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published in
Circulation
2003

DOI (link to publisher)
10.1161/01.CIR.0000081778.35370.1B

document version
Publisher's PDF, also known as Version of record

citation for published version (APA)
IJzerman, R. G., Stehouwer, C. D. A., de Geus, E. J. C., van Weissenbruch, M. M., Delemarre-van de Waal, H. A., & Boomsma, D. I. (2003). Low birth weight is associated with increased sympathetic activity. *Circulation*, *108*(5), 566-571. https://doi.org/10.1161/01.CIR.0000081778.35370.1B

Low Birth Weight Is Associated With Increased Sympathetic Activity
Dependence on Genetic Factors

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***Background*—**Low birth weight may be associated with high blood pressure in later life through genetic factors, an association that may be explained by alterations in sympathetic and parasympathetic activity. We examined the association of birth weight with cardiac pre-ejection period and respiratory sinus arrhythmia (indicators of cardiac sympathetic and parasympathetic activity, respectively) and with blood pressure in 53 dizygotic and 61 monozygotic adolescent twin pairs.

***Methods and Results*—**Birth weight of the twins was obtained from the mothers. Pre-ejection period and respiratory sinus arrhythmia were measured with electrocardiography and impedance cardiography at rest, during a reaction time task, and during a mental arithmetic task. In the overall sample, lower birth weight was significantly associated with shorter pre-ejection period at rest, during the reaction time task, and during the mental arithmetic task ($P=0.0001$, $P<0.0001$, and $P=0.0001$, respectively) and with larger pre-ejection period reactivity to the stress tasks ($P=0.02$ and $P=0.06$, respectively). In within-pair analyses, differences in birth weight were associated with differences in pre-ejection period at rest and during both stress tasks in dizygotic twin pairs ($P=0.01$, $P=0.06$, and $P=0.2$, respectively) but not in monozygotic twin pairs ($P=0.9$, $P=1.0$, and $P=0.5$, respectively). Shorter pre-ejection period explained approximately 63% to 84% of the birth weight and blood pressure relation.

***Conclusions*—**Low birth weight is associated with increased sympathetic activity, and this explains a large part of the association between birth weight and blood pressure. In addition, our findings suggest that the association between birth weight and sympathetic activity depends on genetic factors. **(*Circulation*. 2003;108:566-571.)**

Key Words: blood pressure ■ nervous system ■ genetics

Low weight at birth is associated with raised blood pressure in later life.[1] This association has been attributed to a programmed response to intrauterine malnutrition,[2] but the alternative view is that genetic factors influencing both birth weight and blood pressure are responsible.[3]

Studies in dizygotic and monozygotic twin pairs offer a unique opportunity to investigate the influence of intrauterine and genetic factors. Specifically, differences within dizygotic twin pairs are a function of both genetic and nongenetic factors, whereas differences within monozygotic (genetically identical) pairs can only be caused by nongenetic factors. In our cohort of adolescent twin pairs, within-pair differences in birth weight were associated with differences in blood pressure in dizygotic twin pairs but not in monozygotic twin pairs.[4] These data are consistent with several other twin studies[5–7] and demonstrated that genetic factors play an important role in the association between birth weight and blood pressure in later life.[4]

The mechanisms that underlie the association between birth weight and blood pressure are largely unknown. Changes in autonomic nervous system activity are involved in the development of high blood pressure.[8] However, it is not known whether birth weight is associated with the activity of the sympathetic and parasympathetic nervous systems nor whether any such associations can explain the relationship between birth weight and blood pressure.

To examine the association of birth weight with indicators of cardiac autonomic nervous activity and blood pressure and the possible influence of genetic factors, we investigated birth weight, the cardiac pre-ejection period, and respiratory sinus arrhythmia at rest and during mental stress in dizygotic and monozygotic twin pairs. Cardiac pre-ejection period and

Received October 18, 2002; de novo received February 25, 2003; revision received May 12, 2003; accepted May 12, 2003.

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***Circulation* is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000081778.35370.1B**

respiratory sinus arrhythmia are indicative of sympathetic and parasympathetic nervous system control of the heart, respectively.[9–11]

Methods

Subjects

This study is part of a larger project in which cardiovascular risk factors have been studied in 160 adolescent twin pairs and their parents.[4,12,13] A maternal questionnaire included questions regarding birth weight and gestational age of their children.[4] Opposite-sex dizygotic twin pairs were excluded because of the effects of sex differences within a pair. Individuals using oral contraceptives were excluded. None of the participants used any other medication that may affect measurements of cardiac autonomic nervous system or blood pressure. Thus, 53 dizygotic and 61 monozygotic twin pairs were eligible for analysis. The study was approved by an institutional review committee, and the subjects gave informed consent.

Experimental Protocol

After acclimatization, measurements were performed at rest and during reaction time and mental arithmetic tasks as described in detail previously.[12] During the reaction time task, participants had to press a “yes” button when a high tone and a “no” button when a low tone was heard. During the mental arithmetic task, participants had to add up numbers that were presented on a television screen.

Measurements

The pre-ejection period is the time interval between the onset of ventricular depolarization and the opening of the semilunar valves. The pre-ejection period is an index of cardiac contractility that indicates β-adrenergic inotropic drive to the left ventricle[9,10]; the shorter the pre-ejection period, the stronger the sympathetic control of heart rate. The pre-ejection period was measured as described previously.[14,15] Pre-ejection period was defined as the time in millisecond from the onset of the Q-wave on the ECG to the B-point (the opening of the aortic valves) in the impedance cardiogram. Pre-ejection period reactivity was calculated by subtracting the pre-ejection period during the stress tasks from the pre-ejection period at rest. A larger pre-ejection period reactivity, then, is an indicator of an increased sympathetic activity.[9,10]

Respiratory sinus arrhythmia refers to the cyclic variations in heart rate that are related to respiration. These variations are largely attributable to respiratory modulation of the outflow of the vagal nerve: the larger the respiratory sinus arrhythmia, the stronger the vagal control of heart rate.[11] Respiratory sinus arrhythmia was measured as described previously.[16,17] Respiratory sinus arrhythmia reactivity was calculated by subtracting the respiratory sinus arrhythmia during the stress tasks from the respiratory sinus arrhythmia at rest. Blood pressure measurements from an arm cuff around the nondominant arm were performed automatically with an oscillometric technique.[4]

Statistical Methods

Data are expressed as mean±SD, unless stated otherwise. The paired Student’s *t* test was used to compare measurements before and during mental stress. In the overall sample, linear regression analysis was used to investigate the influence of birth weight on heart rate, respiratory sinus arrhythmia, and pre-ejection period and to analyze within-pair associations. Interaction analysis was performed to investigate whether the associations were modified by zygosity, current body mass index, or current weight. Linear regression analysis was also used to investigate whether the association between birth weight and blood pressure[4] remained when allowing for the pre-ejection period. A 2-tailed P value <0.05 was considered significant. All analyses were performed using the statistical software package SPSS version 9.0 (SPSS Inc).

TABLE 1. Clinical Characteristics of the Twins

	Dizygotic Twins	Monozygotic Twins
n (men)	106 (60)	122 (68)
Age, y	17.0±1.7	16.0±1.8
Birth weight, g	2438±547	2488±519
Gestational age, w	37±3	36±8
Body mass index, kg/m^2	20.2±2.0	19.6±2.2
Systolic blood pressure, mm Hg	118.3±9.0	117.8±7.8
Diastolic blood pressure, mm Hg	67.3±6.5	66.3±5.9
Total cholesterol, mmol/L	4.1±0.7	4.3±0.8
Smoking, n (men)	14 (10)	10 (8)
Heart rate, bpm		
At rest	67.4±11.5	68.7±10.4
During reaction time task	72.8±13.5*	74.0±11.7*
During mental arithmetic task	75.9±15.7*	78.1±13.2*
Reactivity to reaction time task	5.4±4.3	5.4±4.2
Reactivity to mental arithmetic task	8.5±7.9	9.5±6.7
Pre-ejection period, ms		
At rest	118.8±14.3	114.8±15.3
During reaction time task	115.5±17.2*	110.5±20.2*
During mental arithmetic task	111.8±19.3*	105.4±19.5*
Reactivity to reaction time task	3.3±9.1	4.4±10.4
Reactivity to mental arithmetic task	7.0±13.8	9.5±10.8
Respiratory sinus arrhythmia, ms		
At rest	103.3±55.5	116.1±59.2
During reaction time task	89.4±51.5*	94.1±48.8*
During mental arithmetic task	79.4±51.3*	83.7±49.4*
Reactivity to reaction time task	13.5±28.0	21.0±28.8
Reactivity to mental arithmetic task	23.7±32.8	31.9±35.7

*$P<0.001$ vs at rest.

Results

The characteristics of the twins are shown in Table 1. Heart rate was significantly increased and pre-ejection period and respiratory sinus arrhythmia were significantly decreased during mental stress.

Association of Birth Weight With Pre-Ejection Period and Respiratory Sinus Arrhythmia in the Overall Sample

Birth weight was not significantly related to heart rate measurements (Table 2). Birth weight was positively associated with the absolute pre-ejection period and negatively with the pre-ejection period reactivity to mental stress. In other words, low birth weight was associated with a shorter pre-ejection period and a higher reactivity to mental stress, both indicative of an increased sympathetic activity. These associations were not significantly modified by zygosity, current weight, or current body mass index ($P>0.6$). Specifically, the association between birth weight and the pre-ejection period was similar in dizygotic and monozygotic twins (at rest: 6.2 [95% CI, −0.9 to 11.4], $P=0.02$, versus 8.4 [2.8 to 13.9], $P=0.004$; during the reaction time test: 8.0 [1.7 to 14.3], $P=0.03$, versus 12.5 [5.1 to 19.7], $P=0.001$; during

TABLE 2. Associations of Birth Weight With Heart Rate, Pre-Ejection Period, and Respiratory Sinus Arrhythmia in Twins

	β (95% CI)*	P
Heart rate		
At rest	−0.4 (−3.1 to 2.4)	0.8
During reaction time task	−1.2 (−4.4 to 1.9)	0.4
During mental arithmetic task	−2.0 (−5.7 to 1.5)	0.2
Reactivity to reaction time task	−0.9 (−1.95 to 0.2)	0.1
Reactivity to mental arithmetic task	−1.7 (−3.6 to 0.1)	0.06
Pre-ejection period, ms		
At rest	6.8 (3.1 to 10.6)	0.0001
During reaction time task	9.7 (5.0 to 14.5)	<0.0001
During mental arithmetic task	9.8 (4.8 to 14.7)	0.0001
Reactivity to reaction time task	−2.9 (−5.4 to −0.4)	0.02
Reactivity to mental arithmetic task	−3.0 (−6.1 to 0.2)	0.06
Respiratory sinus arrhythmia, ms		
At rest	2.3 (12.7 to 17.3)	0.8
During reaction time task	4.7 (−8.3 to 17.6)	0.5
During mental arithmetic task	4.6 (−8.2 to 17.4)	0.5
Reactivity to reaction time task	−3.3 (−10.7 to 4.0)	0.4
Reactivity to mental arithmetic task	−2.6 (−11.5 to 6.3)	0.6

*β (95% CI) per kilogram of birth weight after adjustment for age, sex, and current body mass index.

the mental arithmetic test: 8.4 [1.4 to 15.4], $P=0.02$, versus 12.5 [5.5 to 19.6], $P=0.001$). Birth weight was not associated with respiratory sinus arrhythmia.

Within-Pair Association of Birth Weight With Pre-Ejection Period and Respiratory Sinus Arrhythmia

Within-pair differences in birth weight were positively associated with differences in the pre-ejection period at rest and during the reaction time task in dizygotic twins but not in monozygotic twins (Table 3). For example, in dizygotic twins, a difference in birth weight of 1 kg within pairs was associated with a pre-ejection period at rest that was 12.8 ms shorter (indicative of increased cardiac sympathetic activity) in the twin with the lowest birth weight compared with the co-twin with the highest birth weight after adjustment for differences in current body mass index. The associations of birth weight with the pre-ejection period at rest, during the reaction time task, and during the mental arithmetic task were different between dizygotic twins and monozygotic twins ($P=0.04$; $P=0.07$, and $P=0.1$, respectively). Within-pair differences in birth weight were not associated with the pre-ejection period reactivity. Within-pair differences in birth weight were also not significantly associated with differences in respiratory sinus arrhythmia (Table 2) or heart rate (data not shown).

When subjects with a gestational age shorter than 37 weeks (21 dizygotic and 24 monozygotic twin pairs) were excluded, the results were similar. When the analyses were performed without adjustment for current body mass index or after adjustment for current weight instead of current body mass index, the results were also similar (data not shown).

Association of Pre-Ejection Period and Respiratory Sinus Arrhythmia With Blood Pressure

The pre-ejection period as well as the pre-ejection period reactivity were associated with systolic blood pressure, indicating that increased sympathetic activity was associated with higher blood pressure. In addition, respiratory sinus arrhythmia was negatively associated with systolic blood pressure (Table 4), indicating that decreased parasympathetic activity was associated with higher blood pressure.

Within-pair differences in the pre-ejection period were negatively associated with differences in systolic blood pressure (Table 5), indicating that increased sympathetic activity was associated with higher blood pressure within twin pairs.

TABLE 3. Associations of Within-Pair Differences in Birth Weight (Independent Variable) With Within-Pair Differences in Pre-Ejection Period and Respiratory Sinus Arrhythmia (Dependent Variables) in Twins

	Dizygotic Twin Pairs		Monozygotic Twin Pairs	
	β (95% CI)*	P	β (95% CI)*	P
Pre-ejection period, ms				
At rest	12.8 (3.0 to 22.7)	0.01	−0.7 (−9.0 to 7.5)	0.9
During reaction time task	13.1 (1.8 to 24.4)	0.02	−0.2 (−9.7 to 9.5)	1.0
During mental arithmetic task	9.7 (−3.6 to 23.0)	0.2	−3.9 (−14.8 to 7.0)	0.5
Reactivity to reaction time task	−0.2 (−6.4 to 5.9)	0.9	−0.6 (−7.6 to 6.5)	0.9
Reactivity to mental arithmetic task	1.3 (−8.1 to 10.7)	0.5	3.1 (−4.9 to 11.2)	0.4
Respiratory sinus arrhythmia, ms				
At rest	8.2 (−37.9 to 54.2)	0.7	24.1 (−25.8 to 74.0)	0.3
During reaction time task	21.5 (−17.3 to 60.3)	0.3	27.2 (−5.4 to 59.8)	0.1
During mental arithmetic task	18.2 (−18.3 to 54.6)	0.3	22.4 (−11.3 to 56.1)	0.2
Reactivity to reaction time task	−18.1 (−41.1 to 4.9)	0.1	−5.5 (−34.7 to 23.8)	0.7
Reactivity to mental arithmetic task	−10.1 (−35.4 to 15.1)	0.4	1.8 (−30.4 to 34.1)	0.9

*β (95% CI) per kilogram of birth weight after adjustment for differences in current body mass index.

TABLE 4. Associations of Pre-Ejection Period and Respiratory Sinus Arrhythmia With Systolic Blood Pressure in the Overall Sample of Twins

	β (95% CI)*	P
Pre-ejection period		
At rest	−0.18 (−0.24 to −0.11)	<0.00001
During reaction time task	−0.16 (−0.21 to −0.11)	<0.00001
During mental arithmetic task	−0.15 (−0.20 to −0.10)	<0.00001
Reactivity to reaction time task	0.20 (0.10 to 0.31)	0.0001
Reactivity to mental arithmetic task	0.12 (0.04 to 0.20)	0.004
Respiratory sinus arrhythmia, ms		
At rest	−0.02 (−0.04 to −0.002)	0.03
During reaction time task	−0.04 (−0.06 to −0.02)	0.0001
During mental arithmetic task	−0.05 (−0.07 to −0.03)	<0.00001
Reactivity to reaction time task	0.03 (−0.002 to 0.07)	0.06
Reactivity to mental arithmetic task	0.05 (0.02 to 0.08)	0.002

*β (95% CI) mm Hg per ms after adjustment for age, sex, and current body mass index.

Within-pair differences in respiratory sinus arrhythmia were negatively associated with differences in systolic blood pressure, but only the association of respiratory sinus arrhythmia during the mental arithmetic task with blood pressure in dizygotic twins was statistically significant (Table 5).

Subsequently, we examined whether birth weight effects on sympathetic activity could explain the association between birth weight and blood pressure. After adjustment for pre-ejection period at rest, during the reaction time task, or during the mental arithmetic task, the regression coefficient of the previously[4] described association between birth weight and blood pressure in the overall sample of twins (slope: −1.9 [95% CI, −3.9 to 0.0]; $P=0.05$) decreased by 63%, 84%, and 74%, respectively (slope after adjustment: −0.7 [−2.7 to 1.2], $P=0.5$; −0.3 [−2.2 to 1.5], $P=0.7$; and −0.5 [−2.4 to 1.4], $P=0.6$, respectively). This is illustrated in the Figure.

Adjustment for pre-ejection period reactivity or respiratory sinus arrhythmia (or reactivity) did not influence the association between birth weight and blood pressure (data not shown). The results were similar when blood pressure during stress was used instead of blood pressure at rest (data not shown). All results were similar when adjusted for smoking and gestational age (data not shown).

Discussion

We report 3 novel findings. First, in our overall sample, low birth weight was strongly associated with a shorter pre-ejection period and a larger pre-ejection period decrease in response to stress, which are indicative of increased sympathetic nervous system activity. Second, a shorter pre-ejection period was related to higher blood pressure and statistically explained a large part of the association between birth weight and blood pressure. Third, within-pair differences in birth weight were associated with differences in the pre-ejection period in dizygotic twins but not in monozygotic twins, which

TABLE 5. Associations of Within-Pair Differences in Pre-Ejection Period and Respiratory Sinus Arrhythmia (Independent Variables) With Within-Pair Differences in Systolic Blood Pressure (Dependent Variable) in Twins

	Dizygotic Twin Pairs		Monozygotic Twin Pairs	
	β (95% CI)*	P	β (95% CI)*	P
Pre-ejection period, ms				
At rest	−0.18 (−0.30 to −0.06)	0.0003	−0.23 (−0.38 to −0.07)	0.005
During reaction time task	−0.18 (−0.28 to −0.08)	0.001	−0.15 (−0.28 to −0.01)	0.03
During mental arithmetic task	−0.15 (−0.24 to −0.06)	0.002	−0.16 (−0.27 to −0.04)	0.01
Reactivity to reaction time task	0.14 (−0.07 to 0.35)	0.2	−0.03 (−0.23 to 0.16)	0.7
Reactivity to mental arithmetic task	0.08 (−0.06 to 0.22)	0.3	0.05 (−0.12 to 0.22)	0.6
Respiratory sinus arrhythmia, ms				
At rest	−0.01 (−0.04 to 0.02)	0.4	−0.004 (−0.03 to 0.02)	0.8
During reaction time task	−0.03 (−0.06 to 0.003)	0.08	−0.02 (−0.06 to 0.02)	0.3
During mental arithmetic task	−0.04 (−0.08 to −0.01)	0.02	−0.03 (−0.07 to 0.01)	0.1
Reactivity to reaction time task	0.04 (−0.02 to 0.09)	0.2	−0.01 (−0.05 to 0.04)	0.8
Reactivity to mental arithmetic task	0.04 (−0.01 to 0.09)	0.1	0.02 (−0.02 to 0.06)	0.2

*β (95% CI) mm Hg per ms after adjustment for differences in current body mass index.

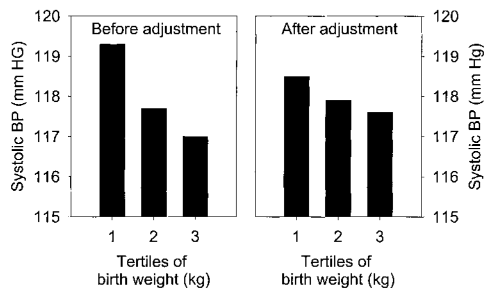

Illustration of the influence of adjustment for cardiac sympathetic activity on the relationship between birth weight and blood pressure. Systolic blood pressure level is shown according to tertiles of birth weight before and after adjustment for the pre-ejection period during the reaction time task. Division points for tertiles are 2.25 and 2.75 kg. BP indicates blood pressure.

demonstrates that the relationship between birth weight and sympathetic activity depends on genetic factors.

The association between low birth weight and increased sympathetic activity in the overall sample is consistent with several experimental studies.[18,19] In addition, low birth weight is associated with high resting heart rate in adult life in middle-aged individuals.[20]

A shorter pre-ejection period was strongly associated with higher systolic blood pressure in these twin subjects. This is consistent with studies in singletons that investigated the association of blood pressure with sympathetic activity, as indicated by muscle sympathetic nerve activity,[21] plasma levels of norepinephrine,[22] or spectral analysis of heart rate.[23]

The association between birth weight and blood pressure in this twin sample was remarkably similar to the well-established association in singletons (≈ -2 mm Hg per kg increase of birth weight[1]). This association diminished greatly (ie, 63% to 84%) after adjustment for the cardiac pre-ejection period. These findings are consistent with the hypothesis that the association between birth weight and blood pressure can be explained, at least partially, by sympathetic nervous system activity.

The within-pair analyses suggest that the association between birth weight and sympathetic activity is dependent on genetic factors. This finding adds to our previous observation of a genetic explanation for the relationship between birth weight and blood pressure in twins.[4] If the relationship between low birth weight and sympathetic activity depends on genetic factors, improvement of fetal nutrition may not prevent the development of increased sympathetic nervous system activity.

Our findings are relevant for understanding the development of hypertension and cardiovascular disease. A recent meta-analysis demonstrated that, on average, a 1-kg higher birth weight is associated with a 2-mm Hg lower blood pressure.[1] In clinical practice, this may seem a small difference, but these are relevant differences between the mean values of populations. For example, lowering mean systolic blood pressure in a population by 2 mm Hg corresponds to a 8% reduction in the risk of stroke.[24] Huxley et al[25] have recently concluded that the size of the association between birth weight and blood pressure may be overestimated because of publication bias, but this conclusion was largely based on findings in very large population studies, in which birth weight data or blood pressure levels were self-reported, causing attenuation of the associations in these studies. In addition, our findings may have important implications that extend beyond blood pressure. An increased sympathetic activity may be important for the development of insulin resistance, atherosclerosis, and cardiac hypertrophy.[26–28]

Differences in birth weight in twins can be used as a model for differences in birth weight in singletons, because several studies have demonstrated that birth weight in twins is associated with many variables that have been related to birth weight in singletons.[4–7,13,29–31]

It could be argued that, besides genetic factors, intrauterine factors in monozygotic twins may also be different from those in dizygotic twins. An important intrauterine difference between monozygotic and dizygotic twins is the placentation. Approximately two thirds of monozygotic twins are monochorionic (ie, share a placenta), whereas all dizygotic twins are dichorionic (ie, have separate placentas). We do not have data on chorionicity in our group of monozygotic twins, but we consider it unlikely that differences in chorionicity between dizygotic and monozygotic twins can fully explain the difference in the association of birth weight with indices of sympathetic activation and blood pressure. First, the overall association between birth weight and indices of sympathetic activation was similar in dizygotic and monozygotic twins. Second, others have shown that chorionicity did not influence the intrapair association between birth weight and blood pressure.[7,32] Furthermore, it should be noted that intrapair differences in birth weight in monozygotic twins have been related to intrapair differences in HDL cholesterol,[13] insulin sensitivity,[30] diabetes,[33] and height,[34] demonstrating that the twin study design in general is quite capable of showing that intrauterine factors can influence adult outcome. In summary, we have shown that low birth weight is associated with increased sympathetic activity and that a large part of the association between birth weight and blood pressure is explained by this increase. In addition, the within-pair analyses suggest that the association between low birth weight and increased sympathetic activity depends on genetic factors.

Acknowledgments

This study was supported by grants (86.083 and 88.042) from the Netherlands Heart Foundation.

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