

## Low birth weight is associated with components of the metabolic syndrome

Xinhua Xiao<sup>a,\*</sup>, Zhen-Xin Zhang<sup>b</sup>, Wen-Hui Li<sup>a</sup>, Kai Feng<sup>a</sup>, Qi Sun<sup>a</sup>, Harvey Jay Cohen<sup>c</sup>,  
Tao Xu<sup>d</sup>, Heng Wang<sup>a</sup>, Ai-Min Liu<sup>e</sup>, Xiao-Ming Gong<sup>f</sup>, Ying Shen<sup>g</sup>, Zeng Yi<sup>h,i</sup>

<sup>a</sup>Key Laboratory of Endocrinology, Ministry of Health, Department of Endocrinology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China

<sup>b</sup>Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China

<sup>c</sup>Center for the Study of Aging and Human Development, Department of Medicine, Duke University, Durham, NC, USA

<sup>d</sup>Epidemiology and Statistics, School of Basic Medicine, Peking Union Medical College

<sup>e</sup>Case Registry Office, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China

<sup>f</sup>Department of Obstetrics, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China

<sup>g</sup>Laboratory Center, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China

<sup>h</sup>Center for the Study of Aging and Human Development, Department of Medicine, Duke University, Durham, NC, USA

<sup>i</sup>China Center for Economic Research of Peking University, Beijing, China

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### Abstract

The purpose of the study was to investigate the association between birth weight and number of metabolic syndrome (MetS) components in an urban Chinese cohort. Individuals (N = 2019) who were born between 1921 and 1954 at the Peking Union Medical College Hospital and who had detailed obstetric records volunteered to take part and were examined by medical personnel in a clinical setting between May 2003 and April 2005. Data of birth outcome and results on clinic examination in adulthood were analyzed using analysis of variance and multivariate ordinal regression to estimate the association between birth weight and MetS. *Metabolic syndrome* was defined as per the National Cholesterol Education Program Adult Treatment Panel III. The prevalence of MetS was 26.74%, whereas 55.43% of the subjects had at least 2 components of MetS. Subjects who presented with all 5 components of MetS exhibited a significantly lower birth weight and higher age, body mass index, and waist circumference at follow-up. Multivariate ordinal regression analysis revealed that, as compared with those with birth weights of 3000 to 3500 g, subjects who had birth weights of less than 2500 g were 66% more likely to develop a greater number of MetS components in adulthood (95% confidence interval, 1.18–2.34;  $P = .004$ ), whereas those with birth weights between 2500 and 3000 g were 33% more likely to develop a greater number of MetS components as adults (95% confidence interval, 1.09–1.63;  $P = .005$ ). The present study demonstrated the relationship between low birth weight and increased presentation of MetS components in Chinese adults. © 2010 Elsevier Inc. All rights reserved.

### 1. Introduction

Risk factors of metabolic syndrome (MetS), such as diabetes, coronary heart disease, insulin resistance, and hypertension, cluster in a way that cannot be explained by chance and have been largely associated with environmental factors such as sedentary lifestyle, diet, and thinness or low weight at birth [1–3]. The latter factor is supported by hundreds

of epidemiologic studies [4], which have given saliency to fetal origin frameworks, such as the thrifty phenotype hypothesis or the Barker hypothesis in particular. Briefly, it has been proposed that postnatal survival physiology, structure, and metabolism are altered under conditions of intermittent or poor fetal nutrition, an adaptive response (in concert with other genetic dispositions) [5] that enhances postnatal survival, but portends long-term consequences in function once nutrition becomes more abundant in the postnatal environment [6]. Such programmed adaptations result in decreased nephron number, defects in insulin secretion and/or insulin sensitivity, decreased arterial elastin concentrations, and increased activity of the hypothalamic-pituitary-adrenal axis [7–10].

\* Corresponding author. Tel.: +86 10 65295073; fax: +86 10 65294070.  
E-mail address: [xiaoxinhua@medmail.com.cn](mailto:xiaoxinhua@medmail.com.cn) (X. Xiao).

Epidemiologic studies of MetS, which have characterized MetS as the “small-baby syndrome” [11], are however variable in terms of the disparity of cohorts (developing countries vs high-income countries) analyzed and the definitions as well as the validity of those definitions of MetS used. We have previously demonstrated low birth weight to be an independent risk factor for adult diabetes or impaired glucose regulation from cohort data from the Peking Union Medical College Hospital (PUMCH) in Beijing [12]. More recently, Mi et al [13] have also investigated the effects of low birth weight in relation to MetS, using the Fetal Origin of Adult Disease cohort of Beijing and working definition of MetS formulated by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III [14]. The NCEP ATP-III addresses the concurrence of interrelated disorders that define MetS by examining obesity, dyslipidemia, hyperglycemia, and hypertension and has been routinely used in this field after its inception [15,16].

We hypothesized that low birth weight is associated with greater number of MetS components in adulthood. Thus, the objective of this study was to extend our previous findings in the PUMCH cohort to corroborate the relationship between low birth weight and increased number of MetS components in adulthood.

## 2. Methods

### 2.1. Design and subjects

As previously described [12], subjects were derived from the PUMCH records (from 1921 to 1954) in Beijing, which provide extensive documentation of obstetric records and data including weight, length, head circumference at birth, placental weight, gestational weeks, blood pressure at delivery and during pregnancy, and various maternal parameters such as parity, age, and date of last menstrual period. Briefly, during the periods of 1921–1941 and 1948–1954, a total of 6570 Chinese neonates were born in PUMCH. Using actuarial census projections, we estimated there would be approximately 2990 survivors at the time of the planned assessment. In 2003–2005, we traced 2503 subjects through community registries and media announcements with the assistance of the Beijing Population Registry. Among traced subjects, 418 were not included: 175 were deceased, 78 refused to participate, and 165 resided outside Beijing. Thus, of the 2085 individuals who were traced and agreed to participate, 2019 had complete MS examinations and were included in this study. Follow-up analysis in May 2003 and April 2005 was conducted. Informed consent from all participants and institutional review board approval were obtained.

### 2.2. Measurements

A team of experienced physicians, nurses, and technicians, all blinded from the obstetric data, performed measurements of the study parameters. Blood samples

were collected from the antecubital vein between 8:30 AM and 12:30 PM after a 12-hour overnight fast and evaluated for high-density lipoprotein (HDL) cholesterol and triglyceride levels using standard enzymatic methods [17] and fasting plasma glucose using a standard oxidase method [18]. According to the NCEP ATP-III, MetS was defined as the presence of 3 of the following 5 components [13,15]: (1) fasting glucose of at least 110 mg/dL or diagnosed diabetes mellitus, (2) elevated blood pressure (systolic blood pressure  $\geq 130$  mm Hg and/or diastolic blood pressure  $\geq 85$ ) or history of hypertension, (3) serum HDL concentration less than 40 mg/dL for men and less than 50 mg/dL for women, (4) serum triglyceride concentration of at least 150 mg/dL, or (5) a waist circumference of at least 102 cm for men and at least 88 cm for women as measured to the nearest 0.1 cm at the level of the navel using a flexible steel tape.

### 2.3. Statistical analysis

Differences were assessed by 1-way analysis of variance (ANOVA) tests. Multiple comparisons of means were performed using the Student-Newman-Keuls test. Results were presented as mean  $\pm$  SD for continuous variables, and as counts and percentages for categorical variables. The correlation between neonatal characteristics and number of MetS components presented in adulthood was evaluated using univariate and, when significance was observed, multivariate ordinal regression, adjusted for possible confounding factors in adult life, including sex, age, central obesity, smoking status, alcohol intake, hypertension, dyslipidemia, family history of diabetes, occupational status, current social class, gestational age, and gestational hypertension. All statistical assessments were 2-sided, and a  $P$  value  $< .05$  was considered statistically significant. Statistical analyses were performed using SPSS 12.0 statistical software (SPSS, Chicago, IL).

## 3. Results

### 3.1. Subjects

As shown in Table 1, basic anthropometric, clinical, and biochemical data as well as prevalence of MetS and its defining features of the study participants were analyzed. Of the 2019 subjects enrolled, 515 (26.74%) fulfilled NCEP ATP-III criteria of MetS ( $\geq 3$  components), approximately half of the subjects ( $n = 997$ , 49.38%) had at least 2 MetS components, and 349 (18.12%) had no MetS components (Table 1). A majority of subjects (67.03%) also had high blood pressure, and 41.59% had elevated serum triglyceride levels.

### 3.2. Birth characteristics and number of MetS components in adulthood

Subjects were stratified according to the number of MetS components in adulthood (Table 2). Statistically significant

Table 1

Patients' basic anthropometric, clinical, and biochemical data and prevalence of MetS and its defining features (N = 2019)

	n (%)
<i>Basic anthropometric</i>	
Sex, male (%)	990 (49.0%)
Measurements at birth	
Birth weight (g)	3111.5 ± 456.0
Birth length (cm)	49.4 ± 2.4
Head circumference (cm)	31.6 ± 1.7
Ponderal index (kg/m <sup>3</sup> )	27.8 ± 3.4
Adult measurements	
Age (y)	59.3 ± 8.1
BMI (kg/m <sup>2</sup> )	25.0 ± 3.5
Waist circumference (cm)	89.1 ± 10.7
SBP (mm Hg)	130.51 ± 20.66
DBP (mm Hg)	79.01 ± 10.91
Maternal age (y)	27.6 ± 5.6
<i>Clinical and biochemical data</i>	
Fasting glucose (mg/dL)	98.07 ± 29.30
HDL (mg/dL)	56.06 ± 15.01
Triglycerides (mg/dL)	155.13 ± 159.00
MetS, n (%)	515 (26.74%)
No. of MetS components presented, n (%)	
0	349 (18.12%)
1	580 (30.11%)
2	482 (25.3%)
3	325 (16.78%)
4	144 (7.48%)
5	46 (2.39%)
Components of the MetS, n (%)	
High fasting glucose (≥110 mg/dL)	459 (23.83%)
High blood pressure (≥130/85 mm Hg)	1291 (67.03%)
Low HDL (<50 mg/dL women; <40 mg/dL men)	210 (10.90%)
High triglycerides (≥150)	801 (41.59%)
Waist circumference (≥88 cm for women and ≥102 cm for men)	567 (29.44%)

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

differences were observed in the number of MetS components stratified by weight at birth ( $P = .001$ ) as well as age, body mass index (BMI), and waist circumference ( $P < .0001$ ) at follow-up. Specifically, subjects who had all 5 components of MetS exhibited a significantly lower birth weight ( $2936 \pm 431.2$  g) compared with those with 0 to 3 MetS components. Subjects with all 5 MetS components also exhibited significantly higher BMI ( $29.2 \pm 3.8$ ) and waist circumference ( $100.5 \pm 7.7$  cm) at follow-up ( $P < .001$ ) compared with those with 0 to 4 MetS components.

### 3.3. Birth measurements in relation to adult MetS

As shown in Table 3, birth measurements in relation to adult MetS were evaluated by univariate and multivariate ordinal regression analysis. After adjusting for possible confounding factors in adult life, including sex, age, central obesity, smoking status, alcohol intake, hypertension, dyslipidemia, family history of diabetes, occupational status, current social class, gestational age, and gestational hypertension, subjects with birth weights less than 2500 g

were 66% more likely to develop greater number of MetS components (95% confidence interval [CI], 1.18–2.34;  $P = .004$ ) and 33% more likely when birth weights were between 2500 and 3000 g (95% CI, 1.09–1.63;  $P = .005$ ), using individuals with a birth weight of 3000 to 3500 g as reference. These results confirm that low birth weight is associated with the development of increased number of MetS components in adulthood. No significant association between head circumference and MetS was observed.

## 4. Discussion

In this cohort of Chinese adults, the prevalence of MetS was 26.74%; and 55.43% of the subjects had at least 2 components of MetS. Subjects who presented with all 5 components of MetS exhibited a significantly lower birth weight and higher age, BMI, and waist circumference. As compared with those with a birth weight of 3000 to 3500 g, subjects with birth weights of less than 2500 g were 66% more likely to develop a greater number of MetS components in adulthood, whereas those with birth weights between 2500 and 3000 g were 33% more likely to develop greater a greater number of MetS components in adulthood; however, low birth weight was not associated with MetS as defined by the NCEP.

At least 224 articles and 5 reviews investigating low body weight and MetS have been published, although few have analyzed Chinese cohorts; 31 studies have recently been subjected to meta-analysis by Silveira and Horta [4]. Studies using NCEP ATP-III have shown a MetS prevalence ranging from 0.3% to 23%, based on hospital registries or other sources, in high-income countries throughout Europe between the 1920s to the 1980s [19–23]. The high prevalence of MetS observed in the present study appears to be consistent with the results of our previous study, which documented a 22.7% prevalence based on the Fetal Origin of Adult Disease records in Beijing between 1948 and 1954 [12]. Adjusted odds ratios of low birth weight and MetS in 3 studies, which used 2500 g as a cutoff point for low birth weight (Gale et al [19], Eriksson et al [20], and Stein et al [23]), were 4.6 (95% CI, 1.02–20.4), 0.99 (95% CI, 0.3–3.3), and 1.92 (95% CI, 0.35–10.6), respectively, which are comparable with the findings of this study. Other large registry-based studies in which birth weight percentiles were used [4,12,13,24] have consistently reported that subjects with low birth weight (<25th percentile of the total samples) demonstrated a 60% higher MetS prevalence than those in the 75th and higher percentile.

The prevalence of MetS observed in this study is comparable with those reported for European countries [19–23]; however, increased MetS prevalence was observed using waist cutoffs recommended for Asians in the revised American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) definition of MetS (data not

Table 2

Characteristics of the study sample according to number of MetS components

	No. of MetS components in adulthood						<i>P</i> value
	0 n = 349	1 n = 580	2 n = 482	3 n = 325	4 n = 144	5 n = 46	
Measurements at birth							
Birth weight (g)	3148.5 ± 452.8	3140.4 ± 442.6	3098.1 ± 462.4	3114.8 ± 483.7	3001.0 ± 415.3 <sup>a,b,d</sup>	2936.9 ± 431.2 <sup>a,b,c,d</sup>	.001*
Birth length (cm)	49.6 ± 2.4	49.6 ± 2.4	49.3 ± 2.4	49.5 ± 2.4	49.0 ± 2.4	49.0 ± 2.8	.028
Head circumference (cm)	31.8 ± 1.7	31.6 ± 1.5	31.7 ± 1.8	31.6 ± 1.8	31.3 ± 1.6	31.3 ± 1.4	.075
Ponderal index (kg/m <sup>3</sup> )	25.9 ± 3.6	25.8 ± 3.7	25.9 ± 3.4	25.7 ± 3.0	25.5 ± 2.7	25.0 ± 2.7	.368
Adult measurements							
Age (y)	56.0 ± 7.2	59.0 ± 8.0 <sup>a</sup>	60.2 ± 8.1 <sup>a</sup>	60.6 ± 8.0 <sup>a</sup>	61.7 ± 8.3 <sup>a,b,c</sup>	61.6 ± 8.4 <sup>a,b,c</sup>	<.001*
BMI (kg/m <sup>2</sup> )	22.3 ± 2.6	24.1 ± 3.0 <sup>a</sup>	25.5 ± 3.2 <sup>a,b</sup>	26.8 ± 3.2 <sup>a,b,c</sup>	28.00 ± 3.3 <sup>a,b,c,d</sup>	29.2 ± 3.8 <sup>a,b,c,d,e</sup>	<.001*
Waist circumference (cm)	80.2 ± 8.4	86.0 ± 9.2 <sup>a</sup>	91.2 ± 9.00 <sup>a,b</sup>	95.3 ± 9.6 <sup>a,b,c</sup>	98.3 ± 9.1 <sup>a,b,c,d</sup>	100.5 ± 7.7 <sup>a,b,c,d,e</sup>	<.001*
Maternal age (y)	27.4 ± 5.2	27.4 ± 5.6	27.6 ± 5.6	27.7 ± 5.5	27.8 ± 6.2	28.20 ± 5.8	.826

*P* values are based on ANOVA and pairwise multiple comparisons between groups using the Student-Newman-Keuls test.\* *P* < .05.<sup>a</sup> Significantly different to subjects with 0 MetS component.<sup>b</sup> Significantly different to subjects with 1 MetS component.<sup>c</sup> Significantly different to subjects with 2 MetS components.<sup>d</sup> Significantly different to subjects with 3 MetS components.<sup>e</sup> Significantly different to subjects with 4 MetS components.

shown). Specifically, according to the AHA/NHLBI definition of MetS (waist circumference >90 cm for men and >80 cm for women), 978 (49.5%) of the study participants had MetS as compared with a 26.74% prevalence using the NCEP ATP-III definition, which is similar to another study of MetS prevalence in China [25]. Using the ATP-III criteria, MetS prevalence was 9.8%; however, MetS prevalence increased to 15.1% upon use of the modified AHA/NHLBI criteria [25]. Thus, further studies addressing the most appropriate criteria for analyzing MetS in Asian populations are warranted.

Table 3

Birth measurements, maternal age, and adult MetS as evaluated by ordinal regression analysis

	Univariate			Multivariate <sup>a</sup>		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Maternal age	1.05	1.04-1.06	<.001*	1.05	1.04-1.06	<.001*
Sex						
Male	1.00	—		1.00	—	
Female	1.17	1.00-1.38	.049	1.20	1.02-1.42	.029*
Neonatal measurements						
Birth weight						
<2500 g	1.47	1.08-2.01	.014*	1.66	1.18-2.34	.004*
2500-3000 g	1.34	1.11-1.62	.003*	1.33	1.09-1.63	.005*
3000-3500 g	1.00	—		1.00	—	
>3500 g	1.00	0.81-1.25	.982	0.97	0.87-1.23	.817
Head circumference						
<31 cm	1.13	0.93-1.37	.215	0.86	0.70-1.07	.179
31-33 cm	1.00	—		1.00	—	
>33 cm	0.91	0.75-1.12	.378	1.06	0.85-1.32	.607

OR indicates odds ratio.

\* *P* < .05.

<sup>a</sup> Adjusted for the possible confounding factors in adult life, including sex, age, central obesity, smoking status, alcohol intake, hypertension, dyslipidemia, family history of diabetes, occupational status, current social class, gestational age, and gestational hypertension.

The Barker hypothesis serves to explain what appears to be a universal trend—low birth weight, a marker of intrauterine growth retardation, is associated with development of chronic diseases, including MetS. Fetal growth in late gestation is limited by maternal size and capacity, a condition commonly referred to as *maternal constraint* [26]. Reproductive outcomes are also predicated upon maternal nutritional status, maternal age, and socioeconomic variables during gestation [27]. The weathering hypothesis (health deteriorates as a physical consequence of cumulative socioeconomic disadvantage) [28] and the life course approach (health deteriorates as a consequence of the cumulative health impacts of social, biological, and psychologic processes from conception to death) [29] are often evoked to explain maternal age and other risk factors for low birth weight. Indeed, both hypotheses indicate that the burdens of poverty and social change—phenomena not alien to an epoch marked by political strife in China (1921-1954) or to a radically developing metropolis such as Beijing—compromise a woman's health and chances of delivering a healthy infant, perhaps well before conception. Thus, it was not unexpected to observe that low birth weight was associated with subsequent severity of MetS development in adulthood in both univariate and multivariate ordinal regression models.

To conclude, the present study demonstrated the relationship between low birth weight and increased number of MetS components in Chinese adults. Risk factors for MetS, such as tobacco use, dietary intake, and a sedentary lifestyle, have however modified this relationship [30], suggesting that, in addition to improving the nutritional status of Chinese women, promoting healthy lifestyles especially in susceptible individuals remains a priority in public health policy making.



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