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Blunted Autonomic Responses and Low-Grade Inflammation in Mongolian Adults Born at Low Birth Weight

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Low birth weight (LBW) has been considered as a risk factor for adult hypertension that is associated with deterioration of autonomic functions and low-grade inflammation. To explore the above effects of LBW, we measured blood pressure (BP) and heart rate variability during postural change from a supine position to a sitting position in 21 healthy Mongolian adults aged 23-34 years: 4 with LBW (birth weight < 2,500 g), 13 with normal birth weight (NBW, 2,500 g ≤ birth weight < 4,000 g), and 4 with high birth weight (HBW, ≥ 4,000 g). Mongolian population is known to have higher prevalence of hypertension. The ratio of low frequency (LF, 0.04-0.15 Hz) to high frequency components (HF, 0.15-0.40 Hz) was used as an index of sympathetic nerve activity, and HF was used as an index of parasympathetic nerve activity. In contrast to the NBW group, the LBW and HBW groups showed no significant increase in heart rate, systolic BP and LF/HF following postural change. We also measured blood cell counts and other blood parameters related to inflammation. After adjusting for age, BMI, sex and family history of hypertension, LBW was retained as an independent predictor only for higher counts of leukocytes ($\beta = -0.51$, $p < 0.05$), basophils ($\beta = -0.62$, $p < 0.01$), eosinophils ($\beta = -0.83$, $p < 0.001$), and platelets ($\beta = -0.61$, $p < 0.05$). We propose that LBW leads to blunted autonomic responses and low-grade inflammation in seemingly healthy Mongolian adults.

Keywords: autonomic function; birth weight; blood pressure; healthy young Mongolian adult; low-grade inflammation

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Introduction

In the 1980s, Barker and Osmond (1988) first described a relationship between birth weight and hypertension in adulthood. Subsequently, a number of epidemiological studies confirmed the association between low birth weight (LBW) and increased risk of adult hypertension (Tamakoshi et al. 2006; Mu et al. 2012). However, the underlying mechanisms linking LBW to the development of hypertension in adulthood are poorly understood and likely to be numerous.

LBW may contribute to hypertension through several suggested mechanisms. Schmidt et al. (2005) observed that impaired intrauterine growth has a negative influence on nephron formation and renal function in humans, which might lead to hypertension. On the other hand, other researchers have demonstrated that vascular structures can be differently programmed in the early stages of development in individuals with LBW (Ligi et al. 2010; Zanardo et al. 2013). LBW has been correlated with increased stiffness in the large arteries in young adults assessed using carotid-femoral pulse wave velocity (Oren et al. 2003), and Leeson et al. (2001) observed that LBW is also associated with reduced endothelium-dependent flow-mediated dilation of the brachial artery in young adults aged 20-28 years.

In recent years, low-grade inflammation and deterioration of autonomic regulation, both of which play key roles in the hypertensive disease process, have attracted the attention of researchers. For instance, in the Northern Finland 1966 Birth Cohort Study, high-sensitivity C-reactive protein (Hs-CRP) levels at 31 years were 16% higher per kg lower birth weight (Tzoulaki et al. 2008). From the same birth cohort, Canoy et al. (2009) found that birth weight was inversely related with adult leukocyte count. Furthermore, it is known that the autonomic nervous system plays an important role in blood pressure (BP) regulation and in the development of hypertension. LBW may increase sympathetic nerve activity and decrease baroreflex sensitivity (IJzerman et al. 2003), thus contribute to the development of adult hypertension in individuals with LBW. However, some experimental studies have contradicted this hypothesis, reporting unchanged (Weyer et al. 2000) or decreased sympathetic nerve activity (Weitz et al. 2003).

Thus far, almost no studies have investigated these processes in Mongolian people, despite the high overall risk of hypertension in these individuals (Zhu et al. 2012).

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Mongolians are a major minority in northern China. The prevalence of hypertension in Chinese individuals aged > 18 years was 18.8% in 2002 (National Bureau of Statistics of China, 2004), and there are marked ethnic and geographical differences in BP and prevalence of hypertension in China (Ueshima et al. 2000), with Mongolians showing a higher prevalence of hypertension than other ethnic groups (Zheng et al. 2010). Previous studies have suggested that the high prevalence of hypertension in Mongolians is attributable to genetic backgrounds, customs, culture, and food consumption (Yang and Sun 2011), even though the etiology of hypertension cannot be fully explained by genetic or adult risk factors such as age, body mass index (BMI), physical activity, and cigarette smoking (Zhao et al. 2002). On the other hand, there are significant differences in birth weight among different regions and ethnic groups in China (Liu et al. 2005). The rates of LBW and high birth weight (HBW) infants were 3.6% and 4.6% in China, and 4.9% and 6.3% in Inner Mongolia, respectively (Liu and Chen 1999; Liu et al. 2005). Nevertheless, previous studies investigating the association between birth weight and hypertension in Chinese individuals did not consider ethnic and regional differences. Further studies are needed to clarify the developmental process of hypertension in a high-risk Mongolian population.

Therefore, our objective was to evaluate the relationship between birth weight and hypertension risk factors, including low-grade inflammation and autonomic regulation, in healthy young Mongolian adults.

Methods

Participants

The participants of this study were 21 healthy Mongolian adults (12 men and 9 women) aged 23-34 years, who were raised in the Inner Mongolia Autonomous Region of China and studied in Japan. The participants responded to a questionnaire about their birth weight, age, height, weight, medical history, physical activity (present continuous exercise), fasting time, family history (FH) of hypertension, and presence or absence of allergy. None of the participants had a history of smoking, continuous exercise, medication use, or respiratory or circulatory disease. We selected female participants with a regular menstrual cycle and performed measurements in the follicular phase when levels of both estrogen and progesterone are lower, because cardiac autonomic regulation might vary within the menstrual cycle (McKinley et al. 2009; Boudreau et al. 2011; Yang et al. 2013).

We used numerical analyses to evaluate all of the participants' resting BP, heart rate (HR) and autonomic nervous activity, as well as humoral risk factors. In addition, in order to prove the hypothesis that the response of HR, BP and autonomic nervous activity following postural changes from supine to sitting position are different by birth weight, categorical method was adopted for the autonomic function studies. Thus, participants should be classified by weight at birth into the LBW (birth weight < 2,500 g, 2 men and 2 women), normal birth weight (NBW, 2,500 g ≤ birth weight < 4,000 g, 8 men and 5 women), and HBW (birth weight ≥ 4,000 g, 2 men and 2 women) groups based on the birth weight range of LBW and HBW (Gill et al. 2013), when studied the autonomic function.

Measurements

The participants were asked to refrain from drinking caffeinated beverages and performing strenuous exercise for 24 h prior to the measurement. They were also asked to obtain sufficient sleep the night before the measurement was performed. If the participants required a meal, they were limited to low-fat foods and asked to finish eating at least 2 hours before the examination. All measurements were performed between 9:00 and 16:00 to avoid circadian influence on the HR and autonomic nervous system (Nussinovitch et al. 2011). The examination was performed in a quiet room maintained at a temperature of 24 ± 2°C and a humidity of 50 ± 5%. After personal data collection, participants were asked to lie down in a bed. Then, electrodes were attached to the chest to obtain the electrocardiogram (ECG), and a BP monitor (OMRON HEM-7430 Tokyo, Japan) was placed on the right upper arm. Participants maintained a supine position for 15 minutes, after which they changed to a sitting position for 15 minutes. They were asked to maintain each position without moving or talking, as possible. BP was measured twice each in the supine position and sitting position, and once in the "immediately after sitting position" defined as the first minute after postural change. ECG measurements (Radarcirc TM, Dainippon Sumitomo Pharmaceutical Co., Osaka, Japan) were recorded for 30 minutes, with the first and last 5 minutes excluded from the analysis. The ratio of low frequency (LF, 0.04-0.15 Hz) to high frequency (HF, 0.15-0.40 Hz) components was used as an index of sympathetic nerve activity, and HF was used as an index of parasympathetic nerve activity (Matveev et al. 2003; Nussinovitch et al. 2011, 2012).

Blood samples obtained from all participants at the end of the experiment were used to analyze total leukocyte, leukocyte subtype, red blood cell, hemoglobin, hematocrit, and platelet counts, as well as total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and Hs-CRP levels. This study was approved by the Tohoku University Graduate School of Medicine's Ethics Committee. All the participants gave written informed consent.

Statistical analysis

Data were analyzed using SPSS Statistics 21.0 (IBM Japan, Ltd.). One-way analysis of variance (ANOVA) and multiple comparison tests were performed to compare the means of three variables. The distributions of TG and Hs-CRP levels were skewed; hence, we used the log-transformed values instead of the raw data. The relationship between birth weight and indices of hypertension risk factors were analyzed using the Pearson correlation coefficient and multivariate regression analyses. One-way repeated-measures ANOVA and multiple comparison tests were performed to identify the influence of postural change. Values are expressed as the mean ± SE. All reported p-values are two-tailed and $p < 0.05$ was considered statistically significant.

Results

Characteristics of participants by birth weight group

Baseline data in the different birth weight groups are presented in Table 1. Birth weight was found to differ significantly among the three birth weight groups ($p < 0.01$). The mean birth weights were 2,335 ± 113.2 g in the LBW group, 3,392 ± 63.5g in the NBW group, and 4,200 ± 122.5 g in the HBW group. Age, height, weight, and BMI were similar among the three birth weight groups. All of the leu-

Table 1. Baseline characteristics of participants by birth weight.

	LBW	NBW	HBW
Birth Weight (g)	2335 ± 113.2**,†††	3392 ± 63.5	4200 ± 122.5**
Age (years)	27.3 ± 1.3	28.2 ± 0.8	27.5 ± 1.3
Height (cm)	160.5 ± 4.9	166.8 ± 1.9	170.5 ± 3.5
Weight (kg)	55.0 ± 5.8	60.6 ± 2.3	69 ± 8.4
BMI (kg/m^2)	21.1 ± 1.1	21.8 ± 0.7	23.7 ± 2.4
FH of hypertension (Yes: No)	2: 2	8: 5	2: 2
HR (bpm)	67.6 ± 1.9	63.7 ± 1.8	61.6 ± 3.5
SBP (mmHg)	114.0 ± 9.4	114.0 ± 3.4	112.3 ± 3.7
DBP (mmHg)	65.0 ± 4.4	64.7 ± 2.5	62.3 ± 2.8
LF/HF	1.2 ± 0.3	0.9 ± 0.1	1.2 ± 0.5
HF (msec^2/Hz)	186.2 ± 118.2	170.6 ± 46.3	156.9 ± 28.3
Leukocyte (/μL)	6222.5 ± 567.0	5433.9 ± 262.7	4572.5 ± 192.2
Basophil (/μL)	48.3 ± 17.6	29.5 ± 4.7	13.8 ± 3.1
Eosinophil (/μL)	358.8 ± 45.7*,†	110.1 ± 22.1	62.3 ± 10.3
Neutrophil (/μL)	3545.0 ± 213.2	3340.9 ± 215.5	2756.5 ± 54.7
Lymphocyte (/μL)	1962.8 ± 250.7	1678.1 ± 103.0	1476.3 ± 120.0
Monocyte (/μL)	307.5 ± 57.5	275.4 ± 17.0	263.8 ± 27.4
Red blood cell(×10^4/μL)	474.0 ± 48.3	477.5 ± 13.5	457.3 ± 22.7
Hemoglobin (g/dL)	14.2 ± 1.5	14.1± 0.5	13.5 ± 0.8
Hematocrit (%)	43.5 ± 4.1	43.0 ± 1.3	41.4 ± 2.4
Platelet (×10^4/μL)	26.4 ± 1.3*	21.0 ± 1.1	21.1 ± 1.4
TC (mg/dL)	157.3 ± 11.7	160.1 ± 7.8	158.3 ± 8.1
HDL-C (mg/dL)	49.0 ± 3.7	47.0 ± 2.4	45.8 ± 2.4
LDL-C (mg/dL)	88.5 ± 8.0	95.4 ± 7.0	96.8 ± 5.1
Fasting time (hours)	7.6±2.3	5.5±1.1	7.6±2.5
Log TG (mg/dL)	2.0 ± 0.2	1.9 ± 0.1	2.0 ± 0.1
Log Hs-CRP (mg/L)	-0.5 ± 0.1	-0.7 ± 0.1	-0.2 ± 0.1

LBW, low birth weight; NBW, normal birth weight; HBW, high birth weight; BMI, body mass index; FH of hypertension, family history of hypertension; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LF/HF, ratio of low to high frequency; HF, high frequency; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Log TG, log-transformed triglyceride; Log Hs-CRP, log-transformed high-sensitivity C-reactive protein.
Variables are expressed as mean ± SE (*$p < 0.05$, **$p < 0.01$ compared with NBW; †$p < 0.05$, †††$p < 0.001$ compared with HBW).

kocyte, red blood cell, hemoglobin, hematocrit, platelet counts, and Hs-CRP levels were within the normal ranges for all 21 participants. As for leukocyte subtypes, the eosinophil count was significantly higher in the LBW group than in the NBW and HBW groups ($p < 0.05$ for both). Moreover, we found that the platelet count was significantly higher in the LBW group than in the NBW group ($p < 0.05$). Leukocyte counts were not significantly different among the three birth weight groups.

Pearson correlation analyses and multivariate regression analyses between birth weight and each hypertension risk factor

Birth weight is positively related to current height ($r = 0.52$, $p < 0.05$; data not shown), weight ($r = 0.54$, $p < 0.05$; data not shown), and inversely related to leukocyte ($r = −0.45$, $p < 0.05$), basophil ($r = −0.55$, $p < 0.05$; data not shown), eosinophil ($r = −0.75$, $p < 0.001$; data not shown), and platelet counts ($r = −0.49$, $p < 0.05$) (Table 2), whereas no correlations between birth weight and other hypertension risk factors, such as TC, HDL-C, LDL-C, TG, and Hs-CRP levels, resting HR, BP, LF/HF, and HF were found.

Even within this young age group, age is positively

related to LDL-C levels ($r = 0.45$, $p < 0.05$). Current height is positively related to resting systolic BP (SBP, $r = 0.53$, $p < 0.05$) and inversely related to basophil and eosinophil counts ($r = -0.53$, $p < 0.05$ and $r = -0.46$, $p < 0.05$, respectively, data not shown). Current body weight is positively related to resting SBP ($r = 0.67$, $p < 0.01$), TC ($r = 0.47$, $p < 0.05$), LDL-C ($r = 0.47$, $p < 0.05$) and log TG ($r = 0.46$, $p < 0.05$) levels, and inversely related to resting HR and HF ($r = -0.57$, $p < 0.01$ and $r = -0.45$, $p < 0.05$, data not shown). Furthermore, adult BMI is positively related to resting SBP ($r = 0.58$, $p < 0.01$), log TG ($r = 0.45$, $p < 0.05$) and log Hs-CRP level ($r = 0.49$, $p < 0.01$), and inversely related to HR ($r = -0.66$, $p < 0.01$), shown as Table 2.

The multivariate regression analyses used HR, BP, autonomic function, leukocyte and platelet counts, TC, HDL-C, LDL-C, log TG and log Hs-CRP separately as dependent variables and birth weight, age, BMI, sex and FH of hypertension as independent variables. After adjusting for age, BMI, sex and FH of hypertension for the total sample in a multivariate regression model, LBW was retained as an independent predictor variable for higher leukocyte ($\beta = -0.51$, $p < 0.05$), basophil ($\beta = -0.62$, $p < 0.01$; data not shown), eosinophil ($\beta = -0.83$, $p < 0.001$; data not shown), and platelet counts ($\beta = -0.61$, $p < 0.05$), shown in Table 3.

Changes in cardiovascular measures following postural change

The LBW and HBW groups showed no significant changes in HR following postural change from a supine

Table 2. Values of Pearson correlation coefficient between individual variables and each risk factor.

	HR	SBP	DBP	LF/ HF	HF	Leukocyte	Platelet	TC	HDL-C	LDL-C	Log TG	Log Hs-CRP
	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)
Birth Weight (g)	-0.40	0.08	-0.06	0.11	-0.22	**-0.45**	**-0.49**	0.07	-0.14	0.16	0.01	0.17
	(0.07)	(0.74)	(0.80)	(0.65)	(0.34)	**(0.04)**	**(0.02)**	(0.77)	(0.54)	(0.50)	(0.98)	(0.46)
Age (years)	-0.10	0.28	0.29	-0.14	-0.16	-0.38	-0.13	**0.48**	0.10	**0.45**	0.11	-0.10
	(0.67)	(0.22)	(0.20)	(0.56)	(0.48)	(0.09)	(0.57)	**(0.03)**	(0.65)	**(0.04)**	(0.64)	(0.66)
BMI (kg/m2)	**-0.66**	**0.58**	0.40	0.39	-0.40	0.01	0.09	0.40	-0.41	0.40	**0.45**	**0.49**
	(0.00)	**(0.01)**	(0.07)	(0.08)	(0.07)	(0.96)	(0.69)	(0.07)	(0.07)	(0.07)	**(0.04)**	**(0.03)**
Sex	0.17	**-0.56**	-0.39	-0.16	**0.46**	-0.02	0.33	**-0.44**	0.10	-0.40	-0.35	0.03
(Women = 1 or Men = 0)	(0.46)	**(0.01)**	(0.08)	(0.49)	**(0.04)**	(0.93)	(0.15)	**(0.05)**	(0.66)	(0.07)	(0.12)	(0.90)
FH of hypertension	-0.09	0.21	0.15	0.11	0.16	-0.09	0.00	**0.47**	-0.04	0.41	0.06	0.24
(Yes = 1 or No = 0)	(0.70)	(0.37)	(0.53)	(0.65)	(0.50)	(0.69)	(1.00)	**(0.03)**	(0.88)	(0.06)	(0.81)	(0.29)

BMI, body mass index; FH of hypertension, family history of hypertension; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LF/HF, ratio of low to high frequency; HF, high frequency; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Log TG, log-transformed triglyceride; Log Hs-CRP, log-transformed high-sensitivity C-reactive protein.

Table 3. Values of Multiple regression coefficients evaluating the effect of individual variables on each risk factor.

	HR	SBP	DBP	LF/ HF	HF	Leukocyte	Platelet	TC	HDL-C	LDL-C	Log TG	Log Hs-CRP
	β (p)	β (p)	β (p)	β (p)	β (p)	β (p)	β (p)	β (p)	β (p)	β (p)	β (p)	β (p)
Birth Weight (g)	-0.17	-0.21	-0.29	-0.03	-0.04	**-0.51**	**-0.61**	-0.24	0.01	-0.03	-0.22	0.01
	(0.43)	(0.30)	(0.23)	(0.90)	(0.87)	**(0.03)**	**(0.01)**	(0.38)	(0.98)	(0.88)	(0.38)	(0.97)
Age (years)	0.02	0.06	0.17	-0.26	0.08	-0.43	0.05	-0.05	0.20	0.35	-0.05	-0.12
	(0.93)	(0.78)	(0.48)	(0.32)	(0.73)	(0.07)	(0.82)	(0.84)	(0.44)	(0.12)	(0.84)	(0.61)
BMI (kg/m2)	**-0.60**	**0.53**	0.42	0.39	-0.33	0.24	0.42	0.47	-0.43	0.27	0.47	**0.51**
	(0.01)	**(0.02)**	(0.10)	(0.15)	(0.17)	(0.29)	(0.07)	(0.07)	(0.12)	(0.23)	(0.07)	**(0.05)**
Sex	-0.00	**-0.42**	-0.25	-0.17	0.47	-0.25	0.37	-0.29	0.08	-0.11	-0.29	0.16
(Women = 1 or Men = 0)	(0.99)	**(0.05)**	(0.32)	(0.54)	(0.06)	(0.29)	(0.11)	(0.26)	(0.76)	(0.62)	(0.26)	(0.53)
FH of Hypertension	0.02	0.02	0.02	0.01	0.32	-0.16	0.03	-0.38	0.05	0.33	-0.09	0.19
(Yes = 1 or No = 0)	(0.92)	(0.90)	(0.93)	(0.98)	(0.15)	(0.44)	(0.90)	(0.71)	(0.83)	(0.12)	(0.71)	(0.40)

Dependent variables: HR, SBP, DBP, LF/HF, HF, Leukocyte and Platelet counts, TC, HDL-C, LDL-C, Log TG and Log hs-CRP; Independent variables: Birth weight, Age, BMI, Sex, FH of Hypertension; BMI, body mass index; FH of hypertension, family history of hypertension; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LF/HF, ratio of low to high frequency; HF, high frequency; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Log TG, log-transformed triglyceride; Log Hs-CRP, log-transformed high-sensitivity C-reactive protein.

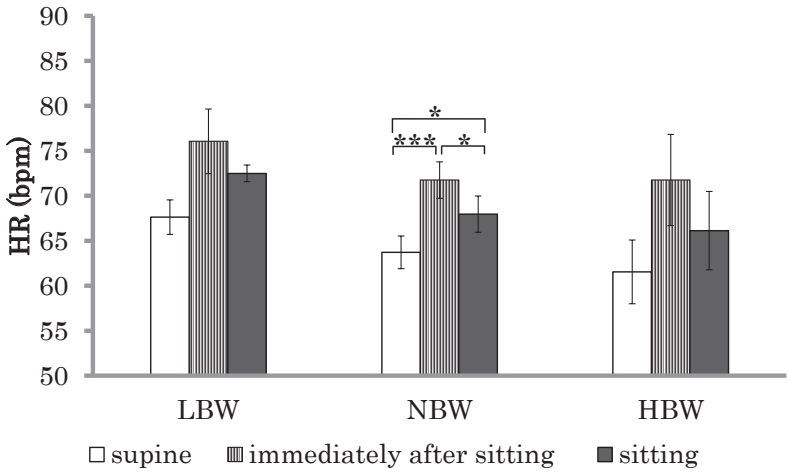

Fig. 1. Changes in heart rate following postural change.
HR, heart rate; LBW, low birth weight; NBW, normal birth weight; HBW, high birth weight.
Variables are expressed as mean ± SE (*p < 0.05, ***p < 0.001).

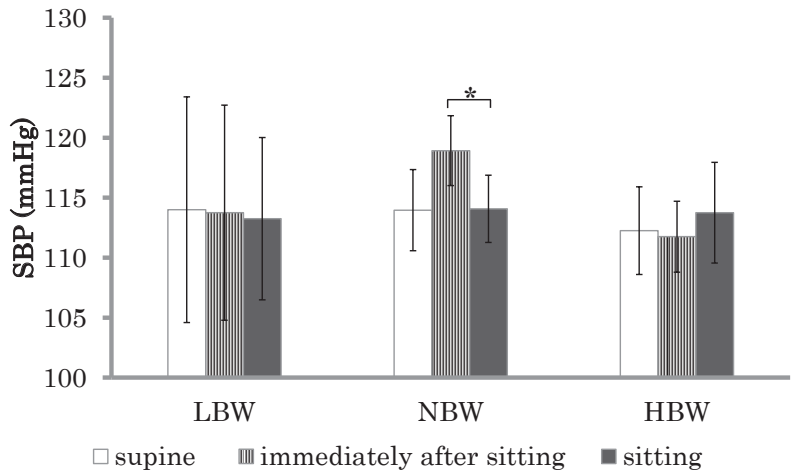

Fig. 2. Changes in systolic blood pressure following postural change.
SBP, systolic blood pressure; LBW, low birth weight; NBW, normal birth weight; HBW, high birth weight.
Variables are expressed as mean ± SE (*p < 0.05).

position to a sitting position, whereas the NBW group showed a significant increase in HR ($p < 0.001$) in the "immediately after sitting position" measurement followed by a significant decrease in HR in the sitting position ($p < 0.05$). In addition, HR in sitting position was significantly higher than in supine position ($p < 0.05$; Fig. 1).

After postural change from supine to sitting position, only in the NBW group, a trend of increase in SBP in the "immediately after sitting position", and a statistically significant decrease in sitting position measurement was observed ($p < 0.05$), as shown in Fig. 2. After postural changes, the LBW, NBW, and HBW groups showed significant increase in diastolic BP (DBP), $p < 0.05$ in the LBW and HBW groups, $p < 0.01$ in NBW group, as shown in Fig. 3.

The LBW and HBW groups showed no significant response in LF/HF and the LBW group conversely displayed a slight decrease in LF/HF in the "immediately after sitting position". In contrast, in the NBW group, LF/HF increased following postural change with a significant difference between the supine and sitting positions (Fig. 4). Changes in HF following postural change showed a similar trend in the three birth weight groups, as for HF gradually decreased in the "immediately after sitting position" and sitting measurements (Fig. 5).

Discussion

Birth weight and biomarkers of low-grade inflammation

In this study, we identified significant and novel associations between LBW and increased total leukocyte, basophil, eosinophil and platelet counts (within the normal ranges) in healthy young Mongolian adults. After adjusting a set of age, BMI, sex and FH of hypertension, the statistically significance of relations between birth weight and leukocyte, basophil, eosinophil and platelet counts were being intense. At present, studies revealing similar relationships

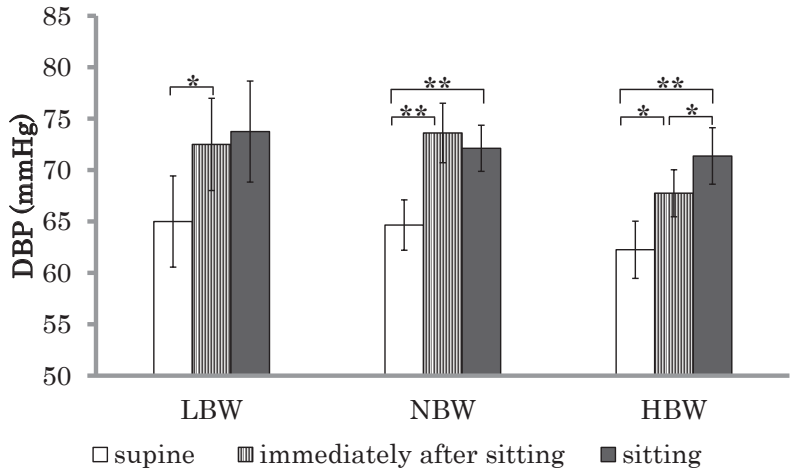

Fig. 3. Changes in diastolic blood pressure following postural change.
DBP, diastolic blood pressure; LBW, low birth weight; NBW, normal birth weight; HBW, high birth weight.
Variables are expressed as mean ± SE (*p < 0.05, **p < 0.01).

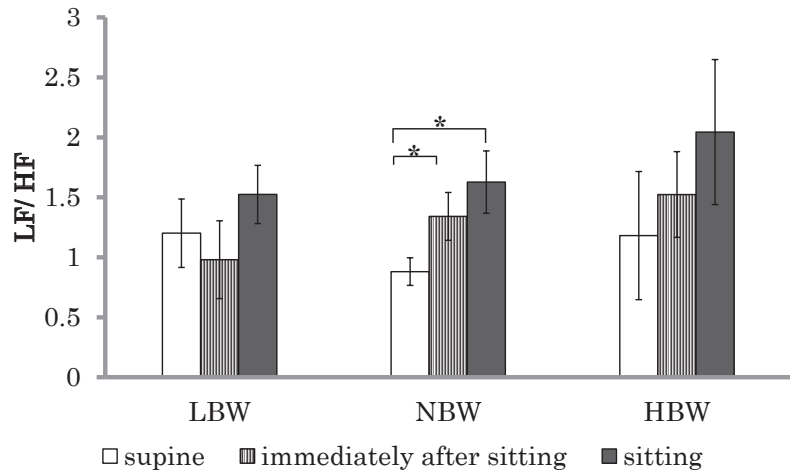

Fig. 4. Changes in sympathetic nerve activity following postural change.
LF/HF, ratio of low to high frequency; LBW, low birth weight; NBW, normal birth weight; HBW, high birth weight.
Variables are expressed as mean ± SE (*p < 0.05).

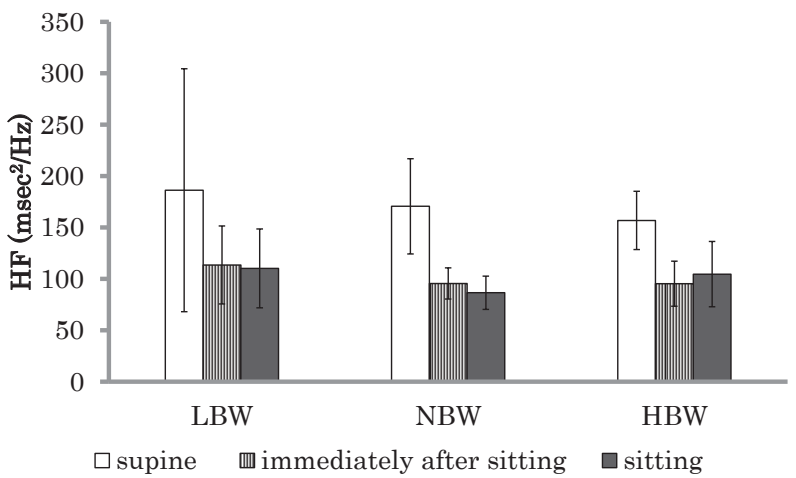

Fig. 5. Changes in parasympathetic nerve activity following postural change.
HF, high frequency; LBW, low birth weight; NBW, normal birth weight; HBW, high birth weight.
Variables are expressed as mean ± SE.

in healthy young adults are sparse. In the Bogalusa Heart Study, inverse relationships between birth weight and total leukocyte count among Caucasian and African American children aged 4-11 years and adults aged 18-38 years were reported (Chen et al. 2009). Our findings are consistent with those of the Bogalusa Heart Study and suggest that higher leukocyte counts may persist in adult life in individuals who were small at birth. The underlying mechanisms linking LBW to high leukocyte count are not well understood. Chen et al. (2009) postulated that it is because individuals with intrauterine growth restriction have consequent deficits in muscle cell replication (Widdowson et al. 1972), and then these individuals when faced with a nutritionally rich environment later in adult life, develop a disproportionately high fat mass induced by adipose tissue cells and chronic low-grade inflammation. We considered that the increased leukocyte count in LBW individuals may lead to the development of endothelial dysfunction, according to the previous study that suggested an effect of low-grade inflammation on endothelial function. Leukocytes, a widely available biomarker of systemic inflammation, might thus be a predictor of hypertension risk in healthy young Mongolian adults with LBW.

We also examined the associations between birth weight and leukocyte subtypes. Information is sparse about the different leukocyte subtypes as hypertension risk factors. Previous studies have discussed basophils and eosinophils in relation to human allergic inflammation (Nadif et al. 2013). In our study, there were no persistent allergic conditions in the participants. Several recent studies have suggested that eosinophils may contribute to endothelial damage and dysfunction, both directly and indirectly, via their cationic proteins. Activated eosinophils have been shown to display direct cytotoxicity toward endothelial cells in vitro (Roufosse 2013) and one study has suggested that eosinophil cationic protein, a sensitive marker of eosinophil activation, could represent a biomarker for coronary atherosclerosis (Niccoli et al. 2010). Furthermore, a new study of young adults by Hou et al. (2013) suggested the possible involvement of leukocytes, particularly eosinophils, in the early stages of atherosclerosis. The cause of the increased percentage of basophils in the LBW group in our study is unknown. Therefore, it is unclear which leukocyte subtypes can predict increased hypertension risk. Our study revealed higher count of eosinophils (within the normal range) in healthy young adults with LBW, which may result in future endothelial damage. Oda et al. (2012) recently observed that lymphocyte count was significantly related to hyper-LDL cholesterolemia in apparently healthy Japanese. In the present study, the counts of total leukocytes and different leukocyte subtypes showed no relationship with TC, HDL-C, LDL-C, or Log TG levels. Further studies will be required to clarify the interaction of each leukocyte subtype with potential hypertension risk factors.

An intriguing aspect of this study was the observation that birth weight was inversely related to platelet count. To our knowledge, no existing research has reported this association in healthy young adults. At present, it is established that platelets are important not only in hemostasis and thrombosis but also in the inflammatory reaction (Projahn and Koenen 2012). Moreover, interactions among platelets, leukocytes, and endothelial cells are considered important steps leading to inflammation and thrombosis (Stokes and Granger 2012). We estimate that LBW may facilitate vascular inflammation in future life through increased platelet and leukocyte counts or the interaction of leukocytes and platelets.

The levels of Hs-CRP, a sensitive marker for systemic inflammation, have not been associated with birth weight in our study. BMI predicted Hs-CRP more eminently than birth weight in healthy young Mongolian adults. The generally accepted markers of low-grade systemic inflammation, such as Hs-CRP and counts of neutrophils, monocytes or lymphocytes, were not correlated with LBW in our study. This may be related to the specific feature of healthy young Mongolian ethnicity with normal range of these values in our participants. However, we cannot exclude the possibility of merely accidental non-associations due to multiple comparisons and the small sample size.

Birth weight and hemodynamic changes at rest and after postural change

After postural change from the supine to the sitting position, the LBW and HBW groups showed no significant increase in HR or LF/HF, whereas the NBW group showed normal responses. Leotta et al. (2007) observed that birth weight was positively and independently associated with baroreflex sensitivity in 211 healthy women aged 22-24 years. Baroreflex responses sense the temporarily decreased venous return during postural change and attempt to maintain BP by increasing HR and sympathetic nerve activity. In the present study, the LBW and HBW groups displayed a dulled reaction in HR and sympathetic nerve activity when changing from a supine to sitting position. The DBP, which reflects peripheral vasoconstriction, showed similar changes among the three birth weight groups. We suggest that peripheral vasoconstriction function was maintained normally in the young age groups regardless of the birth weight.

Due to the presence of classic risk factors such as age, current body weight, and BMI in these participants, the influence of birth weight may be partly masked. Birth weight retained an inverse relationship with adult biomarkers of low-grade inflammation such as leukocyte and platelet counts. Blunted autonomic responses were also observed in young Mongolian adults with LBW.

There are some inevitable limitations to this study. Due to low Mongolian population within the chosen area, only 21 sample sizes fit our study criteria. A statistical evaluation of differences in autonomic responses among the three birth weight groups was difficult because of the small sample size. Increasing our sample size can also give us

greater power to detect the differences. In the current study, we did not measure the glucose levels. So we cannot be certain that blood glucose levels did not affect other risk factors. In addition, it is difficult to judge that which leukocyte subtype plays the most important role in interactions between birth weight and low-grade inflammation. It is uncertain that whether the presence of elevated low-grade inflammation and blunted autonomic response at this young age will track into future life and contribute to hypertension. Therefore, further studies would be needed.

In conclusion, we suggest that LBW relates to increased low-grade inflammation and blunted autonomic function in healthy young Mongolian adults, and these might be preliminary steps of hypertension development in LBW individuals.

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Conflict of Interest

The authors declare no conflict of interest.

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