Association between maternal overweight or obesity and cerebral palsy in children: A meta-analysis

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Abstract

Context

There is no consensus regarding the association between maternal obesity or overweight and cerebral palsy (CP) in children.

Objectives

To investigate whether maternal obesity or overweight is associated with CP and identify the factors that explain the differences in the study results.

Data sources

We conducted a meta-analysis of studies published in English with titles or abstracts that discussed the relationships between maternal obesity or overweight and CP before August 23, 2017, using Ovid Medline, EMBASE and Web of Science.

Study selection

Of 2699 initially identified studies, 8 studies that addressed the association between maternal obesity or overweight and CP met our final inclusion criteria.

Data extraction

Information from the individual studies was abstracted using standardized forms by 2 independent observers who were blinded to the authors’ names and journal titles.

Data synthesis

According to a random effects model, maternal overweight was significantly associated with CP in offspring [RR = 1.29 (95% CI, 1.04–1.60), heterogeneity ($I^2 = 45.5\%, P = 0.103$)]; maternal obesity was significantly associated with CP in offspring [RR = 1.45 (95% CI, 1.25–1.69), heterogeneity ($I^2 = 24.1\%, P = 0.253$)]; and maternal obesity III was significantly associated with CP in offspring [RR = 2.25 (95% CI, 1.82–2.79), heterogeneity ($I^2 = 0\%, P = 0.589$)]. However, maternal underweight was not significantly associated with CP in offspring [RR = 1.11 ...
Factors that explained the differences in the meta-analysis results included study design, study location, and whether individual studies adjusted for potential confounders.

Conclusion
This study suggests that maternal obesity and overweight increase the risk of CP in offspring. Further studies are required to confirm these results and determine the influence of variables across studies.

Introduction
Obesity is becoming an epidemic health problem. This trend is particularly true for maternal obesity and overweight, which may be associated with adverse obstetric complications[1, 2]. Maternal obesity is associated with low Apgar scores at 5 minutes[2, 3], preterm birth[4], low birth weight, periventricular leukomalacia (PVL)[5], autism spectrum disorders (ASDs)[6, 7], and intellectual disability[8], which could alter the offspring’s neurodevelopmental outcomes[6]. Furthermore, maternal obesity is associated with an increased risk of gestational diabetes, hypertension, and preeclampsia, which may be associated with adverse neurodevelopmental outcomes[9]. In addition, maternal obesity is associated with type 2 diabetes, congenital anomalies[10], and asthma[11] in offspring. Maternal obesity and overweight are the leading cause of public health problems. More than half of women receiving prenatal care in the United States are overweight or obese[12], and maternal obesity and overweight are epidemic in Sweden[13] and other countries.

Cerebral palsy (CP), which leads to cognitive impairments and motor deficits[14], is multifactorial. CP occurs in two per 1000 live births in Sweden[13]. This disorder is a tremendous burden on society and families. Studies show that maternal chorioamnionitis[15], maternal preeclampsia[16], maternal age >35 years, a low Apgar score at 5 minutes, preterm birth[17], low birth weight, periventricular/intraventricular hemorrhage[18], and bronchopulmonary dysplasia (BPD) are associated with CP. Among recent studies focusing on the relationship between maternal obesity and CP in offspring[9, 12, 13, 17, 19–22], two studies showed that maternal weight during pregnancy is associated with CP in offspring[23, 24], and other studies indicated a significant association between maternal obesity and CP in children[9, 12, 13, 20, 21]. Maternal obesity may contribute to CP in offspring via maternal preeclampsia, preterm birth, or a low Apgar score at 5 minutes (asphyxia), as these parameters alter the uterine environment[25] and lead to maladaptive programming of the fetal brain[26]. Furthermore, maternal obesity may induce a chronic inflammatory state, such as chorioamnionitis, which may contribute to the development of CP[15]. However, two studies[12, 22] have reported that there is no significant association between maternal obesity and CP in children. The reason for this discrepancy may be that infants with CP whose mothers were not obese may have been affected by other factors that induce adverse neurodevelopmental outcomes.

To date, findings regarding this issue have been little known and inconsistent. Thus, we conducted a meta-analysis of human studies investigating the relationship between maternal obesity or overweight and CP in children.

Methods
Retrieval of studies
We searched Ovid Medline, EMBASE, and Web of Science for articles published before August 23, 2017. We used the following keywords and medical subject headings (MeSH) to
search for the first theme: “overweight”, “over-weight”, “body weight”, “obes$”, “body weight changes”, “body fat distribution”, “body mass index”, “overnutrition”, “body weigh$”, “body-weigh$”, “body mass$”, “bodymass”, “body fat$”, “bodyfat$”, “skinfold thickness”, and “waist-hip ratio”, using “OR” to connect relevant terms within the search field. For the second theme, we used “maternal”, “pregnancy”, “prenatal”, “antenatal”, “antepart”, “gestat”, “fetal development”, “transplacental exposure”, “fetal programming”, “fetal growth”, “foetal development”, “gestational age”, “fetal age”, and “foetal age”, using “OR” to connect relevant terms within the search field. For the third theme, cerebral palsy, we used MeSH and key words such as “cerebral palsy”, “CP”, “spastic”, “quadripleg$”, “quadrplegia”, “tetraplegi$”, “diplegi$”, or “disabled children”. For the fourth theme, etiology, we used “risk”, “mortality”, or “cohort” to acquire the search results. We used “AND” to combine the first theme, the second theme, the third theme and the fourth theme (S1 Data). We restricted the search to human studies published in English. The identified studies were screened by reading the titles and abstracts, and two reviewers (Dongqiong Xiao and Lan Huang) subsequently read the full text of the remaining studies independently and then discussed any disagreements to reach a consensus.

**Definition**

The weight categories were defined as follows: maternal overweight (25 kg/m$^2$<BMI<30 kg/m$^2$), maternal obesity (BMI≥30 kg/m$^2$), maternal obesity class I (30 kg/m$^2$<BMI<35 kg/m$^2$), maternal obesity class II (35 kg/m$^2$<BMI<40 kg/m$^2$), and maternal obesity class III (BMI≥40 kg/m$^2$).

**Study selection criteria**

The study inclusion criteria were as follows: (1) studies that evaluated the association between maternal overweight or obesity and the risk of CP in offspring; (2) a case-control or cohort study design; (3) studies that described the assessment of exposure and outcome; and (4) studies that reported hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs), adjusted and/or unadjusted odds ratios (ORs) and 95% CIs, or adjusted and/or unadjusted relative risk (RR) estimates and 95% CIs for maternal overweight and obesity.

The exclusion criteria for the study were as follows: (1) duplicated studies, (2) review or meta-analysis articles, (3) case reports, (4) studies published in a language other than English, (5) animal experiment studies, (6) studies that did not examine the relationship between maternal obesity/overweight and CP in offspring, (7) studies with overlapping data, and (8) studies with unusable data.

**Data extraction**

Data were independently extracted from the studies by two reviewers (Dongqiong Xiao and Lan Huang). The extracted data included the name of the first author; publication year; the country of the participants; study design; sample size; the method for assessing maternal obesity, overweight and CP; primary outcome; and adjusted confounders.

**Quality evaluation**

The two reviewers (Dongqiong Xiao and Lan Huang) independently used the Newcastle-Ottawa scale (NOS)[3] to examine the methodological quality of all the included studies. The quality score was evaluated by assessing the study population selection (four items), comparability (one item), and the evaluation of exposure and outcome (three items). Studies with
scores of at least 5 were deemed to be of high quality. Disagreements were resolved in the manner previously described.

**Statistical analysis**

The included original studies used ORs, RR, or HRs to assess the association between maternal obesity or overweight and the risk of CP in offspring. Because the P0, which is the incidence of the outcome in the nonexposed group, was very small in our study and because RR = OR/((1-P0)+P0\times OR)[27], RR>OR; thus, the HR, RR and OR were directly considered in the RR [7], and we used ln(RR), ln(OR), and ln(HR) to combine these values. We pooled the RR across studies using the DerSimonian–Laird formula (random effects model)[28]. The statistical heterogeneity[29] of the studies was assessed by using $I^2$. $I^2>50%$ and P<0.1 indicated high heterogeneity. A forest plot was used to display the RR and 95% CIs for each study, as well as the pooled RR and 95% CIs. We conducted subgroup analyses based on study design (case-control or cohort), study location (USA or other), time of maternal BMI measurement (pre-pregnancy or other), and adjusted confounding variables (maternal age, maternal race, child’s sex, maternal smoking status, and maternal diabetes status). We performed sensitivity analyses by omitting one study at a time. Publication bias was assessed with Egger’s[30] and Begg’s[31] tests. P<0.05 was considered statistically significant. The statistical tests were performed with Stata software (version 12).

**Results**

**Literature search**

We identified 2699 potential studies: 105 from Ovid Medline, 218 from EMBASE, and 2376 from Web of Science. After careful screening, 8 studies were selected for inclusion in this study (Fig 1). The extracted data from the 8 included studies are presented in Tables 1 and 2.
| Author, year | Country       | Study design     | Size   | Time of BMI measurement | Ascertainment of exposure; outcome | Primary outcome | Adjusted confounding factors | Risk of bias; quality |
|-------------|---------------|------------------|--------|-------------------------|-----------------------------------|-----------------|-----------------------------|----------------------|
| Crisham Janik, 2013 [19] | United States | Retrospective cohort | 6221001 | Prenatal or perinatal  | Medical data; registry data | BMI ≥ 30, OR = 1.27 (CI, 1.06–1.52) BMI ≥ 40, OR = 2.56 (CI, 1.79–3.66) | Maternal race, maternal age, maternal education, no prenatal care, low insurance status, male infant | Different methods of exposure, only preterm neonates; NOS: 6 |
| Pan, C, 2014 [9] | United States | Retrospective cohort | 83901  | Pre-pregnancy           | Medical data; registry data | BMI < 18.5, OR = 0.46 (CI, 0.06–3.34); BMI = 25–29.9, OR = 1.15 (CI, 0.66–2.01); BMI = 30–34.9, OR = 1.62 (CI, 0.9–2.93); BMI = 35–39.9, OR = 2 (CI, 1–4.01); BMI ≥ 40, OR = 2.95 (CI, 1.45–5.97) | Maternal age, education level, race, ethnicity; maternal intellectual disability; febrile at delivery; diabetic, hypertensive; tobacco user; sexually transmitted diseases; child's sex, gestational age, birth weight | Different methods of exposure; NOS: 7 |
| Forthun, I, 2016 [20] | Norway, Denmark | Prospective cohort | 188788 | Pre-pregnancy           | Self-reported; registry data | BMI < 18.5, RR = 0.91 (CI, 0.5–1.67); BMI = 25–29.9, RR = 1.56 (CI, 1.21–2.01); BMI ≥ 30, RR = 1.55 (CI, 1.11–2.18) | Occupational status, smoking during the first part of pregnancy and age | Different methods of exposure; NOS: 7 |
| McPherson, 2016 [12] | United States | Case-control     | 1669   | Pre-pregnancy           | Registry data | BMI = 30–39.9, OR = 1.1 (CI, 0.8–1.6); BMI ≥ 40, OR = 1.8 (CI, 0.9–3.4) | Preterm birth <28 weeks and magnesium sulfate exposure | Different methods of exposure, only preterm neonates; NOS: 6 |
| Villamor, E, 2017 [13] | Sweden | Retrospective cohort | 1423929 | Early pregnancy | Registry data | BMI < 18.5, HR = 1.09 (CI, 0.84–1.41); BMI = 25–29.9, HR = 1.22 (CI, 1.11–1.33); BMI = 30–34.9, HR = 1.28 (CI, 1.11–1.47); BMI = 35–39.9, HR = 1.54 (CI, 1.24–1.93); BMI ≥ 40, HR = 2.02 (CI, 1.46–2.79) | Maternal age, country of origin, education level, cohabitation with a partner, parity, height, smoking during pregnancy, and year of delivery | Different methods of exposure; NOS: 8 |
| Love, E, 2012 [22] | Scotland | Retrospective cohort | 28967  | Unknown                 | Registry data | BMI < 20, OR = 0.99 (CI, 0.40–2.48); BMI = 25–29.9, OR = 0.81 (CI, 0.37–1.76); BMI ≥ 30, OR = 0.92 (CI, 0.35–2.47) | Maternal age, maternal smoking, gestational age, birthweight | Different methods of exposure; NOS: 7 |
| Nielsen, LF, 2008 [29] | Denmark | Case-control     | 488    | Pre-pregnancy           | Medical records | BMI < 18.5, OR = 1.7 (CI, 0.87–3.32); BMI = 25–29.9, OR = 0.9 (CI, 0.45–1.83) | Gestational age | Different methods of exposure; NOS: 6 |
| Walstab, J, 2002 [31] | Australia | Case-control  | 439     | Pregnancy               | Registry data; medical data | BMI = 25–29.9, RR = 3.48 (CI, 1.25–9.68) | No | Different methods of exposure; NOS: 6 |

CP, cerebral palsy; BMI, body mass index; RR, relative risk; OR, odds ratio; HR, hazard ratio; NOS, Newcastle-Ottawa score.

All primary outcomes were obtained after adjustment for several potentially confounding variables.

https://doi.org/10.1371/journal.pone.0205733.t001
Table 2. Pooled results of the associations between maternal BMI and CP risk.

| Variable                  | Studies | RR(95% CI) | I²(P-value) | Studies | RR(95% CI) | I²(P-value) | Studies | RR(95% CI) | I²(P-value) | Studies | RR(95% CI) | I²(P-value) |
|---------------------------|---------|------------|-------------|---------|------------|-------------|---------|------------|-------------|---------|------------|-------------|
| Total                     | 4       | 1.11(0.88, 1.38) | 0(0.435) | 6       | 1.29(1.04, 1.60) | 0.455(0.103) | 6       | 1.45(1.25, 1.69) | 0.241(0.253) | 4       | 2.25(1.82, 2.79) | 0(0.589) |
| Study location            |         |            |             |         |            |             |         |            |             |         |            |             |
| USA                       | 1       | 0.46(0.06, 3.43) | NA         | 1       | 1.15(0.66, 2.01) | NA         | 3       | 1.47(1.09, 1.98) | 0.603(0.08) | 3       | 2.45(1.84, 3.27) | 0(0.563) |
| Other                     | 3       | 1.12(0.89, 1.40) | 0(0.37)    | 5       | 1.31(1.01, 1.69) | 0.560(0.059) | 3       | 1.51(1.24, 1.83) | 0(0.600) | 1       | 2.02(1.46, 2.79) | NA      |
| Case-control              | 1       | 1.70(0.87, 3.32) | NA         | 2       | 1.68(0.45, 6.29) | 0.781(0.033) | 1       | 1.29(0.82, 2.03) | NA         | 1       | 1.8(1.93, 3.50) | NA      |
| Retrospective cohort      | 3       | 1.05(0.83, 1.33) | 0(0.624)   | 4       | 1.28(1.08, 1.51) | 0.329(0.215) | 5       | 1.48(1.24, 1.76) | 0.374(0.172) | 3       | 2.31(1.84, 2.90) | 0(0.488) |
| Pre-pregnancy             | 3       | 1.14(0.66, 1.97) | 0.255(0.261) | 3       | 1.33(0.99, 1.80) | 0.259(0.259) | 3       | 1.63(1.27, 2.08) | 0.2(0.287) | 2       | 2.27(1.40, 3.68) | 0(0.319) |
| Other                     | 1       | 1.09(0.84, 1.41) | NA         | 3       | 1.34(0.76, 2.38) | 0.607(0.079) | 3       | 1.35(1.16, 1.56) | 0.026(0.358) | 2       | 2.25(1.77, 2.86) | 0(0.336) |
| Maternal age              |         |            |             |         |            |             |         |            |             |         |            |             |
| Yes                       | 3       | 1.05(0.83, 1.33) | 0(0.624)   | 4       | 1.28(1.08, 1.51) | 0.329(0.215) | 5       | 1.48(1.24, 1.76) | 0.374(0.172) | 3       | 2.31(1.84, 2.90) | 0(0.488) |
| No                        | 1       | 1.70(0.87, 3.32) | NA         | 2       | 1.68(0.45, 6.29) | 0.781(0.033) | 1       | 1.29(0.82, 2.03) | NA         | 1       | 1.8(0.9, 3.4) | NA      |
| Child’s sex               |         |            |             |         |            |             |         |            |             |         |            |             |
| Yes                       | 1       | 0.46(0.06, 3.43) | NA         | 1       | 1.15(0.66, 2.01) | NA         | 2       | 1.56(0.98, 2.49) | 0.798(0.026) | 2       | 2.63(1.91, 3.63) | 0(0.726) |
| No                        | 3       | 1.12(0.89, 1.40) | 0(0.37)    | 5       | 1.31(1.01, 1.69) | 0.560(0.059) | 4       | 1.47(1.23, 1.76) | 0(0.705) | 2       | 1.98(1.48, 2.64) | 0(0.76) |
| Maternal race             |         |            |             |         |            |             |         |            |             |         |            |             |
| Yes                       | 1       | 0.46(0.06, 3.43) | NA         | 1       | 1.15(0.66, 2.01) | NA         | 2       | 1.56(0.98, 2.49) | 0.798(0.026) | 2       | 2.63(1.91, 3.63) | 0(0.726) |
| No                        | 3       | 1.12(0.89, 1.40) | 0(0.37)    | 5       | 1.31(1.01, 1.69) | 0.560(0.059) | 4       | 1.47(1.23, 1.76) | 0(0.705) | 2       | 1.98(1.48, 2.64) | 0(0.76) |
| Maternal smoking          |         |            |             |         |            |             |         |            |             |         |            |             |
| Yes                       | 3       | 1.05(0.83, 1.33) | 0(0.624)   | 4       | 1.28(1.08, 1.51) | 0.329(0.215) | 4       | 1.60(1.35, 1.91) | 0.007(0.388) | 2       | 2.16(1.61, 2.90) | 0(0.34) |
| No                        | 1       | 1.70(0.87, 3.32) | NA         | 2       | 1.68(0.45, 6.29) | 0.781(0.033) | 2       | 1.27(1.08, 1.50) | 0(0.95) | 2       | 2.37(1.73, 3.24) | 0(0.36) |
| Maternal diabetes         |         |            |             |         |            |             |         |            |             |         |            |             |
| Yes                       | 1       | 0.46(0.06, 3.43) | NA         | 1       | 1.15(0.66, 2.01) | NA         | 1       | 2.05(1.4, 3.0) | NA         | 1       | 2.95(1.45, 5.99) | NA      |
| No                        | 3       | 1.12(0.89, 1.40) | 0(0.37)    | 5       | 1.31(1.01, 1.69) | 0.560(0.059) | 5       | 1.37(1.21, 1.55) | 0(0.562) | 3       | 2.19(1.75, 2.75) | 0(0.521) |

NA: not available

https://doi.org/10.1371/journal.pone.0205733.t002
Characteristics and quality of the included studies

The included studies were published between 2002 and 2017. All included studies were cohort and case-control studies. The sample sizes varied from a minimum of 439 to a maximum of 6,221,001 patients. In terms of the timing of maternal BMI assessment, four of the included studies\[9, 12, 20,32\] assessed maternal BMI during pre-pregnancy, one study\[13\] assessed maternal BMI during early pregnancy (<14 weeks)\[13], and three studies\[19, 21, 22\] assessed maternal BMI at the hospital without mentioning the testing time. Five studies\[9, 13, 21, 22, 32\] used normal-weight (BMI 18.5–24.9 kg/m\(^2\)) status as the reference, one study\[20\] used a lower normal weight (BMI 18.5–22.9 kg/m\(^2\)) as the reference, and two studies\[12, 19\] used nonobese (BMI <30 kg/m\(^2\)) participants as the reference. For the sources of the data used to determine maternal BMI, one study\[20\] used self-reported maternal weight and height, and seven studies used medical records or registry data. For CP diagnosis, all the studies identified cases from registry data or medical records. Some of the included studies statistically controlled for several potentially confounding variables, as shown in Table 1. The results of the quality assessment of the included studies are shown in Table 1. All the included studies were of high quality (NOS >5)(S1 Data).

Maternal overweight or obesity and CP in children

The original outcomes of the included studies are presented in Table 1 and Fig 2 shows the association between maternal BMI and CP risk in offspring: maternal underweight was investigated in 4 studies, with RR = 1.11 (95% CI, 0.88–1.38) and low heterogeneity (\(I^2 = 0\%), P = 0.435); maternal overweight was investigated in 6 studies, with RR = 1.29 (95% CI, 1.04–1.60) and heterogeneity (\(I^2 = 45.5\%), P = 0.103); maternal obesity was investigated in 6 studies, with RR = 1.45 (95% CI, 1.25–1.69) and heterogeneity (\(I^2 = 24.1\%), P = 0.253); and maternal obesity III was investigated in 4 studies, with RR = 2.25 (95% CI, 1.82–2.79) and heterogeneity (\(I^2 = 0\%), P = 0.589). The results from each study were adjusted for several potentially confounding variables, as shown in Table 2.

Stratified analysis and sensitivity analysis

A stratified analysis was conducted to investigate possible sources of heterogeneity in studies of maternal BMI and CP risk in offspring (Table 2). The association between maternal underweight and CP in offspring was nonsignificant, and this association was consistent when stratified by different factors. The association between maternal obesity III and CP in offspring was statistically significant, and this association was consistent when stratified by different factors.

The association between maternal overweight and CP in offspring was inconsistent when stratified by different factors. Stronger associations between maternal overweight and CP in offspring were found in countries other than the USA. Stronger associations between maternal overweight and CP in offspring were found in retrospective cohort studies than in case-control studies. When the results were stratified by certain cofounding variables, stronger associations were found when adjustments were made for maternal age and maternal smoking status than when these confounding variables were not adjusted, while stronger associations were found without adjustments for the child’s sex, maternal race, and maternal diabetes status than when these confounding variables were adjusted.

The association between maternal obesity and CP in offspring was consistent when stratified by study location, BMI assessment, maternal smoking and maternal diabetes. Stronger associations between maternal obesity and CP in offspring were found in retrospective cohort studies than in case-control studies. When the results were stratified by certain confounding variables, stronger associations were found with adjustments for maternal age than without
adjustments for maternal age; however, stronger associations were found when the child’s sex and maternal race were not adjusted than when these parameters were adjusted.

Considering the small number of studies in our meta-analysis, we omitted one study at a time to perform a sensitivity analysis. For underweight patients and maternal obesity class III patients, no heterogeneity was observed during the sensitivity analysis. For overweight patients, when the study by Walstab et al[21] was omitted, the heterogeneity decreased ($I^2 = 24.3\%$, $P = 0.259$). For maternal obesity patients, when the study by Crisham et al[19] was omitted, the heterogeneity decreased ($I^2 = 0\%$, $P = 0.434$).

Publication bias

Publication bias tests and plots were conducted when the meta-analysis included more than 10 studies; however, these tests were underpowered to detect publication bias when there were only 8 studies included in the meta-analysis (S1 Data).
Discussion

To our knowledge, this study is the first meta-analysis of the relationship between maternal BMI and the risk of CP in offspring. The results of this meta-analysis, which included 8 studies with a total of 7,949,182 participants, showed that maternal overweight and obesity were significantly associated with CP in children. Maternal overweight, maternal obesity, and maternal obesity III were associated with a 29%, 45%, and 125% higher risk of CP in offspring, respectively. Maternal underweight was not associated with CP in offspring.

Stronger associations between maternal obesity and CP risk were found in our meta-analysis, especially in the USA and Europe. Maternal obesity has increased globally in recent years, and the incidence of adverse outcomes is increasing[33]. The number of women with maternal BMI ≥35 kg/m² doubled from 50 to 100 million between 2000 and 2010[34]. The etiology of maternal obesity may be related to maternal age[13], race[17], and lifestyle. These findings may provide motivation for women to maintain an appropriate weight before or during pregnancy. Maternal obesity is significantly related to Apgar scores <7 at 5 minutes[3], preterm delivery, periventricular leukomalacia (PVL)[35], and neurodevelopmental disability[36], which may contribute to CP. Obesity may induce inflammation[37], which may increase the risk of CP. Maternal infections diagnosed during pregnancy were associated with an increased risk of CP in offspring in a study by Bear et al[17]. Maternal chorioamnionitis and obesity increased the risk of PVL beyond that expected for preterm neonates[35].

Maternal obesity might affect fetal neurodevelopment through multiple pathways. Maternal obesity has an impact on fetal anomaly screening[38] and birth defects[39]. Maternal obesity is associated with neurodevelopmental and psychiatric disorders in offspring[40–44] via related alterations in the uterine environment[25] and/or epigenetic processes[26, 45]. The mechanisms through which maternal obesity alters the neurodevelopment of offspring may be related to placental inflammation, lipotoxicity, and oxidative stress, and these changes in the uterine environment may contribute to maladaptive programming of the fetal brain. Another mechanism by which maternal obesity may affect the neurodevelopment of offspring may be related to insulin resistance, which contributes to abnormal central glucose metabolism and transport. One study[46] analyzed the whole placental transcriptome in obese and normal-weight women and showed that maternal obesity had a negative effect on placental development and function. Another study[47] used oxidative stress biomarkers to analyze samples from mothers and offspring and found that maternal obesity could affect the maternal microenvironment and that oxidative stress has a negative impact on the placenta and fetal growth. Brain-derived neurotrophic factor (BDNF) is necessary for placental development and fetal growth. An additional study[48] found that pre-pregnancy/early maternal obesity adversely affects BDNF signaling and affects placental function and fetal growth. A study by Hatanaka et al[49] showed that maternal obesity leads to the abnormal development of the neuronal circuitry and the loss of synapses. A study by Niculescu et al[50] demonstrated that maternal obesity may alter fetal hippocampal development and that maternal exposure to a high-fat diet induces fetal resorption and small-for-gestational age (SGA) offspring. A study[51] by Tozuka et al demonstrated that maternal obesity impairs hippocampal progenitor cell division and neuronal production in young offspring. Thus, the association between maternal obesity and CP risk in children may be mediated by various factors.

The association between maternal overweight and obesity and CP in offspring was inconsistent when the results were stratified by study location, study design, and certain confounding variables. Maternal overweight and obesity could contribute to CP in children via multiple factors, including study location, study design, maternal age, maternal race, maternal smoking status, maternal diabetes status, and child gender. The heterogeneity decreased when the study of Pan et al was omitted, a result that may be related to the adjustment for maternal diabetes. In
addition, the source of heterogeneity may be the factors in the stratified analysis that were mentioned above. Although the meta-analysis adjusted for several confounding variables, potential biases due to other factors that contribute to childhood CP cannot be excluded. Other factors may interact with maternal obesity along the pathogenetic pathway that leads to CP in offspring.

This meta-analysis has several limitations. First, we may have missed some studies because we included only studies that were published in English and obtained from the Ovid Medline, EMBASE, and Web of Science databases. Furthermore, the pooled results of this meta-analysis should be interpreted with caution because they depend on a small number of studies, and the publication year may be a source of bias. Second, quantitative synthesis cannot eliminate the biases inherent to observational studies. Third, it is very difficult to visually assess publication bias when the number of included studies is only 8. Fourth, meta-analytic methods introduce limitations, especially when the source of heterogeneity is unclear or when publication bias is present. Although we did not find statistical evidence of publication bias, there may be publication bias, errors in data abstraction and incomplete ascertainment of published studies.

One of the major advantages of our study is that most of the included original articles used a cohort design, which excludes the possibility of reverse causation. Additionally, the sample size was large, which enhanced the statistical power for precise and reliable estimation.

In conclusion, our pooled analyses provide evidence that maternal obesity and overweight are significantly associated with CP in offspring. Additional studies are required to further investigate this question by identifying more risk factors.

Supporting information

S1 Checklist. PRISMA checklist. (DOC)

S1 Data. Retrieval strategy, New Castle Ottawa(NOS) quality assessment for included. (DOC)

Acknowledgments

This work was supported by the National Science Foundation of China (No. 81330016, 81630038, and 81771634), the Major State Basic Research Development Program (2017YFA0104200), and grants from the Science and Technology Bureau of Sichuan Province (2016TD0002). The search strategy was evaluated by a trained librarian from Sichuan University, and we would like to thank American Journal Experts (www.aje.com) for English language editing.

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References

1. McPherson JA, Smid MC, Smiley S, Stamilio DM. Association of Maternal Obesity with Child Cerebral Palsy or Death. American Journal of Perinatology. 2017; 34(6):563–7. https://doi.org/10.1055/s-0036-1594015 PMID: 27855463.

2. Persson M, Johansson S, Villamor E, Cnattingius S. Maternal overweight and obesity and risks of severe birth-asphyxia-related complications in term infants: a population-based cohort study in Sweden. PLoS Med. 2014; 11(5):e1001648. Epub 2014/05/23. https://doi.org/10.1371/journal.pmed.1001648 PMID: 24845218; PubMed Central PMCID: PMC34028185.

3. Zhu T, Tang J, Zhao F, Qu Y, Mu D. Association between maternal obesity and offspring Apgar score or cord pH: a systematic review and meta-analysis. Sci Rep. 2015; 5:18386. Epub 2015/12/23. https://doi.org/10.1038/srep18386 PMID: 26692415; PubMed Central PMCID: PMCPMC4686911.

4. Kanadya WM, Leszczynska-Gorzelak B, Jedrych M, Oleśzczyk J. Maternal pre-pregnancy obesity and the risk of preterm birth: a systematic overview of cohort studies with meta-analysis. Ginekol Pol. 2012; 83(4):270–8. Epub 2012/06/21. PMID: 22712259.

5. Herzog M, Cerar LK, Srsen TP, Verdenik I, Lucovnik M. Impact of risk factors other than prematurity on periventricular leukomalacia. A population-based matched case control study. European Journal of Obstetrics Gynecology and Reproductive Biology. 2015; 187:54–9. PMID: 70936272.

6. Edlow AG. Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. Prenat Diagn. 2017; 37(1):95–110. https://doi.org/10.1002/pd.4932 PMID: 27684946.

7. Wang Y, Tang J, Xu S, Weng S, Liu Z. Maternal Body Mass Index and Risk of Autism Spectrum Disorders in Offspring: A Meta-analysis. Sci Rep. 2016; 6:34248. Epub 2016/10/01. https://doi.org/10.1038/srep34248 PMID: 27683989; PubMed Central PMCID: PMCPMC4686911.

8. Mann J, McDermott S, Pan C, Hardin J, Zhang Z. Obesity and weight gain in pregnancy: Are they risk factors for intellectual disability in children? Developmental Medicine and Child Neurology. 2012; 54:58–9. PMID: 70936272.

9. Pan C, Deroche CB, Mann JR, McDermott S, Hardin JW. Is prepregnancy obesity associated with risk of cerebral palsy and epilepsy in children? J Child Neurol. 2014; 29(12):Np196–201. Epub 2013/12/18. https://doi.org/10.1177/0883073813510971 PMID: 22343434.

10. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. Jama. 2009; 301(6):636–50. Epub 2009/02/13. https://doi.org/10.1001/jama.2009.113 PMID: 19211471.

11. Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW, Eriksson JG, et al. Influence of maternal obesity on the long-term health of offspring. Lancet Diabetes Endocrinol. 2017; 5(1):53–64. Epub 2016/10/17. https://doi.org/10.1016/S2213-8587(16)30107-3 PMID: 27743978; PubMed Central PMCID: PMCPMC5245733.

12. McPherson JA, Smid MC, Smiley S, Stamilio DM. Association of Maternal Obesity with Child Cerebral Palsy or Death. Am J Perinatol. 2016. Epub 2016/11/18. https://doi.org/10.1055/s-0036-1594015 PMID: 27855463.

13. Villamor E, Tedroff K, Peterson M, Johansson S, Neovius M, Petersson G, et al. Association Between Maternal Body Mass Index in Early Pregnancy and Incidence of Cerebral Palsy. Jama. 2017; 317(9):925–36. Epub 2017/03/08. https://doi.org/10.1001/jama.2017.0945 PMID: 28267854.

14. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: Incidence, impairments and risk factors. Disability and Rehabilitation. 2006; 28(4):183–91. https://doi.org/10.1080/09638280500158422 PMID: 16467053.

15. Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy in children. Pediatrics. 2015; 136(6):1132–43. Epub 2015/11/26. https://doi.org/10.1542/peds.2015-0944 PMID: 26598455.

16. Mukerji A, Shah V, Shah PS. Periventricular/Intraventricular Hemorrhage and Neurodevelopmental Outcomes: A Meta-analysis. Pediatrics. 2015; 136(6):1132–43. Epub 2015/11/26. https://doi.org/10.1542/peds.2015-0944 PMID: 26598455.

17. Crisham Janik MD, Newman TB, Cheng YW, Xing G, Gilbert WM, Wu YW. Maternal diagnosis of obesity and risk of cerebral palsy in the child. J Pediatr. 2013; 163(5):1307–12. Epub 2013/08/13. https://doi.org/10.1016/j.jpeds.2013.06.062 PMID: 23932316; PubMed Central PMCID: PMCPMC3812421.
20. Forthun I, Wilcox AJ, Strandberg-Larsen K, Moster D, Nohr EA, Lie RT, et al. Maternal Prepregnancy BMI and Risk of Cerebral Palsy in Offspring. Pediatrics. 2016; 138(4). Epub 2016/09/10. https://doi.org/10.1542/peds.2016-0874 PMID: 27609826; PubMed Central PMCID: PMC5051208 conflicts of interest to disclose.

21. Walstab J, Bell R, Reddihough D, Brenneck S, Bessell C, Beischer N. Antenatal and intrapartum antecedents of cerebral palsy: a case-control study. Aust N Z J Obstet Gynaecol. 2002; 42(2):138–46. Epub 2002/06/19. PMID: 12069139.

22. Love ER, Crum J, Bhattacharya S. Independent effects of pregnancy induced hypertension on childhood development: a retrospective cohort study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2012; 165(2):219–24. https://doi.org/10.1016/j.ejogrb.2012.08.015 PubMed PMID: WOS:000313370300013. PMID: 22948131

23. Hasegawa J, Toyokawa S, Ikenoue T, Asano Y, Satoh S, Ikeda T, et al. Relevant Obstetric Factors for Cerebral Palsy: From the Nationwide Obstetric Compensation System in Japan. Plos One. 2016; 11(1). https://doi.org/10.1371/journal.pone.0148122 PubMed PMID: WOS:000369528400071. PMID: 26821386

24. Ahlin K, Himmelmann K, Hagberg G, Kacerovsky M, Cobo T, Wenerholm UB, et al. Non-infectious risk factors for different types of cerebral palsy in term-born babies: a population-based, case-control study. BJOG. 2013; 120(6):724–31. Epub 2013/02/20. https://doi.org/10.1111/1471-0528.12164 PMID: 23418811.

25. Howell KR, Powell TL. Effects of maternal obesity on placental function and fetal development. Reproduction. 2017; 153(3):R97–108. Epub 2016/11/20. https://doi.org/10.1530/REP-16-0495 PMID: 27864335.

26. Duquenne M, Dehouck B, Prevot V. Programming the Brain from the Womb: Maternal Obesity Perturbs the Hypothalamic Blood-Brain Barrier. Endocrinology. 2016; 157(6):2201–3. Epub 2016/06/04. https://doi.org/10.1210/en.2016-1262 PMID: 27258761.

27. Willi C, Bodenmann P, Ghali WA, Farts PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. Jama. 2007; 298(22):2654–64. Epub 2007/12/13. https://doi.org/10.1001/jama.298.22.2654 PMID: 18073361.

28. Hartzel J, Agresti A, Caffo B. Multinomial logit random effects models. Statistical Modelling. 2001; 1(2):81–102. https://doi.org/10.1177/1471082x0100100201 PubMed PMID: WOS:0000000000000001.

29. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003; 327(7414):557–60. Epub 2003/09/06. https://doi.org/10.1136/bmj.327.7414.557 PubMed PMID: WOS:000129851000006. PMID: 12958120; PubMed Central PMCID: PMCPMC192859.

30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997; 315(7109):629–34. Epub 1997/10/06. PMID: 9310563; PubMed Central PMCID: PMCPMC2127453.

31. Beggb CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50(4):108–101. Epub 1994/12/31. PMID: 7786990.

32. Nielson LF, Schendel D, Grove J, Hvidtjorn D, Jacobsson B, Josiasen T, et al. Asphyxia-related risk factors and their timing in spastic cerebral palsy. BJOG-an International Journal of Obstetrics and Gynaecology. 2008; 115(12):1518–28. https://doi.org/10.1111/j.1471-0528.2008.01896.x PubMed PMID: WOS:000260098200008. PMID: 19035988.

33. Catalano PM, Shankar K. Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. Bmj. 2017; 356:j1. Epub 2017/02/10. https://doi.org/10.1136/bmj.j1 PMID: 28179267.

34. Di Cesare M, Bentham J, Stevens GA, Zhou B, Danaei G, Lu Y, et al. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016; 387(10026):1377–96. PubMed PMID: WOS:000373217500031. https://doi.org/10.1016/S0140-6736(16)30054-X PMID: 27115820.

35. Herzog M, Cerar LK, Srnen TP, Verdenik I, Lucovnik M. Impact of risk factors other than prematurity on periventricular leukomalacia. A population-based matched case control study. Eur J Obstet Gynecol Reprod Biol. 2015; 187:57–9. Epub 2015/03/10. https://doi.org/10.1016/j.ejogrb.2015.02.008 PMID: 25748489.

36. Hinkle SNo, Sharma AJ, Kim SY, Schieve LA. Maternal prepregnancy weight status and associations with children’s development and disabilities at kindergarten. International Journal of Obesity. 2013; 37(10):1344–51. https://doi.org/10.1038/ijo.2013.128 PubMed PMID: WOS:000325542200008. PMID: 23860335.

37. Teo JD, Morris MJ, Jones NM. Maternal obesity increases inflammation and exacerbates damage following neonatal hypoxic-ischaemic brain injury in rats. Brain Behav Immun. 2016. Epub 2016/10/22. https://doi.org/10.1016/j.bbi.2016.10.010 PMID: 27746186.
38. Eastwood KA, Daly C, Hunter A, McCance D, Young I, Holmes V. The impact of maternal obesity on completion of foetal anomaly screening. J Perinat Med. 2017. Epub 2017/02/02. https://doi.org/10.1515/jpm-2016-0048 PMID: 28145880.

39. Parnell AS, Correa A, Reece EA. Pre-pregnancy Obesity as a Modifier of Gestational Diabetes and Birth Defects Associations: A Systematic Review. Matern Child Health J. 2017. Epub 2017/01/26. https://doi.org/10.1007/s10995-016-2209-4 PMID: 28120287.

40. Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VWV, Eriksson JG, et al. Influence of maternal obesity on the long-term health of off spring. Lancet Diabetes & Endocrinology. 2017; 5(1):53–64. https://doi.org/10.1016/s2213-8587(16)30107-3 PubMed PMID: 28743978

41. Edlow AG. Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. Prenat Diagn. 2017; 37(1):95–110. Epub 2016/09/30. https://doi.org/10.1002/pd.4932 PMID: 27684946.

42. Daraki V, Roumeliotaki T, Koutra K, Georgiou V, Kampouri M, Kyriklaki A, et al. Effect of parental obesity and gestational diabetes on child neuropsychological and behavioral development at 4 years of age: the Rhea mother-child cohort, Crete, Greece. Eur Child Adolesc Psychiatry. 2017. Epub 2017/01/05. https://doi.org/10.1007/s00787-016-0934-2 PMID: 28050707.

43. Mina TH, Lahti M, Drake AJ, Raikkonen K, Minnis H, Denison FC, et al. Prenatal exposure to very severe maternal obesity is associated with adverse neuropsychiatric outcomes in children. Psychol Med. 2017; 47(2):353–62. Epub 2016/10/26. https://doi.org/10.1007/s00787-016-0934-2 PMID: 27776561.

44. Adane AA, Mishra GD, Tooth LR. Maternal pre-pregnancy obesity and childhood physical and cognitive development of children: a systematic review. Int J Obes (Lond). 2016; 40(11):1608–18. Epub 2016/08/17. https://doi.org/10.1038/ijo.2016.140 PMID: 27528251.

45. Elshenawy S, Simmons R. Maternal obesity and prenatal programming. Mol Cell Endocrinol. 2016; 435:2–6. Epub 2016/07/10. https://doi.org/10.1016/j.mce.2016.07.002 PMID: 27392495.

46. Altmae S, Segura MT, Esteban FJ, Bartel S, Brandi P, Irmler M, et al. Maternal Pre-Pregnancy Obesity Is Associated with Altered Placental Transcriptome. PLoS One. 2017; 12(1):e0169223. Epub 2017/01/27. https://doi.org/10.1371/journal.pone.0169223 PMID: 28125991; PubMed Central PMCID: PMCPMC5268451 Helmoltz Center Munich and from Research Center Borstel during the conduct of the study. Dr. Koletzko is a member of the National Breastfeeding Committee and tends to be biased towards breastfeeding. The Ludwig-Maximilians-University of Munich, Germany and its employee Dr. Koletzko has received support for scientific and educational activities by companies that market products for infants and children, including Abbott, Baxter, B. Braun, Coca Cola, Dairy Goat Cooperative, Danone, Fresenius Kabi, Fonterra, Hipp, Hochdorf, Mead Johnson, Nestle, and Yakult, predominantly as part of publicly funded research projects with support of the European Commission or German governmental research support, outside the submitted work. The rest of the co-authors have nothing to disclose. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

47. Hernandez-Trejo M, Montoya-Estrada A, Torres-Ramos Y, Espejel-Nunez A, Guzman-Grenfell A, Morales-Hernandez R, et al. Oxidative stress biomarkers and their relationship with cytokine concentrations in overweight/obese pregnant women and their neonates. BMC Immunol. 2017; 18(1):3. Epub 2017/01/08. https://doi.org/10.1186/s12865-016-0184-6 PMID: 28061809; PubMed Central PMCID: PMCPMC5219784.

48. Prince CS, Maloyan A, Myatt L. Maternal obesity alters brain derived neurotrophic factor (BDNF) signaling in the placenta in a sexually dimorphic manner. Placenta. 2017; 49:55–63. Epub 2016/12/26. https://doi.org/10.1016/j.placenta.2016.11.010 PMID: 28012455; PubMed Central PMCID: PMCPMC5193148.

49. Hatanaka Y, Kabuta T, Wada K. Disturbance in Maternal Environment Leads to Abnormal Synaptic Instability during Neuronal Circuitry Development. Front Neurosci. 2017; 11:35. Epub 2017/02/22. https://doi.org/10.3389/fnins.2017.00035 PMID: 28220059; PubMed Central PMCID: PMCPMC5292599.

50. Niculescu MD, Lupu DS. High fat diet-induced maternal obesity alters fetal hippocampal development. Int J Dev Neurosci. 2009; 27(7):627–33. Epub 2009/08/22. https://doi.org/10.1016/j.ijdevneu.2009.08.006 PMID: 19695321; PubMed Central PMCID: PMCPMC2754591.

51. Tsuchiya Y, Wada E, Wada K. Diet-Induced obesity in female mice leads to peroxidized lipid accumulations and impairment of hippocampal neurogenesis during the early life of their offspring. Faseb J. 2009; 23(6):1920–34. Epub 2009/01/23. https://doi.org/10.1096/fj.08-124784 PMID: 19158155.