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REVIEW

Birth weight and risk of coronary heart disease in adults: a meta-analysis of prospective cohort studies

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Some studies have found a significant relationship between birth weight (BW) and the risk of coronary heart disease (CHD) in adulthood, but results were inconsistent. The purpose of this study was to characterize the association between BW and the risk of CHD in adults. Among 144 papers detected by our search, 27 papers provided data on the relationship between BW and CHD, of which 23 papers considered BW as a continuous variable, and 14 articles considered BW as a categorical variable for this meta-analysis. Based on 23 papers, the mean weighted estimate for the association between BW and the combined outcome of non-fatal and fatal CHD was 0.83 [95% confidence interval (CI), 0.80–0.86] per kilogram of BW ($P < 0.0001$). Low birth weight (LBW <2500 g) was associated with increased risk of CHD [odds ratio (OR), 1.19; 95% confidence interval (CI), 1.11–1.27] compared with subjects with BW ⩾2500 g. LBW, as compared with normal BW (2500–4000 g), was associated with increased risk of CHD (OR, 1.16; 95% CI, 1.08–1.25). High birth weight (HBW ⩾4000 g) was associated with decreased risk of CHD (OR, 0.89; 95% CI, 0.81–0.98) compared with subjects with BW <4000 g. In addition, there was an indication (not quite significant) that HBW was associated with a lower risk of CHD (OR, 0.89; 95% CI, 0.79–1.01), as compared with normal BW. No significant evidence of publication bias was present. These results suggest that LBW is significantly associated with increased risk of CHD and a 1 kg higher BW is associated with a 10–20% lower risk of CHD.

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Key words: a meta-analysis, birth weight, coronary disease, coronary heart disease

Introduction

Coronary heart disease (CHD) is the leading cause of death globally, with 7.2 million deaths occurring worldwide every year.[1] In China, CHD causes death in over 1 million people each year.[2] Although CHD mortality has been declining in the United States and in Western Europe since 1970s, it remains the leading cause of death.[3,4] And for all we know, CHD is considered as a multifactorial chronic disease that may be associated with hypertension, dyslipidemia, impaired glucose tolerance,[5–7] a small body size at birth,[8,9] and some traditional factors (e.g. high fat diet, low occupational status, low household income and mother's parity).[10–12] A recent study reported that physical inactivity could increase the risk of CHD.[13]

According to the 'fetal origins' hypothesis, the fetus makes metabolic adaptations when it is undernourished and these persist to adult life and predispose to CHD.[14] Early studies have shown that low birth weight (LBW) was considered to result from slow intrauterine growth.[7,15] However, slow growth *in utero* may result in accelerated weight gain during childhood, which may contribute to a relatively greater risk of CHD, hypertension and type 2 diabetes mellitus.[16] In addition, extensive epidemiological studies have reported that babies who later developed CHD tended to be thin in men and be short in women at birth.[8,17]

To date, many studies have suggested that there is a significant relationship between birthweight (BW) and the risk for CHD.[18–28] Nevertheless, this relationship is inconsistent. Although some epidemiological studies have reported an inverse association between BW and risk of CHD,[18,23,26] others have reported no significant association or a positive association between BW and risk of CHD.[21,22] Moreover, in the reports of Danish birth cohort by Osler *et al.*,[27] a U-shaped relationship was observed between BW and risk of CHD. Therefore, we carried out a meta-analysis to further identify the association between BW and subsequent risk of CHD.

Methods

This systematic review and meta-analysis was performed according to the Cochrane methodology and the recommendations for reporting proposed by the Meta-analysis of observational studies in epidemiology group.[29]

Study selection

An electronic literature search was conducted in PUBMED to identify human studies published from January 1995 up to October 2013, using a search strategy that combined text word and MeSH heading of BW and of CHD. No restrictions on the

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language or location of the study were imposed. In addition, we manually searched all references cited in original studies and reviews identified.

Two of the authors (L. Shu and M. Mu) read the abstracts of articles retrieved in the initial search to identify studies that examined the association between BW and risk of CHD. When all agreed (S.F. Wang, L. Shu and M. Mu), the articles were reviewed against inclusion and exclusion criteria for this meta-analysis. To be eligible, studies had to fulfill the following criteria: (1) the study was published as an original article. (2) The association between BW and risk of CHD has been reported in studies. (3) Odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals (or data can be calculated) for BW and CHD were provided. Moreover, if BWs were reported as categorical data in studies, BWs should be categorized according to the international standards (LBW: <2500 g; normal BW: 2500–4000 g; high BW: ⩾4000 g). (4) CHD was diagnosed based on clinical manifestations (including angina or myocardial infarction, or myocardial ischemia, or cardiac failure and arrhythmia, or a death certificate cause of death as CHD), electrocardiogram and coronary arteriography. Papers were excluded for the following reasons: (1) Title and abstract did not contain data on BW and CHD; (2) there were insufficient data on HRs or ORs for the association of BW and CHD; (3) there was no measure of CHD; (4) the paper was a review or commentary article; (5) there were insufficient dichotomous data on BW and CHD; and (6) the paper reported data using different BW categories. Among 144 papers detected by our search, 27 provided data reporting the relationship of BW to CHD, of which 23 cohort studies considered BW as a continuous variable, and of which 14 cohort studies considered BW as a categorical variable for this meta-analysis.

Quality assessment

The Newcastle-Ottawa Quality Assessment scale was used for quality assessment.[30] Eight questions were assessed and each satisfactory answer received 1 point (may receive 2 points in comparability categories), resulting in a maximum score of 9. Only these studies in which most of the questions were deemed satisfactory (i.e. with a score of 6 or higher) were considered to be of high methodological quality.

Assessment of heterogeneity

Heterogeneity of study results was estimated by the χ^2-test. *P*-values <0.05 were considered to be significant. In our meta-analysis, a random-effects model was used to account for possible heterogeneity between studies, whereas a fixed-effects model was adopted in the absence of heterogeneity.[31]

Statistical analysis

Statistical analyses were performed by using Review Manager, version 5.0 (Nordic Cochrane Centre Copenhagen, Denmark) and STATA, version 12 (Stata Corp, College Station, TX, USA). ORs and 95% confidence intervals (CIs) from individual studies were combined to produce an overall OR. Sensitivity analysis was conducted to determine whether differences in study design, age, statistical methods and sex of the study population affected study conclusions. Publication bias was assessed by inspection of the funnel plot and by formal testing for 'funnel plot' asymmetry using Begg's test and Egger's test.[32] All statistical tests were two-sided and *P*-values <0.05 were considered significant.

Results

Overview of studies included in the meta-analysis

A search in the database of PUBMED identified 144 papers, 117 of which were excluded based on the reasons shown in Fig. 1. Finally, there are 27 articles[5,7–9,17,20,24–28,33–48] reporting the relationship between BW and risk of CHD, of which 14 papers[5,7–9,17,20,27,28,36–40] considered BW as a categorical variable, and 23 papers[5,7–9,17,20,24–26,28,33–35,37–39,41–47] considered BW as a continuous variable (10 articles repeat). Descriptive information for each included study was presented in Table 1.

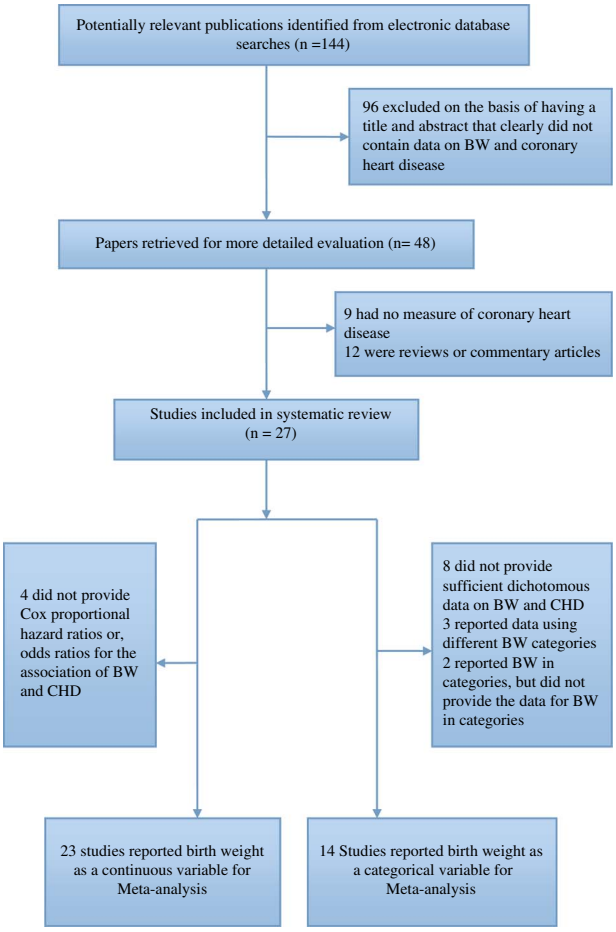

Fig. 1. Flow chart of the article screening and selection process. BW, birth weight; CHD, coronary heart disease.

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Table 1. *Characteristics of 27 studies reporting the association between BW and subsequent risk of CHD (1993–2010)*

Source	Location	Total number of subjects	Age	Year of study baseline	Race	BW ascertainment method	Diagnostic criteria for CHD	BW reference category for adjusted estimate	Confounding factors
Osmond *et al.*[28]	United Kingdom	16 652 women/men	21–81 years	1911–1930	White	Hospital birth records	ICD-9 codes 410–414 Occupation recorded on the death certificate	<2500 g; 2500–4000 g; >4000 g	None
Fall *et al.*[36]	England	5654 men	52–62 years	1982	White	Questionnaire	Electrocardiography, chest pain questionnaire, history of surgery for coronary revascularization, coronary artery bypass graft or coronary angioplasty	⩽5.5 lb; 5.5–6.5 lb 6.5–7.5 lb; 7.5–8.5 lb 8.5–9.5 lb; >9.5 lb	Smoking and social class
Frankel *et al.*[5]	England	1258 men	45–59 years	1979–1983	White	Recorded from medical records	ECG changes, questionnaire of CHD	<2500 g; 2500–4000 g; >4000 g	Age
Stein *et al.*[7]	India	517 women/ men	38–60 years	1934–1954	Yellow	Hospital birth records	ECG changes, chest pain questionnaire, history of coronary revascularization surgery	⩽5 lb; 5.1–5.5 (2.5 kg) lb 5.6–6.0 lb; 6.1–6.5 lb 6.6–7.0 lb; >7.0 (3.1 kg) lb	Age and sex
Rich-Edwards *et al.*[39]	United States	70 297 women	30–55 years	1976	White	Questionnaire	Questionnaire of angina myocardial infarction, coronary revascularization, coronary artery bypass graft, coronary angioplasty	<2268 g; 2268–2495 g; 2495–3175 g; 3475–3856 g; 3856–4536 g; >4536 g	Age, time period, BMI, cigarette smoking, hypertension, diabetes, menopausal status, and use of postmenopausal hormones
Wadsworth and Kuh[48]	United Kingdom	3157 women/ men	53 years	1949	White	Hospital birth records	ICD-8 codes 410–414 Hospital records	None	Unpublished
Leon *et al.*[26]	Sweden	6531 women; 7012 men	29–80 years	1915–1929	White	Hospital birth records	ICD-7 codes 410–414 Hospital admission or death from CHD	<3250 g; 3250–3749 g; 3750–4249 g; ⩾4250 g	Period of birth, maternal marital status, parental SES, current SES

Table 1. *Continued*

Source	Location	Total number of subjects	Age	Year of study baseline	Race	BW ascertainment method	Diagnostic criteria for CHD	BW reference category for adjusted estimate	Confounding factors
Eriksson *et al.*[20]	Finland	3641 men	38–71 years	1971–1997	White	Hospital birth records	ICD-8 and ICD-9 codes 410–414 ICD-10 codes I21–I25 Hospital records	⩽2500 g; 2500–3500 g; 3000–3500 g; 3500–4000 g; >4000 g	Gestational age
Forsén *et al.*[9]	Finland	3447 women	37–62 years	1971–1995	White	Hospital birth records	ICD-8 and ICD-9 codes 410–414, hospital records of myocardial infarctions	⩽2500 g; 2500–3000 g; 3000–3500 g; 2500–4000 g; >4000 g	Gestation and placental weight
Roseboom *et al.*[42]	Holland	736 women/ men	50 years	1943–1947	White	Hospital birth records	ECG changes, history of coronary revascularization, questionnaire of angina pectoris	None	Sex
Eriksson *et al.*[8]	Finland	4630 men	37–53 years	1971–1997	White	Hospital birth records	ICD-8 and ICD-9 codes 410–414 ICD-10 codes I21–I25 Hospital admission or death from CHD	⩽2500 g; 2500–3500 g; 3000–3500 g; 3500–4000 g; >4000 g	Gestational age
Gunnarsdottir *et al.*[34]	Iceland	4775 women/ men	32–53 years	1967	White	Midwives' original birth records	ECG changes, hospital record of myocardial infarction	⩽3450 g; 3450–3750 g; 3750–4000 g; >4000 g	Year of birth
Hubinette *et al.*[38]	Sweden	4594 women/ men	>54 years	1967–1973	White	Telephone questionnaire	Telephone interviews about angina pectoris	<2000 g; 2000–2900 g; ⩾3000 g	Sex, age, zygosity, BMI and smoking status
Andersen and Osler[45]	Denmark	10 753 men	15–49 years	1953	White	Hospital birth records	ICD-10 codes I21–I25 cause-of-death registers	<2500 g; 2500–2999 g; 3000–3499 g; 3500–3900 g; >4000 g	Maternal marital status, paternal occupation at birth, parental life span
Eriksson *et al.*[35]	Sweden	1586 men	20–85 years	1969	White	Obstetrical records	Hospital discharge and cause-of-death registers, ICD-9 codes 410–414	⩽3000 g; 3001–4249 g; ⩾4250 g	Gestational age
Forsén *et al.*[17]	Finland	4130 women	37–54 years	1971–1998	White	Clinic records	ICD-10 codes I21–I25 hospital admission or death from CHD	⩽2500 g; 2500–3000 g; 3000–3500 g; 2500–4000 g; >4000 g	Gestation and placental weight

Table 1. *Continued*

Source	Location	Total number of subjects	Age	Year of study baseline	Race	BW ascertainment method	Diagnostic criteria for CHD	BW reference category for adjusted estimate	Confounding factors
Forsén *et al.*[43]	Finland	2345 men	37–62 years	1971	White	Hospital birth records	ICD-8 and ICD-9 codes 410–414, hospital admission or death from CHD	None	Gestation and placental weight
Lawlor *et al.*[24]	United Kingdom	1394 women	11–49 years		White	Questionnaire	Medical record of myocardial infarction or angina	<3250 g; 3250–3749 g; 3750–4249 g; ⩾4250 g	Age, maternal survival status, childhood SES
Lawlor *et al.*[25]	United Kingdom	10 803 women/men	11–50 years	1950–1956	White	Hospital birth records	ICD-9 codes 410–414 hospital record of myocardial infarction or angina	<3250 g; 3250–3749 g; 3750–4249 g; ⩾4250 g	Age, gestational age, childhood: SES, BMI, and height; maternal: hypertension, age and parity
Martin *et al.*[47]	United Kingdom	639 women/ men	71 years	1937–1939	White	Self-report	ICD-9 codes 410–414 Records of angina, ischemic or heart disease, or myocardial ischemia	None	Unpublished
Rich-Edwards *et al.*[46]	United States	65 788 women	54–79 years	1976	White	Questionnaire	Hospital records of coronary artery by-pass graft angioplasty, non-fatal myocardial infarction	<2268 g; 2268–2495 g; 2495–3175 g; 3475–3856 g; 3856–4536 g; >4536 g	Age
Ferrie *et al.*[44]	United Kingdom	1084 women; 2290 men	35–55 years	1997–1999	White	Hospital birth records	Chest pain questionnaire, hospital record: ECG change, cardiac enzymes	None	Age and sex
Morley *et al.*[41]	Australia	2937 women/ men	>40 years	1857–1900	White	Hospital birth records	ICD-8 codes 410–414 Records of angina, ischemic or heart disease, or myocardial ischemia	None	Fathers' social class

Table 1. *Continued*

Source	Location	Total number of subjects	Age	Year of study baseline	Race	BW ascertainment method	Diagnostic criteria for CHD	BW reference category for adjusted estimate	Confounding factors
Yang *et al.*[40]	Sweden	48 052 women	30–50 years	1991–1992	White	Self-administered questionnaire	ECG changes, chest pain, questionnaire history of coronary revascularization surgery, coronary artery by-pass graft or angioplasty, non-fatal myocardial infarction	<2500 g; 2500–3000 g; >3000 g	Age, smoking, alcohol, education, use of oral contraceptives, exercise, diabetes, hypertension and BMI
Osler *et al.*[27]	Denmark	9143 men	25–52 years	1978–2005	White	Recorded from medical records	Hospital discharge register, ICD-8, codes 410–414 ICD-10, codes I21–I25	<2500 g; 2500–3999 g; ⩾4000 g	Fathers' social class at birth, and educational level at age 19
Andersen *et al.*[33]	Denmark; Finland	485 044 women/men	25–77 years	1924–1976	White	Hospital birth records	Hospital discharge and cause-of-death registers, ICD-8, codes 410–414 ICD-10, codes I21–I25	2000–2500 g; 2510–3000 g; 3010–3500 g; 3510–4000 g; 4010–4500 g; 4510–5000 g; 5010–5500 g	Sex and BMI
Fan *et al.*[37]	China	2033 women/men	50–84 years	2002–2004	Yellow	Obstetric records	ECG changes, chest pain, questionnaire history of coronary revascularization surgery, coronary artery by-pass graft or angioplasty, non-fatal myocardial infarction	⩽2500 g; 2500–3000 g; 3000–3500 g; ⩾3500 g	Sex, age, and obesity

BW, birth weight; CHD, coronary heart disease, LB, pound; ICD, International Classification of Disease; ECG, electrocardiogram; SES, socioeconomic status; BMI, body mass index.

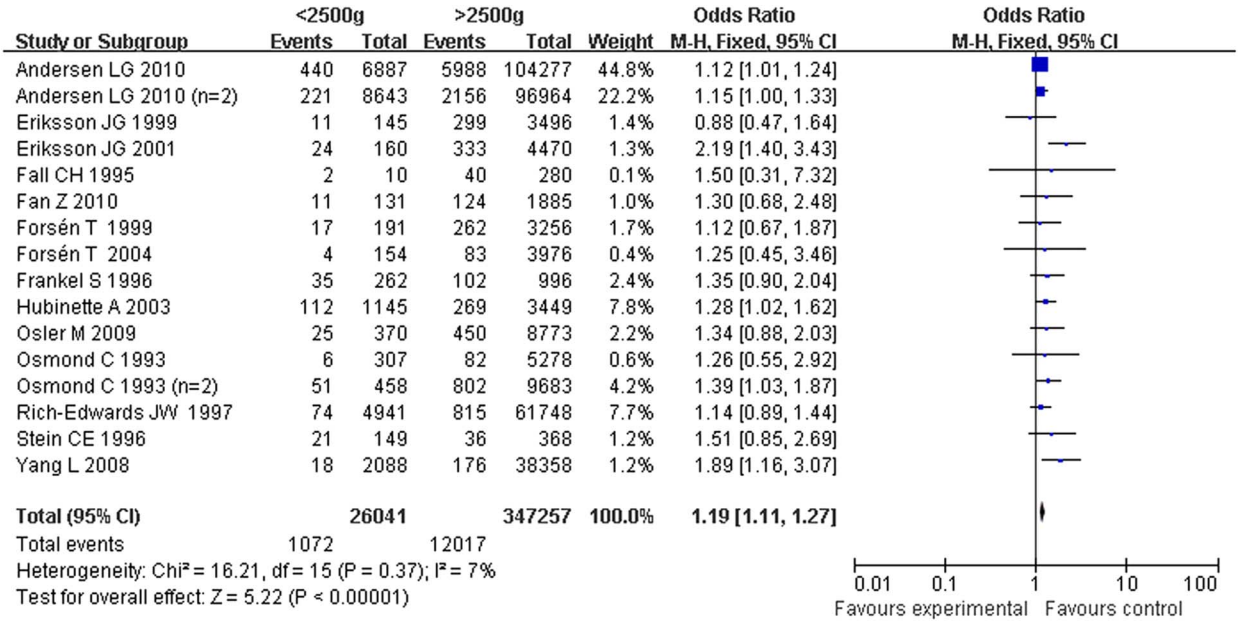

Fig. 2. The forest plot for risk of coronary heart disease in subjects with low birth weight (<2500 g) compared with subjects with birth weight >2500 g. The pooled odds ratios are calculated by a fixed-effects model; 95% confidence interval (95% CI) are shown in parentheses and horizontal bars.

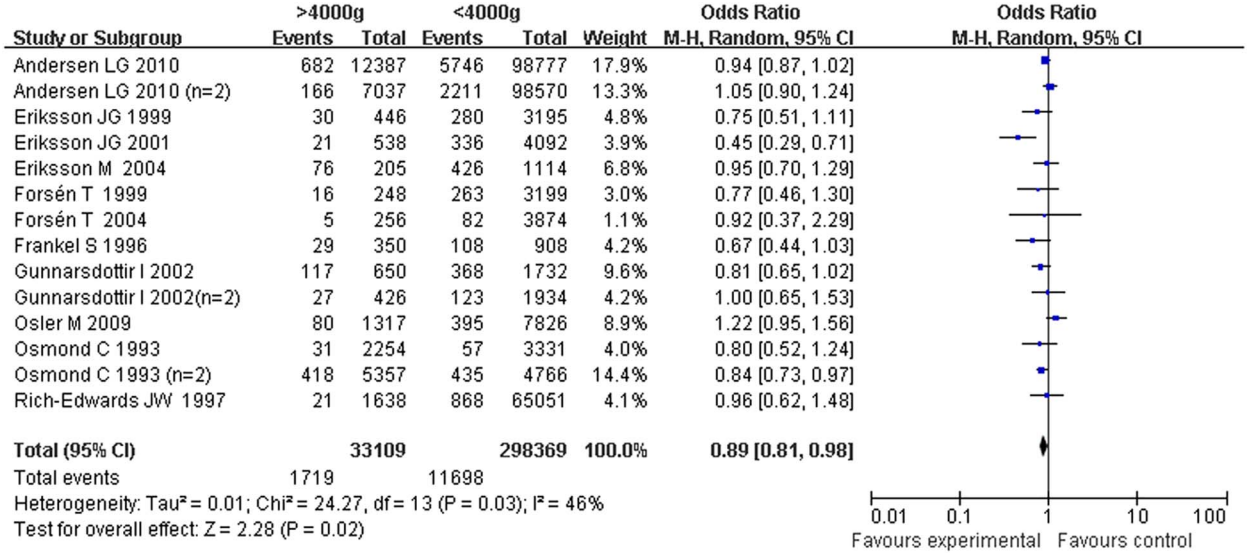

Fig. 3. The forest plot for risk of coronary heart disease in subjects with high birth weight (>4000 g) compared with subjects with birth weight <4000 g. The pooled odds ratios are calculated by a random-effects model; 95% confidence interval (95% CI) are shown in parentheses and horizontal bars.

Figure 2 showed the forest plot for risk of CHD in subjects with LBW (<2500 g) compared with subjects with BW ⩾2500 g. There was less evidence of heterogeneity ($P = 0.37$, $I^2 = 7\%$), and hence data from 14 studies[5,7–9,17,20,27–31,23,36–40] were assessed using the fixed-effects model. The results showed that LBW was associated with increased risk of CHD (OR, 1.19; 95% CI, 1.11–1.27, $P < 0.00001$).

Eleven articles (reporting 14 original data) analyzed the risk of CHD in subjects with high birth weight (HBW; ⩾4000 g) compared with that of subjects with BW <4000 g.[5,8,9,17,20,27,28,33,34,39] There was significant heterogeneity ($P = 0.03$, $I^2 = 46\%$) and hence the effect was assessed using the random-effects model. The results from this analysis revealed the relationship between HBW and risk of CHD (OR, 0.89; 95% CI, 0.81–0.98; $P = 0.02$; Fig. 3).

To assess the risk of CHD associated with both ends of the BW spectrum, using normal BW (2500–4000 g) as the reference category, all studies that provided data for both high

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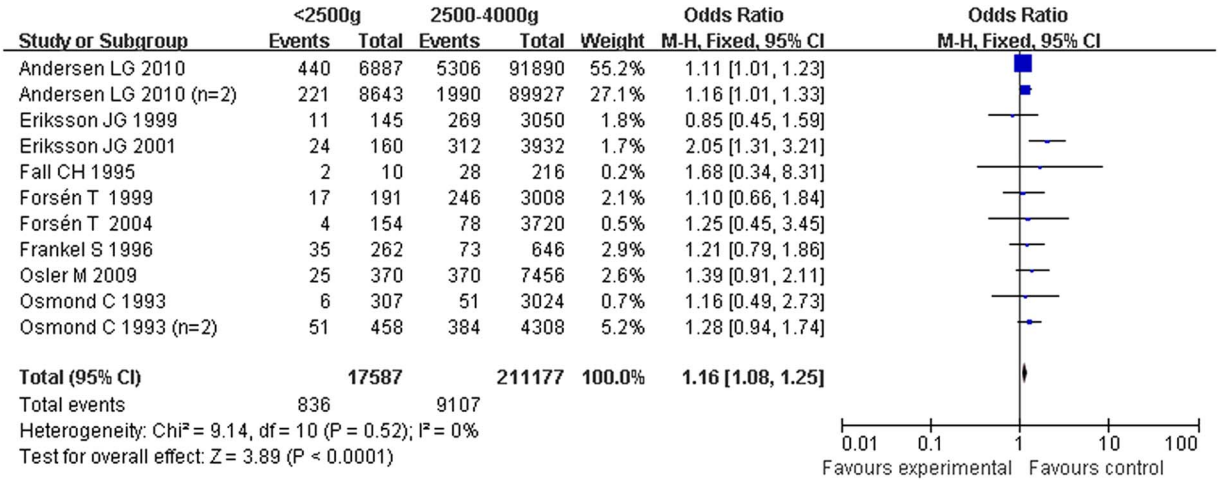

Fig. 4. The forest plot for risk of coronary heart disease in subjects with low birth weight (<2500 g) compared with subjects with normal birth weight (2500–4000 g). The pooled odds ratios are calculated by a fixed-effects model; 95% confidence interval (95% CI) are shown in parentheses and horizontal bars.

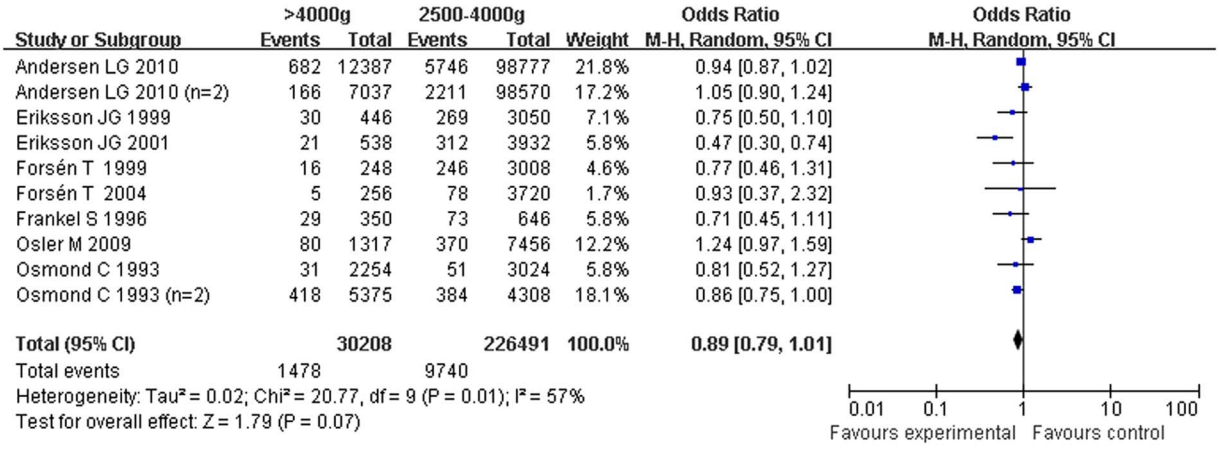

Fig. 5. The forest plot for risk of coronary heart disease in subjects with high birth weight (>4000 g) compared with subjects with normal birth weight (2500–4000 g). The pooled odds ratios are calculated by a random-effects model; 95% confidence interval (95% CI) are shown in parentheses and horizontal bars.

and LBW were analyzed[3]. Figure 4 showed the forest plot for risk of CHD in subjects with LBW (<2500 g) compared with normal BW (2500–4000 g). Nine studies (reporting 11 original data)[5,8,9,17,20,27,28,33,36] analyzed the risk of CHD in subjects with LBW (<2500 g) compared with subjects with normal BW (2500–4000 g). There was no significant heterogeneity ($P = 0.52$, $I^2 = 0\%$) and hence the effect was assessed using the fixed-effects model. The results showed that LBW was associated with increased risk of CHD (OR, 1.16; 95% CI, 1.08–1.25; $P < 0.0001$).

Figure 5 showed the forest plot for risk of CHD in subjects with HBW (⩾4000 g) compared with normal BW (2500–4000 g). Eight studies (including 10 original data)[5,8,9,17,20,27,28,33] reported the ORs for CHD in subjects with HBW (>4000 g), as compared with subjects with normal BW. There was significant heterogeneity ($P = 0.01$, $I^2 = 57\%$) and hence the effect was assessed using the random-effects model. The results suggested (not quite significant) that HBW was associated with decreased risk of CHD (OR, 0.89; 95% CI, 0.79–1.01; $P = 0.07$).

All of the identified studies suggested an inverse association between BW and risk of CHD. In 23 studies[5,7–9,17,20,24–26,28,33,34,37–39,41–47] that examined the relation of per kilogram of BW with the combined outcome for non-fatal and fatal CHD, the overall relative risk for CHD was 0.83 (95% CI, 0.80–0.86) per 1 kg higher BW (Fig. 6).

Quality assessment

Quality of each study in terms of population and sampling methods, description of exposure and outcomes and statistical adjustment of data, was summarized in Appendix 1. Out of

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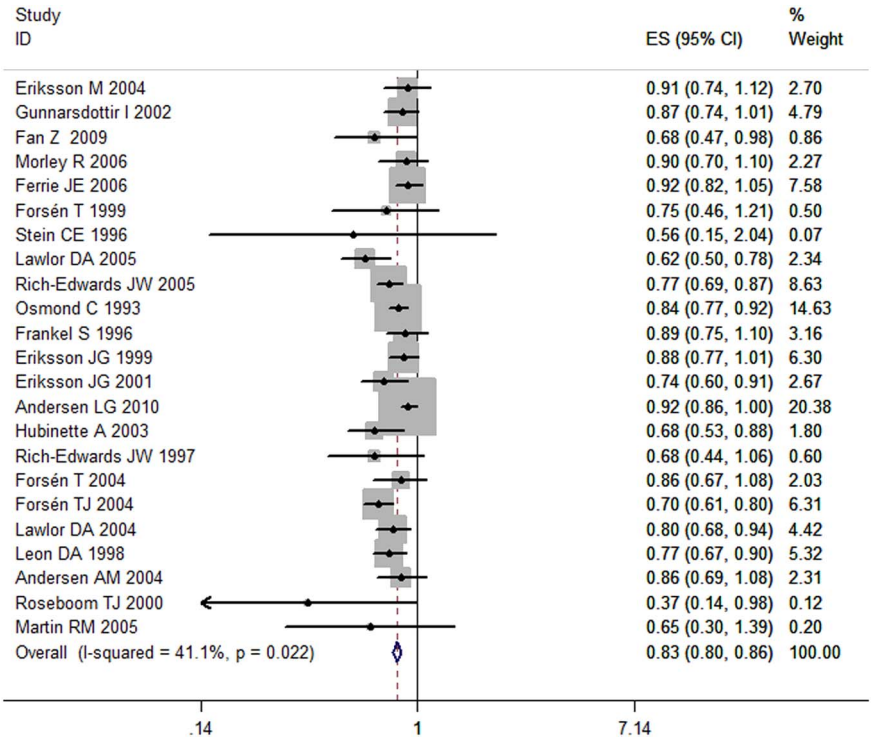

Fig. 6. Relative risks and 95% confidence intervals (CIs) for risk of coronary heart disease associated with 1 kg higher birth weight.

sixteen studies, 14 studies received 6 scores or higher on the Newcastle-Ottawa Quality Assessment scale and were considered to be of high methodological quality.[5,8,9,17,20,27,28,33–37,39,40]

Sensitivity analysis

Sensitivity analyses revealed that differences in sample size, sex and source of data for BW had an effect on the BW/CHD association. When comparing HBW (>4000 g) with BW <4000 g and normal BW (2500–4000 g), the BW/CHD association was more obvious when sample size was <5000 and age was >50 years. In addition, when comparing LBW (<2500 g) with normal BW (2500–4000 g), the BW/CHD association was more obvious when source of data for BW were hospital birth records, sample size was >5000, and sex was male. As these variables have a strong impact on the association between BW and risk of CHD, their differences can partially explain the observed heterogeneity between studies (Appendix 2).

Publication bias

Inspection of funnel plots did not reveal evidence of asymmetry (Appendix 3). Egger's tests for publication bias was not statistically significant (Egger's tests, $P = 0.218$ for studies comparing LBW (<2500 g) with BW >2500 g; $P = 0.342$ for studies comparing HBW (>4000 g) with BW <4000 g; $P = 0.130$ for studies comparing LBW with normal BW (2500–4000 g); $P = 0.50$ for studies comparing HBW with normal BW).

Discussion

Previous studies have reported the associations between BW and risk of CHD. Among these studies, some studies showed that LBW was associated with increased risk of CHD.[21,27,34] In contrast, other studies showed no significant association of BW with later CHD risk.[17,35–37] In addition, Hubinette and Osler *et al.* found a U-shaped relationship between BW and CHD.[27,28] However, in the present study, the results indicate that there is an inverse association between BW and the subsequent risk of CHD. To our knowledge, Rachel Huxley *et al.*[49] in 2007 have reported an excellent review of BW and the risk of ischemic heart disease. In this study, however, we have an update on the earlier meta-analysis and further explore the associations between LBW, HBW and the risk of CHD.

In our analyses, LBW was significantly associated with increased risk of CHD. Consistent with our findings, many epidemiological studies have reported an inverse association between BW and risk of CHD.[21,34,50] Rachel Huxley *et al.*[49] in 2007 reported 15–20% risk reduction (HR, 0.84; 95% CI, 0.81–0.88) per kg higher BW in a meta-analysis of ischemic heart disease. Another meta-analysis of cardiovascular mortality showed a 12% lower risk (HR, 0.88; 95% CI, 0.85–0.91) per kg higher BW.[51] More than BW, postnatal growth patterns are also related to the risk of CHD as adults. There is now clear evidence that people who develop CHD grew differently to other people in their early life. They tended to grow slowly *in utero*, so that their birthweights were lower. In addition, they tended to remain small for the first 2 years after birth.

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After that, they gained weight and body mass index rapidly. This pattern of growth during childhood was associated with insulin resistance in later life.[10]

Like other living creatures, humans are plastic during their development. Malnutrition and other adverse influences during development can alter gene expression and permanently change body structure and function, a phenomenon known as 'programming',[52] that are related to adverse cardiovascular risk later in life. In animals, it is surprisingly easy to produce lifelong changes in the physiology and metabolism of the offspring by minor modifications to the diet of the mother before and during pregnancy.[53] Malnutrition and other adverse influences during development also lead to slowing of fetus growth, which is why some chronic diseases are associated with LBW.

During development, there are critical periods during which a system or organ has to mature. These periods are brief. For human, much of the development is completed during the first 1000 days after conception (i.e. during intrauterine life and infancy). There are several reasons to explain the increased risk of cardiovascular disease among persons who were small at birth and during infancy. First, they have reduced function in important organs, such as the kidney.[54] Second, they have altered settings in their metabolism and hormonal feedback.[55] Third, they are more susceptible to adverse environmental influences in later life.[56] Fourth, their 'catch-up growth' occurs when undernutrition during early development is followed by adequate nutrition in childhood.[8] Children who are undernourished in the first 2 years of life and put on weight rapidly later in childhood and adolescence have a disproportionately high fat mass in relation to muscle mass, which leads to insulin resistance, a known risk factor for CHD.[10] Finally, people with LBW may be those who experienced intrauterine growth retardation, partly due to maternal hypertensive disorder during pregnancy, thus may be genetically predisposed to CHD.[27] Thus, our findings of the inverse association between BW and the risk of CHD may emphasize the importance of reducing LBW for the primary prevention of CHD in adults. Protecting the nutrition and health of girls and young women will contribute to the reduction of LBW and the prevention of chronic disease in the offspring and should be the cornerstone of public health.[57]

Consistent inverse associations between BW and CHD were found across most studies. The present meta-analysis shows that HBW is associated with decreased risk of CHD in later life. However, women who have gestational diabetes are more likely to give birth to large babies who are at increased risk of developing diabetes later in life.[58] HBW could be a result of gestational diabetes, and therefore potentially a risk factor for CHD in the child. Curhan *et al.*[59] found HBW was associated with an increased risk of adult obesity. In addition, HBW has also been described to be a risk factor for type 2 diabetes and hypertension.[18,60] In this context, HBW may be considered as a key linking factor for CHD. To date, however, very few studies have confirmed that HBW is directly assocaited with increased risk of CHD. In addition, some studies reported the relationship between BW and the subsequent risk of CHD after adjusting for gestational age. A further limitation of this analysis is the lack of information on the association between HBW and gestational diabetes in most of the studies; thus, further studies are needed to confirm the association between HBW and risk of CHD.

Strengths and limitations

This meta-analysis holds its own strengths. First, this is the latest meta-analysis reporting the associations between BW and the risk of CHD. We not only have an update on the earlier meta-analysis (Huxley *et al.* in 2007), but also further explore the associations between LBW, HBW and the risk of CHD in adults. Second, BW has been classified according to international standards in our analyses, avoiding underestimation or distortion of effect of LBW. Third, no signs of publication bias were evident in the funnel plot, and the statistical test for publication bias was non-significant. Finally, studies included in this meta-analysis are all cohort studies, reducing the possibility of recall bias.

However, some limitations need to be considered in our meta-analysis. First, the principal limitation of this study was the use of potentially biased evidence. No additional information could be obtained from the studies' authors. Confounding factors were poorly handled in some of the selected studies and four articles about birth characteristics were obtained by parental recall or questionnaire. As a result, the data included in our analyses might suffer from differing degrees of completeness and accuracy. Second, two articles were low quality in this meta-analysis, and low quality grade studies increased inter-study heterogeneity. Third, this meta-analysis involved 27 studies, most from Europe and North America. Thus, the BW/CHD association might be only reflected in European and American people and could not be expanded to all populations.

Conclusion

In conclusion, the present meta-analysis has indicated that LBW is significantly associated with increased risk of CHD and a 1 kg higher BW is associated with 10–20% lower risk of CHD. Our findings underline the importance of reducing LBW for the primary prevention of CHD. Therefore, further research should elucidate the mechanisms underlying this association.

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Conflicts of Interest

None.

Ethical Standards

The study was approved by the institutional review and ethics committee of Anhui Medical University.

Supplementary material

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