Smoking and Orofacial Clefts: A United Kingdom–Based Case-Control Study

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Objective: **To investigate the association between smoking and orofacial clefts in the United Kingdom.**

Design: **Case-control study in which the mother's exposure to tobacco smoke was assessed by a structured interview.**

Setting: **Scotland and the Manchester and Merseyside regions of England.**

Participants: **One hundred ninety children born with oral cleft between September 1, 1997, and January 31, 2000, and 248 population controls, matched with the cases on sex, date of birth, and region.**

Main Outcome Measure: **Cleft lip with or without cleft palate and cleft palate.**

Results: **There was a positive association between maternal smoking during the first trimester of pregnancy and both cleft lip with or without cleft palate (odds ratio 1.9, 95% confidence interval 1.1 to 3.1) and cleft palate (odds ratio 2.3, 95% confidence interval 1.3 to 4.1). There was evidence of a dose-response relationship for both types of cleft. An effect of passive smoking could not be excluded in mothers who did not smoke themselves.**

Conclusion: **The small increased risk for cleft lip with or without cleft palate in the offspring of women who smoke during pregnancy observed in this study is in line with previous evidence. In contrast to some previous studies, an increased risk was also apparent for cleft palate. In these U.K. data, there was evidence of a dose-response effect of maternal smoking for both types of cleft. The data were compatible with a modest effect of maternal passive smoking, but the study lacked statistical power to detect or exclude such an effect with confidence. It may be useful to incorporate information on the effects of maternal smoking on oral clefts into public health campaigns on the consequences of maternal smoking.**

KEY WORDS: *case-control study, maternal smoking, orofacial clefts*

Orofacial clefts (OFCs) are among the most common types of congenital anomalies, occurring with a prevalence of about 1.7/1000 live births (Mossey and Little, 2002). Affected individuals require multidisciplinary care from birth until adulthood, and they and their families may suffer psychological effects. The defects therefore pose a substantial burden to the individual and their family and require significant expenditure in terms of health and related services. Thus, it is important to identify strategies for primary prevention, and this requires an understanding of etiology.

A positive association between maternal cigarette smoking and OFCs has been observed in a number of studies (Khoury et al., 1987, 1989; Van Den Eeden et al., 1990; Hwang et al., 1995; Shaw et al., 1996; Källén, 1997; Lieff et al., 1999; Romitti et al., 1999; Chung et al., 2000; Lorente et al., 2000; Honein et al., 2001; Wyszynski and Wu, 2002). In meta-analyses, marked variation in relative risks have been observed (Wyszynski et al., 1997; Källén, 2002), but in the larger studies, the relative risks for cleft lip with or without cleft palate (CL±P) have been in the range of 1.2 to 1.7 and somewhat

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lower for cleft palate (CP). The evidence as to whether there is a linear dose-response relationship is inconsistent (Wyszynski et al., 1997). Although the magnitude of these relative risks is not large, the proportion of OFCs attributable to smoking may be substantial because large numbers of women smoke during pregnancy. In Scotland in 1999, 28% of women smoked at the start of their pregnancy (ISD, 2000). Estimates of smoking in females are generally similar for northern England and Scotland (Boreham, 2000). An association between OFCs and smoking therefore has important implications globally, in light of the increased targeting of women by tobacco companies, both in developed and developing countries (Kaufman and Nichter, 2001).

The risk of OFCs attributable to smoking may be underestimated because exposure of pregnant women to passive smoking in the home and workplace has not usually been taken into account (Windsor, 2001). This appears to have been investigated in only one previous study, carried out in China, where the proportion of women who smoke has been low (Zhang et al., 1992). The study found a suggestion of a positive association between OFCs and paternal smoking (odds ratio [OR] about 1.5) although it was not statistically significant.

A positive association between OFCs and deprivation (assessed on the basis of census characteristics of area of residence) was observed for births in Scotland for the period 1989 to 1998 (Clark et al., 2003). There is a strong, positive association between socioeconomic status (SES) and tobacco smoking. In 1996 in Scotland, based on maternity inpatient discharge records, 9.5% of women in deprivation category 1 (least deprived) smoked during pregnancy, compared with 49.6% in category 7 (most deprived; ISD, 1998). This suggests that maternal tobacco smoking during pregnancy may account, at least in part, for the association between OFCs and deprivation. The relationship between smoking and OFCs has not yet been investigated in the United Kingdom. We now present the results of a case-control study of smoking and OFCs in Scotland and Northern England.

Methods

A population-based, case-control study was carried out between September 1, 1997, and January 31, 2000, and included 190 nonsyndromic patients with OFCs (112 CL±P and 78 CP) and 248 unaffected controls. Clinical records of patients were reviewed by experienced dysmorphologists to determine whether they were syndromic or nonsyndromic. Patients with isolated clefts or clefts associated with multiple anomalies that were not part of a recognized syndrome were included, including 10 infants with the Pierre Robin association.

Subjects were recruited from predetermined postcode sector regions, selected to represent urbanized areas of Scotland and Manchester/Merseyside and used as geographical recruitment boundaries. Areas included the following: Scotland (Grampian, Tayside, Fife, Lothian, Forth Valley, Greater Glasgow, Ayrshire and Arran, Lanarkshire, and Borders) and England (Manchester and Merseyside Health Board areas).

All infants born with clefts in these areas are referred to specialist centers for treatment. Patients were ascertained via the regional cleft teams who informed the study coordinator or local research interviewer of any affected child born within the predetermined geographical boundaries. Scottish patients were verified against the CLEFTSiS register (formerly the Scottish Cleft Lip and Palate Association Register), to which all clinicians in Scotland involved in the care of patients with OFCs contribute and which supports the management of care. This register has been validated against the National Birth Register for Scotland and has been found to have a high level of completeness for live-born infants (Clark et al., 2003). English patients were verified against the Craniofacial Anomalies Network register.

In Scotland, potentially eligible controls were identified from the Community Health Index (CHI), a register of the general population that allows assessment of capitation payments for general practitioners. The CHI is also used for the provision of primary care services such as breast and cervical cancer screening and recall and in the organization of child health surveillance and immunization. It has been shown to have a high level of completeness (Roworth and Jones, 1988; Garton, 1993; Ramsay et al., 1999). In England, potentially eligible controls were identified by contacting general practices in the same postcode sector region as the recruited case infant. Controls were matched with cases on sex, date of birth (±1 month) and region (postcode sector).

The initial approach, in which a study pack was either handed or posted to the subject's mother, was made by various agencies, depending on the region. Completed consent forms were returned to the regional study interviewer, who was trained in interview techniques. The interviewer then telephoned to arrange a visit during which a structured interview was conducted. The interviews took place at a mean of 5.5 months after the birth for cases and 6.5 months after birth for controls. Information was sought on maternal smoking history prior to and during pregnancy. If the mother had smoked during pregnancy, the timing and duration of exposure as well as number and type of cigarette smoked (filter/nonfilter) was recorded. Assessment of the mother's passive exposure to tobacco smoke during pregnancy included questions on whether she was regularly exposed to other people's tobacco smoke in the home, at work, or in other environments. The number of hours of exposure per day, the number of people who were usually smoking at the same time, and the degree of smokiness of the air (on a 3-point scale) were recorded. Current habitual diet was assessed using a validated, semiquantitative food frequency questionnaire (Aberdeen FFQ, version 5.4 [Masson et al., 2003]). The questionnaire includes 150 food items, and respondents were asked how often and how many ''measures'' they ate of each food item. Any changes to the usual diet during pregnancy were recorded. Sociodemographic information, use of supplemental nutrients, and birth weight of the child were also recorded.

The relationship between CL±P, CP, and OFCs of all types and maternal smoking both in the first trimester and at any

TABLE 1 Comparison of Sociodemographic Characteristics and Smoking Behavior in Cases and Controls

Characteristics	*Cases*		*Controls*	
Sex				
Boys	91		119	
Girls	99		129	
Quarter of birth				
March to May	36		56	
June to August	40		50	
September to November	70		79	
December to February	44		63	
Region				
East Scotland	29		38	
West Scotland	64		55	
Manchester and Merseyside	97		155	
Maternal education (highest level)				
Primary	4		5	
Secondary	102		106	
College/university	76		116	
Postgraduate	7		21	
Ethnicity				
Both parents of U.K. origin	148		215	
One parent U.K. origin, one of other ethnicity	17		17	
At least one parent of unknown ethnicity	25		16	
Maternal Smoking	yes	no	yes	no
Mother ever smoked	103	87	93	155
Mother smoked during pregnancy	85	105	60	188
Mother smoked during first trimester	80	110	59	189
Passive smoking	yes	no	yes	no
Nonsmoking mothers	38	49	70	85
Smoking mothers	94	9	77	16

TABLE 2 Association Between Maternal Smoking During the First Trimester of Pregnancy and Oral Clefts in the Offspring*

Cleft	*Smoking Status*		*Odds Ratio*† (95% CI)
	Yes	*No*	
OFC	80	110	2.0 (1.3–3.1)
CL±P	45	67	1.9 (1.1–3.1)
CP	35	43	2.3 (1.3–4.1)
Controls	59	189	

* OFC = orofacial cleft; CL±P = cleft lip with or without cleft palate; CP = cleft palate; CI = confidence interval.

† Adjusted for sex, season of birth, maternal education, and child's ethnic group.

time during pregnancy was assessed. Conditional and unconditional analyses produced similar ORs. Results of the unconditional analyses are reported because this allowed use of the full data set because not every case had a matched control, and increased the statistical power. A dose-response relationship was tested for by treating the number of cigarettes smoked per day as both a continuous and categorical variable (nonsmoker; ≤10 cigarettes/day; >10 cigarettes/day). The cut points were decided *a priori*, and allowed comparison with other studies. The analysis was stratified by sex to assess the internal consistency of association. We adjusted for the matching variable sex and season of birth; adjustment for region and year of birth was not made because this had little effect on the results. Potential confounding by SES was also considered using three measures: maternal education; the child's ethnic group defined according to the country of birth of the parents; and the Carstairs index, an area-based measure of material deprivation (Carstairs and Morris, 1990). Maternal education and the child's ethnic group affected the results and were therefore included in the model; adjustment for the Carstairs index had little influence on the results. We also considered potential confounding by reported total energy intake, folate intake, supplemental vitamin use, and alcohol consumption. The primary analysis of the effects of passive smoking was stratified on whether the mother had smoked during pregnancy. Hours of exposure to passive smoke during pregnancy was considered both alone and in combination with the degree of smokiness reported (hours of exposure multiplied by the degree of smokiness) and also considered these as categories of exposure (unexposed, then tertiles of exposure). We also considered the effects of combinations of passive and active smoking. As a check on the internal validity of the study, the relationship between birth weight and maternal smoking in the controls was examined to determine whether this well-established association held in the participating subjects.

The study was approved by the local research ethics committees for each Health Board region within Scotland and by the corresponding committees for Manchester and Merseyside. Approval was also obtained from GP subcommittees in Grampian.

RESULTS

Maternal interviews were completed for 190 of 349 eligible infants (54%) with OFCs born in the relevant areas during the study period (112 of 191 CL±P, 78 of 158 CP). Interviews were completed for 248 mothers of control infants, 75% of which were the first controls approached, 25% the second, and 1% the third. The distribution of sociodemographic factors and maternal smoking for cases and controls are summarized in Table 1. The proportion of mothers who smoked at any time during pregnancy was 45% for cases and 24% for controls. Almost all women who smoked during pregnancy smoked during the first trimester (139 of 145, 96%).

The OR of OFCs associated with maternal smoking during the first trimester was 2.0 (95% confidence interval [CI] 1.3 to 3.1), adjusted for sex, season of birth, maternal education, and ethnic group of the child. The ORs were similar for CL±P and CP (Table 2) and were little changed when considering smoking at any time during pregnancy (data not shown). A dose-response relationship was apparent for both CL±P and CP (Table 3), p value for trend .012 for CL±P and .004 for CP). The ORs were little changed after adjustment for potential confounding by total energy intake, total folate intake, supplemental vitamin use, and maternal alcohol consumption (data not shown). A weak effect of hours of passive smoking in mothers who did not actively smoke was also observed. The adjusted ORs for the highest tertile of exposure, compared with no exposure were 1.7 (95% CI 0.9 to 3.2) for OFCs, 1.5 (0.7

TABLE 3 Association Between Oral Clefts and Amount Smoked During the First Trimester*

	Nonsmokers			*≤10 Cigarettes/Day*			*11+ Cigarettes/Day*			*Trend*	
	n	*OR†*	*(95% CI)*	*n*	*OR†*	*(95% CI)*	*n*	*OR†*	*(95% CI)*	χ^2	*p*
OFC	110	1.0	(reference)	52	1.8	(1.1–2.9)	28	2.8	(1.4–5.6)	11.5	.001
CL±P	67	1.0	(reference)	28	1.7	(0.9–3.0)	17	2.5	(1.1–5.6)	6.5	.011
CP	43	1.0	(reference)	24	2.1	(1.1–3.9)	11	3.1	(1.2–7.8)	8.5	.004
Controls	189			43			16				

* OFC = orofacial cleft; CL±P = cleft lip with or without cleft palate; CP = cleft palate; OR = odds ratio; CI = confidence interval.
† Odds ratio adjusted for sex, season of birth, maternal education, and child's ethnic group.

to 3.2) for CL±P, and 1.8 (0.7 to 4.7) for CP. There were no statistically significant trends across categories (data not shown). Results were similar for a measure comprising hours of exposure combined with degree of smokiness, the adjusted ORs for the highest tertile of exposure, compared with no exposure, being 1.6 (95% CI 0.8 to 3.1) for OFCs, 1.4 (95% CI 0.6 to 3.0) for CL±P, and 1.8 (95% CI 0.7 to 4.6) for CP. There were no statistically significant trends across categories (data not shown). Data on the association between OFCs and maternal exposure to combinations of active and passive smoking are presented in Table 4. Ex-smokers did not have an increased risk of having a child with an OFC.

The ORs for smoking during the first trimester were greater for females than for males, the association being driven almost entirely by CL±P (Table 5).

Among both cases and controls, birth weight of offspring of smokers was significantly lower than birth weight of offspring of nonsmokers (cases: smokers mean 3183 g [938 to 4546 g], nonsmokers mean 3449 g [994 to 4659 g], t = 3.06, $p = .003$; controls: smokers mean 3329 g [1676 to 4631 g], nonsmokers mean 3507 g [2045 to 4858 g], t = 2.21, $p = .028$). The birth weight of offspring of mothers exposed only to passive smoke was also lower than that of unexposed mothers, although the difference was not statistically significant (controls: nonexposed mean 3542 g, passive smokers mean 3482 g; cases: nonexposed mean 3473 g, passive smokers mean 3434 g).

Discussion

A positive association was found between maternal smoking during the first trimester of pregnancy and both CL±P and CP. A dose-response relationship was observed for both types of cleft. The data were compatible with a modest effect of maternal passive smoking, but the study lacked statistical power to detect or exclude such an effect.

Strengths of the present study include the population-based design and the assessment of potential confounding by lifestyle factors including total dietary (energy) intake, folate intake, supplemental vitamin use, and alcohol consumption. Potential limitations include the participation rate and recall bias. Participation bias is possible in view of the incomplete participation of both cases and controls, although the magnitude of the association observed between OFCs and maternal smoking is similar to that of other studies. The information leaflet that was supplied with the consent form made no explicit mention of smoking. The study was primarily designed to examine maternal nutrition (and folic acid in particular) and, therefore, the issue of whether women smoked would not be expected to influence their decision to participate. The well-established association between birth weight and maternal smoking was observed in controls. In addition, the proportion of control mothers who reported that they smoked (24%) is similar to estimates from other studies in the United Kingdom (Office for National Statistics, 2000). The proportion of nonsmoking control mothers reporting exposure to passive smoking was 45%. This is somewhat higher than the 30% of adult women in the United States who reported that they lived in a home with at least one smoker or reported passive exposure at work (Pirkle et al., 1996). However, our study included passive smoking in social settings, whereas the U.S. study includes only exposure in the home or at work. The 1997 Health Education Population Survey for Scotland found that 66% of nonsmokers were exposed to passive smoking, although this varied with age group (85% in the 16- to 24-year-olds; 45% in the 65- to 74-year-olds; Health Education Board for Scotland, 1999). Evidence suggesting that women may report passive tobacco smoke exposure accurately is indicated by studies that find close agree-

TABLE 4 Association Between Oral Clefts and Combinations of Maternal Passive and Active Smoking During the First Trimester*

	No Passive Smoke No Active Smoke			*Passive Smoke No Active Smoke*			*No Passive Smoke Active Smoke*			*Passive Smoke Active Smoke*		
Cleft	*n*	*OR†*	*(95% CI)*	*n*	*OR†*	*(95% CI)*	*n*	*OR†*	*(95% CI)*	*n*	*OR†*	*(95% CI)*
OFC	43	1.0	(reference)	67	1.0	(0.6–1.6)	4	0.8	(0.2–3.1)	76	2.2	(1.3–3.8)
CL±P	27	1.0	(reference)	40	0.9	(0.5–1.7)	1	0.2	(0.0–2.3)	44	2.1	(1.1–3.9)
CP	16	1.0	(reference)	27	1.1	(0.5–2.2)	3	2.1	(0.5–9.4)	32	2.5	(1.2–5.3)
Controls	78			111			8			51		

* OFC = orofacial cleft; CL ± P = cleft lip with or without cleft palate; CP = cleft palate; OR = odds ratio; CI = confidence interval.
† Odds ratio adjusted for sex, season of birth, maternal education, and child's ethnic group.

TABLE 5 Association Between Smoking During First Trimester and Oral Clefts, by Sex*

	Controls Smokers		OFC			CL±P			CP		
			Smokers		Odds Ratio†	Smokers		Odds Ratio†	Smokers		Odds Ratio†
Sex	Yes	No	Yes	No	(95% CI)	Yes	No	(95% CI)	Yes	No	(95% CI)
Males	28	91	36	55	1.7 (0.9–3.2)	25	42	1.4 (0.7–2.9)	11	13	2.2 (0.8–5.9)
Females	31	98	44	55	2.4 (1.3–4.4)	20	25	2.5 (1.2–5.4)	24	30	2.3 (1.1–4.8)

* OFC = orofacial cleft; CL±P = cleft lip with or without cleft palate; CP = cleft palate; CI = confidence interval.
† Adjusted for season of birth, maternal education, and child's ethnic group.

ment between women's and their partner's reports of the partner's smoking behavior (Filippini et al., 1994; Passaro et al., 1997).

Recall bias has been subject to considerable discussion, although few studies have attempted to demonstrate or to quantify it. However, studies of comparisons of information collected retrospectively with that collected before the pregnancy outcome was known generally indicate no severe bias for those with an adverse pregnancy outcome (Little, 1992; Swan et al., 1992; Khoury et al., 1994).

After stratification by sex, the association between CL±P and smoking was stronger in females than in males. This pattern was not seen for CP. The numbers available for this part of the analyses were small, and the results should be interpreted with caution. The association among maternal smoking, OFCs, and sex of the offspring has not been well studied. We are aware of one other such report (Romitti et al., 1999), which found increased risks in males, although the size of the difference was not reported.

The present study adds to evidence from studies in other parts of northern Europe and North America that maternal smoking in pregnancy increases the risk for OFCs. The formulation of tobacco control policies suggests that, as yet, the association between OFCs and smoking does not have widespread recognition. Despite being included among the specific birth defects that have been related to maternal smoking in the recent report of the U.S. Surgeon General on women and smoking (U.S. Department of Health and Human Services, 2001), OFCs were not mentioned in the most recent report of the World Health Organization (2001) on women and the tobacco epidemic (Samet and Yoon, 2001). Assuming causality, the population fraction of clefts attributable to maternal smoking in the present study is of the order of 22%. This may be an overestimate because of possible participation and recall biases that are general issues in the interpretation of case-control studies. However, associations of similar magnitude have been observed in other studies of CL±P (Shaw et al., 1996; Christensen et al., 1999; Lorente et al., 2000) and CP (Romitti et al., 1999; Beaty et al., 2001). Based on a large cohort study in Sweden (Källén, 1997), the population attributable fraction for CLP was about 5%, substantially lower than in our study, reflecting a lower magnitude of the association.

We suggest that OFCs should be incorporated into public health campaigns on the consequences of maternal smoking. It is noteworthy that the images of faces of children with cleft lip have been used to promote some of the world's largest medical charity organizations. This powerful image might help counterbalance the active targeting of women by tobacco companies.

CONCLUSIONS

A case-control study of the association between OFCs and maternal exposure to tobacco smoke during the first trimester of pregnancy was carried out. There was a small but statistically significant positive association between active smoking during pregnancy and the risk of OFCs. The data were compatible with a modest effect of maternal passive smoking, but the study lacked statistical power to detect or exclude such an effect with confidence.

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