Birth Weight and Blood Pressure in Young Adults
A Prospective Twin Study

Ruth J.F. Loos, MSc; Robert Fagard, PhD, MD; Gaston Beunen, PhD; Catherine Derom, PhD; Robert Vlietinck, PhD, MD

Background—The intrauterine environment may be a critical period for the development of hypertension in later life. In the present study, we applied the twin approach to estimate the contribution of genetic and environmental causes that may underlie the birth weight–adult blood pressure association.

Methods and Results—Birth weights of 418 twin pairs were obtained prospectively, and resting and 24-hour ambulatory blood pressures were obtained at the age of 18 to 34 years. In women, resting systolic blood pressure decreased 4.27 mm Hg (P<0.001) and diastolic pressure decreased 2.18 mm Hg (P=0.02) per kilogram increase in birth weight. Similar associations were found for ambulatory measurements, although these were somewhat less pronounced. Pair-wise analysis confirmed these findings: twin pairs of whom both members had a low birth weight (<2500 g) had a higher systolic blood pressure compared with twins who both had a high birth weight (≥2500 g). Systolic blood pressure of the lightest of a low-birth-weight pair was 4.7 mm Hg (P<0.02) higher and of the heaviest 2.4 mm Hg higher (P=0.2) than similar measurements in high-birth-weight pairs. Intrapair differences in blood pressure between the lightest and the heaviest at birth were only present in low-birth-weight pairs. The results were similar for monozygotic and dizygotic twin pairs. In men, no associations were found between birth weight and adult blood pressure.

Conclusions—These findings suggest that prenatal programming of adult blood pressure occurs at least in female twins. We suggest that particularly maternal influences, experienced by both twin members, may underlie the association between birth weight and blood pressure. The fetoplacental unit seems to influence blood pressure only when both fetuses had low birth weight. (Circulation. 2001;104:1633-1638.)

Key Words: prenatal care ▪ twins ▪ birth weight ▪ blood pressure

The relationship between low birth weight and elevated blood pressure (BP) in adult life, which was first shown by Barker et al and Law et al about a decade ago, has been confirmed by an extensive series of epidemiological investigations. More recently, the fetal origins of BP have also been studied in twins. Twins offer a unique opportunity to distinguish between individual fetoplacental, maternal, and genetic influences. Twin members share the same maternal environment, and monozygotic twins are genetically identical. By comparing the heavier and the lighter twin member within a pair, the influence of birth weight can be estimated while potential confounding maternal and genetic characteristics are controlled for. Thus far, the results of these studies have been inconclusive, and there were several shortcomings (eg, zygosity was inaccurately determined and birth weights were self-reported). As in most singleton studies, only resting BP was measured, although 24-hour ambulatory registration is considered more representative of a subject’s usual or true BP.

In the present study, we examined the association between birth weight and adult resting and ambulatory BP in young adult twins. Twin data were obtained from the East Flanders Prospective Twin Survey, which is a population-based register known for its prospectively collected perinatal data and accurate zygosity determination.

Methods

Participants
The study sample consisted of 418 twin pairs between 18 and 34 years of age (Figure 1) who were randomly selected from the East Flanders Prospective Twin Survey. This population-based survey has prospectively registered all twins born in the Belgian Province of East Flanders since 1964. Perinatal data were collected at birth, and placental examination was performed within 24 hours after delivery. Zygosity was determined through sequential analysis based on sex, fetal membranes, umbilical cord blood groups, placental alkaline phosphatase, and DNA fingerprints. Between July 1964 and May 1982, the Twin Survey had registered 2141 twin pairs who met the World Health Organization criteria for liveborn infants (birth weight...
Recording began between 6:00 and 9:00 AM and was finished 24 hours later. The recorders were programmed to obtain measurements every 15 minutes from 8:00 AM to 10:00 PM and every 30 minutes between 10:00 PM and 8:00 AM. Whenever a reading could not be successfully completed, the measurement was repeated after 2 minutes. Readings were automatically rejected when systolic BP was $>220$ mm Hg or $<70$ mm Hg and diastolic BP was $>140$ mm Hg or $<40$ mm Hg. In addition to the automatic exclusion of readings by the monitor, subjects were excluded from further analysis when there were no valid measurements in any 2-hour period. Day and night were defined with short fixed-clock time periods that ranged from 10:00 AM to 8:00 PM and from midnight to 6:00 AM. Morning and evening intervals were excluded from analysis.

### Statistical Analyses

Twins were considered both as individuals and as members of a pair for particular analyses. First, regression analysis was used to estimate the relationship between birth weight and BP in men and women separately. When adjustment for adult body mass was applied, subjects weighing $\geq 100$ kg (n=6) were excluded because of nonlinearity above this value.

In a second analysis, we compared the adult BP of the heavier twin at birth with that of the lighter sibling. Regression analysis was used to relate intrapair differences in adult BP to intrapair differences in birth weight. The regression line was constrained to pass through the origin so that the results were independent of whether the twin was the first or second born.

Finally, we compared the BP of pairs in whom both members had a low birth weight ($<2500$ g; concordant low birth weight, LL), pairs of whom both members had a high birth weight ($\geq 2500$ g; discordant birth weight, LH), and pairs of whom one member had a low ($<2500$ g) and the other a high birth weight ($\geq 2500$ g; discordant birth weight, LH). In each birth weight group, we distinguished the lightest and heaviest twin member. This resulted in 6 groups (ie, the lightest and heaviest of LL pairs, the lightest and heaviest of LH pairs, and the lightest and heaviest of HH pairs). ANOVA was used to compare the BP characteristics of the different birth weight groups (ie, the lightest and heaviest twins were considered separately). A paired $t$ test was used to compare the heaviest and lightest within a pair.

Pairwise analyses were restricted to same-sex pairs of whom both members had participated. Data analyses were performed using SAS version 6.12 (SAS Institute Inc, 1997). All tests were 2-sided; $P<0.05$ was considered significant.

### Results

Perinatal, anthropometric, and BP characteristics are shown in Table 1. Perinatal and maternal characteristics of the participants are representative for the East Flanders twin population and were not significantly different from subjects that were excluded.

#### Birth Weight and BP

In women, birth weight was negatively associated with BP. As shown in Table 2, this was more pronounced for resting than for ambulatory measurements, more for systolic than for diastolic BP, and more for daytime than for nighttime BP. The relationships remained significant for resting and daytime systolic BP after adjustment for adult body mass and gestational and adult age (Table 2). The independent contribution ($r^2$) of birth weight to the variance of BP did not exceed 3.4% for systolic BP and 1.5% for diastolic BP. Similar results were obtained when body mass index was used for adjustment. In men, birth weight did not show any significant relationship with BP.

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**Figure 1.** Flowchart illustrating the allocation of subjects. MZ indicates monozygotic; DZ, dizygotic.

$\geq 500$ g or gestational age $\geq 22$ weeks, if birth weight unknown). Pairs of whom one or both members were stillborn, died in neonatal or later life, or suffered from major congenital malformation were excluded. We randomly contacted 803 pairs using an envelope system (randomly drawing identification numbers out of an envelope). To assure equally distributed groups, we stratified for birth year and zygosity/chorionicity. Subjects were excluded when they currently suffered from cardiovascular diseases ($n=1$), endocrinological disorders (thyroid disease, adrenal disease, or diabetes; $n=11$), or multiple sclerosis ($n=1$) or when they were taking drugs with potential effects on BP (n=20). Three women were excluded because of early pregnancy. Eventually, 768 twins of 418 pairs (overall response, 52.1%) participated in the Prenatal Programming Twin Study. The twins gave informed consent, and the project was approved by the Local Committee of Medical Ethics.

**Measures**

Birth weights were obtained from obstetric records, and gestational age was reported by the obstetrician and calculated as the number of completed weeks of pregnancy based on the last menstrual period. For 42 pairs, gestational age was reported by the mother because no data were available in the obstetric record. Gestational age was missing for 7 pairs.

Between February 1997 and April 2000, all twins visited our research center for a 2-hour examination in the morning. After 5 minutes of supine rest, BP was measured on the right arm in triplicate by sphygmomanometry and auscultation (Korotkoff phases I and V) by 1 of 4 trained investigators. The reported resting BP is the average of the 3 measurements. Standing height (cm) was measured with a Harpenden fixed stadiometer to the nearest 0.1 cm, and body mass (kg) was measured on a balance scale (SECA) to the nearest 0.1 kg. Body mass index was calculated as body mass divided by squared height.

Ambulatory BP was monitored using the SpaceLabs 90207 device (SpaceLabs, Inc). Subjects applied the monitor at home on the nondominant arm. They were instructed to perform normal activity ($\sim \geq 100$ kg) and not to engage in vigorous physical exercise or contact sports. Recording began between 6:00 and 9:00 AM and was finished 24 hours later. The recorders were programmed to obtain measurements every 15 minutes from 8:00 AM to 10:00 PM and every 30 minutes between 10:00 PM and 8:00 AM. Whenever a reading could not be successfully completed, the measurement was repeated after 2 minutes. Readings were automatically rejected when systolic BP was $>220$ mm Hg or $<70$ mm Hg and diastolic BP was $>140$ mm Hg or $<40$ mm Hg. In addition to the automatic exclusion of readings by the monitor, subjects were excluded from further analysis when there were no valid measurements in any 2-hour period. Day and night were defined with short fixed-clock time periods that ranged from 10:00 AM to 8:00 PM and from midnight to 6:00 AM. Morning and evening intervals were excluded from analysis.

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TABLE 1. Data at Birth and Adulthood in Men and Women

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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</tr>
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<tbody>
<tr>
<td>Birth</td>
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<tr>
<td>Birth weight, g</td>
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<td>2489±481</td>
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<tr>
<td>Gestational age, wk</td>
<td>37.2±2.4</td>
<td>37.3±2.4</td>
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<td>Adulthood</td>
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<td></td>
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<tr>
<td>Age, y</td>
<td>26.2±4.8</td>
<td>25.9±4.8</td>
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</tr>
<tr>
<td>Body mass, kg</td>
<td>71.0±10.7</td>
<td>60.6±10.1</td>
<td>&lt;0.001</td>
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<tr>
<td>Height, cm</td>
<td>178.3±6.4</td>
<td>165.6±6.2</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI, kg/m²</td>
<td>22.3±3.1</td>
<td>22.1±3.6</td>
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<tr>
<td>Birth weight</td>
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<tr>
<td>Resting BP, mm Hg</td>
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<tr>
<td>Systolic*</td>
<td>129.7±10.9</td>
<td>119.7±11.2</td>
<td>&lt;0.001</td>
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<tr>
<td>Diastolic†</td>
<td>70.1±9.9</td>
<td>65.7±8.5</td>
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<tr>
<td>Ambulatory BP, mm Hg</td>
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<tr>
<td>Daytime‡</td>
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<tr>
<td>Systolic</td>
<td>124.4±8.9</td>
<td>119.1±8.4</td>
<td>&lt;0.001</td>
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<tr>
<td>Diastolic</td>
<td>72.7±7.3</td>
<td>74.0±7.0</td>
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<tr>
<td>Nighttime§</td>
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<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>109.3±8.8</td>
<td>105.0±8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>59.0±6.3</td>
<td>58.4±6.8</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. P values were determined by t test for difference between men and women.
Data are missing for: *1 woman; †1 man and 1 woman; ‡19 men and 24 women; §27 men and 42 women.

Intrapair Birth Weight Difference Versus Intrapair Difference in BP

Table 3 shows that there was no significant relationship between the intrapair birth weight difference and the intrapair difference in adult BP (ie, BP of the heavier and lighter twin at birth were similar, regardless of their intrapair birth weight difference). This was true for monozygotic and dizygotic twins and for both sexes.

TABLE 2. Slopes of Relationships of Systolic and Diastolic BP With Birth Weight in Men and Women

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted*</td>
<td>Unadjusted</td>
<td>Adjusted*</td>
</tr>
<tr>
<td>Resting BP, mm Hg</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>0.46</td>
<td>0.70</td>
<td>−0.89</td>
<td>0.55</td>
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<tr>
<td>Diastolic</td>
<td>0.90</td>
<td>0.39</td>
<td>−0.80</td>
<td>0.56</td>
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<tr>
<td>Ambulatory BP, mm Hg</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>1.18</td>
<td>0.23</td>
<td>−0.89</td>
<td>0.48</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.91</td>
<td>0.25</td>
<td>−0.40</td>
<td>0.71</td>
</tr>
<tr>
<td>Nighttime</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>0.02</td>
<td>0.99</td>
<td>−0.90</td>
<td>0.49</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.04</td>
<td>0.95</td>
<td>−0.27</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*Adjusted for gestational age, adult body mass, and age, excluding 6 subjects with adult body mass ≥100 kg.
Missing subjects from each group are given in Table 1.

Concordant Heavy Twins Versus Concordant Light Twins

Subsequently, pairs were compared according to the concordance for low or high birth weight. There were 111 LL pairs, 70 LH pairs, and 130 HH pairs. In women, LL twins both had a higher BP compared with the other birth weight groups (LH, HH). This tendency was most apparent for resting measurements. Figure 2 shows the results after controlling for adult age and body mass.

Systolic BP of the lightest of a LL pair was ≥4.7 mm Hg higher (P=0.02) that of the lightest of the LH and HH pairs. For the heavier sibling in a LL pair, this difference was less and did not reach significance (≥2.4 mm Hg; P=0.2; Figure 2A). Diastolic BP of both members of a LL pair was significantly higher than that of the heaviest twin of LH and HH pairs (≥3.5 mm Hg; P<0.05) but not significantly higher than that of the leanest twin of LH and HH pairs (≥1.95 mm Hg; P=0.2; Figure 2B). Although the intrapair birth weight difference between the lighter and heavier of an LL pair was small, the intrapair difference for systolic BP was significant (2.1 mm Hg; P=0.02). Similar results were found when monozygotic and dizygotic twins were considered separately, but the differences did not reach statistical significance due to small sample sizes.

In men, no differences in BP were found according the concordance for low or high birth weight.

Discussion

Our findings support the hypothesis that low birth weight, as marker of the intrauterine environment, is associated with an increased adult BP, at least in female twins. When both twin members had a low birth weight, they both had a higher BP compared with pairs in whom both members had a high birth weight. This indicates that the inverse association between birth weight and BP may be mediated through maternal environmental or genetic factors that influence both members of a pair. The fact that the results were similar in monozygotic
and dizygotic twins suggests that maternal factors are more important than genetic influences. Only when both members had a low birth weight did the intrapair comparison between the lightest at birth and the heavier sibling show a lower BP in favor of the heavier, suggesting the influence of the fetoplacental environment that was unique to each fetus. No associations were found in men. In addition, the relationships in women were weak: the contribution of birth weight to the variance of adult BP was 3.4% at the most. The significance for cardiovascular risk is therefore limited, particularly in view of the weaker association with ambulatory BP, which was not even significant for night-time pressure.

### Birth Weight and Adult BP

Several studies have reported an inverse association between birth weight and adult BP. Although the majority of studies have reported significant relationships only after adjustment for current body size, we found that in women, this inverse association was significant whether or not the influence of adult body mass was taken into account. Furthermore, in agreement with other twin studies, the slope of the association was steeper than that observed in singletons. This difference between twins and singletons may be due to the marked deceleration of twin fetal growth during the last trimester of pregnancy. A limited capacity in the maternal/placental supply line of nutrients has been postulated to underlie the fetal growth retardation, rather than “crowding in the uterus.”

#### The Twin Model and Prenatal Programming

An innovative feature of the current study is the use of twins to test the prenatal programming hypothesis. Twins...
share the same maternal environment, and monozygotic twins are genetically identical. Nevertheless, each fetus has its own fetoplacental environment, as reflected by its birth weight, that may differ substantially between twin members. By comparing the BP of the heaviest twin at birth with that of the lighter sibling, potential confounding maternal and genetic characteristics can be controlled. So far, only 4 studies have applied this twin approach for BP,\textsuperscript{4–7} but their results have not been consistent. Dwyer et al\textsuperscript{4} and Poulter et al\textsuperscript{5} found a tendency for the monozygotic twin who was lightest at birth to have the highest BP later in life, suggesting that the association between birth weight and adult BP is at least partly independent from maternal and genetic influences. Ijzerman et al\textsuperscript{6} observed an inverse relationship between intrapair birth weight difference and intrapair difference in BP in only dizygotic, not monozygotic, twins and concluded that genetic factors might explain the birth weight–BP relationship. Baird et al\textsuperscript{7} found no differences in BP between both twin members in relation to birth weight, which suggests that both twins may be influenced by genetic or maternal characteristics. These analyses\textsuperscript{8} were restricted to comparing the BP of the heavier twin with the lighter sibling.

However, fetal programming may not only result from an adverse fetoplacental unit, which is unique to each fetus, but also from an adverse maternal environment, which influences both fetuses. Therefore, we compared the BP of twin pairs in whom both members had a low birth weight (<2500 g), reflecting an adverse maternal environment, with that of pairs in whom one or both members had a relatively high birth weight (\geq2500 g). Female twin pairs concordant for low birth weight both had a higher BP compared with pairs who had at least one member weighing \geq2500 g. This was only found in women but was true for monozygotic and dizygotic twins. Our data suggest that maternal environmental factors may influence the causal pathway between birth weight and adult BP. More than in singleton pregnancies, maternal constraint may influence fetal growth in twins. A limitation in the maternal supply of nutrients will affect the intrauterine growth of both members of a pair, which in turn may result in an increased BP later in life. This ties in with the findings of human\textsuperscript{17–19} and animal\textsuperscript{20–22} studies that investigated the influence of maternal characteristics, such as overexposure to maternal glucocorticoids and maternal protein restriction, on birth weight.

In addition, the fetoplacental unit seems to affect adult BP when both twins have a lower birth weight.

**Influence of Sex**

Inverse relationships between birth weight and adult BP have been reported in men and in women. In agreement with others,\textsuperscript{1,13,23,24} we found an association in women, but not in men. The rate of fetal growth differs between sexes (ie, girls grow slowly in the first part of pregnancy\textsuperscript{25,26} but show a more pronounced acceleration in the third trimester compared with boys).\textsuperscript{27} In twins, growth retardation occurs mainly in the last trimester. Therefore, we speculate that the female fetus may be more vulnerable to an adverse prenatal environment than the male fetus. Nevertheless, more research is required to confirm these sex differences, because others\textsuperscript{10,28,29} found an inverse association in men but not in women. This inconsistency in findings with regard to sex may be due to the fact that, although significant, the relationship between birth weight and adult BP is small.

In conclusion, our data confirm that reduced fetal growth is related to raised BP, at least in female twins. We suggest that maternal influences experienced by both twin members may underlie the prenatal programming of BP, rather than disturbances within the fetoplacental unit of each fetus. The latter may, however, contribute in pairs that were concordant for low birth weight.

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**References**


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