Tobacco smoking and oral clefts: a meta-analysis

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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*).

Mots clés Tabagisme/effets indésirables; Bec de lièvre/ étiologie/ épidémiologie; Fente palatine/ étiologie/ épidémiologie; Grossesse; Nouveau-né; Relation dose-effet médicaments; Méta-analyse; Etude cas-témoins; Etude cohorte (*source: MeSH, INSERM*).

Palabras clave Tabaquismo/efectos adversos; Labio fisurado/ etiología/ epidemiología; Paladar fisurado/ etiología/ epidemiología; Embarazo; Recién nacido; Relación dosis-respuesta a droga; Meta-análisis; Estudios de casos y controles; Estudios de cohortes (*fuente: DeCS, BIREME*).

الكلمات المفتاحية: التدخين، التأثيرات الضائرة للتدخين، تشققات الشفة، سببيات تشققات الشفة، ايبدميولوجيا تشققات الشفة، تشققات الحنك، سببيات تشققات الحنك، ايبدميولوجيا تشققات الحنك؛ الحمل؛ الوِلدان؛ الرُّضَّع؛ العلاقة بين الجرعة والاستجابة لها، الأدوية؛ التحليل التلوي؛ دراسات الحالات والشواهد، الدراسات الأترابية. (المصدر: رؤوس الموضوعات الطبية، المكتب الإقليمي لشرق المتوسط).

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 RRs 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 analysed 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 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 or 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

Fig. 1. **Results of fixed effects meta-analysis of the relative risk of cleft lip, with or without cleft palate, in the offspring of mothers who smoked during pregnancy compared with the offspring of mothers who did not smoke** (see ref. *11, 14, 20–31*)

Odds ratio
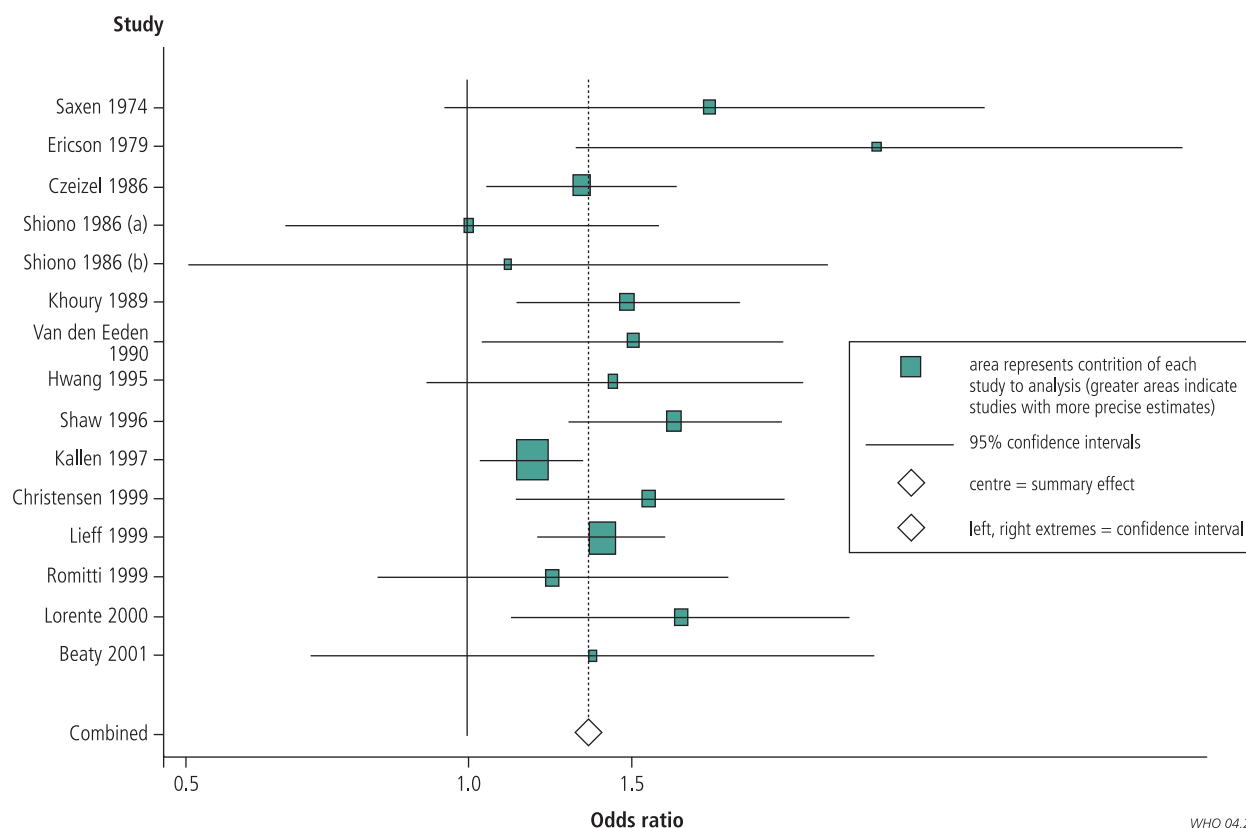
WHO 04.20

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.

Fig. 2. **Funnel plot (with pseudo 95% confidence intervals) to detect possible publication bias for the association between cleft lip, with or without cleft palate, and maternal smoking**

Standard error log [odds ratio]
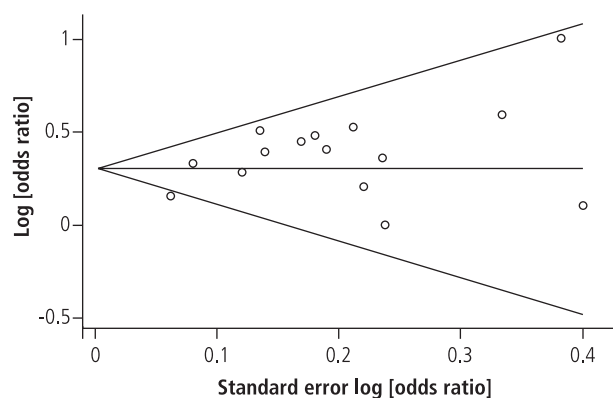
WHO 04.21

Fig. 3. **Results of fixed effects meta-analysis of the relative risk of cleft palate in the offspring of mothers who smoked during pregnancy compared with the offspring of mothers who did not smoke**
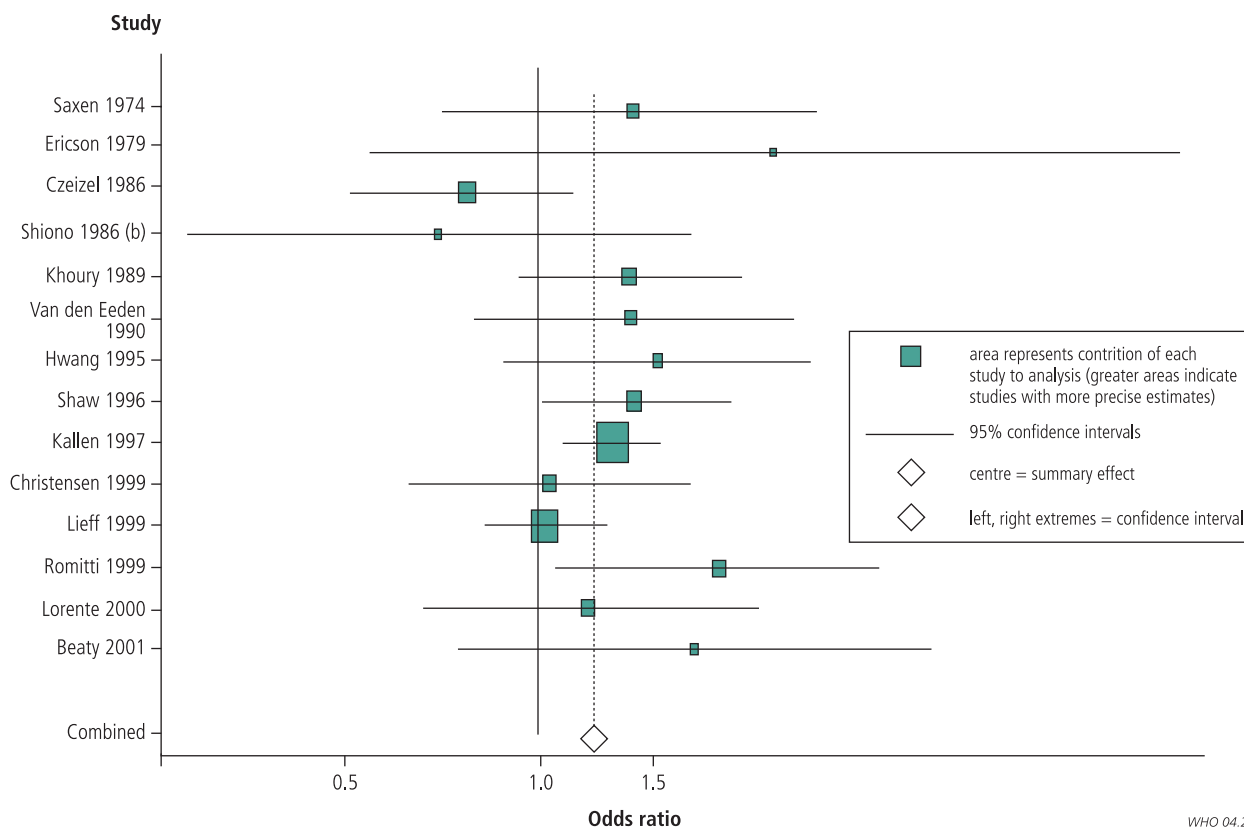
WHO 04.22

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

Fig. 4. **Funnel plot (with pseudo 95% confidence intervals) to detect possible publication bias for the association between cleft palate and maternal smoking**

WHO 04.23

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 (*TGFα*, *TGFβ3*, *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
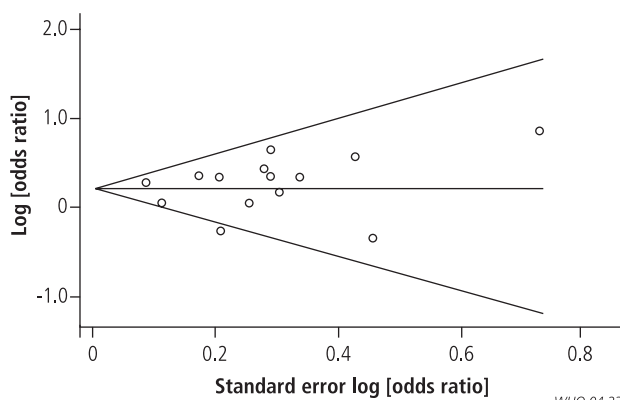
two control groups, one with and one without malformations that were thought to be unrelated to smoking. Essentially the same RRs were obtained for both groups (*38*).

Maternal smoking has been considered in relation to other types of congenital malformation. No consistent association has been observed with NTDs, cardiovascular anomalies or Down syndrome. Some studies suggest a positive association with limb defects. In four of five studies on gastroschisis a positive association was observed. We are not aware of any evidence for common etiological factors between clefts and gastroschisis, which is also a midline defect (*40*).

It has been suggested that some aspects of the etiology of NTDs and OFCs may be shared, on the basis of involvement of cranial neural crest cells in pathogenesis. However, there are differences in the pattern of geographical variation in prevalence at birth, in distribution by sex, and in time trends (*7*). In addition, while folate and folic acid have a clear role in the etiology of NTDs, evidence on the role of folate in the etiology of OFCs is conflicting (*6*). The contrast in the findings on maternal smoking provides further evidence of differing etiologies for these anomalies.

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

Méta-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 Méta-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 antitabáquicas.

ملخص

تدخين التبغ وتشققات الفم: تحليل تلوي

الغرض: اختبار العلاقة بين تدخين الأم وظهور تشققات الفم والوجه في الرُضع.

الطريقة: تم إجراء تحليل تلوي للارتباط بين تدخين الأم أثناء الحمل وظهور تشققات الفم والوجه في الرُضّع، وذلك باستخدام معطيات مستقاة من ٢٤ دراسة أترابية أُجريت على الحالات والشواهد.

الموجودات: لوحظ ارتباط ثابت ومتوسط وذو أهمية إحصائية بين تدخين الأم وتشقق الشفاه، سواء المصحوب أو غير المصحوب بتشقق الحنك (بلغ الاختطار النسبي ١,٣٤ عند فاصل ثقة ٩٥٪، إذ تراوح من ١,٢٥ إلى ١,٤٤)، كما لوحظ ارتباط بين تدخين الأم وتشقق الحنك (بلغ الاختطار النسبي ١,٢٢ عند فاصل ثقة ٩٥٪، إذ تراوح من ١,١٠ إلى ١,٣٥). كما وجدت بينات على ارتباط بسيط بين مستوى جرعة التدخين وظهور تشققات الفم المصحوب أو غير المصحوب بتشقق الحنك.

الحصيلة: توجد بينات قوية على الارتباط بين تدخين الأم للتبغ وظهور تشققات الفم والوجه، مما يبرر استخدام هذه الحقيقة في حملات مكافحة التدخين.

Research
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Research

Julian Little et al.　　　　　　　　　　　　　　　　　　　　　　　Tobacco smoking and oral clefts: a meta-analysis

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

Author	Study area	Period	Sample details/ source	CLP type [a,b]	No. of cases	Case partici-pation	Control type	No. of controls	Control partici-pation	Expo-sure assess-ment	Tim-ing [c]	Infor-mation re-corded	Con-founder assess-ment	Sub-groups
Europe														
Evans et al., 1979 (1)	UK, Cardiff	1965–76	Cardiff Birth Survey	TC|NS	111	98% [d]	Cohort	>65 000	98%	Interview in puerperium	P	Dose	No	No
Saxén 1974 (2)	Finland	1967–71	Finnish Register of Congenital Malforma-tions	CL ± P|I CP|I TC|M+S	599	100%	Matched on resi-dence area and delivery time	590	98%	Interview after delivery	P	5+/day versus none	No	TC by pres-ence of other malfor-mations
Ericson et al., 1979 (3)	Sweden	1975	Swedish delivery records	CL ± P|NS CP|NS	66	88%	No malfor-mations, matched on delivery unit and time, maternal age and parity	130	87%	Health clinic records of first visit during pregnancy	EP	Dose	Yes	No
Kallén 1997 (4)	Sweden	1983–92	Swedish health registries: cases without chromo-somal anomalies	CL+P|I,M CL|I,M CP|I,M PRS	1834	NS	Cohort	1 002 742	99%	Interview at first antenatal clinic visit	EP	Dose	Yes	Each cleft type by pres-ence of other malfor-mations
Czeizel & Nagy, 1986 (5)	Hungary	1970–76	Hungarian Congenital Malforma-tion Registry	CL ± P|I CP|I TC|S	630 179 392	58% 49% 78%	Matched on birth place and week, sex, birth outcome	824	42%	Question-naire	PreC T1 P	Dose	No	No
Christensen et al., 1999 (6)	Denmark	1991–94	Hospital live births	CL±P|I CP|I TC|I,M	302	96%	Live births, no malfor-mations, matched on time and place of birth	567	94%	Interview, usually within two weeks of birth	T1	Dose	Yes	Each cleft type by TGF geno-type
Lorente et al., 2000 (7)	France, Italy, Netherlands and United Kingdom	1989–92	Live births or stillbirths from congenital malforma-tion registries	CL ± P|I,M+S CP|I,M+S	161	63% [e]	Live births, no malfor-mations, matched on residence area and delivery time	1134	90% France, Italy; 60% Nether-lands; 86% United Kingdom	Interview within one month of birth	T1	Dose	Yes	Each cleft type by pres-ence of other malfor-mations
USA														
Kelsey et al., 1978 (8)	Connecticut	1974–76	Hospital and clinic births	TC|NS	40	71% [f]	Random sample of hospital-born normal infants [g]	2968	90%	Interview within one year of birth	Month 3	Dose	Yes	No
Christianson 1980 (9)	San Francisco	1959–66	Members of Kaiser Health Plan	TC|NS	24	NS	Cohort	14 735	NS	Interview in early pregnancy, usually first trimester	EP	Yes/No	No	No
Shiono et al., 1986 (10) a	Multicentre	1959–66	Collabo-rative Perinatal Project: liveborn 20+ weeks gestation	CL ± P|NS	NS	NS	Cohort	53 572	98% [h]	Interview at regis-tration for prenatal care	EP	Yes/No [i]	No	No

(Table 1, cont.)

Author	Study area	Period	Sample details/ source	CLP type [a,b]	No. of cases	Case partici- pation	Control type	No. of controls	Control partici- pation	Expo- sure assess- ment	Tim- ing[c]	Infor- mation re- corded	Con- founder assess- ment	Sub- groups
Shiono et al., 1986 (10) b	California	1974–77	Kaiser Clinics: live births of 20+ weeks gestation	CL ± P|NS CP|NS	56	NS	Cohort	34 434	94%	Self-adminis- tered question- naire as part of routine prenatal care	T1	Yes/No (i)	Yes	No
Shaw et al., 1996 (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 malfor- mations, matched on time period and area of birth	734	78%	Interview, mean of 3.5 years after delivery	PeriC [j]	Dose	Yes	Each cleft type by pres- ence of malfor- mations; TGF geno- type
Khoury et al., 1987 (12). Overlap with Hwang 1995.	Maryland	1984	Maryland Birth Defects Reporting and Infor- mation System: births of 20+ weeks gestation or >500g 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 pres- ence of other malfor- mations
Hwang et al., 1995 (13)	Maryland	1984–92	Maryland Birth Defects Reporting and Infor- mation System: births of 20+ weeks gestation or >500g birthweight	CL ± P|I CP|I	183	NS	Births with other isolated defects, matched on year and county of birth, maternal age	284	NS	Interview	P	Yes/No Dose for CP	Yes	Each cleft type by TGF geno- type
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 smok- ing
Khoury et al., 1989 (15)	Metropolitan Atlanta	1968–80	Metropolitan Atlanta Congenital Defects Program	CL ± P|I,M CP|I,M	345	70% [k]	Live births, matched on birth period, hospital and ethnicity	2809	70% [l]	Interview	PeriC [m]	Dose	Yes	Each cleft type by pres- ence of other malfor- mations
Malloy et al., 1989 (16)	Missouri	1980–83	Single births from Missouri Birth Defects Registry	TC|NS	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 Epidemio- logy Unit Birth Defects Study: Whites, live births or stillbirths	CL|I,M CL + P|I,M CP|I,M CL±P|I,M	1479	84% [n]	Live births or stillbirths with other malfor- mations thought unrelated to mater- nal smok- ing [p]	2295	77% (n)	Interview within six months of delivery	P 1976–92; T1 1988–92	Dose	Yes	Each cleft type by pres- ence of other malfor- mations

(Table 1, cont.)

Author	Study area	Period	Sample details/source	CLP type [a,b]	No. of cases	Case partici-pation	Control type	No. of controls	Control partici-pation	Exposure assessment	Tim-ing[c]	Infor-mation re-corded	Con-founder assess-ment	Sub-groups
Van den Eeden et al., 1990 (18)	Washington State	1984–86	Birth records: single births from Washington State	CL ± P|I,M+S CP|I,M+S	173	97% [p]	Singleton liveborn, no malfor-mations	4500	96%	Birth certificate	P	Yes/No	Yes	Each cleft type by pres-ence of other malfor-mations
Romitti et al., 1999 (19)	Iowa	1987–94	Iowa Birth Defects Registry: Whites, live births, stillbirths, aborted fetuses	CL ± P|I	225	71% [q]	Live births, no malfor-mations	393	58%	Interviews/question-naires, mean 29 months after birth (cases) or 35 months (controls)	Two months after con-ception	Dose	Yes	Each cleft type by TGF and MSX1 geno-type
Chung et al., 2000 (20)	46 states	1996	National Centre for Health Statistics 1996 Natality Database: live births	TC|I	2207	~99%	Live births, no malfor-mations	4414	NS	Recorded by physician/nurse at birth	P	Dose	Yes	No
							Live births with genitouri-nary, gastro-intestinal or chromosomal anomalies	9183	NS	Recorded by physician/nurse at birth	P	Dose	Yes	No
Honein et al., 2001 (21)	45 states plus New York City and District of Columbia	1997–8	National Centre for Health Statistics 1997-98 Natality Database: live births	TC	5238	NS	Cohort	6 161 506	NS	Birth certificate	P	Dose	Yes	No
Woods and Raju 2001 (22)	Cincinnati	1998–99	Liveborn hospital births	TC|NS	7	NS	Cohort	18 009	NS	Recorded at admis-sion	P	Yes/No	Yes	No
Canada														
McDonald et al., 1992 (23)	Montreal	1982–84	Pregnancies >20 week gestation	TC|NS	96	NS	Cohort	89 221	NS	NS	T1	Dose	Yes	No
Eastern Mediterranean														
Seidman et al., 1990 (24)	Israel, West Jerusalem	1974–76	Live births or stillbirths from three obstetric units	TC|NS	17 or 18 [r]	NS	Cohort	17 152	98%	Interview in puerperium	P	Dose	No	No

[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)

Author	Cleft type[a]	Relative risk			Trend (χ^2 test)	P-value
		Low	Medium	High		
Ericson 1979 (*3*)	NS	3.4	2.3	-	4.10	0.043
Czeizel 1986 (*5*)	I	1.5	0.9	1.1	1.10	0.295
Khoury 1987[b] (*12*)	I	1.2	4.2	4.8	8.58[c]	0.003[c]
Khoury 1989[c] (*15*)	I	1.6	1.6	1.9	8.03	0.005
Shaw 1996 (*11*)	I	1.6	2.1	-	15.47	0.000
Christensen 1999 (*6*)	I	1.1	1.6	1.5	5.01	0.025
Lieff 1999 (*17*)	I	1.5	1.4	1.1	5.76	0.016
Romitti 1999 (*19*)	I	1.2	1.3	-	0.97	0.324
Lorente 2000 (*7*)	I	1.4	2.0	-	6.36	0.012

[a] I = isolated, NS = not stated.
[b] Subset of Hwang et al. (*13*).
[c] From Wyszynski et al. (*25*).
Categories
  Ericson: Low 1−9: Medium 10+.
  Czeizel: Low 1−10; Medium 11−20; High 21+.
  Khoury 1987: Low 1−10; Medium 11−20; High 21+.
  Khoury 1989, Leiff: Low 1−14; Medium 15−24; High 25+.
  Shaw: Low 1−19; Medium 20+.
  Christensen: Low 1−9; Medium 10−19; High 20+.
  Romitti, Lorente: Low 1−9; Medium 10+.

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

Author	Cleft type[a]	Relative risk			Trend (χ^2 test)	P-value
		Low	Medium	High		
Ericson 1979 (*3*)	NS	2.5	2.1	-	0.68	0.41
Czeizel 1986 (*5*)	I	0.8	0.9	0.3	3.26	0.071
Hwang 1995 (*13*)	I	1.4	1.5	-	1.69	0.194
Shaw 1996 (*11*)	I	1.4	2.2	-	6.84	0.009
Christensen 1999 (*6*)	I	0.9	1.0	0.6	0.24	0.621
Lieff 1999 (*17*)	I	1.3	1.1	1.0	0.43	0.511
Romitti 1999 (*19*)	I	1.5	2.3	-	5.23	0.022
Lorente 2000 (*7*)	I	1.3	1.4	-	0.64	0.423

[a] I = isolated, NS = not stated.
Categories as Table 2, plus Hwang: Low 1−10; Medium $\geqslant$11.

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