Special Article

Maternal Tobacco Smoke Exposure during Pregnancy and the Occurrence of Orofacial Clefts: A Systematic Review of Reported Meta-analyses

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Background: *The association between maternal tobacco smoke exposure and the occurrence of orofacial clefts (OFCs) is evident from several meta-analyses; however, a review of these findings is lacking.*
Objective: *To review the evidence in the literature systematically for the main findings of these meta-analyses.*
Material and Method: *A systematic literature search between 1966 and 2016 was conducted through PubMed, using the search terms 'cleft lip palate' or 'orofacial clefts', and 'tobacco smoke'.*
Results: *Based on a meta-analysis of 14 studies, passive tobacco smoke exposure increased the risk of non-syndromic orofacial clefts (NSOFC) 2.11 times (odds ratio [OR] (95% confidence interval [CI]: 1.54-2.89). A pooled analysis of 2 studies, however, revealed no association between passive tobacco smoke exposure and the risk of OFCs (OR: 1.09 [95% CI: 0.93–1.27]). Two meta-analyses comprising a respective 38 and 5 studies found significant positive associations between active tobacco smoke exposure and the occurrence of OFCs (OR: 1.28 [95% CI: 1.20-1.36]) and NSOFC (OR: 1.64 [95% CI: 1.33-2.02]), respectively.*
Conclusion: *The current systematic review of reported meta-analyses revealed a positive association between maternal smoke exposure and an increased risk of occurrence of OFCs and NSOFC. These findings confirm that pregnant women should avoid tobacco smoke.*

Keywords: *Tobacco smoke exposure, Non-syndromic orofacial clefts, Orofacial clefts, Meta-analysis, Systematic review, Pregnant woman*

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Orofacial clefts (OFCs) including cleft lip (CL) or cleft lip with cleft palate (CLP) and isolated cleft palate (CP) are common birth defects of the head and neck, and have complex etiologies with environmental and genetic factors[1-4]. The birth prevalence of OFCs varies between 0.57 and 1.57 cases per 1,000 live births, according to population and ethnicity[1,2]. OFCs can occur as an isolated anomaly without any associated syndrome or other apparent structural or developmental abnormalities (non-syndromic orofacial clefts). OFCs may be associated with a syndrome or other apparent congenital abnormalities (syndromic orofacial clefts)[3,4].

The association between maternal tobacco exposure and the increasing prevalence of orofacial clefts has been documented in many studies[5-42], and confirmed through meta-analyses[43-49]. Several meta-analyses, however, indicate variability of results between maternal tobacco smoke exposure and the occurrence of OFCs. To obtain an overall estimate for the association between tobacco smoke exposure and the occurrence of OFCs, the authors conducted a systematic literature review to evaluate the reported results of the association between maternal tobacco smoke exposure and the occurrence of orofacial clefts.

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Material and Method

Data sources

A systematic literature search was conducted for the years 1966 to 2016, using the electronic database PubMed and the key search terms 'cleft lip palate' or 'orofacial clefts' and 'tobacco smoke'. Papers containing these terms in any language were included and searched. The titles and abstracts of 191 relevant

articles were screened independently by two authors (OP and MP) to identify articles for which there were full text publications. The same authors then selected relevant articles reporting a meta-analysis, including on the association between maternal tobacco smoke exposure and prevalence of orofacial clefts. Reference lists of included papers were screened for additional papers that may have been missed in the databases searched[1,2].

Definition

The definition of active smoke exposure was fulfilled if there was maternal tobacco smoking as opposed to environmental tobacco smoke or second-hand smoke exposure, which are considered passive tobacco smoke exposure.

Non-syndromic orofacial clefts (NSOFC) were defined as OFCs occurring as isolated anomalies without associated syndromes or other apparent structural or developmental abnormalities.

Study selection

The studies included meta-analyses on the association between maternal tobacco smoke exposure (active or passive) and the prevalence of orofacial clefts. The two authors performed the search independently using these inclusion criteria. Disagreements were resolved by consensus.

Data extraction

Using a standardized data extraction form, we included data on the (a) type of tobacco smoke exposure, (b) number of cases included, (c) number of studies included, (d) relative risk for the occurrence of orofacial clefts, (e) relative risk for the occurrence of cleft lip with/or without cleft palate, (f) relative risk for the occurrence of cleft palate, (g) quality rating, (h) heterogeneity, (i) publication bias, and (j) sensitivity test.

Each meta-analysis was reviewed according to (a) the databases used; (b) whether the meta-analysis guidelines were used (*i.e.*, Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[49,50] or the Quality of Reporting of Meta-analyses (Quorom) statement, 2009[51]; (c) whether it was rated on quality (e.g., Newcastle-Ottawa scale[49], or Cochrane Handbook guidelines[49]); (d) the statistics used to test for heterogeneity in the data (i.e., Cochran's Q[52] or I^2[53]), (e) whether fixed [54] or random effects models[55] were used for pooling individual studies; and, (f) which tests of publication bias were used (i.e., funnel plots[56], Egger's test[57], or Begg's test[58]). Furthermore, we checked whether sensitivity analyses had been conducted.

Quality assessment

Studies were assessed on completeness and origins of the data.

Statistical analysis

Relative risk for orofacial clefts, cleft lip with or without cleft palate, and cleft palate were presented with their respective odds ratio (OR) and 95% confidence interval (CI).

Results

The search combination in the databases identified 191 relevant articles. A thorough evaluation of these articles using the inclusion and exclusion criteria led to the exclusion of 183 articles leaving 8 papers that met the inclusion criteria. After a critical review of the full text of the 8, 2 were excluded because of incomplete data. Other than these 6 papers, no additional papers were found after reference checking (Fig. 1).

Sabbagh et al reviewed 14 studies and found a near two-fold increase in the risk of NSOFC (non-syndromic orofacial clefts) associated with passive tobacco smoke exposure (OR: 2.11, 95% CI: 1.54-2.89) and the magnitude of the association was similar between cleft lip with or without cleft palate (CL/P) and cleft palate (CP). By comparison, Leonardi-Bee et al. conducted a pooled analysis of 2 studies, which revealed no associations between overall passive smoke exposure and the risk of orofacial clefts (OR: 1.09, 95% CI: 0.93-1.27).

Hackshaw et al reviewed 38 studies and found that active maternal smoking during pregnancy was associated with orofacial clefts (OR: 1.28, 95% CI: 1.20-1.36), while Zeiger et al., who reviewed 5 studies found that active maternal smoking during pregnancy was associated with NSOFC (OR:1.64, 95% CI: 1.33-2.02).

Little et al. and Wyszynski et al. reviewed respective 24 and 11 studies and reported an association between maternal active tobacco smoking exposure during pregnancy and the increase in the risk of NSOFC (Table 1).

Discussion

Of the 6 reported meta-analyses included, the number of studies in each meta-analysis varied from 2 to 38, with the majority (67%) of meta-analyses being

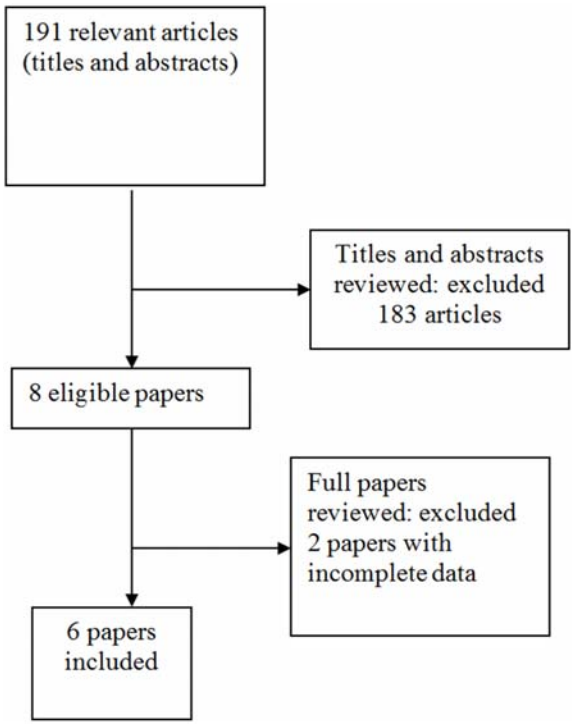

Fig. 1 Flow diagram of papers searched and papers included into the systematic review.

available for active maternal tobacco smoking exposure during pregnancy. Only a relatively small number (17%) of the studies completely followed the meta-analyses guidelines[49,50]. This systematic review of reported meta-analyses confirmed statistically significant positive associations between active or passive maternal tobacco smoke exposure and the increased risk of occurrence of OFCs and NSOFC [43-48].

Maternal tobacco smoking during pregnancy is an established risk factor for miscarriage, premature births, small for gestational age, and congenital malformations [3-42]. Tobacco smoke can produce various biological chemicals including nicotine, and carbon monoxide that injure the fetus [3-42]; however, the pathogenesis of tobacco smoke in the increase of abnormalities in babies is not well understood. Nicotine can cause blood vessels to constrict, which may reduce the oxygen supply to the fetus and carbon monoxide can bind to hemoglobin resulting in a lower amount of oxygen to the fetus [5]. Some investigations have found susceptible genes like nitric oxide synthase (*NOS*) which are more susceptible to the toxic effects of tobacco smoke exposure than others[59]. Cigarette smoking has a broad impact on DNA methylation of genes at many loci and this might be a potential mechanism for the adverse health outcomes[60,61]. The precise underlying mechanism (s) for the teratogenic effects remains unclear.

The relatively wide-range effect (OR 1.09 to 2.11) of maternal smoke exposure in the associations of the occurrence of orofacial clefts may be explained by the presence of underlying etiologic heterogeneity in orofacial clefts and the differential susceptibility of each individual to tobacco smoke exposure.

Study limitations

Most of the data obtained from these meta-analyses were self-reported data, and are often retrospective in nature and, therefore, subject to recall or response bias due to the socially-sensitive nature of the questions and answers.

Conclusion

The results of the present study based on the series of meta-analyses published to date indicate that cigarette smoke exposure during pregnancy is associated with increased risk of orofacial clefts including CLP and CP. It is suggested that maternal smoke exposure is one of many factors in the etiology of cleft lip and cleft palate in humans. Maternal smoke exposure in pregnancy is an important risk factor for several major birth defects and public health educational information should encourage all women to avoid tobacco smoke during pregnancy. The findings from the foregoing meta-analyses could provide further insight into better policy making.

What is already known on this topic?

Cigarette smoke exposure during pregnancy is associated with increased risks of OFCs.

What this study adds?

The current systematic review of reported meta-analyses found a positive association between maternal tobacco smoke exposure and the increased risk of occurrence of OFCs and NSOFC.

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Potential conflicts of interest

None.

Table 1. Associations based on meta-analyses of maternal tobacco smoke exposure and occurrence of orofacial clefts

References	Type of tobacco smoke exposure	Number of cases/number of studies	Main outcome: relative risk for orofacial clefts, OR (95% CI)	Relative risk for cleft lip with or without cleft palate, OR (95% CI)	Relative risk for cleft palate, OR (95% CI)	Quality rating	Heterogeneity	Publication bias	Sensitivity analyses
Sabbagh et al (2015)[43]	Passive smoking	1,869/14	NSOFC, 2.11[a] (1.54-2.89)	2.05 (1.27-3.30)	2.11 (1.23-3.62)	Yes (Newcastle -Ottawa Scale)	Yes (I^2 >75%)	Yes (funnel plots and Egger's test)	Yes
Hackshaw et al (2011)[44]	Active smoking	23,441/38	OFC, 1.28 (1.20-1.36)	NA	NA	NA	Yes	Yes (funnel plots)	NA
Leonardi-Bee et al (2011)[45]	Passive smoking	1,651/2[b]	OFC, 1.09 (0.93-1.27)	NA	NA	Yes	Yes (I^2 = 0%)	Yes (funnel plots)	NA
Zeiger et al (2005) [46]	Active smoking	1,384/5	NSOFC, 1.64 (1.33-2.02)	NA	1.42 (1.06-1.90)[c]	NA	Yes	Yes (funnel plots, Begg's test, and Egger's test)	NA
Little et al (2004)[47]	Active smoking	15,771/24	NSOFC, NA	1.34 (1.25-1.44)	1.22 (1.10-1.35)	Yes	Yes (Q test)	Yes (funnel plots and Egger's test)	NA
Wyszynski et al (1997)[48]	Active smoking	3,566/11	NSOFC, NA	1.29 (1.18-1.42)	1.32 (1.10-1.62)	Yes	Yes (Breslow and Day test)	Yes	NA
Total[43-48]	Active and Passive	47,682/94 (range, 2-38)	OFC and NSOFC	1.29 (1.18-1.42) to 2.05 (1.27-3.30)	1.22 (1.10-1.35 to 2.11 (1.23-3.62)	Yes	Yes	Yes	NA

NA = Not available; OFC = Orofacial clefts; NSOFC = Non-syndromic orofacial clefts; OR = Odds ratio

[a] adjustment for potential confounders attenuated the magnitude of association to about a 1.5-fold increase in risk

[b] Four of 19 studies assessed the effect of passive smoke exposure on the risk of defects of the face, eyes, ears, and neck

[c] 1.95 (1.22-3.10) (the infant carried the TGFA Taq1 C2 allele)

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การได้รับควันบุหรี่ของมารดาขณะตั้งครรภ์และการเกิดปากแหว่งเพดานโหว่: การศึกษาทบทวนอย่างเป็นระบบจากรายงาน meta-analyses

อวยพร ปะนะมณฑา, ภัทร วิริมย์รัตน์, ยุทธพงศ์ วงศ์สวัสดิวัฒน์, อรรฆมิศา ไชกิจภิญโญ, มนัส ปะนะมณฑา, กุณฑล วิชาจารย์

ภูมิหลัง: ความสัมพันธ์ของมารดาที่ได้รับควันบุหรี่ขณะตั้งครรภ์กับการเกิดปากแหว่งเพดานโหว่ (OFCs) นั้นได้มีรายงานใน meta-analyses แต่ยังไม่มีการศึกษาทบทวน meta-analyses

วัตถุประสงค์: เพื่อศึกษาอย่างเป็นระบบของรายงาน meta-analyses

วัสดุและวิธีการ: ศึกษาจากรายงานในฐานข้อมูล PubMed ตั้งแต่ปี พ.ศ. 2509 ถึง 2559 โดยใช้คำที่ค้นหาคือ cleft lip palate or orofacial clefts and tobacco smoke

ผลการศึกษา: meta-analysis ที่ศึกษา 14 รายงานพบว่ามารดาที่ได้รับควันบุหรี่ทางอ้อมมีโอกาสเกิด non-syndromic orofacial clefts (NSOFC) มากกว่าคนปกติเท่ากับ 2.11 (odds ratio [OR] (95% confidence interval [CI]: 1.54-2.89)แต่จาก pooled analysis ของการศึกษาหนึ่งที่ศึกษา 2 รายงานพบว่า OFCs ในกลุ่มที่ได้รับควันบุหรี่ทางอ้อมไม่ได้เพิ่มขึ้น (OR: 1.09 [95% CI: 0.93 ถึง 1.27]). meta-analyses จำนวน 2 เรื่องที่ศึกษา 38 รายงานและ 5 รายงาน พบว่ามารดาที่สูบบุหรี่ขณะตั้งครรภ์ (สูบเอง) มีความเสี่ยงที่จะเกิด OFCs (OR: 1.28 [95% CI: 1.20 ถึง 1.36] และ NSOFC (OR: 1.64 [95% CI: 1.33 ถึง 2.02] สูงกว่ามารดาที่ไม่ได้สูบบุหรี่ตามลำดับ

สรุป: การศึกษาทบทวนอย่างเป็นระบบของ meta-analyses ต่างๆ นี้พบว่ามารดาที่ได้รับควันบุหรี่มีความเสี่ยงที่ทารกจะเกิด OFCs และ NSOFC มากกว่าคนที่ไม่ได้รับควันบุหรี่ ดังนั้นผู้หญิงตั้งครรภ์ควรหลีกเลี่ยงควันบุหรี่