Maternal obesity is a risk factor for orofacial clefts: a meta-analysis

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Abstract

Orofacial clefts are the most prevalent birth defects that affect craniofacial structures and implicate genetic and environmental factors in their aetiology. Maternal metabolic state and nutrition have been related to these and other structural malformations, and studies of maternal obesity before pregnancy have shown controversial results about its association with the risk of orofacial clefts in their offspring. Our aim was to assess the combined effect of several single studies of maternal obesity on the risk of orofacial clefts using meta-analysis. We searched for these reports in the PubMed database, and selected 8 studies that met our criteria for eligibility. As a result of this analysis, and using maternal normal weight as a reference, we found that maternal obesity does increase the risk of orofacial clefts in their offspring (OR 1.18, 95% CI 1.11 to 1.26). When these clefts are considered separately, maternal obesity is associated with cleft lip with or without cleft palate (OR 1.13, 95% CI 1.04 to 1.23), and with cleft palate alone (OR 1.22, 95% CI 1.09 to 1.35). Our results support the relation between maternal obesity and orofacial clefts, and confirm two previous meta-analyses that considered fewer studies. However, the molecular mechanisms underlying this statistical evidence have not been fully elucidated.

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Introduction

Among birth defects cleft lip with or without cleft palate and cleft palate alone grouped together as orofacial clefts are the most common birth defects that affect the craniofacial skeleton. The prevalence of cleft lip and palate (1/1000 births) and of cleft palate alone (1/1600 births) varies according to the ethnic origin, geographical location, and socioeconomic group, among other factors.1 Around 350 syndromes include orofacial clefts among their features, and they comprise about 30% of all clefts. The remaining 70% are isolated (non-syndromic) orofacial clefts.1 Given their prevalence and the complexity of their rehabilitation plus medical costs and the emotional burden to patients and their families, these malformations are a worldwide public health problem.2 The aetiology of orofacial clefts can be explained by the interaction between functionally-altered genes and environmental factors.3 Maternal conditions such as diabetes, alcohol consumption, and smoking before and during pregnancy, have also been associated with these birth defects.1,4

According to the World Health Organization (WHO) about 27% of the world’s adult population is overweight or obese, with about 300 million obese women.5 Maternal overweight and obesity before pregnancy have been associated with an increased risk of maternal complications such as pre-
eclampsia and gestational diabetes, together with perinatal death and congenital malformations. 6 Although the reported effect is modest (around 27% incremental risk), maternal obesity before pregnancy has been identified as a risk factor for orofacial clefts in cohort studies, 7,8 but some case-control studies have failed to pick up the association. 9,10

Our aim was to evaluate the effect of maternal obesity before pregnancy on the risk of development of orofacial clefts in the offspring using a meta-analysis that combined the individual effects of several relevant studies reported in a scientific database.

Subjects and methods

Extraction of data

We searched the database PubMed up to October 2014 with no restrictions for date of entry and including the “Related articles” option. For this purpose we used the following terms: “orofacial clefts” OR “cleft lip palate” OR “cleft palate only” OR “oral clefts” AND “maternal obesity” OR “maternal body mass index”, and included case-control and cohort studies. This search was made independently by two of us who identified the authors, year of publication, journal, sample size, maternal normal weight before pregnancy, classification criteria for obesity, and results (number of cases and controls among mothers of normal weight and obese).

Statistical analyses

To estimate the effect of maternal obesity before pregnancy we calculated the combined odds ratio (OR) with 95% confidence interval (95% CI), using the effect of maternal normal weight as reference. The presence of heterogeneity among the selected studies was assessed based on the Cochran Q statistic, which is calculated by summing the squared deviations for the effect of each study related to the pooled effect. 11 In addition, heterogeneity was quantified using the $I^2$ test, which indicates the percentage of between-studies variability that is explained by heterogeneity. 11 The combined effect was therefore estimated using fixed-effects or random effects methods according to the respective absence ($I^2 < 50$) or presence of heterogeneity ($I^2 > 50$). 12 Publication bias was evaluated by visual inspection of the Begg’s funnel plot, on which each trail is presented around a central estimator (Napierian logarithm of pooled OR in the ordinate) compared with the standard error (as estimator or study size). If reports are located symmetrically (as a funnel) one can conclude the absence of publication bias (that is, that studies have been published independently of their sample size and of their positive or negative effect). 12 In addition, visual inspection of a funnel plot was complemented by the computation of Eggers statistic, which detects asymmetry from this plot based on a regression model of precision (inverse of standard error) compared with the effect. 12 All tests were calculated with the aid of the statistical package Epidat 3.1.

Results

The initial result of our search showed 26 reports. The reading of the full text of each of these papers permitted us to exclude several studies for the reasons detailed in Fig. 1. Eight reports were then considered for the meta-analysis (Table 1). All these papers classified mothers according to their body mass index (BMI) before pregnancy as normal (BMI 18.5-24.9 kg/m²) or obese (BMI ≥ 30 kg/m²), the only exception being Cedergren and Källén 19 who classified normal as BMI 19.8-26 kg/m² and obese as BMI > 29 kg/m², respectively. The number of affected and non-affected children delivered by these mothers is shown in Table 1 as total orofacial clefts, and as cleft lip and palate, and cleft palate alone, separately.

When we considered the total number of orofacial clefts, the meta-analysis showed no evidence of heterogeneity among the 8 studies ($Q = 9.38; p = 0.227; I^2 = 25.4\%$), so the combined effect was estimated by means of fixed effects. Using maternal normal weight as the reference, maternal obesity significantly increased the risk of orofacial clefts in the offspring (OR = 1.18; 95% CI 1.11 to 1.26) (Fig. 2). The individual OR for each study and its contribution (weight (%)) are shown in Fig. 2. The analyses of publication bias showed a borderline asymmetry as can be seen in the Beggs funnel plot (Fig. 3). However, we found no significance in the result of the Egger test ($p = 0.907$), which shows that this kind of bias is not present in our selection.

Many authors have considered cleft lip and palate and cleft palate alone as two different entities, 3 and so we also assessed the combined effect of segregating by type of orofacial cleft. Six of the 8 studies included data about cleft lip and palate and cleft palate alone separately (Table 1). When we evaluated the overall effect for 6 studies about maternal obesity and the risk for cleft lip and palate in the offspring, the results allowed

![](image_url)

Fig. 1. Algorithm showing how the studies were selected.
Table 1
Studies that met the criteria for meta-analysis and their characteristics.

<table>
<thead>
<tr>
<th>First author and date</th>
<th>Country</th>
<th>Type of study</th>
<th>No. of controls</th>
<th>No. of orofacial clefts</th>
<th>No. with cleft lip and palate</th>
<th>No. with cleft palate alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal weight/obese</td>
<td>total</td>
<td>Normal weight/obese</td>
<td>Normal weight/obese</td>
</tr>
<tr>
<td>Watkins (2003)</td>
<td>USA</td>
<td>Case-control</td>
<td>212/36</td>
<td>59/8</td>
<td>37/6</td>
<td>22/2</td>
</tr>
<tr>
<td>Honein (2007)</td>
<td>USA</td>
<td>Case-control</td>
<td>1584/484</td>
<td>774/229</td>
<td>492/139</td>
<td>282/90</td>
</tr>
<tr>
<td>Waller (2007)</td>
<td>USA</td>
<td>Case-control</td>
<td>2241/572</td>
<td>922/269</td>
<td>592/165</td>
<td>330/104</td>
</tr>
<tr>
<td>Oddy (2009)</td>
<td>Australia</td>
<td>Case-control</td>
<td>229/30</td>
<td>22/6</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Carmichael (2012)</td>
<td>USA</td>
<td>Case-control</td>
<td>3442/984</td>
<td>1303/438</td>
<td>860/276</td>
<td>404/162</td>
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Fig. 2. Forest plot showing association between maternal obesity and total orofacial clefts. Odds ratio (OR) and 95% confidence intervals (95% CI) are shown for each study and for their combined effect. Weight (%) indicates the contribution of each study to the overall OR.

Pooled OR based on fixed-effects models (I² = 25.4%; p = 0.227).

Discussion

The results about the risks associated with maternal obesity before pregnancy and orofacial clefts are controversial. Although some reports have shown the association, others have not. The aim of this study was to analyse the results of a set of reports about the association by doing a meta-analysis in a large sample size to evaluate the combined effect of single studies.

We considered normal maternal weight before pregnancy as the reference, and have pooled the effects of 8 studies to verify this. Pooled data showed that obese mothers have a moderate increase in the risk for all clefts (18%, Fig. 2). The historical division between cleft lip and palate and cleft palate alone led us to analyse each type of cleft separately. Six of the 8 studies separated the data for each category, and cleft lip and palate, and cleft palate alone, were also related to maternal obesity with a mild increase in risk (13% and
To the best of our knowledge, there have been two previous meta-analyses in this field, and they also describe maternal obesity as a risk factor for orofacial clefts. Stothard et al. considered 3 of the 8 studies that we also evaluated: Watkins et al., Cedergren and Källen, and Waller et al. They found OR of 1.20 for cleft lip and palate and 1.23 for cleft palate alone. Molina-Solana et al. included just 2 of the reports that we did (Cedergren and Källen, and Stott-Miller et al.), and described an overall OR of 1.26. We included more reports, with a consequent increase in the total size of the sample. For example, the study of Molina-Solana et al. considers 1810 cases and 636 086 controls, while we included 7204 cases and 1 396 933 controls. Despite this greater total sample size, the risk of maternal obesity in orofacial clefts has not changed substantially compared with the previous meta-analysis. We can infer therefore that this variable has only a mild effect on facial clefts at birth.

Maternal obesity has been associated not only with orofacial clefts, but also with other major structural birth defects, such as those of the neural tube and heart. However, the obesity-teratogenic mechanism has not been fully elucidated. A possible explanation can be the close relation between obesity and gestational diabetes with the consequent hyperglycaemia during pregnancy. In rats, maternal hyperglycaemia leads to the delivery of offspring with agnathia, micrognathia, and cleft lip and palate. These malformations are related to defects in the fetal expression of developmental genes such as bone morphogenetic protein 4 and the sonic hedgehog gene and those that encode enzymes for the management of reactive oxygen species, which shows that glucose has a teratogenic effect at several levels.

However, there have been some controversial results. Some reports have found that diabetic mothers have an increased risk of having a child with cleft lip and palate.
comparing with non-diabetic mothers. However, some authors have found no differences in metabolic variables such as glucose concentrations and glucose tolerance between mothers of babies with cleft lip and palate and control mothers. In addition to glucose concentrations in obesity, the condition has been associated with a deficiency in certain nutrients. Obese women have deficiencies mainly in folate and iron. Diabetic mothers who take folic acid (in supplements or vitamins) during the month before conception or within the first 3 months of pregnancy (periconceptional period) had a 6-fold reduction in the risk of orofacial clefts compared with diabetic mothers who did not take supplements. This can be linked to evidence from murine models that has shown that palatal development is regulated by epigenetic changes in embryonic DNA such as methylation, which modulates gene expression. It has been widely documented that folic acid and folates are fundamental for the homeostasis of methyl-group donors (or one-carbon metabolism). In neural tube defects, another prevalent birth defect that implicates embryological structures closely, epigenetic changes have been seen in animals but at levels at which histone acetylation occurs, a mechanism that could be explored in orofacial clefts.

Despite the fact that we have combined reports from case-control studies, cohort studies, and studies that used different criteria to define obesity (BMI ≥ 30 kg/m² and BMI > 29 kg/m²) in the current meta-analysis, we found no evidence of heterogeneity for our 3 analyses (total orofacial clefts, cleft lip and palate, and cleft palate alone). In addition, we found no publication bias in these 3 analyses according to the tests that we used. These factors, plus the fact that, compared with previous meta-analyses, we increased the number of single reports, strengthen our results. However, despite this increment, the number of pooled studies is still modest. This could have an impact on the power to detect heterogeneity using statistics such as Q or I², and this could possibly be the main limitation of the study.

In summary, we made a meta-analysis of eight single studies the results of which support the association between maternal obesity before pregnancy and the risk of orofacial clefts in the offspring when analysed as a group of facial clefts or separated into the subgroups cleft lip and palate, and cleft palate alone. Further analyses are necessary to elucidate the molecular mechanism or mechanisms that explain these statistical findings.

Conflict of interest
We have no conflicts of interest.

Ethics statement/confirmation of patient permission
Not required.

Appendix A. Supplementary data
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bjoms.2015.05.017.

References


