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REVIEW

The impact of cesarean section on offspring overweight and obesity: a systematic review and meta-analysis

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Studies have reported inconsistent results concerning the association of cesarean section with offspring obesity. We performed a systematic review and meta-analysis to examine whether cesarean section increases the risk of later overweight and obesity. Pubmed, Embase and Web of Science were searched using different combinations of two groups of keywords: 'cesarean' and 'overweight/obesity'. Cohort or case–control studies that reported the association of cesarean section with childhood (3–8 years), adolescence (9–18 years) and/or adult (>19 years) overweight/obesity were eligible. Where possible, adjusted risk estimates were pooled using a random effects model; otherwise unadjusted estimates were pooled. Statistical heterogeneity was assessed with I^2 statistics; the values of 25%, 50% and 75% were considered to indicate low, medium and high heterogeneity, respectively. We conducted a subgroup analysis to identify the sources of heterogeneity according to study quality defined on the basis of the Newcastle-Ottawa Scale. In total, two case–control and seven cohort studies were identified for the literature review and 15 separate risk estimates were included in the meta-analysis. The overall pooled odds ratio (OR) of overweight/obesity for offspring delivered by cesarean section compared with those born vaginally was 1.33 (95% confidence interval (CI) 1.19, 1.48; $I^2 = 63\%$); the OR was 1.32 (1.15, 1.51) for children, 1.24 (1.00, 1.54) for adolescents and 1.50 (1.02, 2.20) for adults. In subgroup analysis, the overall pooled OR was 1.18 (1.09, 1.27; $I^2 = 29\%$) for high-quality studies and 1.78 (1.43, 2.22; $I^2 = 24\%$) for medium-quality (P for interaction = 0.0005); no low-quality studies were identified. The ORs for children, adolescents and adults all tended to be lower for high-quality studies compared with medium-quality studies. Our results indicated that cesarean section was moderately associated with offspring overweight and obesity. This finding has public health implications, given the increase in cesarean births in many countries.

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Keywords: cesarean section; offspring; systematic review; meta-analysis

INTRODUCTION

In recent years, concerns have been raised about the potential long-term impacts of cesarean section on the health of offspring, especially given the widespread increase in the number of cesarean births.[1] In many countries, the cesarean section rate has exceeded 15%,[2] the maximum recommended level,[3] and cesarean delivery has become even more common than vaginal delivery in some settings.[4]

The most plausible mechanism linking cesarean section with later diseases is the hygiene hypothesis.[5] The basis of this hypothesis is that during the birth process the mouths of newborns delivered vaginally are directly exposed to maternal vaginal and intestinal microbiota, whereas the mouths of newborns delivered by cesarean section are exposed to non-maternally derived environmental bacteria. This early-life difference in bacteria acquisition could have lasting impacts on offspring gut microbiota composition and its related disorders.[6]

A series of previously published systematic reviews and meta-analyses have shown that cesarean section is associated with a modestly increased risk of asthma,[7] allergic rhinitis,[8] food allergy or atopy[8] and type 1 diabetes mellitus[9] in later life. These risks have been explained by the common hygiene hypothesis. Specifically, in cesarean-delivered newborns, the lack of or delay in early-life exposure to maternal vaginal and intestinal bacteria could alter the normal development of their immune system and thus increase susceptibility to atopic, allergic and autoimmune diseases.[5]

Recent studies suggests that gut microbiota might have a crucial role in the pathophysiology of obesity by influencing gut energy harvest from diet,[10–12] and cesarean section has been speculated to be associated with offspring obesity on the basis of the hygiene hypothesis.[6,13] Several epidemiological studies have examined the association between cesarean section and later overweight/obesity,[14–21] yet their conclusions as well as the magnitude of the association were somewhat inconsistent, possibly due to insufficient statistical power, inadequate adjustment for confounding factors, or variations in study quality. In this situation, a systematic review and meta-analysis is needed to summarize the available evidence. We conduct this review to comprehensively assess whether there exists an association between cesarean section and overweight/obesity in offspring, and to determine the strength of the association.

MATERIALS AND METHODS

The study was done and reported according to the proposal for conducting and reporting meta-analyses of observational studies in epidemiology.[22]

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Literature search and inclusion criteria

We searched for relevant publications using Pubmed, Embase and Web of Science databases from inception to the end of June 2012. We used different combinations of two groups of free text search terms: (1) 'cesarean', 'caesarean', 'cesarian', 'caesarian', 'delivery mode', 'mode of delivery', 'delivery method', 'method of delivery', 'delivery type' or 'type of delivery'; and (2) 'overweight', 'over weight', 'over-weight' or 'obesity'. We had no additional restrictions on language. After excluding duplicate records, we scanned titles and abstracts to determine the relevance of content, and then retrieved full texts of potentially relevant articles for detailed evaluation. We also hand-searched the references of the retrieved articles for additional relevant studies. All searches were conducted by HL and double-checked by YZ. The two reviewers reached a consensus at each stage before proceeding.

Studies were considered for inclusion if: (1) the study was an original research published in English or in other languages with an English abstract; (2) the study used a cohort (historical or prospective) or case–control design and examined the association of cesarean section compared with vaginal delivery with overweight/obesity in childhood (3–8 years), adolescence (9–18 years) and/or adult (>19 years); and (3) the authors reported ORs with 95% confidence intervals (CIs) or other effect measures such as prevalence ratios, or reported necessary information from which unadjusted ORs and 95% CIs could be calculated.

Data extraction

Information on effect estimates and study characteristics was independently extracted by two reviewers (HL and YZ) using a pretested structured form. Discrepancies were resolved on the basis of a consensus discussion between the two reviewers or with the third reviewer (JL). Where possible, we extracted the adjusted effect estimates; otherwise, we extracted or calculated the unadjusted one. If several multivariate-adjusted estimates were available, we extracted the most fully adjusted one only. If a study simultaneously reported several estimates based on different cohorts, we extracted all estimates. If a study longitudinally assessed overweight/obesity risk for children, adolescents and adults based on the same cohort, we extracted all estimates. If a study reported more than one estimate within the same group (that is, childhood, adolescence or adulthood), we extracted only the estimate with the longest follow-up. If a study divided participants into three mutually exclusive groups (that is, normal weight, overweight and obesity), and estimated both the overweight and obesity risks using the normal weight group as a reference, we extracted the latter. In addition to overall estimates, we also extracted gender-specific estimates whenever possible. The extracted information on study and participant characteristics included study setting, population source, sample size, age at assessment, outcome assessment and adjustment for confounders.

Quality assessment

The quality of each included study was independently assessed by two reviewers (HL and YZ) according to the Newcastle-Ottawa Scale.[23] Separate Newcastle-Ottawa Scale scales had been developed for case–control and cohort studies; both scales awarded a maximum of 9 stars to each study: 4 stars for study group selection, 2 for the comparability between groups and 3 for the ascertainment of exposure for case–control studies or the ascertainment of outcome measure for cohort studies. We defined $\geqslant$7 stars as high quality, 4–6 stars as medium and $\leqslant$3 stars as low. Any discrepancies concerning the quality assessment between the two reviewers were resolved after a discussion with the third reviewer (JL).

Data analyses

The effect estimates of cesarean section on later obesity were likely to be overestimated if a study did not adjust for or did not adequately adjust for crucial confounding factors such as maternal body mass index and indicators of social economic status.[15] Therefore, the most completely adjusted effect estimates were used to calculate the log ORs and corresponding s.e.'s for all syntheses, where possible; otherwise, unadjusted estimates were used. A random-effects model meta-analysis based on the generic inverse variance method was done to estimate the pooled ORs for all syntheses. Statistical heterogeneity across estimates was assessed by I^2 statistics, and the values of 25%, 50% and 75% indicated low, medium and high heterogeneity, respectively.[24]

Our primary analysis was to estimate: (1) overall pooled OR for offspring delivered by cesarean versus vaginal delivery; and (2) specific pooled ORs for children, adolescents and adults. We explored the sources of statistical heterogeneity for these pooled ORs by conducting subgroup analyses according to the study design (cohort versus case–control), type of outcome measures (overweight versus obesity), type of effect estimates (adjusted versus unadjusted) and study quality (high versus medium). We conducted subgroup meta-analyses by pooling gender-specific estimates to assess whether the association varied between male and female participants. The heterogeneity across subgroup pooled estimates was examined using chi-square tests with $n-1$ degrees of freedom, where n is the number of subgroups.[25]

We also conducted sensitivity analyses to assess the robustness of the results by excluding: (1) the study carrying the greatest weight; and (2) the study with $\geqslant$2 effect estimates extracted from the same cohort, as these estimates were not independent.[26] Publication bias was assessed using funnel plot and Begg's rank correlation test.[27] The influence of potential publication bias on pooled results was assessed using the trim-and-fill method. The Begg's test and trim-and-fill analysis were performed using R statistical software (version 2.15.1) with the Metafor package (version 1.6-0),[28] and all other analyses using RevMan 5. *P* values were two-sided, with a significance level of 0.05.

RESULTS

Our search yielded a total of 2454 non-duplicate records (Figure 1). After reviewing the titles, abstracts and full texts, eight studies[14–21] met the inclusion criteria for this literature review and meta-analysis; we also included one unpublished study.[29] In total, there were seven cohort[14–17,19,20,29] and two case–control[18,21] studies. Rooney *et al.*[19] longitudinally evaluated the impact of cesarean section on childhood, adolescence and adulthood obesity, from which three estimates were extracted. Barros *et al.*[15] followed three cohorts of children born in 1982, 1993 and 2004 and reported six separate obesity risk estimates for children, adolescents or adults, from which five estimates were extracted (the adolescent obesity risk was assessed twice for individuals of the 1993 cohort, and only the estimate of the longest follow-up was extracted). Huh *et al.*[17] reported the risks of both overweight and obesity with the normal weight as a reference group using a multinomial logistic regression model, from which only the latter was extracted. In the remaining six studies, five reported childhood overweight/obesity risk[14,18,20,21,29] and one reported adult obesity risk.[16] Overall, 10 childhood,

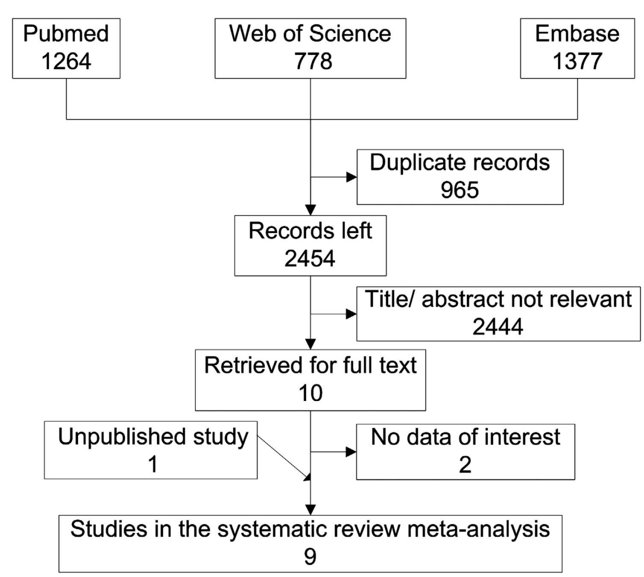

Figure 1. Literature search and study selection flowchart.

Table 1. Characteristics of studies included in the meta-analysis

Studies	*Study and population description*	*Quality*	*No. of participants*	*Range of or mean age (years)*	*Outcome assessment*	*Adjustment for confounders*	*Risk estimates (95% CI)*
Ajslev *et al.*[14]	PCS; Danish National Birth Cohort; children born during 1997–2002, singleton, term delivery; excluded mothers having diabetes, gestational diabetes or preeclampsia	High	VD: 24829 CS: 3525	7.0	Overweight; defined according to IOTF cutoffs	Maternal age, socioeconomic status, BMI (Body Mass Index), gestational weight gain, smoking; father's BMI; child's parity, birth weight, sex, breastfeeding and age at follow-up	Multiple logistic regression; adjusted OR: 1.01 (0.82, 1.24)
Barros *et al.*[15]	PCS; three birth-cohort studies of individuals born in 1982, 1993 and 2004 in southern Brazil	High	4y/1982 cohort: 4742 4y/1993 cohort: 1237 4y/2004 cohort: 3756 11y/1993 cohort: 4100 15y/1993 cohort: 4349 23y/1982 cohort: 4297	4, 11, 15, 23	Obesity at 4, 11 and 15 years defined according to WHO standard; obesity at 23 years defined as BMI$\geqslant$30 kg m^{-2}	Family income and maternal schooling at birth, type of payment for delivery, maternal skin color, birth order, maternal age, maternal prepregnancy weight, maternal height, smoking during pregnancy, birth weight	Multiple poisson regression; adjusted prevalence ratios: 4y/1982 cohort: 1.22 (0.97, 1.53) 4y/1993 cohort: 1.31 (0.90, 1.92) 4y/2004 cohort: 1.21 (0.99, 1.48) 11y/1993 cohort: 1.06 (0.86, 1.30) 15y/1993 cohort: 1.23 (0.98, 1.54) 23y/1982 cohort: 1.10 (0.87, 1.41)
Goldani *et al.*[16]	PCS; community participants, Brazil; singletons born during June 1978-May 1979	High	VD: 1400 CS: 657	23.9 ± 0.71	Obesity; defined as BMI$\geqslant$30 kg m^{-2}	Maternal education and smoking during pregnancy; adult's birth weight, sex, physical activity, smoking, education and income	Multiple poisson regression; adjusted prevalence ratio: 1.58 (1.23, 2.02)
Huh *et al.*[17]	PCS; project viva, U.S.; singletons whose mothers were fluent in English	Medium	VD: 982 CS: 284	VD: 3.3 ± 0.38 CS: 3.3 ± 0.32	Obesity; defined as age-sex-specific BMI $\geqslant$95th percentile of U.S. national reference	Maternal age, race/ethnicity, education, maternal BMI, gestational diabetes, gestational weight gain, gestation length; birth weight, duration of breastfeeding, paternal BMI, child age and sex	Multiple logistic regression; adjusted OR: 2.10 (1.36, 3.23)
Li *et al.*[18]	CCS; cases were from national survey on obesity, China; excluded children with secondary or pathological obesity	Medium	Cases: 3414 Controls: 3414	0 – 7	Obesity; defined according to National Center for Health Statistics/WHO standard	Maternal BMI, paternal BMI, birth weight, excess hours of watching TV, intensity of outdoor exercise, sleeping and eating behavior	Multiple logistic regression; adjusted OR: 1.47 (1.19, 1.83)
Li *et al.*[29] unpublished study	PCS; 2 southern provinces in China; singletons born in 1993 with gestational age$\geqslant$28 weeks	High	VD: 142680 CS: 38700	VD: 5.0 ± 0.67 CS: 4.8 ± 0.70	Overweight; defined according to IOTF cutoffs	Maternal age, height, weight at first prenatal visit, weight gain during pregnancy, education, occupation, parity, folic acid supplementation; child's gender, birth length, birth weight, gestational age and age at follow-up	Multiple logistic regression; adjusted OR: 1.13 (1.08, 1.18)
Rooney *et al.*[19]	PCS; 27 clinics and a hospital in the Midwest, U.S.; singletons born since 1988; excluded mothers with gestational diabetes, preeclampsia and cervical incompetence	Medium	Childhood: 359; Adolescence: 450; Adulthood: 453	Childhood: 4 – 5; Adolescence: 9 – 14; Adulthood: 19 – 20	Childhood and adolescence obesity defined as BMI$\geqslant$85th percentile of all participants; adulthood obesity as BMI$\geqslant$30.0 kg m^{-2}	Childhood obesity model: maternal marital status at birth, insurance status at birth and child's gender	Logistic regression; adjusted OR for childhood: 2.49 (1.10, 5.62); Unadjusted OR for adolescence: 1.32 (0.67, 2.61); Unadjusted OR for adulthood: 2.78 (1.30, 5.94)
Steur *et al.*[20]	PCS; PIAMA birth cohort study, Netherlands; children born in 1996/1997	Medium	VD: 1542 CS: 145	8.0	Overweight; defined according to IOTF cutoffs	None	Unadjusted OR: 1.7 (1.1, 2.6)
Zhou *et al.*[21]	CCS; 10 kindergartens in a city in southern China; excluded children with secondary obesity; with digestive system, metabolic, cardiovascular and endocrine diseases; or with severe rickets	Medium	Cases: 81 Controls: 81	3–6	Obesity; defined according to IOTF cutoffs	Maternal age, education, pregnancy complication, father's education, obesity status of parents, family income, single birth, asphyxia birth injuries, birth weight, gestational age, types of feeding within 6 months	Multiple logistic regression; adjusted OR: 5.23 (1.24, 22.04)

Abbreviations: BMI, body mass index; CCS, case–control study; CS, cesarean section; IOTF, International Obesity Task Force; PCS, prospective cohort study; VD, vaginal delivery; y, years.

2 adolescence and 3 adulthood estimates were included in the meta-analysis; 3 estimates were for overweight and 12 for obesity. Moreover, five sets of gender-specific estimates for children, one set for adolescents, and one set for adults from three cohort studies were included in subgroup meta-analysis.[14,15,29]

Literature review

Of the nine studies included, three were conducted in China,[18,21,29] two in Brazil,[15,16] two in the United States,[17,19] one in Denmark[14] and one in Netherlands;[20] adult obesity was defined as a body mass index $\geqslant 30\,\mathrm{kg\,m^{-2}}$,[15,16,19] and overweight/obesity for children and adolescents was mainly defined by International Obesity Task Force cutoffs or WHO growth references.[14,15,18,20,21,29] The two Brazil studies used prevalence ratios as effect measures,[15,16] and the remaining seven studies used ORs.[14,17–21,29] Four studies were assessed to be high-quality[14–16,29] and five medium-quality;[17–21] no studies were deemed to be low-quality. The detailed characteristics for each study are shown in Table 1.

The five medium-quality studies included two case–control[18,21] and three cohort[17,19,20] studies. Of the five studies, four were likely to have overestimated the obesity risk due to inadequate adjustment for important confounding factors such as social economic status, birth weight or maternal body mass index;[18–21] one followed only ~40% of the participants of the original cohort, leading to a possibility of selection bias.[17] The four high-quality studies all received 9 stars. The seven sets of gender-specific estimates were all extracted from high-quality studies.

Meta-analysis

Overall risk. The pooled OR of overweight/obesity for offspring delivered by cesarean section compared with those born vaginally was 1.33 (95% CI 1.19, 1.48). We observed a moderate to high heterogeneity ($I^2 = 63\%$) across the 15 estimates (Figure 2). In subgroup analysis, the pooled OR was 1.29 (95% CI 1.16, 1.44; $I^2 = 59\%$) for cohort studies and 2.25 (95% CI 0.70, 7.28; $I^2 = 66\%$) for case–control (*P* for interaction = 0.35); the pooled OR of overweight was 1.22 (95% CI 0.99, 1.50; $I^2 = 64\%$) and the pooled OR of obesity was 1.37 (95% CI 1.21, 2.56; $I^2 = 45\%$) (*P* for interaction = 0.33); the pooled OR was 1.28 (95% CI 1.15, 1.43; $I^2 = 63\%$) for adjusted estimates and 2.00 (95% CI 1.43, 2.81; $I^2 = 0\%$) for unadjusted (*P* for interaction = 0.01); the pooled OR

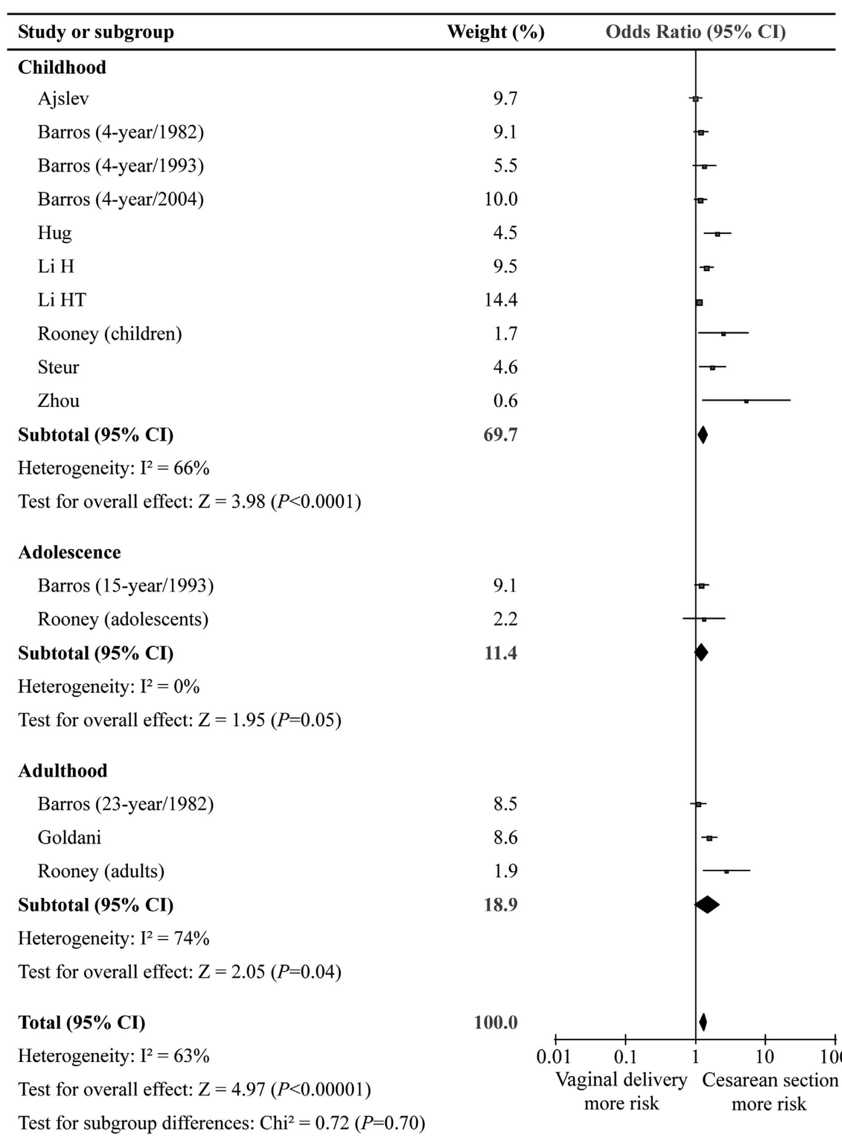

Figure 2. Cesarean section compared with vaginal delivery on offspring overweight and obesity.

was 1.18 (95% CI 1.09, 1.27; $I^2 = 29\%$) for high-quality studies and 1.78 (95% CI 1.43, 2.22; $I^2 = 24\%$) for medium-quality, and the difference was statistically significant (*P* for interaction = 0.0005) (Table 2). In sensitivity analyses, the pooled OR (1.36, 95% CI 1.16, 1.60) was slightly changed after excluding non-independent estimates from Rooney's and Barros's studies;[15,19] when we further excluded the study carrying the greatest weight,[29] the pooled OR (1.45, 95% CI 1.18, 1.77) was not substantially changed.

Childhood risk. The pooled OR for childhood overweight/obesity was 1.32 (95% CI 1.15, 1.51). We observed a moderate to high heterogeneity ($I^2 = 66\%$) across the 10 estimates (Figure 2). In subgroup analyses, the pooled OR was 1.26 (95% CI 1.10, 1.44; $I^2 = 59\%$) for cohort studies and 2.25 (95% CI 0.70, 7.28; $I^2 = 66\%$) for case–control (*P* for interaction = 0.33); the pooled OR of overweight was 1.22 (95% CI 0.99, 1.50; $I^2 = 64\%$) and the pooled OR of obesity was 1.40 (95% CI 1.17, 1.67; $I^2 = 50\%$) (*P* for interaction = 0.31); the pooled OR was 1.29 (95% CI 1.12, 1.48; $I^2 = 65\%$) for adjusted estimates and 1.70 (95% CI 1.11, 2.61) for unadjusted (*P* for interaction = 0.23); the pooled OR for high-quality studies (1.13, 95% CI 1.09, 1.18; $I^2 = 0\%$) was lower than that for medium-quality studies (1.78, 95% CI 1.39, 2.28; $I^2 = 30\%$), and the difference was statistically significant (*P* for interaction = 0.0004) (Table 2). In sensitivity analysis, the pooled OR (1.39, 95% CI 1.17, 1.65) was slightly changed after excluding the study with the greatest sample size.[29]

Table 2. Subgroup analysis for total and childhood estimates

Subgroups[a]	*Number of estimates*	*Pooled OR (95% CI)*	I^2 (%)	P *values*[b]
Total estimates				
Design				0.35
Cohort	13	1.29 (1.16, 1.44)	59	
Case–control	2	2.25 (0.70, 7.28)	66	
Outcome measure[c]				0.33
Overweight	4	1.22 (0.99, 1.50)	64	
Obesity	11	1.37 (1.21, 1.56)	45	
Type of estimates				0.01
Adjusted	12	1.28 (1.15, 1.43)	63	
Unadjusted	3	2.00 (1.43, 2.81)	0	
Study quality				0.0005
High	8	1.18 (1.09, 1.27)	29	
Medium	7	1.78 (1.43, 2.22)	24	
Childhood estimates				
Design				0.33
Cohort	8	1.26 (1.10, 1.44)	59	
Case–control	2	2.25 (0.70, 7.28)	66	
Outcome measure[d]				0.31
Overweight	4	1.22 (0.99, 1.50)	64	
Obesity	6	1.40 (1.17, 1.67)	50	
Type of estimates				0.23
Adjusted	9	1.29 (1.12, 1.48)	65	
Unadjusted	1	1.70 (1.11, 2.61)	–	
Study quality				0.0004
High	5	1.13 (1.09, 1.18)	0	
Medium	5	1.78 (1.39, 2.28)	30	

Abbreviations: CI, confidence interval; OR, odds ratio. [a]Subgroup analyses for adolescence and adulthood estimates were not conducted due to limited number of studies. [b]*P* values for testing heterogeneity between subgroups were calculated using χ^2 tests. [c]Overweight defined as body mass index $\geqslant$85th percentile for children (adolescents) or $\geqslant 25.0\,kg\,m^{-2}$ for adults; obesity as body mass index $\geqslant$95th percentile for children (adolescents) or $\geqslant 30.0\,kg\,m^{-2}$ for adults. [d]Overweight and obesity were defined as body mass index $\geqslant$85th and $\geqslant$95th percentile, respectively.

Adolescence and adulthood risk. The pooled OR for adolescence and adulthood obesity was 1.24 (95% CI 1.00, 1.54; $I^2 = 0\%$) and 1.50 (95% CI 1.02, 2.20; $I^2 = 74\%$), respectively (Figure 2). We did not conduct formal subgroup analyses and interaction tests for adolescence and adulthood estimates due to the limited number of available studies, but the ORs for high-quality studies (1.23 (0.98, 1.54) for adolescents; 1.32 (0.92, 1.88) for adults) also appeared to be relatively lower than those for medium-quality studies (1.32 (0.67, 2.61) for adolescents; 2.78 (1.30, 5.59) for adults).

Subgroup meta-analysis regarding gender-specific estimates. The pooled OR was 1.16 (95% CI 1.08, 1.24; $I^2 = 5\%$) for male offspring and 1.13 (95% CI 1.07, 1.19; $I^2 = 0\%$) for female; the difference was not significant (*P* for interaction = 0.54) (Table 3). For childhood obesity, the pooled OR was 1.18 (95% CI 1.07, 1.30; $I^2 = 20\%$) for male and 1.12 (95% CI 1.06, 1.19; $I^2 = 0\%$) for female (*P* for interaction = 0.39) (Table 3). For adolescence and adulthood, the gender-specific pooled ORs were not calculated due to the limited number of available studies.

Publication bias. For childhood estimates, the funnel plot (Figure 3) indicated a publication bias, and the Begg's test was significant ($P = 0.009$). However, the trim-and-fill analysis still showed a significant effect (OR = 1.20, 95% CI 1.00, 1.44; $P = 0.048$), indicating that the publication bias was not likely to substantially affect the results. For adolescent and adulthood estimates, we did not assess a publication bias due to the limited studies available.

Table 3. Subgroup meta-analyses for gender-specific estimates

Subgroups[a]	*Number of estimates*	*Pooled OR (95% CI)*	I^2 (%)	P *values*[b]
Total estimates				*0.54*
Male	7	1.16 (1.08, 1.24)	5	
Female	7	1.13 (1.07, 1.19)	0	
Childhood estimates				*0.39*
Male	5	1.18 (1.07, 1.30)	20	
Female	5	1.12 (1.06, 1.19)	0	

Abbreviations: CI, confidence interval; OR, odds ratio. [a]Subgroup meta-analyses for adolescence and adulthood gender-specific estimates were not conducted due to limited number of studies. [b]*P* values for testing heterogeneity between subgroups were calculated using chi-square tests.

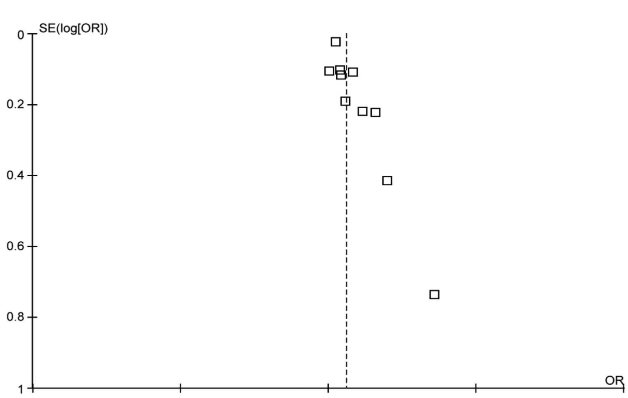

Figure 3. Funnel plot for childhood estimates.

DISCUSSION

In this systematic review and meta-analysis, we found that cesarean section versus vaginal delivery was moderately associated with an increased risk of subsequent overweight and obesity in offspring.

Our overall analysis showed that cesarean section was associated with a 33% increased risk of subsequent overweight and obesity. The magnitude of this risk remained almost unchanged after removal of the non-independent estimates from Rooney's and Barros's study.[15,19] Because a moderate to high level of heterogeneity existed across individual risk estimates, we conducted various subgroup analyses to explore the sources of heterogeneity. We observed that the heterogeneity was not reduced in at least one stratum of each pair of subgroups stratified by design, type of outcome measures and type of estimates, suggesting that the overall heterogeneity could not be explained by these characteristics. However, the heterogeneity in both high- and medium-quality strata was at a rather lower level, indicating that the overall heterogeneity could likely be explained by variations in study quality. The magnitude of the pooled risk for high-quality studies was modest in size and substantially lower than that for medium quality. We assessed the robustness of the pooled results from high-quality studies by excluding the study with the largest sample size,[29] and also observed a modestly increased obesity risk (OR = 1.21, 95% CI, 1.09, 1.35). We further conducted a subgroup meta-analysis regarding gender-specific estimates that were all from high-quality studies, and again observed a similar-sized increased risk in both male and female participants.

Moreover, we conducted separate pooled analyses to investigate whether the moderately increased obesity risk persisted from childhood to adulthood, and observed similar pooled risk estimates for children, adolescents and adults (range: 1.24–1.50). For childhood obesity, the pooled risk estimate for high-quality studies was more modest and substantially lower than that for medium-quality studies; the magnitude of the risk was similar in both male and female individuals. For adolescence and adulthood obesity, modestly increased risks were also observed for high-quality studies.

The underlying mechanism of the association between cesarean section and later obesity remains unclear. However, the hygiene hypothesis provides one possible mechanism.[5,6] Cesarean section deprives the opportunity for the newborn to be exposed to maternal vaginal feces, the bacteria from which are a major source for the intestinal bacteria of the newborn;[5] consequently, compared with those born vaginally, newborns delivered by cesarean section had fewer intestinal Bifidobacteria and Bacteroides,[30] both of which were reported to be protective factors against later obesity.[31] In addition to the hygiene hypothesis, the association was also supported by indirect epidemiological evidence.[32] Cesarean section was associated with a lower umbilical leptin concentration[33] and a reduced rate of early breastfeeding,[34] both of which were reported to be associated with an increased risk of later obesity.[35,36]

To the best of our knowledge, this is the first systematic review and meta-analysis based on currently available observational studies in different settings that assessed the association of cesarean section with later overweight/obesity. Our review and meta-analysis has limitations. First, we might have missed some studies published in non-English language. Second, some non-independent longitudinal results were included in calculating childhood, adolescence and adulthood pooled effect sizes, which may lead to biased subgroup estimates. We observed that the pooled ORs for children were almost the same with or without inclusion of studies with longitudinal estimates (1.32 (95% CI 1.15, 1.51) and 1.32 (95% CI 1.12, 1.56), respectively); however, we did not assess the robustness of the pooled ORs for adolescents and adults due to the limited studies available in the literature. In addition, as in any meta-analysis of observational studies, we could not eliminate the possibility of residual confounding effects, even though adjusted effect estimates from most studies were used for data syntheses. However, our analyses consistently showed that cesarean section was moderately associated with subsequent obesity risk, and this risk did not vary by gender and might persist from childhood to adulthood.

In summary, this systematic reviewe and meta-analysis of observational studies indicated cesarean section as a moderate early-life risk factor for later overweight and obesity. The causal relationship between cesarean section and obesity in offspring, especially in adolescents and adults, needs to be examined in future prospective studies. It is worthy to note that even a modest risk would have significant public health implications, given the high prevalence of both cesarean section and obesity in many countries.[2,37] Future studies also need to explore the underlying mechanism of cesarean–obesity association and to investigate whether the associations of cesarean section with various offspring health outcomes share a common pathway.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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