Original Contribution

Passive Smoke Exposure as a Risk Factor for Oral Clefts—A Large International Population-Based Study

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Maternal cigarette smoking is a well-established risk factor for oral clefts. Evidence is less clear for passive (secondhand) smoke exposure. We combined individual-level data from 4 population-based studies (the Norway Facial Clefts Study, 1996–2001; the Utah Child and Family Health Study, 1995–2004; the Norwegian Mother and Child Cohort Study, 1999–2009; and the National Birth Defects Prevention Study (United States), 1999–2007) to obtain 4,508 cleft cases and 9,626 controls. We categorized first-trimester passive and active smoke exposure. Multivariable logistic models adjusted for possible confounders (maternal alcohol consumption, use of folic acid supplements, age, body size, education, and employment, plus study fixed effects). Children whose mothers actively smoked had an increased risk of oral clefts (odds ratio (OR) = 1.27, 95% confidence interval (CI): 1.11, 1.46). Children of passively exposed nonsmoking mothers also had an increased risk (OR = 1.14, 95% CI: 1.02, 1.27). Cleft risk was further elevated among babies of smoking mothers who were exposed to passive smoke (OR = 1.51, 95% CI: 1.35, 1.70). Using a large pooled data set, we found a modest association between first-trimester passive smoking and oral clefts that was consistent across populations, diverse study designs, and cleft subtypes. While this association may reflect subtle confounding or bias, we cannot rule out the possibility that passive smoke exposure during pregnancy is teratogenic.

birth defects; cleft lip; cleft palate; oral clefts; passive smoking; secondhand smoke; smoking

Abbreviations: CI, confidence interval; MoBa, Norwegian Mother and Child Cohort Study; NBDPS, National Birth Defects Prevention Study; NFCS, Norway Facial Clefts Study; OR, odds ratio; UCFHS, Utah Child and Family Health Study.
and risk of oral clefts (8), but the biological mechanisms by which smoking increases risk of clefts remains unclear (13).

A related (if more speculative) risk factor for oral clefts is passive or secondhand exposure to tobacco smoke. Passive smoke exposure is relevant given that more women are exposed to cigarette smoke passively than actively (14). Several studies have reported increased risks of oral clefts among the offspring of women who were passively exposed to tobacco smoke, although the associations are often seen within one subtype and not others. In the National Birth Defects Prevention Study (NBDPS), using a much smaller sample than is included here, Honein et al. (12) reported that maternal passive smoke exposure was associated with cleft palate but not with clefts overall. In an analysis of the Norwegian case-control data also included in the current analysis, passive smoking was associated with cleft lip with palate but not with clefts overall (13). In a recent meta-analysis of previous studies, Sabbagh et al. (15) reported a 1.5-fold increase in risk of nonsyndromic orofacial clefts for passive smoking. In a Brazilian case-control study, passive smoke exposure among nonsmoking mothers was found to be associated with an increase in cleft lip with palate but not with cleft palate alone (16). Perhaps the most interesting positive association is the report of a nearly 2-fold higher risk of cleft lip with or without cleft palate in Chinese infants whose mothers had passive smoke exposure (17). Few women in China are active smokers, but many are passively exposed, reducing the chance of misclassification between passive and active smoking.

In 2014, the US Surgeon General’s Report noted that the role of passive smoking in the etiology of oral clefts remains inconclusive (11). While previous studies are suggestive, all have been limited by relatively small sample sizes (fewer than 1,000 cases), multiple testing, and consequent imprecision and lack of statistical power. In addition, only a few studies had population-based samples (12, 13, 18). The meta-analysis also was based on mostly small studies that differed in terms of whether and how much they controlled for potential confounders, as well as in their sample design and risk measures (15). The adjusted risk estimate for passive smoke exposure in the meta-analysis (odds ratio OR) = 1.5) far exceeds the risk for active smoking reported in previous meta-analyses (OR ≈ 1.3) (10), suggesting confounding in these estimates. Furthermore, small studies are particularly prone to false-positive findings, increasing the potential for bias in a meta-analysis estimate.

We used a pooled data set comprising more than 4,500 cases and nearly 10,000 controls from 4 population-based studies to evaluate the association between maternal exposure to passive smoke in the first trimester of pregnancy and risk of oral clefts. Our study had several strengths over previous work, including the recent meta-analysis (15). These advantages included focusing on population-based studies to enhance representativeness; a pooled regression analysis of individual-level data that included harmonized measures of active smoking and passive smoke exposure, both alone and combined, and controlled for similar confounders across studies; and a larger total sample of cases and controls than any previous analysis, which allowed us to investigate differences by cleft type (which was not done in the meta-analysis (15)). Furthermore, most of our data have not been included in any previous analyses of passive smoke exposure. The earlier work from the NBDPS included a much smaller sample than what we include here (12). Furthermore, we include new data from Norway beyond what was published previously (13), as well as new data from Utah.

**METHODS**

**Design**

Data for this analysis came from an international consortium of 4 studies (the Norway Facial Clefts Study (NFCS) (19, 20), the Norwegian Mother and Child Cohort Study (MoBa) (21), the Utah Child and Family Health Study (UCFHS) (22), and the NBDPS (23)), which together supplied individual exposure and outcome data for 4,508 cleft cases and 9,626 controls. All studies provided detailed data on household demographic and socioeconomic factors and maternal exposures, including active cigarette smoking and passive exposure to cigarette smoke during the first trimester of pregnancy, collected through in-person interviews, telephone interviews, or surveys completed by the mothers. These data sets are briefly described below.

The NFCS was a population-based study that enrolled 573 infants born with oral clefts in 1996–2001, comprising 88% of eligible newborns with oral clefts treated in Norway during this period (19, 20). Controls were a random sample of 763 Norwegian newborns without oral clefts. Exposure data were obtained from case and control mothers through self-administered paper questionnaires completed about 3 months after delivery. The analytical sample with complete data for all relevant variables included 546 cases and 733 controls.

MoBa was a population-based birth cohort study of approximately 100,000 pregnancies with deliveries that took place during 1999–2009 in Norway, including babies with oral clefts and unaffected live births (21). MoBa collected data on first-trimester exposures through interviews with mothers at 15–18 weeks of pregnancy, during their first prenatal visit. Additional interviews were completed around the 30th week of gestation. MoBa provided data on 184 babies with clefts and a randomly selected sample of 551 infants without clefts. The analytical sample with complete data included 134 cases and 419 controls. None of the cases were born in 1999 and 2000; only 4 cases in the analytical sample were enrolled in 2001. Thus, there was minimal overlap with the NFCS; subject identifiers for the NFCS are no longer available for confirmation of whether those 4 cases were also enrolled in the NFCS.

The UCFHS enrolled 561 infants with oral clefts delivered during 1995–2004 in Utah and identified from a statewide birth-defects registry, together with 660 unaffected live births randomly selected from birth certificates and frequency-matched to cases by sex and month/year of birth (22). Mothers provided data on first-trimester exposures and other maternal variables through telephone interviews after delivery. The UCFHS analytical sample with complete data included 557 cases and 658 controls. Utah births of infants with clefts occurring after 2005 and unaffected controls were enrolled in the NBDPS, described below; there was no overlap between the UCFHS and NBDPS Utah samples.
The NBDPS was a case-control study carried out among infants in 10 US states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Cases with major birth defects (including oral clefts) were identified through participating state birth-defect registries; cases recognized as having a single-gene condition or chromosome abnormality were excluded (23). Controls were randomly selected from birth certificates or birth hospital logs in each participating state during the same time period as the cases. First-trimester exposure data and other relevant pregnancy information was obtained via telephone interviews with case and control mothers 6 weeks to 24 months after delivery. The overall sample from the NBDPS included 3,491 cleft cases and 8,357 controls born between 1997 and 2007. The analytical sample with complete data included 3,271 cases and 7,816 controls.

Main outcome and risk factor measures

We evaluated all cleft cases combined, as well as specific cleft types (cleft lip alone, cleft palate alone, cleft lip with cleft palate, and cleft lip with or without cleft palate (which are commonly combined)). We also conducted subanalyses on isolated cases only, without other birth defects or syndromes, in order to estimate associations in a more homogeneous subgroup.

Our study combined individual-level data from the 4 studies described above in which similar but not identical questions had been asked about passive smoke exposure. We harmonized the measures from these studies to create a dichotomous indicator representing any maternal exposure to passive smoke during the first trimester at home or at work. Web Table 1 (available at http://aje.oxfordjournals.org/) shows the questions used to collect passive smoke exposure data in each study and our strategy for mapping these questions to a single passive smoke measure. Questions about active smoking were more consistent across all studies, allowing a finer level of data harmonization. Maternal active smoking during the first trimester was analyzed as a dichotomous indicator (any smoking vs. none) in the main models, and also as continuous and categorical measures of number of cigarettes smoked per day.

Statistical analysis

We used logistic regression to evaluate the associations between first-trimester maternal exposure to cigarette smoke and risk of clefts. The regression analysis included indicators for the following 3 exposure groups: 1) nonsmoking mothers exposed to passive smoke; 2) active smokers not exposed to passive smoke; and 3) active smokers exposed to passive smoke. Nonsmokers with no exposure to passive smoke served as the reference group in all comparisons.

Since passive and active smoke exposures are correlated with alcohol consumption, use of folate supplements, body weight, and socioeconomic status (all of which have been suggested as risk factors for clefts), we adjusted for these potentially confounding factors. Specifically, we adjusted for any maternal use of alcohol in the first trimester (yes/no), any use of folic acid supplements in the first trimester (yes/no), maternal body size based on body mass index (weight (kg)/height (m)^2; underweight (<18.5), normal-weight (18.5–25), overweight (25–30), or obese (≥30)), maternal education (less than high school diploma, high school diploma, or college graduate (4-year college degree or higher)), maternal age (≤18, 19–25, 26–30, 31–35, or 36–49 years), and maternal employment anytime during pregnancy (yes/no).

In addition, we adjusted for binary indicators for the study populations in all models (study fixed effects) to account for differences in case-control ratios and potentially unobservable confounders across studies. These fixed effects accounted for population differences in risk factors (e.g., smoking prevalence), cleft prevalence, and study period and ensured that such differences did not bias the overall estimated association between the smoking indicators and oral cleft risk. Furthermore, because of these fixed effects and because cases and controls were practically balanced by birth year within each study, birth year did not confound the average estimate of association between smoking and cleft risk from the pooled regression.

Using Wald tests, we examined whether the logistic regression coefficient for active smokers who were also exposed to passive smoke was significantly different from the coefficients of each of the 2 groups of single-exposure mothers. The logistic regression model was fitted for all clefts combined, as well as for each cleft type. Alternative models were also fitted, in which the binary indicator for any active smoking was replaced with dosage indicators.

Analyses were conducted with SAS 9.2 (SAS Institute, Inc., Cary, North Carolina) (24), Stata 12 (StataCorp LP, College Station, Texas) (25), and R (R Foundation for Statistical Computing, Vienna, Austria) (26) statistical software. Ninety-five percent confidence intervals were calculated.

RESULTS

Web Table 2 shows numbers of cases by cleft type and isolated status. The distributions of smoking exposures and model covariates are presented by study in Table 1. Web Table 3 shows the prevalence of smoking exposures in cases and controls in all study populations combined. Web Table 4 shows descriptive statistics for controls.

Table 2 provides results comparing the 3 smoke exposure groups (passive alone, active alone, and both active and passive) with the unexposed (results for isolated clefts are shown in Web Table 5). We focus on the results adjusted for known risk factors. Estimates adjusted for study fixed effects alone were consistent with the adjusted results and are shown in Web Table 6.

Women exposed only to passive smoke were at greater risk of having a child with a cleft. Exposure to passive smoke alone was associated with a 14% increase in risk of all clefts combined (OR = 1.14, 95% confidence interval (CI): 1.02, 1.27). Odds ratios for separate types of clefts ranged from 1.08 for cleft lip with palate to 1.18 for cleft palate only.

Active smoking was associated with increased risk of oral clefts, for clefts as a whole as well as the separate cleft types. Active smoking alone (without exposure to passive smoke) was associated with a 27% increase in cleft risk (OR = 1.27, 95% CI: 1.11, 1.46). Odds ratios ranged from 1.18 for cleft lip with palate to 1.65 for isolated cleft lip only.

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### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UCFHS (n=1,215)</th>
<th>NFCS (n=1,279)</th>
<th>MoBa (n=553)</th>
<th>NBDPS (n=11,087)</th>
<th>Total (n=14,134)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
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<td>Smoking exposure</td>
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<td></td>
<td></td>
</tr>
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<td>Both active and passive</td>
<td>86</td>
<td>7</td>
<td>339</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>Active only</td>
<td>42</td>
<td>4</td>
<td>114</td>
<td>9</td>
<td>96</td>
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<tr>
<td>Passive only</td>
<td>67</td>
<td>6</td>
<td>252</td>
<td>20</td>
<td>25</td>
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<tr>
<td>None</td>
<td>1,020</td>
<td>84</td>
<td>574</td>
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<td>399</td>
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<td>Other exposures</td>
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<td>Alcohol use</td>
<td>84</td>
<td>7</td>
<td>430</td>
<td>34</td>
<td>77</td>
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<td>Supplements containing folic acid</td>
<td>921</td>
<td>76</td>
<td>498</td>
<td>39</td>
<td>446</td>
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<td>Maternal body size&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Underweight</td>
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<td>6</td>
<td>50</td>
<td>4</td>
<td>25</td>
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<td>Normal</td>
<td>713</td>
<td>59</td>
<td>883</td>
<td>69</td>
<td>350</td>
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<td>Overweight</td>
<td>268</td>
<td>22</td>
<td>249</td>
<td>20</td>
<td>117</td>
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<tr>
<td>Obese</td>
<td>156</td>
<td>13</td>
<td>97</td>
<td>8</td>
<td>61</td>
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<td>Maternal age, years</td>
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<tr>
<td>≤18</td>
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<td>10</td>
<td>1</td>
<td>1</td>
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<td>19–25</td>
<td>512</td>
<td>42</td>
<td>270</td>
<td>21</td>
<td>83</td>
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<td>26–30</td>
<td>369</td>
<td>30</td>
<td>506</td>
<td>40</td>
<td>206</td>
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<tr>
<td>31–35</td>
<td>197</td>
<td>16</td>
<td>357</td>
<td>28</td>
<td>195</td>
</tr>
<tr>
<td>36–49</td>
<td>95</td>
<td>8</td>
<td>136</td>
<td>11</td>
<td>68</td>
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<tr>
<td>Maternal education</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Less than high school diploma</td>
<td>87</td>
<td>7</td>
<td>167</td>
<td>13</td>
<td>13</td>
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<tr>
<td>High school diploma</td>
<td>778</td>
<td>64</td>
<td>595</td>
<td>47</td>
<td>178</td>
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<tr>
<td>College graduation or higher</td>
<td>350</td>
<td>29</td>
<td>517</td>
<td>40</td>
<td>362</td>
</tr>
<tr>
<td>Maternal employment</td>
<td>1,056</td>
<td>87</td>
<td>1,062</td>
<td>83</td>
<td>456</td>
</tr>
</tbody>
</table>

<sup>a</sup> Maternal body size was based on body mass index (weight (kg)/height (m)<sup>2</sup>) categories: underweight, <18.5; normal-weight, 18.5–<25; overweight, 25–<30; and obese, ≥30.

### Table 2

<table>
<thead>
<tr>
<th>Cleft Status</th>
<th>Smoking Exposure Category</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cleft</td>
<td>None&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.14</td>
<td>1.02, 1.27</td>
<td>1.27</td>
<td>1.11, 1.46</td>
<td>1.51</td>
<td>1.35, 1.70</td>
</tr>
<tr>
<td>Cleft lip with or without cleft palate</td>
<td>Passive Only</td>
<td>1.11</td>
<td>0.98, 1.27</td>
<td>1.28</td>
<td>1.09, 1.51</td>
<td>1.55</td>
<td>1.36, 1.77</td>
</tr>
<tr>
<td>Cleft lip only</td>
<td>Passive Only</td>
<td>1.14</td>
<td>0.93, 1.39</td>
<td>1.52</td>
<td>1.19, 1.94</td>
<td>1.63</td>
<td>1.33, 2.00</td>
</tr>
<tr>
<td>Cleft lip with cleft palate</td>
<td>Passive Only</td>
<td>1.11</td>
<td>0.95, 1.29</td>
<td>1.18</td>
<td>0.97, 1.43</td>
<td>1.52</td>
<td>1.30, 1.78</td>
</tr>
<tr>
<td>Cleft palate only</td>
<td>Passive Only</td>
<td>1.18</td>
<td>1.00, 1.39</td>
<td>1.25</td>
<td>1.01, 1.55</td>
<td>1.43</td>
<td>1.20, 1.70</td>
</tr>
</tbody>
</table>

<sup>a</sup> Maternal body size was based on body mass index (weight (kg)/height (m)<sup>2</sup>) categories: underweight, <18.5; normal-weight, 18.5–<25; overweight, 25–<30; and obese, ≥30.

<sup>b</sup> Maternal education (less than high school diploma, high school diploma, or college graduate), maternal age (≤18, 19–25, 26–30, 31–35, or 36–49 years), employment (yes/no), alcohol consumption (yes/no), folic acid use (yes/no), and study population were adjusted in all analyses.

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Risk of clefts was highest for the offspring of active smokers who were also exposed to passive smoke (OR = 1.51, 95% CI: 1.35, 1.70). This risk was statistically higher than the risk for active smoking alone ($P = 0.0378$) or passive smoke exposure alone ($P = 0.0001$). The increased risk for a combination of active smoking and passive smoke exposure was consistent across the several cleft types.

We also considered the dose of active smoking by replacing any active smoking with indicators for cigarette quantity: low-level smoking ($\leq 4$ cigarettes/day) and moderate or heavy smoking ($\geq 5$ cigarettes per day). This produced 5 categories of exposure (passive smoke exposure alone; low-level active smoking, not exposed to passive smoke; low-level active smoking, exposed to passive smoke; moderate/heavy active smoking, not exposed to passive smoke; and moderate/heavy active smoking, exposed to passive smoke, plus the reference group of unexposed to either (Web Table 7)). The results for passive smoke alone were consistent with those from the previous model based on any active smoking.

In the absence of passive smoke exposure, there was a dose-response pattern of higher risk with higher exposure to active smoking, and there was an added risk with passive smoking in each active-smoking stratum for any cleft and any isolated cleft. This pattern was not observed across all cleft types, probably because of the reduced numbers of cases in subgroups defined by extent of active smoking, passive smoke exposure, and cleft type.

### Heterogeneity between studies

Figure 1 shows study-specific and overall odds ratios for associations with passive smoke exposure alone, combining all cleft types and adjusting for covariates. All study-specific estimates exceeded 1.00 (odds ratios ranged from 1.09 in UCFHS to 1.20 in NFCS). This analysis indicated little heterogeneity in estimates among studies. A slightly wider range was observed when limiting the analysis to isolated clefts (odds ratios ranged from 1.04 to 1.21), but with substantially overlapping confidence intervals (Web Figure 1). Web Figures 2–5 show study-specific and overall odds ratios for passive smoke exposure by cleft type. Except for cleft lip only and cleft palate only in the Utah study (probably due to small sample sizes), all study-specific estimates were above 1. Stratifying by study illustrates the problem of small samples when using specific studies, especially for studying cleft types. For example, MoBa had no cases of cleft lip only that were exposed to passive smoke alone; therefore, the risk estimate for cleft lip with/without cleft palate was below 1, even though it was above 1 for cleft lip with palate and could not be estimated for cleft lip only.

In order to formally test for heterogeneity by study, we reran the logistic regression analysis after combining the 4 studies and adding interaction terms for interaction between smoke exposure measures and the study fixed effects. None of these interactions were significant in the models for any cleft or isolated clefts, indicating no heterogeneity in estimates among studies.

### Sensitivity checks

Because MoBa collected data prospectively while the other studies obtained data retrospectively, we examined the influence of MoBa on the average association by rerunning the pooled regression without MoBa. The estimates were virtually the same as those including MoBa (Web Table 8).

Because the US government mandated folic acid fortification of certain foods beginning in January 1998 (27), we investigated whether the association estimates were sensitive to this mandate by rerunning the regressions after excluding observations from infants in the US studies born before 1999 (Web Table 9). We found similar estimates (the association for cleft palate only became slightly more pronounced and

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### Table: Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCFHS</td>
<td>1.09 (0.65, 1.82)</td>
</tr>
<tr>
<td>NFCS</td>
<td>1.20 (0.88, 1.64)</td>
</tr>
<tr>
<td>MoBa</td>
<td>1.18 (0.45, 3.13)</td>
</tr>
<tr>
<td>NBDPS</td>
<td>1.13 (1.00, 1.28)</td>
</tr>
<tr>
<td>Total</td>
<td>1.14 (1.02, 1.27)</td>
</tr>
</tbody>
</table>

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**Figure 1.** Adjusted odds ratios (ORs) for maternal passive exposure to cigarette smoke and offspring risk of any cleft in 4 population-based studies (Norway Facial Clefts Study (NFCS), 1996–2001; Utah Child and Family Health Study (UCFHS), 1995–2004; Norwegian Mother and Child Cohort Study (MoBa), 1999–2009; and National Birth Defects Prevention Study (NBDPS), 1999–2007), overall and by study. Sample sizes for each study are shown in Table 1. Bars, 95% confidence intervals (CIs).
significant). We observed a similar pattern when we excluded the 2 Norwegian studies and included only US births occurring in 1999 and later, after implementation of the food fortification mandate (Web Table 10). Furthermore, we examined whether controlling for dietary folate intake (from natural folate in foods or fortified products), on which data were available from the NBDPS, had an influence on the association between smoking and oral cleft risk in that study and found no meaningful difference (Web Table 11).

Finally, we examined whether racial/ethnic variation in the US studies was a confounder by refitting the models after controlling for white versus nonwhite race/ethnicity, first combining all 4 studies (considering all participants from Norway to be white, since we had no data on race/ethnicity for Norway) and then including only the US studies. We found results similar to those of the main estimates (Web Tables 12 and 13).

DISCUSSION

Oral clefts are the only category of birth defects known to be caused by active smoking. The 2014 US Surgeon General’s Report concluded that “evidence is sufficient to infer a causal relationship between maternal smoking in early pregnancy and orofacial clefts” (11, p. 10). Consistent with this statement, we found a modest but robust 27% increase in the risk of oral clefts with active maternal smoking. We also found that maternal passive exposure to cigarette smoke was associated with a 14% increased risk of clefts in a pooled analysis of 4,500 cases and nearly 10,000 controls (OR = 1.14, 95% CI: 1.02, 1.27). This association was consistent across all cleft subtypes and across individual studies and was little affected by adjustment for possible confounding factors.

Furthermore, we also observed an association of passive smoking with facial clefts among mothers who were themselves active smokers (Table 2). An obvious concern with such a result is that active smokers are already exposed passively to their own smoke. By what biological mechanism might additional passive exposure increase risk among smokers? While unexpected, such an association is not without precedent. A study from Hong Kong found that smokers exposed to the passive smoke of other smokers had substantially higher risk of respiratory symptoms than unexposed smokers (14). The authors speculated that passive exposure from smokers’ own cigarettes “may be qualitatively different from that caused by other people’s smoking due to settling and aging of the smoke as it disperses” (14, p. 312). Other explanations for that observation must also be considered—in particular, unmeasured confounding. For example, passive exposure may be a surrogate for residual confounding by active smoking. That is, smokers who are themselves heavier smokers may also be more likely to be surrounded by smokers. We explored this possibility in our own data by stratifying smokers into lighter and heavier smokers (Web Table 7); the added risk with passive exposure remained in both strata. There is the possibility of other unmeasured confounding factors, although our results were adjusted for known confounders. While we cannot identify an artifact to explain the higher risk of clefts with passive smoke exposure among smokers, this observation remains tentative in the absence of a plausible biological mechanism.

Our study was unique in its large sample and its pool of subjects from 4 of the largest population-based epidemiologic studies of oral clefts. A large sample size is essential for detecting small but clinically relevant associations with exposures (such as passive smoke) that require adjustments for other risk factors (such as active smoking). In comparison with a recent meta-analysis (15), we observed a more modest association of passive smoking with oral clefts, which may be due to differences in sample designs and the smaller sizes of the studies included in the meta-analysis and greater potential for important confounders. The estimate in our study is probably more realistic than that of the meta-analysis, as it is smaller than the risk from active smoking, as one would expect, unlike the meta-analysis estimate. Our larger sample size also enabled us to investigate individual cleft types and combined associations for active smoking and passive smoke exposure. Our estimates were mainly based on new data not included in the meta-analysis, and the availability of detailed data on potential confounders that could be harmonized among studies allowed us to more fully adjust for these factors in multivariable models.

Limitations of our study included the inability to quantify passive smoking exposure (to further elucidate levels of harmful exposure) and the use of self-reported measures of exposure, which may have resulted in recall or report biases. The case-control design of 3 of our component studies meant that knowledge of the outcome could have influenced the report of exposure. MoBa collected exposure data before the outcome was known, and the estimated risk with passive smoke exposure was consistent with the other studies. Our analysis combined studies from populations that varied in terms of their background risks. Furthermore, one study, the NBDPS, contributed much more to the sample and estimates than the other studies. However, as we noted above, there was little heterogeneity in estimates across studies.

Maternal exposure to passive smoking has been hypothesized to interact with genetic factors in causing birth defects. Interaction with the infant’s microRNA-140 gene (MIR140) has been suggested to contribute to cleft palate risk, possibly as a result of passive smoke’s decreasing levels of microRNA-140 during palatal development (17). Interaction between the zinc finger protein 533 gene (ZNF533) and maternal passive smoking during the first trimester has also been observed among Chinese cleft lip with/without cleft palate case-parent trios (28). Evaluating whether genetic interactions modify the association observed in our study is a promising area for future research.

While the estimated increase in cleft risk from passive smoke exposure is relatively small, the exposure is widespread. One-third of all women worldwide are exposed to passive smoke, with the proportion ranging from 9% in Africa to 66% in Eastern Europe (29). In our study populations, controls provided information on the proportion of exposure among pregnant women in their respective populations. Seventeen percent of our control mothers smoked during the first trimester of pregnancy, and 24% were passively exposed to cigarette smoke. Despite public health initiatives in many countries to reduce smoking in public areas, passive smoke exposure remains widespread among pregnant women. Bias or confounding cannot be excluded as a possible explanation for
the association we observed between passive smoking and oral clefts. Still, the consistency of this association in our data, together with the established role of active smoking as a cause of oral clefts, supports the possibility that passive exposure to cigarette smoke during pregnancy can be teratogenic.

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REFERENCES


