Birth by caesarean section and offspring overweight and obesity in adult life: a systematic review and meta-analysis

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Abstract: Overweight/obesity is one of the most important health problem worldwide. Birth by cesarean section has been shown to influence long-term health outcome including obesity. The aim of this systematic review-meta-analysis is to examine whether cesarean section increases the risk of offspring’s overweight/obesity.

The study follows the PRISMA and MOOSE guidelines. A systematic literature search was conducted on Scopus, PubMed, and WoS until December 2020. For inclusion, studies must have reported either (I) both Birth by cesarean section and adult (≥ 18 years) offspring BMI, (II) cohort or case-control study design and (III) a risk estimate. Heterogeneity testing was performed using Cochran’s Q and I2 statistics. Publication bias was assessed by Egger’s test and Begg’s test. Meta-analysis was performed through a random effect model.

Eleven studies with a combined population of 180,408 subjects were included in the meta-analysis. The overall analysis (n = 18) yielded a combined risk estimate for overweight/obesity of 1.19 (95% CI 1.08-1.31) and the test of heterogeneity resulted Q=53,37 (I2 = 70,37 %, P≤0.0001). The risk of offspring obesity is 1.23 (95% CI 1.09-1.39) and the test of heterogeneity resulted Q=39.50 (I2= 72,15%, P≤0.0001).

Children born by cesarean section have an increased risk of developing obesity in adulthood

Keywords: cesarean section, body mass index, obesity, meta-analysis

1. Introduction

Overweight and obesity represent relevant public health concerns worldwide. The prevalence of obesity has been increasing significantly in the past two decades and overweight/obesity is now recognized as a global epidemic. In 2016, 13% of the world’s adult population were obese. The prevalence of obesity was about 30% in China and in USA and 25% in Europe. [1, 2]. A recent NEJM report estimated that, by 2030, nearly half of adults in the USA will have obesity, with a prevalence not below 35% in any state, and nearly one in four will have severe obesity, with a prevalence higher than 25% in 25 states [3]. Overweight and obesity are associated with an increased risk of Non-Communicable Diseases (NCDs) and are responsible for about 4 million deaths every year worldwide. Reducing by one third premature deaths by NCDs is one of the targets of the 2030 Agenda for Sustainable Development of the United Nations [4, 5, 6]. Birth by cesarean section (CS) has been shown to influence health outcome; CS rates are increasing globally, accounting for more than 20% worldwide births.[7]. Given the increasing use of CS and the growing
evidence on its effects on the health of mother and the effects on children, a deeper knowledge of its long-term effects/impact on offspring’s adulthood health status has become crucial [8]. Recent literature showed that babies born by CS have different hormonal and bacterial patterns and that this fact can change neonatal physiology and health outcomes [9-13]. Subjects born by CS present increased risk of immune-related diseases in later life such as allergies [9], asthma [10], celiac disease [11], type 1 diabetes [12], and metabolic and cardiovascular disease risk factors such as elevate systolic blood pressure, excess fat mass and high body mass index BMI (13). Two meta-analyses, published in 2012 and 2015, to date investigate the association between CS and BMI in offspring, considering overall the period of childhood, adolescence, and to some extent adulthood [14, 15]. A recent meta-analysis (2014) found a strong association between CS and increased BMI of offspring’s adulthood, reporting a mean increase of 0.44 kg/m² in BMI of adults born by CS (95% CI: 0.17, 0.72; P = 0.002; I² = 39%) [16] whereas a recent (2015) systematic review found a slight influence between CS and the risk of overweight and obesity, which changes with age [17]. A recent update [18] of the previous review [17], included articles only to 2019, and founding similar results. Since then, several other studies with wider sample sizes and longer follow-up times have been published. Therefore, a systematic review and meta-analysis was conducted to summarize the evidence on the association between CS delivery and offspring BMI in adulthood and to assess the risk of overweight and obesity in offspring’s adulthood.

2. Materials and Methods

Literature search strategy

Our literature search was aimed at identifying available research studies that investigated the effects of CS on offspring BMI. We identified the studies included in our meta-analysis by searching, without restrictions, multiple literature databases including Scopus, Web of Knowledge and PubMed, and selecting all the articles published until 2nd January 2021. We searched for abstracts and articles including the following terms: caesarean OR cesarean OR caesarian OR cesarian) AND (obesity OR Body Mass Index OR Overweight) AND (Adult) AND (Offspring). In addition, we supplemented this research by checking the references cited in retrieved papers and recent reviews.

Data extraction

We systematically reviewed and selected the studies meeting the following eligibility criteria: (I) assessed both mode of delivery and adult (≥ 18 years) offspring BMI, (II) used a cohort or case–control study design and (III) reported a risk estimate (hazard ratio, relative risk, prevalence ratio or OR) for the association between mode of delivery and BMI, as well as its 95% CI. When studies reported data from the same population, only the most comprehensive study was enrolled. Studies providing insufficient or overlapping data and conference abstract were excluded. Two investigators (M. C and B. DS) reviewed the eligibility of all studies according to the predetermined eligibility criteria independently. We extracted information about study characteristics (study name, authors, publication year, study design), study population characteristics, type of exposure (mode of delivery), outcomes (BMI…), and variables of adjustment. The mode of delivery was categorized in vaginal delivery (VD), as reference (including natural, forceps and vacuum extraction), and cesarean section (CS) including Planned CS (elective) and non-planned CS (non-elective). The outcomes of interest in our analysis were overweight and obesity classified according to the International Classification of BMI [19], namely ‘overweight’ (BMI=25.0-29.9) and ‘obese’ (BMI≥30).

Quality Evaluation
We used the Newcastle-Ottawa Scale Assessment [20] for the evaluation of quality of the enrolled studies. Newcastle-Ottawa Scale adopted a star system scoring from 0 to 9 and a total score ≥7 indicated a high-quality study. Two investigators (B. DS. and I.G.) performed the quality evaluation of each selected study and disagreements were settled by a joint reevaluation of the original article with a third reviewer. No study was excluded based on quality criteria, in order to avoid selection bias.

Statistical Analysis

We evaluated the association between born by CS and BMI using the statistical program ProMeta version 3.0 (IDo Statistics-Internovi, Cesena, Italy). For the overall estimation, the hazard ratio was taken as an approximation to the OR, and the meta-analysis was performed as if all types of ratios were ORs. The combined risk estimate was calculated using a random-effects model in which the effect measures were ORs or hazard ratio. We assessed heterogeneity between studies by the Cochran’s Q statistic (χ²), deeming p < 0.05 as significant, and I² test, which yields results ranged from 0 to 100% (I²= 0–25%, no heterogeneity; I²= 25–50%, moderate heterogeneity; I²= 50–75%, large heterogeneity; and I²= 75–100%, extreme heterogeneity) [21]. To explore the sources of heterogeneity among studies and to test the robustness of the associations, we conducted subgroup analyses and sensitivity analyses. We further examined the influence of individual studies on the overall risk estimate, which was investigated by recalculating the pooled estimates for the remainder of the studies by omitting one study at each turn. Publication bias was evaluated using the methods of Begg and Mazumdar [22] and Egger et al. [23], which both test for funnel plot asymmetry, the former based on the rank correlation between the effect estimates and their sampling variances, and the latter based on a linear regression of a standard normal deviate on its precision. If the intercept of Egger’s regression line deviated from zero with a p value < 0.10, the funnel plot was considered asymmetrical. In case of a small number (25 or fewer) of studies enrolled in the meta-analysis, as in the current review, this test for asymmetry possesses relatively low power to detect a real publication bias. If a potential bias was detected, sensitivity analyses were performed to assess the robustness of our findings. p values reported are from 2-sided statistical tests and differences with p < 0.05 were considered significant. This review is reported according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [24] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25].

3. Results

Study profiles

The study selection process is shown in Figure 1. Our initial research returned 316 citations. After excluding 142 duplicates, the analysis of titles and abstracts identified 10 studies on the potential association of CS with offspring BMI. Through the reference lists of recent relevant reviews and already selected articles, 5 additional articles were included for the analysis. From the 15 potentially eligible articles, 4 studies were excluded from the analysis after the full-text assessment, as follows (Fig. 1):

- 2 studies report overlapping data
- 1 study is an abstract conference
- 1 study reports no risk estimate

Eleven studies with a combined population of 180,408 subjects were included in the meta-analysis.
Figure 1: Flow diagram of the systematic literature search on birth by Cesarean Section (CS) and offspring overweight/obesity.

Study Characteristics

The detailed characteristics of included studies are summarized in Table 1.

Table 1: Main characteristics of studies included in the systematic review and meta-analysis on birth by Cesarean Section (CS) and offspring overweight/obesity.
TABLE 1. Main characteristics of studies included in the systematic review and meta-analysis on birth by Cesarean Section (CS) and offspring overweight/obesity.

| First author | Year | Country of study | Study design name and population | Follow-up Age | Identification of cases | Exposure assessment | Outcome | OR/RR/PR (95% CI) | Matched or adjusted variables | Quality Score (NOS) |
|--------------|------|------------------|---------------------------------|---------------|-------------------------|--------------------|---------|-------------------|-------------------------------|-------------------|
| Ahlvist VH et al (29) | 2019 | Sweden | Cohort study | Population: n. 97291 males born between 1982 and 1987 Follow-up: 18y Age 18 y | Weight (kg) and height (cm) using a standardized scale and a stadiometer under supervision of a nurse or physician | Using the Swedish Medical Birth Register, we obtained information on recorded mode of delivery (vaginal or cesarean delivery), which was supplemented with information on indication for cesarean delivery (elective or nonelective) | Overweight Obesity | RR | VD*: Ref CS elective: 0.99 (0.90-1.08) CS non elective: 0.99(0.90-1.08) VD: Ref CS elective: 1.02 (0.88-1.18) CS non elective: 0.96(0.83-1.10) | Adjusted for MATERNAL Age at delivery, education, smoking, parity, Pre-pregnancy BMI, diabetes at delivery, hypertension at delivery, OFFSPRING: birth weight standardized according to gestational age, preeclampsia, and gestational age. | 6 |
| Goldani H et al (30) | 2011 | Brazil | Cohort study | Population: n. 2057 subjects born from 1 June 1978 to 31 May 1979. Follow-up: 25 y Age: 23-25 y | physical examination for anthropometric assessment and lifestyle questionnaire and a socioeconomic questionnaire | Trained personnel collected data from mothers and children at the time of birth. | Obesity | PR | VD: Ref CS: 1.58 (1.23, 2.02) | Adjusted for MATERNAL: education, smoking OFFSPRING: birth weight, sex, physical activity, smoking, schooling, and income | 9 |
| Study Authors | Year | Country | Study Design | Population | Follow-up | Age | Data Collection | Outcome | RR/PR | Adjustments | Notes |
|--------------|------|---------|--------------|------------|-----------|-----|----------------|---------|-------|-------------|-------|
| Rooney B et al (31) | 2011 | United States | Cohort study | n. 453 subjects between 18-20 y | 20 y | 18-20 y | Weight and height measurements available at any time during adolescence (ages 9–14 years) and at the offspring's last appointment (ages 18–20 years) were also gathered | Obesity | Ref | Not adjusted | 4 |
| Barros FC et al (32) | 2012 | Brazil | Cohort study | 4297 subjects from 1982 | 23 y | mean 22.8 y (21.9–23.7y) | All individuals were weighed and measured with standardized techniques | Obesity | Ref | Adjusted for MATERNAL: Age, education, smoking pre-pregnancy BMI, type of payment for delivery OFFSPRING: family income at birth, skin color, birth order, birth weight, schooling, physical activity, smoking and alcohol consumption | 8 |
| Manun A et al. (33) | 2013 | Australia | Cohort study | n. 2625 subjects born between 1981 and 1983 | | | Detailed physical and developmental examinations | Overweight Obesity | Ref | Adjusted for MATERNAL: age at delivery, race, education, smoking during | 7 |
| Study | Design | Population | Follow-up: 16 y | N° 14763 participants | Age: 19-28 y | Baseline questionnaire | Pregnancy, hypertensive disorder in pregnancy, gestational weight gain, pre-pregnancy BMI | Offspring: birth weight, | RR | Adjusted for | 5 |
|-------|--------|------------|----------------|----------------------|--------------|----------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----|----------------|----|
| Yuan et al (34) 2016 United States | Cohort study | GUTs (Growing Up Today Study); | Offspring responded to a yearly self-administered follow-up questionnaire between 1997 and 2001 and biennial questionnaires thereafter | Baseline questionnaire | Obesity | CS: 0.9 (0.6-1.4) | Pregnancy, hypertensive disorder in pregnancy, gestational weight gain, pre-pregnancy BMI | Offspring: birth weight, | RR | Adjusted for | 5 |
| Hansen S et al (35) 2018 Denmark | Cohort study | Danish Fetal Origins Cohort | self-administered web-based questionnaire with questions on height and weight and a clinical | Information about maternal health and birth outcomes was obtained from hospital records and the Danish | Overweight, Male overweight | OR | Age, parity, education, smoking, | 7 |
| Study | Design | Participants | Follow-up | Age | Examination | Medical Registry | Females overweight | VD: Ref | CS: 3.61 (1.31 -10.0) | Pre-pregnancy BMI, maternal, pre-eclampsia and gestational diabetes | Offspring: sex, birth weight, gestational age, | Adjusted for | Observations |
|-------|--------|--------------|-----------|-----|-------------|------------------|-------------------|---------|----------------------|-----------------------------------------------|------------------------------------------------|-------------|-------------|
| Chavarro JE et al. (36) | Cohort study | Participants: n. 33 226 subjects from Nurses’ Health Study II (NHS-II) | Follow-up: 26 y | Age: 33.8 (4.6) y (range, 24.0-44.0 years) | Self-administered questionnaires every 2 years regarding lifestyle factors, anthropometric variables, and disease prevalence | Mothers of NHS-II participants completed a questionnaire regarding their pregnancy with their NHS-II participant daughter and additional information regarding their daughter’s infancy, forming the Nurses’ Mothers Cohort study. | Obesity | RR | VD: Ref | CS: 1.11 (1.03-1.19) | Maternal: age at delivery, race, education, smoking during pregnancy, pre-pregnancy BMI, gestational weight gain maternal height, gestational diabetes, preeclampsia, pregnancy-induced hypertension | Gestational age at delivery, birth weight, region of residence at birth | 5 |
| Martin-Calvo N et al (37) | Cohort study | Population: N. 2791 subjects Seguimiento Universidad de | | | Data on diet, lifestyle and clinical diagnoses are collected at enrollment | Questionnaire included questions regarding pregnancy and delivery | Overweight and obesity | RR | VD: Ref | CS: 2.67 (1.10-5.12) | Maternal: age at delivery, pre-gestational BMI, updated smoking habit | | 4 |
| Study | Type of Study | Population | Follow-up | Age | Measurements | Mode of Delivery | Adjusted for |
|-------|---------------|-------------|-----------|-----|--------------|-----------------|-------------|
| Sogunle E et al (38) | Case/Control Study | Participants 889 subjects from the prospective South African birth cohort (Birth to Twenty Plus 1990) | 24 y | 21–24 y | Administered questionnaires, contact with parents or caregivers, telephone calls, and field visits. Measurements were taken by trained research personnel. | Information on mode of delivery was copied by the investigators of the South African birth cohort from the official birth notification forms compiled at the local authority. | Males obesity OR | MATERNAL: education and parity | OFFSPRING sex and birth weight; |
| Svensson E et al (39) | Case/Control Study | Population: 21051 Danish men born in 1977-1983 | 18 y | 18 y | Height and weight measured to calculate BMI | Medical Birth Registry, Danish National Registry of Patients | PR | MATERNAL: Age, marital status, parity, diabetes, gestational hypertensive disorder, hospitalization for infection during pregnancy | OFFSPRING: |
In our selection, 9 studies [29, 30, 31, 32, 33, 34, 35, 36, 37] have prospective study design and two studies have retrospective study design [38, 39]. Two studies reported subtype of CS (Elective CS and Non elective CS) [29, 39], four studies investigated the association of CS with overweight and obesity [29, 33, 37, 39], one the association of CS with overweight [35] and six the association of CS with obesity [30, 31, 32, 34, 36, 38]. Four studies were conducted in Europe (in particular, two in Denmark [35,39], one in Spain [37], one in Sweden [29]), 3 studies in USA [31, 34, 36], 2 studies in south America (Brazil) [30, 32], one in Australia [33] and the remaining one in Africa (South Africa) [38]. Five studies reported RR [29, 31, 34, 36, 37], three reported OR [33, 35, 38] and three reported PR [30, 32, 39]. Among the studies, five reported overall risk estimates in offspring [30, 31, 33, 34, 37], one study reported risk estimates for females’ sex only [36] and two studies for males’ sex only [29, 39], while the three studies reported risk estimates for both sexes [32, 35, 38]. Four studies investigated the risk of overweight in adults aged 18-20 years [29, 35, 37, 39] and one study in adults aged 21 or more years [33]. Obesity was the outcome of interest in four studies investigating adults aged 18-20 years [29, 31, 37, 39] and five studies investigating adults aged 21 or more years [30, 32, 36, 38, 39].

Quality Assessment

The range of quality score was from 4 to 9 (median: 7). High-quality studies (i.e., those studies that had a score ≥7) included 2 case-control [38, 39] and 4 cohort studies [30, 32, 34, 35].

Meta-Analyses

The overall analysis of the 11 studies (n = 18) yielded a combined risk estimate for overweight/obesity of 1.19 (95% CI 1.08-1.31) and the test of heterogeneity resulted Q=53.37 (I² = 70.37 %, P≤0.0001).

The forest plots are shown in Figure 2.

**Figure 2:** Forest plots of the association between Cesarean Section and offspring “Overweight” (A) and “Obesity” (B). ES, effect size.

A:

| Study Description | ES     | 95% CI     | W        |
|-------------------|--------|------------|----------|
| Alqatif 2019/Cohort Europe/Age 18-20/Overweight M | 0.69   | 0.69 / 1.08 | 34.93%   |
| Calvo 2020/Cohort Europe/Age 18-20/Overweight M+F | 1.71   | 1.10 / 2.52 | 11.57%   |
| Hansen 2018/Cohort Europe/Age 18-20/Overweight F | 3.61   | 1.31 / 10.00 | 2.56%   |
| Hansen 2018/Cohort Europe/Age 18-20/Overweight M | 1.62   | 0.62 / 4.23 | 2.85%   |
| Mamun 2013/Cohort Australia/Age >21/Overweight M+F | 0.90   | 0.60 / 1.20 | 14.68%   |
| Svesson 2013/Case-control Europe/Age 18-20/Overweight M+F | 1.05   | 0.64 / 1.17 | 33.42%   |
| Overall (random-effects model) | 1.11   | 0.94 / 1.32 | 100.00%   |

B:
Further analyses were performed stratifying by study design, sex, age, geographic area and level of BMI (Overweight/Obesity) (Table 2).

Table 2: Results of overall analysis and stratified analysis of the “Overweight” and “Obesity” risk estimates for the Birth by cesarean section.

| Combined risk estimate | Test of heterogeneity | Publication bias |
|------------------------|------------------------|------------------|
|                        | Value (95% CI)         | p               | Q     | I² % | p     | (Egger test) | (Begg test) |
| All (n=18)             | 1.19 (1.08-1.31)       | 0.0004          | 53.37 | 70.37 | <0.0001 | 0.005 | 0.063 |
| Study Profile          |                        |                  |       |      |       |      |      |
| Case Control (n=4)     | 1.27 (0.99-1.64)       | 0.058           | 10.71 | 71.99 | 0.013  | 0.208 | 0.497 |
| Cohort (n=14)          | 1.17 (1.05-1.31)       | 0.04            | 45.16 | 71.21 | <0.0001 | 0.028 | 0.090 |
| Sex                    |                        |                  |       |      |       |      |      |
| Male (n=5)             | 1.00 (0.90-1.11)       | 0.968           | 5.81  | 31.20 | 0.213  | 0.140 | 0.142 |
| Female (n=4)           | 1.32 (1.00-1.75)       | 0.051           | 6.90  | 56.53 | 0.075  | 0.063 | 0.174 |
| Age                    |                        |                  |       |      |       |      |      |
| Age>20 (n=8)           | 1.18 (0.99-1.40)       | 0.062           | 16.41 | 57.34 | 0.022  | 0.450 | 0.458 |
| Age 18-20 (n=9)        | 1.27 (1.08-1.49)       | 0.004           | 38.88 | 79.42 | <0.0001 | 0.002 | 0.095 |
| Geographic Area        |                        |                  |       |      |       |      |      |
| Europe (n=8)           | 1.22 (1.04-1.42)       | 0.012           | 32.74 | 76.62 | <0.0001 | 0.006 | 0.048 |
| USA (n=3)              | 1.13 (0.98-1.31)       | 0.094           | 5.82  | 65.65 | 0.054  | 0.324 | 0.602 |
| Brazil (n=3)           | 1.29 (0.96-1.73)       | 0.086           | 4.85  | 58.80 | 0.088  | 0.253 | 0.117 |
| Level of BMI           |                        |                  |       |      |       |      |      |
| Overweight (n=6)       | 1.11 (0.94-1.32)       | 0.217           | 13.87 | 63.96 | 0.0160 | 0.098 | 0.091 |
| Obesity (n=12)         | 1.23 (1.09-1.39)       | 0.001           | 39.50 | 72.15 | <0.0001 | 0.032 | 0.217 |
| Overweight (n=6)       | 1.11 (0.94-1.32)       | 0.217           | 13.87 | 63.96 | 0.0160 | 0.098 | 0.091 |
| Case-Control (n=1)    | 1.05 (0.94-1.17)       | 0.382           |       |      |       |      |      |
| Cohort (n=5)           | 1.28 (0.91-1.79)       | 0.156           | 13.72 | 70.84 | <0.0001 | 0.142 | 0.142 |
| Male (n=2)             | 0.99 (0.90-1.09)       | 0.914           | 1.00  | 0.17  | 0.317  |      |      |
| Female (n=1)           | 3.61 (1.31-10.0)       | 0.013           |       |      |       |      |      |
| Age>20 (n=1)           | 0.90 (0.60-1.20)       | 0.551           |       |      |       |      |      |
| Age 18-20 (n=5)        | 1.16 (0.96-1.41)       | 0.120           | 13.25 | 69.82 | 0.010  | 0.029 | 0.050 |
The results showed a significantly increased risk of overweight/obesity in association with birth by CS in cohort studies, with a risk estimate of 1.17 (95% CI 1.05, 1.31; *P*=0.04). Stratifying by sex a significant association was found in females (OR 1.32; 95% CI 1.00-1.75), while no significant association was found in males (OR 1.00; 95% CI 0.90-1.11). CS was associated with a significantly increased risk of overweight/obesity in adults aged 18-20 years (OR 1.27; 95% CI 1.08-1.49), but not in adults aged >20 years (OR 1.18; 95% CI 0.99-1.40). The stratified analysis by geographic area showed a significantly increased risk of overweight/obesity in Europe (OR 1.22; 95% CI 1.04-1.42) but not in USA (OR 1.13; 95% CI 0.98-1.31) and Brazil (OR 1.29; 95% CI 0.96-1.73). Stratifying by BMI values, CS was associated with a significantly higher risk of developing obesity in adulthood (OR 1.23; 95% CI 1.09-1.39) while no significant effect on overweight (OR 1.11; 95% CI 0.94-1.32) was observed.

### Cesarean birth and overweight offspring

The overall analysis of the 5 studies pooled together (n = 6) yielded a combined risk estimate for overweight of 1.11 (95% CI 0.94-1.32) and the test of heterogeneity resulted *Q*=13.87 (I²= 63.96%, *P*=0.0160). The forest plots are reported in Figure 2.

### Cesarean birth and obesity offspring

The overall analysis of the 10 studies pooled together (n = 12) yielded a combined risk estimate for obesity of 1.23 (95% CI 1.09-1.39) and the test of heterogeneity resulted *Q*=39.50 (I²= 72.15%, *P*≤0.0001). The forest plots are reported in Figure 2.

| Region      | OR (95% CI) | *P*     | *ORR*  | *P*     | *Q* (I²%) | *P*     |
|-------------|-------------|---------|--------|---------|-----------|---------|
| Europe      | 1.22 (1.04-1.42) | 0.023   | 0.290  | 0.652   | 13.96%   | 0.017   |
| USA         | 1.13 (0.98-1.31)  | 0.054   | 0.324  | 0.602   | 11.73%   | 0.117   |
| Brazil      | 1.29 (0.96-1.73)  | 0.088   | 0.253  | 0.117   | 11.73%   | 0.117   |
| Case-Control| 1.46 (1.07-1.99)  | 0.240   | 0.336  | 0.117   | 11.73%   | 0.117   |
| Cohort      | 1.18 (1.04-1.35)  | 0.098   | 0.501  | 0.117   | 11.73%   | 0.117   |
| Male        | 1.07 (0.75-1.53)  | 0.023   | 0.290  | 0.652   | 11.73%   | 0.117   |
| Female      | 1.12 (1.05-1.20)  | 0.034   | 0.023  | 0.090   | 11.73%   | 0.117   |
| Age>20      | 1.23 (1.02-1.48)  | 0.024   | 0.087  | 0.497   | 11.73%   | 0.117   |
| Age 18-20   | 1.50 (1.06-2.13)  | 0.091   | 0.259  | 0.117   | 11.73%   | 0.117   |
| USA         | 1.35 (0.95-1.91)  | 0.094   | 0.054  | 0.324   | 11.73%   | 0.117   |
| Brazil      | 1.29 (0.96-1.73)  | 0.086   | 0.253  | 0.117   | 11.73%   | 0.117   |

A Significant association was found in case control studies (OR 1.46; 95% CI 1.07-1.99) and in cohort studies (OR 1.18; 95% CI 1.04-1.35). A Significant association was found in age 18-20 years (OR 1.50; 95% CI 1.06-2.13), in age >20 years (OR 1.23; 95% CI 1.02-1.48) and in females (OR 1.12; 95% CI 1.05-1.20), but not in males (OR 1.00; 95% CI 0.90-1.11). No significant association was found in different geographical area (Europe, USA, Brazil) Table 2.
Publication Bias

Bias detection revealed a significant effect ($P=0.005$) using the method of Egger, while no bias was detected by the Begg and Mazumder test ($P=0.063$) (Figure 3). In the stratified analysis on the association between CS and obesity a significant publication bias was detected by Egger test; ($P=0.032$), but not by Begg and Mazumder test; $P=0.217$) The funnel plots of the meta-analyses are shown in figure 3.

**Figure 3:** Funnel plots of the meta-analyses on the “Overweight” (A) and “Obesity” (B) offspring.

A:

![Funnel plot for overweight offspring](image)

B:

![Funnel plot for obesity offspring](image)
Sensitivity analyses

Sensitivity analyses by omitting one study in turn suggested that the overall risk estimates were not substantially modified by any single study, with a range from 1.15 (95% CI 1.05-1.27) to 1.22 (95% CI 1.10-1.35). Heterogeneity was still observed after omitting each study in turn.

4. Discussion

Several studies confirmed that CS is related to different hormonal, physical and bacterial exposures and that this fact can change neonatal physiology and health outcomes [8-13]. Recently, the relationship between CS and offspring’s BMI has attracted a great deal of attention. Therefore, we conducted a systematic review and meta-analysis to summarize the evidence on the association between mode of birth and BMI in offspring’s adulthood and to assess the risk of obesity and overweight in offspring’s adulthood associated with CS. The overall results of the current meta-analysis indicate that CS was associated with a significantly higher risk (1.19; 95% CI 1.08-1.31) of overweight/obesity in offspring’s adulthood. The overall analysis (population= 180,408 subjects) showed a statistically significant increase of overweight/obesity risk in the cohort studies, in females, in age group 18-20 and in Europe. In case of obesity, significant effects were observed also in case control study

and age>21. Our study shows a decrease in significance of overweight/obesity risk as age increases. The

obesity risk is inversely associated to increasing age groups probably in correlation with the fact that the influence of environmental factors on obesity risk increases. This observation could be because lifestyle and environmental factors such as high food consumption, high sweetened beverages, less activity, television watching that are causative of obesity may have assumed greater importance [40]. This may be that the association between CS and overweight/obesity risk factors is more pronounced in prosperous societies, as found in our study with significant results in Europe, where breastfeeding is less common and where there is limited exposure to diverse bacteria in the immediate postnatal period. The underlying causes for obesity are complex, involving social and cultural aspects, and biological context involving epigenetics mechanisms, regulation of food
intake, and even the gut microbiota [40]. Significant differences have been documented between the microbiome of infants born by caesarean section and infants born vaginally. Such differences were also proven to appear in the gut flora of normal weight people with respect to obese subjects. Children born by CS have similar patterns of intestinal colonization caused by lack of contact with maternal vaginal and intestinal flora [41, 42]. The intestinal flora of infants born through caesarean section is less rich and diverse. Bacterial species protective against later obesity such as Bifidobacteria spp. and Bacteroides, are almost absent and the microbes such as that colonize their gut allows them to harvest more nutrients from diet, this is therefore presumed to persist in adulthood [41, 43]. The mechanism by which CS increases the risk of overweight/obesity could be related to altered epigenetic regulation of obesity gene expression due to higher DNA methylation. CS, in fact, affects epigenetic activity in newborn infants who exhibited a higher DNA methylation than infants vaginally born [44], on the other hand a higher DNA methylation may be associated to higher risk of overweight and obesity. The mechanism by which CS increases the risk of overweight/obesity could be related to lower rate of breastfeeding in children born by CS. The prevalence of obesity is significantly lower in breastfed people and breastfeeding is associated with a reduction in obesity risk [45].

5. Strengths and Limitations

Our studies collectively represent a large population of 180,408 subjects, from eight countries, and four different continents. In addition, our review separately assessed the effects of CS on the different categories of BMI (overweight, obesity) in an adult-only population and in the subcategories of sexes and age groups. Our study is the fifth meta-analysis about the relation between CS delivery and overweight/obesity in offspring.
adults, but it is the only one that have tried to study some subgroups, such as geographical area.

The studies limitations are the small number of studies included, the few risks estimated considered and the failure to investigate how much environmental factors affect obesity risk by age. Furthermore, the prevalence of CS is strongly and directly related to socioeconomic position, residual confounding may affect associations with any outcomes that also vary according to wealth. In any case the control of potential confounders is of considerable importance in studies investigating the association of C-section and obesity.

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