Low Birth Weight Predicts Elevated Plasma Cortisol Concentrations in Adults From 3 Populations


Abstract—Low birth weight is linked with raised blood pressure in adult life. Recent evidence has suggested that a neuroendocrine disturbance involving the hypothalamic-pituitary-adrenal axis could mediate this link. We therefore investigated the relation between birth weight and fasting plasma cortisol concentrations and the association of cortisol with current blood pressure in population samples of 165 men and women born in Adelaide, South Australia, from 1975 to 1976, 199 men and women born in Preston, UK, from 1935 to 1943, and 306 women born in East Hertfordshire, UK, from 1923 to 1930. Fasting plasma cortisol was measured in plasma samples obtained between 8 and 10 AM. Blood pressure was measured with an automated sphygmomanometer. Low birth weight was associated with raised fasting plasma cortisol concentrations in all 3 populations. A combined analysis that allowed for differences in the gender composition, age, and body mass index between the studies showed that cortisol concentrations fell by 23.9 nmol/L per kilogram increase in birth weight (95% CI 9.6 to 38.2, \( P<0.001 \)). Fasting plasma cortisol concentrations also correlated positively with the subjects’ current blood pressure. However, the association between cortisol and blood pressure was most marked in subjects who were obese (\( P=0.038 \) for interaction between body mass index and cortisol, \( P=0.01 \) for interaction between waist-to-hip ratio and cortisol). These results show that low birth weight is associated with raised cortisol concentrations. Increased activity of the hypothalamic-pituitary-adrenal axis may link low birth weight with raised blood pressure in adult life. (Hypertension. 2000;35:1301-1306.)

Key Words: hypothalamus • cortisol • adrenal glands • blood pressure

Epidemiological studies in more than 30 populations have established that low birth weight in babies born at term is associated with raised blood pressure in childhood and adult life.\(^1\) Because birth size is largely determined by the nutrient supply to the fetus, these studies have led to the hypothesis that hypertension may originate in utero as a result of fetal undernutrition.\(^2\) It is suggested that endocrine or other physiological changes involved in the fetal adaptation to undernutrition persist and predispose to the development of adult hypertension.

Recent animal experiments have suggested that a neuroendocrine disturbance involving the hypothalamic-pituitary-adrenal axis may play a part in explaining the epidemiological associations. It is known that the fetus responds to undernutrition or other stressful stimuli by increasing cortisol secretion.\(^3\) Fetal exposure to stressful stimuli or glucocorticoids permanently alters the set point of the hypothalamic-pituitary-adrenal axis (HPAA), resulting in the birth of offspring who have increased basal and stress-induced glucocorticoid secretion\(^4\)–\(^6\) and raised blood pressure.\(^7\) These changes in the function of the HPAA appear to be a consequence of lifelong alterations in the central feedback mechanisms controlling the axis.\(^4\)–\(^8\) Because it is well known that individuals exposed to pathological concentrations of cortisol, for example, in Cushing’s syndrome, have raised blood pressure, raised cortisol concentrations could mediate the association between low birth weight and raised blood pressure.

A study of 64-year-old men born in Hertfordshire showed that those who had lower birth weight had raised fasting plasma concentrations of cortisol.\(^9\) Mean fasting plasma cortisol concentrations fell progressively from 408 nmol/L among those whose birth weights were \( \leq 2.50 \) kg (5.5 lb) to 309 nmol/L among those who weighed \( \geq 4.31 \) kg (9.5 lb) at birth. This trend was independent of the subjects’ age and body mass index (BMI). It was not a result of changes in their plasma concentration of corticosteroid-binding globulin. Moreover, elevated plasma cortisol concentrations were associated with higher blood pressure. These findings in men in Hertfordshire provide human evidence that altered development of the HPAA may be a mechanism underlying the association between low birth weight and raised blood press-
sure. We describe studies that reveal a relationship between low birth weight and elevated plasma cortisol concentrations in population samples of women born in Hertfordshire and men and women born in Adelaide, South Australia, and in Preston, Lancashire. Two of the populations also have data on head size, length at birth, and placental weight, which give insight into the nature of the growth retardation in utero associated with raised cortisol concentrations in later life.

Methods

Hertfordshire

From 1911 onward, each birth in Hertfordshire was notified by the attending midwife, and the birth weight was recorded. As previously described, we traced women born in East Hertfordshire during 1923 to 1930. A group of 309 women born in Hertfordshire between 1923 and 1930 agreed to attend a local clinic for study of cardiovascular risk factors. Field workers visited the subjects at home and obtained information on medical and social history and on smoking and drinking habits. The father’s occupation was used to define social class at birth and current social class was derived from the women’s occupation if she was single or the husband’s occupation is she was married (most married women were housewives). Five graded social class groupings were used: (1) professional; (2) employers and managers; (3) skilled occupations (a, nonmanual, and b, manual); (4) partly skilled occupations; and (5) unskilled occupations. The interviewers also measured the women’s heights with a portable stadiometer and their weights with a portable scale. BMI was defined as the weight in kilograms divided by the square of the height in meters. Subjects were categorized as overweight (BMI between 25 and 30 kg/m²) or obese (BMI >30 kg/m²). Waist and hip circumferences were measured with a steel tape measure, and the ratio of waist-to-hip circumference was recorded as a marker of central obesity. Blood pressure was measured with an automated recorder (Dinamap model 18465X; Critikon) in seated subjects with central obesity. Blood pressure was measured with an automated recorder (Dinamap model 18465X; Critikon) in seated subjects with central obesity.

Adelaide

The study sample was drawn from an existing cohort of young adults known as the Adelaide Children’s Hospital Family Heart Study. As previously described, the obstetric records of births between 1975 to 1976 maintained at the Queen Victoria Hospital, Adelaide, were used to trace 764 individuals currently living in Adelaide who were singletons and had been born after 37 completed weeks of gestation. Information available on the subjects included birth weight, length, head circumference, placental weight, and length of gestation at the time of delivery. A stratified sample of 165 men and women agreed to attend a local clinic for an intravenous glucose tolerance test. The subjects’ height, weight, waist circumference, hip circumference, and blood pressure were recorded as in the Preston study. The subjects were asked to fast and to refrain from smoking and alcohol overnight before attending the department between 8 and 9 AM for blood sampling. None of the subjects reported a history of pituitary or adrenal disease and none were taking oral glucocorticoids.

Cortisol Assay

Cortisol was measured in the fasting plasma sample by radioimmunoassay, which had an inters assay coefficient of variation of between 7.4% and 10.3%. The samples from all 3 populations were measured in the same laboratory and with the use of the same method as the previous study of men in Hertfordshire.

Statistical Analysis

The data were analyzed by simple or multiple linear regression. Logistic regression was used to analyze the relationship between birth size and use of antihypertensive treatment. Probability values refer to analyses performed with continuously distributed variables. In all 3 populations, the studies were approved by the local ethics committees, and all subjects gave written informed consent.

Results

Table 1 compares the subjects studied in Adelaide, Preston, and Hertfordshire. The mean age of the subjects ranged from 20.9 years in Adelaide to 63.6 years in Hertfordshire. The

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adelaide Men (SE)</th>
<th>Adelaide Women (SE)</th>
<th>Preston Men (SE)</th>
<th>Preston Women (SE)</th>
<th>Hertfordshire Women (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>87 (SE)</td>
<td>78 (SE)</td>
<td>92 (SE)</td>
<td>107 (SE)</td>
<td>306 (SE)</td>
</tr>
<tr>
<td>Age, y</td>
<td>20.9 (0.03)</td>
<td>20.9 (0.03)</td>
<td>51.6 (0.2)</td>
<td>51.2 (0.2)</td>
<td>63.6 (0.2)</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.57 (0.05)</td>
<td>3.37 (0.04)</td>
<td>3.21 (0.05)</td>
<td>3.20 (0.05)</td>
<td>3.40 (0.03)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.0 (0.4)</td>
<td>23.3 (0.5)</td>
<td>26.4 (0.4)</td>
<td>25.6 (0.4)</td>
<td>27.0 (0.26)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.82 (0.01)</td>
<td>0.71 (0.01)</td>
<td>0.93 (0.01)</td>
<td>0.82 (0.01)</td>
<td>0.80 (0.01)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>124 (1.0)</td>
<td>114 (1.0)</td>
<td>154 (2.2)</td>
<td>143 (2.1)</td>
<td>159 (1.4)</td>
</tr>
<tr>
<td>Fasting plasma cortisol, nmol/L</td>
<td>332 (11.0)</td>
<td>441 (20.7)</td>
<td>427 (13.0)</td>
<td>400 (12.9)</td>
<td>350 (7.3)</td>
</tr>
</tbody>
</table>
older Preston and Hertfordshire populations had a higher BMI and higher systolic blood pressure measurements. The overall fasting plasma cortisol concentrations ranged from 109 to 848 nmol/L (mean 377, SD 138). Fasting plasma cortisol concentrations were unrelated to the subjects’ height but fell by 3.6 nmol/L per unit increase in BMI ($P = 0.001$). They were also strongly inversely related to the waist-to-hip ratio in men ($P = 0.002$), but this was less marked in women ($P = 0.07$). Cortisol concentrations did not differ significantly by gender (men 381 ± 9.3 nmol/L, women 375 ± 6.5 nmol/L) or age. Table 2 shows that in these 3 populations, birth weight significantly predicted both systolic blood pressure (fall in blood pressure per kilogram increase in birth weight $= 3.6$ mm Hg, 95% CI 0.5 to 6.7, $P = 0.003$) and the percentage of subjects receiving antihypertensive treatment ($P < 0.001$).

**Birth Weight and Cortisol**

Figure 1 shows the regression coefficients (and 95% CIs) for the change in fasting cortisol concentration per kilogram increase in birth weight in men and women in the Adelaide and Preston studies and the women in Hertfordshire. The results are compared with the data from the previously published study of 370 men born in Hertfordshire. The studies are presented in ascending order of the subjects’ ages. In each of the studies, the data are adjusted for BMI and age and are presented separately for each gender. In all the studies, the regression coefficients were negative: That is, fasting cortisol concentrations fell with increasing birth weight in each population. A combined analysis that included the data for the Hertfordshire men (total $= 1040$ men and women) and allowed for differences in the gender composition, age, and BMI between the studies showed a significant correlation between birth weight and fasting plasma cortisol concentrations ($r = -0.11$, $P < 0.001$, Figure 2). Overall cortisol concentrations fell by 23.9 nmol/L per kilogram increase in birth weight (95% CI 9.6 to 38.2).

The additional data on body size at birth available in the Preston and Adelaide studies, enabled us to analyze the relationship between these measurements and fasting plasma cortisol concentrations in adult life. Table 3 shows the results of regression analyses in the combined populations of the Preston and Adelaide studies. The differences in age, level of obesity, and gender between the Preston and Hertfordshire populations had a higher BMI and higher systolic blood pressure measurements. The overall fasting plasma cortisol concentrations ranged from 109 to 848 nmol/L (mean 377, SD 138). Fasting plasma cortisol concentrations were unrelated to the subjects’ height but fell by 3.6 nmol/L per unit increase in BMI ($P = 0.001$). They were also strongly inversely related to the waist-to-hip ratio in men ($P = 0.002$), but this was less marked in women ($P = 0.07$). Cortisol concentrations did not differ significantly by gender (men 381 ± 9.3 nmol/L, women 375 ± 6.5 nmol/L) or age. Table 2 shows that in these 3 populations, birth weight significantly predicted both systolic blood pressure (fall in blood pressure per kilogram increase in birth weight $= 3.6$ mm Hg, 95% CI 0.5 to 6.7, $P = 0.003$) and the percentage of subjects receiving antihypertensive treatment ($P = 0.003$).

**Table 2. Prevalence of Hypertension and Mean Systolic Blood Pressure According to Birth Weight in Adelaide, Preston, and Hertfordshire Populations**

<table>
<thead>
<tr>
<th>Birth Weight, kg</th>
<th>No. of Subjects</th>
<th>No. (%) on Antihypertensive Treatment†</th>
<th>Mean Systolic Blood Pressure, mm Hg (SE)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.0</td>
<td>150</td>
<td>26 (17.3)</td>
<td>145.0 (1.7)</td>
</tr>
<tr>
<td>−3.5</td>
<td>273</td>
<td>47 (17.2)</td>
<td>144.5 (1.2)</td>
</tr>
<tr>
<td>−4.0</td>
<td>167</td>
<td>21 (12.6)</td>
<td>142.8 (1.5)</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>80</td>
<td>6 (7.5)</td>
<td>138.0 (2.6)</td>
</tr>
<tr>
<td>All</td>
<td>670</td>
<td>100 (14.9)</td>
<td>146.4 (1.0)</td>
</tr>
</tbody>
</table>

Measurements of systolic blood pressure exclude subjects receiving hypertensive treatment and are adjusted for location and gender, age, and BMI within each location.

*Test for trend, $r = -0.12$, $F = 9.1$, $P = 0.003$.

†Test for trend, $P = 0.03$.

Figure 2. Scattergram showing relationship between fasting plasma cortisol concentrations and birth weight in combined populations of Adelaide, Preston, and Hertfordshire. Regression line is adjusted for location and for gender, age, and BMI in each location.

**Table 3. Regression Models for Variables Predicting Fasting Plasma Cortisol Concentrations in Combined Populations of 165 People Born in Adelaide and 199 People Born in Preston**

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta$</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, kg</td>
<td>−34.7</td>
<td>−65.3 to −4.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Placental weight, g</td>
<td>−0.04</td>
<td>−0.24 to 0.16</td>
<td>0.70</td>
</tr>
<tr>
<td>Length, cm</td>
<td>−7.5</td>
<td>−14.1 to −1.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>−5.7</td>
<td>−14.4 to 3.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Ponderal index, kg/m³</td>
<td>−1.0</td>
<td>−6.0 to 4.0</td>
<td>0.70</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>−7.8</td>
<td>−17.2 to 1.7</td>
<td>0.11</td>
</tr>
</tbody>
</table>

$\beta$, Estimated regression coefficient.

Each regression is adjusted for location and for gender, age, and BMI within each location.
and Adelaide studies were controlled for in these analyses. Table 3 shows that low birth weight and shortness at birth were associated with elevated plasma cortisol concentrations in adult life. There was no independent effect of gestational age within the limited range of gestational age of this study, and the trends with birth weight or length at birth were present after adjustment for gestational age. Neither placental weight, ponderal index, nor head circumference was associated with plasma cortisol concentrations.

Cortisol and Blood Pressure

In the combined populations of Adelaide, Preston, and Hertfordshire (men and women), the fasting plasma cortisol concentration was a significant predictor of systolic blood pressure in adult life. In a multiple regression analysis that included terms for the different populations, systolic blood pressure (excluding the 195 men and women receiving antihypertensive treatment) was positively associated with BMI (P<0.0001), plasma cortisol (P<0.0001), age (P=0.006), and male gender (P<0.0001). Table 4 shows how the current systolic blood pressure is related to plasma cortisol concentrations and current BMI.

Social Class and Lifestyle

Birth weight did not correlate with either current social class or social class at birth. There were no significant trends in cortisol concentrations with social class at birth. The mean ± SEM fasting plasma cortisol concentration in men and women in current social classes I, II, and II (nonmanual) was 358 ± 6.6 nmol/L, and was similar to that in social class III (manual): 358 ± 7.4 nmol/L. Social classes IV and V had somewhat but not significantly higher mean fasting plasma cortisol concentrations: 372 ± 8.3 nmol/L. Current smokers and ex-smokers had higher cortisol concentrations than did nonsmokers (369 ± 8.7 nmol/L in current and 360 ± 6.4 nmol/L in ex-smokers compared with 349 ± 8.7 nmol/L in nonsmokers, P<0.001). However, cortisol concentrations were unrelated to alcohol intake. Allowing for social class or smoking did not alter the trends between birth weight and cortisol concentrations or between cortisol concentrations and systolic blood pressure.

Discussion

We have shown that low birth weight is associated with raised plasma cortisol concentrations in adult life in people living in 3 different populations and in women as well as in men. The association is not caused by possible confounding variables such as weight, body fat distribution, smoking, or social class. Because the association has been observed in young men and women in Adelaide as well as in the older Preston and Hertfordshire populations, it suggests that the factors that lead to low birth weight and adult hypercortisolemia affect men and women in young adult life as well as populations in middle age.

In our 3 populations, birth weight was a significant predictor of systolic blood pressure. Although the correlation coefficient is low (r=−0.12), the size of the effect in our study (3.6 mm Hg per kilogram increase in birth weight) is consistent with other published studies. The relation between birth weight and fasting plasma cortisol concentrations was similar in all 3 populations (Figure 1). A combined analysis indicated that plasma cortisol concentrations fell progressively with increasing birth weight by 23.9 nmol/L per kilogram increase in birth weight. Although the correlation was highly statistically significant, the correlation coefficient was low. This is likely to be caused by the imprecision of both birth weight as a measure of fetal growth and a single fasting cortisol measurement as a measure of cortisol secretion. It is likely, therefore, that we have underestimated the strength of the association between prenatal events associated with reduced birth size and hypercortisolemia in adult life. It is not yet clear whether the high circulating cortisol concentrations we have observed are due to delayed cortisol metabolism or increased cortisol secretion. However, we recently investigated a subset of the Hertfordshire men and showed that those who were small at birth had increased adrenocortical responses to adrenocorticotropic hormone, suggesting increased cortisol secretion. In many of the animal models of prenatal HPAA programming the affected offspring have increased stress-induced cortisol secretion. Because it is probable that the combination of

<table>
<thead>
<tr>
<th>TABLE 4. Systolic Blood Pressure According to Fasting Plasma Cortisol Concentrations and Current BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol, nmol/L</td>
</tr>
<tr>
<td>≤300</td>
</tr>
<tr>
<td>−400</td>
</tr>
<tr>
<td>&gt;400</td>
</tr>
<tr>
<td>All</td>
</tr>
</tbody>
</table>

Data exclude 195 subjects receiving antihypertensive treatment. Parentheses show number of subjects. Blood pressure measurements are adjusted for differences in location and for gender and age within each location.
fasting and the novel clinic setting in which our blood samples were obtained will have acted as a stress test, we suggest that the elevated morning fasting plasma cortisol concentrations that we have observed in individuals who were small at birth are due to an increased stress response.

In Hertfordshire, the only measurement recorded at birth was birth weight. The birth records in Preston and Adelaide were more detailed and included duration of gestation, head circumference, length, and placental weight. We restricted our study to babies born at term (37 or more completed weeks of gestation). Therefore, the association between weight at birth and adult cortisol concentrations must have been with reduced rates of fetal growth rather than prematurity. Analysis of the birth size data in Preston and Adelaide studies (Table 3) suggests that raised cortisol concentrations in adult life are not only linked with low birth weight but also with shortness at birth but not with ponderal index, suggesting a proportional reduction in all birth measurements. Shortness at birth is known to be linked with raised blood pressure, the insulin resistance syndrome, and coronary artery disease in adult life.17,18

Although Cushing’s syndrome or treatment with synthetic glucocorticoids are known to increase blood pressure whereas hypoadrenalism is associated with low blood pressure, there is still controversy as to whether physiological variations in plasma cortisol concentrations regulate blood pressure. Yet, in our study, we found that blood pressure was strongly and significantly related to fasting plasma cortisol concentrations. These findings add to the accumulating evidence that neuroendocrine stress mechanisms may contribute to the development of raised blood pressure and cardiovascular disease.19 It is likely that several factors contribute to raised fasting plasma cortisol concentrations, including the impact of current or recent life stress and cigarette smoking, which has been previously linked with altered HPAA function.20 However, our data showing strong and consistent links between birth size and fasting plasma cortisol concentrations suggest that prenatal resetting of the HPAA is an important cause of hypercortisolemia. It is also likely to be one of the mechanisms explaining the association between birth size and raised blood pressure, although it is likely that other factors are involved in this link, including alterations in the central sympathetic drive.21

A novel finding in our study was that the influence of raised plasma cortisol concentrations on current systolic blood pressure appeared to depend on an interaction with obesity: The correlation was strongest in subjects who had the highest BMI or waist-to-hip ratio (Table 4). Yet, we found that increasing obesity was associated with a reduction in plasma cortisol concentrations, which has been a consistent finding in several studies.22 This suggests the existence of a group of men and women who become obese and yet paradoxically maintain elevated plasma cortisol concentrations. It is this group that had the highest blood pressure. Whereas these findings require confirmation and further study, this phenomenon might explain the consistent finding that obesity amplifies the influence of low birth weight on cardiovascular or metabolic disease.23

In summary, we have confirmed the association between low birth weight and raised fasting plasma cortisol concentrations in 3 populations and shown that the association does not depend on the gestational age of the baby. Analysis of detailed measurements of body size at birth suggests that people who were light or short at birth but not of low ponderal index have raised cortisol concentrations in adult life. Our results also suggest that raised plasma cortisol concentrations are associated with raised blood pressure and that this association may depend on an interaction with obesity. Further detailed studies of the HPAA in these subjects will determine the nature of the long-term changes in glucocorticoid secretion associated with reduced fetal growth.

Acknowledgments
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References


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