Tobacco smoking and oral clefts: a meta-analysis
Julian Little,1 Amanda Cardy,2 & Ronald G. Munger3

Objective To examine the association between maternal smoking and non-syndromic orofacial clefts in infants.
Methods A meta-analysis of the association between maternal smoking during pregnancy was carried out using data from 24 case-control and cohort studies.
Findings Consistent, moderate and statistically significant associations were found between maternal smoking and cleft lip, with or without cleft palate (relative risk 1.34, 95% confidence interval 1.25–1.44) and between maternal smoking and cleft palate (relative risk 1.22, 95% confidence interval 1.10–1.35). There was evidence of a modest dose–response effect for cleft lip with or without cleft palate.
Conclusion The evidence of an association between maternal tobacco smoking and orofacial clefts is strong enough to justify its use in anti-smoking campaigns.

Keywords Smoking/adverse effects; Cleft lip/etiology/epidemiology; Cleft palate/etiology/epidemiology; Pregnancy; Infant, Newborn; Dose–response relationship, Drug; Meta-analysis; Case–control studies; Cohort studies (source: MeSH, NLM).

Introduction Smoking is practised by about a third of the world's population aged 15 years or older, including some 12% of women (1). The proportion of women who smoke in developed countries is currently estimated to be 24%, while the proportion in developing countries is about 7% (1). Although tobacco consumption by women may be declining in some countries, there are signs overall that the proportion of women who smoke is increasing, particularly in developing countries (2), where it is estimated that tobacco consumption is rising by about 3.4% per year (3). Globally, each year approximately 12 million women smoke during pregnancy (4). In view of the known adverse effects of smoking on reproductive health, as well as on health more generally, there is a need to consider new methods for tobacco control. In this paper we review the evidence for a relationship between oral clefts and tobacco smoking. We propose that this evidence might be used as a basis for raising awareness of the adverse consequences of tobacco smoking in a subgroup of the population known to have a relatively high motivation to cease smoking (5). This would reinforce a message delivered in a recent report on craniofacial anomalies (6).

Orofacial clefts (OFCs) occur at an average frequency of about 1 per 600 live births (7) but there is substantial geographical variation. Some hospital-based surveys in developing countries have revealed markedly higher frequencies (8). Affected infants require multidisciplinary surgical and non-surgical care from birth until adulthood. Thus, in addition to the burden on families, OFCs represent an important cost for health and related services.

OFCs are commonly divided into two etiologically distinct groups: cleft lip with or without cleft palate (CL ± P) and cleft palate only (CP). A further division can be made within these groups into isolated clefts (those not associated with other malformations), syndromic clefts (those that are part of a recognized syndrome) and those associated with multiple defects that are not part of a recognized syndrome (henceforth “multiple”). Minor variations occur in the definitions of these groups given by different workers.

A previous meta-analysis of the association between maternal cigarette smoking and nonsyndromic oral clefts, based on 11 studies, indicated odds ratios (ORs) for both cleft lip and cleft palate of about 1.3 (9). The present meta-analysis, which also focuses on maternal smoking, is based on 24 studies.

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Methods

Publications of potential relevance to our study were identified by using both exploded MeSH headings and text words in a search of MEDLINE (1966–2002) and EMBASE (1980–2002) databases. The main search terms were “cleft lip”, “cleft palate”, “smoking”, “tobacco”, “cigarette”, “mother” and “maternal”. Since OFCs may not be indexed specifically when a study is related to a number of different types of congenital anomaly, we also conducted searches on congenital anomalies and malformations in general. Further articles of potential relevance were identified by manual searches of reference lists in articles identified during the electronic searches and of current journals covering the fields of epidemiology and teratology. A literature search conducted in the preparation of a monograph on neural tube defects (NTDs) was also used to identify earlier work (10).

The present review is limited to case–control and cohort studies that include data on smoking by women during pregnancy. It does not cover animal studies and studies of case series. Where studies overlapped, only the largest data set, or that with the most relevant data, was included. The OR estimates of relative risk (RR) and associated 95% confidence intervals (CIs) for use in the meta-analysis were calculated from the data presented in each paper and were therefore unadjusted, with the exception of three studies where only adjusted ORs were available (11–13). A qualitative assessment was made of the effect of potential confounding.

We carried out analyses by etiological type (isolated or multiple) wherever possible. In most studies that considered clefts associated with additional defects a distinction was made between multiple and syndromic cases and the latter were excluded from analysis. We also omitted syndromic cases where possible, although we could not always distinguish between multiple and syndromic groups (11, 14, 15). A meta-analysis was not conducted for syndromic cases alone because of the small numbers of studies presenting relevant data and because the number of cases in these studies was small.

We carried out meta-analyses for CL ± P, CP and total clefts. However, the last-mentioned were only examined in respect of studies that did not distinguish between CL ± P and CP. The analyses of CL ± P and CP were repeated following stratification by the presence or absence of malformations in addition to the cleft, after the exclusion of studies that used malformed controls. All analyses were performed by means of Stata Version 7 software (16). The “meta” command was used in order to obtain fixed and random effects models. Heterogeneity was assessed using the Q test (17) and, in accordance with convention, a random effect model was used if the P-value was less than 0.1, because this is a weak test. We tested for publication bias by means of Begg’s funnel plot and the formal tests proposed by Begg (18) and Egger (19). Tests for the presence of a linear dose–response effect were carried out where suitable data were available.

Results

Ten cohort and 22 case–control publications were identified as potentially eligible for inclusion, one of which included data from two separate cohort studies (20). One cohort study and seven case–control studies were excluded, leaving 24 studies for the meta-analysis. A list of the excluded papers is available from the authors. The reasons for exclusion included insufficient data (one publication), data very similar to or superseded by those in other publications (six publications) and the use of a control group unlikely to be representative with regard to smoking exposure (one publication).

Most studies derived their cases from various registers of malformations. The methods of exposure assessment varied widely, ranging from the use of specifically designed questionnaires or interviews to the examination of standard records collected during the medical histories of mothers or children. The time of data collection ranged from the first trimester to more than three years after birth. The amount of exposure detail varied from the simple presence or absence of smoking during pregnancy to the number of cigarettes smoked and exposure by month of pregnancy (Table 1, web version only, available at: http://www.who.int/bulletin).

Our meta-analysis of maternal smoking and CL ± P included thirteen case–control studies (11, 14, 15, 21–30) and two cohort studies (20, 31), one of which (20) included data from two separate cohorts. The initial analysis was based on the maximum number of cases per study after the exclusion of syndromic cases. Data were included for six studies on isolated and multiple defects combined, six studies on isolated defects and three studies in which the presence or absence of additional defects was not stated. Each study was represented only once. A formal test for heterogeneity did not give a significant result (Q = 16.6, P = 0.28) and a fixed effects model was therefore used. We found an overall RR of 1.34 (95% CI = 1.25–1.44) with a range of 1.0 (20) to 2.73 (22) (Fig. 1). The RR was 1.2 or above in 13 of the studies, ranging from 1.3 to 2.3 for case–control studies and from 1.0 (20) to 1.17 (31) for cohort studies. The RR was substantially unchanged on limiting the analysis to studies that considered only isolated CL ± P (1.35; 95% CI = 1.25–1.46; twelve studies) or multiple CL ± P (1.38; 95% CI = 1.14–1.66; seven studies), and on excluding studies that used malformed controls (1.34; 95% CI = 1.22–1.46; nine studies). The Begg funnel plot showed no striking evidence of publication bias (Fig. 2). Neither Begg’s adjusted rank correlation test nor Egger’s regression asymmetry test gave a statistically significant result.

The evidence for a relationship between maternal smoking and CP appears somewhat similar to that for CL ± P. The studies used were the same as those used for the analysis of CL ± P. A formal test for heterogeneity did not give a significant result (Q = 15.5, P = 0.28) and a fixed effects model was therefore used. The combined estimate of RR was 1.22 (95% CI = 1.1–1.35) and the range was from 0.7 (20) to 2.3 (22) (Fig. 3). Ten of the studies had RR values of 1.2 or more. The two cohort studies had RRs of 0.7 (20) and 1.3 (31). The RR was little changed when analysis was limited to studies that did not use malformed controls (1.34; 95% CI = 1.18–1.52; nine studies). Analysis by subgroups of CP indicated an increased RR for isolated CP (1.31; 95% CI = 1.17–1.47; twelve studies) but not for multiple CP (0.97; 95% CI = 0.77–1.21; seven studies). The Begg funnel plot shows no striking evidence of publication bias (Fig. 4). Neither Begg’s adjusted rank correlation test nor Egger’s regression asymmetry test gave a statistically significant result.

Studies of total clefts indicated an overall RR that was intermediate between those for CL ± P and CP (1.26; 95% CI = 1.10–1.43). Seven cohort (12, 13, 32–36) and two case–control studies (37, 38) were included. One of the case–control studies (38) included data from two separate control groups. A random effects model was used because of the P-value of 0.003 in the Q test for heterogeneity.

Nine studies of CL ± P included sufficient information to allow dose–response analysis (Table 2, web version only, available at: http://www.who.int/bulletin). Five suggested a
weak dose–response relationship, two showed increasing risk with dose but a reduced risk in the highest exposure group, and one found equal (raised) risks in the low-exposure and medium-exposure groups and an increased risk in the high-exposure group. Our dose–response analysis of CP included eight studies (Table 3, web version only, available at: http://www.who.int/bulletin). No clear evidence was observed: four studies suggested a weak positive dose–response relationship and four did not indicate any such relationship. We did not carry out our own dose–response analysis for total clefts as insufficient raw data were available, although a positive association was reported in four of the eight studies of total clefts which considered this matter and were included in the meta-analysis (13, 32, 37, 38).

Some consideration was given to confounding in all but six of the studies in Table 1 (see web version). In most of the studies there was adjustment for maternal sociodemographic characteristics, predominantly maternal age and education, but some studies also considered parity, marital status and race/ethnicity. Alcohol consumption was also considered as a potential confounder in five studies, and one study omitted women who had consumed alcohol during pregnancy. Adjustment for multivitamin use was made in three studies. In general, adjusted relative risks were similar to crude relative risks.

**Discussion**

The present study lends support to the hypothesis that maternal smoking increases the risk of OFCs. Although the studies included in our analysis varied in terms of case definition, control selection and exposure assessment, the relationship, although of only moderate strength, is largely consistent. The effect was observed for both isolated and multiple clefts and was stronger and more consistent for CL ± P than for CP. We did not conduct a separate analysis for syndromic clefts. Evidence of a dose–response effect for CL ± P may be seen as support for a causal relationship, although a reduced risk was seen in some of the high-exposure groups. This reduced risk may, however, be an artefact attributable to the small sample sizes of these groups or may indicate that high levels of exposure are so toxic to the fetus that they result in fetal death (39). There was little evidence of a dose–response effect for CP.
Our analysis was limited to published studies. However, we found no strong evidence of publication bias, although the statistical tests for detecting this have limited power (18), especially for relatively small numbers of studies.

Since smoking is correlated with alcohol use, diet and other lifestyle factors in many settings, the control of confounding is an important issue. In most of the studies there was adjustment for various sociodemographic factors that may be related to lifestyle. Of the five studies that controlled for maternal alcohol intake, three treated intake as a dichotomous variable, potentially making residual confounding an issue. However, studies of the association between alcohol and OFCs are inconsistent and publication bias may be an issue (6). There is some evidence of possible associations with binge drinking but none of the studies included in our meta-analysis considered this. Potentially, vitamin supplementation may also confound the association between OFCs and maternal smoking. In the studies that considered this, however, the adjusted and unadjusted RRs were similar. Moreover, as with alcohol consumption, the relationship is unclear (40). In the study that was most comprehensive in its assessment of confounding, which included a consideration of alcohol consumption, similar adjusted and unadjusted RRs were found (25).

Since the mid-1990s a number of epidemiological studies have sought to investigate interactions between various genes (TGF\(\alpha\), TGF\(\beta\)3, RARA, MSX1, CYP, GST and EPHX1) and smoking by women during pregnancy in relation to OFCs in their offspring (41). The findings have been inconsistent and suggest that any interaction would probably explain only a small proportion of OFCs. However, this is a promising area of research that can be expected to expand.

There has been considerable discussion about the potential importance of recall bias in case–control studies but few studies have attempted to demonstrate or quantify it. The available evidence comparing information collected before pregnancy with that collected retrospectively does not demonstrate any severe bias in relation to women who have had adverse pregnancy outcomes compared with women who have had normal births (10). Furthermore, it has been shown that recall bias can lead to spurious inferences only under extreme conditions (42–44). One study covered by the present review included
We found consistent, moderate and statistically significant associations between both CL ± P and CP and maternal smoking. Assuming causality and a 24% prevalence of smoking during pregnancy, the overall RRs from the meta-analyses suggest population excess fractions of 7.5% for CL ± P and 5% for CP. Young women continue to smoke even though the adverse effects of smoking on reproductive health are well known. The demonstration of an association between tobacco smoking during pregnancy and OFCs, and the provision of an easily understandable measure of the association, may create the basis for a new approach to reducing the uptake and continuation of smoking. The way in which the association is presented for the purpose of risk communication is likely to be important. For example, its presentation as a change in absolute risk from 1 per 600 births to 1 per 450 births may have a smaller impact than pointing out that a woman has approximately a 30% increased risk of having a child with CL ± P and a 20% increased risk of having one with CP if she smokes during pregnancy.

Conflicts of interest: none declared.

Résumé
Meta-analyse du lien entre le tabagisme et les fentes faciales

Objectif Examen du lien entre le tabagisme pendant la grossesse et les fentes faciales non syndromiques chez le nourrisson.

Méthodes Métro-analyse de cette association à partir de 24 études cas-témoins et études de cohortes.

Résultats Des liens cohérents, modérés et statistiquement significatifs ont été trouvés entre le tabagisme pendant la grossesse et la fente labiale, avec ou sans fente palatine (risque relatif 1,34, intervalle de confiance à 95% : 1,25 – 1,44) et entre le tabagisme maternel et la fente palatine (risque relatif 1,22, intervalle de confiance à 95% : 1,10 – 1,35). Il semble qu’il y ait une relation dose-effet modeste pour la fente labiale avec ou sans fente palatine.

Conclusion L’association entre le tabagisme maternel et les fentes faciales est suffisamment bien établie pour pouvoir être utilisée dans les campagnes antitabac.

Resumen
Tabaquismo y hendiduras bucales: metanálisis

Objetivo Estudiar la relación entre el tabaquismo materno y las hendiduras orofaciales en los recién nacidos.

Métodos Partiendo de los datos de 24 estudios de casos y testigos y de cohortes, se realizó un metanálisis de la relación entre el hábito de fumar en las mujeres durante el embarazo y la incidencia de hendiduras orofaciales en su descendencia.

Resultados Encontramos relaciones coherentes, moderadas y estadísticamente significativas entre el tabaquismo materno y el labio leporino, con o sin hendidura del paladar (riesgo relativo: 1,34, intervalo de confianza del 95%: 1,25-1,44), y entre el tabaquismo materno y la hendidura del paladar (riesgo relativo: 1,22, intervalo de confianza del 95%: 1,10-1,35). La evidencia reunida muestra una relación dosis-respuesta moderada para el labio leporino, con o sin palatosquisis.

Conclusión Las pruebas de la existencia de una relación entre el tabaquismo materno y las hendiduras orofaciales son lo bastante sólidas para justificar su uso en las campañas antitabacicas.
References


**Table 1. Studies of orofacial clefts and maternal smoking included in the meta-analysis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study area</th>
<th>Period</th>
<th>Sample details/source</th>
<th>CLP type</th>
<th>No. of cases</th>
<th>Case participation</th>
<th>Control type</th>
<th>No. of controls</th>
<th>Control participation</th>
<th>Exposure assessment</th>
<th>Timing</th>
<th>Information recorded</th>
<th>Confounder assessment</th>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al., 1979 (1)</td>
<td>UK, Cardiff</td>
<td>1965–76</td>
<td>Cardiff Birth Survey</td>
<td>TC:NS</td>
<td>111</td>
<td>98%</td>
<td>Cohort</td>
<td>&gt;65 000</td>
<td>98%</td>
<td>Interview in puerperium</td>
<td>P</td>
<td>Dose</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Saxén 1974 (2)</td>
<td>Finland</td>
<td>1967–71</td>
<td>Finnish Register of Congenital Malformations</td>
<td>CL + PI</td>
<td>599</td>
<td>100%</td>
<td>Matched on residence area and delivery time</td>
<td>590</td>
<td>98%</td>
<td>Interview after delivery</td>
<td>P</td>
<td>5+/day versus none</td>
<td>No</td>
<td>TC by presence of other malformations</td>
</tr>
<tr>
<td>Ericson et al., 1979 (3)</td>
<td>Sweden</td>
<td>1975</td>
<td>Swedish delivery records</td>
<td>CL + PI:NS</td>
<td>66</td>
<td>88%</td>
<td>No malformations, matched on delivery unit and time, maternal age and parity</td>
<td>130</td>
<td>87%</td>
<td>Health clinic records of first visit during pregnancy</td>
<td>EP</td>
<td>Dose</td>
<td>Yes</td>
<td>No</td>
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<td>Källén 1983–92 (4)</td>
<td>Sweden</td>
<td>1983–92</td>
<td>Swedish health registers: cases without chromosomal anomalies</td>
<td>CL + PI,M</td>
<td>1834</td>
<td>NS</td>
<td>Cohort</td>
<td>1 002 742</td>
<td>99%</td>
<td>Interview at first antenatal clinic visit</td>
<td>EP</td>
<td>Dose</td>
<td>Yes</td>
<td>Each clft type by presence of other malformations</td>
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<td>Czeizel &amp; Nagy, 1986 (5)</td>
<td>Hungary</td>
<td>1970–76</td>
<td>Hungarian Congenital Malformation Registry</td>
<td>CL + PI,M</td>
<td>630</td>
<td>58%</td>
<td>Matched on birth place and week, sex, birth outcome</td>
<td>824</td>
<td>42%</td>
<td>Questionnaire</td>
<td>PreC</td>
<td>T1</td>
<td>Dose</td>
<td>No</td>
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<tr>
<td>Christiansen et al., 1999 (6)</td>
<td>Denmark</td>
<td>1991–94</td>
<td>Hospital live births</td>
<td>CL + PI,M</td>
<td>302</td>
<td>96%</td>
<td>Live births, no malformations, matched on time and place of birth</td>
<td>567</td>
<td>94%</td>
<td>Interview, usually within two weeks of birth</td>
<td>T1</td>
<td>Dose</td>
<td>Yes</td>
<td>Each clft type by TGF genotype</td>
</tr>
<tr>
<td>Lorente et al., 2000 (7)</td>
<td>France, Italy, Netherlands and United Kingdom</td>
<td>1989–92</td>
<td>Live births or stillbirths from congenital malformation registries</td>
<td>CL + PI,M</td>
<td>161</td>
<td>63%</td>
<td>Live births, no malformations, matched on residence area and delivery time</td>
<td>1134</td>
<td>90%</td>
<td>France, Italy; 60% Netherlands; 86% United Kingdom</td>
<td>Interview within one month of birth</td>
<td>T1</td>
<td>Dose</td>
<td>Yes</td>
</tr>
<tr>
<td>Kelsey et al., Connecticut 1978 (8)</td>
<td>Connecticut</td>
<td>1974–76</td>
<td>Hospital and clinic births</td>
<td>TC:NS</td>
<td>40</td>
<td>71%</td>
<td>Random sample of hospital-born normal infants</td>
<td>2968</td>
<td>90%</td>
<td>Interview within one year of birth</td>
<td>Month 3</td>
<td>Dose</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Christianson 1980 (9)</td>
<td>San Francisco</td>
<td>1959–66</td>
<td>Members of Kaiser Health Plan</td>
<td>TC:NS</td>
<td>24</td>
<td>NS</td>
<td>Cohort</td>
<td>14 735</td>
<td>NS</td>
<td>Interview in early pregnancy, usually first trimester</td>
<td>EP</td>
<td>Yes/No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Shiono et al., Multicentre 1986 (10)</td>
<td>Multicentre</td>
<td>1959–66</td>
<td>Collaborative Perinatal Project: Live born at 20+ weeks gestation</td>
<td>CL + PI:NS</td>
<td>53</td>
<td>572</td>
<td>98%</td>
<td>Cohort</td>
<td>Interview at registration for prenatal care</td>
<td>EP</td>
<td>Yes/No</td>
<td>No</td>
<td>No</td>
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</table>
# Tobacco smoking and oral clefts: a meta-analysis

**Author** | **Study area** | **Period** | **Sample details/source** | **CLP type** | **No. of cases** | **Case participation** | **Control type** | **No. of controls** | **Control participation** | **Exposure assessment** | **Timing** | **Information recorded** | **Confounder assessment** | **Subgroups** |
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
Shiono et al., 1986 (10 b) | California | 1974–77 | Kaiser Clinics: live births of 20+ weeks gestation | CL ± P(N)S CP(N)S | 56 | NS | Cohort | 34 434 | 94% | Self-administered questionnaire as part of routine prenatal care | T1 | Yes/No (i) | Yes | No |
Shaw et al., 1986 (11) | California | 1987–89 | California Birth Defects Monitoring Program (includes fetuses) | CL ± P(I),(M,S) CP(I),(M,S) | 731 | 85% | Live births, no malformations, matched on time period and area of birth | 734 | 78% | Interview, mean of 3.5 years after delivery | PeriC | Dose | Yes | Each cleft type by presence of malformations; TGF genotype |
Khoury et al., 1987 (12), Overlap with Hwang 1995. | Maryland | 1984 | Maryland Birth Defects Reporting and Information System: births of 20+ weeks gestation or >500 g birthweight | CL ± P(I),(M,S) CP(I),(M,S) | 53 | 98% | Births with other defects, excluding Down syndrome | 198 | 95% | Interview after birth | P | Dose | Yes | Each cleft type by presence of other malformations |
Hwang et al., 1984–92 | Maryland | 1984–92 | Maryland Birth Defects Reporting and Information System: births of 20+ weeks gestation or >500 g birthweight | CL ± P(I) CP(I) | 183 | NS | Births with other isolated defects, matched on year and county of birth, maternal genotype | 284 | NS | Interview | P | Yes/No Dose for CP | Yes | Each cleft type by TGF genotype |
Beaty et al., 2001 (14) | Maryland | 1992–98 | Cases of various ethnicities from various sources: figures for Whites presented | CL ± P(I) CP(I) | 171 | NS | Healthy infants from newborn nursery or attending well baby clinic | 182 | NS | Brief interview at first visit, then detailed telephone interview | T1 | Yes/No | Yes | Also passive smoking |
Khoury et al., 1989 (15) | Metropolitan Atlanta | 1968–80 | Metropolitan Atlanta Congenital Defects Program | CL ± P(I),(M) CP(I),(M) | 345 | 70% | Live births, matched on birth period, hospital and ethnicity | 2809 | 70% | Interview | PeriC | Dose | Yes | Each cleft type by presence of other malformations |
Malloy et al., 1989 (16) | Missouri | 1980–83 | Single births from Missouri Birth Defects Registry | TC(N)S | 451 | NS | Cohort | 288 067 | 95% | Birth certificate | P | Yes/No | Yes | No |
Lieff et al., 1999 (17) | USA and Canada, multicentre | 1976–92 | Slone Epidemiology Unit Birth Defects Study: Whites, live births or stillbirths | CL wi | 1479 | 84% | Live births or stillbirths with other malformations thought unrelated to maternal smoking | 2295 | 77% (n) | Interview within six months of delivery | P | 1976–92; T1 1988–92 | Dose | Yes | Each cleft type by presence of other malformations |
<table>
<thead>
<tr>
<th>Author</th>
<th>Study area</th>
<th>Period</th>
<th>Sample details/source</th>
<th>CLP type a,b</th>
<th>No. of cases</th>
<th>Case participation</th>
<th>Control type</th>
<th>No. of controls</th>
<th>Control participation</th>
<th>Exposure assessment</th>
<th>Timing</th>
<th>Information recorded</th>
<th>Confounder assessment</th>
<th>Subgroups</th>
</tr>
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<tbody>
<tr>
<td>Van den Eeden et al., 1990 (18)</td>
<td>Washington State</td>
<td>1984–86 Birth records: single births from Washington State</td>
<td>CL ± P; M+S</td>
<td>173</td>
<td>97% a</td>
<td>Singleton liveborn, no malformations</td>
<td>4500</td>
<td>96%</td>
<td>Birth certificate</td>
<td>P</td>
<td>Yes/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Each cleft type by presence of other malformations</td>
</tr>
<tr>
<td>Romitti et al., 1999 (19)</td>
<td>Iowa Birth Defects Registry: Whites, live births, stillbirths, aborted fetuses</td>
<td>1987–94</td>
<td>CL ± Pj</td>
<td>225</td>
<td>71% a</td>
<td>Live births, no malformations</td>
<td>393</td>
<td>58%</td>
<td>Interviews/questionnaires, mean 29 months after birth (cases) or 35 months (controls)</td>
<td>Two months after conception</td>
<td>Dose</td>
<td>Yes</td>
<td>Yes</td>
<td>Each cleft type by TGF and MSX1 genotype</td>
</tr>
<tr>
<td>Chung et al., 2000 (20)</td>
<td>National Centre for Health Statistics 1996 Natality Database: live births</td>
<td>1996</td>
<td>TCj</td>
<td>2207</td>
<td>&lt;99%</td>
<td>Live births, no malformations</td>
<td>4414</td>
<td>NS</td>
<td>Recorded by physician/nurse at birth</td>
<td>P</td>
<td>Dose</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Honein et al., 2001 (21)</td>
<td>National Centre for Health Statistics 1997–98 Natality Database: live births</td>
<td>45 states plus New York City and District of Columbia</td>
<td>TC</td>
<td>5238</td>
<td>NS</td>
<td>Cohort 6 161 506</td>
<td>NS</td>
<td>Birth certificate</td>
<td>P</td>
<td>Dose</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woods and Raju 2001 (22)</td>
<td>Liveborn hospital births</td>
<td>1998–99</td>
<td>TCj</td>
<td>7</td>
<td>NS</td>
<td>Cohort 18 009</td>
<td>NS</td>
<td>Recorded at admission</td>
<td>P</td>
<td>Yes/No</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>McDonald et al., 1992 (23)</td>
<td>Montreal</td>
<td>Pregnancies &gt;20 week gestation</td>
<td>TCj</td>
<td>96</td>
<td>NS</td>
<td>Cohort 89 221</td>
<td>NS</td>
<td>NS</td>
<td>T1</td>
<td>Dose</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>Seidman et al., 1990 (24)</td>
<td>Israel, West Jerusalem</td>
<td>Live births or stillbirths from three obstetric units</td>
<td>TCj</td>
<td>17 or 18</td>
<td>NS</td>
<td>Cohort 17 152</td>
<td>98%</td>
<td>Interview in puerperium</td>
<td>P</td>
<td>Dose</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

a CL ± P = cleft lip with/without cleft palate; CP = cleft palate only; CL = cleft lip only; CL ± P = cleft lip and cleft palate; TC = total clefts; PRS = Pierre Robin Syndrome.

b I = isolated clefts; M = clefts associated with multiple defects (unknown etiology); S = syndromic clefts; M+S = syndromic and multiple cases probably included; NS = not stated.

c PreC = preconceptional; PeriC = periconceptional; P = pregnancy; EP = early pregnancy; T1 = first trimester.

d Information on smoking habits of mother obtained for 98% of singleton deliveries recorded in Cardiff Birth Survey.

e All types of congenital anomalies combined.

f Participation rate for malformations of all types.

g Same five hospitals in which 90% of cases of malformations were born; excludes births in private clinics, which accounted for 10% of cases of malformation.

h This is overestimated, as an unspecified number of women refused follow-up. It is stated that in 4689 of 59 391 pregnancies the mothers refused follow-up or the pregnancies ended in miscarriage or stillbirth.

i Dose-response relationship was analysed but data not presented for oral clefts.

j One month before conception to three months after pregnancy began.

k Includes subjects with syndromic, multiple and isolated clefts.

l Participation rate for mothers of infants with all types of congenital anomalies and mothers of controls combined.

m Three months before conception to three months after pregnancy began.

n In 1983.

p Excluded infants with CNS, CVS and musculoskeletal defects, inguinal hernia, pyloric stenosis and syndromes associated with oral clefts (despite absence of cleft).

q Calculated with inclusion of cases having associated malformations; these cases were excluded from analysis.

r Case number calculated from other figures presented in paper.
### Table 2. Relative risk of CL ± P by level of maternal smoking during pregnancy (data from first trimester used when available)

<table>
<thead>
<tr>
<th>Author</th>
<th>Cleft type</th>
<th>Relative risk</th>
<th>Trend ($\chi^2$ test)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Ericson 1979 (3)</td>
<td>NS</td>
<td>3.4</td>
<td>2.3</td>
<td>-</td>
</tr>
<tr>
<td>Czeizel 1986 (5)</td>
<td>I</td>
<td>1.5</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Khoury 1987&lt;sup&gt;a&lt;/sup&gt; (12)</td>
<td>I</td>
<td>1.2</td>
<td>4.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Khoury 1989&lt;sup&gt;c&lt;/sup&gt; (15)</td>
<td>I</td>
<td>1.6</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Shaw 1996 (17)</td>
<td>I</td>
<td>1.6</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>Christensen 1999 (6)</td>
<td>I</td>
<td>1.1</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Lieff 1999 (17)</td>
<td>I</td>
<td>1.5</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Romitti 1999 (19)</td>
<td>I</td>
<td>1.2</td>
<td>1.3</td>
<td>-</td>
</tr>
<tr>
<td>Lorente 2000 (7)</td>
<td>I</td>
<td>1.4</td>
<td>2.0</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> I = isolated, NS = not stated.

<sup>b</sup> Subset of Hwang et al. (13).

<sup>c</sup> From Wyszynski et al. (25).

### Table 3. Relative risk of CP by level of maternal cigarette smoking pregnancy (data from first trimester used when available)

<table>
<thead>
<tr>
<th>Author</th>
<th>Cleft type</th>
<th>Relative risk</th>
<th>Trend ($\chi^2$ test)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Ericson 1979 (3)</td>
<td>NS</td>
<td>2.5</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>Czeizel 1986 (5)</td>
<td>I</td>
<td>0.8</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Khoury 1995 (13)</td>
<td>I</td>
<td>1.4</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>Shaw 1996 (17)</td>
<td>I</td>
<td>1.4</td>
<td>2.2</td>
<td>-</td>
</tr>
<tr>
<td>Christensen 1999 (6)</td>
<td>I</td>
<td>0.9</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Lieff 1999 (17)</td>
<td>I</td>
<td>1.3</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Romitti 1999 (19)</td>
<td>I</td>
<td>1.5</td>
<td>2.3</td>
<td>-</td>
</tr>
<tr>
<td>Lorente 2000 (7)</td>
<td>I</td>
<td>1.3</td>
<td>1.4</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> I = isolated, NS = not stated.

Categories as Table 2, plus Hwang: Low 1–9; Medium 10–19; High 20+.

### References in Tables 1 and 2

Julian Little et al.


