Is There a Sex Difference in the Association between Birth Weight and Systolic Blood Pressure in Later Life? Findings from a Meta-Regression Analysis

Debbie A. Lawlor, Shah Ebrahim, and George Davey Smith

From the Department of Social Medicine, University of Bristol, Bristol, United Kingdom.

Received for publication November 29, 2001; accepted for publication July 22, 2002.

The aim of this study was to determine whether a sex difference exists in the association between birth weight and systolic blood pressure. A meta-analysis of all observational studies \((n = 57)\) in which the study population contained both males and females and the association between birth weight and blood pressure was presented as a linear regression coefficient was undertaken. There were no differences in the pooled regression coefficients between males and females combining all studies; the regression of blood pressure on birth weight for males was \(-1.27\) (95% confidence interval: \(-1.77, -0.77\)) mmHg/kg and for females was \(-1.24\) (95% confidence interval: \(-1.90, -0.58\)) mmHg/kg. When studies in which blood pressure had been measured in childhood were considered separately from those in which it was measured in adulthood, there were no sex differences in either age group. The pooled regression coefficient tended to be weaker in studies reporting sex-specific results than in those reporting combined results. These findings suggest that reports of sex differences in the association between birth weight and blood pressure are chance findings.

birth weight; blood pressure; meta-analysis

Low birth weight is associated with high blood pressure and other cardiovascular disease outcomes in later life, but the underlying mechanisms responsible for this association are not established (1). One suggestion is that poor intrauterine nutrition leads to small birth size and also, depending upon the timing, “programs” selective physiologic changes leading to later disease (2, 3). Alternative hypotheses include common genetic factors independently causing both low birth weight and increased cardiovascular disease risk (4) and programming due to nonnutrition factors, such as altered exposure to glucocorticoids or other hormonal factors (5).

The lack of good evidence for an effect of maternal diet on either birth weight or offspring cardiovascular disease has cast doubt on the importance of nutritional programming (6). However, this line of argument fails to distinguish between maternal and fetal nutrition (6). Even large changes in maternal diet may have little impact on fetal growth if biologic mechanisms are in place that protect the fetal supply of nutrients, whereas insults to fetal nutrition will have a large impact (2, 3, 6). Fetal nutrition is determined by a number of factors but in particular by placental function and fetal demand. Fetal demand is, in part, determined by the fetal growth trajectory, with faster growing fetuses being more vulnerable to impaired fetal nutrition (2, 3, 6).

Some, but not all, studies have reported sex differences in the association between birth weight and blood pressure in later life (1). Since the growth trajectories differ between males and females, with male fetuses growing on average at a faster rate than female fetuses, sex differences may be anticipated in this association if fetal nutritional programming is the underlying mechanism (2, 3). Animal studies suggest that there is a sex difference in the magnitude of the association between birth weight and later life cardiovascular disease, and one commentator has suggested, “One possibility is that the greater vulnerability of such fetuses on a fast growth trajectory could contribute to the rise in coronary heart disease with Westernisation and the higher death rates in men” (2, p. 146). An alternative explanation for the sex difference reported in some studies is that it is due to random variation associated with subgroup analyses (7).

The aim of this study was to determine whether a sex difference exists in the association between birth weight and systolic blood pressure.

MATERIALS AND METHODS

All studies included in a recent systematic review of the association between size at birth and systolic blood pressure...
were retrieved (1). In addition, a Medline search from March 1999 (1 year prior to the cutoff date of the review) to June 2001 was conducted using the following key words: “birth weight,” “blood pressure,” and “hypertension.” Bibliographies of retrieved articles were used to further identify relevant studies. Studies, in any language, were included if the study population contained both males and females and the association between birth weight and blood pressure was presented as a linear regression coefficient. Studies in which blood pressure was measured in only the first year of life were excluded, because blood pressure during this period is very labile and difficult to measure with accuracy.

For studies presenting sex-specific results, these were pooled separately for males and females. Results from studies with combined results only were also pooled to determine whether there was any systematic difference between the studies that published sex-specific results and those that did not. In addition, it was noted for all studies presenting combined results only whether the authors commented upon sex differences.

For studies with repeat measures at different ages, the result of the first (youngest age) outcome assessment was included in the meta-analysis, and sensitivity analyses were conducted by replacing this, in turn, with each repeat measure. Results were pooled using the random effects method of DerSimonian and Laird. Heterogeneity was assessed using meta-regression analysis (8). All analyses were undertaken using Stata version 7 software (8).

RESULTS

Ninety-one papers were retrieved and, of these, 44 papers describing 57 studies fulfilled our inclusion criteria (figure 1) (9–52). These studies included populations from the United Kingdom (9–11, 19, 22, 29, 37, 39, 40, 45, 46, 48, 51–53), Japan (12, 24), Finland (13, 33, 54), the United States (14, 34), Jamaica (15, 22, 41–43), Italy (16, 35), Israel (17), Croatia (20), Australia (21, 36, 44), India (25, 26), China (27, 47), Guatemala (27), Chile (27), Nigeria (27), South Africa (28), Zimbabwe (30), Argentina (31), the Netherlands (32, 50), France (38), and Denmark (49).

Nineteen of the included studies presented results stratified by sex (9–23). Of these 19, two did not discuss sex differences (9, 16), and only five undertook formal tests of statistical interaction (10, 11, 15, 18, 19). Of the 38 studies presenting combined results (24–52), 23 (61 percent) stated that there was no sex difference in the association between birth weight and blood pressure (22–26, 29–35, 37, 40, 42–44, 47, 49–52); four of these reported formal tests of statistical interaction (24, 31, 32, 37). Our results did not differ when a different one of a set of repeat measures was entered, so all results are presented with the first measure from those
studies in which repeat measures were undertaken. There were no substantial differences in the pooled regression between males and females combining all studies or when studies in which blood pressure had been measured in childhood or adolescence (under 18 years) were considered separately from those in which it was measured in adulthood (table 1). There was considerable heterogeneity between studies. This was largely explained by differences between studies in the age at which blood pressure was assessed (table 1). When a term for geographic location of the study (categorized as “Europe, North America, or Australia,” “Latin America or West Indies,” “Japan, China, India, or Africa”) was entered into the meta-regression analysis, this did not importantly influence heterogeneity. Pooled regression coefficients from studies with combined results tended to be higher than those from studies with sex-specific results.

**DISCUSSION**

We found no sex difference in the association between birth weight and systolic blood pressure in later life. Our findings, among studies presenting combined results only, of a 2-mmHg increase in blood pressure with each 1 kg of lower birth weight, after adjustment for current size, and of a tendency for stronger effects among adults compared with children are consistent with the conclusions of a recent systematic review of the association between birth weight and blood pressure (1). The tendency for the pooled regression coefficient to be weaker in studies reporting sex-specific results than in those reporting combined results suggests that investigators may be more likely to undertake subgroup analyses when overall results are relatively weak.

It has been suggested that birth weight is not a sensitive measure of poor fetal nutrition or of the effect of fetal growth trajectory, because the same birth weight can reflect many different paths of growth (2, 3). For example, a long, thin baby may have the same birth weight as a baby whose height and weight are more proportioned, these two alternatives representing different growth trajectories. Most studies have used birth weight as a measure of fetal growth and have identified an inverse association between this and adult cardiovascular disease. One study has suggested that the body proportions of newborn boys and girls differ and are associated with different adult cardiovascular disease outcomes (54). Investigators in this study suggested that shortness (female pattern) at birth was associated with persistent liver changes, resulting in increased cholesterol and fibrinogen levels, and thinness (male pattern) with increased insulin resistance. However, these results may be due to post hoc subgroup analyses and the same investigators, using a cohort from the United Kingdom, have also concluded that low birth weight in women is more strongly associated with insulin resistance than in men (53).

Our findings suggest that either programming is not affected by fetal growth trajectory, which would imply that fetal nutrition was not an important part of the mechanism

| TABLE 1. Pooled regression coefficient of systolic blood pressure (mmHg) per kg of increase in birth weight for studies with sex-specific results and studies with combined results only |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                               | No. of studies  | Pooled adjusted regression* | Test for heterogeneity Q† | Probability of heterogeneity (p value) | Between-study variation (% without including median age in meta-regression analysis) | Between-study variation (% with median age included as continuous variable in meta-regression analysis) |
| All studies                                   |                 | Coefficient 95% CI†         |                     |                             |                             |                             |
| Sex-specific studies                          |                 |                              |                     |                             |                             |                             |
| Male                                          | 19              | −1.27 −1.77, −0.77          | 56.1                | <0.01                       | 0.64                        | 0.29                        |
| Female                                        | 19              | −1.24 −1.90, −0.58          | 93.1                | <0.01                       | 1.36                        | 0.49                        |
| Combined studies                              | 38              | −2.00 −2.49, −1.50          | 108.5               | <0.01                       | 1.15                        | 0.71                        |
| Studies with outcome blood pressure measured in childhood (under 18 years) |                 |                              |                     |                             |                             |                             |
| Sex-specific studies                          |                 |                              |                     |                             |                             |                             |
| Male                                          | 10              | −0.99 −1.45, −0.53          | 16.5                | 0.06                        |                             |                             |
| Female                                        | 10              | −0.70 −1.50, 0.11           | 37.9                | <0.01                       |                             |                             |
| Combined studies                              | 27              | −1.64 −2.16, −1.12          | 65.5                | <0.01                       |                             |                             |
| Studies with outcome blood pressure measured in adulthood |                 |                              |                     |                             |                             |                             |
| Sex-specific studies                          |                 |                              |                     |                             |                             |                             |
| Male                                          | 9               | −2.21 −3.56, −0.86          | 38.5                | <0.01                       |                             |                             |
| Female                                        | 9               | −2.33 −3.55, −1.10          | 28.4                | <0.01                       |                             |                             |
| Combined studies                              | 11              | −3.26 −3.94, −2.58          | 11.5                | 0.3                         |                             |                             |

* Regression coefficients were adjusted for current size (weight, ponderal index, or body mass index) in all studies.
† Q, test for heterogeneity statistic; CI, confidence interval.
associating birth weight with blood pressure, or that the association between low birth weight and later blood pressure is not entirely explained by programming. If programming is influenced by fetal nutrition, as claimed (2,3,6), then a sex difference would be expected because of a faster growth trajectory’s having a requirement for greater fetal nutrition on average.

An alternative explanation for our results is that the remaining heterogeneity between studies, due to differences between study populations, obscures any sex difference. This is unlikely because age contributed importantly to the heterogeneity between studies, and sex differences were not apparent when the analyses were considered by age group. Geographic variations between studies, which will to some degree encompass racial, ethnic, and economic differences between study populations, did not explain the heterogeneity between studies. It may be that, since the majority of studies did not present results stratified by sex, we had insufficient data to determine a true sex difference. However, the majority of the studies that presented combined sex results (60 percent) stated that there were no sex differences.

Our results suggest that subgroup analyses on the bases of sex may be undertaken only when the overall results are weak. Further, very few studies, even when discussing sex differences, undertook formal tests of statistical interaction. This finding has implications for other epidemiologic studies, and it demonstrates the importance of a priori hypotheses regarding sex differences and of formal tests of statistical interaction in epidemiologic studies.

ACKNOWLEDGMENTS

D. A. L. is funded by a Medical Research Council research training fellowship.

REFERENCES