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Birth weight and metabolic syndrome in adults: meta-analysis

ABSTRACT

OBJECTIVES: To assess published evidences of the effect of birth weight on metabolic syndrome in adults.

METHODS: PubMed and LILACS databases were searched for articles published from 1966 through May 2006. The terms used were: "birth weight", "birthweight", "intra-uterine growth restriction (IUGR)", "fetal growth retardation", "metabolic syndrome", "syndrome X", "Reaven's X syndrome". Two hundred and twenty-four studies reporting estimates of the association between birth weight and metabolic syndrome or its components were considered eligible. Eleven studies provided odds ratios and were included in the meta-analysis.

RESULTS: All but two studies reported an inverse relationship between birth weight and metabolic syndrome. A comparison between low birth weight vs. normal birth weight subjects showed the random effects odds ratio for metabolic syndrome was 2.53 (95% CI: 1.57;4.08). The funnel plot graphic suggests a publication bias but, even in the studies with more than 400 subjects, the results remained significant (pooled odds ratio: 2.37 (95% CI: 1.15;4.90).

CONCLUSIONS: Low birth weight increases the risk of metabolic syndrome in adults.

KEY WORDS: Birth weight. Metabolic syndrome. Nutritional and metabolic diseases. Meta-analysis.

INTRODUCTION

Low birth weight (LBW) is a marker of intra-uterine environment, and a predictor of neonatal and child mortality⁵⁷. Barker³ proposed that low birth weight would be associated with adult chronic diseases such as coronary heart disease, hypertension, stroke²¹ and type 2 diabetes.⁴⁴

Children with intra-uterine growth retardation are at greater risk to gain adiposity after birth. This can cause obesity in childhood and adolescence and insulin resistance (IR), which are the main suggested mechanisms of metabolic syndrome.^{46,58}

Metabolic syndrome is described as a cluster of the following components: central obesity, IR, atherogenic dyslipidemia, hypertension, vascular inflammatory markers, and impaired glucose tolerance, which are associated to greater risk of cardiovascular disease (CVD) and type 2 diabetes.¹³

Many studies on the association between birth weight (BW) and components of metabolic syndrome were published in the last decade.

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In regard to hypertension, Adair & Dahly¹ recently reviewed the evidence on the association between hypertension and BW and found negative regression coefficients ranging from 0.35 mmHg to 5.9 mmHg per kg. Schluchter⁴⁵, in a meta-analysis of 55 studies on the association of BW and hypertension, including subjects aged 0 to 75, found a reduction of 1.38 mmHg in the systolic blood pressure for each increase of 1 kilogram in the BW. This author pointed out that there was probably publication bias since the effect of BW was higher in small studies. Huxley²³ found similar results in another meta-analysis of 55 studies: the pooled coefficient was -1.9 mmHg per kg of BW in the studies with less than 1000 subjects whereas among those with more than 3000 subjects the pooled coefficient was -0.6 mmHg per kg.

With respect to the relationship between BW and cholesterol levels, Huxley et al.²⁴ conducted a systematic review and meta-analysis and found a pooled effect of -1.39 mg/dL (95% CI -1.81 to -0.97 mg/dL), i.e., each increase of one kg in BW was associated with a decrease of 1.39 mg/dL in total cholesterol. Studies of infants and those with small sample size showed the larger effect sizes and the conclusion was that publication bias and results from uncontrolled studies for confounders have resulted in a strong negative relationship between BW and seric cholesterol. Besides, the effect of intrauterine growth in the cholesterol levels was weak and unlike to affect the risk of vascular disease. According to Laurén et al.³¹, there is no evidence that BW is associated with seric lipids levels in later life while the evidence is inconclusive for triglycerides.

Newsome et al.³⁸ in a systematic review of BW and glucose metabolism disturbances, found that most of the 48 studies reported an inverse relationship between BW and fasting and postchallenge glucose, fasting insulin, prevalence of type 2 diabetes, and insulin resistance and secretion measures, although these last measures had inconsistent results in adults.

Kuh et al.²⁹ in the United Kingdom, did not find an association between waist circumference and BW, only an negative effect on waist-hip ratio in women after adjusting for current body weight. A study with adults in China found that those who had the highest and the lowest BW presented a higher risk of developing abdominal obesity.⁵²

According to Kramer²⁸ part of the skepticism about the evidence of association between BW and later chronic adult disease shifted from criticism of the analytical approaches – with many studies showing the association only after adjustment for current obesity –, to questioning the impact of this association on public health.

The studies in the literature on the association between BW and metabolic syndrome are not consistent. Some studies show a direct relationship between LBW and

metabolic syndrome while others show a protective, though not significant, effect with large confidence intervals. Although several meta-analysis and reviews on the association between BW and components of metabolic syndrome have been published, to the authors' best knowledge, none of them has assessed the evidence on the direct association between BW and metabolic syndrome. Also, there may be publication bias: small studies or those with negative results are less likely to be published.³⁰

The purpose of the present study was to review the published evidences of the effect of BW on the occurrence of metabolic syndrome in adults.

METHODS

MEDLINE and LILACS databases were searched following the Meta-analysis of Observational Studies in Epidemiology⁵⁰ (MOOSE) Group guidelines to identify studies published from 1966 through May 2006 on the association between BW and metabolic syndrome. The following MeSH terms were used: “fetal growth retardation,” “intrauterine growth restriction” (IUGR), “birth weight,” “birthweight” with “metabolic syndrome,” “syndrome X” e “Reaven's syndrome X”.

Any paper reporting on the association between BW and metabolic syndrome (using any diagnostic criteria) or its components was eligible to be included in this review. Of 918 published studies identified, 694 were excluded after reading their abstracts. Most were studies in animals, reporting metabolic and syndromic alterations in newborns or management of critically ill neonates. There was no restriction of age groups in the selection of the articles. However, since there is no consensus on metabolic syndrome criteria in children and adolescents, only studies with adults were included in the meta-analysis. There were included only papers published in English, Portuguese, French, Italian or Spanish.

After reading the 224 articles and their references, 31 studies that reported data on BW and where the outcome was metabolic syndrome or its components were reviewed; of them, only one had complete data for the meta-analysis. Authors were contacted by e-mail (26) and letter (4), and were asked to provide odds ratios (OR) and their confidence intervals for the association of LBW (<2.5 kg compared to BW higher than 3.4 kg) with metabolic syndrome according to the National Cholesterol Education Program Expert Panel III (NCEP-ATP III criteria),³⁷ adjusted for some measures of socioeconomic condition. Four authors provided the required data,^{15,18,41,47} six justified they did not have the required data^{10,22,25,29,48,51} and two were reviews.^{40,46} One of them studied only twins and was excluded.⁶ Another five authors had their data extracted from the original article;^{26,43,54,59} and 13 authors did not answer.

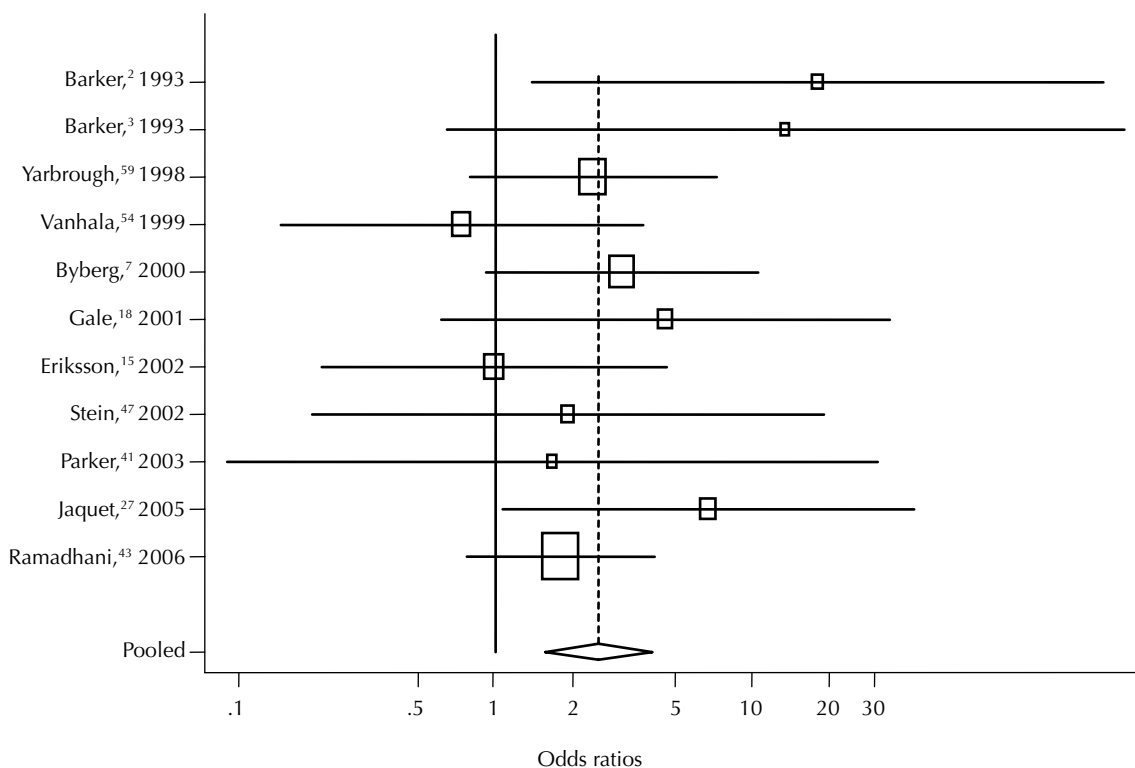


Figure 1. Odds ratios of metabolic syndrome in low birth weighted compared to normal.

A total of 11 studies provided OR. Since Byberg et al⁷ population was interviewed at the age of 50 and 70, there were included only the results of 70. Barker et al⁴ article comprised two different populations, and both were included. When a metabolic syndrome criterion was not that from NCEP-ATPIII, the simultaneous occurrence of one criterion of dyslipidemia, dysglycemia and hypertension was considered.

The studies were reviewed by two authors. A checklist was used comprising the following criteria: author's name, year of publication, study country, study type, year of birth of the study population, mean age of the population, number of subjects, sex, losses, BW classification, metabolic syndrome criteria, confounders and mediators, BW categories, ORs and confidence intervals.

Losses were estimated based on the original population minus deaths. STATA v 9.0 was used in data analyses. Q test was used to check for heterogeneity between studies³⁹ and, in case of heterogeneity, randomic models were preferred.¹¹ Publication bias was evaluated by Egger's and Begg's tests and funnel plot.¹⁴ The analyses were stratified by sample size to detect the impact of publication bias on the pooled effect.

Influence analysis was performed excluding each study from the data set, and recalculating the pooled estimated of the remaining studies.

RESULTS

Study design and baseline characteristics of the 10 articles (11 studies) included in the meta-analysis are shown in Table 1. A total of 5,867 subjects were involved, with a mean age of 50.7 years, and median birth year of 1939. The average losses were 68.4%. Figure 1 shows that there was heterogeneity among studies: two studies reported a non-statistically significant, protective effect of LBW. Nine studies showed a greater chance of metabolic syndrome in people with LBW. However, the Q test was 16.612, p=0.083 and a randomic model was used. The pooled effect was 2.53 (95% CI 1.57;4.08, p<0.0001).

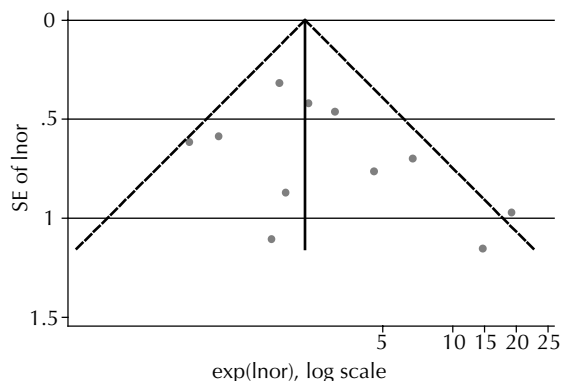


Figure 2. Funnel plot of the studies on birth weight and metabolic syndrome.

Table 1. Summary of 11 studies included in the meta-analysis on the association between birth weight and metabolic syndrome.

Author Publication year, country	Study type	Year of birth	Age (years)	Sex	Sample size (% loss)	Source of birth weight	Criteria for metabolic syndrome	Birth weight (kg)	Confounders	Control for mediators	Metabolic syndrome prevalence (%)	OR (95% CI)	Adjusted OR* (95% CI)
Barker, ⁴ 1993, England	Cohort	1920– 1930	64	Male	407 (64.8)	Midwife	Impaired glucose tolerance(IGT) or DM, SBP 160 or treatment, TG \geq median 1.4 mmol	≥ 2.5 > 4.31	Tobacco and alcohol use, social condition (current and at birth)	BMI	LBW 6/20(30) AGA 2/32(6)	-	18.0 (2.6-118. 0)
Barker, ⁴ 1993, England	Cohort	1935– 1943	50	Both	266 (47.1)	Midwife	SPB 150 or treatment, TG \geq median 1.4 mmol, Impaired glucose tolerance(IGT) or DM(ADA)	≥ 2.5 > 3.41	Tobacco and alcohol use, social condition (current and at birth)	BMI and sex	≥ 2.5 4/30 (13) >3.41 1/82 (1)	-	13.5 (1.4-129. 0)
Yarbrough, ⁵⁹ 1998, US	Cohort	1917	67	Female	303 (80.1)	53% recall, 47% other records	SBP ≥ 160 or DBP ≥ 90 or treatment, TGS ≥ 2.3 mmol or HDL-C ≤ 1.4 mmol; IGT or diabetes, or treatment	LT 1.12-3.06 HT 3.6-5.85	Adjusted each component for age	No	LT 11/92 (12) HT 4/99 (4.3)	-	2.41 (1.06- 5.51)
Vanhala, ⁵⁴ 1999, Finland	Cohort	1947, 1952, 1957	41	Both	428 (57.5)	Other records*	BP ≥ 140 or ≥ 90 or treatment, TG ≥ 1.7 mmol/L, HDL-C < 1.0 mmol in men and < 1.2 in women; IR, DM, IGT or hyperinsulinemia ≥ 13 mU/L	< 3.3 for men < 3.05 for women > 3.9 for men > 3.7 for women	Age and sex	BMI	LW 6/108 (5.6) HW 8/109 (7.3)	-	0.74 (0.22- 2.47)
Byberg, ⁷ 2000, Sweden	Cohort	1922	70	Male	734 (61.4)	Hospital registry	SBP ≥ 154 or treatment; low insulin sensitivity index < 3.65 mg/min or IGT or DM; TG ≥ 1.57 mmol/L or treatment or HDL-C < 1.1 ; PAI1 > 19.2 U/ml	≥ 2.5 > 4.31	Socioeconomic condition	No	LT 35/174 (20.1) HT 7/68 (10.3)	2.17 (0.93- 5.26)	3.12 (1.25- 7.69)
Gale, ¹⁸ 2001, England	Cohort	1924	72	Both	143 (93.6)	Hospital registry	NCEP-ATP III	≥ 2.5 > 4.31	Socioeconomic condition	No	-	4.5 (1.02- 19.8)	4.6 (1.02- 20.4)
Eriksson, ¹⁵ 2002, Finland	Cohort	1924– 1933	70	Both	474 (93.3)	Hospital registry	NCEP-ATP III	≥ 2.5 > 4.31	Socioeconomic condition	No	Total 107/464 (23)	-	0.99(0.3- 3.3)
Stein, ¹⁷ 2002, Guatemala	Cohort	1973	24	Both	385 (49.5)	Other records**	NCEP-ATP III	≥ 2.5 > 4.31	Socioeconomic condition	No	LBW 2/28(7.1) HBW 5/99 (5)	1.46 (0.30- 7.09)	1.92 (0.35- 10.6)
Parker, ⁴¹ 2003, England	Cohort	1947	50	Both	358 (68.6)	Other records**	NCEP-ATP III	≥ 2.5 > 4.31	Socioeconomic condition	No	Total 41/358 (11.5)	1.19 (0.14- 9.98)	1.67 (0.19- 14.0)
Jaquet, ²⁶ 2005, France	Case- control	1971– 1985	22	Both	1620 (65.2)	Hospital registry	NCEP-ATP III	SGA (< 10 th percentile) AGA (25th < 75 th)	Age, sex, tobacco, oral contraception, family history of metabolic and CVD	BMI	SCA17/734 (2.3) AGA 3/886 (0.3)	1.8 (1.0- 3.5)	6.76(1.93- 30.02)
Ramadhani, ⁴³ 2006, Netherlands	Cohort	1970– 1973	28	Both	749 (82.2)	Other records**	NCEP-ATP III	LT 1.25-3.20 HT: 3.65-5.50	Sex, family history of CVD, education	-	LT (11.6) HT (7.1)	-	1.8 (1.0- 3.5)

IGT: impaired glucose tolerance; DM: diabetes mellitus; SBP: systolic blood pressure, in mmHg; TG: triglycerides; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; IR: insulin resistance; PAI 1: plasminogen activator inhibitor1; LBW: low birth weight; HBW: high birth weight; BMI: body mass index; LT: lower tertile; HT: upper tertile; HT: higher weight; SGA: small for gestational age; AGA: appropriate for gestational age; CVD: cardiovascular disease; NCEP-ATP III: National Cholesterol Education Program Expert Panel III.

* Adjusted for socioeconomic factors

** Several sources: midwife, birth card or birth certificates, baby books or unknown

Table 2. Stratified meta-analysis of birth weight and metabolic syndrome studies

Variable	Odds ratio	p-value	Number of studies
Sample size			
< 400	2.87 (1.56;5.30)	0.001	5
≥ 400	2.37 (1.15;4.90)	0.020	6
Age (years)			
≤ 50	2.25 (1.08;4.65)	0.030	6
> 50	2.92 (1.44;5.91)	0.003	5
Birth year			
1917-1929	2.92 (1.44;5.91)	0.003	5
1943-1952	2.10 (0.39;11.2)	0.390	3
1973-1978	2.52 (1.14;5.58)	0.020	3
Publication year			
≤ 1999	3.18 (1.29;7.86)	0.012	5
≥ 2001	2.14 (1.27;3.62)	0.005	6
Sex			
Male	6.08 (1.15;32.24)	0.034	2
Female	2.41 (1.06;5.50)	0.036	1
Both	2.12 (1.17;3.83)	0.013	8
Losses to follow-up (%)			
< 60	2.92 (0.80;10.70)	0.105	4
60-79	4.26 (1.34;13.60)	0.014	3
≥ 80	1.94 (1.25;3.01)	0.003	4
Adjustment for confounders			
No	1.62 (0.77;3.42)	0.204	3
Yes	3.19 (1.72;5.90)	<0.0001	8
Birth weight exposure			
LBW	3.37 (1.29;8.83)	0.013	6
Others	2.22 (1.30;3.80)	0.004	5
Birth weight comparison			
LBW x HBW	3.37 (1.29;8.83)	0.013	6
LBW x AGA	2.22 (1.43;3.44)	<0.0001	3
Metabolic syndrome classification			
NCEP-ATPIII	2.14 (1.27;3.62)	0.005	6
Other	3.18 (1.29;7.86)	0.012	5

LBW: low birth weight; HBW: high birth weight; AGA: adequate birth weight; NCEP-ATP III: National Cholesterol Education Program Expert Panel III

The funnel plot (Figure 2) suggests publication bias with few small studies reporting a protective effect. But neither Begg's ($p=0.28$) nor Egger's test ($p=0.20$) were statistically significant. In a homogeneous set of trials the points will scatter about a line that runs through the origin at standard normal deviate zero. If there is no selection bias, the plot of the trials' effect estimates against sample size will resemble a symmetrical inverted funnel.

The pooled effect was slightly higher among small studies: OR=2.87 (95%CI: 1.56;5.30) for studies with less than 400 subjects compared to OR=2.37 (95%CI: 1.15;4.90) for those with 400 or more (Table 2). There was no statistically significant difference in the OR in the analysis stratified by age, sex and controlled for confounders or according to the year of birth. There were no differences among studies concerning the definition criteria for metabolic syndrome or BW categories (LBW or tertile) or comparison categories (LBW and high BW, or lower tertile and upper tertile). Losses to follow-up were associated with the heterogeneity of the studies: the effect of LBW was higher in those studies with losses between 60% and 79% (pooled OR=4.26; 95%CI: 1.34;13.60). Studies published in the 1990s showed an OR=3.18 (95%CI: 1.29;7.86) compared to an OR=2.14 (95%CI: 1.27;3.62) in those published from 2000.

DISCUSSION

The results of the present review confirm the inverse relationship between BW and metabolic syndrome: LBW children are two and a half times more to have metabolic syndrome in their adult life (OR=2.53; 95%CI: 1.57;4.08).

The funnel plot suggests publication bias. Although Egger's and Begg's tests did not show any statistical significance, they are less powerful in small sample analysis (less than 20 studies).⁴⁹ In the analysis stratified by sample size, there was still a significant effect (OR) in studies with larger sample size, suggesting that only a small part of the effect was due to publication bias. Heterogeneity of the studies was seen as the pooled effect was greater in studies with intermediate losses, and published in earlier years.

The majority of the studies, except for Gale et al,¹⁸ Parker et al,⁴¹ Stein et al,⁴⁷ Eriksson et al,¹⁵ and Ramadhani et al,⁴³ adjusted for the effect of BW to current body mass index (BMI). This is considered statistically inappropriate⁹ since adult weight can be associated to BW and then an outcome would be adjusted for a mediator³⁵ as most components of metabolic syndrome are related to obesity. This methodological difference may explain the greater effect found in early studies. Some authors such as Parker et al,⁴¹ Eriksson et al,¹⁵ and Ramadhani et al,⁴³ excluded diabetics and patients receiving cholesterol drugs, and this possibly could reduce the effect. Some studies^{7,43,59} did not use LBW (≤ 2.5 kg) but rather the first tertile as a comparison category and this could underestimate the effect of BW. But the stratified analysis did not show heterogeneity in BW classifications and probably it did not affect the pooled effect of the present analysis.

Most studies obtained BW information from hospital records or health clinics to reduce recall bias. Yarbrough et al.⁵⁹ used data from family records (47%) and parents

information (53%) but this possibly did not influence this study results because the pooled effect was 2.61 (95%CI: 1.49;4.58; $p=0.001$) after excluding their data from the analysis.

The 13 studies whose authors did not provide any information may have introduced a selection bias with negative studies tending not to be included. But nine of these studies were with children and adolescents and would have been excluded^{15,10,12,17,20,32,34,55,56} from the meta-analysis. Two studies^{36,53} found an association between LBW and metabolic syndrome components. Fagerberg et al.¹⁶ found an association between BW and metabolic syndrome only in those LBW subjects who had a catch-up growth, and selection bias is thus unlikely.

The relationship between LBW and metabolic syndrome is not yet fully understood. In a recent review, Lévy-Marchal & Czernichow³³ described some theories, from the fetal origins proposed by Barker et al³ and Hales et al.²¹ Barker et al³ suggested that LBW was a marker of poor fetal nutrition which caused the fetus to adapt in order to survive in deleterious situations which would have consequences later in life. The “thrifty phenotype hypothesis,” proposed by Hales et al,²¹ suggested that the key mechanism was impaired insulin secretion due to a small beta cell mass but this has not been confirmed in children who were small for

gestational age (SGA).^{5,27} It has also been proposed that genetic factors play a role in the relationship between BW and chronic adult diseases and genes that promote fetal growth would favor insulin resistance in postnatal environment.^{2,8} More recently, with the development of euglycemic clamp techniques, studies suggested that insulin resistance occurs in SGA children and adults,⁴² especially if they become obese or had a catch-up growth and abnormal adipose tissue deposition at birth would modify the metabolic role of adipocytes.^{26,55}

Today, it is believed that a greater risk of metabolic syndrome and cardiovascular risk seems to be a consequence of genetic and environmental interactions that influence BW.

In conclusion, the results of this unprecedented meta-analysis confirm the 2.53 risk of metabolic syndrome in adults born with LBW. This finding has a major impact in terms of cardiovascular diseases, the leading cause of mortality nowadays.

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