Smoking and the Risk of Oral Clefts

Exploring the Impact of Study Designs

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Background: Maternal cigarette smoking is a suspected cause of oral clefts, although this association has not been firmly established. We used case-crossover, case-time-control, and bidirectional case-crossover designs to supplement findings from a case-control study of maternal smoking and oral clefts among offspring in a large birth registry.

Methods: Data are from the Swedish Medical Birth Registry. From 1983 through 1997 there were 678 recorded cases of cleft palate and 1175 cases of cleft lip with or without palate. Maternal smoking status was ascertained in early pregnancy. Controls for the case-control study were a random sample of infants born without a cleft; controls for the case-crossover designs were nonmalformed infants born to case mothers.

Results: Cleft palate was positively associated with maternal smoking in all study designs, whereas cleft lip with or without cleft palate was associated with smoking only in the case-control design. In the case-control design, the odds ratios for cleft palate were 1.2 (95% confidence interval = 1.0–1.5) for women who smoked 1 to 9 cigarettes per day and 1.4 (1.1–1.8) for women who smoked 10+ cigarettes per day. In the case-time–control analysis, the odds ratio for cleft palate with maternal smoking was 3.2 (1.3–7.4) and in the bidirectional case-crossover design, the odds ratio was 2.2 (1.1–4.1).

Conclusions: An association between smoking and cleft palate was supported by all designs, whereas that between smoking and cleft lip with or without cleft palate was not. Case-only designs are a viable option in birth registries and may yield more information than a case-control design alone.

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Maternal smoking during early pregnancy has received much attention in the oral cleft literature.[1–21] Although most studies have shown a positive relation with oral clefts, confidence in the association has been hampered by the modest strength of effect estimates, the lack of statistical power in many studies, and the potential for recall bias or uncontrolled confounding.

Administrative databases often lack data on potential confounding variables. For example, we are unaware of any birth registry that includes information on maternal alcohol consumption or multivitamin supplement use—factors that may be associated with the risk of oral clefts and may also vary with smoking habits. Here, we consider study design approaches that may, in part, address the lack of data on confounding factors in administrative birth registries.

Maclure[22] introduced the case-crossover approach to study exposure-disease relations using data from case subjects only. In this design, exposure at the time of an event is compared with exposure during some nonevent period. Because each case period is matched to a control period within the same individual, all time-invariant confounding is controlled, although confounding by time-varying factors remains possible. In Maclure's discussion of the design, control periods were those that preceded case periods. Maclure notes that systematically sampling controls from periods before the event is acceptable for stable exposures but will be vulnerable to bias if there are changes over time in the exposure of interest or in confounding variables. In light of this concern, investigators have suggested methods to control for time trends in exposure. Suissa[23] proposed adjusting case-crossover findings for exposure trends by estimating the degree of trend from data on subjects without an event. The case-time-control design implicitly assumes that the exposure trend observed in the noncase subjects will accurately portray the exposure trend in the case subjects. To the extent that the

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trends differ between the 2 groups, the case-time-control approach will inadequately adjust for the exposure trend.[24] Another proposed method of controlling for exposure trends includes referent periods from both before and after the event period.[25] Assuming a relatively constant exposure trend and similar time windows between the event and control periods, this bidirectional design should equalize the exposure trend in the case and control periods. However, the approach will be valid only if the event does not influence subsequent exposure. Both approaches fit into the genre of case-only designs, as reviewed by Greenland.[26]

Using the population-based Swedish Medical Birth Registry, we examined the relation between maternal smoking during pregnancy and birth to an infant with an oral cleft using case-control, case-crossover, case-time-control, and bidirectional case-crossover designs. These designs differ in their potential for confounding and selection bias and in their eligible populations, the case-only designs being limited to women who have both case and control births. Our objectives were to explore the consistency of findings using these various methodologic approaches, and to consider the advantages and disadvantages of each design in evaluating the smoking-oral clefts association in a large birth registry.

METHODS

The Swedish Medical Birth Registry

The Swedish Medical Birth Registry, established in 1973, contains data on virtually all births in Sweden. Starting with the first antenatal visit, information is prospectively collected on demographics, reproductive history, and complications during pregnancy, delivery, and the neonatal period. Such information is forwarded to the Registry through copies of standardized antenatal, obstetric, and pediatric records that have been in use since 1982. All births and perinatal deaths reported to the Registry are validated annually against the Registry of the Total Population by use of unique personal identification numbers.[26,27]

Nurse midwives collect early pregnancy data from women at their first antenatal clinic visit, generally during weeks 8 to 12 of pregnancy. From 1983 through 1997, women reported their current smoking status as no smoking, fewer than 10 cigarettes per day, or 10 or more cigarettes per day. Smoking data were missing on 6% of all births in this time interval. In addition to smoking status, the Registry includes data on several relevant covariates: maternal age, singleton/multiple birth status, maternal diabetes, the mother's country of origin, offspring birth year, and cohabiting status of the parents. Additionally, birth order and history of malformations were determined from each woman's available birth history as recorded in the Registry from 1973. Diagnoses are classified according to the Swedish version of the *International Classification of Diseases* (ICD). Infant diagnoses are noted by a pediatrician at the time when the infant is discharged from the hospital, using a standardized form, on which the definitions of the diagnoses are written beside the ICD code. Sweden used ICD-8 in 1983–1986, ICD-9 in 1987–1996, and thereafter the ICD-10. We excluded multiple births (n = 3246), mothers who immigrated to Sweden (n = 17), births with missing smoking data (n = 8402), and recurrent cleft births (n = 25). Note that with the exception of immigrants to Sweden, all exclusions were on the birth, not maternal, level. Other design-specific exclusions are described subsequently.

Cases

Our analysis focused on 2 major case groups: cleft palate alone (ICD-8 code 749.0, ICD-9 code 749A, ICD-10 code Q35) and cleft lip with or without cleft palate (ICD-8 codes 749.1 and 749.2, ICD-9 codes 749B and 749C, ICD-10 codes Q36 and Q37). We also included analyses for cleft lip alone and cleft lip with palate. We further distinguished those infants in whom the cleft was the only malformation noted in the Registry from infants who had additional noncleft malformations listed in the Registry.

We regarded the findings for the isolated cleft groups as less susceptible to 2 types of bias. First, limiting the sample to isolated clefts would mean that possible associations between smoking and other malformations will not affect the observed relation between oral clefts and smoking. Second, the Registry includes only births; data on spontaneous or elective abortions are not available. We expect spontaneous or elective abortions to be less likely for isolated oral clefts than for infants with clefts and other malformations, thereby reducing the potential for selection bias resulting from removal of aborted fetuses with malformations related to maternal smoking.

Case-Control Study

We included all cleft cases and a random 10% sample of noncleft births as controls. Between 1983 and 1997, there were 872 cleft palate, 678 isolated cleft palate, 1456 cleft lip with or without palate, and 1175 isolated cleft lip with or without cleft palate. The same group of 128,688 noncleft births served as controls for all cleft subtypes. Each mother contributed only 1 birth to the analysis. Because only women with at least 2 children (1 case and 1 control) were eligible for inclusion in the case-only designs, we also examined the effect of restricting the case-control population to women who had at least 2 children.

We used unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the effect of smoking on each case group. Women who reported smoking 1 to 9 or 10+ cigarettes per day were compared with women who reported no smoking at registration. In other analyses, we compared any smoking with no smoking. Mul-

tivariate-adjusted models included maternal age, birth year, maternal diabetes, parents' cohabiting status, maternal history of infants with birth defects, and parity (including study infant); these variables were categorized as shown in Table 1. We included separate dummy variables for each level of multilevel covariables in the regression models and also adjusted for maternal age, offspring birth year, and parity as continuous variables.

Case-Crossover Studies

For the case-only designs, we restricted the study population to women who gave birth to at least 1 child with a cleft. We then selected 2 control populations from each woman's noncleft births: 1) the noncleft infant that immediately preceded the cleft birth (when available); and 2) all noncleft infants, before and after the cleft birth. It is important to note that our case and control periods were separate births with the same mother, not separate periods (with different etiologic relevancy) within the same pregnancy. For the present study, we applied the case-crossover design and (to control exposure trend bias) the case-time-control and bidirectional case-crossover designs.

The case-crossover design restricts the case population to births preceded by at least 1 noncleft birth; women who had only 1 child or whose first child had a cleft were excluded. We further restricted controls to those births that immediately preceded the case birth. This limited, but did not eliminate, possible bias resulting from declining rates of smoking over time.

The case-time-control design provided additional control for exposure trends by estimating the smoking trend among women who did not give birth to an infant with a cleft and by adjusting the observed case-crossover odds ratios for this trend. We addressed the possibility of differing smoking trends among women who did and did not have an infant with a cleft by matching the control and case births of each woman who had a cleft infant to 2 consecutive births among women who did not have a cleft infant. Women were matched on age, cohabiting status, and maternal diabetes, and infant's birth year and birth order. We also applied the bidirectional case-crossover design to control exposure trend bias, including as controls all noncleft births before and after the cleft birth. We used our data to test the assumption (required for valid

TABLE 1. Distribution of Potential Risk Factors for Oral Clefts for Cases and Controls, Swedish Medical Birth Registry, 1983–1997

Variable	Cleft Lip ± Cleft Palate (n = 1175) %	Cleft Palate (n = 678) %	Controls (n = 128,688) %
Smoking (no. of cigarettes/day)			
0	72	71	76
1–10	17	17	15
>10	11	13	9
Age (years)			
< 20	3	2	3
20–24	23	23	23
25–29	37	35	37
30–34	26	27	26
35+	11	13	11
Birth year			
1983–1985	24	25	22
1986–1988	21	16	18
1989–1991	20	21	20
1992–1994	22	24	22
1995–1997	14	15	19
Parents cohabit	95	95	95
Maternal diabetes	1.0	1.3	1.0
Maternal history of birth defects	2.7	3.5	2.7
Parity (no. of births)			
1	58	58	60
2	30	33	31
3+	12	10	9

analyses based on this design) that having a cleft infant did not influence a woman's subsequent smoking.

We used conditional logistic regression to estimate the odds ratios (and 95% CIs) from the case-only designs, comparing smoking status in case and control births within strata of mother. For the case-time-control design, we adjusted the natural log odds ratio from the case-crossover design for smoking trend as follows. First, from women who did not have a cleft infant, we identified birth histories that matched the birth histories of women who had a cleft infant with respect to several variables. That is, for estimates of exposure trend, we matched case women's birth histories to control women's birth histories (explicit matching); this matching procedure is in contrast to matching case births to other (control) births within the same woman (implicit matching) as in the case-crossover analyses. Among the women who did not have an infant with cleft, we then assigned the last birth from the matched birth histories "case" status (that is, coded it "1," in which control status was coded "0"), and conducted the same conditional logistic regression analysis among these women. This provided us with an estimate of the trend in smoking over the period during which women gave birth to an infant with a cleft. Finally, we adjusted our case-crossover estimates by dividing the case-crossover odds ratio by the trend estimate. The variance for the case-time-control estimates was estimated by adding the variance components contributed by the case-crossover and trend estimates on the natural log scale. The resulting confidence intervals reflect the uncertainty in both the case-crossover odds ratio and the exposure trend estimate.

RESULTS

Daily smoking in early pregnancy was slightly more common among women who gave birth to a child with any cleft palate than among control women (Table 1). Overall, the distributions of other covariables did not differ appreciably between case and control women.

We observed modest positive associations between maternal smoking and oral cleft subtypes in the case–control analysis (Table 2). Crude and multivariate-adjusted results were similar, as were effect estimates for isolated clefts and clefts that occurred with other malformations. Modeling maternal age, offspring birth year, and parity as continuous, rather than categorical, variables, also did not alter odds ratios. Compared with nonsmokers, multivariate-adjusted odds ratios (95% CIs) for isolated cleft palate were 1.2 (1.0–1.5) and 1.4 (1.1–1.8) for those who smoked 1 to 9 and 10 or more cigarettes per day, respectively. Odds ratios for cleft lip with or without palate were 1.1 (1.0–1.3) and 1.2 (1.0–1.5) across levels of smoking. Estimates were similar when we restricted the analysis to first births to explore confounding or effect modification by birth order. Among first births, adjusted odds ratios for isolated cleft palate were 1.3 (1.0–1.7) and 1.5 (1.1–2.1) across smoking categories. Odds ratio did not differ among women who had at least 2 children, mirroring the eligible population for the case-cross-

TABLE 2. Crude and Multivariate-Adjusted Odds Ratios and 95% Confidence Intervals for Oral Clefts According to Maternal Smoking at Registration in the Swedish Medical Birth Registry; Case-Control Analysis

	No Smoking*	<10 cig/day	10+ cig/day
Non-malformed sample (n)	97,595	19,207	11,886
Isolated cleft palate			
No. of cases	480	113	85
Crude OR (95% CI)	1.0	1.2 (1.0–1.5)	1.5 (1.2–1.8)
Multivariate adjusted OR (95% CI)	1.0	1.2 (1.0–1.5)	1.4 (1.1–1.8)
All cleft palate			
No. of cases	633	136	103
Crude OR (95% CI)	1.0	1.1 (0.9–1.3)	1.3 (1.1–1.7)
Multivariate adjusted OR (95% CI)	1.0	1.1 (1.0–1.4)	1.4 (1.1–1.7)
Isolated cleft lip with or without palate			
No. of cases	847	195	133
Crude OR (95% CI)	1.0	1.2 (1.0–1.4)	1.3 (1.1–1.6)
Multivariate adjusted OR (95% CI)	1.0	1.1 (1.0–1.3)	1.2 (1.0–1.5)
All cleft lip with or without palate			
No. of cases	1051	238	167
Crude OR (95% CI)	1.0	1.2 (1.0–1.3)	1.3 (1.1–1.5)
Multivariate adjusted OR (95% CI)	1.0	1.1 (1.0–1.3)	1.3 (1.1–1.5)

*Reference category.

over, case-time–control, and bidirectional designs: odds ratios for isolated cleft palate were 1.2 (1.0–1.6) and 1.3 (1.0–1.8) across the 2 levels of smoking and for isolated cleft lip with or without cleft palate 1.2 (1.0–1.4) and 1.3 (1.0–1.6). Finally, odds ratios for the subgroups cleft lip alone and cleft lip with palate did not differ from the odds ratio for cleft lip with or without palate.

We created a dataset of women's first and second births to test assumptions of the case-crossover study. We found no evidence of carryover effects of smoking from one pregnancy to the next; among women who did not give birth to a cleft infant on their first pregnancy, the odds of having a cleft infant in their second pregnancy did not depend on their smoking status during their first pregnancy (OR = 0.8; CI = 0.5–1.4). Furthermore, having a cleft infant did not appear to influence a woman's decision to smoke during subsequent pregnancies; controlling for smoking during the first pregnancy, the odds of smoking during the second pregnancy was not different between women who did or did not have a cleft infant in their first pregnancy (1.0; 0.8–1.3).

Case-only analyses included women who had given birth to at least 1 cleft infant. Table 3 presents the distribution of cleft births within these women's birth histories. For example, 684 women had their cleft infant during their second pregnancy; 503 of these women had only 2 children, 152 women had 3 children, and so on. Table 3 provides rough estimates of the sample sizes available for the various case-only designs, although numbers for analysis were often somewhat lower as a result of missing data on exposure or covariables.

We began with a case-crossover sample, including all women who had at least 1 nonmalformed infant before their cleft infant. From these women, we selected the noncleft birth that immediately preceded the cleft birth. There were 914 such infant pairs; 646 mothers did not smoke in either pregnancy, 197 mothers smoked in both pregnancies, 49 mothers smoked only in the first pregnancy, and 22 mothers smoked only in the second pregnancy. Odds ratios (95% CIs) for specific isolated cleft subgroups, comparing smokers with nonsmokers, were 0.5 (0.2–1.0) for cleft lip with or without palate and 1.4 (0.6–3.5) for cleft palate.

We considered that a decline in smoking over time may have biased these findings. Indeed, the prevalence of smoking decreased by approximately 50% across calendar time (birth year), from 31% or 32% in 1983 to 14% in 1997 (Fig. 1), a trend that could bias case-crossover estimates if not addressed in the analysis. Smoking during pregnancy was also inversely related to maternal age. Most relevant to our analysis, the prevalence of smoking decreased over a woman's birth history (data available with the electronic version of this article). For example, among women who had 3 children, the average smoking prevalence decreased from 25% or 26% during the woman's first pregnancy to 22% or 23% and 21% during the woman's second and third pregnancies, respectively. A smoking trend would most affect those case-crossover strata with a long interval between the control and case birth. Indeed, when we stratified case-crossover data on time, we found an odds ratio of roughly 0.6 for control-case birth intervals of 1 to 2 years and an odds ratio of 0.4 for control-case birth intervals of 3 years or more.

Thus, we attempted to correct case-crossover findings for exposure trend bias by using the case-time-control and

TABLE 3. Distribution of Cases Among Births for Women Who Had at Least One Infant With a Cleft

Total No. of Control Births	Birth Position of Cleft Infant					
	1	2	3	4	5	6
0	751					
1	489	503				
2	150	152	155			
3	18	24	22	39		
4	2	4	4	4	5	
5		1	1	2	2	
6					1	
7						1
Total cases	1360	684	182	45	8	1

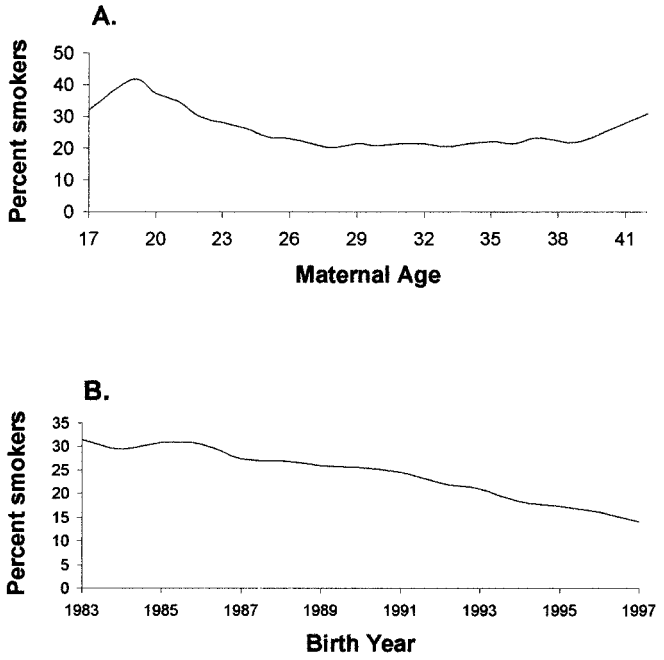

FIGURE 1. Percent of pregnant women who reported smoking at their prenatal visit by (**A**) age and (**B**) birth year, Swedish Medical Birth Registry.

bidirectional approaches. First, we estimated the smoking trend among women who did not give birth to a cleft infant and who had the same distribution of demographic and reproductive factors in 2 subsequent births as mothers of cleft infants. Between these 2 births, there were roughly twice as many instances of women who stopped smoking as those who started smoking. That is, the odds of smoking only in the second pregnancy were half the odds of smoking only in the first pregnancy. Using this ratio to adjust the original case-crossover estimates for the smoking trend, the odds ratio was approximately 1.0 for cleft lip with or without palate (Fig. 2), and also for cleft lip and palate, and cleft lip separately (data not shown). After the adjustment, the odds ratio for cleft palate with smoking was 3.2 (1.3–7.4). Findings were similar when we sampled controls from both before and after the cleft birth (bidirectional design) in an effort to adjust for the smoking trend (Fig. 2). Again, a relation was observed for cleft palate only, with an odds ratio of 2.2 (1.1–4.1). Odds ratios for cleft palate were higher in both of the case-only designs that controlled for smoking trend compared with the case-control design; however, confidence intervals were large in the case-only designs, and both results included the cleft palate point-estimate from the case-control design. As expected, findings from the bidirectional design did not differ when we stratified on control-case birth interval length.

DISCUSSION

Subjecting a study question to a combination of design and analytic approaches can be informative.[28,29] Using multiple approaches is particularly useful for exploring inconsistent findings or for addressing specific limitations of a single design.[30] Findings for oral cleft and smoking have been mixed, with positive associations for both cleft lip with or without cleft palate and cleft palate,[9,12,14,16,18,21] positive findings for only 1 cleft subtype,[1,5] and no association with either subtype.[4,13,15,17] This lack of consistency may be, at least in part, the result of design issues such as low statistical power, inadequate control for potential confounding factors, and possible selection and recall biases. It is also possible that differences in the population prevalence of genetic susceptibility factors has contributed to divergent study findings. The present case–control study did not suffer from lack of statistical power, nor, as we discuss further, selection or recall bias.

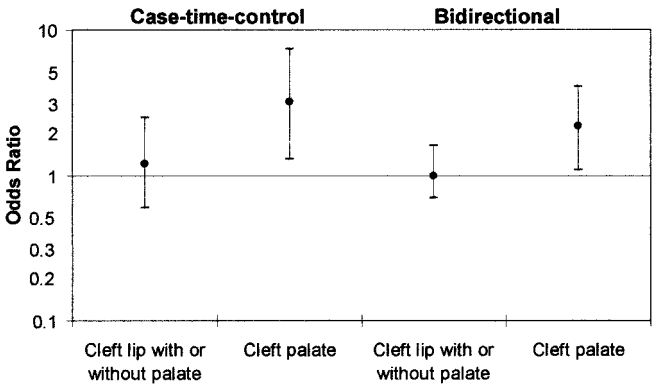

FIGURE 2. Case-time-control and bidirectional case-crossover analyses of maternal smoking (any vs. none) and oral clefts in offspring.

We considered the possibility that our case-control design could be limited by the absence of information on potential confounding variables in the registry. Even so, several aspects of these data suggested, *a priori*, that the case-control design was the most reasonable option.[31] First, more women gave up smoking than initiated smoking during their reproductive years, producing a selection bias in the standard case-crossover design. Second, relatively few women changed their smoking status over time, and the small number of discordant sibling pairs resulted in a large degree of uncertainty in effect estimates. Finally, case-only designs would not necessarily adjust for important potential confounders (such as alcohol and vitamin supplement use) for which changes over time are likely to correlate with changes in smoking.

We included 2 referent groups in our case-only designs: the noncleft birth that preceded the cleft birth and all noncleft births (before and after the cleft birth). We based this decision on considerations of bias and precision. Including up to 12 control periods per case can increase relative efficiency, although the improvement will be hampered by autocorrelation of exposure.[32] Autocorrelation among exposure periods will also violate the assumption of independence among observations and can lead to biased estimates.[33] Maternal smoking was highly correlated in sequential pregnancies, as shown by the minimal degree of crossover. Bias from autocorrelation is of most concern when controls are selected from one side of the case period, like in our case-time-control design. This bias is not appreciable when controls are selected from both sides of the case period, like in our bidirectional design.[34] Restricting the case-time-control analysis to 1 control period decreased autocorrelation bias, but also decreased precision. By including all control periods in the bidirectional design, we increased precision without the expense of autocorrelation bias.

Our case-only population was nontraditional in that the case and control periods were from different infants, in contrast to case-only designs in which the same individual serves as both case and control. An example of such a design in the context of exposure during pregnancy and birth defects is the study by Hernandez-Diaz and colleagues[35] of maternal use of folic acid antagonists at different times during pregnancy among women whose infant had a neural tube defect. This approach was not possible in the Swedish Birth Registry, which lacks data on the specific timing of exposure during pregnancy.

We may not have successfully eliminated selection bias as a result of the decreasing smoking trend over time in the case-crossover designs. In the case-time-control design, we sought to mirror the exposure distribution of the source population of case mothers by matching control mothers to case mothers on factors that may relate to a women's smoking habits over time. However, the limited number of variables in the Registry may have prevented our representing the case population. With respect to the bidirectional design, including all noncleft births as controls may not have completely adjusted for time trends in exposure. Ideally, to adjust for a monotonic trend, one would include control periods that are symmetric in count and temporal distance from the case period. However, restricting our population to situations in which a woman had evenly spaced births would have severely limited the size of our study population.

The Registry has data on only a few potential confounding factors, leaving the case-control design vulnerable to confounding. The case-crossover study will control for confounders that are stable over time such as socioeconomic status, but not time-varying factors such as maternal alcohol consumption, multivitamin supplement use, or medication use. One could consider a woman's propensity to consume alcohol or use vitamin supplements during pregnancy as somewhat stable over time, but it is also reasonable to assume that these variables will change. To the extent that trends in these potential risk factors mirror trends in smoking, there may be intractable confounding.

In addition to design-specific biases, misclassification or biased entry into the Registry would affect all designs. Smoking data were collected prospectively, which limits the potential for differential misclassification of smoking based on birth outcome. In general, studies report high reliability and validity of retrospective maternal reports of smoking during pregnancy,[36,37] and it is reasonable to assume that data collected prospectively would be at least as valid.

It is possible that, when learning of their pregnancy, some women stopped smoking before their visit to the nurse midwife but after some portion of the etiologic period. Smoking status was ascertained during weeks 8 to 12 of pregnancy, which is the etiologic period for cleft palate but follows cleft lip development during weeks 5 to 8.[38] Women who stopped smoking after the initiation of lip formation but before palate formation would be classified as nonsmokers, although they did smoke during some part of weeks 5 through 8. Thus, some cases of cleft lip could have been incorrectly classified as nonsmokers, attenuating any positive association between cleft lip and smoking. However, those classified as smokers would be true smokers, and the much larger proportion of true nonsmokers would dampen the effect of misclassification of smokers as nonsmokers.

The Registry includes virtually all births in Sweden, and bias in selection into the Registry is unlikely. Although smoking may be associated with spontaneous abortion and, through social factors, with elective abortion, isolated oral clefts are not believed to result in either spontaneous or elected abortion.[39]

Our findings are consistent with a positive association between maternal smoking during pregnancy and cleft palate in offspring. Weaker positive relations with other cleft subtypes were observed only in a case-control design. This study illustrates the use of case-only designs to explore findings from case-control studies in registries with maternal birth history data.

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