

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.

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

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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 (Quorum) 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

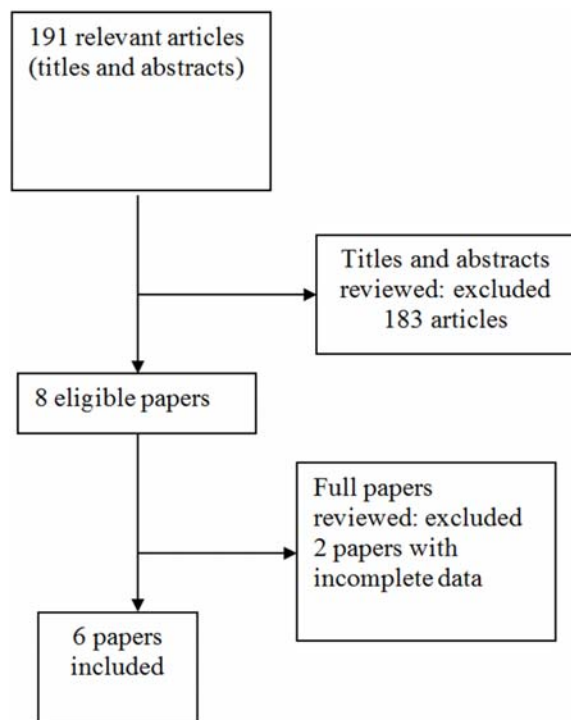


Fig. 1 Flow diagram of papers searched and papers included into the systematic review.

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 ($I^2 > 75\%$)	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, Egger'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)

References

1. Panamonta V, Pradubwong S, Panamonta M, Chowchuen B. Global birth prevalence of orofacial clefts: A systematic review. *J Med Assoc Thai* 2015; 98 (Suppl 7): S11-21.
2. Panamonta V, Pradubwong S, Panamonta M, Chowchuen B. Prevalence of congenital heart diseases in patients with orofacial clefts: a systematic review. *J Med Assoc Thai* 2015; 98 (Suppl 7): S22-7.
3. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. *Lancet* 2009; 374: 1773-85.
4. Mossey P. Epidemiology underpinning research in the aetiology of orofacial clefts. *Orthod Craniofac Res* 2007; 10: 114-20.
5. Evans DR, Newcombe RG, Campbell H. Maternal smoking habits and congenital malformations: a population study. *Br Med J* 1979; 2: 171-3.
6. Saxen I. Cleft lip and palate in Finland: parental histories, course of pregnancy and selected environmental factors. *Int J Epidemiol* 1974; 3: 263-70.
7. Ericson A, Kallen B, Westerholm P. Cigarette smoking as an etiologic factor in cleft lip and palate. *Am J Obstet Gynecol* 1979; 135: 348-51.
8. Kallen K. Maternal smoking and orofacial clefts. *Cleft Palate Craniofac J* 1997; 34: 11-6.
9. Czeizel A, Nagy E. A recent aetiological study on facial clefting in Hungary. *Acta Paediatr Hung* 1986; 27: 145-66.
10. Christensen K, Olsen J, Norgaard-Pedersen B, Basso O, Stovring H, Milhollin-Johnson L, et al. Oral clefts, transforming growth factor alpha gene variants, and maternal smoking: a population-based case-control study in Denmark, 1991-1994. *Am J Epidemiol* 1999; 149: 248-55.
11. Lorente C, Cordier S, Goujard J, Ayme S, Bianchi F, Calzolari E, et al. Tobacco and alcohol use during pregnancy and risk of oral clefts. Occupational Exposure and Congenital Malformation Working Group. *Am J Public Health* 2000; 90: 415-9.
12. Kelsey JL, Dwyer T, Holford TR, Bracken MB. Maternal smoking and congenital malformations: an epidemiological study. *J Epidemiol Community Health* 1978; 32: 102-7.
13. Christianson RE. The relationship between maternal smoking and the incidence of congenital anomalies. *Am J Epidemiol* 1980; 112: 684-95.
14. Shiono PH, Klebanoff MA, Berendes HW. Congenital malformations and maternal smoking during pregnancy. *Teratology* 1986; 34: 65-71.
15. Shaw GM, Wasserman CR, Lammer EJ, O'Malley CD, Murray JC, Basart AM, et al. Orofacial clefts, parental cigarette smoking, and transforming growth factor-alpha gene variants. *Am J Hum Genet* 1996; 58: 551-61.
16. Khoury MJ, Weinstein A, Panny S, Holtzman NA, Lindsay PK, Farrel K, et al. Maternal cigarette smoking and oral clefts: a population-based study. *Am J Public Health* 1987; 77: 623-5.
17. Hwang SJ, Beaty TH, Panny SR, Street NA, Joseph JM, Gordon S, et al. Association study of transforming growth factor alpha (TGF alpha) TaqI polymorphism and oral clefts: indication of gene-environment interaction in a population-based sample of infants with birth defects. *Am J Epidemiol* 1995; 141: 629-36.
18. Beaty TH, Wang H, Hetmanski JB, Fan YT, Zeiger JS, Liang KY, et al. A case-control study of nonsyndromic oral clefts in Maryland. *Ann Epidemiol* 2001; 11: 434-42.
19. Khoury MJ, Gomez-Farias M, Mulinare J. Does maternal cigarette smoking during pregnancy cause cleft lip and palate in offspring? *Am J Dis Child* 1989; 143: 333-7.
20. Malloy MH, Kleinman JC, Bakewell JM, Schramm WF, Land GH. Maternal smoking during pregnancy: no association with congenital malformations in Missouri 1980-83. *Am J Public Health* 1989; 79: 1243-6.
21. Lief S, Olshan AF, Werler M, Strauss RP, Smith J, Mitchell A. Maternal cigarette smoking during pregnancy and risk of oral clefts in newborns. *Am J Epidemiol* 1999; 150: 683-94.
22. Van den Eeden SK, Karagas MR, Daling JR, Vaughan TL. A case-control study of maternal smoking and congenital malformations. *Paediatr Perinat Epidemiol* 1990; 4: 147-55.
23. Romitti PA, Lidral AC, Munger RG, Daack-Hirsch S, Burns TL, Murray JC. Candidate genes for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype-environment interactions from a population-based case-control study of orofacial clefts. *Teratology* 1999; 59: 39-50.
24. Chung KC, Kowalski CP, Kim HM, Buchman SR. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. *Plast Reconstr Surg* 2000; 105: 485-91.
25. Honein MA, Paulozzi LJ, Watkins ML. Maternal smoking and birth defects: validity of birth

- certificate data for effect estimation. *Public Health Rep* 2001; 116: 327-35.
26. Woods SE, Raju U. Maternal smoking and the risk of congenital birth defects: a cohort study. *J Am Board Fam Pract* 2001; 14: 330-4.
 27. McDonald AD, Armstrong BG, Sloan M. Cigarette, alcohol, and coffee consumption and congenital defects. *Am J Public Health* 1992; 82: 91-3.
 28. Little J, Cardy A, Arslan MT, Gilmour M, Mossey PA. Smoking and orofacial clefts: a United Kingdom-based case-control study. *Cleft Palate Craniofac J* 2004; 41: 381-6.
 29. Seidman DS, Ever-Hadani P, Gale R. Effect of maternal smoking and age on congenital anomalies. *Obstet Gynecol* 1990; 76: 1046-50.
 30. Mirilas P, Mentessidou A, Kontis E, Asimakidou M, Moxham BJ, Petropoulos AS, et al. Parental exposures and risk of nonsyndromic orofacial clefts in offspring: a case-control study in Greece. *Int J Pediatr Otorhinolaryngol* 2011; 75: 695-9.
 31. Chevrier C, Bahuau M, Perret C, Iovannisci DM, Nelva A, Herman C, et al. Genetic susceptibilities in the association between maternal exposure to tobacco smoke and the risk of nonsyndromic oral cleft. *Am J Med Genet A* 2008; 146A: 2396-406.
 32. Leite IC, Koifman S. Oral clefts, consanguinity, parental tobacco and alcohol use: a case-control study in Rio de Janeiro, Brazil. *Braz Oral Res* 2009; 23: 31-7.
 33. Wang W, Guan P, Xu W, Zhou B. Risk factors for oral clefts: a population-based case-control study in Shenyang, China. *Paediatr Perinat Epidemiol* 2009; 23: 310-20.
 34. Honein MA, Rasmussen SA, Reefhuis J, Romitti PA, Lammer EJ, Sun L, et al. Maternal smoking and environmental tobacco smoke exposure and the risk of orofacial clefts. *Epidemiology* 2007; 18: 226-33.
 35. Jianyan L, Zeqiang G, Yongjuan C, Kaihong D, Bing D, Rongsheng L. Analysis of interactions between genetic variants of BMP4 and environmental factors with nonsyndromic cleft lip with or without cleft palate susceptibility. *Int J Oral Maxillofac Surg* 2010; 39: 50-6.
 36. Li L, Zhu GQ, Meng T, Shi JY, Wu J, Xu X, et al. Biological and epidemiological evidence of interaction of infant genotypes at Rs7205289 and maternal passive smoking in cleft palate. *Am J Med Genet A* 2011; 155A: 2940-8.
 37. Zhang B, Jiao X, Mao L, Xue J. Maternal cigarette smoking and the associated risk of having a child with orofacial clefts in China: a case-control study. *J Craniomaxillofac Surg* 2011; 39: 313-8.
 38. Li Z, Liu J, Ye R, Zhang L, Zheng X, Ren A. Maternal passive smoking and risk of cleft lip with or without cleft palate. *Epidemiology* 2010; 21: 240-2.
 39. Lie RT, Wilcox AJ, Taylor J, Gjessing HK, Saugstad OD, Aabyholm F, et al. Maternal smoking and oral clefts: the role of detoxification pathway genes. *Epidemiology* 2008; 19: 606-15.
 40. Taghavi N, Mollaian M, Alizadeh P, Moshref M, Modabernia S, Akbarzadeh AR. Orofacial clefts and risk factors in Tehran, Iran: a case control study. *Iran Red Crescent Med J* 2012; 14: 25-30.
 41. Honein MA, Devine O, Grosse SD, Reefhuis J. Prevention of orofacial clefts caused by smoking: implications of the Surgeon General's report. *Birth Defects Res A Clin Mol Teratol* 2014; 100: 822-5.
 42. McKinney CM, Pisek A, Chowchuen B, DeRouen T, Muktabhant B, Pradubwong S, et al. Case-control study of nutritional and environmental factors and the risk of oral clefts in Thailand. *Birth Defects Res A Clin Mol Teratol* 2016; 106: 624-32.
 43. Sabbagh HJ, Hassan MH, Innes NP, Elkodary HM, Little J, Mossey PA. Passive smoking in the etiology of non-syndromic orofacial clefts: a systematic review and meta-analysis. *PLoS One* 2015; 10: e0116963.
 44. Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. *Hum Reprod Update* 2011; 17: 589-604.
 45. Leonardi-Bee J, Britton J, Venn A. Secondhand smoke and adverse fetal outcomes in nonsmoking pregnant women: a meta-analysis. *Pediatrics* 2011; 127: 734-41.
 46. Zeiger JS, Beaty TH, Liang KY. Oral clefts, maternal smoking, and TGFA: a meta-analysis of gene-environment interaction. *Cleft Palate Craniofac J* 2005; 42: 58-63.
 47. Little J, Cardy A, Munger RG. Tobacco smoking and oral clefts: a meta-analysis. *Bull World Health Organ* 2004; 82: 213-8.
 48. Wyszynski DF, Duffy DL, Beaty TH. Maternal cigarette smoking and oral clefts: a meta-analysis. *Cleft Palate Craniofac J* 1997; 34: 206-10.
 49. Nieuwenhuijsen MJ, Dadvand P, Grellier J, Martinez D, Vrijheid M. Environmental risk factors of pregnancy outcomes: a summary of recent meta-analyses of epidemiological studies. *Environ*

- Health 2013; 12: 6.
50. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008-12.
 51. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. *Lancet* 1999; 354: 1896-900.
 52. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954; 10: 101-29.
 53. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539-58.
 54. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; 22: 719-48.
 55. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177-88.
 56. Light RJ, Pillemer DB. *Summing up: The science of reviewing research*. Cambridge, MA: Harvard University Press; 1984.
 57. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629-34.
 58. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088-101.
 59. Shaw GM, Iovannisci DM, Yang W, Finnell RH, Carmichael SL, Cheng S, et al. Endothelial nitric oxide synthase (NOS3) genetic variants, maternal smoking, vitamin use, and risk of human orofacial clefts. *Am J Epidemiol* 2005; 162: 1207-14.
 60. Joehanes R, Just AC, Marioni RE, Pilling LC, Reynolds LM, Mandaviya PR, et al. Epigenetic signatures of cigarette smoking. *Circ Cardiovasc Genet* 2016; 9: 436-47.
 61. Joubert BR, Felix JF, Yousefi P, Bakulski KM, Just AC, Breton C, et al. DNA methylation in newborns and maternal smoking in pregnancy: Genome-wide consortium meta-analysis. *Am J Hum Genet* 2016; 98: 680-96.

การได้รับควันบุหรี่ของมารดาขณะตั้งครรภ์และการเกิดปากแหว่งเพดานโหว่: การศึกษาทบทวนอย่างเป็นระบบจากรายงาน meta-analyses

อวยพร ปะนะมณฑา, ภัทร วิรมย์รัตน์, ยุทธพงศ์ วงศ์สวัสดิวัฒน์, อรรษิศา 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 นี้พบว่ามารดาที่ได้รับควันบุหรี่มีความเสี่ยงที่จะเกิด OFCs และ NSOFC มากกว่าคนที่ไม่ได้รับควันบุหรี่ ดังนั้นผู้หญิงตั้งครรภ์ควรหลีกเลี่ยงควันบุหรี่
