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Relationship between birth size and coronary heart disease in China

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Abstract

Background—Clinical epidemiological studies suggested a link between fetal growth conditions and later coronary heart disease (CHD) in adult life. However, no such studies have been conducted in a Chinese population.

Objectives—We investigated the association between various birth characteristics and CHD occurrence in a Chinese cohort.

Design—Retrospective cohort study.

Setting—Peking Union Medical College Hospital, Beijing, China.

Participants—A total of 2,033 subjects who were born at Peking Union Medical College Hospital between 1921 and 1954.

Measurements—Neonatal birth-weight, placental weight, length from crown to heel, head circumference, and biparietal and occipitofrontal diameters were routinely recorded at the time of birth. All participants were followed up between May 2002 and April 2004 for the occurrence of CHD.

Results—CHD was identified in 135 patients. The occurrence of CHD was inversely related to birth sizes, such as birth-weight, head circumference, placental weight ($P < 0.05$), but was not significantly related to birth length or ponderal index (birth-weight/birth length³). After

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multivariable logistic regression, the ratio of birth-weight to birth length was an independent predictor of CHD along with two other variables: obesity and age.

Limitations—This was a single-center retrospective study.

Conclusions—In China low birth size or birth disproportion, which is suggestive of fetal growth retardation, has an effect on CHD occurrence during adulthood. This suggests that environmental factors operate in both the prenatal and postnatal periods with regard to the development of CHD.

Keywords

Birth size; coronary artery disease; fetal growth retardation; risk factors

The origins of cardiovascular disease are related to genetic factors, postnatal environment, behavioral influences, and the environment experienced *in utero*. Small size at birth is linked to increased death and higher prevalence rates (1–11) of coronary heart disease (CHD), stroke (12), and other atherosclerosis (13), together with levels of known cardiovascular risk factors, impaired glucose tolerance and diabetes (14,15), hypertension (14,16,17), high plasma clotting factor (18), blood cholesterol level (19,20), etc. Small head size, birth length, and birth-weight are markers of the lack of nutrients or oxygen at particular stages of gestation (21). They reflect adaptations made by the fetus to sustain its development. Those adaptations may be permanent. Findings from epidemiological studies are strongly supported by animal studies (22). An improved and updated understanding of the relationship between a mother's nutrition and the maturation of fetal development may allow for the prevention of adult cardiovascular disease through interventions made early in life. In China, babies are small at birth (23) when compared to those in Western countries, although the prevalence of CHD is low. Babies in China (23), however, tend to be proportionately small in head size, length, and weight. No studies of relationship between birth size and CHD have been conducted in a Chinese population. The purpose of this analysis is to explore the association between the characteristics at birth and CHD occurrence during adulthood in a Chinese population with adjustment for adult characteristics.

Subjects and Methods

This study was a sub-cohort of randomly selected participants in the retrospective study. The study protocol was reviewed and approved by the National Institutes of Health (NIH) scientific review committee. Written informed consent was obtained from all subjects.

From all the obstetric records, 12,097 babies were born at Peking Union Medical College Hospital from 1921 to 1954. We submitted their birth record identification data to the Beijing Population Registry Office and found 2,033 individuals excluding 57 twins who were alive when the present study was conducted. The vast majority of them were living in the Beijing area. The medical birth records provided information of the parents' names, their ages and occupations, home addresses, date of birth, course of pregnancy, baby size at birth, and mother's previous pregnancies. The records also showed whether they had been born full-term or more than 2 weeks prematurely and whether or not they were twins. We calculated the gestation period from the date of the last menstrual period or by the obstetrician's estimation from the first prenatal visit to the physical examination of the child at birth.

Neonatal birth-weight, placental weight, length from crown to heel, head circumference, and biparietal and occipitofrontal diameters were routinely recorded at the time of birth. We

calculated ponderal index as birth-weight/length³ (kg/m³), and birth-weight/length as the ratio of birth-weight to birth length (kg/m).

We also obtained information on medical and social history including smoking and drinking habits of the participants. The social class at birth was defined by the father's occupation. Current social class was defined by the subject's occupation or (in the case of married women) the spouse's occupation.

We subsequently approached the 2,033 participants who agreed to participate in the study and provided follow-up during the study period from May 2002 to April 2004. All participants were invited to come to our hospital for the following health examinations. The Rose/WHO chest pain questionnaire (24) and standard 12-lead electrocardiograms according to the 1982 Minnesota protocol were administered. Electrocardiograms were Minnesota-coded independently in duplicate by two trained coders who were not aware of the birth or current measurements of the participants. CHD was defined (1–5) as the presence of one or more of the following: typical angina according to the questionnaire on chest pain; electrocardiography Minnesota codes 1-1, 1-2 (Q and QS codes); more than 50% coronary artery stenosis on angiography, or a history of coronary revascularization, either coronary artery by-pass graft or coronary angioplasty; or non-fatal myocardial infarction, which was confirmed by the World Health Organization criteria as symptoms, and either diagnostic electrocardiographic changes or raised cardiac enzyme activities.

Blood samples were taken in the morning after 12 hours of overnight fasting and 120 minutes after a standard (75 g) oral glucose load. Samples were analyzed for plasma glucose levels, while fasting plasma samples were analyzed for serum triglyceride, total cholesterol, and high low-density lipoprotein cholesterol. Plasma glucose concentrations were analyzed in hospital by a standard glucose oxidase method. Serum cholesterol was measured by standard enzymatic methods. Participants were asked to confirm that they performed moderate-intensity aerobic (endurance) physical activity for a minimum of 30 min on five days each week or vigorous-intensity aerobic activity for a minimum of 20 min on three days each week in the 5-year period preceding the study.

Blood pressure was measured four times in the right arm at intervals of 5 minutes while the participants were both lying down and standing up. Height, weight, and body mass index were measured. Information on smoking habits (categorized as former smokers, current smokers, or never smokers), alcohol consumption, and socio-economic status was obtained by questionnaire. Alcohol consumption was converted to the total number of units per week. The observers and interviewers at the hospital were unaware of the birth measurements of the participants. Before the study started, the procedure for the measurements was standardized and the field-workers were trained.

Diabetes was defined as the presence of one or more of the following: having a history of diabetes, with or without medication; fasting plasma glucose levels greater than 126 mg/dL (7.0 mmol/L); or plasma glucose levels more than 200 mg/dL (11.1 mmol/L) following a standard (75 g) oral glucose load. Hypertension was defined as the presence of one or more of the following: having a history of hypertension with or without medication, diastolic blood pressure greater than 90 mmHg, or systolic blood pressure greater than 140 mmHg. Dyslipidemia was defined as the presence of one or more of the following: total serum cholesterol greater than 220 mg/dL (5.70 mmol/L), low-density lipoprotein (LDL) cholesterol greater than 140 mg/dL (3.68 mmol/L), serum triglyceride greater than 150 mg/dL (1.70 mmol/L), or high-density lipoprotein (HDL) cholesterol less than 40 mg/dL (1.05 mmol/L). Obesity (25) was defined as a body mass index greater than 28 kg/m².

Mean $\pm$ SD values were used to describe the data. The *t* test and chi-square test were used to compare anthropometrical data for men and women and to compare maternal, birth size, and adult measurements between the two groups with or without CHD. Logistic regression was used for calculating odds ratios (ORs) and 95% confidence intervals (CIs) for the birth size categories. Birth-weight, birth length, placental weight, and the ponderal index were categorized into four or five groups. Trend tests for these birth measurements were calculated on the basis of the continuous variable. Multiple logistic regression was used to assess the combined effect of size at birth and other variables of some CHD risk factors such as smoking habits, body mass index, dyslipidemia, hypertension, and so on. Significance was defined as $P < 0.05$. The statistical software used was SPSS for Windows, version 11.5.

Results

Anthropometrical measurements for the subjects

A total of 2,033 subjects were identified in this study. In Table I, birth-weight, birth length, head circumference, placental weight, ponderal index, and birth-weight/length, birth-weight/occipitofrontal diameter (BW/OF) in the male babies were greater than those in the female babies ($P < 0.01$). Men were heavier and taller than women and had greater adult body mass index than in women ($P = 0.001$). Ages of the 2,033 subjects ranged from 50–84 years (mean 60 years) and were not different between men and women.

The association of CHD with maternal, birth, and adult conditions

Of the 2,033 subjects included in the study, 73 men and 62 women suffered from CHD. The maternal condition analysis had been conducted on average age of the mothers (1,933 cases), length of gestation (1,974 cases), and birth times (1,990 cases), as well as previous pregnancies (1,990 cases). The data are summarized in Table II, which shows that the prevalence of CHD was not related to the maternal age at pregnancy, duration of gestation, birth times, or the number of previous pregnancies.

In terms of the neonatal conditions, we found that subjects with CHD in adult life had significantly lower birth-weight, placental weight, birth length, smaller head circumference, and birth-weight/length, compared to those subjects who did not have CHD. There was also a trend toward decreased occurrence of CHD with greater ponderal index, though this was not statistically relevant.

Regarding the adulthood conditions, Table II also presents mean values of known coronary risk factors in subjects with and without CHD. In the subjects with CHD, the average body mass index, total cholesterol, and triglyceride were higher and HDL cholesterol was lower, respectively, compared to those without CHD, $P < 0.05$. In the group of 124 subjects with CHD, 37 individuals suffered from diabetes, while 281 individuals suffered from diabetes in the group of 1,832 subjects without CHD. Hypertension was identified in 89 participants in the group of 130 individuals with CHD, while hypertension was identified in 985 subjects in the group of 1,894 participants without CHD. The association between CHD occurrence and birth size in men was similar to that in women.

CHD with reference to birth-weight, birth length, ponderal index, and placental weight

The prevalence of CHD was inversely associated with birth-weight, birth length, and placental weight ($P < 0.05$), but not associated with ponderal index ($P > 0.05$).

Multivariable logistic regression

We examined the correlation between birth size and CHD, taking into account other possible risk factors for CHD. In a simultaneous regression analysis with the occupation, maternal age, education of the parents, birth times, pregnancy times, and gestational duration, birth-weight/birth length, placental weight, milk consumption, regular physical exercise in the 5-year period preceding the study, diabetes, obesity, hypertension, and dyslipidemia, age, gender, the association with the ratio of birth-weight to birth length remained statistically significant. The other significant associations in this analysis were with age and obesity (Table IV).

Discussion

All birth measurements in this study were low by Western standards, although in line with Chinese community averages (23). Birth-weights were especially low, as 8.0% of the babies weighed less than 2,500 g. Birth lengths were especially low, as 21.3% of the babies' lengths were less than 48 cm. Placental weights were also low, with 17.8% of the placentas weighing less than 450 g. In the 4,130 women born in Helsinki (4) between 1934 and 1944, the mean (SD) birth-weight was 3,327 (458) g, while head circumference, birth length, placental weight, and ponderal index were 34.8 (1.4) cm, 49.9 (1.8) cm, 640 (118) g, and 26.7 (2.2) kg/m³, respectively, with only 3.7% of the group having a birth-weight under 2,500 g. The mean birth-weight and the rate of birth-weight under 2,500 g were 3,332 g and 7.4% in the 66,689 women born in the United States (2) in 1921–1946, 3,313 g and 5.5% in the 5,594 women born in the United Kingdom (1) in 1923–1930, and 3,429 g and 4.7% in 13,363 women and men born in Sweden (3) during 1915–1929, respectively.

Our finding that CHD was associated with low birth-weight, small head circumference, short body length, and low placental weight at birth is consistent with findings in the UK (1), USA (2), Sweden (3), Finland (4), India (5), the Netherlands (7), and Australia (8). These associations were seen in babies born at term and therefore reflect low rates of fetal growth. Small head circumference, short length at birth, and low birth-weight are thought to result from fetal adaptations to malnutrition with reduction in growth of the head, body length, or soft tissues. These adaptations occur at different stages of gestation, since growth of the head precedes growth in length.

CHD in this study was associated with some of the conventional risk factors including age, hypertension, diabetes, altered concentration of serum lipids, and obesity.

It is becoming more evident that individuals whose growth was impaired *in utero*, and who were exposed to an adverse environment in childhood and adult life, would have a higher prevalence of cardiovascular disease. Associations between reduced early growth and cardiovascular risk factors are being found in different study populations. In the present study, the associations are independent of social class and other measures of adult lifestyle.

Simultaneous regression analysis suggested that the associations between reduced fetal growth and conventional coronary risk factors do not explain the association between reduced fetal growth and CHD. We therefore conclude that this association must be partly mediated by processes other than the known risk factors. Our results suggest that any strategy to prevent further increases in rates of CHD in China must include measures to improve prenatal care and the resulting, exceptionally low rates of fetal growth. Fetal growth depends on the steady supply of nutrients, and improved fetal growth may therefore require improvement in the nutrition and health of young women.

Our study was based on a group of adults who were born in one hospital and provided sufficient information to enable matches to their birth records. The study group is therefore unrepresentative of all people in the city, although the birth measurements were similar to those of all individuals born in other hospitals. Our analysis, however, is based on internal comparisons; bias would be introduced only if the association between fetal growth and CHD differed in those born in and outside the hospital, and in those traced and not traced. We have no reason to suspect such differences. We defined CHD by the standard criteria for epidemiological studies. Misclassification of some individuals is possible and could tend to weaken the associations found.

Although these data suggest that cardiovascular benefits might be reaped from interventions to reduce low birth-weight, it is not clear which environmental or genetic factors that determine birth-weight might also affect cardiovascular risk. Birth size is only a crude marker of intra-uterine development. Further research is needed to identify whether there is a specific mechanism that affects both birth size and the risk of cardiovascular disease in adulthood.

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Key messages

- The studies of fetal growth conditions and later coronary heart disease in adult life have not been conducted in a Chinese population.
- In China low birth size or birth disproportion, which is suggestive of fetal growth retardation, has an effect on coronary heart disease occurrence during adulthood.

Table 1

Body measurements at birth and in adulthood.

	Men		Women		P value
	Mean $\pm$ SD	No.	Mean $\pm$ SD	No.	
Newborn infant					
Birth-weight (g)	3195.4 $\pm$ 456.0	991	3065.5 $\pm$ 435.0	1025	<0.001
Birth length (cm)	49.9 $\pm$ 2.5	994	49.1 $\pm$ 2.3	1020	<0.001
Head circumference (cm)	31.9 $\pm$ 1.7	987	31.4 $\pm$ 1.6	1016	<0.001
Ponderal index (kg/m ³)	25.8 $\pm$ 3.7	991	26.0 $\pm$ 3.7	1017	0.270
Placental weight (g)	539.6 $\pm$ 103.1	928	525.7 $\pm$ 101.8	953	0.003
Gestation (weeks)	39.2 $\pm$ 2.0	970	39.3 $\pm$ 2.1	1004	0.191
Birth-weight/height (kg/m)	6.4 $\pm$ 0.8	991	6.2 $\pm$ 0.7	1017	<0.001
BW/OF	28.6 $\pm$ 3.9	987	27.9 $\pm$ 3.7	1019	<0.001
BPD/BL	0.2 $\pm$ 0.01	988	0.2 $\pm$ 0.01	1017	0.546
Adult measurement					
Age (y)	59.9 $\pm$ 8.4	996	59.9 $\pm$ 8.1	1032	0.328
Height (cm)	170.2 $\pm$ 6.5	950	158.4 $\pm$ 6.2	1002	<0.001
Weight (kg)	73.9 $\pm$ 11.4	950	61.4 $\pm$ 9.6	1002	<0.001
Body mass index (kg/m ²)	25.5 $\pm$ 3.4	950	24.5 $\pm$ 3.6	1002	<0.001

Ponderal index = birth-weight/height³; BW/OF = birth-weight/occipitofrontal diameter; BPD/BL = biparietal diameter/birth length.

Table II

Maternal, neonatal, and adult characteristics for participants with CHD and non-CHD.

	CHD			Non-CHD		
	No.	Mean $\pm$ SD	No.	Mean $\pm$ SD	P value	
Mother						
Maternal age (years)	131	27.1 $\pm$ 5.8	1862	27.6 $\pm$ 5.6	0.358	
Pregnant times	132	2.6 $\pm$ 1.8	1858	2.8 $\pm$ 2.1	0.889	
Delivery times	132	2.3 $\pm$ 1.6	1858	2.5 $\pm$ 1.9	0.656	
Gestation (weeks)	130	39.0 $\pm$ 1.9	1844	39.2 $\pm$ 2.1	0.137	
Newborn infant						
Birth-weight (g)	135	2989 $\pm$ 409	1881	3139 $\pm$ 446	<0.001	
Birth length (cm)	132	49.1 $\pm$ 2.5	1882	49.5 $\pm$ 2.4	0.034	
Head circumference (cm)	134	31.3 $\pm$ 1.4	1870	31.7 $\pm$ 1.7	0.009	
Placental weight (g)	126	510 $\pm$ 98	1755	534 $\pm$ 102	0.010	
Ponderal index (kg/m ³)	132	25.4 $\pm$ 2.9	1876	25.9 $\pm$ 3.8	0.093	
Birth-weight/height (kg/m)	132	6.1 $\pm$ 0.7	1876	6.3 $\pm$ 0.8	<0.001	
BW/OF	134	27.1 $\pm$ 3.6	1872	28.3 $\pm$ 3.8	<0.001	
BPD/BL	132	0.2 $\pm$ 0.01	1870	0.19 $\pm$ 0.01	0.407	
Preterm (%)	15/130	11.5%	115/1844	6.2%	0.018	
Asphyxia (%)	9/86	10.5%	76/1394	5.5%	0.052	
Adulthood						
Men/women	73/62		928/970		0.245	
Age (years)	130	64.4 $\pm$ 8.1	1898	59.4 $\pm$ 8.2	<0.001	
Body mass index (kg/m ²)	129	25.7 $\pm$ 3.9	1832	24.9 $\pm$ 3.5	0.016	
Weight (kg)	129	66.6 $\pm$ 13.7	1823	67.5 $\pm$ 12.1	0.844	
Height (cm)	129	161.9 $\pm$ 8.5	1823	164.3 $\pm$ 8.7	0.002	
Obesity (BMI > 28 kg/m ²)	38/129	30%	333/1823	18%	0.002	
Hypertension (%)	89/130	69%	985/1894	52%	<0.001	
Diabetes (%)	37/124	30%	281/1832	15%	<0.001	
T-C (mg/dL)	127	214 $\pm$ 68	1860	207 $\pm$ 36	0.042	
LDL-C (mg/dL)	127	140 $\pm$ 45	1860	140 $\pm$ 35	0.990	
HDL-C (mg/dL)	127	53 $\pm$ 15	1860	56 $\pm$ 15	0.041	

	CHD		Non-CHD		<i>P</i> value
	No.	Mean $\pm$ SD	No.	Mean $\pm$ SD	
Triglyceride (mg/dL)	127	213 $\pm$ 479	1860	151 $\pm$ 108	0.001

Values are mean $\pm$ SD, except where given as percentages.

CHD = coronary heart disease; PI = birth-weight/height³; T-C = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; BPD/BL = biparietal diameter/birth length; BW/OF = birth-weight/occipitofrontal diameter.

Table III

Unadjusted association of coronary heart disease with birth-weight, birth length, ponderal index, or placental weight (Pearson chi-square tests).

	No. of participants	No. of CHD (%)	Odds ratio (95% CI)
Birth-weight (g)			
< 2,500	131	11 (8.4%)	1.31 (0.66–2.56)
2,500–3,000	633	54 (8.5%)	1.33 (0.90–1.96)
3,000–3,500 (ref.)	838	55 (6.6%)	1.00
≥ 3,500	414	15 (3.6%)	0.54 (0.29–1.00)
<i>P</i> value for trend			0.036
Ponderal index (kg/m ³)			
< 22	131	9 (6.9%)	1.13 (0.54–2.40)
22–24	357	28 (7.8%)	1.31 (0.79–2.16)
24–26 (ref.)	638	39 (6.1%)	1.00
26–28	534	34 (6.4%)	1.04 (0.65–1.68)
≥ 28	348	22 (6.3%)	1.04 (0.60–1.78)
<i>P</i> value for trend			0.870
Birth length (cm)			
< 48	400	39 (9.8%)	1.75 (1.01–3.03)
48–49	291	22 (7.6%)	1.32 (0.71–2.46)
49–50 (ref.)	361	21 (5.8%)	1.00
50–51	360	15 (4.2%)	0.70 (0.36–1.39)
≥ 51	602	35 (5.8%)	1.00 (0.57–1.76)
<i>P</i> value for trend			0.023
Placental weight (g)			
< 450 (ref.)	343	33 (9.6%)	1.00
450–560	861	59 (6.9%)	0.69 (0.44–1.08)
560–670	511	26 (5.1%)	0.50 (0.30–0.86)
≥ 675	167	8 (4.8%)	0.47 (0.21–1.05)
<i>P</i> value for trend			0.050

CHD = coronary heart disease.

Table IV

Multivariate analyses about the relationship between perinatal characteristics and coronary heart disease in adulthood (adjusted for confounders both at birth and in adulthood).

	Chi-square	P	B	SE	OR	95% CI
Age	22.319	0.000	0.070	0.015	1.072	1.042–1.103
Gender	0.494	0.482				
Male (ref.)					1	1.0–1.0
Female			–0.152	0.231	0.850	0.541–1.337
Education of the parents	2.333	0.311				
Primary school (ref.)					1	1.0–1.0
Secondary school	1.223	0.269	–0.464	0.420	0.629	0.276–1.431
College	0.050	0.823	0.072	0.320	1.074	0.574–2.011
Occupation of the parents	1.544	0.672				
Worker					1	1.0–1.0
Manager	0.047	0.828	0.093	0.429	1.098	0.473–2.547
Academic	0.347	0.556	–0.246	0.418	0.782	0.345–1.773
Servant	0.001	0.981	0.010	0.424	1.010	0.440–2.319
Delivery times	3.052	0.384				
1					1	1.0–1.0
2–3	0.585	0.445	0.215	0.282	1.240	0.714–2.155
4–5	2.050	0.152	0.532	0.371	1.702	0.822–3.525
>5	0.180	0.720	–0.205	0.571	0.815	0.266–2.495
Maternal age at birth (years)	2.896	0.235				
21–35					1	1.0–1.0
< 21	2.718	0.099	0.575	0.349	1.778	0.897–3.524
> 35	0.062	0.804	–0.075	0.305	0.928	0.513–1.677
Gestational weeks	2.113	0.348				
37–42					1	1.0–1.0
< 37	0.338	0.561	–0.232	0.398	1.261	0.577–2.753
> 42	1.697	0.193	–0.986	0.757	0.373	0.085–1.644
Birth-weight/birth length	4.323	0.038	–0.385	0.185	0.680	0.473–0.978
Milk consumption	0.554	0.457	–0.204	0.274	0.816	0.477–1.395

	Chi-square	P	B	SE	OR	95% CI
Dyslipidemia	0.016	0.899	0.081	0.634	1.084	0.313–3.752
Hypertension	0.548	0.459	0.182	0.246	1.200	0.741–1.944
Diabetes	2.436	0.119	0.414	0.265	1.513	0.900–2.544
Obesity	7.242	0.007	0.679	0.252	1.972	1.203–3.233
Placental weight	2.330	0.127	−0.002	0.001	0.998	0.995–1.001
Physical exercise	2.883	0.090	−0.452	0.266	0.636	0.377–1.072
Constant	0.150	0.699	−0.826	2.132	0.438	