Original Contribution

Exposure to Maternal Smoking During Pregnancy as a Risk Factor for Tobacco Use in Adult Offspring

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Nicotine from maternal smoking during pregnancy can cross the placental barrier, possibly resulting in fetal brain sensitization, as indicated by studies in which prenatal exposure to maternal smoking was associated with an increased risk of tobacco use among adolescent offspring. We investigated whether this association persists beyond adolescence by studying cigarette smoking and the use of snus (Swedish oral moist snuff) among 983 young adults from a prospective cohort study conducted in Stockholm, Sweden, between 2006 and 2010. Self-reported questionnaire data were linked with data from national population-based registers from 1983 onward. Maternal smoking during pregnancy was consistently associated with snus use in offspring (e.g., for lifetime daily snus use, adjusted odds ratio = 2.04, 95% confidence interval: 1.32, 3.16; for use of >3 cans of snus per week vs. less, odds ratio = 3.85, 95% confidence interval: 1.57, 10.15). No association was apparent with offspring’s smoking, or changes in use between 2006 and 2010. These findings indicate that prenatal exposure to maternal smoking is associated with regular and heavy nicotine intake from smokeless tobacco rather than from smoking. This should be further explored in epidemiologic studies that simultaneously address the roles of genetics and social environments.

cigarette smoking; prenatal exposure delayed effects; smoking; tobacco; tobacco, smokeless


Editor’s note: An invited commentary on this article appears on page 1418, and the authors’ response appears on page 1422.

Maternal smoking during pregnancy is associated with offspring tobacco use and dependence later in life, as shown in animal studies (1, 2), studies on the human cell system (3), and epidemiologic studies (4–17). Because nicotine can cross the placental barrier and reach the fetus, it is conceivable that nicotine may permanently alter the fetal mesolimbic dopaminergic system, which could result in an enhanced vulnerability to tobacco dependence (18).

Epidemiologic studies have mainly investigated the impact of fetal nicotine exposure on tobacco use in adolescence (4–7, 9, 10, 12, 14, 19, 20), a developmental period during which tobacco behavior is not yet stabilized (21). Of the studies that included adults, only 5 used a prospective design (11, 16, 22–24), and they presented conflicting results. In fact, 3 of those studies found maternal smoking during pregnancy to be linked with regular or heavy tobacco use in adult offspring (11, 16, 24), whereas 2 found no evidence of such an association (22, 23). None of these studies included use of tobacco products other than cigarettes. Sweden is in a unique position to study the use of smokeless tobacco, as 1 in 5 men is a current daily user of snus, which is Swedish oral moist snuff (25). Snus is also used in other Nordic countries (26), and it has recently been marketed internationally. In the United States, the prevalence of daily use was 1.8% in 2009 (27). Studies of smokeless tobacco may be important because if maternal smoking during pregnancy were found to be a determinant for snus use in offspring, the hypothesis of a biological pathway would be further strengthened.
In the present prospective study, we used the experience of a population-based cohort to investigate the association between prenatal exposure to maternal smoking and use of cigarettes and smokeless tobacco in young adults after controlling for postnatal influences. In particular, we aimed to investigate the relation between exposure in utero and heavy tobacco use in the offspring, as well as other patterns of use that were not addressed previously, such as age at onset, duration, and changes in tobacco use over time.

METHODS

Study population

The derivation of the study cohort is illustrated in Figure 1. The Stockholm Public Health Cohort (28) was accrued in 2006 by means of a questionnaire survey initially mailed to a random sample of 56,634 inhabitants of Stockholm County, Sweden, who were 18 years of age or older. In total, 34,707 (61.3%) participated and gave their consent to be included in the longitudinal study. Of these, 25,167 participated in a follow-up survey in 2010. Because register-based information on prenatal exposure was only available for individuals born in Sweden in 1983 or later (i.e., for participants 23 years of age or younger at baseline), the study population comprised 1,124 individuals who met these criteria. The final analytical sample encompassed 983 respondents who provided complete information about exposure. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Data collection

Data on health- and lifestyle-related information (including tobacco use) were collected from the questionnaires. These data were complemented with register data retrieved by record linkages using personal identification numbers, a unique number assigned to all Swedish residents (29).

Exposure. Information about maternal smoking during pregnancy was retrieved from the Medical Birth Register. This register was initiated in 1973 and contains information about pregnancy and delivery for all births in Sweden (30). Since 1983, information on maternal smoking has been registered in the antenatal records as a routine part of obstetrical care at the first antenatal visit (usually between the 8th and 12th gestational week). Smoking was self-reported by the women and categorized as no current daily smoking (75% of participants in this study), current smoking of fewer than 10 cigarettes per day (15%), and current smoking of at least 10 cigarettes per day (10%). Prenatal exposure was analyzed both as a dichotomous variable (no daily smoking vs. any daily smoking) and as a 3-category variable to explore the presence of a dose-response relationship.

Outcome. Self-reported outcome measures in offspring included lifetime and current daily use of cigarettes and snus, age at onset of daily use, duration and intensity of daily use, and changes in use between 2006 (baseline survey) and 2010 (follow-up survey). Lifetime tobacco use, defined as daily use for at least 6 months, was self-reported by the participants at the baseline survey in 2006 (age 18–23 years) separately for cigarettes and snus. The same information was collected again in the follow-up survey in 2010.
when the participants were between 22 and 27 years of age. Participants who reported lifetime daily use of cigarettes and/or snus at any survey were considered lifetime daily users. Current daily tobacco use was reported in 2010. Separate dichotomous variables (daily use vs. no daily use) were created for smoking and snus use. Further, combined variables of any tobacco use (cigarette smoking, snus use, or both) were created for both current and lifetime use.

In the follow-up survey in 2010, daily users of tobacco were asked to provide information about the age at which they started smoking or using snus daily. Former users also provided information on age at cessation. Early age at onset of daily smoking among users was defined based on the median value of the age at initiation (17 years for smoking); that is, initiation of daily smoking before this age was considered to be early onset. Age at onset of daily snus use and of any tobacco use was categorized accordingly. Duration of use was calculated as the difference between the participant’s attained age in 2010 (for current users) or age when quitting (for former users) and the participant’s age at initiation of daily use. A combined variable for duration of any daily tobacco use was also created, discounting overlapping periods of smoking and snus use. Duration of smoking, snus use, or any daily tobacco use was dichotomized at the median value (<6 years vs. ≥6 years). Intensity of tobacco use, assessed as cigarettes per day or cans of snus per week, was self-reported in 2010 and categorized as light (1–10 cigarettes per day or 1–3 cans per week) versus heavy (>10 cigarettes per day or >3 cans per week) based on median values. Using self-reported information about current tobacco use in 2006 and 2010, a variable was created to indicate changes in use between these 2 time points, categorized as stable nonuse (no current use at both time points), started (no current use in 2006 but current use in 2010), quit (current use in 2006 but not in 2010), and stable use (current tobacco use in both years).

**Covariates.** Recall of parental tobacco use during childhood and adolescence was elicited through a questionnaire survey in 2010. Information was provided separately for mothers and fathers and for smoking and snus use. Parental tobacco use during upbringing was categorized as neither parent used tobacco, 1 parent used tobacco, or both parents used tobacco.

Biological parents were identified by linkage to the Multi-Generation Register. The register includes all individuals born since 1932 and living in Sweden at any point since 1961 and contains near-complete information on both biological and social first-degree relatives (31).

The mother’s highest educational level when the participants were 8 years of age was retrieved from the Longitudinal Integrated Database for Sick Insurance and Labor Market Studies, which contains data regarding the labor market and educational and social sectors for all Swedish residents from 1990 onward (32). For the purpose of the present study, maternal educational level was categorized as postsecondary education or higher versus secondary education or lower. Parents’ nationalities were retrieved from the Medical Birth Register and categorized as both parents with citizenship in 1 of the Nordic countries versus at least 1 parent with another citizenship.

Parental psychiatric morbidity was assessed by record linkage with the Swedish National Patient Register, which includes hospital admissions with psychiatric diagnoses from 1973 and all hospital admissions from 1987. The register contains information on date of admission as well as the main and secondary diagnoses classified according to the Swedish version of the eighth, ninth, and tenth revisions of the *International Classification of Diseases* (ICD) (33). A history of psychiatric disorder was defined as a hospital admission between 1973 and 2008 with any of the following diagnostic codes as either the primary or secondary diagnosis:

![Figure 2](image-url)

Participant’s yearly disposable income in 2004 and highest achieved educational level in 2010 were retrieved from the database described above. Information about whether the participant had been living with both biological parents during his or her upbringing was self-reported in 2010.

Statistical analyses

Odds ratios with corresponding 95% confidence intervals were calculated using logistic regression. Selection of covariates included in the statistical models was based on a theoretical causation model. The association between prenatal exposure to maternal smoking and tobacco use in adult life is likely confounded by both influences in the social environment and genetic factors, as illustrated in the direct acyclic graph (34) shown in Figure 2. The Figure is a theoretical illustration of causal pathways based on previous knowledge (18, 35, 36), in which each arrow represents a possible causal effect. On the basis of this conceptual framework, the following variables were considered as potential confounders: parental postnatal tobacco use, maternal educational level, offspring educational level, parental psychiatric morbidity, parents’ nationalities, and cohabitation with parents during upbringing. To illustrate the importance of parental postnatal tobacco use as potential confounder of the exposure-outcome association, we first adjusted for this factor alone and thereafter for all potential confounders simultaneously, with results shown separately in tables. Because maternal smoking during pregnancy and parental postnatal tobacco use might be highly correlated and thus impair the efficiency of adjustments, we also conducted stratified analyses in subgroups of parental postnatal tobacco use. All analyses were done separately for men and women. SAS, version 9.2 for Windows (SAS Institute, Inc., Cary, North Carolina) was used for all analyses.

RESULTS

Table 1 shows selected characteristics of study participants and their parents. The majority of the participants were women, had completed secondary education, and had both parents of Nordic citizenship. Mean age at baseline was 20.3 (standard deviation, 1.75) years, and the mean disposable income in 2004 was 151,136 (standard deviation, 98,017) SEK. In total, 246 (25%) were exposed to any maternal daily smoking during pregnancy (compared with 30% of persons who were lost to follow-up), and 284 (29%) and 196 (20%) were lifetime daily users of cigarettes and snus, respectively. Participants exposed to maternal daily smoking during pregnancy were more likely to also be exposed to parental postnatal tobacco use and to have parents with a history of psychiatric diagnoses. Unexposed participants were more likely to have highly educated mothers, to have lived...
with both of their biological parents during upbringing, and to have achieved a high educational level.

Crude and adjusted odds ratios of lifetime and current daily use of tobacco with exposure to maternal daily smoking during pregnancy are shown in Tables 2 and 3. In unadjusted models, prenatal exposure to maternal smoking was associated with a nearly 2-fold increase in the odds of lifetime daily smoking, snus use, and any tobacco use. Adjustment

Table 2. Odds Ratios and 95% Confidence Intervals for Lifetime Daily Tobacco Use in Relation to Maternal Smoking During Pregnancy, Stockholm Public Health Cohort, Stockholm, Sweden, 2006–2010

<table>
<thead>
<tr>
<th>Lifetime Daily Useb</th>
<th>No. of Exposed Cases</th>
<th>Crude</th>
<th>Adjusted for Parents’ Postnatal Tobacco Use</th>
<th>Adjusted for All Potential Confoundersa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco: any vs. none</td>
<td>Overall 126</td>
<td>2.01</td>
<td>1.90, 4.51</td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td>Men 52</td>
<td>2.17</td>
<td>1.36, 3.49</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td>Women 74</td>
<td>1.91</td>
<td>1.31, 2.78</td>
<td>1.11</td>
</tr>
<tr>
<td>Smoking: any vs. none</td>
<td>Overall 95</td>
<td>1.84</td>
<td>1.36, 2.50</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>Men 27</td>
<td>1.79</td>
<td>1.04, 3.04</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>Women 68</td>
<td>1.90</td>
<td>1.30, 2.77</td>
<td>1.00</td>
</tr>
<tr>
<td>Snus: any vs. none</td>
<td>Overall 72</td>
<td>2.04</td>
<td>1.45, 2.85</td>
<td>2.02</td>
</tr>
<tr>
<td></td>
<td>Men 44</td>
<td>2.17</td>
<td>1.34, 3.50</td>
<td>1.93</td>
</tr>
<tr>
<td></td>
<td>Women 28</td>
<td>2.20</td>
<td>1.30, 3.67</td>
<td>2.30</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

a Adjusted for parents’ psychiatric morbidity, parents’ postnatal tobacco use, socioeconomic characteristics (maternal educational level, own educational level, and parents’ nationality), and characteristics of upbringing (living with both parents during upbringing), as illustrated in Figure 2.

b Analyses of any tobacco use, smoking, and snus use were based on 980, 979, and 981 participants, respectively.


<table>
<thead>
<tr>
<th>Current Daily Useb</th>
<th>No. of Exposed Cases</th>
<th>Crude</th>
<th>Adjusted for Parents’ Postnatal Tobacco Use</th>
<th>Adjusted for All Potential Confoundersa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco: any vs. none</td>
<td>Overall 88</td>
<td>2.36</td>
<td>1.71, 3.24</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>Men 42</td>
<td>2.72</td>
<td>1.66, 4.44</td>
<td>1.58</td>
</tr>
<tr>
<td></td>
<td>Women 46</td>
<td>2.16</td>
<td>1.41, 3.30</td>
<td>1.24</td>
</tr>
<tr>
<td>Smoking: any vs. none</td>
<td>Overall 42</td>
<td>1.83</td>
<td>1.21, 2.74</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Men 13</td>
<td>2.15</td>
<td>1.00, 4.47</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Women 29</td>
<td>1.71</td>
<td>1.03, 2.78</td>
<td>0.82</td>
</tr>
<tr>
<td>Snus: any vs. none</td>
<td>Overall 49</td>
<td>2.20</td>
<td>1.48, 3.25</td>
<td>1.97</td>
</tr>
<tr>
<td></td>
<td>Men 31</td>
<td>2.29</td>
<td>1.35, 3.86</td>
<td>1.82</td>
</tr>
<tr>
<td></td>
<td>Women 18</td>
<td>2.39</td>
<td>1.24, 4.51</td>
<td>2.30</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

a Adjusted for parents’ psychiatric morbidity, parents’ postnatal tobacco use, socioeconomic characteristics (maternal educational level, own educational level, and parents’ nationality), and characteristics of upbringing (living with both parents during upbringing), as illustrated in Figure 2.

b Analyses of any tobacco use, smoking, and snus use were based on 979, 979, and 980 participants respectively.
for parents using tobacco during the proband’s upbringing remarkably attenuated the estimates for any tobacco use and for smoking but not for snus use. The same was true after adjustment for potential confounders simultaneously. In fact, the 2-fold increased odds of snus use remained stable (and formally significant) both after adjustment for parent’s postnatal tobacco use and in the fully adjusted model (Table 2). Analyses of current daily tobacco use (Table 3) resulted in similar results, as did stratified analyses by parental postnatal tobacco use (data not shown). In separate analyses by sex (Tables 2 and 3), there were no differences between men and women. However, these results were based on small sample sizes and were therefore very imprecise. There was a hint of a dose-response relationship between intensity of maternal pregnancy smoking and offspring’s tobacco use for smoking only. The adjusted odds ratio for lifetime daily tobacco use was 0.99 (95% confidence interval: 0.64, 1.52) for those exposed to 1–9 cigarettes per day and 1.53 (95% confidence interval: 0.92, 2.57) for those exposed to 10 or more cigarettes per day. For snus use, the association was similar in both levels of exposure.

Table 4 shows the crude and adjusted odds ratios for duration and intensity of tobacco use. Compared with unexposed subjects, participants who were exposed to maternal smoking during pregnancy had a more than 3-fold increase in the odds of being heavy snus users (≥3 cans of snus per week) after adjustment for all potential confounders. The association between prenatal exposure and heavy snus use appeared stronger among women, although estimates were very imprecise (Table 4). Offspring’s heavy smoking and duration of use were not associated with the exposure. Early age at onset of daily cigarette smoking or snus use was not significantly associated with prenatal exposure to maternal smoking (data not shown).

Prenatal exposure to maternal smoking was not associated with increased odds of being a stable daily user of tobacco, quitter, or starter rather than a nonuser between 2006 and 2010. Furthermore, there was no difference between being a stable user and being a quitter during the same interval (data not shown).

DISCUSSION

We found that maternal smoking during pregnancy was associated with regular and established snus use in adult offspring but not with smoking. The absence of an association between prenatal exposure to maternal smoking and regular smoking in the offspring was not completely surprising, as results from previous longitudinal studies that included adults were not consistent. In fact, 2 studies did not find any significant association (22, 23). In a study based on 262 women, Tehranifar et al. (16) reported a more than 4-fold higher risk of daily smoking for persons exposed to maternal smoking during pregnancy compared with those who were unexposed (16). Kandel et al. (11) found a similar association, with particularly high odds among those exposed to intense smoking during pregnancy (≥10 cigarettes per day). We did not find any association with intensity of use or with age at

<table>
<thead>
<tr>
<th>Duration and Intensity of Tobacco Use</th>
<th>No of Exposed Cases</th>
<th>Crude</th>
<th>Adjusted for Parents Postnatal Tobacco Use</th>
<th>Adjusted for All Potential Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>&gt;5 years of daily tobacco use vs. less</td>
<td>86</td>
<td>1.66 1.02, 2.74</td>
<td>1.25 0.71, 2.21</td>
<td>1.06 0.58, 1.94</td>
</tr>
<tr>
<td>Overall</td>
<td>38</td>
<td>2.39 1.11, 5.44</td>
<td>1.41 0.55, 3.66</td>
<td>0.83 0.27, 2.52</td>
</tr>
<tr>
<td>Men</td>
<td>48</td>
<td>1.29 0.69, 2.46</td>
<td>1.11 0.55, 2.27</td>
<td>1.16 0.54, 2.52</td>
</tr>
<tr>
<td>Women</td>
<td>39</td>
<td>2.70 1.56, 4.70</td>
<td>1.68 0.90, 3.13</td>
<td>1.21 0.61, 2.36</td>
</tr>
<tr>
<td>Smoking &gt;10 cigarettes per day vs. less</td>
<td>12</td>
<td>2.14 0.80, 5.84</td>
<td>1.40 0.44, 4.28</td>
<td>0.96 0.20, 4.37</td>
</tr>
<tr>
<td>Overall</td>
<td>27</td>
<td>3.00 1.55, 5.87</td>
<td>1.80 0.85, 3.81</td>
<td>1.39 0.60, 3.16</td>
</tr>
<tr>
<td>Men</td>
<td>45</td>
<td>3.60 1.93, 6.90</td>
<td>2.89 1.27, 6.81</td>
<td>3.85 1.57, 10.15</td>
</tr>
<tr>
<td>Women</td>
<td>28</td>
<td>4.02 1.81, 9.37</td>
<td>2.41 0.85, 7.06</td>
<td>3.93 1.20, 14.37</td>
</tr>
<tr>
<td>Consumption of &gt;3 cans of snus per week vs. less</td>
<td>17</td>
<td>3.14 1.14, 9.09</td>
<td>4.45 1.11, 22.57</td>
<td>6.15 1.38, 35.81</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

A Adjusted for parents’ psychiatric morbidity, parents’ postnatal tobacco use, socioeconomic characteristics (maternal educational level, own educational level, and parents’ nationality), and characteristics of upbringing (living with both parents during upbringing), as illustrated in Figure 2.

B Analyses of duration of daily tobacco use, heavy smoking, and heavy snus use were based on 39 participants.
onset of daily use. In a prospective study, Cornelius et al. (24) found higher odds of heavy smoking among those prenatally exposed to maternal smoking during pregnancy. Associations between prenatal smoking exposure and early age at onset of smoking in offspring were previously reported in a cross-sectional study of adult smokers (15) and in prospective cohort studies of adolescents (4, 19). A third longitudinal study of adolescents did not find such an association (19). Finally, exposure was seemingly not associated with another indicator of dependent tobacco use, namely sustained tobacco use over time rather than its discontinuation, an outcome that has not been studied previously.

To the best of our knowledge, the present study is the first analysis of adult smokeless tobacco use in relation to prenatal exposure to maternal smoking. Therefore, comparisons with previous studies cannot be established. The association we found between maternal smoking during pregnancy and offspring’s use of snus may support the hypothesis of a causal effect of early brain exposure to nicotine on the subsequent risk of transition to nicotine dependence. Why this enhanced risk would manifest with smokeless tobacco rather than smoking is a matter of speculation. There are reasons to surmise that snus might be more addictive than cigarettes because of the manner in which nicotine is delivered with oral tobacco. In fact, peak levels of nicotine in plasma after snus consumption are similar to those achieved after smoking a cigarette with an equivalent dose, but the high concentration is sustained for a longer period (37, 38). There is empirical evidence that snus users are less prone to quit than are smokers (39). A study from India found higher baseline craving among smokeless tobacco users than among smokers that was not decreased by pictorial warning, as it was among smokers (40). A Swedish study found higher odds of symptoms of nicotine dependence in adolescent snus users than in smokers (41), but such differences were not confirmed in a US study (42). A further reason why the potential effect of prenatal exposure would be evident on snus use in this sample rests on the underlying population patterns of use. In fact, during the last 20 years, there has been a generational shift in tobacco use in Sweden. Although smoking has become less common, the prevalence of snus use has risen, particularly among young adults who are the age of our study population (43). Because initiation of tobacco use is usually by smoking (39), it is possible that young snus users represent a subgroup of people that abandoned smoking at an early stage but couldn’t stop all tobacco use. Compared with continued or escalating smokers, snus users might be less exposed to pro-smoking social influences, such as that of parents or peers. In fact, despite the small sample size, snus use was the only outcome not sensitive to adjustments, that is, less confounded by psychosocial influences.

At odds with our previous study of adolescents (17), we could not detect major differences between men and women in this cohort. Besides the low power, possible explanations for this apparent discrepancy between the 2 studies are differences in age span and outcome measures. In the present study, we did not have information on symptoms of nicotine dependence among tobacco users other than heaviness of smoking. Early onset of dependence may indicate particular susceptibility to the addictive properties of nicotine during adolescence, which may be higher among females, potentially because of an interaction with female hormones (2, 44, 45). The sex-specific pattern in adolescence may therefore simply indicate the relative speed at which dependence is established, with little bearing on the prevalence of dependence in adulthood. In a US study, the median time to early symptoms of nicotine dependence after monthly smoking in early adolescence was more than 8 times shorter among girls than among boys (46).

To our knowledge, this is the first study to investigate the association between prenatal exposure to maternal smoking and the use of tobacco products other than cigarettes in adults. Further strengths include the prospective cohort design, with information on exposure and other relevant covariates retrieved from registers with high quality and coverage. Moreover, a number of potential confounders were analyzed and were chosen a priori in accordance with a theoretical causation model.

However, some limitations should be kept in mind when interpreting the results from this study. The strong covariation between parental postnatal tobacco use and maternal smoking during pregnancy rendered stratified analyses in subgroups of parental postnatal tobacco use noninformative and adjustment for parental postnatal tobacco use inefficient. Furthermore, parental psychiatric morbidity only included hospital diagnoses and therefore probably only the most severe cases. Also, self-selection due to low participation at recruitment and follow-up could have introduced bias because of a correlation among determinants of participation, exposure, and outcome, which calls for a cautious generalization of the findings. However, the prevalence of daily tobacco use among the study participants and the prevalence of maternal smoking during pregnancy were very similar to those in the general population of Sweden during corresponding time periods, which suggests that selection bias would be a minor issue. Several of the measures used in the present study were based on self-reports without biochemical validation, including exposure and outcomes, which are likely to be underreported (47, 48). Information about parental postnatal tobacco use reported by the participants might differ from parents’ actual use, but this would not necessarily constitute a disadvantage because perceived parental use, rather than actual use, is likely to represent role-modeling influences. The inclusion of nondaily smokers among nonsmokers might have diluted the possible effects of low levels of smoking during pregnancy. Exposure was only measured during the first trimester of pregnancy, which precludes us from discerning prenatal effects throughout development. All of these sources of misclassification would likely dilute the estimated associations. Finally, residual confounding from unmeasured determinants, such as genetic or social factors or other early-life exposures, cannot be ruled out.

In summary, findings from the present study indicate that prenatal exposure to nicotine is associated with snus use among adults, supporting the hypothesis of a biological pathway that links prenatal tobacco exposure with brain vulnerability to nicotine that persists into adulthood. This should be further explored in epidemiologic studies that simultaneously address the roles of genetics and early social environments.
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REFERENCES


