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Etiology and Pathophysiology

Size at birth and abdominal adiposity in adults: a systematic review and meta-analysis

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Summary

We performed a systematic literature review on the associations between birth size and abdominal adiposity in adults, while also investigating the role of the adjustment for adult body mass index (BMI). MEDLINE, Scopus, Web of Science, LILACS and SciELO databases were searched for articles published up to February 2013. Only prospective studies were included. After screening 2,570 titles, we selected 31 publications for the narrative synthesis, of which 13 were considered to be of high methodological quality. Six main indicators of birth size were identified, and birth weight (BW) was the most extensively studied. Most studies relied on anthropometric measurements as proxies for abdominal fatness or as indicators of body fat distribution. Few studies assessed abdominal adiposity through imaging methods, generally with small sample sizes. Eleven articles could be included in the meta-analyses. BW was found to be positively associated with waist circumference in adulthood, but the association disappeared after adjustment for adult BMI. In contrast, there was no association between BW and waist-to-hip ratio, whereas a strong negative association became evident after controlling for adult BMI. In conclusion, BW seems to be associated with larger adult size in general, including both waist and hip circumferences. The marked change in coefficients after adjustment for adult BMI suggests that post-natal growth strongly affects relative central adiposity, whereas BW *per se* does not play a role. Given the potential impact of post-natal growth, further research is needed to identify different growth trajectories that lead to abdominal adiposity, as well as studies on interactions of foetal and post-natal growth patterns.

Keywords: Birth weight, meta-analysis, obesity, review.

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Introduction

Obesity is defined as an excess of body fat, traditionally classified based on the body mass index (BMI) (1). Its prevalence nearly doubled from 1980 to 2008, reaching epidemic levels and affecting countries independently of income or developmental levels (2). Several studies have shown associations between BMI and adverse outcomes, such as mortality and cardiovascular diseases (CVD) (3–7). However, BMI alone does not account for regional distribution of body fat, which has been pointed as a key correlate of the health risk associated with overweight and obesity (8,9).

Central fat accumulation, and in particular intra-abdominal or visceral fat depots, has been identified as an independent risk factor for insulin resistance, CVD and hypertension (10–14). Many methods are available for central body fat assessment (15). Anthropometric measures and derived indicators, such as waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR) and

ratio of subscapular to triceps skin-folds (STSR), are largely used as proxies for abdominal fat in order to assess risk for adverse outcomes (9,16).

In a recent review, Seidell (17) reported an increased risk of all mortality related to WC and WHR, throughout the range of adult BMIs. WC and WHR have been shown to be better markers of metabolic risk than BMI, among both sexes and different ethnic groups (18–20). However, WC and WHR cannot capture the distinct components of abdominal fat depots (21). Developing of imaging methods, such as computed tomography, magnetic resonance imaging (MRI) and ultrasound, allowed assessing the different risks associated with visceral and subcutaneous abdominal fat (22,23). Visceral rather than subcutaneous fat has been associated with insulin resistance and type 2 diabetes, atherogenic dyslipidaemia and CVD, among others (9).

Following the hypothesis of the early onset of adult diseases (24,25), several studies assessed the association between size at birth and adult obesity or its comorbidities (26–29). According to this hypothesis, early life experiences may induce permanent changes in organ functions, through a process of biological programming (30,31). The prenatal phase is referred to as 'critical period' when adverse events may have a lifelong effect on later body composition and contribute to the development of obesity (32).

Birth weight (BW) is largely used as a proxy for intrauterine growth, and its relation with adult BMI has been extensively studied (26,33). BW distributions are remarkably different across developed and developing countries, and the associations between BW and later adiposity may differ in these populations (34). Although most studies showed positive associations when BW is treated as a continuous variable (26), some have also raised the hypothesis that low BW infants may be at higher risk of adult obesity and its comorbidities, compared with those in the normal range (35,36). Interpretation of the existing literature is complex because few studies separated lean from fat mass in adults, and even fewer examined fat distribution. Those who did so suggested that low BW infants tend to develop central adiposity (36,37). In 2003, Rogers and EURO-BLCS Study Group (33) identified 10 publications dealing with the association between BW and abdominal adiposity, showing a positive association with WC but little evidence of an association with WHR or STSR. Since this review, many other studies have been published on this topic.

In the present study, we aimed to (i) systematically review the literature on the associations between birth size and abdominal adiposity in adults, updating the review carried out by Rogers and EURO-BLCS Study Group (33) and extending it to other measures of birth size in addition to BW; (ii) perform a meta-analysis in order to summarize the effects of birth size on abdominal adiposity in adults and (iii) investigate the role of adjustment for adult BMI in the association between birth size and abdominal adiposity in adults.

Methods

This systematic review and meta-analysis was carried out and reported following Cochrane methodology and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group proposal for reporting (38).

Eligibility criteria

In the present review, we considered all articles dealing with the association between size at birth and abdominal adiposity in adults. In order to avoid information bias, we only included those in which the size at birth was assessed prospectively for research purposes or extracted from birth registers rather than based on recall.

There were no restrictions in terms of methods used to measure abdominal adiposity. These included anthropometric methods, computed tomography, abdominal MRI, ultrasound and dual-energy X-ray absorptiometry (DXA).

No limits for language, date of publication or location of the study were applied, but the search was restricted to humans. We excluded literature reviews, intervention studies and those in which the outcome was measured in children or adolescents. Studies that included special groups such as twins or extreme low BW were also considered.

Information sources and search strategies

We searched MEDLINE (since 1966), Scopus (since 1966), Web of Science (since 1974), LILACS (since 1982) and SciELO (since 1909) databases for articles published from inception to 5 February 2013.

The following keywords were used for assessing size at birth: 'birth weight' OR 'birth size' OR 'birthweight' OR 'infant, low birth weight' OR 'premature birth' OR 'prematurity, neonatal' OR 'preterm birth'. These keywords were identified through a comprehensive search of electronic databases using broad search terms, in accordance with the Medical Subject Headings (MeSH) of the U.S. National Library of Medicine. Each keyword was combined with terms related to abdominal adiposity and body fat distribution: 'body fat distribution' OR 'abdominal obesity' OR 'central obesity' OR 'visceral obesity' OR 'abdominal fat'. We did not conduct hand searching or searching of grey literature.

Study selection

Separate searches in each electronic bibliographic database were carried out. The results were pooled into a

single library file in the software EndNote X5® (Thomson Reuters, San Francisco, CA, USA), and the duplicate references were removed. Two independent reviewers then conducted an initial screening based on article titles, excluding those clearly irrelevant. Afterwards, the same reviewers screened study abstracts. Subsequently, the full text of selected articles was retrieved for detailed examination regarding relevance and inclusion based on the eligibility criteria mentioned above.

The references cited in all included articles were also inspected to identify additional relevant studies, and these were included if applicable. Two authors performed all stages of study selection independently (GVAF and MCR-M), and a third author (CLM) was consulted in case of disagreement.

Data items and collection process

The two reviewers independently extracted data from full-text articles using a standard form, which included year of publication, country, sample size, subjects' gender, age at examination, outcome(s), exposure(s), association(s) investigated and adjustment for confounders. Disagreements were solved by re-extraction and consensus. Studies were classified by region and income levels according to the World Bank classification (39). For studies reporting on anthropometric measurements, the exact placement of the measuring tape was recorded (Supporting Information Table S1).

For meta-analysis purposes, linear regression coefficients (β) and standard error or 95% confidence intervals (95% CI) were extracted. Crude and adjusted coefficients were extracted when available. The estimates adjusted for adult BMI were recorded separately.

Quality assessment

The Newcastle–Ottawa Scale was used to assess the methodological quality of the articles. This scale contains nine questions and each satisfactory answer receives 1 point, adding up to a maximum score of 9 points. It allows evaluating epidemiological quality in three main domains: selection (0–4), comparability (0–2) and ascertainment of the outcome (0–3). As part of the comparability domain, the instrument allows an extra point to studies that controls for a specific variable relevant for the review, and we did so for those that included adjustment by adult BMI. Those with a score of 8 or 9 were considered as high methodological quality studies.

Two authors independently assessed the methodological quality of all eligible studies (CLM and MCR-M), and disagreements were resolved by consensus, with input from a third reviewer (GVAF).

Meta-analysis

All analyses were performed using the software Stata version 12.1 (StataCorp, College Station, TX, USA). Because of the small number of studies for some of the associations of interest, we decided to perform meta-analysis only for the association between BW and WC or WHR. We included articles that reported BW and WC/WHR analysed as continuous variables, providing linear regression coefficient (β) and a measure of dispersion (standard error or 95% CI).

The authors of three papers (40–42) reporting on the association between BW and WC/WHR but did not perform linear regression or did not report dispersion measures were contacted by email, and all responded. Studies that presented estimates of linear regression coefficients based on measures of BW in pounds (lb) or in units of standard deviation were converted into the metric system. Two articles presented the linear regression coefficient and the exact two-sided *P*-value, so the bounds of the 95% CI were estimated taking into account the number of observations included in the model.

Linear regression coefficients and 95% CI were pooled through random effects meta-analysis. This model was used because it accounts for sampling error and possible heterogeneity between studies, and it defaults to a fixed effects model in the absence of heterogeneity (43–45). The I^2 statistic was applied to assess heterogeneity between study. This statistic varies from 0% to 100%, with higher values suggesting heterogeneity among studies. We classified heterogeneity according to Higgins *et al.*'s (46) proposal, considering moderate and high heterogeneity values of I^2 of 50–75% and 75% or higher, respectively.

Publications that reported only combined estimates for both sexes were treated as a single study. Those providing estimates for men and women were treated as two separate results in the meta-analysis. We also analysed separately those studies that adjusted for adult BMI, presenting pooled sex-stratified effects, with and without adjustment.

Assessing risk of bias across studies

We used the funnel plot (47,48) to check for publication bias. In addition, we formally tested funnel plot asymmetry using Begg's test and Egger's test (49). We also investigated the influence of each individual study on the pooled estimate, omitting each study at a time and repeating the analyses (50).

Results

Study selection

A total of 4,346 articles were identified through database searching. After removing the duplicates, 2,570 records

were pre-screened by reading of the titles from which 219 remained for abstract screening. From this, a total of 60 full-text articles were retrieved for detailed examination and 32 were excluded. The main reasons for exclusion were reviews (16 articles) and absence of measure of abdominal obesity (11 articles). Two articles were excluded because size at birth was neither assessed prospectively nor extracted from birth register. Three studies were added by checking of references of the 28 selected articles. Therefore, 31 studies (40–42,51–78) were selected for the narrative synthesis (Fig. 1).

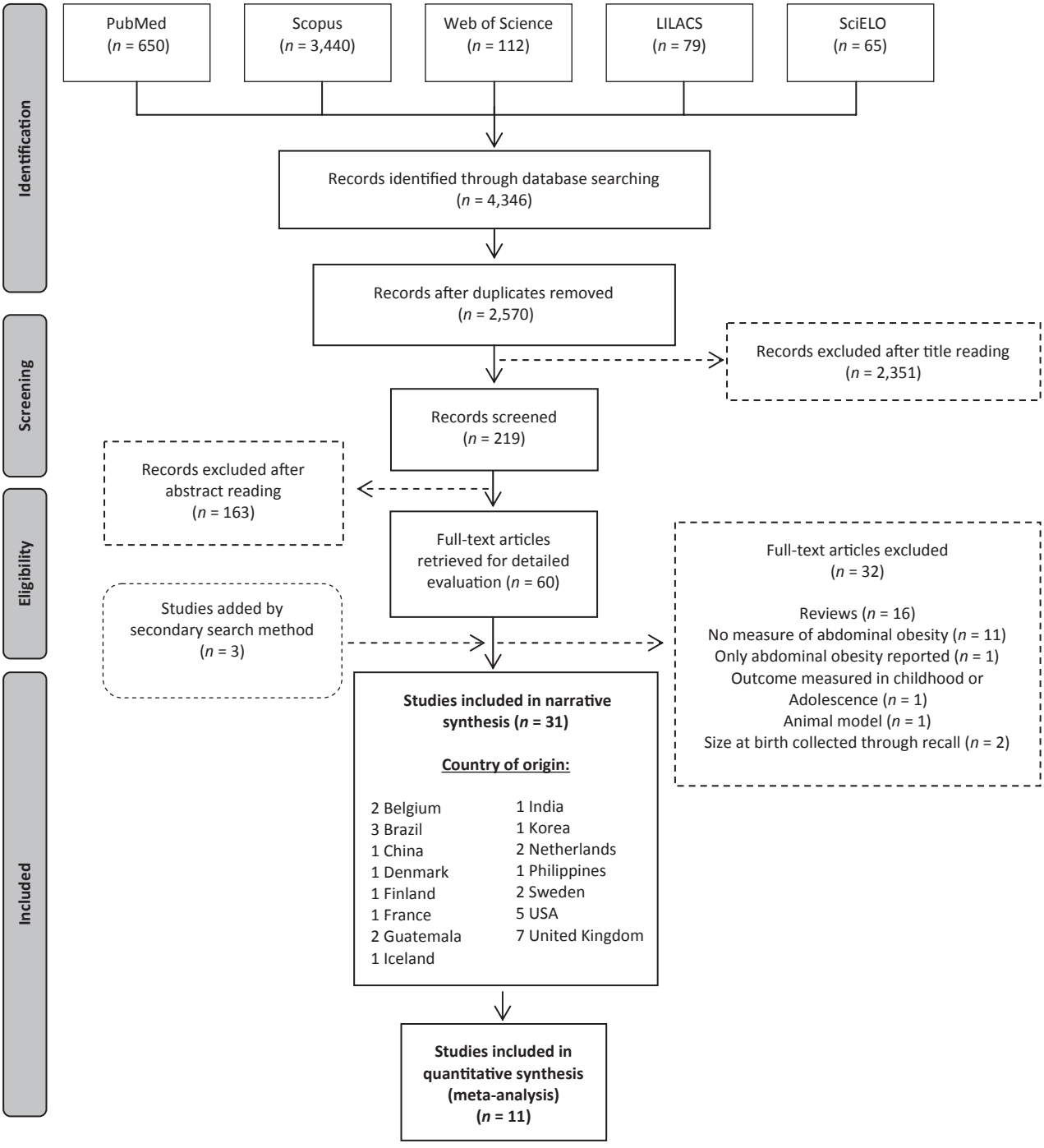


Figure 1 Flow diagram of search strategy and selection process. February 2013.

Study characteristics

Descriptive information of the 31 selected articles is presented in Table 1. All articles were written in English and most of them from 2000 to 2009. Twenty-three studies were conducted in high-income countries, mostly from the European region (55%). The majority of articles included both sexes (68%) and presented a sample size bellow 1,000 subjects (68%).

Regarding the definition of anthropometric measurements, most studies measured WC at a point between the costal margin and the iliac crest, or at the level of the umbilicus. HC was commonly measured at the level of the greater trochanter (Supporting Information Table S1).

BW was the main exposure investigated (24 articles). Thirteen articles assessed the association between BW and WHR, followed by BW and WC ($n = 9$). Six studies reported on HC as an outcome. Only four and two articles reported visceral and subcutaneous fat, respectively, both measured by abdominal MRI, computed tomography or ultrasound.

Quality assessment

The detailed methodological quality of each study is summarized in Supporting Information Table S2. Thirteen articles (42%) (42,51,52,55,58,59,62–64,68,72,74,77) were considered to be of high methodological quality (scores of 8 or 9 points). The majority of studies ($n = 24$; 77%) received high score in the selection scale, based on representativeness and ascertainment of exposure. Regarding the comparability scale, 12 articles (39%) presented measurements adjusted by adult BMI and 6 (19%) (53,65,69,71, 75,78) only presented crude estimates. Ascertainment of outcome and non-response were poorly rated in most studies, with high scores in only seven (23%) of them as only seven articles received high scores (Table 1).

Findings according to main exposure

Description of the 21 articles that assessed the effect of birth size on anthropometric measurements of abdominal adiposity is presented in Supporting Information Table S3. The table only includes analyses that reported linear regression coefficients. In Supporting Information Table S4, we present the studies that applied other methods for measuring outcomes, such as abdominal MRI and ultrasound. These articles will be described in the following sections according to the exposure that was studied. We initially address the associations between the different early life exposures and measurements of abdominal adiposity, followed by a specific section describing adjustment for adult BMI.

Table 1 Key features of 31 papers selected by systematic review on effects of birth size on adult abdominal adiposity

Category	No. of studies	%
Year of publication		
Before 2000	5	16.1
2000–2009	22	71.0
2010 or after	4	12.9
Region*		
East Asia and Pacific	3	9.7
Europe and Central Asia	17	54.8
Latin America and Caribbean	5	16.1
North America	5	16.1
South Asia	1	3.2
Income level*		
High income: OECD	23	74.2
Lower middle income	4	12.9
Upper middle income	4	12.9
Gender		
Both	21	67.7
Only males	7	22.6
Only females	3	9.7
Sample size		
<100	4	12.9
100 to 999	17	54.8
1,000 or more	10	32.3
Exposure investigated†		
Birth weight	24	77.4
Birth length	4	12.9
BMI at birth	3	9.7
Ponderal index at birth	3	9.7
Small for gestational age	2	6.4
Birth weight for gestational age	2	6.4
Association investigated†		
Birth weight → Waist-hip ratio	13	41.9
Birth weight → Waist circumference	9	29.0
Birth weight → Hip circumference	6	19.3
Birth weight → Subscapular to triceps skin-fold ratio	5	16.1
Birth weight → Visceral fat	4	12.9
Quality assessment (Newcastle–Ottawa Scale)		
Total score		
High (8 or 9 points)	13	41.9
Moderate/low (<8 points)	18	58.1
Quality assessment (Newcastle–Ottawa Scale)		
Selection		
High (4 points)	24	77.4
Moderate/low (<4 points)	7	22.6
Comparability		
High (2 points)	12	38.7
Moderate (1 point)	13	41.9
Low (0 point)	6	19.4
Ascertainment		
High (3 points)	7	22.6
Moderate/low (<3 points)	24	77.4

*According to World Bank classification.
†Percentage in each category refers to proportion in relation to the total number of studies ($n = 31$).
BMI, body mass index; OECD, Organisation for Economic Co-operation and Development.

Birth length

Four studies (42,51,54,72) investigated the effect of birth length (BL) on abdominal adiposity in adults. Corvalán *et al.* (54) showed a positive association between BL and WC in Guatemala, after controlling for several confounders.

In India, Sachdev *et al.* (42) found a negative association between BL and STSR for both sexes combined. The sex-stratified analysis showed a negative association among men but little evidence of an association among women. The patterns by sex are consistent with results reported by Adair (51) in the Cebu (Philippines) cohort.

Using WHR as the outcome, Sachdev *et al.* (42) reported no statistical evidence of an association with BL in both sexes combined, but there was a positive association among women. In Guatemala, Schroeder *et al.* (72) found no statistical evidence of association between BL and WHR. In summary, few studies assessed the association between BL and abdominal adiposity in adults. Most analyses showed absence of association, although some of them had small sample sizes. We highlight the negative association between BL and STSR among men, observed in two studies from low-income countries (42,51).

Birth weight

Twenty-four articles presented BW as exposure of interest (40–42,51–53,55–62,64–67,70,72,73,75–77). Regarding HC, Euser *et al.* (56) found a positive association among subjects who were born very preterm, analysing both sexes combined. Among women, two studies reported positive associations: one study in the United Kingdom (62) and one in Brazil (58). In men, three studies (52,58,62) showed positive associations between BW and HC, one of them presenting estimates adjusted for adult BMI (52).

Nine studies assessed the association between BW and WC (52,56,58,61,62,70,75–77). Euser *et al.* (56) and Tian *et al.* (77) showed positive associations for both sexes combined, using different approaches. Euser *et al.* (56) analysed a prospective cohort of men and women born with less than 32 weeks of gestation in Holland. They found an average increase of 2.41 cm in WC per kilogram change in BW in an unadjusted analysis. Tian *et al.* (77) conducted a cross-sectional study in Chinese adults, showing that low BW (BW < 2.500 g) was associated with an odds ratio of 2.26 for abdominal obesity compared with those in the BW category of 2,500–3,499 g, after adjustment for several confounders. Rolfe *et al.* (70) reported lack of association between BW and WC in United Kingdom. Stern *et al.* (75) carried out a study in Mexican–Americans, showing a weak but significant correlation between BW and WC (data not shown in table because an effect measure was not presented).

Sex-stratified analyses were performed in five studies (52,58,61,62,76), of which one only provided estimates adjusted for adult BMI (52). Among women, two studies carried out in United Kingdom (62) and the Netherlands (76) showed no statistical evidence of association between BW and WC. In contrast, González *et al.* (58) found a positive association in a Brazilian birth cohort. In men, three studies (58,61,62) presented positive associations. In contrast, two articles reported no statistical evidence of association, one of them with a very small sample size (76) and the other only reporting BMI-adjusted results (52).

Five studies reported the effects of BW on STSR (42,51,52,59,78). Gunnarsdottir *et al.* (59) in Iceland and Sachdev *et al.* (42) in India found negative associations for both sexes combined, without adjustment for adult BMI. In the sex-stratified analysis, two articles (42,51) found no statistical evidence of association among women. In contrast, Valdez *et al.* (78) reported a negative association among Mexican–American women but did not provide effect measures. Among men, three studies (42,51,52) found negative associations and one reported no evidence of association without providing effect estimates (78). One study only presented estimates adjusted for adult BMI (52), which were similar to the unadjusted results.

The effect of BW on WHR was assessed by 13 studies (40–42,52,57,58,62,64–66,71,72,76). Most of them showed no statistical evidence of association (40–42,58, 62,64–66,71,76), except one analysis for men (52) and two for women (57,72). Byberg *et al.* (52) reported a negative association among Swedish men, after adjusting for age and adult BMI. Among women, Schroeder *et al.* (72) in Guatemala also showed a negative association. In contrast, Fall *et al.* (57) reported no statistical evidence of association between BW and WHR at age 60–71 years among women in the Hertfordshire (United Kingdom) cohort.

Kahn *et al.* (61) studied 192 male applicants for military service in United States, including abdominal diameter index (ADI) and sagittal abdominal diameter (SAD) as measures of abdominal adiposity. The authors reported no statistical evidence of association between BW and ADI, but a positive association with SAD, after controlling for race and height.

Four studies including both sexes reported measurements of abdominal adiposity collected through other methods: abdominal MRI (55), computed tomography (53,67), ultrasound (70) and DXA (60,70). Regarding the association between BW and abdominal visceral adipose tissue (VAT), two studies with small samples in the Unites States estimated the mass of VAT through abdominal MRI (55) or the area of VAT using computed tomography (67). They found no statistical evidence of association. Rolfe *et al.* (70) applied ultrasonography to measure VAT thickness in the United Kingdom, reporting a negative association with BW after adjusting for adult BMI.

Demerath *et al.* (55) showed a positive association between BW and abdominal subcutaneous adipose tissue (SAT) measured through MRI, but Rolfe *et al.* (70) did not confirm this result using ultrasound. Demerath *et al.*

(55) also obtained several other measurements. The authors reported no statistical evidence of association between BW and percentage of abdominal fat, percentage of abdominal VAT in relation to total body fat, log of VAT and percentage of abdominal VAT in relation to abdominal subcutaneous adipose tissue.

Rolfe *et al*. (70) also used DXA to assess the total abdominal fat, showing a negative association with BW. The following studies were not included in Supporting Information Table S4 because they failed to provide measures of effect. Kensara *et al*. (60) carried out a small study comparing men born with low and high BW in Hertfordshire, United Kingdom. BW was associated with higher trunk-to-limb fat ratio based on DXA after adjusting for total fat mass or percentage of body fat.

Choi *et al*. (53) studied a small sample of young Korean adults and found that BW correlates poorly with visceral fat area ($r = -0.22$) and visceral-to-subcutaneous fat ratio ($r = -024$), both estimated through computed tomography.

In Brazil, Silva *et al*. (73) studied adults from the 1978–1979 Ribeirão Preto cohort. They applied structural equation modelling for assessing the association between BW and adiposity, treated as a latent variable including BMI, WC and sum of triceps and subscapular skin-folds. The results showed a small but significant effect of BW on adiposity.

Summarizing, we found that BW is associated with larger HC in both sexes, and with WC in men. In terms of indicators of relative abdominal adiposity, there is evidence of a positive association between BW and STRS among men but not among women. Most studies reported no statistical evidence of association with WHR, consistent for both sexes. We also highlight the small number of studies assessing abdominal adiposity through imaging methods, generally using small sample sizes.

Small for gestational age and birth weight for gestational age

We identified two studies that assessed small for gestational age (SGA) infants (63,68). Laitinen *et al*. (63) found that being born SGA was not associated with WHR among Finnish women, but SGA men had an independent risk of abdominal obesity (higher WHR) than those born with weight appropriate for gestational age (AGA), either adjusting or not for adult BMI. Meas *et al*. (68) found that AGA subjects in a French cohort presented a significantly larger WC compared with the SGA subjects at age 22 years, but not at 30 years. This was due to a greater increase in WC between the two ages in the SGA group compared with those born AGA. The authors did not provide effect measures.

Two articles assessed BW for gestational age (40,69). Loos *et al*. (40) analysed the East Flanders Prospective Twin Survey and reported a negative association with WHR, after adjusting for adult BMI. In Denmark, Rasmussen *et al*. (69) used DXA to determine whole-body fat content and regional fat distribution in a random sample of young men from the Danish Medical Birth Registry. Subjects with BW for gestational age below the 10th centile had significantly higher proportion of trunk and abdominal fat mass, compared with other subjects. Effect measures were not provided.

Body mass index and Ponderal index at birth

Three studies reported the association between BMI at birth and later abdominal adiposity (42,54,74). Sachdev *et al*. (42) found a negative association between BMI at birth and STSR, and no statistical evidence of association with WHR, either in combined or sex-stratified analyses. Regarding abdominal and WC, both Corvalán *et al*. (54) and Simões *et al*. (74) found no statistical evidence of association with BMI at birth, for either sex.

Three studies (42,59,72) assessed Ponderal index at birth. Analyses combining both sexes showed negative associations with STSR in two different countries: Iceland and India. In sex-stratified analyses, Sachdev *et al*. (42) found a negative association among women and absence of association among men for STSR. For women, two studies also reported lack of association with WHR (42,72).

Adjustment for adult body mass index

We identified three studies that presented estimates of the association between BW and WC (62,70,76) before and after adjusting for adult BMI (Supporting Information Table S5). In the analyses that were not adjusted for BMI, all five effect estimates were positive, although most were not statistically significant. After adjustment, four of the estimates became negative, and the positive effect in the fifth was greatly reduced.

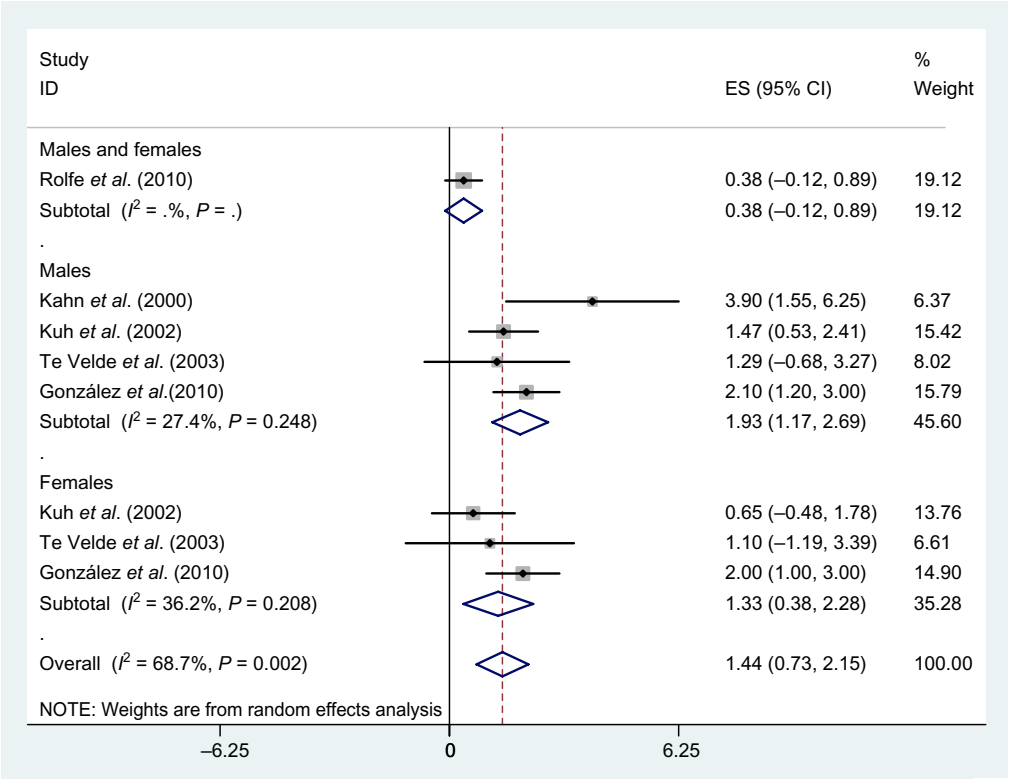
Regarding the association between BW and WHR (40,42,62,76), eight sex-stratified analyses were identified. Two analyses including only men and one among women showed a negative association after adjusting for adult BMI, whereas the unadjusted analyses had previously shown no statistical evidence of association. Even when adjusting for adult BMI did not alter the direction or significance of the linear regression coefficient, we observed that the size of the effect measure tended to be smaller after adjustment.

Meta-analyses

The meta-analyses were restricted to the association between BW and WC, and that between BW and WHR, because none of the other combinations of exposure and outcome had more than a couple of studies.

Eleven studies met the inclusion criteria for the meta-analyses (40–42,56,58,61,62,64,70,72,76). Figure 2a

(a)



(b)

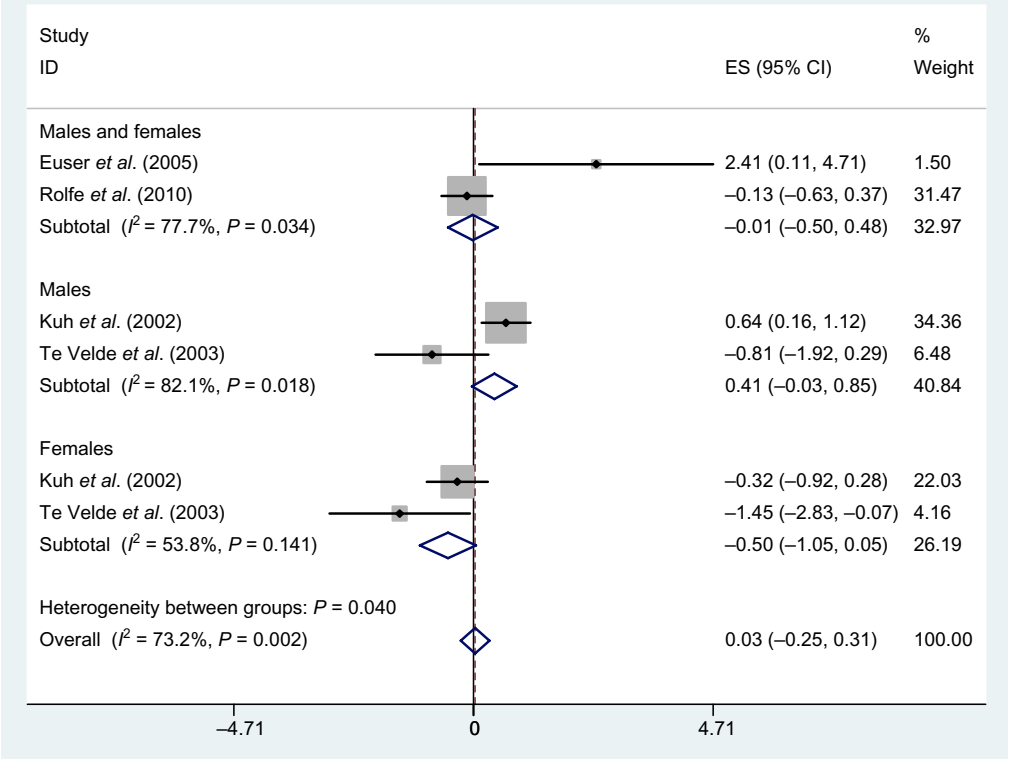


Figure 2 Grouped and sex-stratified effect for the association between birth weight (kg) and waist circumference (cm) without (a) or with adjustment (b) for adult body mass index among adults. February 2013.

presents the grouped and sex-stratified effect for the association between BW and WC without adjustment for adult BMI. We found a positive pooled effect of BW on WC (β = 1.44 cm; 95% CI: 0.73–2.15 cm) with moderate heterogeneity (I^2 = 68.7%), including eight linear regression coefficients from five studies (one study only reported sex-combined estimates) (70). Sex-stratified analyses showed positive pooled effects for men (β = 1.93 cm; 95% CI: 1.17–2.69 cm) and women (β = 1.33 cm; 95% CI: 0.38–2.28 cm), both analyses with low heterogeneity.

Only four studies presented estimates adjusted for adult BMI (56,62,70,76) (Fig. 2b). Both sex-combined and sex-stratified pooled effects showed moderate or high heterogeneity, and the resulting estimates include the null value.

Figure 3a presents the meta-analyses of the association between BW and WHR without adjustment for adult BMI based on seven articles (40–42,58,62,72,76). The overall pooled effect (β = –0.07; 95% CI: –0.34–0.20) showed no statistical evidence of association and low heterogeneity (I^2 = 37.9%; P = 0.1). The sex-stratified analysis also showed no association between BW and WHR, with low heterogeneity among men (I^2 = 0%; P = 0.42) and moderate among women (I^2 = 56.6%; P = 0.04).

Figure 3b presents the forest plot of six articles that presented estimates adjusted for adult BMI (40–42, 62,64,76). We found a negative association (β = –0.59; 95% CI: –0.84 to –0.34) between BW and WHR with low heterogeneity (I^2 = 0; P = 0.523). Sex-stratified analyses showed that the effect was similar among men (β = –0.60; 95% CI: –0.90 to –0.29) and women (β = –0.55; 95% CI: –1.11 to 0.01), both with low heterogeneity.

Assessment of bias across studies

Supporting Information Figs S1 and S3 present the funnel plot for the meta-analysis of the effect of BW on WC and WHR, respectively, without (a) or with adjustment (b) for adult BMI. There was no evidence of publication bias in the funnel plots, confirmed by Egger's and Begg's tests. We also investigated the influence of each individual study on the overall meta-analysis summary estimate (Supporting Information Figs S2 and S4), observing only small changes in overall estimates when any single study is omitted.

Discussion

Studies in animal models have shown that the metabolism of adipose, lean and hepatic tissues may be programmed by maternal nutrition during gestation and lactation (79,80). Epidemiological evidence from the last decades has shown that environmental exposures from conception to adulthood influence the susceptibility to obesity and chronic diseases (81). However, the relevant mechanisms in humans are unclear, and the associations between birth size and later adiposity have been inconsistent. An effect of early life exposures on body fat distribution, especially on the central accumulation of fat, could lead to altered risks for obesity-related metabolic diseases in adult life.

In 2003, Rogers and EURO-BLCS Study Group (33) carried out a literature review and reported that several studies had found positive associations between BW and WC. Unadjusted analyses showed little evidence of direct association with measures of relative distribution of fat, such as WHR or STSR. Analyses adjusted for current body mass showed consistent evidence of negative association between BW and STSR, but less consistent evidence of negative associations with WHR. The authors also highlighted the heterogeneity of the subjects studied, the variability in the indicators of fat distribution and the generally small sample sizes.

A literature review performed by Fall (82) addressed studies relating BW to later body composition in adults. The results were mixed. Whereas some studies showed positive associations between BW and WC or WHR, others failed to detect an association. Additionally, some studies found that low BW was associated with higher WHR after adjustment for current BMI or weight. The author concluded that there is some evidence that low BW contributes to abdominal fatness. Although presenting a comprehensive perspective of the evidence for the early determinants of adiposity in later life, the review was not systematically performed and reported.

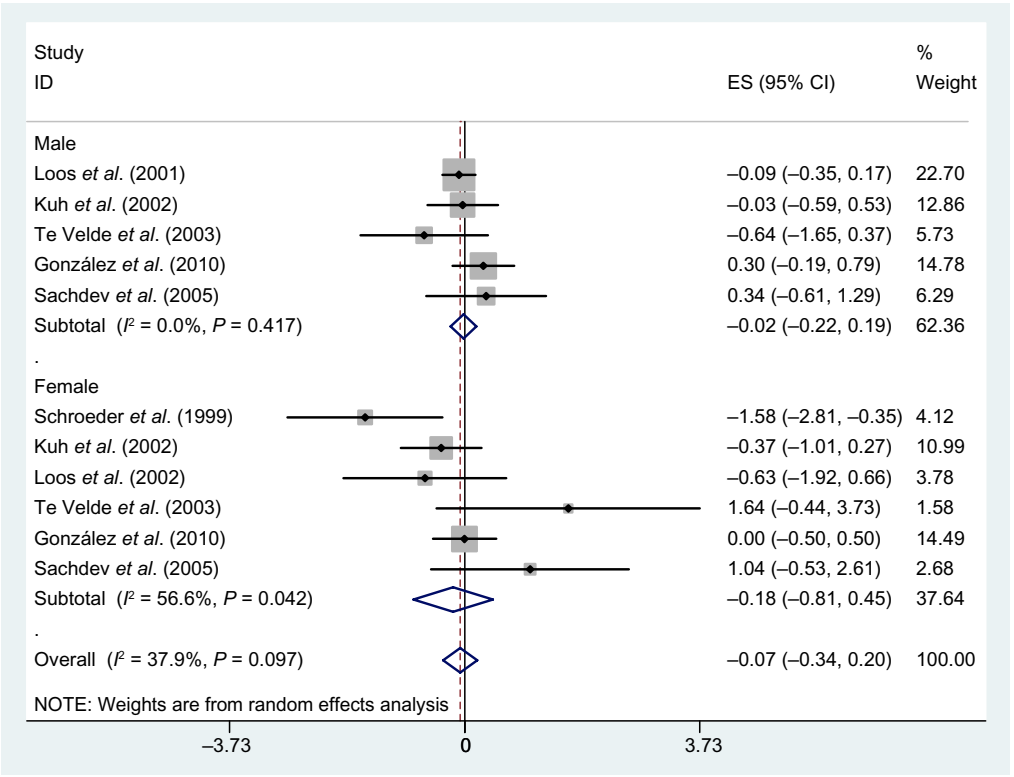
We performed a systematic review of the literature on associations between birth size and adult abdominal adiposity, including several measurements of both exposures and outcomes. We also presented comprehensive estimates of associations between BW and WC/WHR, and used meta-analysis to obtain pooled effects, with and without adjustment for adult BMI.

Our results may be summarized as follows. Pooling both sexes, we found a positive association between BW and WC. The overall estimate obtained through meta-analysis presents moderate heterogeneity among studies, and in the qualitative narrative review, it appeared that the association was stronger among men. However, there was little heterogeneity associated with sex in the meta-analyses. Regarding the relative distribution of fat, there is no evidence of association between BW and WHR, in either sex. Our estimates present low heterogeneity among studies in both sex-combined and sex-stratified analyses.

The present results are compatible with a positive association between BW and overall adult body size, including WC and HC, but do not support a specific effect of BW on central adiposity.

The reviewed articles differ in many ways: from the definition of exposures and outcomes, to the study design, age composition of samples and potential confounders. Most studies were carried out in high-income countries

(a)



(b)

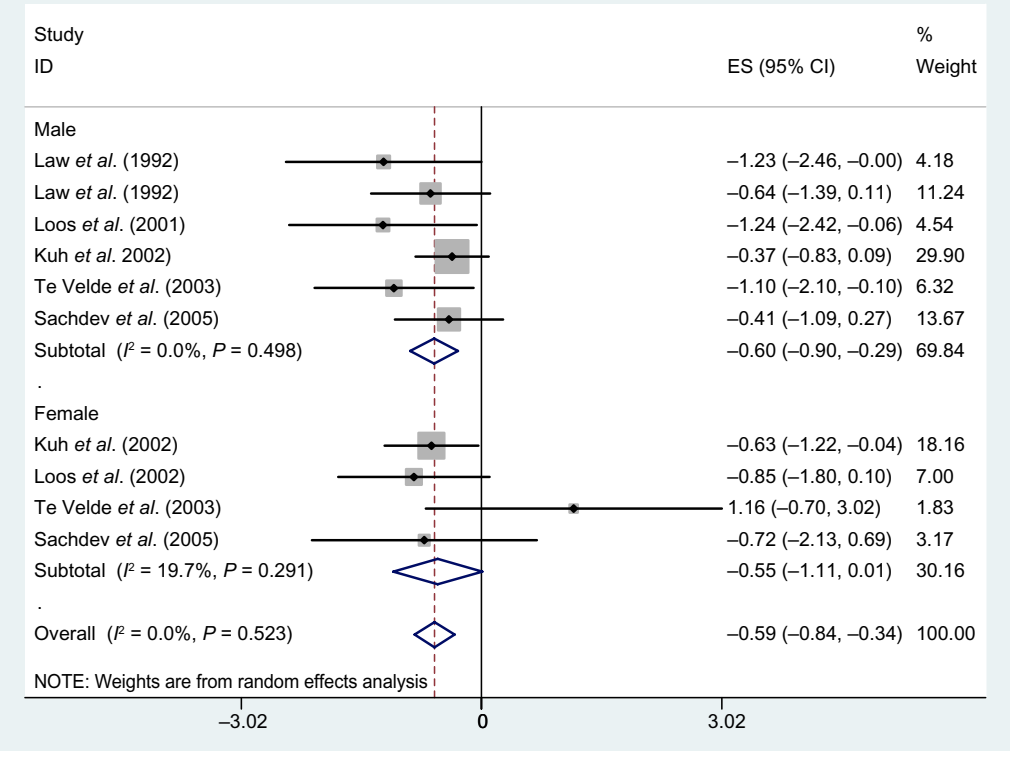


Figure 3 Grouped and sex-stratified effect for the association between birth weight (kg) and waist-to-hip ratio without (a) or with adjustment (b) for adult body mass index among adults. February 2013.

from Europe and North America. This must be taken into account when interpreting the results of the present review because life-course research from low- and middle-income countries may show different patterns of associations and confounders in comparison to findings from high-income countries (36,83).

We identified six main indicators of birth size, of which BW was the most extensively studied. This can be explained by the fact that studies from high-income countries often rely on birth records. BW has been historically considered as an important indicator of prenatal conditions, and as a predictor for survival, growth and development later in life (26,84).

Most studies included in the present review relied on anthropometric measurements as proxies for abdominal fatness and/or indicators of body fat distribution. We find that a distinction between absolute and relative measures of abdominal fatness is useful in interpreting the results of different studies. WC represents an absolute measure of abdominal fat, being considered as the best anthropometric correlate of absolute amount of VAT (11).

Two ratio measures are often used as indicators of relative distribution of fat, comparing central to peripheral fat. The WHR is used to assess the ratio of intra-abdominal to peripheral fat (9,33) because HC reflects fat deposition in the buttocks, as well as pelvic size and gluteal muscle (84). A second anthropometric ratio is the STSR, or ratio between a centrally located skin-fold (subscapular) and a peripheral skin-fold (triceps), thus reflecting the ratio of truncal to peripheral subcutaneous fat (11). Therefore, whereas WHR and STSR both reflect ratios of central or truncal to peripheral fat, they have different anatomical connotations.

Highly precise measurements of relative body fat distribution can also be obtained through imaging methods. For example, Kaess *et al*. (85) demonstrated in a large community-based sample that the VAT/SAT ratio measured by computed tomography is a correlate of cardiometabolic risk above and beyond obesity defined using BMI and absolute visceral fat mass. However, we identified few studies that reported measurements obtained through imaging methods. Those that did so generally used small sample sizes, probably because of the high costs of the methods and, for computed tomography, the risks associated with radiation exposure (9).

We assessed the association between BL and relative central adiposity measured through STSR. The number of studies was insufficient for meta-analysis; however, based on the narrative synthesis, there was evidence of an inverse association, but only among men. We are not aware of any previous reviews on this topic, but a recent review on BL and adult BMI or overweight or obesity found that eight of nine studies failed to detect an association (26). A potential biological mechanism for these findings is that BL would contribute primarily to lean mass but not to fat mass (86), and therefore would not affect BMI as a whole, nor lead to central adiposity.

Despite the small number of articles, we highlight the consistent positive association between BW and HC in both men and women. Several studies have shown that HC presents a strong inverse association with the cardiovascular risk, once the deleterious effect of WC has been accounted for (87–89). The protective effect of larger hips in relation to WC seems to be related to the regulation of fatty acid release and uptake, and a beneficial adipokine profile related to gluteofemoral adipose tissues (90).

Few studies addressed the association between BW and Ponderal index/BMI at birth, SGA or BW for gestational age. We could not identify clear patterns for these associations. The results presented are also inconclusive.

We now address the consequences of adjustment for adult BMI when analysing the association between BW and central adiposity. Previous studies have shown how such adjustment affects the association between BW and later measurements, such as blood pressure (91–93).

We start with the association between BW and WHR. There was no statistical evidence of association when adult BMI was not adjusted for, whereas a strong negative association emerged after adjustment. This statistical artefact has been described as the 'reversal paradox' (94) in which the association between two variables is reversed, diminished or enhanced by the adjustment for another related variables (95). Adult BMI is not a true confounder in the association between BW and abdominal adiposity in adulthood because it is not independently related to both variables. In fact, when both BW and BMI are in the same model with outcomes related to non-communicable diseases, BW often becomes negatively associated with the outcome. This should be interpreted as an effect of post-natal weight gain, rather than a protective effect of BW *per se* (96), given that in the analyses that were unadjusted for BMI there was no effect of BW (97–100). The results of our meta-analyses of WHR clearly show that this is the case.

An analogous finding was observed in the meta-analysis for absolute abdominal adiposity, measured through WC. BW showed a positive association with WC in both sexes before adjusting for adult BMI, but there was no statistical evidence of association after adjustment. The apparent disappearance of the association after adjustment would also be consistent with the reversal paradox, signalling that post-natal growth also plays a role. These findings from the meta-analyses must be interpreted with caution. We identified moderate heterogeneity for the overall effect, although performing a meta-regression is not a recommended option considering the small number of studies included (101).

In summary, the meta-analyses showed that the adjustment for adult BMI leads to disappearance of the initially

positive association between BW and WC, showing that both BW and post-natal growth are important for absolute central adiposity. In contrast, we observed a negative association with WHR after controlling for adult BMI, whereas unadjusted analyses showed no statistical evidence of association. These findings could suggest that post-natal growth is important in relative central adiposity, whereas BW does not play a role. Therefore, BW could be associated with larger adult size in general, including both waist and HCs.

This is consistent with results from the cohorts showing a stronger association between BW and lean mass than with fat mass, which could be due to either greater concentration of lean mass in non-abdominal regions or accumulation of fat mass in the abdomen (86).

Our review has some limitations. All studies included in the analyses are observational; therefore, we cannot rule out the possibility that results were affected by residual confounding. Most articles failed to describe follow-up rates or non-response rates, so we could not determine if selection bias may have influenced their findings. Control for confounding varied widely across studies, and some of them did not present estimates adjusted for important confounders such as socioeconomic status and maternal characteristics. We identified very few studies from low- and middle-income countries, where the effect of birth size on later adiposity may be different than that observed in high-income countries (36,83).

The small sample sizes of some studies, especially those using imaging methods, could explain the lack of statistical associations; it is noteworthy that none of the articles in the review reported power calculations. Lastly, we could not obtain a pooled effect for several of the associations because of the limited number of studies assessing the same combination of exposure and outcome. Also because of the few studies available, we could not perform meta-regressions to better explore the heterogeneity between studies.

The strengths of this review include its systematic nature, the restriction to studies with reliable ascertainment of size at birth and the overall proportion of high methodological quality studies. Most of the studies reviewed used standard protocols for assessment of anthropometric measurements (102,103), so that these were generally comparable across studies. We were able to compare pooled effects between those studies that adjusted for adult BMI and those that not, as adult BMI is an important factor in the causal path between BW and abdominal adiposity. Finally, publication bias was found not to be important for most outcomes when we examined the effect of study size on the estimates.

In conclusion, epidemiological and clinical studies show that abdominal obesity is an important risk factor for various diseases. Because dietary interventions for obese patients have limited success (19,104), it is also important to identify early risk factors for later abdominal adiposity that may be amenable to intervention through a life course approach. Given the potential impact of post-natal growth, further research is needed to identify different growth trajectories that lead to abdominal adiposity, as well as studies on interactions of foetal and post-natal growth patterns (105). More studies from low- and middle-income countries are needed, and in particular more studies using imaging methods to assess abdominal adiposity.

Conflict of interest statement

The authors declare no conflict of interest.

Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12109

Figure S1. Funnel plot for the association between birth weight and waist circumference without (1A) or with adjustment (1B) for adult body mass index (BMI) among adults. February 2013.
Figure S2. Sensitivity analysis for the association between birth weight and waist circumference without (2A) or with adjustment (2B) for adult body mass index (BMI) among adults. February 2013.
Figure S3. Funnel plot for the association between birth weight and waist-to-hip ratio without (3A) or with adjustment (3B) for adult body mass index (BMI) among adults. February 2013.
Figure S4. Sensitivity analysis for the association between birth weight and waist-to-hip ratio without (4A) or with adjustment (4B) for adult body mass index (BMI) among adults. February 2013.
Table S1. Definition of the anthropometric outcomes measured.
Table S2. Methodological quality of the papers assessed using the Newcastle–Ottawa Scale.
Table S3. Description of papers selected by systematic review on effects of birth size on anthropometric measurements of adult abdominal adiposity. February 2013.
Table S4. Descriptive information of papers* selected by systematic review on effects of birth size on abdominal fat measured by abdominal magnetic resonance imaging (MRI), computed tomography, dual-energy X-ray absorptiometry (DXA) or ultrasound. February 2013.
Table S5. Studies assessing the association between birth weight and waist circumference or waist-to-hip ratio among adults, with and without adjustment for adult body mass index (BMI). February 2013.

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