



Maternal active smoking and risk of oral clefts: a meta-analysis

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Objective. To assess the association between maternal active cigarette smoking and the risk of oral clefts in the offspring.

Study Design. Oral clefts are divided into three subgroups: total clefts, cleft lip with or without cleft palate (CL ± P), and cleft palate only (CP). Data from studies on different levels of smoking were gathered to examine the dose–response effect.

Results. The present meta-analysis included 29 case-control and cohort studies through Cochrane, PubMed, and Ovid Medline searches. A modest but statistically significant association was found between maternal active smoking and CL ± P (odds ratio [OR] 1.368; 95% confidence interval [CI] 1.259-1.486) as well as CP (OR 1.241; 95% CI 1.117-1.378). Half the studies showed positive dose–response effect for each subgroup (test for linear trend, $P < .05$).

Conclusions. There is a moderate risk for having a child with a CL ± P or CP in women who smoke during pregnancy. We could not confirm whether there was a positive dose–response effect between maternal smoking and clefts. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:680-690)

Oral clefts are one of the most common birth defects worldwide. Its incidence ranges from 1.0 in 1000 births to 2.21 in 1000 births in different regions and is relatively high among American Indian, Japanese, and Chinese populations.^{1,2} Oral clefts can be divided into cleft lip with or without cleft palate (CL ± P) and cleft palate only (CP), according to differences in anatomy, genetics, and embryology.^{3,4} Each category can be further classified into three groups: (1) isolated: clefts that occur alone or with secondary or minor defects⁵; (2) multiple: clefts with other major defects that are not recognized as syndromes; (3) syndromes: clefts with other major defects that are recognized as syndromes.⁶ The etiology of oral clefts is complex and remains unclear despite a wide range of studies on epidemiology and animal experiments.^{7,8} In recent years, more studies are concentrating on the combined effects of genetics and maternal environmental exposure.

Maternal smoking, especially in early pregnancy, is causing more concern in prenatal care because of its increasing incidence among young women. In an analysis of 4268 cases in China, smoking was the second biggest risk factor during the first 3 months of pregnancy.⁹

Two previous meta-analyses included 11 and 24 studies, respectively, to find the association between maternal smoking and oral clefts, and both showed a weak but statistically significant association.^{10,11} Only a limited number of studies were included in Wyszynski et al.'s meta-analysis¹⁰; however, a large number of

new studies have been published since in the twenty-first century. Our study aims to assess the association between maternal active smoking during pregnancy, especially in the first trimester, and the incidence of cleft lip and palate in their offspring. As a result of its explicit inclusion criteria and discussion, this meta-analysis may provide more comprehensive information and guidance to women of childbearing age.

MATERIALS AND METHODS

We searched in the Cochrane, PubMed, and Ovid Medline databases from January 1966 to May 2015 for relevant studies. The main search terms were “cleft lip,” “cleft palate,” “birth defects,” “congenital malformation,” “tobacco,” “cigarette smoking,” and “maternal.” Orofacial clefts needed to be one of the major congenital anomalies of focus in research studies searched, using the terms “birth defects” and “congenital malformation.” As a supplement to computerized searches, manual searches helped us identify five more related articles. When the raw data overlapped, only the largest or most relevant data set was included. For each study, two authors independently extracted data regarding the author, journal, publication year, title, study type, data resource, sample size, information on smoking exposure, and results.

Statement of Clinical Relevance

More attention should be brought to maternal smoking, because active smoking during pregnancy has been proven to be associated with oral clefts in the offspring. This awareness will support the efforts toward smoking cessation during pregnancy and will promote healthy births.

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Received for publication Jan 3, 2016; returned for revision Mar 20, 2016; accepted for publication Aug 8, 2016.

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2212-4403/\$ - see front matter

<http://dx.doi.org/10.1016/j.oooo.2016.08.007>

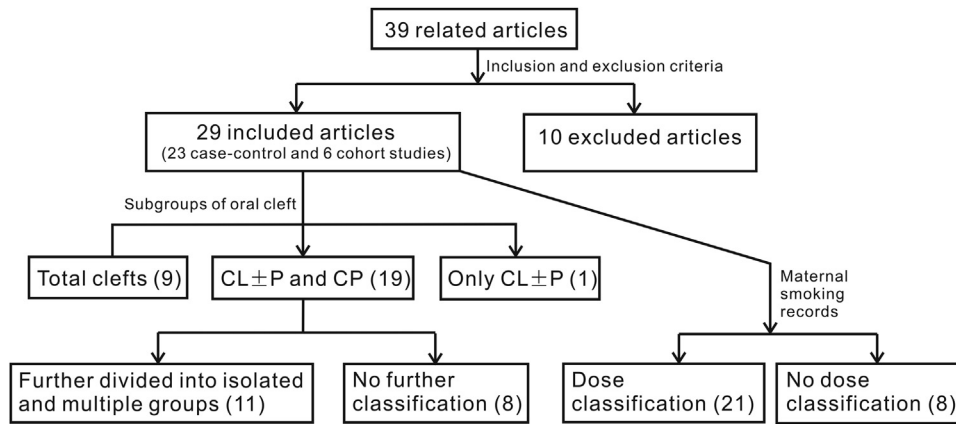


Fig. 1. The specific process of methods, with the numbers of included and excluded articles as well as the subgroups classification.

Our study focused on case-control and cohort studies with records of maternal active smoking (including levels of exposure) before and after conception, especially the periconception period. Paternal smoking and exposure to environmental tobacco smoke (ETS) were excluded in this review. The *periconception period* had a slightly different definition in each study, and we defined it as the period from 3 months before conception to the first trimester of pregnancy. Articles were excluded if precise information on maternal smoking was lacking. For example, the study by Kelsey et al. did not show the exact period of smoking, so we could not determine whether the mothers included in the study had smoked during pregnancy.¹² Ex-smokers or those who stopped smoking before conception were included in the non-smokers group for the possibly marginal effect of their past smoking on the occurrence of clefts in their offspring.^{11,13} Information regarding smoking had been obtained from hospital records, questionnaires, or conversations with the mothers through telephone, e-mail, or patient–doctor dialogue. Some studies displayed the average number of cigarettes smoked per day, whereas others only reported whether or not the mothers smoked.

We carried out a meta-analysis for total clefts, CL ± P, and CP, as well as isolated CL ± P and CP, if available. Total cleft cases were only analyzed when CL ± P and CP were not distinguished. We accepted not only normal live births but also malformed or non-malformed sick controls to reduce reporting bias.^{14,15} The specific process of inclusion of articles is presented in Figure 1.

The odds ratio (OR) and associated 95% confidence interval (CI) were calculated from raw data from each study by means of Stata/SE 12.0 software (Statacorp LP, College Station, TX) in spite of existing unadjusted OR and CI. When the existing data were inconsistent with the software calculations, the latter were adopted.

All meta-analyses were performed by using the Stata software, and heterogeneity was estimated by the

Q test. The fixed effect model was used if the *P* value was <.1. Our study used the random effect model for conservative estimates, as some *P* values were >.1. Publication bias was tested for quality assessment of the included studies by means of both Begg’s¹⁶ and Egger’s funnel plot.¹⁷ The results were the same; thus, only Begg’s funnel plot is shown here. To evaluate the impact of different study types, sensitivity analysis was conducted. Trend chi-square (χ^2) and *P* values were assessed by SPSS software version 16.0 (SPSS Inc., Chicago, IL) to evaluate the dose–response effect.

RESULTS

Of the 39 articles left after preliminary screening, 10 were excluded (Table I).¹⁸⁻²⁷ The study by Shi et al. included three sources of cases, of which one was excluded because siblings were used as controls.²⁸ Finally, 29 reports (1974-2011) met our inclusion criteria, as shown in Table II.^{5,6,11,13-15,28-50} Twenty-three case-control studies and six cohort studies were finally chosen for our meta-analysis. Because nine of them did not distinguish CL ± P from CP, the data were only eligible for the total clefts group in the analysis. The rest discussed CL ± P and CP separately, except for one study in which only the CL ± P category was presented.⁴⁶ Eleven studies further divided each category into two groups: isolated cleft and multiple clefts. Different levels of maternal cigarette smoking during pregnancy were given in 21 studies. These 29 reports collected sources from various registers of malformations in different countries, and the period of maternal smoking ranged from 6 months before conception to the end of pregnancy.

TOTAL CLEFTS

For the nine studies on total oral clefts,^{12,14,15,30,33,35,41,43,48} the random effect model

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