The Influence of Low Birth Weight and Smoking on the Male Patients with Premature Coronary Heart Disease: a retrospective case-control study

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Abstract

Background: Low birth weight (LBW) is one of the risk factors for coronary heart disease (CHD). The association of LBW and other risk factors with male patients with premature CHD has not been fully determined. This study aims to assess the association of LBW and other risk factors with the incidence of male patients with premature CHD.

Methods We identified hospitalized male patients with premature CHD (CHD group) and healthy male subjects (control group) from January 2013 to December 2018. The differences of demographics, birth weight (BW) and other traditional risk factors were compared between the CHD group and the control group and logistic regression was used to estimate their effects on the risk of premature CHD.

Results A total of 384 male subjects were enrolled in the study (183 in the CHD group vs 201 in the control group). There were significant differences in BW, smoking, diabetes and hyperlipidemia between the two groups (2.98±0.35 vs 3.37±0.39kg, *P*<0.001, 73.22% vs 27.36%, *P*<0.001, 8.74% vs 3.48%, *P*=0.033, 53.55% vs 37.31%, *P*=0.001) respectively. The risk of premature CHD increased significantly with the LBW (OR=4.530, 95% CI 1.331-15.412 *P*=0.016) and smoking (OR=6.748, 95% CI 4.258-10.693 *P*<0.001) respectively according to the multivariate logistic regression model.

Conclusion LBW and smoking are independently and positively correlated with male patients with premature CHD. A history of LBW should be paid particularly attention in younger men for primordial prevention of premature CHD, especially away from tobacco.

Background

Coronary heart disease (CHD) is a global pandemic causing 7.2 million deaths every year in the world and the age at onset is increasingly younger. In China, one million deaths occur because of CHD each year. The origins of CHD may be related to maladaptive changes in utero, behavioral factors, genetic factors, and the postnatal environment[1].

Recently, more attention has been paid to exposure to risk factors in early life; these include the fetal environment and its impact on birth weight (BW) and the development of chronic diseases. The hypothesis of the fetal origins of adult diseases focuses on maladaptive changes in utero, which lead to permanent changes predisposing an individual to the onset and development of CHD[1]. These changes persist throughout life. Individual cardiometabolic disorders are thought to have origins during fetal life[2]. Low birth weight (LBW) is a rough indicator of fetal growth impairment that is linked to adult cardiometabolic disorders, including CHD, hypertension, type 2 diabetes and metabolic syndrome[2–4].

Several cohort studies reported an inverse association between BW and the risk of CHD[5–10]. Historical cohort studies in the United States showed that BW and body mass index (BMI) at the age of seven appeared to be independently associated with the risk of CHD in adulthood[7]. Recently, a meta-analysis of a prospective cohort study suggested that LBW was strongly related to an increased risk of CHD, and

the study also showed that a 1 kg increase in BW was associated with a 10–20% reduction in the risk of CHD[5]. In China, a retrospective cohort study showed that the incidence of CHD was inversely associated with size at birth (such as BW, head circumference) but was not significantly associated with birth length or the ponderal index (BW/birth length).[8] More recently, premature CHD (onset of disease before the age of 45 years in males and 55 years in females) have got more and more concern worldwide[11–13]. Premature CHD can have devastating consequences for the individual, the family, and the society[14]. Additionally, there is a male predominance as shown in a study of 2 series of patients with coronary artery disease at 40 years of age, but female consisted only of 5.6% and 11.4% respectively[15]. Historically, the studies of risk factors of CHD were largely concentrated on both the middle-aged and the elderly population. There are no data regarding the association of BW with the incidence of premature CHD in male patients.

In this study, we used data from male patients with premature CHD and healthy male subjects with measures of BW and records of other risk factors to analyze the risks of male patients with premature CHD in Fujian Province, China.

Methods

Study populations

This was a retrospective study involved male patients with premature CHD(CHD group)and healthy male subjects (control group) from January 2013 to December 2018 respectively from Department of Cardiology and Health Examination Center of Fujian Medical University Union Hospital, China. We retrospectively reviewed the information in the corresponding medical records. For the CHD group, we enrolled patients who were aged ≤ 45 years in their first onset of chest pain and were hospitalized in the Department of Cardiology. All patients were diagnosed via digital subtraction angiography (DSA) of the coronary artery by their treating cardiologists in their first hospital stay. They consisted of patients with stable angina pectoris and acute coronary syndrome. Patients with syphilis, Kawasaki disease, connective tissue diseases and other diseases that can lead to lesion of coronary artery were excluded. In addition, there were subjects of different genders, ages, occupations, educational backgrounds and marital status and so on. from Health Examination Center of our hospital. For the control group, we enrolled healthy male subjects after medical history collection and detailed clinical examination including blood test, electrocardiogram and Doppler echocardiography. Exclusive criteria of the control group: age > 45 years; a history of CHD or coronary atherosclerosis, a history of chest pain, serum cardiac enzymes or troponin elevation; ST-T change on electrocardiogram; abnormal periodic ventricular wall motion observed by the Doppler echocardiography.

Data Collection Process

The data collection from the medical record of Department of Cardiology and Health Examination Center in our hospital was performed by trained medical staff. Demographic data regarding education background, marital status and age were collected. Medical history of associated risk factors such as smoking, hypertension, diabetes, hyperuricemia and dyslipidemia were also documented. Moreover, details of diagnostic tests, laboratory tests including fasting plasma glucose (FPG), plasma glucose level after a standard load (75 g) of oral glucose, total serum cholesterol, low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, uric acid were obtained. There was no participant who was born premature or a twin. BW of patients was obtained through telephone interviews, while BW of health subjects was obtained by wechat questionnaire surveys designed and accepted by the relevant ethics committees.

LBW was defined as < 2.5 kg, while medium birth weight (MBW) was defined as 2.5 to 4 kg, and high birth weight (HBW) was defined as > 4 kg, regardless of gestational age, size and maturity (WHO)[16]. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg or a history of self-reported hypertension with or without treatment with antihypertensive medications. Diabetes was defined as a FPG level ≥ 7.0 mmol/L, plasma glucose ≥ 11.1 mmol/L after a standard load (75 g) of oral glucose, or a history of diabetes mellitus with or without treatment. Hyperuricemia was defined as a fasting uric acid level ≥ 0.43 mmol/L or a self-reported history of hyperuricemia or urarthritis diagnosed by a physician. Dyslipidemia was defined as total serum cholesterol ≥ 5.70 mmol/L, LDL-C ≥ 3.68 mmol/L, HDL-C ≤ 1.05 mmol/L, or serum triglyceride ≥ 1.70 mmol/L. Smoking was defined as current cigarette smoking.

Statistical analysis

Continuous variables were expressed as the means ± standard deviations (SDs) in the case of a normal distribution, and two-sample T-tests were used to compare the characteristics of the two groups. Data are expressed as the medians (interquartile ranges, P_{25}, P_{75}) in the case of a skewed distribution and were compared by the Mann-Whitney U-test. Categorical variables are presented as counts (percentages) and were compared by the Pearson chi-square test. Logistic regression was used to assess the association of the LBW and other factors with premature CHD. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated to estimate the effect of LBW and other factors on the risk of premature CHD. Statistical analyses were performed using SPSS software for Windows (version 22.0, SPSS Inc., Chicago, Illinois). A probability value of $P < 0.05$ on the two-side was considered statistically significant in all analyses.

Results

The baseline clinical characteristics are shown in Table 1. A total of 384 cases were enrolled in this study, including 183 male patients (mean age: 38.85 ± 4.59 years) in the CHD group and 201 (mean age: 38.56 ± 4.17 years) in the control group. The patients with ST elevation myocardial infarction, non-ST elevation myocardial infarction, and stable angina pectoris in the CHD group were 39(21.3%), 38(20.8%) and 67(36.6%) respectively. Among them, 60(32.8%) patients had multivessel disease. The proportion of

smokers, diabetes and hyperlipidemia in the CHD group were higher than those in the control group (73.22% vs 27.36%,$P < 0.001$, 8.74% vs 3.48%，$P = 0.033$, 53.55% vs 37.31%，$P = 0.001$). The mean BW was significantly lower in the CHD group than in the control group (2.98 ± 0.35 vs 3.37 ± 0.39 kg, $P < 0.001$) (Fig. 1). The proportions of patients with premature CHD in each group (Table 2) stratified by BW (< 2.5, ≥ 2.5 kg) were significantly different (78.9% vs 46%, $P = 0.005$).

Table 1
Baseline characteristics of study participants

Variables	Control group (n = 201)	CHD group (n = 183)	*P* values
Age,year	38.56 ± 4.17	38.85 ± 4.59	0.525
Height,cm	170.21 ± 2.47	170.34 ± 4.61	0.724
Weight,kg	71.7 ± 9.77	73.3 ± 10.44	0.121
BMI,kg/m^2	24.76 ± 3.42	25.22 ± 3.22	0.169
Smoking,n(%)	55(27.36)	134(73.22)	< 0.001
Hypertension,n(%)	32(15.92)	43(23.5)	0.071
Diabetes,n(%)	7(3.48)	16(8.74)	0.033
Hyperuricemia,n(%)	49(24.38)	54(29.51)	0.299
Hyperlipemia,n(%)	75(37.31)	98(53.55)	0.001
Education level,n(%)			0.333
Junior high school and below	159(79.1)	137(74.86)	
Vocational high school and above	42(20.9)	46(25.14)	
Marriage status,n(%)			0.597
Others	34(16.92)	35(19.13)	
Married and spouse still living	167(83.08)	148(80.87)	
FPG,mmol/L	5.03(4.56,5.37)	5.08(4.65,5.62)	0.063
LDL-C,mmol/L	3.07 ± 0.77	2.91 ± 1.29	0.134
Triglyceride,mmol/L	1.64(1.26,2.11)	1.65(1.16,2.32)	0.961
Uric acid,mmol/L	0.39 ± 0.09	0.40 ± 0.10	0.345
BMI body mass index, FPG fasting plasma glucose, LDL-C low density lipoprotein cholesterol			

Table 2
Proportion of premature CHD in two group

Variables	Control group (n = 201)	CHD group (n = 183)	*P* value
Birth weight,n(%)			0.005
< 2.5 kg	4(21.1)	15(78.9)	
≥ 2.5 kg	197(54.0)	168(46.0)	

LBW(OR = 4.397, 95% CI: 1.432–13.504,*P* = 0.010), smoking（OR = 7.259, 95% CI（4.625–11.394）P < 0.001）, diabetes（OR = 2.655, 95% CI（1.067–6.609）P = 0.036） and hyperlipemia（OR = 1.937, 95% CI（1.289–2.911）P = 0.001） were relationship to premature CHD according to the single factor logistic regression model (Table 3). Then, the multivariate logistic regression was used to analyze the significant variables after single factor logistic regression analysis. As shown in Table 4, both LBW（OR = 4.530, 95% CI（1.331–15.412）*P* = 0.016）and smoking （OR = 6.748, 95% CI（4.258–10.693）*P* < 0.001）were independently and positively correlated with premature CHD according to the multivariate logistic regression model.

Table 3
Single factor logistic regression analysis

Variables	OR	95% CI	*P* values
Birth weight			0.010
≥ 2.5 kg	Ref		
< 2.5 kg	4.397	1.432–13.504	
Age, per 10y	1.162	0.733–1.840	0.524
BMI	1.043	0.982–1.109	0.170
Smoking	7.259	4.625–11.394	< 0.001
Hypertension	1.622	0.978-2.700	0.063
Diabetes	2.655	1.067–6.609	0.036
Hyperuricemia	1.299	0.826–2.041	0.258
Hyperlipemia	1.937	1.289–2.911	0.001
Education level			0.573
Junior high school and below	Ref		
Vocational high school and above	0.861	0.511–1.450	
Marriage status			0.255
Others	Ref		
Married and spouse still living	1.598	0.712–3.587	
FPG	1.141	1.000-1.303	0.051
LDL-C	0.858	0.704–1.045	0.128
Triglyceride	1.115	0.957–1.299	0.161
Uric acid	2.824	0.328–24.300	0.344

Table 4
Multivariate logistic regression analysis

Variables	OR	95% CI	*P* values
Birth weight			0.016
≥ 2.5 kg	Ref		
< 2.5 kg	4.530	1.331–15.412	
Smoking	6.748	4.258–10.693	< 0.001
Diabetes	1.742	0.619–4.904	0.293
Hyperlipemia	1.539	0.970–2.443	0.067

Discussion

Our results showed that LBW was positively correlated with the male patients with premature CHD, and the male subjects with LBW had a 4.5-fold increased risk of premature CHD. It was consistent with the current mainstream findings from most epidemiological studies of patients with CHD without age limits[5–8, 17–21]. Smoking had a highest OR for the CHD, which was 6.7 times of the non-smoker.

In addition to the traditional risk factors for CHD, such as hypertension, hyperlipidemia, diabetes mellitus, obesity and smoking, the hypothesis of the fetal origin of disease initially focused on fetal deprivation in LBW infants[1]. The explanations of the association between LBW and CHD include genetic influences, placental function, LBW-related metabolic syndrome and other interruptions of the fetal supply of necessary substances[6]. The “Barker hypothesis” proposed that adult disease originated from fetal origin and was supported by numerous epidemiological studies demonstrating the detrimental consequences of abnormal BW[1, 4, 22–25]. The hypothesis was that a defective uterine environment shaped the most important fetal organ systems, such as the nervous system, which received more nutrients at the expense of other systems. This imbalance may result in metabolic and cardiovascular functional deficiencies in postnatal life. In particular, LBW is increasingly associated with the risk for chronic disease, including metabolic syndrome, type 2 diabetes, and cardiovascular disease[26]. In animals, it is surprisingly easy to produce permanent changes in the metabolism and physiology of the offspring by slightly modifying the diet of the mother during pregnancy[27]. Many adverse conditions, including malnutrition, can induce the slowing of fetal growth, leading to LBW, with which some chronic diseases such as CHD are associated. LBW has been considered a substitute biomarker of fetal malnutrition[1]. It can occur in response to a series of conditions, including poor prenatal care, complications during pregnancy, stress, maternal alcohol consumption or parental smoking. Developmental plasticity leads to permanent changes in the individual’s structure and function owing to the intrauterine and early postnatal environments[2]. Influences that alter growth and development during fetal life lead to long-term consequences with regard to individual health, including CHD. Meanwhile, impaired fetal growth also influences the coronary arteries in the next generation, suggesting an

epigenetic mechanism of disease that has its origins in the fetal and early developmental periods[28]. Experiments showed not only that adverse influences during fetal life led to long-term programmed consequences with regard to CHD but also that the renin angiotensin system, the sympathetic nervous system, the increased production of endothelin and the increased level of oxidative stress contributed to the etiology of CHD originating in fetal life[29, 30]. Barker hypothesized that when the fetal nutritional supply was less than the nutritional demand, the fetus would adapt to survive during gestation, leading to a redistribution of the bloodstream to adequately supply the brain at the expense of other organs, thereby altering the structure, metabolism, endocrinology and physiology of the affected areas in a way that would “program” the individual to have a greater risk for high blood pressure and CHD after birth[2]. Numerous studies have found an inverse association between BW and blood pressure[31].

We found that the BW of the CHD group was significantly lower than that of the control group, which was consistent with the results of other related cohort studies. Andersen’s study showed that the risk of CHD was inversely related to BW less than 3.4 kg, whereas the association weakened for BW above 3.4 kg and tended to disappear in those with BWs above 4 kg in the Nordic countries[7]. Due to differences in BW between Eastern and Western countries, a study in Peking Union Medical College Hospital in China showed that the BW of 135 patients with CHD was 2989 ± 409 g, which was significantly different from that of the non-CHD group[8]. A number of studies have shown that LBW infants are at increased risk for the onset and development of metabolic syndrome, including hypertension, insulin resistance, dyslipidemia, and obesity[31]. Decreased fetal growth is related to insulin resistance and type 2 diabetes in later life, both of which may be involved in the link between LBW and CHD[7]. The mechanisms of the inverse association between BW and CHD are still unclear; however, insulin resistance and its related metabolic risk factors are most likely important contributors. In our study, the proportion of traditional risk factors including diabetes mellitus and hyperlipidemia in the CHD group was significantly higher than that in the control group. There was no significant correlation between LBW both with diabetes mellitus and hyperlipidemia. We are looking forward to more large-scale studies. In our study, smoking was still the main traditional risk factor, and the risk of premature CHD in male smokers was 6.7 times higher than the non-smokers. This result was consistent with another report, where smoking is noted in 65–92% of younger patients with acute myocardial infarction compared with 24–56% of patients older than 45 years[15]. It showed that smoking had a greater impact on younger patients. It has been suggested that the risk of CHD in adults is related to the BMI at age seven[7]. A study of the 1950s cohort of Aberdeen children demonstrated that adjustment for BMI at the time of entrance into an educational institution did not alter the inverse association between BW and CHD[18]. A Finnish cohort study showed that weight gain from age 3 to 11 years and body size at birth had independent effects on the cumulative incidence of CHD[32]. Thus, the treatment and prevention of obesity in children should be accorded sufficient attention, especially in individuals whose BW was below the average[7]. The latest survey of adult Inuit in Greenland showed that BW was inversely associated with peripheral insulin resistance and hepatic adiposity as well as other adult types of adiposity[33]. We did not record BMI values in childhood in our study because of the lack of available data.

Numerous experimental models of fetal undernutrition have shown that males are more susceptible to the development of hypertension and CHD. In view of the anti- atherosclerosis effect of estrogen, the incidence rate of CHD in pre-menopausal women, especially younger women, is extremely low. A recent published review indicated that acute myocardial infarction in younger patients almost exclusively occurs in males, with STEMI being the main diagnosis[34]. Among the retrospective cases in our study, the number of younger female patients with premature CHD was vary rare. Thus, we only study the younger male patients.

The main limitation of this study stems from a single center with a small sample size, and all patients were male and from Fujian, China. The change in BMI with age could not be investigated due to the lack of relevant data, although BMI is obviously an important risk factor for CHD. Multi-center studies with larger sample sizes including female are needed in the future.

Conclusions

LBW and smoking are independently and positively correlated with male patients with premature CHD. A history of LBW should be paid particularly attention in younger men for primordial prevention of premature CHD, especially away from tobacco.

Abbreviations

LBW: Low birth weight; BW; birth weight; CHD: Coronary heart disease; BMI: body mass index; FPG: fasting plasma glucose; LDL-C: low density lipoprotein cholesterol; DSA: digital subtraction angiography; HDL-C: high-density lipoprotein cholesterol; MBW: medium birth weight; HBW: high birth weight; SBP: systolic blood pressure; DBP: diastolic blood pressure

Declarations

Authors' contributions

GWY, HSH, XHL, LLC and WWW were responsible for the conception and design of the study. GWY and XHL contributed to the statistical analyses. GWY, XHL and WWW contributed to the data collection and interpretation. GWY, HSH, and XHL drafted the manuscript. HSH and XHL contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare no competing interests.

Availability of data and materials

The dataset used and analyzed for the current study is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethics committee of Fujian Medical University Union Hospital (Ethics Code: 2019KY102). Because this was a retrospective study involved only secondary analysis of data available (no individual details, images or videos, et al.) in the public domain, the ethics committee of Fujian Medical University Union Hospital considered that written informed consent could be exempted.

Consent for publication

Not applicable.

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Figures

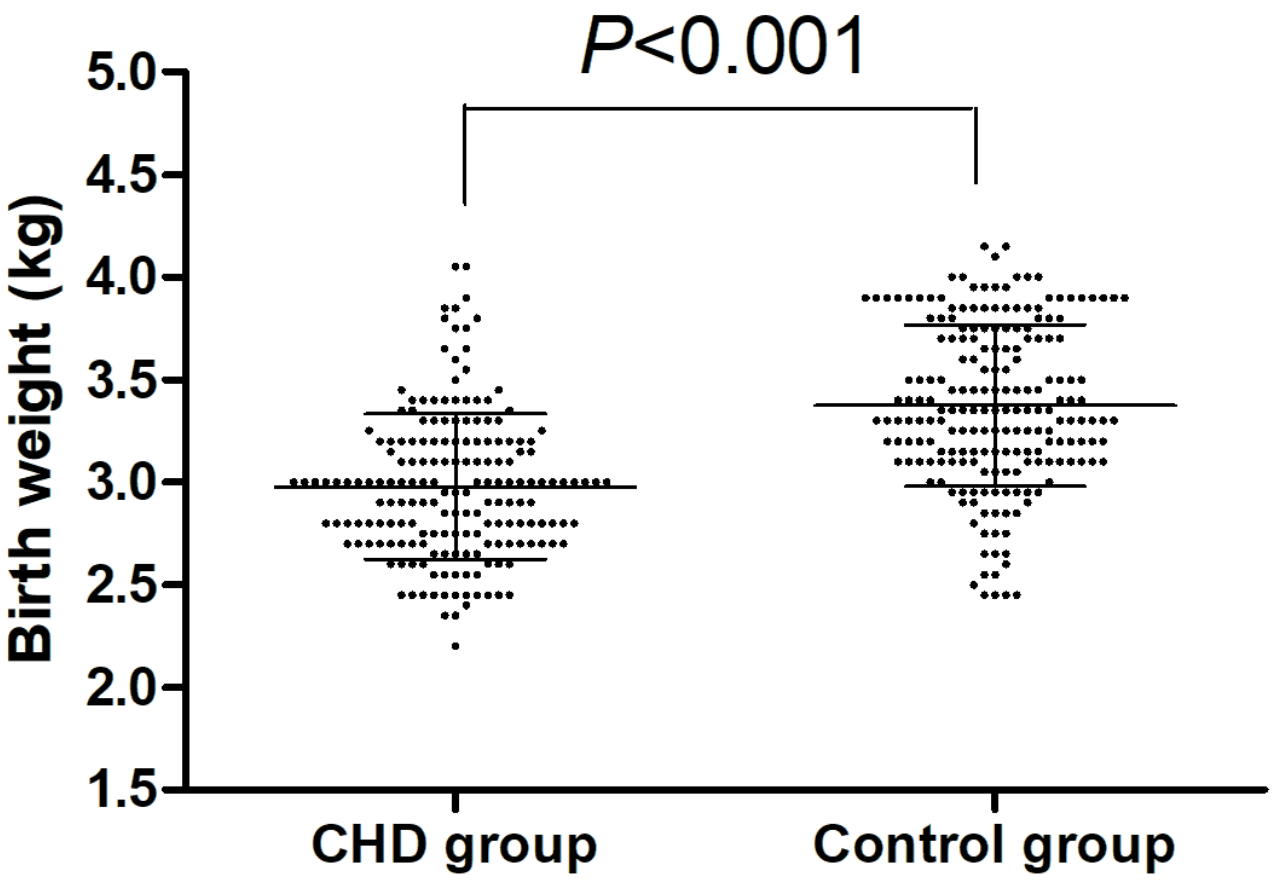

Figure 1

Mean birth weight of two groups