Blood Pressure in Relation to Birth Weight in Twins and Singleton Controls Matched for Gestational Age

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Associations between adult blood pressure and birth weight were investigated in 122 same-sex twin pairs aged 18–50 years and 86 singleton controls matched according to maternal age and parity, gender, gestational age, and current age who were recruited via an obstetric database in Aberdeen, Scotland, in 1999. Twins weighed on average 425 g less than controls at birth (p < 0.001) but did not differ significantly in adult height or systolic or diastolic blood pressure from the controls. Among controls, the differences in systolic and diastolic blood pressure per kg of difference in birth weight, adjusted for gender, gestational age, current age, body mass index, smoking, physical activity level, and alcohol intake, were –4.3 (95% confidence interval (CI): –12.8, 4.3) and –6.1 (95% CI: –10.8, –1.5) mmHg/kg, respectively. In unpaired analysis among all twins, the equivalent values were –0.1 (95% CI: –4.0, 3.8) mmHg/kg for systolic pressure and –0.4 (95% CI: –2.9, 2.2) mmHg/kg for diastolic pressure, while in within-pair analysis the values were –0.9 (95% CI: –6.4, 4.6) mmHg/kg for systolic pressure and –0.2 (95% CI: –4.1, 3.7) mmHg/kg for diastolic pressure. The results suggest that in-utero growth restriction in twins is not a major determinant of their blood pressure as adults.

birth weight; blood pressure; twins

The “fetal origins” or “programming” hypothesis proposed by Barker et al. (1) suggests that poor intrauterine growth resulting from suboptimal maternal nutrition leads to metabolic changes which have adverse effects on blood pressure, lipid levels, and glucose tolerance in later life. The original observational studies cited in support of this hypothesis reported inverse associations between birth weight and blood pressure of up to 5 mmHg of systolic blood pressure per kg of birth weight (2, 3). Subsequent studies have generally found similar but smaller effects: A systematic review of the literature published in 2000 suggested that the size of the effect was approximately 2 mmHg of difference per kg of birth weight (4), while a more recent meta-analysis of 37 studies suggested that the true effect could be even lower, possibly less than 1 mmHg/kg (5).

The possibility that maternal nutrition is the causal factor in this association is supported by the finding that maternal protein restriction in pregnancy can increase blood pressure among offspring in rats (6). However, observations of the offspring of mothers who were undernourished during the Dutch famine (7) or the siege of Leningrad (8) failed to demonstrate a clear influence of maternal dietary restriction on adult blood pressure. A number of alternative explanations for the association have been suggested: The possibility of confounding by socioeconomic factors was tested but was not supported by a large Finnish study (9), while the role of genetic influences (10–12) or other intergenerational factors (13, 14) remains unresolved.

Twins provide investigators with an opportunity to explore some of these possibilities, since they have lower birth weights for gestational age than singletons and often exhibit substantial birth weight differences within pairs. Twins are automatically matched according to maternal nutrition (though not necessarily for placental transfer of nutrients) and socioeconomic and other environmental conditions in childhood; furthermore, dizygotic twins share 50 percent of their genes, while monozygotic twins share all of their genes. If the lower birth weight among twins compared with singletons is not associated with a higher risk of adult disease, this argues against a direct association between low birth weight...
and adult disease risk, though it does not rule out an influence of maternal nutrition. Alternatively, if the association between birth weight and adult disease risk is attenuated in within-pair analyses in dizygotic twins and absent in monozygotic twins, it is more likely that genetic factors play a role.

Results from nine studies of within-pair birth weight and blood pressure differences among twins, ranging in size from 16 to 861 monozygotic pairs and from 39 to 449 dizygotic pairs, have recently been reported (14–22). None of these studies found a significant association between birth weight differences and blood pressure differences within monozygotic pairs, though one study found a significant negative association in dizygotic pairs (14). However, only four of these studies were carried out in subjects over age 20 years (15, 17–19); of these, only two were able to use obstetric records rather than self-reported values for birth weight (17, 18), and only one included adjustment for differences in adult smoking status and alcohol consumption (19).

The Aberdeen Maternity and Neonatal Databank is a computerized register of all births that have occurred at Aberdeen Maternity Hospital in Aberdeen, Scotland, since 1949. It contains detailed information on gestation and birth weight recorded at delivery. We traced all same-sex twins born between 1949 and 1980 at this hospital who were currently living in the Grampian Region to study the influence of birth weight differences on differences in cardiovascular disease risk factors among adults, using DNA fingerprinting to assess zygosity. We also recruited singleton controls matched according to sex, gestational age, mother’s age, and parity to compare the associations between twins and singletons in the same population.

MATERIALS AND METHODS

Subjects

Between 1949 and 1980, there were 792 same-sex twin livebirths at Aberdeen Maternity Hospital. We were able to trace one or both twins from 619 (78 percent) of these pairs via National Health Service records. Fifteen pairs in which one or both twins were unsuitable for medical reasons were excluded by the family doctor. Information about the study was sent to all other persons who were currently living in the Grampian Region to study the influence of birth weight differences on differences in cardiovascular disease risk factors among adults, using DNA fingerprinting to assess zygosity. We also recruited singleton controls matched according to sex, gestational age, mother’s age, and parity to compare the associations between twins and singletons in the same population.

The protocol for the study was approved by the Grampian Research Ethics Committee, and all subjects gave written consent to participate.

Measurements

All subjects completed a questionnaire on medical history, occupation, and lifestyle that included questions on smoking based on those in the Scottish MONICA study (23). The physical activity questions were modified versions of those used for the Framingham Physical Activity Index (24), which provided a physical activity level expressed as the ratio of total energy expenditure to basal metabolic rate. Daily alcohol intake (g) was assessed by means of a semiquantitative food frequency questionnaire (25). Height was measured to the nearest 1 mm; weight was measured to the nearest 0.1 kg, and body mass index was calculated as weight (kg)/height (m)². Blood pressure was measured with an Omron HEM 705 CP automatic sphygmomanometer (Omron Healthcare GmbH, Hamburg, Germany) with the subject resting supine on an examination couch. Two readings were taken 10 minutes apart, and the average was used in the analysis. A venous blood sample was taken for zygosity analysis by DNA fingerprinting in the Department of Medical Genetics at the University of Aberdeen. Information on the birth weights and gestational ages of twins and controls was obtained from the Aberdeen Maternity and Neonatal Databank records.

Data analysis

Three monozygotic and four dizygotic twin pairs in which one or both twins were on antihypertensive medication and three controls who were on antihypertensive medication were excluded from the analysis. Two dizygotic twin pairs in which the difference in body mass index was greater than 15 were also excluded from the analyses.

Differences in all variables within twin pairs were calculated as firstborn minus secondborn. This was chosen in preference to differences between heavier and lighter twins because the distribution of birth weight differences is normally distributed for the former but not the latter (26). The distribution of all variables was tested for normality using the Kolmogorov-Smirnov test. Difference in smoking status was assessed by coding current smokers, ex-smokers, and nonsmokers as 2, 1, and 0, respectively, and subtracting the code for the secondborn twin from that for the firstborn twin.

Differences in birth weight, adult weight, height, body mass index, body fat, and blood pressure between twins and controls were assessed by t test or Mann-Whitney test for nonnormally distributed data. The association between blood pressure and birth weight in unpaired twins and in controls was assessed by multiple regression analysis with age, gender, gestational age, body mass index, smoking category, physical activity level, and alcohol intake included as confounding variables. The association between blood pressure difference and birth weight difference within twin pairs was also assessed by multiple regression analysis with age, gender, body mass index difference, smoking category...
TABLE 1. Mean values for birth weight and adult characteristics of twins and controls in a study of adult blood pressure and birth weight, Aberdeen, Scotland, 1949–2000

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monozygotic twins (n = 42)</td>
<td>Dizygotic twins (n = 56)</td>
<td>All twins (n = 98)</td>
<td>Controls (n = 43)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>2.52 (0.08)</td>
<td>2.69 (0.08)</td>
<td>2.62 (0.06)</td>
<td>2.96 (0.08)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>37.5 (0.5)</td>
<td>37.0 (0.4)</td>
<td>37.2 (0.3)</td>
<td>36.7 (0.4)</td>
</tr>
<tr>
<td>Current age (years)</td>
<td>33.9 (1.3)</td>
<td>36.9 (1.2)</td>
<td>35.6 (0.9)</td>
<td>35.4 (1.5)</td>
</tr>
<tr>
<td>Adult height (cm)</td>
<td>177.0 (1.1)</td>
<td>177.3 (0.9)</td>
<td>177.2 (0.7)</td>
<td>176.0 (0.9)</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>24.5 (0.5)</td>
<td>26.0 (0.5)</td>
<td>25.4 (0.4)</td>
<td>25.9 (0.6)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132.4 (2.1)</td>
<td>135.9 (1.9)</td>
<td>134.4 (1.4)</td>
<td>142.7 (2.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.1 (1.2)</td>
<td>84.9 (1.3)</td>
<td>82.8 (0.9)</td>
<td>85.7 (1.6)</td>
</tr>
<tr>
<td>Physical activity level (× basal metabolic rate)</td>
<td>1.72 (0.07)</td>
<td>1.70 (0.05)</td>
<td>1.71 (0.04)</td>
<td>1.64 (0.05)</td>
</tr>
<tr>
<td>Alcohol intake (g/day)</td>
<td>23.1 (2.5)</td>
<td>17.6 (1.8)</td>
<td>20.0 (1.5)</td>
<td>19.7 (2.6)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, standard error.
† Weight (kg)/height (m)².

RESULTS

The birth weights and adult characteristics of the participating twins and singleton controls are shown in table 1. Males were slightly older than females among both twins (p < 0.001) and controls (p < 0.05), which may reflect difficulties involved in tracing older women who had changed their names upon marriage. Although the twins and controls were matched for gestational age, the controls had a significantly higher birth weight than the twins in both males and females (p < 0.001 for both). However, there was no evidence that this was associated with lower blood pressure, since systolic blood pressure was significantly higher in controls than in twins among the males (p < 0.01). There were no differences in diastolic pressure, adult height, or body mass index between the two groups in either males or females.

The regression coefficients for the relation between birth weight and blood pressure in unpaired twins and singleton controls are given in table 2. Inclusion of lifestyle factors and adult body mass index created little difference in the coefficients. In twins, the effects were close to zero and were not statistically significant. In controls, there was a more negative association between birth weight and both systolic and diastolic blood pressure, though this was statistically significant only for diastolic blood pressure (p < 0.02).

TABLE 2. Regression coefficients (β) for the increase in adult blood pressure per 1-kg increase in birth weight among twins and controls (unpaired analysis), Aberdeen, Scotland, 1949–2000

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Monozygotic twins (n = 114)</th>
<th>Dizygotic twins (n = 130)</th>
<th>All twins (n = 244)</th>
<th>Controls (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
<td></td>
<td>Adjusted,†</td>
<td>Adjusted,‡</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>0.73</td>
<td>-3.93, 5.40</td>
<td>-1.79</td>
<td>-7.59, 4.01</td>
</tr>
<tr>
<td></td>
<td>3.87</td>
<td>-1.09, 8.82</td>
<td>0.21</td>
<td>-5.45, 5.87</td>
</tr>
<tr>
<td></td>
<td>2.42</td>
<td>-0.97, 5.81</td>
<td>-0.30</td>
<td>-4.22, 3.62</td>
</tr>
<tr>
<td></td>
<td>-4.26</td>
<td>-12.77, 4.25</td>
<td>-1.11</td>
<td>-7.32, 0.88</td>
</tr>
</tbody>
</table>

* CI, confidence interval.
† Adjusted for gestational age, gender, and current age.
‡ Adjusted for gestational age, gender, current age, physical activity level, alcohol intake, and smoking category.
§ Adjusted for gestational age, gender, current age, physical activity level, alcohol intake, smoking category, and body mass index.

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Table 3 shows the within-pair differences in birth weight, adult height, body mass index, blood pressure, smoking, physical activity, and alcohol intake among twins. Although the median differences were very small, there was a wide range of differences in all variables—for example, up to 1.8 kg in birth weight and up to 50 mmHg in systolic pressure. There was no evidence that the range of within-pair differences differed between monozygotic twins and dizygotic twins for any of these variables.

Table 4 shows the regression coefficients for the relation between birth weight difference and blood pressure difference within twin pairs, both unadjusted and adjusted for possible confounding variables. In the analysis of all twins, both unadjusted and adjusted regression coefficients were small and were not statistically significantly different from zero. There was also no evidence for attenuation of the association in monozygotic pairs relative to dizygotic pairs.

**DISCUSSION**

Although this sample was drawn from a population register, the relatively low response rate in both twins and controls raises the possibility of selection bias in the study population. However, there was no significant difference between participants and nonparticipants in birth weight, current age, or gender (data not shown), indicating that in these respects the subjects were representative of the local obstetric population. We cannot exclude the possibility that participants differed from nonparticipants in terms of adult health, and the higher systolic blood pressure among singleton controls compared with twins in the male participants raises the possibility that male controls who were at increased risk of cardiovascular health problems could have been more likely to participate than those at lower risk.

The fact that the regression coefficients for the association between birth weight and blood pressure were close to zero...
in the unpaired analysis in all twins (table 2) is similar to the findings of one study in twins of average age 43 years (18) and another study in twins aged 7 and 17 years (21), though three other studies in twins aged 8–18 years found a significant negative association between birth weight and blood pressure in unpaired analysis (14, 16, 22). A difference in the relation between birth weight and blood pressure in unpaired twins compared with singletons would be expected if the variation in birth weight among twins was related to factors influencing birth weight in twins only that are not related to adult disease risk. Although twin-twin transfusion syndrome in monochorionic monozygotic twin pairs is commonly believed to play a large part in differences in birth weight among twins, a study of 539 twin pregnancies found no difference in within-pair differences in birth weight among monochorionic twins as compared with dichorionic twins (27), and another study of monochorionic placentas found no association between vascular anastomoses and discordant growth (28). Differences in birth weight among both monochorionic and dichorionic twins were found in one study to be related to the number of placental lesions (infarction, abruption, thrombosis, and fibrosis) in the lighter twin, particularly among dichorionic pairs (29). Another study of discordant twin pairs found that lighter twins tend to have lower levels of essential amino acids than co-twins, indicating that placental transport of nutrients may be a limiting factor in intrauterine growth restriction in twins (30).

Among the singleton controls in this study, the regression coefficients for the association between birth weight and blood pressure were larger than those in the unpaired analysis of twins and were in the same range as those found in the early studies in singletons. The attenuation in twins could be interpreted as evidence that there are factors influencing birth weight in twins but not in singletons which are not related to blood pressure. However, the number of controls in this study was small, so these results must be interpreted with caution. No other twin study included singleton controls, but in a study of male Swedish twins aged 17–19 years, the authors commented that the association between birth weight and systolic blood pressure among twins was similar in magnitude to that seen among singletons in the same population (22).

The paired analysis in twins was designed to assess whether controlling for some or all shared genetic factors and all maternal factors and childhood socioeconomic influences reduced the influence of birth weight differences on adult blood pressure differences. The regression coefficients were not appreciably altered by adjustment for differences in physical activity level, alcohol intake, or smoking, though adjusting for adult body mass index differences reduced the regression coefficients for both systolic and diastolic pressure in all twins (table 4). For systolic blood pressure, the regression coefficient for all 122 pairs was –0.86 (95 percent confidence interval: –6.35, 4.64) mmHg per kg of birth weight difference, which is similar to the value of –0.6 mmHg/kg for singletons suggested by Huxley et al. (5) in their recent meta-analysis but is also not significantly different from zero. Six of the published twin studies reported regression coefficients for monozygotic and dizygotic twins combined which ranged from –7.3 mmHg/kg to 3.3 mmHg/kg, all of which were also not statistically significant (14, 15, 18, 19, 21, 22). One possible reason for attenuation of associations between birth weight and later health status in within-pair analyses is “crossover” of birth weight within a pair due to errors in attribution of birth order, though a large study of male twins which excluded the 38 percent of pairs in whom this effect was considered possible reported an association between within-pair differences in birth weight and systolic blood pressure of –0.2 mmHg/kg (95 percent confidence interval: –2.1, 1.7) (22).

The results from this study can also be used to address the question of whether postnatal catch-up growth is an important influence on adult blood pressure. The fact that the twins were lighter at birth but not different in adult height from the controls suggests that these twins experienced in-utero growth restriction but subsequently exhibited postnatal catch-up growth to achieve their full genetic potential in adult size. A recent study in singletons found that postnatal catch-up growth was associated with an increased risk of mortality from coronary heart disease among persons who were small at birth (31), but there is no evidence in the present study that the catch-up growth experienced by the twins was associated with higher blood pressure in adult life.

In summary, this study found no evidence for an association between lower birth weight in twins and higher blood pressure in adult life in comparison with singletons matched for gestational age. As in other twin studies in this area, the association between within-pair differences in birth weight and systolic blood pressure among all twins was not significantly different either from zero or from the value of –0.6 mmHg/kg recently suggested for singletons (5). Since even the largest of twin studies has limited power to detect such small differences and since all twin data on birth weight may include effects of intrauterine influences on birth weight, which are less common in singletons, the most valuable use of twin data in relation to the programming hypothesis may lie in meta-analyses of the existing data on monozygotic and dizygotic twins for the possible contribution of genetic factors to the associations between birth weight and adult blood pressure.

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