Family History, Maternal Smoking, and Clubfoot: An Indication of a Gene-Environment Interaction

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Although epidemiologic studies of some birth defects have suggested a gene-smoking interaction, the possibility of this interaction in clubfoot has not been examined. The authors analyzed risk factors among 346 infants with isolated clubfoot and 3,029 infants without defects from the Atlanta Birth Defects Case-Control Study. All infants were born during 1968–1980, and mothers were interviewed in 1982–1983. The authors examined the family history-smoking interaction as an indication of a gene-environment interaction. They defined “smoking” as smoking any time during the first 3 months of pregnancy and “family history” as having a first-degree relative with clubfoot. Conditional logistic regression (matching variables: race, birth hospital, and birth period) was used to obtain effect estimates. The adjusted odds ratios were 1.34 (95% confidence interval (CI): 1.04, 1.72) for smoking only, 6.52 (95% CI: 2.95, 14.41) for family history only, and 20.30 (95% CI: 7.90, 52.17) for a joint exposure of smoking and family history. The effect estimate for the joint exposure was higher than would be expected under either an additive or a multiplicative model of interaction and showed a statistically significant departure from additivity. This study confirms the importance of familial factors and smoking in the etiology of clubfoot and identifies a potentially important interaction. Am J Epidemiol 2000;152:658–65.

Isolated talipes equinovarus, or clubfoot, is a major structural birth defect with a birth prevalence of approximately 1.2 per 1,000 live births among Caucasians (1, 2). Affected children have abnormal bone structure in their ankle such that the affected feet are fixed in an extended, adducted position. Correction requires repeated medical treatment and quite often surgery (3). Clubfoot affects about twice as many males as females (1, 4–7). About half of the infants with clubfoot have bilateral involvement, and some studies have reported that the right leg is more likely to be affected than the left (8). Birth prevalence of clubfoot varies by race/ethnicity with low rates (about 0.6 per 1,000 live births) among Asians and high rates (more than 6 per 1,000 live births) among Pacific Islanders (1, 5).

The concordance of clubfoot is about 33 percent for monozygotic twins versus 3 percent for dizygotic twins (9), and there is a higher recurrence risk among first-degree relatives than among more distant relatives (2, 7, 10, 11). There is also variation by sex, with a higher risk for first-degree relatives of female clubfoot cases (4.3 percent) than male clubfoot cases (1.3 percent) (6). These factors suggest a strong genetic component, especially for female cases.

Smoking during pregnancy has been associated with an increased risk for certain birth defects such as abdominal wall defects, limb reduction defects, and some cardiac defects (12); however, the strongest evidence to date is for an increased risk for oral clefts with maternal smoking (13, 14). A gene-environment interaction in the etiology of oral clefts has been seen in some studies, with the highest risk among those who have a specific polymorphism at the transforming growth factor alpha locus and are also exposed to maternal smoking (15, 16). However, a recent study of oral clefts (17) did not find any interaction between maternal smoking and transforming growth factor alpha.

Although some previous studies have identified an association between maternal smoking and clubfoot (18, 19) or between maternal smoking and all foot deformities (20, 21), the possibility of a gene-environment interaction in the etiology of clubfoot has not been examined.

MATERIALS AND METHODS

We used existing data from the Atlanta Birth Defects Case-Control Study (ABDCCS). The ABDCCS methods have been described in detail elsewhere (22, 23). In brief, infants with birth defects were identified by the Centers for Disease Control and Prevention’s population-based Metropolitan Atlanta Congenital Defects Program. This surveillance system uses active case-finding among records of
all birth hospitals in metropolitan Atlanta to identify affected infants and includes a clinical review of each abstracted case. All defects were coded using the Metropolitan Atlanta Congenital Defects Program procedure manual. All infants were born in the five metropolitan Atlanta counties between 1968 and 1980. During the initial data collection, infants without defects who were randomly selected from live births to residents of metropolitan Atlanta were matched to infants with birth defects on birth year, race, and birth hospital. The infants’ mothers were interviewed by telephone in 1982 and 1983. Maternal interviews were completed for 4,929 infants with serious defects (69.1 percent of eligible mothers) and 3,029 infants without defects (71.3 percent of eligible mothers) in the ABDCCS.

The ABDCCS included 528 cases of clubfoot coded as talipes equinovarus or as clubfoot not otherwise specified (NOS)/talipes NOS. We restricted the cases to infants with isolated talipes equinovarus or clubfoot. We excluded infants with any of the known or suspected causes of clubfoot: central nervous system defects, chromosomal anomalies and syndromes, arthrogryposis, metabolic disorders, bone dysplasias, lower limb deficiencies, bilateral absence of the kidneys, Potter’s facies, prune belly syndrome, congenital rubella syndrome, amniotic bands, or posterior urethral obstruction. We also excluded all infants with syndromic patterns of defects, as well as those with “multiple” defects (i.e., those with two or more major defects affecting at least two different organ systems). A dysmorphologist (C. A. M.) reviewed the diagnoses of all infants with multiple defects to determine which infants should be excluded. After the exclusion process, 346 cases of isolated clubfoot remained in the study. All 3,029 controls with completed maternal interviews were included in the analysis.

In the ABDCCS, mothers were asked about the occurrence of many different exposures during a 6-month period that included the 3 months before pregnancy and the first 3 months of pregnancy. The mothers were asked, “Did you smoke cigarettes during this period?” If they said “yes,” they were then asked about each month of this time period. We defined maternal smoking as the mother’s reporting that she smoked cigarettes any time during the first 3 months of pregnancy, because the first trimester is the critical period for the development of talipes equinovarus according to current etiologic theories.

For each live birth the mother reported, she was asked, “Did he/she have a health problem at birth or a birth defect that was diagnosed during the first year of his/her life?” For each stillbirth the mother reported, she was asked, “Did he/she have a birth defect?” If the mother said “yes” to either of these questions, she was then asked, “What kind of birth defect (or health problem) was that?” and her answer was recorded verbatim. The mother was also asked the same questions about herself and the index child’s father. Infants were considered to have a family history of a foot anomaly if the mother reported that any first-degree relative of the infant (mother, father, sibling) had a birth defect or health problem that was consistent with possible clubfoot. A physician (L. J. P.) who was blinded to case-control status determined which family history reports were consistent with a relevant foot anomaly. Descriptions that were consistent with our definition of foot anomaly included: “club foot,” “feet curved in,” “feet turned out,” “right foot was twisted,” “bone problem with foot needed corrective shoes,” and “feet were placed in cast to correct turning in and out.” Next, we defined a family history of clubfoot per se as a maternal report of clubfoot in a first-degree relative of the infant, with the word “club” specified in the mother’s response. Both definitions of family history were assessed to determine if risk for clubfoot was greater when a more specific definition was used.

Other variables assessed during the analysis as potential confounders based on previous literature included gravidity, sex, birth weight, gestational age, maternal education, and maternal age. The following were considered the “exposed” category for these variables: primigravida, male sex, birth weight less than 2,500 g, gestational age less than 36 weeks, maternal education of less than or equal to 12 years, and maternal age greater than or equal to 35 years. We controlled for race, hospital of birth, and period of birth in all analyses because the controls were frequency matched to all birth defects on these variables in the original study. We also assessed maternal alcohol use during the first 3 months of pregnancy because of the correlation that often exists between tobacco and alcohol use.

The initial descriptive, crude, and stratified analysis of the data was done using SAS computer software. We analyzed maternal smoking and family history as a four-level variable; those who were not exposed to maternal smoking and had no family history of clubfoot were used as the reference. We did not have information on genotype, but we examined the family history-smoking interaction as an indication of a gene-environment interaction. For analysis stratified by the sex of the infant, both cases and controls were restricted to the same sex. We fit a conditional logistic regression model using LogXact software. The regression was stratified on the matching variables (race, birth hospital, birth period) and also included the following: joint exposure to maternal smoking and a family history of clubfoot, a family history of clubfoot with no exposure to maternal smoking, maternal smoking with no family history of clubfoot, gravidity, and sex of the infant. Inclusion of additional variables did not contribute meaningful information to the model.

Interaction is defined as the departure from additivity of effects. To assess the statistical significance of the interaction between maternal smoking and family history, we calculated the proportion of clubfoot attributable to the interaction among those with the joint exposure to maternal smoking and family history. The 95 percent confidence intervals for this attributable proportion, which has a null value equal to zero, were estimated using a method based on the Taylor Series expansion.

We used a cohort approach to assess the potential bias resulting from using a yes/no variable for family history in a case-control study where cases and controls might have different family sizes. The crude risk ratio obtained by
the cohort approach can be compared with the crude odds ratio obtained using the yes/no variable for family history. To assess the possible impact of shared environmental risk factors (32), we calculated the risk of case mothers having children other than the index infants who were affected by clubfoot, stratified by the smoking status of the case mother during the index pregnancy.

RESULTS

The case infants included 170 infants with bilateral clubfoot (49.1 percent), 74 left-affected infants (21.4 percent), 69 right-affected infants (19.9 percent), and 33 infants with an unspecified laterality. The cases were more likely to be White, male, and the first born child than were the controls (table 1). There were no significant differences between cases and controls with respect to gestational age, birth weight, maternal education, or maternal age. Mothers of infants with clubfoot reported a higher prevalence of smoking during pregnancy and much higher prevalence of having a family history of both clubfoot and all foot anomalies consistent with possible clubfoot.

In the conditional logistic regression model, clubfoot was associated with maternal smoking alone, family history of foot anomalies alone, and having both an exposure to maternal smoking and a family history of foot anomalies (table 2), with 95 percent confidence intervals that excluded the null value. The effect estimate for those both exposed to maternal smoking and having a family history of foot anomalies (odds ratio (OR) = 7.95, 95 percent confidence interval (CI): 3.96, 15.97) was slightly greater than the odds ratio of 6.85 that would be expected under an additive model.

When the family history variable was narrowed to include only those infants whose mothers specifically reported a family history of clubfoot (table 3), the effect estimates for those either only exposed to maternal smoking or only having a family history of clubfoot were quite similar to those observed for having a family history of any foot anomaly consistent with possible clubfoot (table 2). However, the effect estimate for those both exposed to maternal smoking and having a family history of clubfoot (OR = 20.30, 95 percent CI: 7.90, 52.17) was much larger and was greater than would be expected under either an additive or a multiplicative model of interaction.

### TABLE 1. Descriptive characteristics of infants with clubfoot and infants without birth defects, Atlanta, Georgia, 1968–1980

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 346)</th>
<th>Controls (n = 3,029)</th>
<th>M-H</th>
<th>( \chi^2 )</th>
<th>( \rho ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>221</td>
<td>63.9</td>
<td>1,551</td>
<td>51.2</td>
<td>19.9</td>
</tr>
<tr>
<td>White</td>
<td>292</td>
<td>84.4</td>
<td>2,301</td>
<td>76.0</td>
<td>12.4</td>
</tr>
<tr>
<td>Primigravida</td>
<td>147</td>
<td>42.5</td>
<td>1,092</td>
<td>36.1</td>
<td>5.5</td>
</tr>
<tr>
<td>Gestational age &lt; 36 weeks</td>
<td>22</td>
<td>6.4</td>
<td>177</td>
<td>5.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Birth weight &lt; 2,500 g</td>
<td>43</td>
<td>12.4</td>
<td>354</td>
<td>11.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Maternal education ≤ 12 years</td>
<td>212</td>
<td>61.3</td>
<td>1,738</td>
<td>57.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Maternal age ≥ 35 years</td>
<td>12</td>
<td>3.5</td>
<td>147</td>
<td>4.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>132</td>
<td>38.2</td>
<td>866</td>
<td>28.6</td>
<td>13.6</td>
</tr>
<tr>
<td>Family history of foot deformity</td>
<td>40</td>
<td>11.6</td>
<td>63</td>
<td>2.1</td>
<td>94.3</td>
</tr>
<tr>
<td>Family history of clubfoot</td>
<td>25</td>
<td>7.2</td>
<td>27</td>
<td>0.9</td>
<td>82.1</td>
</tr>
</tbody>
</table>


### TABLE 2. Odds ratios (ORs) and 95% confidence intervals (CIs) by the conditional logistic regression model for the association among isolated clubfoot, maternal smoking, and a family history of foot anomalies consistent with possible clubfoot, Atlanta, Georgia, 1968–1980

<table>
<thead>
<tr>
<th>Family history of foot anomaly and maternal smoking</th>
<th>Cases (no.)</th>
<th>Controls (no.)</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of foot anomaly and maternal smoking</td>
<td>16</td>
<td>21</td>
<td>7.95</td>
<td>3.96, 15.97</td>
</tr>
<tr>
<td>Family history of foot anomaly, no maternal smoking</td>
<td>24</td>
<td>42</td>
<td>6.44</td>
<td>3.72, 11.15</td>
</tr>
<tr>
<td>Maternal smoking, no family history of foot anomaly</td>
<td>116</td>
<td>845</td>
<td>1.41</td>
<td>1.09, 1.81</td>
</tr>
<tr>
<td>No family history of foot anomaly, no maternal smoking</td>
<td>190</td>
<td>2,121</td>
<td>Referent</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 3. Odds ratios (ORs) and 95% confidence intervals (CIs) by the conditional logistic regression model for the association among isolated clubfoot, maternal smoking, and a family history of clubfoot, Atlanta, Georgia, 1968–1980

<table>
<thead>
<tr>
<th>Family history of clubfoot and maternal smoking</th>
<th>Cases (no.)</th>
<th>Controls (no.)</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of clubfoot, no maternal smoking</td>
<td>14</td>
<td>7</td>
<td>20.30</td>
<td>7.90, 52.17</td>
</tr>
<tr>
<td>Maternal smoking, no family history of clubfoot</td>
<td>11</td>
<td>20</td>
<td>6.52</td>
<td>2.95, 14.41</td>
</tr>
<tr>
<td>No family history of clubfoot, no maternal smoking</td>
<td>118</td>
<td>859</td>
<td>1.34</td>
<td>1.04, 1.72</td>
</tr>
</tbody>
</table>

* Adjusted for gravidity of the mother and sex of the infant.

There were major differences in some effect estimates by the sex of the infant (table 4) and the laterality of the defect (table 5). The strongest effect estimate for maternal smoking alone was observed among infants with bilateral clubfoot (OR = 1.43, 95 percent CI: 1.07, 2.01), though similar effects were observed for male infants, left-affected infants, and right-affected infants. A weaker effect for maternal smoking alone that did not exclude the null value was observed for female infants (OR = 1.14, 95 percent CI: 0.74, 1.74). Having a first-degree family history of clubfoot was a consistent risk factor across all subgroups analyzed, but the magnitude of the effect estimates varied. The effect estimate for having only a family history of clubfoot was much greater for left-affected infants (OR = 13.62) than right-affected infants (OR = 2.28) and was greater for male infants (OR = 7.78) than female infants (OR = 4.15), though there was considerable overlap in the 95 percent confidence intervals. The effect of a joint exposure to maternal smoking and family history of clubfoot was greater than would be expected under either an additive or multiplicative model for all subgroups analyzed except for left-affected cases.

Approximately 66 percent of the clubfoot among those with the joint exposure to maternal smoking and a family history of clubfoot can be attributed to the interaction of these factors (table 6). The proportion of these cases attributable to the interaction ranged from 75 percent to 87 percent for female infants, male infants, bilateral cases, and right-affected cases. The 95 percent confidence intervals for all these estimates excluded the null value. The attributable proportion was not calculated for the left-affected cases because no interaction was noted.

Maternal alcohol use during the first 3 months of pregnancy was not associated with an increased risk for clubfoot. Additionally, the analysis did not provide evidence of an interaction between maternal alcohol use and a family history of clubfoot (data not shown).

The average first-degree family size was 4.80 for case infants and 4.87 for control infants. The standard deviations

TABLE 4. Odds ratios (ORs) and 95% confidence intervals (CIs) by the conditional logistic regression model for the association among isolated clubfoot, maternal smoking, and a family history of clubfoot by sex of the index infant, Atlanta, Georgia, 1968–1980

<table>
<thead>
<tr>
<th>Family history of clubfoot and maternal smoking</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (no.)</td>
<td>Controls (no.)</td>
<td>OR*</td>
</tr>
<tr>
<td>Family history of clubfoot and maternal smoking</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Family history of clubfoot, no maternal smoking</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Maternal smoking, no family history of clubfoot</td>
<td>39</td>
<td>412</td>
</tr>
<tr>
<td>No family history of clubfoot, no maternal smoking</td>
<td>77</td>
<td>1,050</td>
</tr>
</tbody>
</table>

* Adjusted for gravidity of the mother.
for family size were 1.43 and 1.52 for cases and controls, respectively. The crude estimate for the risk ratio using the cohort approach to analyzing family history was 8.19. The crude odds ratio for the effect of family history, analyzed as a yes/no variable, was 8.66 (table 7).

To determine whether the effect of family history was attributable only to recurring smoking from one pregnancy to the next, we calculated the occurrence risk for the mother’s having another child affected by clubfoot either before or after the index case. First, we used the broad definition of family history, meaning a reported foot anomaly that was consistent with possible clubfoot in siblings and, second, we used the narrow family history definition that included only specific reports of clubfoot in siblings. Excluding the index cases, 22 of 318 (6.9 percent) of the children of nonsmoking case mothers had a foot anomaly consistent with possible clubfoot compared with 11 of 198 (5.6 percent) of the children of smoking case mothers. Restricting the definition specifically to reported clubfoot and still excluding the index cases, 7 of 318 (2.2 percent) of the children of nonsmoking case mothers had clubfoot, while 9 of 198 (4.5 percent) of the children of smoking case mothers had clubfoot.

### DISCUSSION

This study provides further evidence in support of a causal role of smoking in clubfoot. Exposure to maternal smoking in the absence of a family history of clubfoot is associated with isolated clubfoot in all subgroups analyzed. This study also confirms the well-known role of family history in the etiology of clubfoot. Among infants not exposed to maternal smoking, a family history of either clubfoot or any foot anomaly is associated with having isolated clubfoot. The effect estimates for a joint exposure of maternal smoking and a family history of clubfoot are greater than would be expected under either an additive or a multiplicative model for all infants except left-affected infants, indicating for the first time a significant interaction between these two risk factors.

### TABLE 5. Odds ratios (ORs) and 95% confidence intervals (CIs) by the conditional logistic regression model for the association among isolated clubfoot, maternal smoking, and a family history of clubfoot by laterality of the defect, Atlanta, Georgia, 1968–1980

<table>
<thead>
<tr>
<th>Laterality of clubfoot</th>
<th>Bilateral clubfoot</th>
<th>Left affected</th>
<th>Right affected</th>
<th>Other cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (no.)</td>
<td>OR†</td>
<td>95% CI</td>
<td>Cases (no.)</td>
</tr>
<tr>
<td>Family history of clubfoot and maternal smoking</td>
<td>10</td>
<td>30.55</td>
<td>10.99, 84.96</td>
<td>2</td>
</tr>
<tr>
<td>Family history of clubfoot, no maternal smoking</td>
<td>4</td>
<td>5.81</td>
<td>1.82, 18.51</td>
<td>4</td>
</tr>
<tr>
<td>Maternal smoking, no family history of clubfoot</td>
<td>61</td>
<td>1.43</td>
<td>1.07, 2.01</td>
<td>24</td>
</tr>
<tr>
<td>No family history of clubfoot, no maternal smoking</td>
<td>95 Referent</td>
<td>44 Referent</td>
<td>42 Referent</td>
<td>22 Referent</td>
</tr>
</tbody>
</table>

*Other* refers to those cases with unspecified laterality; number of cases is given but no odds ratios are calculated.

† Adjusted for gravidity of the mother and sex of the infant.

### TABLE 6. Proportion of clubfoot among those with a joint exposure to maternal smoking and a family history of clubfoot that is attributable to the interaction between these two exposures, Atlanta, Georgia, 1968–1980

<table>
<thead>
<tr>
<th></th>
<th>AP</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>0.66</td>
<td>0.26, 1.0</td>
</tr>
<tr>
<td>Female infants</td>
<td>0.77</td>
<td>0.31, 1.0</td>
</tr>
<tr>
<td>Male infants</td>
<td>0.75</td>
<td>0.30, 1.0</td>
</tr>
<tr>
<td>Bilateral cases</td>
<td>0.80</td>
<td>0.50, 1.0</td>
</tr>
<tr>
<td>Left affected</td>
<td>No interaction noted</td>
<td></td>
</tr>
<tr>
<td>Right affected</td>
<td>0.87</td>
<td>0.56, 1.0</td>
</tr>
</tbody>
</table>

*AP*, attributable proportion; CI, confidence interval.

### TABLE 7. Comparison of cohort and case-control approaches to estimating the risk of family history of clubfoot, Atlanta, Georgia, 1968–1980

<table>
<thead>
<tr>
<th>Disease status of index baby</th>
<th>Case (no.)</th>
<th>Control (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clubfoot in first degree relatives</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>No</td>
<td>1,182</td>
<td>10,625</td>
</tr>
<tr>
<td>Total first degree relatives</td>
<td>1,208</td>
<td>10,653</td>
</tr>
<tr>
<td>Crude risk ratio = 8.19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history of clubfoot</th>
<th>Case (no.)</th>
<th>Control (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>No</td>
<td>321</td>
<td>3,002</td>
</tr>
<tr>
<td>Total no. of index babies</td>
<td>346</td>
<td>3,029</td>
</tr>
<tr>
<td>Crude odds ratio for family history of clubfoot as a yes/no variable = 8.66</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The etiology of isolated clubfoot, or idiopathic talipes equinovarus, is not known, but there are many different etiologic theories (33). Vascular disruption or compromise due to smoking may be a plausible mechanism by which smoking contributes to the occurrence of clubfoot. Most patients with clubfoot who require surgery have an abnormal arterial pattern (34), which may be a sign of vascular disruption. Nicotine is vasoactive and may reduce both placental and fetal circulation (35–37). Carbon monoxide may cause fetal tissue hypoxia (38). The blood levels of many volatile organic compounds are much higher in smokers than in non-smokers (39); these components of cigarette smoke may contribute to vascular disruption or be teratogenic in some other way.

Both the magnitude and direction of the effect of maternal smoking on the risk of clubfoot are consistent with the literature. Two previous studies have identified statistically significant associations between maternal smoking and foot deformities with odds ratios of 1.2 and 1.7, respectively (20, 21). One study of clubfoot in Washington State found an odds ratio of 1.4 for maternal smoking reported on the birth certificate, with a 95 percent confidence interval that excluded the null value (18). A study of talipes equinovarus in Washington State found a stronger effect of maternal smoking in males (OR = 2.6) than females (OR = 1.4) (18). The effects of maternal smoking may vary with the sex of the fetus (40), with the male fetus being more vulnerable to some effects of maternal smoking such as decreased fetal growth (41, 42). This sex difference may account for the weaker association with maternal smoking among female infants observed in both this study and the Washington State study of talipes equinovarus.

Erroneous or biased reporting of maternal smoking history is an unlikely explanation for the association observed between maternal smoking and clubfoot. During a telephone interview, mothers reported whether or not they smoked during the first 3 months of pregnancy. In general, assessment of maternal smoking through an interviewer-administered questionnaire is preferable to the information reported on administrative sources such as birth certificates. A recent meta-analysis of self-reported smoking found a mean sensitivity of 88 percent and a mean specificity of 89 percent (43), with higher sensitivity and specificity for interviewer-administered questionnaires and reports by adults. Moreover, a recent capture-recapture analysis of maternal smoking found that confidential questionnaires had a sensitivity of 86–90 percent (44). A study that examined smoking during pregnancy for women pregnant in the 1960s found a high kappa correlation coefficient between reported smoking during pregnancy and levels of biomarkers associated with active smoking (45).

The National Natality Surveys of married women found that smoking during pregnancy declined from 45 percent in 1967 to 30 percent in 1980 among White women (46). By 1994, the National Health Interview Survey found that approximately 15 percent of pregnant women reported smoking during pregnancy (47). Given the observed declines in reported maternal smoking in the United States over the past 30 years, it is interesting to note a parallel decline in the birth prevalence of clubfoot. The prevalence of clubfoot in metropolitan Atlanta has declined dramatically over the last 30 years from more than two cases per 1,000 live births in 1968 to about one case per 1,000 live births in 1996 (Centers for Disease Control and Prevention, unpublished surveillance data). The observed decline in maternal smoking may be a contributing factor, although it is probably not sufficient to explain the magnitude of decline in clubfoot that has been observed.

Although the information on family history of birth defects or other serious health problems at birth was also obtained by maternal interview, family history is likely to be less complete than smoking history. An evaluation of birth defect history of index cases in the ABDCCS as reported by mothers indicated that overall sensitivity for all major birth defects was only about 61 percent, but specificity was 98 percent (48). The sensitivity and specificity for clubfoot were not specifically addressed in this earlier study, but both may be higher than estimates for all major birth defects since clubfoot is external and severe enough to require medical treatment and often surgery.

Among case infants, the prevalence of one or more first-degree relatives with clubfoot (7.2 percent) is somewhat lower than the 12.5 percent and 20.9 percent that were reported by previous family studies (5, 10); however, the absolute risk of clubfoot among first-degree relatives of the case infants (2.2 percent) is similar to that found in previous studies, which reported that 2.1 percent to 3.6 percent of all first-degree relatives were affected by clubfoot (7, 9, 49). The occurrence of clubfoot among siblings of the case infant (3.1 percent) was also within the range described by previous studies, which reported that 2.9 percent to 7.3 percent of the siblings of index patients were affected by clubfoot (2, 5, 10, 49).

There is potential bias in using a yes/no variable to assess family history (50), because the family history of birth defects is dependent on many variables, including relatives' specific risk factors, relatives' genetic relation to the index case, and family size. Relatives' specific risk factors and genetic relation to the index case are unknown, so their potential impact cannot be assessed; however, the role of family size can be and was addressed. The average first-degree family size for cases (n = 4.81) was nearly identical to the average family size for controls (n = 4.87), and the distribution of family size was remarkably similar. Using a cohort approach to compare the risk of disease among case relatives with the risk of disease among control relatives yielded a crude risk ratio estimate of 8.19 that was nearly identical to the crude odds ratio estimate of 8.66.

In this study, we used family history as a proxy for the as-yet unidentified gene or genes that have a causal role in clubfoot; however, use of family history as a proxy undoubtedly leads to some genotype misclassification, which might dilute the true effect of the genotype (51). Additionally, the measurement of first-degree family history includes affected parents and siblings of the index case, and this assessment may be biased if there is a reduction in fertility among those affected by clubfoot. A reduction in childbearing among females with clubfoot has been suggested by a recent cohort study (52).
Another issue is that some of the risk associated with family history could be due to shared environmental factors rather than shared genes (32). Cigarette smoking may cluster within families, and exposure to maternal smoking may recur in subsequent pregnancies. To explore the possibility that the effect of family history may have been due to this clustering/recurrence of smoking, we calculated the risk of a case mother’s having a second affected child by maternal smoking status. We found that nonsmoking mothers had a higher risk for having another child affected by any foot anomaly than did smoking mothers; however, this relation was reversed when restricting the analysis to siblings with reported clubfoot, with case mothers who reported smoking during pregnancy having about double the risk of having another child with clubfoot than case mothers who did not smoke during the index pregnancy. While this raises the possibility that some of the observed effect of family history may be due to recurrence of smoking from one pregnancy to the next, it is insufficient to explain the magnitude of the effect observed for family history.

While the effect estimates for family history alone were very similar for having a family history of any foot anomaly and having a family history of clubfoot, the magnitude of the effect for the joint exposure of maternal smoking and family history was much greater for those with a family history of clubfoot. This change in magnitude likely occurs because the inclusion of some less serious and etiologically distinct foot anomalies in the broader family history definition created some bias toward the null. The mechanism for the observed interaction between a family history of clubfoot and maternal smoking is not known. The reason for the observed variability between left-affected and right-affected cases for both family history alone and the joint exposure is also not known, but it may have been affected by the limited number of cases in each category.

The timing of interviews may have led to recall bias since mothers were interviewed in 1982 and 1983 about births that occurred from 1968 through 1980; however, any recall bias present should be nondifferential for cases and controls since they were matched on year of birth. Recall bias may also occur if the mothers of affected infants are more likely to remember and report exposures than the mothers of unaffected infants; however, methodological research has demonstrated that such bias will only seriously affect inferences under extreme conditions and that the selection bias introduced by using affected controls is likely to be greater than the recall bias that is possible when using unaffected controls (53, 54).

The medical records of case infants often did not provide enough information to definitively code the infants as having talipes equinovarus rather than clubfoot NOS or talipes NOS, and about three fourths of the cases included were coded as clubfoot NOS/talipes NOS. While an estimated 95 percent of clubfoot NOS cases are actually talipes equinovarus (55) and these terms are used interchangeably in the literature, there undoubtedly remain some less severe cases in the “NOS” category. This misclassification probably biased the effect estimates toward the null.

This study provides further evidence that both maternal smoking and family history are important risk factors for clubfoot and identifies a potentially important interaction between these two variables. It also gives additional clues to the etiology of clubfoot and serves to emphasize the importance of considering sex, laterality, and higher-order interactions in etiologic studies of defects. Additionally, the information from this study may be important for the genetic counseling of women who have had a child affected by clubfoot. Finally, it adds to the already substantial body of evidence about the risks of smoking during pregnancy.

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