Original Article

Lower Birth Weight Is Associated with Higher Resting Heart Rate during Boyhood

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There is substantial evidence that low birth weight is associated with the development of cardiovascular disease in adult life. Moreover, resting heart rate is a prognostic factor of cardiovascular morbidity and mortality. However, there are scarce data regarding the association between birth weight and resting heart rate in later life. Therefore, we investigated the association of anthropometric data at birth and hemodynamic indices including resting heart rate in Japanese boys. The data of 1,107 male students of a junior high school in Tokyo, Japan, who underwent a medical check-up in the year of admission to the school (12 or 13 years old) were used. Information on anthropometric data at birth based on "The Maternal and Child Health Handbook" was obtained from 573 students. From a standard 12-channel resting electrocardiogram, 8 cardiac cycles were used to estimate heart rate. Resting heart rate correlated positively with body mass index at the same age (r=0.100, p=0.017) and correlated negatively with birth weight (r=−0.102, p=0.015), height at birth (r=−0.125, p=0.003), and head circumference at birth (r=−0.095, p=0.025). The negative correlation of anthropometric data at birth with heart rate at the age of 12 or 13 was independent of body mass index at the same age. The mean value of resting heart rate at the age of 12 or 13 adjusted for body mass index at the same age was significantly higher in the lower tertile of birth weight than in the higher tertile of birth weight (81.7 *vs.* 78.5 beats/min, p=0.028). In conclusion, lower birth weight is associated with higher resting heart rate during boyhood, suggesting that elevated heart rate may be one mechanism linking small size at birth with the development of cardiovascular disease in future life. (*Hypertens Res* 2007; 30: 945–950)

Key Words**: birth weight, heart rate, sympathetic nerve activity, boyhood, cardiovascular disease**

Introduction

There is now substantial evidence from studies in different populations that a low growth rate during fetal life is associated with development of cardiovascular diseases such as coronary heart disease in adult life (*1–7*). Moreover, the association between elevated resting heart rate and cardiovascular morbidity and mortality has been demonstrated in a large number of epidemiologic studies (*8*). For instance, the Chicago and the Framingham studies found a significant association between resting heart rate and cardiovascular or total mortality (*9*, *10*). In addition, further Framingham study data showed that, in hypertensive subjects, heart rate was independently associated with all-cause mortality, cardiovascular mortality, or coronary heart disease mortality (*11*). A noticeable increase in the awareness of the association between elevated heart rate and cardiovascular mortality took place in the late 1990s, when a number of studies in general populations including younger subjects confirmed those observations showing a positive relationship between resting heart rate and either all-cause or cardiovascular mortality (*8*, *12*). However, there are scarce data in the literature regarding the association between birth weight and resting heart rate

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Table 1. Anthropometric and Hemodynamic Data at the Age of 12 or 13 in the Study Subjects (n=573)

Body weight (kg)	45.8±9.8
Height (cm)	153.0±7.9
Body mass index (kg/m^2)	19.4±3.1
Systolic blood pressure (mm Hg)	109.8±11.7
Diastolic blood pressure (mm Hg)	58.1±8.6
Resting heart rate (beats/min)	80.1±12.5

Values are means±standard deviations.

Table 2. Anthropometric Data at Birth in the Study Subjects (n=573)

Weight (g)	3,193±393
Height (cm)	49.7±2.0
Ponderal index (kg/m^3)	25.9±2.7
Head circumference (cm)	33.6±1.3
Chest circumference (cm)	32.4±1.9

Values are means±standard deviations.

in later life.

The purpose of the present study was to investigate, for the first time, the association between anthropometric data at birth and hemodynamic indices including resting heart rate obtained from electrocardiographic records during boyhood.

Methods

A medical check-up program for students of Dokkyo Junior High School is conducted annually in cooperation with the medical staff of Dokkyo University School of Medicine. All students of Dokkyo Junior High School are male. Check-ups are performed by medical doctors and registered nurses. This program includes a medical interview, physical examination, and blood pressure measurement. The students in the first year of the junior high school undergo an electrocardiogram. These medical examinations are performed in April of each year.

From 1995 to 2001, a total of 1,107 male Japanese students who were 12 or 13 years of age and who were in their first year at Dokkyo Junior High School underwent a medical check-up including an electrocardiogram.

In April 2001, a questionnaire requesting anthropometric data from the time of birth of the student was sent to the parents of these 1,107 subjects. They were asked to complete the questionnaire on the basis of "The Maternal and Child Health Handbook," which is provided to every pregnant woman by the Ministry of Health and Welfare of Japan, and in which important information on measures of birth size is recorded by obstetricians. In Japan, most mothers keep the handbook throughout their lives. In the present study, the data for later analysis were limited to records obtained from the handbook. The ponderal index was calculated as the weight in kg/m^3.

In the medical check-up program, body weight was measured using an electronic scale with 10 g precision with the subject wearing indoor clothes without shoes. Height was determined using a stadiometer accurate to the nearest 0.1 cm. After the student had been sitting quietly for at least 5 min, blood pressure was measured twice by nurses with a mercury sphygmomanometer. Blood pressure was measured in the right arm using an appropriate cuff size. Systolic and diastolic blood pressures (SBP and DBP) were based on the first and fifth Korotkoff phases, respectively. The average values of 2 measurements were used for analysis. From a standard 12-channel resting electrocardiogram, 8 cardiac cycles were used to estimate heart rate. This value was obtained from the automatic output of the electrocardiogram device (ECG-9000 series; Nihon Kohden Co., Ltd., Tokyo, Japan).

The research was approved by the Ethics Committees of Dokkyo Junior High School and Dokkyo University School of Medicine. Written informed consent was obtained from all students enrolled in the study, as well as from their parents.

Statistical Analysis

Values are expressed as the means±standard deviations or 95% confidential intervals. Simple linear regression analysis was performed to compare the hemodynamic data at the age of 12 or 13 and other relevant variables. Multiple linear regression analysis was performed to identify the independent factors that affected the hemodynamic data at the age of 12 or 13. In model 1, weight was used as an independent factor of anthropometric data at birth. In model 2, height was used as an independent factor of anthropometric data at birth. In model 3, head circumference was used as an independent factor of anthropometric data at birth.

The subjects were divided into three nearly equally sized groups according to their birth weight. Differences in hemodynamic data at the age of 12 or 13 among the three groups were analyzed by analysis of covariance adjusted for body mass index at the age of 12 or 13 followed by Newman-Keuls's post hoc test. The statistical package SPSS version 11.0.1 for Windows (SPSS Inc., Chicago, USA) was used for analyses. A value of $p<0.05$ was considered significant.

Results

We obtained and analyzed anthropometric data at birth in "The Maternal and Child Health Handbook" for 573 subjects.

Table 1 shows the anthropometric and hemodynamic data at the age of 12 or 13 in the study subjects. The resting heart rate was 80.1±12.5 beats/min, with a range of 51 to 128 beats/min. In the present study, there were no differences in the anthropometric and hemodynamic data at the age of 12 or 13 between the students whose anthropometric data were obtained from "The Maternal and Child Health Handbook" (n=573) and those whose anthropometric data were not

Table 3. Results of Simple Regression Analysis of the Association between Hemodynamic Data at the Age of 12 or 13 and Other Relevant Variables (n=573)

Independent factor	Systolic blood pressure		Diastolic blood pressure		Resting heart rate	
	r	p	r	p	r	p
Body weight at the age of 12 or 13	0.354	<0.001	0.187	<0.001	0.059	0.156
Height at the age of 12 or 13	0.335	<0.001	0.148	<0.001	−0.030	0.474
BMI at the age of 12 or 13	0.254	<0.001	0.150	<0.001	0.100	0.017
Birth weight	0.052	0.214	0.077	0.065	−0.102	0.015
Height at birth	0.038	0.365	0.071	0.090	−0.125	0.003
Ponderal index at birth	0.013	0.755	0.007	0.866	0.015	0.716
Head circumference at birth	0.000	0.999	0.071	0.092	−0.095	0.025
Chest circumference at birth	0.048	0.257	0.043	0.303	−0.072	0.086

BMI, body mass index.

Table 4. Results of Multiple Regression Analysis of the Association between Hemodynamic Data at the Age of 12 or 13 and Other Relevant Variables (n=573)

Independent factor	Systolic blood pressure			Diastolic blood pressure			Resting heart rate		
	β	t value	p value	β	t value	p value	β	t value	p value
Model 1									
Birth weight	0.036	0.895	0.371	0.068	1.642	0.101	−0.108	−2.608	0.009
BMI at the age of 12 or 13	0.252	6.218	<0.001	0.145	3.515	<0.001	0.106	2.560	0.011
Model 2									
Height at birth	0.029	0.722	0.470	0.066	1.590	0.112	−0.129	−3.115	0.002
BMI at the age of 12 or 13	0.251	6.183	<0.001	0.148	3.565	<0.001	0.108	2.609	0.009
Model 3									
Head circumference at birth	0.002	0.038	0.970	0.072	1.726	0.085	−0.094	−2.247	0.025
BMI at the age of 12 or 13	0.247	6.047	<0.001	0.143	3.423	0.001	0.093	2.216	0.027

BMI, body mass index. In model 1, weight was used as an independent factor of anthropometric data at birth. In model 2, height was used as an independent factor of anthropometric data at birth. In model 3, head circumference was used as an independent factor of anthropometric data at birth.

obtained from the handbook (n=534).

Table 2 shows the anthropometric data at birth in the study subjects. The birth weight was 3,193±393 g, with a range of 1,870 to 4,660 g. In simple regression analysis, body weight at the age of 12 or 13 was positively correlated with birth weight (r=0.105, p=0.012).

Table 3 shows the results of simple linear regression analysis of the association between hemodynamic data at the age of 12 or 13 and other relevant variables. SBP and DBP at the age of 12 or 13 correlated positively with body weight, height, and body mass index at the same age. They did not show significant correlation with any measurement at birth. Resting heart rate at the age of 12 or 13 correlated positively with body mass index at the same age. It showed negative correlations with birth weight, height at birth, and head circumference at birth.

Table 4 shows the results of multiple linear regression analysis between hemodynamic data at the age of 12 or 13 and other relevant variables. In each of the three models, SBP and DBP at the age of 12 or 13 correlated positively with body mass index at the same age. Also in all three models, resting heart rate at the age of 12 or 13 correlated negatively with birth weight, height at birth, and head circumference at birth independently of body mass index at the same age. In addition, resting heart rate at the age of 12 or 13 correlated positively with body mass index at the same age independently of measurements at birth.

Figure 1 shows SBP and DBP at the age of 12 or 13 adjusted for body mass index at the same age by birth-weight tertile. The lower tertile consisted of subjects with a birth weight ranging from 1,870 to 3,040 g (n=192); the middle tertile of subjects with a birth weight ranging from 3,046 to 3,350 g (n=191); and the upper tertile of subjects with a birth weight ranging from 3,354 to 4,660 g (n=190). Blood pressure was 108.7±9.9 (95% confidential interval: 86.5–131.0) mmHg systolic and 57.5±7.8 (40.7–74.3) mmHg diastolic in the lower tertile, 109.6±6.3 (87.3–131.8) mmHg systolic and 58.0±4.9 (41.7–74.8) mmHg diastolic in the middle tertile, and 111.1±14.7 (88.8–133.4) mmHg systolic and 58.9±8.4 (42.0–75.8) mmHg diastolic in the upper tertile. Neither SBP

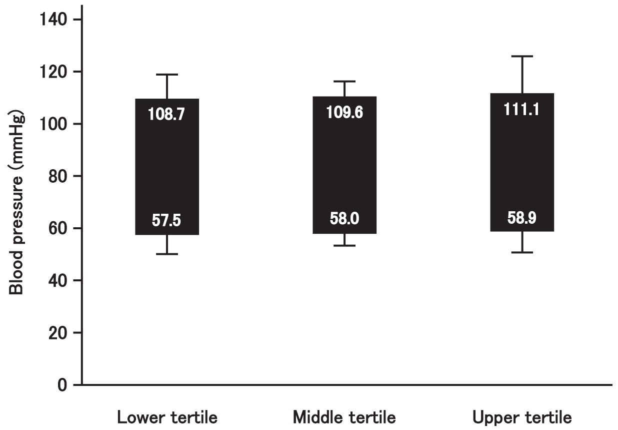

Fig. 1. *The mean values±standard deviations of systolic and diastolic blood pressures (SBP and DBP) at the age of 12 or 13 adjusted for body mass index at the same age in the subjects distributed by their birth weights (n=573). The lower tertile consisted of subjects with a birth weight ranging from 1,870 to 3,040 g (n=192); the middle tertile of subjects with a birth weight ranging from 3,046 to 3,350 g (n=191); and the upper tertile of subjects with a birth weight ranging from 3,354 to 4,660 g (n=190). Neither SBP nor DBP differed significantly among the tertiles.*

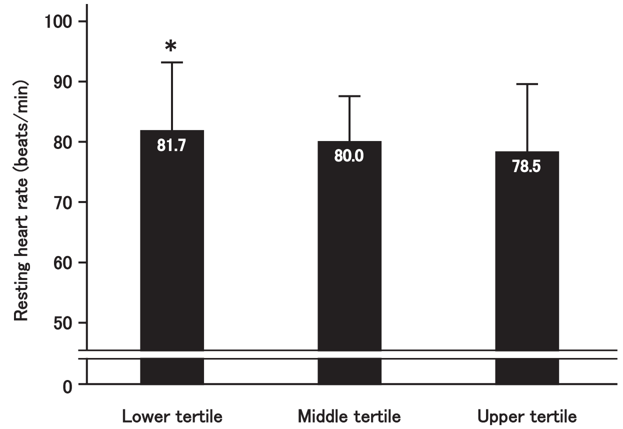

Fig. 2. *The mean values±standard deviations of resting heart rate at the age of 12 or 13 adjusted for body mass index at the same age in the subjects distributed by their birth weights (n=573). The lower tertile consisted of subjects with a birth weight ranging from 1,870 to 3,040 g (n=192); the middle tertile of subjects with a birth ranging from 3,046 to 3,350 g (n=191); and the upper tertile of subjects with a birth weight ranging from 3,354 to 4,660 g (n=190). The mean value of resting heart rate was significantly higher in the lower tertile of birth weight than in the higher tertile of birth weight (81.7 vs. 78.5 beats/min, p=0.028).*

nor DBP differed significantly among the tertiles.

Figure 2 shows the resting heart rate at the age of 12 or 13 adjusted for body mass index at the same age in the tertile groups. Resting heart rate was 81.7±11.3 (57.3–106.2) beats/min in the lower tertile, 80.0±7.7 (55.6–104.4) beats/min in the middle tertile, and 78.5±11.2 (54.0–102.9) beats/min in the upper tertile. Resting heart rate was significantly higher in the lower tertile of birth weight than in the higher tertile of birth weight ($p=0.028$).

Discussion

The main finding of the present study is that there was a significant association between lower birth weight and elevated resting heart rate obtained from the record of the electrocardiogram during boyhood. In addition, other measurements of birth size, such as length and head circumference, also had significant relations with resting heart rate during boyhood.

To the best of our knowledge, only one study has investigated the relationship between birth weight and pulse rate in adult life. Phillips and Barker (*13*) studied the resting pulse rate of 449 men and women aged 46–54 (mean 50) years whose birth size was recorded in detail. Pulse rate was measured simultaneously with blood pressure using an automated recorder at home by trained fieldworkers. The pulse rate rose progressively from 71 beats/min among subjects who weighed 3.3 kg or more at birth to 76 beats/min among those who weighed 2.5 kg or less. The association was independent of the current body mass index, the waist-to-hip ratio, and potential confounding variables including smoking, alcohol consumption, and social class.

The results of the present study agree well with Phillips and Barker's observations (*13*). However, there are some differences between their findings and ours. First, our subjects were all boys at almost the same age (12 or 13 years old). Our sample size was somewhat larger. Our subjects were students of the same private school located in the center of Tokyo, Japan, and it was assumed that their socioeconomic status as well as their educational levels were homogeneous. Second, we assessed not pulse rate but heart rate obtained from the electrocardiographic record. Resting heart rate based on electrocardiographic recording is thought to be more precise than pulse rate measured simultaneously with blood pressure.

Recently, it has been shown that elevated resting heart rate is associated with an increased risk of mortality not only in patients with cardiovascular disease but also in the general population (*8*). For instance, in the Framingham study, in a cohort composed of 5,070 subjects who were free from cardiovascular disease at the time of entry into the study, cardiovascular and coronary mortality increased progressively with resting heart rate based on the electrocardiogram (*10*). Kristal-Boneh *et al*. (*14*) reported that resting heart rate estimated from the electrocardiogram was strongly associated with both all-cause and cardiovascular mortality after controlling for confounding factors in an 8 year follow-up of 3,527 Israeli male industrial employees. Seccareccia *et al*. (*15*) reported that in a low-risk Italian male population aged 40–69 years, heart rate increment was associated with a relative risk increase of 1.52 (95% confidential interval: 1.29–1.78) for all-cause mortality, 1.63 (1.26–2.10) for cardiovascular mortality, and 1.47 (1.19–1.80) for non-cardiovascular mortality. Also in Japan, higher heart rate was found to be an independent marker of cardiovascular and all-cause death for middle-aged men and women in the general population (*16*). Although the study subjects of those reports were largely restricted to persons who were middle-aged at baseline examination, the Chicago study revealed that resting heart rate obtained from electrocardiogram was a significant risk factor for mortality from coronary disease, all cardiovascular diseases, and all causes both in younger men aged 18–39 years and in middle-aged men aged 40–59 years (*9*). However, there is very limited data in the literature regarding the relationship between resting heart rate during boyhood and the development of cardiovascular disease in later life. Therefore, further studies are needed to reveal the clinical significance of the present finding that lower birth weight was associated with higher resting heart rate during boyhood.

Possible explanations for the association between low birth weight and elevated heart rate should be discussed. Elevated heart rate seems to be a result of increased sympathetic nerve activity, reduced vagal activity, or both. Furthermore, a rapid heart rate may reflect autonomic imbalance. To date, there have been several studies investigating the association between birth weight and autonomic nervous activity in later life. For instance, IJzerman *et al*. (*17*) reported increased cardiac sympathetic nerve activity in individuals with low birth weight on the basis of measurements of the cardiac pre-ejection period and respiratory sinus arrhythmia with electrocardiography and impedance cardiography at rest and during mental stress in 53 dizygotic and 61 monozygotic pairs. Boguszewski *et al*. (*18*) reported that young adults born small for gestational age had increased muscle sympathetic nerve activity compared to young individuals born appropriate for gestational age by the use of a cross-sectional, comparative study of 32 subjects.

As we evaluated resting heart rate only at the age of 12 or 13, it is unknown when the association between lower birth weight and higher resting heart rate or higher sympathetic nerve activity becomes apparent in subjects with low birth weight. However, it is suggested that the association between lower birth weight and higher heart rate or higher sympathetic nerve activity is already present in early life. For example, Spassov *et al*. (*19*) reported that heart rate was higher in newborn infants with small weight for gestational age compared to those with average weight for gestational age. Furthermore, Galland *et al*. (*20*) reported that the sympathetic component of the control of heart rate variability was already higher in infants with low birth weight at 1 and 3 months of age. The mechanisms responsible for these findings are unknown, but evidence from animal studies and preliminary evidence in humans suggest that an imbalance between fetal demands and supply leads to an adaptive series of stress responses that appear to permanently alter neuroendocrine development (*21*, *22*).

In the present study, SBP and DBP during boyhood showed no significant correlation with any anthropometric measurement at birth, although an inverse relationship between birth weight and blood pressure in children has been reported in several studies (*23*). However, as young subjects at the age of 12 or 13 were studied in the present study, the influence of elevated heart rate on blood pressure may emerge in later life. To date, epidemiologic studies such as the Framingham study have shown that elevated heart rate is followed by an increase in blood pressure and by the onset of hypertension (*24*).

Recently, it was shown that low birth weight was a higher risk for the metabolic syndrome. In our previous study, birth weight showed an inverse relation with serum total cholesterol and triglyceride levels in 207 male medical students (*25*). Tanaka *et al*. reported that both lower birth weight and visceral fat accumulation were independently related to hyperinsulinemia and insulin resistance in obese Japanese children (*26*). More recently, Ramadhani *et al*. (*27*) also reported that lower birth weight predicted the metabolic syndrome in 749 young adults aged 26–31 years who participated in the Atherosclerosis Risk in Young Adults (ARYA)-study, particularly through higher serum triglycerides and higher SBP. In addition, the association of elevated heart rate with the clustering of metabolic abnormalities has been well documented (*28*). Using the mixture analysis test in numerous Western populations, Palatini *et al*. (*29*) reported that subjects with tachycardia had high values of body mass index, serum triglycerides, blood pressure, and blood glucose and low values of serum high-density lipoprotein cholesterol, which are characteristic features of metabolic syndrome. Taking these findings together, we consider that elevated heart rate in individuals with low birth weight may be a precursor for development of the metabolic syndrome.

One of the limitations in the present study is that we did not assess regular physical activity in the study subjects. It is supposed that some boys were physically active in a sport club, while others were not. Regular physical activity might have had some influences on autonomic nervous activity and hemodynamic variables, especially heart rate during boyhood, in our study subjects. It has been reported that regular physical activity contributes to enhanced autonomic nervous activity in Japanese children (*30*).

In conclusion, birth weight and height and head circumference at birth were inversely associated with resting heart rate during boyhood, suggesting that elevated heart rate may be one mechanism linking small size at birth with the development of cardiovascular disease in later life.

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