Fetal, Developmental, and Parental Influences on Childhood Systolic Blood Pressure in 600 Sib Pairs
The Uppsala Family Study

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Background—Little is known about the contribution of maternal and paternal factors to the inverse association between birth weight and later blood pressure in human offspring. A study of within- and between-family associations of birth weight with blood pressure, which collected data on both parents, would address this gap in our knowledge.

Methods and Results—The study examined families composed of mother, father, and 2 full sibs delivered between 38 and 41 weeks’ gestation within 36 months of each other. A total of 1967 families meeting our inclusion criteria were contacted and 602 were examined (children 5 to 14 years old, 1998 to 2000). Birth weight and gestational age were available from obstetric records. Systolic blood pressure in childhood was inversely associated with birth weight within families (β = −2.3 mm Hg/kg, 95% CI −4.4 to −0.3) after adjustment for gestational age, sex, height, and weight at examination. The between-family effect (β = −1.5 mm Hg/kg, −3.1 to 0.0) was strengthened on adjustment for maternal and paternal height and weight, whereas adjustment for paternal and maternal systolic blood pressure at examination independently attenuated the effect.

Conclusions—The existence of an inverse association of birth weight with systolic blood pressure within families (adjusted for height and weight at examination) demonstrates that factors that vary between pregnancies in the same woman (including fetal genotype) can influence the later blood pressure of offspring. We conclude that this apparent fetal programming effect on blood pressure will not be eliminated solely by interventions aimed at modifying growth and cumulative nutritional status from conception through childhood or other fixed characteristics of future mothers.

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

A large number of studies have reported an inverse association between birth weight and later blood pressure,1,2 with this effect being greatest after adjustment for body size at the time of blood pressure measurement. Barker and colleagues propose that the association is the result of in utero “programming”; suboptimal nutrition in utero leads to adaptive changes in growth and development that produce a susceptibility to elevated blood pressure.3 An alternative explanation is that common genetic factors may both influence size at birth and affect blood pressure.4,5 There remains controversy about the nature of this statistical association, and it has even been suggested that publication bias may have resulted in an overstatement of its size and importance.6

A number of twin studies have been reported that have investigated whether fetal genotype could explain the association of size at birth with blood pressure by looking for an effect within monozygotic twin pairs. In a meta-analysis6 of twin studies7–13 published in 2002, the inverse-variance-weighted combined estimate for the effect within monozygotic twin pairs was −0.6 mm Hg (95% CI −2.2 to 1.0) systolic blood pressure (SBP) per 1-kg difference in birth weight having adjusted for concurrent size. Two other estimates of effect within monozygotic twins have been published subsequently, one14 showing an effect of −1.3 mm Hg (95% CI −4.2 to 1.6) and the other15 an effect of −3.5 mm Hg (95% CI −10.4 to 3.5) SBP per 1 kg difference in birth weight. Overall, this evidence remains inconclusive, not the least because of limited sample sizes, although it is consistent with an in utero programming effect.
If fetal programming does underlie part of the inverse association between size at birth and later blood pressure, then what are the in utero influences that drive this process? Fetal growth is a complex outcome that is influenced by factors that vary from one pregnancy to the next (eg, placental function, fetal genotype, maternal smoking, exercise, diet) and those that can be considered to be fixed maternal characteristics (eg, maternal genotype, height and pelvic dimensions and other factors determined by the mother’s in utero and post-natal growth, cumulative nutritional history up to adulthood).

If fixed maternal characteristics are the primary influences on any fetal programming on blood pressure, then differences in size at birth between full sibs will not be correlated with differences in their childhood blood pressure; these maternal characteristics will by definition not vary from pregnancy to pregnancy. In this case the observed association between size at birth and blood pressure will be driven by differences in fixed maternal characteristics such as mothers’ own genotype and intrauterine, infant, and childhood nutrition and development. However, if differences in size at birth between full sibs do correlate with differences in their later blood pressure, then this effect could be caused by differences in fetal (but not maternal) genotype as well as by features of the in utero environment that vary from pregnancy to pregnancy in the same woman. Resolving these uncertainties is of relevance to public health. Interventions aimed at improving the growth and development of mothers in their pre- and post-natal life would not on their own eliminate the fetal programming of later blood pressure if it could be demonstrated that there is a within-family effect.

The Uppsala Family study was set up to address these issues. Its primary aims were to determine whether an association between birth weight and blood pressure in childhood was observed within full sibships (within-family effect), in which offspring have the same biological mother and father, and to compare the extent of this association with that observed between families.

Methods

Sampling Frame, Eligibility, and Recruitment

The Swedish Medical Birth Registry16 provided information about the deliveries of all women who gave birth to ≥2 infants in the Uppsala Academic Hospital during the period 1987 to 1995. Using these data, we identified mothers who had had ≥2 consecutive live births delivered at 38 to 41 completed weeks’ gestation within 36 months of each other. Among these, we identified 5226 mothers who were living with these index children in Uppsala County.

In a family study of this design, most of the statistical information about the association between birth weight and later blood pressure within families comes from those families whose offspring have discordant birth weights. In the same way, most of the information about the association between birth weight and later blood pressure between families comes from families in which both sibs are either toward the top or bottom ends of the birth weight distribution (ie, from families in which the mean family birth weights are in the upper or lower parts of the distribution). Families in which both offspring have similar birth weights and are close to the population mean are relatively uninformative about either within- or between-family effects. Thus, to increase statistical efficiency we decided that we would recruit only families who fell into 1 of 3 categories: (1) both sibs in bottom one fourth of sex-specific birth weight distribution (ie, <3.42 kg for boys and <3.30 kg for girls); (2) both sibs in the top one fourth of sex-specific birth weight distribution (ie, >3.98 kg for boys and >3.85 kg for girls); and (3) sibs discordant in birth weight (ie, sex-adjusted difference >0.40 kg). Birth weight cutoff points were chosen to result in adequate numbers of families split equally between those with discordant and concordant birth weights of sibs, with the concordants being additionally split equally between those with birth weights in the top and bottom one fourth of the distribution. In total, these 3 groups contained 38% of all families that met our basic inclusion criteria. The Figure shows the distribution of the 600 families included in the analyses according to the mean birth weight of the sib pairs and the birth weight difference within sib pairs.

Starting in March 2000, letters and information sheets were sent to the mothers inviting them, their index children, and the children’s biological father to take part in the study. A small number of families that wished to take part were excluded at this stage either because the biological father of both children was not living within the study area or because one or both parents were born outside of the Nordic area. During an 18-month period, a total of 1967 families who fell into one of our sampling groups were invited to take part. After reminder letters and telephone contacts, responses were received from 71% of families, and just under half of these agreed to take part. In total, 602 (31%) of those families invited were examined between May 2000 and November 2001, when the children were 5 to 14 years old. Participation rates were similar across the sampling groups defined in terms of offspring birth weights.

Physical Examination

For the vast majority of families (95%), all family members were examined on the same occasion. Examinations took place at the Uppsala Academic Hospital and were generally held in the evening (5 to 9 pm). The examination of each family was conducted by a pair of nurses working together. A total of 5 nurses undertook the examinations, each of whom was trained by members of the research team. On arrival, the examination protocol was explained to the family, and any concerns or questions received responses. Signed informed consent of the mother (and father, if present) was obtained.

Measurements were made in a fixed sequence: blood pressure, height, sitting height, weight, triceps and subscapular skinfolds, and waist and hip circumference. Children’s Tanner stage (pubic hair for boys and girls and breast development for girls) was assessed directly by visual inspection. Blood samples (3 × 7.5 mL vacutainers) were taken last. For children, anesthetic cream (EMLA) was applied a minimum of 60 minutes before venipuncture.

Blood pressure and pulse rate were measured with a Dinamap “Compact T” Monitor (Critikon Ltd), which measures SBP with greater precision than does the Model 8100.17 The device was
checked by the suppliers two thirds of the way through the field work and found to be accurately calibrated. Three measurements were taken with the subject in a sitting position, on the left arm with an interval of ~1 to 2 minutes between each reading. The size of the blood pressure cuff (Dura-Cuf, Johnson & Johnson) used was in accordance with the recommendations of the 1987 Task Force on Blood Pressure Control in Children.26 In line with previous practice in similar studies26 and with recent recommendations,20 we used the mean of the 3 readings in the analysis.

All anthropometric measurements were taken 3 times and the mean of the 3 measurements was used in the analysis. Height was measured with a wall-fixed, standardized stadiometer (Ulmer) to an accuracy of 0.1 cm with subjects walking around the room between measurements. Weight was measured (with the subject wearing undergarments) to an accuracy of 0.1 kg with an electronic scale (Seca). Standard triceps and subscapular skinfolds were measured using a Harpenden caliper. The sum of the means of the skinfold measurements at both sites was used in the analysis.

Additional Information Sources

Parents were given questionnaires that were completed and returned to us by 97% of the participating families. These questionnaires covered the demographic and socioeconomic circumstances of the family members and their lifestyle, health-related behaviors, and medical history. The highest levels of education obtained by both the mother and father were classified as university, high school (minimum 10 to 11 years’ full-time education), and below. Occupational social class of each parent was classified on the basis of the Swedish socioeconomic classification.23

Birth weight and gestational age (based on date of last menstrual period or when available on ultrasound) of the children and maternal smoking at the time of first booking were obtained from the Swedish Medical Birth Registry.16

Statistical Methods

Random effects linear regression models that take account of the family structure of the data were used to investigate the effect of birth weight on blood pressure as described elsewhere.22 Each model involved running 2 regressions simultaneously. The first regression obtains the within-family association, regressing the difference in blood pressure between the sib pairs on the differences in their birth weights. The second regression obtains the between-family effect, regressing the mean blood pressure of the sib pairs on their mean birth weights. The random effects regression coefficients (combined coefficients) were then obtained as the weighted average of the within- and between-family effects, each coefficient weighted by the inverse of its variance.22,23 The Hausman test was used to test whether the within-family and the between-family coefficients differed.24 All models were adjusted for age and sex at examination. This approach was also used in descriptive analyses to assess the association of a number of covariates with birth weight and separately with blood pressure. For these initial analyses, we have reported the estimates from the combined model only because there was no evidence of heterogeneity of between- and within-family effects.

In this study of children with a wide range of ages extending into puberty it is particularly important to take account of size relative to children of the same age. We therefore converted children’s weight, height, and body mass index (BMI) at examination into standard deviation scores (SDS) based on Swedish population reference values.25,26 Birth weight SDSs were also calculated relative to the Swedish reference values.27

The regression analyses reported in this article used absolute birth weight (adjusted for gestational age) to make results directly comparable with the bulk of the existing literature. A parallel set of analyses (not reported) was undertaken using birth weight for gestational age SDS instead that led to the same conclusions. Analyses were conducted with the statistical software package Stata.28

The target sample size was 650 families. This was estimated to provide an 80% probability of detecting a significant (P<0.05) difference in the strength of association of birth weight with systolic blood pressure within and between families of 3.4 mm Hg/kg difference (the effect size estimated in a pilot study); however, we were able to recruit only 602 families.

Modeling Strategy

The sequence in which variables were added to successive models was guided by our assessment of the likely causal pathways and confounders that exist. We did not use any automatic variable selection procedures based on statistical significance or goodness-of-fit statistics. Our interest was to see how the strength of the association between birth weight and blood pressure changed on the addition of each variable or set of variables to each model.

Starting from our basic model (adjusted for age and sex), we looked first at the effect of adding gestational age and concurrent height and weight (as standard deviation [SD] scores). Adjustment for these factors is common in other similar studies and provided the most generally comparable results. At this stage, we also looked at whether there was any indication of Tanner stage playing a mediating role, with pubertal development being on a pathway between fetal growth and childhood blood pressure. This was a plausible speculation because blood pressure is known to rise during the course of pubertal development,28 and there is evidence that impaired fetal growth is associated with earlier onset of puberty.30–32

Our next main interest was to see how far the effects adjusted for age, sex, gestational age, and concurrent size were attenuated by adjusting for parental characteristics. We did not include Tanner stage in these later models because it had been examined as a potential factor on the causal pathway rather than as a confounder per se. Of particular importance was to see whether paternal factors had any effect independent of maternal characteristics because this would provide some evidence for a genetic mechanism operating through fetal genes inherited from the father.

Ethical Approval and Data Protection

The study received full approval from the Uppsala University ethics committee and from the Swedish Datainspektion Agency.

Results

Complete blood pressure data for both children (618 boys and 582 girls) were obtained for 600 families. Mean children’s age at examination was 10.1 years (range 5.5 to 13.8). Mean weight was 36.5 kg (SD 10.4) and mean height was 142 cm (SD 12.1). Relative to the current national Swedish reference data26 (based on children born from 1973 to 1975), the children in the study were slightly larger for their age, having a mean weight SDS (standardized for age and sex) of 0.30 (SD 1.2) and a mean height SDS of 0.09 (SD 1.1). With regard to pubertal stage, 80% of boys and 70% of girls were classified as Tanner stage 1 (no pubic hair), whereas 5% of boys and 10% of girls were Tanner stage 3 or above (coarse, curly pubic hair). The mean age difference at examination between sibs within families was 2.1 years (range 0.9 to 3.0).

The mean age at examination of mothers (N=600) was 39 years (range 28 to 53) and of fathers (N=567) was 41 years (range 29 to 69). In 76% of the families, the sib pairs were the mother’s first- and second-born, in 16% they were second- and third-born, whereas the remaining 8% of families had pairs of consecutive higher-order births.

Systolic Blood Pressure

The mean SBP of the 1200 children was 112.4 mm Hg (SD 11.8), increasing by 2.4 mm Hg (95% CI 2.0 to 2.7) per year of age. Childhood SBP increased with Tanner stage and
showed a monotonic positive association with weight SDS, BMI SDS, and height SDS (Table 1).

It is clear from Table 1 that the association of childhood SBP with weight SDS is at least as strong as the SBP association with BMI SDS. In a random effects linear regression model a 1-SD increase in childhood weight SDS is associated with a 2.78 mm Hg (95% CI 2.26 to 3.30) increase in childhood SBP, whereas the corresponding increase per 1 SD in childhood BMI SDS was slightly smaller: 2.30 mm Hg (95% CI 1.76 to 2.83) per 1 SD increase. On additional adjustment for childhood height SDS, the effect of weight SDS on SBP was attenuated to 2.44 (95% CI 1.72 to 3.17) and of BMI SDS to 1.79 (95% CI 1.24 to 2.35).

Childhood SBP was independently associated with both maternal and paternal systolic blood pressure. When both parents’ SBPs were entered into a random effects linear regression model together, for every 1 mm Hg increase in maternal SBP, offspring SBP increased by 0.11 (95% CI 0.07 to 0.16) mm Hg, the equivalent effect for paternal SBP was 0.15 (0.11 to 0.19) mm Hg. Both of these estimates were adjusted for children’s sex, age, and Tanner score and parents’ sex and age at examination and took account of family clustering. The strength of these positive associations was only minimally attenuated when adjusted for child SDS height and weight and parental height and weight. The fully adjusted maternal effect was 0.10 (0.05 to 0.14) mm Hg offspring SBP per 1 mm Hg increase in maternal SBP, the equivalent estimate for the paternal effect being 0.15 (95% CI 0.05 to 0.19). These data suggest that the independent associations of maternal and paternal SBP with offspring SBP are not caused by confounding through correlations in body habitus among family members.

Size at Birth

The mean birth weight of the children was 3.70 kg (SD 0.6). Relative to the Swedish reference standard this was an SDS of 0.42 (SD 1.23). Birth weight showed the expected associations with fetal and maternal characteristics (not shown). Boys were heavier than girls, and birth weight increased with gestational age, parity, and maternal height. Maternal weight was positively associated with birth weight despite that it was measured at examination between 5 and 13 years after delivery; mean birth weight of offspring whose mothers were in the bottom fifth of maternal weight was 3.40 kg compared with 3.94 kg for those whose mothers were in the top fifth. There was also a clear association of paternal height with birth weight (3.54 kg in bottom fifth versus 3.94 kg in top fifth), although this was not as pronounced as seen for maternal height (3.48 kg versus 3.97 kg). Paternal weight at examination showed little evidence of a systematic association with offspring’s birth weight.

Data on maternal self-reported smoking habits in early pregnancy were available for 1155 offspring (96%) from the Medical Birth Registry. As would be expected, nonsmokers had larger babies than smokers, measured both in terms of absolute birth weight and by birth weight for gestational age SDS. Overall, the prevalence of smoking in pregnancy was 12% (135/1155). Among the 556 families in which complete maternal smoking data were available, the smoking habits of mothers were the same in both pregnancies in 516 (483 nonsmokers, 18 smoked 1 to 9 cigarettes per day, and 15 smoked ≥10 per day). In 16 families, women took up smoking or increased their consumption from the earlier to

### TABLE 1. Mean SBP of Children by Selected Characteristics

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the later pregnancy, whereas in 24 families mothers gave up or decreased their consumption between pregnancies. Because of this strong concordance in smoking habit between consecutive pregnancies, within-families differences in smoking between pregnancies had almost no aggregate effect on differences in birth weight between sibs; however, between-families smoking in pregnancy was associated with a 250-g (95% CI 132 to 375) deficit in mean family birth weight, having adjusted for gestational age and sex.

To be included in the study, children had to be born between 38 and 41 completed weeks of gestation. Sibs had the same gestations in 33% of families, a difference of 1 week in 44%, and a difference of ≥2 weeks in 22% of families.

Size at Birth and Childhood Blood Pressure

Based on a series of regression models, the association of the children’s birth weight with their SBP at examination is shown in Table 2. For each model, 3 estimates are given: the within-family, the between-family, and the combined effect. This latter combined effect is estimated on the assumption (confirmed by the Hausman test in all analyses) that the within- and between-family effects are not significantly different.

In an analysis adjusted for age and sex alone, there was no evidence of an association of birth weight with blood pressure (model 1). Adjustment for concurrent size (height and weight SD scores) resulted in an inverse association between birth weight and SBP (model 3). Additional adjustment for gestational age strengthened these associations (model 4), whereas adjustment for Tanner stage reduced the size of the associations (model 5).

In the main analyses presented in Table 2 and later, we chose a priori to adjust for weight SDS rather than BMI SDS because this provided an intuitively simpler approach to the data. An additional reason to select weight SDS rather than BMI SDS is that as shown in the analyses reported above, weight SDS appears to be a little more strongly associated with SBP in these children than is childhood BMI SDS. Interestingly, if in model 4 instead of adjusting for weight SDS we adjusted for BMI SDS, the size of the association of birth weight with SBP was not as large. The within-family effect was $-2.16$ (95% CI $-4.21$ to $-0.12$) mm Hg/kg, the between-family effect was $-1.46$ (−3.04 to 0.12), and the combined effect was $-1.63$ (−2.85 to −0.41). Adding the sum of skinfold thicknesses to any of the models that already contained height SDS and weight SDS, or height SDS and BMI SDS, increased the strength of the association between birth weight and systolic pressure by ≈1%.

The influence of smoking on the association of birth weight with children’s blood pressure was investigated by adding it to model 4 as a 3-level categorical variable. This had only a small effect on the strength of association between birth weight and children’s SBP (not shown). In the smaller subset of children for whom parental socioeconomic data were available (N=1158 for maternal and N=1086 for maternal plus paternal), the effect of adding educational level (as a 3-level categorical variable) together with occupational social class (as a 4-level categorical variable) of either mother or both parents had almost no effect on the between-family or combined estimates (not shown).

Parallel analyses of the association of birth weight with children’s diastolic blood pressure showed similar qualitative changes in the sign and magnitude of the changes from model 1 to model 5, although in absolute terms effects were much smaller and none were statistically significant.

Parental Weight, Height and Blood Pressure

Table 3 shows the effects of adding to the models examination characteristics of the mother and/or father in the subset of 566 families with complete information for fathers as well as other family members. These characteristics are fixed within each family (because they were measured at one point only) and therefore cannot influence the association of birth weight with SBP within families. Hence, the within-family estimates shown in Table 3 are the same for all models. In this subset, the associations between birth weight and children’s SBP adjusted for age, sex, gestational age, and childhood height and weight SDS (model 6) are almost identical to those based on the same model that includes all 600 families (model 4, Table 2).

Adjustment for maternal weight, height, and age at examination (model 7) considerably strengthened the between-family effect, whereas adjustment for fathers’ size (model 8) strengthened it to a smaller extent. Simultaneous adjustment for fathers’ and mothers’ height and weight (model 9) strengthened it more than did adjustment for size of either parent alone. Adjustment for maternal SBP (model 10) or paternal SBP (model 11) alone resulted in a moderate attenuation of the association between birth weight and SBP in the children.
Simultaneous adjustment for mothers’ and fathers’ SBP (model 12) reduced the association of birth weight with SBP more than did adjustment for either on its own.

**Discussion**

This study confirms the existence of an inverse association of birth weight with SBP in childhood (−1.80 mm Hg/kg), having adjusted for gestational age and concurrent height and weight. A systematic review of this association found an effect adjusted for height and weight (but not gestational age) of −1.45 mm Hg/kg for children 10 years old. This is similar to the equivalent estimate in our study (−1.52 mm Hg/kg).

A novel contribution of this study is to demonstrate that the difference in size at birth between full sibs is inversely associated with the difference in childhood SBP. This has important implications for our understanding of the nature of the association. Specifically, the within-family effect must be driven by characteristics that change from one pregnancy to the next. It cannot be explained by maternal genotype or the mother’s cumulative nutritional history and growth in utero and childhood because by definition these are fixed and cannot vary from one pregnancy to the next in the same woman.

It has been argued that “in utero” programming of blood pressure in one generation may be in part a reflection of the in early life circumstances of previous maternal generations. This was recently emphasized in an article in *Nature* that considered the biological basis for the developmental origins of adult disease: “Poor nutrition during her own early development may reduce the capacity of a female to assimilate nutrients, and so resulting in an impaired ability to provision her offspring.” This argument has been used to propose that improving the early life nutrition of mothers is the key intervention that follows from the fetal origins hypothesis. Our data clearly show, however, that fixed differences between mothers (eg, variation in early life maternal nutrition) are in no way necessary components of any in utero programming effects. Instead, from the perspective of any future intervention in well-nourished populations, as found in Sweden today, additional optimization of maternal nutrition in early life and childhood will not eliminate the fetal programming of later blood pressure.

What factors can account for this inverse association between birth weight and blood pressure seen within families? The genotype of the fetoplacental unit differs between full sibs. Thus, the association could be caused by fetal genes from one pregnancy to the next is at present unclear. Nevertheless, it is possible that interventions aimed at modifying factors that vary from one pregnancy to the next in the same woman may have beneficial long-term effects on the blood pressure of offspring.

This study has a number of limitations. We do not have definitive genetic confirmation of paternity for identifiable individuals, although at recruitment we explicitly said that we only wanted to recruit sibs who had the same biological father. In an analysis of de-identified data carried out for
other purposes, paternal genotypes were inconsistent only for one family. This makes it unlikely that our results will be affected to any important degree by inclusion of half-sibs or nonbiological fathers.

One might argue that our results are not generalizable to the population of all singleton term births because our design selected mothers and fathers whose offspring were either concordant or discordant in birth weight. As discussed in Methods, this was done to improve statistical efficiency and should not in itself introduce bias. Indeed, the cutoffs selected for defining concordance or discordance were not extreme, with 38% (1967/5226) of all families who had 2 full-term births born within 3 years of each other being selected as eligible for inclusion on the basis of their offsprings’ birth weights. Moreover, the response rate to invitation was similar across the sampling groups.

Consistent with other studies, the inverse association between birth weight and later blood pressure only became apparent on adjustment for concurrent body size. It has been proposed that this shows that it is change in size between birth and some later point in life that is causally related to blood pressure rather than size at birth per se. Statistical adjustment for concurrent size can be seen as the equivalent of looking at effects holding concurrent size constant. This could be then extended to a hypothetical situation in which we study a population composed entirely of people of the same age, height, and weight. Here, any effect of birth weight (or size at any later age) on subsequent blood pressure would indicate that blood pressure was related to the particular growth trajectory taken by individuals to reach this specified height and weight. This way of looking at the problem shifts the debate away from whether concurrent or earlier size is the most important. One can acknowledge the powerful effect of contemporary size and at the same time investigate the separate issue of whether differences in the growth trajectory from conception to reach a specific body size has any effect on blood pressure.

As found in other studies, we have shown that SBP increases strongly with Tanner stage. Few studies, however, have been able to look at the role of pubertal stage on the association of birth weight with childhood blood pressure. We found that adjustment for Tanner stage attenuated the strength of this association. We interpret this as evidence that pace of pubertal development mediates at least part of the association of birth weight with SBP. This is consistent with the emerging evidence that impaired fetal growth may result in earlier onset of puberty, in part through accelerated postnatal growth.

Ours is the first study that has systematically investigated the influence of parental size on the association of birth weight with later blood pressure. We have found that this association is strengthened by taking account of parental weight and height at examination. What is particularly striking is that it is paternal as well as maternal size that has this effect. We interpret these results as suggesting that it is fetal growth relative to that expected based on the size of both parents that is important for later blood pressure, rather than birth weight for gestational age per se. Thus, elevated blood pressure may be seen as being related to impairment of fetal growth, not just being small for gestational age, which does not differentiate between babies who are small because their parents are small and those who are small because of impaired growth.

A genetic contribution to the inverse association of birth weight with blood pressure is suggested by the fact that adjustment for paternal SBP reduces the strength of the between-family effect to an even greater degree than does adjustment for maternal SBP. This interpretation is strengthened by our finding that the influence of paternal and maternal SBP on the SBP of offspring are of the same order and, most important, are independent of each other and of body size, ruling out an influence of assortative mating and confounding by family clustering of body habitus. Only one other study has looked at the effect of simultaneous adjustment for maternal and paternal blood pressure as a continuous variable on the strength of the association of birth weight with blood pressure. This study found a similar reduction in strength of association between ages 16 and 26 years on joint adjustment for maternal and paternal blood pressure (from −2.24 mm Hg/kg to −1.71 mm Hg/kg).

In conclusion, this study shows for the first time that birth weight differences between consecutive full sibs are inversely associated with differences in SBP in childhood having adjusted for concurrent size. These within-family effects may be driven by fetal genotype, maternal characteristics such as diet and exercise, as well as variations in the performance of the fetal supply line. Some of these within-family influences on fetal growth and nutrition may be modifiable; however, they cannot be explained by fixed maternal characteristics such as maternal genotype and cumulative nutritional status and growth from conception through childhood. Thus, interventions aimed solely at improving the early-life nutrition and growth of females will not eliminate the fetal programming of later blood pressure. Finally, the results suggest that some of the inverse association of birth weight with later blood pressure may be explained by fetal genotype because adjustment for paternal SBP attenuates the between-family effect.

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