Published in final edited form as:

Epidemiology. 2015 May ; 26(3): 441–447. doi:10.1097/EDE.0000000000000270.

Elevated Risk of Nicotine Dependence Among Sib-pairs Discordant for Maternal Smoking During Pregnancy:

Evidence from a 40-year Longitudinal Study

Edmond D. Shenassa^{a,b,c,d}, George D. Papandonatos^e, Michelle L. Rogers^c, and Stephen L. Buka^c

^aMaternal and Child Health Program, School of Public Health, University of Maryland, College Park, MD

^bDepartment of Epidemiology and Biostatistics, School of Public Health, University of Maryland, College Park, MD

^cDepartment of Epidemiology and Public Health, University of Maryland School of Medicine, College Park, MD

^dDepartment of Epidemiology, Brown University School of Public Health, Providence, RI

^eDepartment of Biostatistics, Brown University School of Public Health, Providence, RI

Abstract

Background—Compelling evidence links maternal smoking during pregnancy with elevated risk of nicotine dependence among the offspring. However, no study to date has examined the maternal smoking during pregnancy-nicotine dependence link among sibling-pairs discordant for maternal smoking during pregnancy. We tested two hypotheses that, if supported, suggest that the maternal smoking during pregnancy-nicotine dependence link may be physiologically mediated.

Methods—Study participants were adult offspring of women enrolled in the Providence and Boston sites of the Collaborative Perinatal Project (1959–1966). Approximately 10% of these adult offspring (average age: 39.6 years) were enrolled in the New England Family Study (n = 1,783), a follow-up study that oversampled families with multiple siblings. Logistic regression models predicting maternal smoking during pregnancy risk on various prospectively collected smoking and marijuana use outcomes, including nicotine dependence, were fit using models that allowed between-mother effects of maternal smoking during pregnancy exposure to differ from within-mother effects. In the absence of significant effect heterogeneity, we calculated a combined estimate.

Results—Maternal smoking during pregnancy predicted progression from weekly smoking to nicotine dependence (odds ratio = 1.4 [95% confidence interval = 1.2, 1.8]), but not weekly smoking or progression to marijuana dependence.

Conclusions—Current evidence from sibling-pairs discordant for maternal smoking during pregnancy is consistent with previous reports of a dose–response association between maternal smoking during pregnancy and nicotine dependence, as well as of up-regulation of nicotine receptors among animals exposed to maternal smoking during pregnancy. Together, they provide support for the existence of a physiologically mediated link between maternal smoking during pregnancy and nicotine dependence.

Two lines of evidence suggest a link between maternal smoking during pregnancy and elevated risk of nicotine dependence among offspring. First, nicotinic receptors of laboratory animals exposed to nicotine in utero are up-regulated, suggesting a latent vulnerability to nicotine dependence among animals exposed to nicotine in utero.^{1,2} Second, despite one null finding,³ epidemiologic evidence from cross-sectional^{4–6} as well as longitudinal studies,^{7,8} supports existence of a link between maternal smoking during pregnancy and nicotine dependence, and suggests that this link is physiologically mediated. In particular, maternal smoking during pregnancy is associated specifically with risk of nicotine dependence, but not with marijuana dependence,⁷ supporting the view that the maternal smoking during pregnancy–nicotine dependence link among humans may also be mediated by up-regulation of nicotinic receptors. In addition, evidence of a dose–response association between maternal smoking during pregnancy and risk of nicotine dependence⁷ further suggests that this link has a physiologic substrate. However, extant epidemiologic evidence cannot rule out intergenerational transmission of genetic (eg, depression) and social vulnerabilities (eg, current maternal smoking) to nicotine dependence as an alternate explanation for the observed link. Although some studies have controlled for inheritable pathologies associated with an elevated risk of nicotine dependence (eg, depression⁴), no study to date has used a family design to control for familial vulnerabilities, either genetic or social that predict risk of nicotine dependence.

In this study, we replicate our earlier longitudinal study⁷ among 1,783 adult offspring (age at interview: mean 39.6, range 34–49 years) of 1,308 women enrolled in a large, socioeconomically diverse, population-based birth cohort, for whom data on maternal smoking during pregnancy have been prospectively collected and chemically validated. Unlike our previous report, the current sample includes a large number of offspring from multiplex families showing within-family variation in maternal smoking during pregnancy. This allows us to use a family design to investigate siblings who are discordant with respect to maternal smoking during pregnancy, accounting for familial vulnerabilities to nicotine dependence, both measured and unmeasured.

We tested two hypotheses that, if supported, provide further evidence that the maternal smoking during pregnancy–nicotine dependence link is physiologically mediated. First, we reasoned that risk of smoking *initiation* is mediated primarily by social determinants, such as parental smoking and peer influences, whereas, *progression* to nicotine dependence is primarily physiologically mediated. Therefore, we hypothesized that maternal smoking during pregnancy would be a stronger predictor of progression to nicotine dependence, than of smoking initiation or regular use. Second, we reasoned that, if the link is indeed mediated by up-regulation of nicotinic receptors,^{1,2} maternal smoking during pregnancy would display substance-specificity, and act as a stronger predictor of progression to nicotine than

progression to marijuana dependence. By assessing risk of progression to nicotine dependence, rather than simply nicotine dependence, we condition on risk of ever or regular use, and therefore, control for all reasons for initiation and regular use.

METHODS

Study Sample

Study participants were offspring of mothers enrolled in the Providence and Boston sites of the Collaborative Perinatal Project between 1959 and 1966.^{9,10} Detailed social and medical histories, including responses to questions regarding smoking levels, were collected from the mothers at the time of enrollment and throughout pregnancy.¹¹ We refer to the mothers as “Generation 1” (G1s) and to their offspring as “Generation 2” (G2s).

Approximately, 10% of these G2 offspring were enrolled in the New England Family Study (n = 1,883), a follow-up study in which participants were selected using a multistage sampling procedure that oversampled families with multiple siblings, in particular sibships that were discordant for maternal smoking during pregnancy. Eligibility criteria for this study included being from intact sibling sets or current smokers. Screening questionnaires were mailed to 4,579 of the 15,321 Boston and Providence G2 offspring who survived until age seven. On the basis of 3,153 questionnaires returned, 2,271 G2s were eligible for participation. After further exclusions (Table 1), the analytic sample included 1,783 G2 participants distributed across 1,308 families, composed of 887 singletons, 373 sibling pairs, 43 sibling trios, four sibling quartets, and one sibling quintet.

Measures

At each prenatal visit throughout pregnancy, G1 mothers reported whether they were currently smoking and, if so, the number of cigarettes smoked daily. The number of visits varied by pregnancy. From these reports, we determined the maximum number of cigarettes smoked per day at any time during each pregnancy. Expressed in terms of cigarette packs per day, this became our key maternal smoking measure. Age and number of pregnancies were reported by the G1 mother at study enrollment, along with race/ethnicity and various other socioeconomic indicators. Offspring (G2) smoking histories were obtained by the Life Interview of Smoking Trajectories Questionnaire, an instrument with excellent reliability ($\kappa = 0.78\text{--}0.92$).¹² This instrument obtains detailed information on participants' experiences with smoking, beginning from experimentation, progression to weekly smoking, levels of consumption, and nicotine dependence. Weekly smoking was defined as a positive response to the question, “Did you ever become a weekly smoker (that is, smoke at least once per week for 2 months or longer)?” Lifetime nicotine dependence was defined based on *Diagnostic and Statistical Manual, Fourth Edition (DSM-IV)* criteria¹³ and was assessed using the Composite International Diagnostic Interview.¹⁴ Finally, the fourth version of the Diagnostic Interview Schedule (DIS-IV) was used to assess marijuana use and dependence.

Analytic Plan

All analyses were conducted using SAS/STAT V9.3.¹⁵ We estimated logistic regression models using Proc GenMod. Robust standard errors based on a working independence

correlation matrix were used to correct for dependence in substance use outcomes across multiple pregnancies of the same mother using Generalized Estimating Equation methodology.¹⁶ In particular, the total effect of the j^{th} G1 mother's smoking level during her i^{th} pregnancy (X_{ij}) upon subsequent G2 substance use (Y_{ij}) was modeled as:

$$\text{logit}(P[Y_{ij}=1]) = a + \beta_T (X_{ij} - \bar{X}_{..}), i=1, \dots, N_j, j=1, \dots, J \quad (1)$$

with maternal smoking during pregnancy centered by the overall sample mean $\bar{X}_{..}$ (grand-mean centering, no decomposition approach). This model can also be expressed as

$$\text{logit}(P[Y_{ij}=1]) = a + \beta_B (\bar{X}_{.j} - \bar{X}_{..}) + \beta_W (X_{ij} - \bar{X}_{.j}), i=1, \dots, N_j, j=1, \dots, J \quad (2)$$

where $\bar{X}_{.j}$ represents the average MSP level across all N_j pregnancies of the j^{th} G2 mother (cluster-mean centering, decomposition approach).

Model (1) is nested within model (2), in that the latter allows the between-mother effect (β_B) to differ from the within-mother effect (β_W), whereas the former assumes them to be equal (ie, sets $\beta_B = \beta_W = \beta_T$). Raudenbush and Bryk¹⁷ have called β_B the “contextual” effect and β_W the “individual” effect, the latter representing the effect of a unit change in maternal smoking from one pregnancy to another. If model (2) holds, but the test of equality fails to attain significance due to lack of power, then falsely accepting model (1) leads to a pooled estimate $\hat{\beta}_T$ that is proportional to a weighted average of the estimates of $\hat{\beta}_B$ and $\hat{\beta}_W$ from model (2).^{18,19} In particular, when there is little within-mother variability in maternal smoking during pregnancy, $\hat{\beta}_W$ is relatively imprecise and $\hat{\beta}_T$ is weighted more heavily toward $\hat{\beta}_B$. More commonly, this is also the case when the test is not performed in the first place, as researchers often fit model (1) without considering model (2). The test of equality has low power when cluster sizes are small (ie, when there are few pregnancies per G1 mother), and a low-prevalence outcomes binary outcome is being modeled (eg, progression to marijuana dependence). A more conservative approach, which we adopt in this article, is to simply report both the within and between effects individually, irrespective of test results.

A further advantage of model (2) is that the effect of any mother-level factors correlated with maternal smoking during pregnancy is absorbed by β_B , and does not bias the estimates of β_W . To the extent that inferences about effects are based upon within-mother comparisons, we do not need to explicitly control in the model for any family-level covariates (eg, family history of psychiatric problems, and parental race/ethnicity). This is not necessarily the case for covariates that vary across pregnancies (eg, maternal age at pregnancy, offspring sex, and birth order).^{20–22} Finally, there are several potential within-mother confounders that showed little variability across G1 pregnancies (eg, household crowding, family socioeconomic status, employment status, and marital status); we chose not to include these in our model.

Another issue to consider in these analyses is the inclusion of singleton pregnancies. To the extent that variation in family size is uninformative about outcome, inclusion of singletons is desirable, in that it does not bias the model intercept, whereas improving the precision of estimates of the between-mother effects. This was the case in the New England Family

Study, where only children born to G1 mothers between 1960 and 1966 were included in the sample, and “singleton” pregnancies are not necessarily indicative of small family size.

RESULTS

As shown in Table 1, there were very few differences between the 1,783 G2 offspring included in the current analyses, and the 1,270 considered for inclusion in the New England Family Study that were ultimately determined to be ineligible. Most notably, women were over-represented in the analytic sample (58%) compared with those not interviewed (46%). Furthermore, included G2s were of slightly higher socioeconomic status than those excluded (mean = 54.8 vs. 50.6 on a 100-point scale). However, no important differences in smoking patterns emerged for either categorical or continuous maternal smoking during pregnancy measures. Of note, 61% of the G2 offspring had mothers who smoked during pregnancy, whereas 34% had mothers who smoked a pack a day or more.

Table 2 shows the number of G2 offspring endorsing various cigarette and marijuana use outcomes, among those with pertinent data. Rates of progression from one stage of substance use to another were calculated by conditioning the analysis on the earlier stage of use⁷; for example, only women who ever smoked were used to estimate the rate of progression from ever-smoking to nicotine dependence. We used a similar approach to estimate the rate of progression from ever using marijuana (at least five times in a lifetime) to marijuana dependence. Missing data rates did not exceed 2.5%, with the exception of progression from ever-use to marijuana dependence (5.2%), and from daily use to marijuana dependence (8.2%). To convey the effective sample sizes available for various study outcomes, we provide the number of G1 families and G2 sib-pairs available for each analysis. The total number of available G2 sib-pairs was obtained by adding across family configurations (one for pairs, three for trios, six for quartets, and 10 for quintets), with exposure sib-pairs reported separately.

Table 3 presents results of generalized estimating equation logistic regression models predicting smoking outcomes. Fitting both models (1) and (2) provides four odds ratios per outcome: $OR_B = \exp(\beta_B)$, $OR_W = \exp(\beta_W)$, $OR_{Ratio} = OR_B/OR_W = \exp(\beta_B - \beta_W)$, and $OR_T = \exp(\beta_T)$, each measuring the effects of a single pack increase in maternal smoking during pregnancy on the odds of registering a positive smoking outcome. Although the heterogeneity test statistic OR_{Ratio} appeared to vary considerably from the null value of unity for several outcomes, none of the corresponding *P* values attained statistical significance, suggesting low power for testing differences in between- and within-mother maternal smoking during pregnancy effects. Combining these two effects into an overall MSP effect OR_T , as was done by default in past studies that did not use a decomposition approach, might be easier to justify in low-power scenarios if OR_B and OR_W both point in the same direction, and are distinguished only by small differences in magnitude.

Table 3 shows that only two smoking outcomes satisfied these conditions: lifetime ND prevalence ($OR_T = 1.3$ [95% confidence interval = 1.1, 1.5]), and progression from ever-smoking to lifetime nicotine dependence ($OR_T = 1.4$ [1.2, 1.6]). As for progression from weekly smoking to lifetime nicotine dependence ($OR_T = 1.4$ [1.2, 1.8]), this last outcome is

one for which $OR_W = 3.1$, known to be insensitive to omitted family-level confounder, is more than twice as large as $OR_B = 1.4$, which is not as robust. However, the combined estimate may well provide an adequate summary of the data, given that both odds ratios point in the same direction and that OR_W is relatively imprecise, as it is based upon a small number of within-mother comparisons. Given observed discrepancies in both the direction and magnitude of their between- and within-mother effects, reliance of the combined estimate is best avoided for ever-smoking initiation ($OR_B = 0.75$, $OR_W = 1.5$). Results for weekly smoking initiation appear less discrepant ($OR_B = 1.1$, $OR_W = 0.80$), and indicate an overall lack of association with maternal smoking during pregnancy ($OR_T = 1.1$, [0.94, 1.3]). Covariate adjustment for within-mother covariates did not materially affect any of these conclusions.

In Table 4, we present comparable analyses for marijuana initiation (ever used five times), daily use and dependence, as well as for progression to marijuana dependence. Results were consistent across all outcomes of interest, with OR_B and OR_W both suggesting maternal smoking during pregnancy as a risk factor, and OR_W being slightly higher in magnitude than OR_B . However, overall maternal smoking during pregnancy effects ($OR_T = 1.1$, 1.3) were uniformly weak, reaching statistical significance only for initiation of daily use ($OR_T = 1.2$ [1.0, 1.5]).

DISCUSSION

Extant evidence supports the notion that the link between maternal smoking during pregnancy and nicotine dependence in the offspring is physiologically mediated.⁷ However, this evidence cannot rule out possibly unmeasured familial factors as an explanation for the observed link among humans. Accordingly, we examined the link between maternal smoking during pregnancy and smoking initiation, weekly use, and progression to nicotine dependence using a within-family/discordant-sibling design that more fully accounts for shared genetic and social vulnerabilities. Furthermore, we aimed to increase the precision of our within-family estimates by combining them with between-family estimates, when evidence for effect heterogeneity was weak. We hypothesized that maternal smoking during pregnancy would predict progression to nicotine dependence, but not smoking initiation. We also hypothesized that maternal smoking during pregnancy would show weaker associations with progression to marijuana dependence than for progression to nicotine dependence. For both substances, we assessed risk of progression to dependence by conditioning on risk of ever or regular use, and therefore, controlled for all reasons for initial use.

Based on within-family information free of potentially omitted confounders, we found support for our hypothesis that maternal smoking during pregnancy predicts progression to nicotine dependence. Furthermore, the within- and between-family information pointed in the same direction, with the within-family effect being stronger in magnitude than the between-family effect. Therefore, the two sources of information were combined to provide a conservative and more precise estimate of maternal smoking during pregnancy risk than one based on within-family information alone. Evidence of a maternal smoking during pregnancy-nicotine dependence link is in accord with studies reporting a positive association between maternal smoking during pregnancy and elevated risk of nicotine dependence.⁴⁻⁸

We also found no evidence that maternal smoking during pregnancy is associated with weekly smoking initiation. However, results for ever-smoking initiation were inconclusive, with between-family effects supporting a negative association with maternal smoking during pregnancy, and within-family effects pointing in the opposite direction, but failing to attain statistical significance. Between-family evidence that maternal smoking during pregnancy is negatively associated with risk of ever-smoking initiation is in agreement with some previous investigations, which have reported positive,^{5,23,24} null,^{25–27} or negative^{28,29} associations. We argue that reported associations between maternal smoking during pregnancy and ever-smoking initiation^{5,23,24} are due to residual confounding by correlates of maternal smoking during pregnancy, as they are driven by potentially biased between-family information. Smoking initiation is promoted by familial factors that are correlated with maternal smoking during pregnancy, but are not a consequence of maternal smoking during pregnancy, such as current maternal smoking.^{30,31} The importance of controlling for confounding by correlates of maternal smoking during pregnancy (that are not a consequence of maternal smoking during pregnancy) is further emphasized by evidence that women who continue to smoke during pregnancy are more prone to psychopathology than women who quit.³² Because psychopathology is a heritable risk for nicotine dependence, this places their offspring at a higher risk of nicotine dependence not directly attributable to maternal smoking during pregnancy per se. Confounding by correlates of maternal smoking during pregnancy have indeed led to reporting of spurious associations between maternal smoking during pregnancy and smoking initiation, which were reduced to null after adequate controls were introduced to statistical models.^{26,27,33}

In contrast, evidence of a maternal smoking during pregnancy-nicotine dependence link based on within-family information is less likely to be influenced by heritable genetic and social vulnerabilities to nicotine dependence, at least those passed on by the mother. We found no evidence of a link between maternal smoking during pregnancy and smoking initiation based on within-family estimates. Our findings are in agreement with the only other study of smoking-related outcomes conducted among sibling-pairs discordant for maternal smoking during pregnancy. Among a population-based sample of adults aged 19–27, Rydell et al³⁴ found no within-family association between maternal smoking during pregnancy and risk of current or lifetime smoking. However, they did not explicitly assess progression to nicotine dependence. We reiterate the important distinction between progression to nicotine dependence and less severe smoking outcomes. As this conditional analysis controls for all reasons for initial use, it is the appropriate proxy for existence of a latent physiologic vulnerability to dependence. Ours is the only study to use both a between-within decomposition of familial association with offspring outcomes and a conditional analysis, offering a clear methodological advance in examining progression to dependence.

To determine whether maternal smoking during pregnancy evinces substance specificity, we also assessed the link between maternal smoking during pregnancy and progression to marijuana dependence among the offspring. Marijuana is of particular relevance, because it has a similar route of administration (inhalation) and known co-occurrence with tobacco use.³⁵ However, because its active ingredient (THC) is distinct from nicotine, this suggests that if the maternal smoking during pregnancy-nicotine dependence link is physiologically

mediated, then maternal smoking during pregnancy would be a stronger predictor of progression to nicotine dependence than progression to marijuana dependence.

Our findings in this regard are only suggestive, as the unbiased within-family estimates tend to become rather imprecise as we consider more severe outcomes, based on increasingly fewer discordant sib-pairs (Table 2). Still, for both lifetime dependence prevalence and progression to dependence, the estimates of between-family and within-family effects point in the same direction, and can be combined to provide more precise estimates of risk due to maternal smoking during pregnancy (Tables 3 and 4). In the full sample, the association of maternal smoking during pregnancy with prevalence of marijuana dependence is almost identical to that of nicotine dependence. This is in accord with evidence from the only study to have examined the link between maternal smoking during pregnancy and marijuana use among offspring.³⁶ However, our hypothesis of interest centers on likelihood of *progression* to dependence among those whom have initiated marijuana use. This conditional analysis is the appropriate approach for testing the existence of a latent physiologic vulnerability to dependence. Therefore, the similar risk for nicotine dependence and prevalence of marijuana dependence does not contradict our hypothesis that maternal smoking during pregnancy is a more specific predictor of progression to nicotine dependence. The combined estimates suggest slightly stronger maternal smoking during pregnancy links with progression to nicotine dependence than with progression to marijuana dependence among those initiating substance use ($OR_{ND} = 1.38$ vs. $OR_{MJ} = 1.24$). Furthermore, this divergence in the odds of smoking-related relative to marijuana-related outcomes widens further as we consider outcomes that are less likely to be driven by psychosocial determinants, eg, progression to dependence among regular users ($OR_{ND} = 1.42$ vs. $OR_{MJ} = 1.12$).

We examined the links between maternal smoking during pregnancy, nicotine dependence, and marijuana dependence among offspring of women enrolled in the Collaborative Perinatal Project, a large, socioeconomically diverse, population-based birth cohort for whom maternal smoking during pregnancy data has been collected prospectively and chemically validated. Separation of between- and within-family information allowed us to obtain estimates less confounded by familial vulnerabilities that can influence substance use initiation, regular use, and dependence.

We also note shortcomings of our study. First, we had no measure of second-hand smoke exposure. However, because the same nicotinic pathways are activated irrespective of source of nicotine exposure, we maintain that an independent maternal smoking during pregnancy-nicotine dependence link is evident in this sample. Second, low within-mother variation in maternal smoking during pregnancy levels across pregnancies did not allow us to assess within-mother maternal smoking during pregnancy effects associated with more than half-a-pack of cigarettes smoked per day. In contrast, between-mother maternal smoking during pregnancy effects were based upon a much larger range of variation in the data (0–3 packs per day), but are potentially open to bias from omitted confounders. Third, we had no prospective data on G1 marijuana use during pregnancy. However, retrospective reports were available on 47% of the pregnancies analyzed herein; only 0.48% of these involved G1 marijuana use, with only 0.36% involving both cigarette smoking and marijuana use. This is typical of the early 1960s, when the Collaborative Perinatal Project data were collected:

smoking was normative and marijuana use was rare. Finally, although within-pair estimates are not confounded by factors shared by the siblings, these estimates can be biased by omitted non-shared confounders.³⁷ For example, family socioeconomic status can change over time, and could act as a within-family covariate. However, such changes are often a function of time; in our sample, the maximum age difference among sibs in multiplex families was 3 years (median = 2 years). Thus, variation in the value of time-varying confounders is likely to be negligible.

In conclusion, a study design that discounts the role of shared genetic and social vulnerabilities to nicotine dependence provided further support for the notion that the maternal smoking during pregnancy-nicotine dependence link among humans is likely to be physiologically mediated. Evidence of substance-specificity of maternal smoking during pregnancy provided further support for a physiologically mediated maternal smoking during pregnancy-nicotine dependence link, although it would have benefited from stronger within-family information.

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TABLE 1

Demographic and Smoking Characteristics of G2 Offspring in the Boston and Providence Cohorts of the Collaborative Perinatal Project (N=3,153 Eligible for Interview)

Characteristic ^a	Interviewed (n = 1,783) ^b	Not Interviewed (n = 1,270)
Race/ethnicity, no. (%)		
Non-white	240 (14)	172 (14)
White	1,543 (86)	1,098 (86)
Sex, no. (%)		
Male	754 (42)	689 (54)
Female	1,029 (58)	581 (46)
Maximum number of cigarettes mother smoked on any pregnancy day, no. (%)		
0	735 (41)	496 (39)
1–9	209 (12)	178 (14)
10–19	231 (13)	156 (12)
20–29	393 (22)	271 (22)
30+	215 (12)	158 (13)
Offspring's age at interview (years)	39.6 (34–49)	
Mother's age at pregnancy (years)	24.9 (14–43)	24.3 (14–43)
Family socioeconomic index at birth ^c	54.8 (3–93)	50.6 (5–93)
Gravida	2.2 (0–14)	2.4 (0–16)
Maximum number of cigarettes mother smoked on any pregnancy day	10.9 (0–61)	10.9 (0–61)

^a Mean (range) unless otherwise specified.

^b Data from 100 interviewed G2s were not included in these analyses: 49 were excluded due to interview administration issues, and an additional 39 were excluded due to missing data on maternal or offspring smoking. Finally, one sibling of 12 twin pairs was randomly selected for inclusion, resulting in final analytic sample of n = 1,783.

^c A composite index of socioeconomic status was calculated on the basis of methods developed by the US Census Bureau (possible range = 0–100).

TABLE 2

NEFS Sample Description by Substance Use Outcome (n = 1,783)

Substance Use Outcome	Outcome (%)	No. G2s Positive	No. G2s Available	No. G1 Families	No. G2 Sib-pairs	No. G2 Discordant Sib-pairs
Cigarettes						
Ever smoked	89.8	1,601	1,783	1,308	536	200
Weekly smoking	58.6	1,045	1,783	1,308	536	200
Lifetime nicotine dependence	38.5	678	1,760	1,290	531	199
Progression from:						
Ever smoked to nicotine dependence	43.0	678	1,577	1,193	433	157
Weekly smoking to nicotine dependence	66.4	678	1,021	842	197	70
Marijuana						
Ever used 5 times	63.0	1,108	1,759	1,294	526	197
Daily use	23.0	403	1,749	1,291	517	194
Lifetime marijuana dependence	5.4	91	1,700	1,267	484	181
Progression from:						
Ever used 5 times to marijuana dependence	8.7	91	1,050	866	203	68
Daily use to marijuana dependence	21.9	81	370	345	26	6

G1 = generation 1 (index mothers); G2 = generation 2 (offspring); Discordant sib-pairs = sibling pairs showing within-mother variation in smoking levels during pregnancy; outcome rate = % of available G2s with positive responses.

TABLE 3

GEE Logistic Regression Models for Cigarette Smoking Outcomes

	Unadjusted	Adjusted
	OR (95% CI)	OR (95% CI)
Ever smoked		
Between	0.75 (0.59, 0.96)	0.71 (0.56, 0.91)
Within	1.52 (0.48, 4.82)	1.51 (0.48, 4.79)
Ratio	0.49 (0.15, 1.60)	0.47 (0.15, 1.53)
Total	0.77 (0.61, 0.98)	0.74 (0.58, 0.94)
Ever weekly smoking		
Between	1.12 (0.95, 1.31)	1.09 (0.93, 1.28)
Within	0.80 (0.38, 1.71)	0.80 (0.38, 1.70)
Ratio	1.39 (0.64, 3.04)	1.36 (0.63, 2.94)
Total	1.10 (0.94, 1.28)	1.07 (0.91, 1.26)
Nicotine dependence		
Between	1.26 (1.08, 1.48)	1.24 (1.06, 1.45)
Within	1.51 (0.72, 3.16)	1.51 (0.73, 3.13)
Ratio	0.84 (0.39, 1.79)	0.82 (0.39, 1.73)
Total	1.28 (1.09, 1.49)	1.25 (1.07, 1.46)
Progression from:		
Ever smoked to nicotine dependence		
Between	1.38 (1.17, 1.63)	1.36 (1.15, 1.60)
Within	1.44 (0.64, 3.26)	1.46 (0.65, 3.25)
Ratio	0.96 (0.42, 2.19)	0.93 (0.41, 2.11)
Total	1.38 (1.18, 1.63)	1.36 (1.16, 1.60)
Weekly smoking to nicotine dependence		
Between	1.38 (1.11, 1.71)	1.37 (1.10, 1.69)
Within	3.12 (1.07, 9.12)	3.13 (1.08, 9.11)
Ratio	0.44 (0.15, 1.31)	0.44 (0.15, 1.29)
Total	1.42 (1.15, 1.76)	1.41 (1.14, 1.74)

Adjusted models control for number of pregnancies and offspring sex.

Between indicates between-mother effects; within, within-mother effects; ratio, ratio of between-mother to within-mother effects; total, total effects; GEE, generalized estimating equation; OR, odds ratio; CI, confidence interval.

TABLE 4**GEE Logistic Regression Models for Marijuana Smoking Outcomes**

	Unadjusted	Adjusted
	OR (95% CI)	OR (95% CI)
Ever used marijuana 5 times		
Between	1.12 (0.95, 1.31)	1.10 (0.93, 1.30)
Within	1.34 (0.70, 2.56)	1.31 (0.68, 2.51)
Ratio	0.83 (0.43, 1.62)	0.84 (0.43, 1.66)
Total	1.13 (0.96, 1.32)	1.11 (0.95, 1.31)
Ever daily use		
Between	1.21 (1.01, 1.44)	1.18 (0.99, 1.41)
Within	1.65 (0.71, 3.82)	1.57 (0.65, 3.76)
Ratio	0.73 (0.31, 1.73)	0.76 (0.31, 1.85)
Total	1.23 (1.03, 1.46)	1.20 (1.01, 1.43)
Marijuana dependence		
Between	1.26 (0.90, 1.77)	1.24 (0.89, 1.73)
Within	1.92 (0.30, 12.4)	2.01 (0.30, 13.5)
Ratio	0.66 (0.10, 4.47)	0.62 (0.09, 4.31)
Total	1.29 (0.92, 1.79)	1.26 (0.91, 1.75)
Progression from:		
Used 5 times to marijuana dependence		
Between	1.22 (0.86, 1.72)	1.24 (0.88, 1.73)
Within	1.75 (0.24, 12.8)	1.89 (0.27, 13.1)
Ratio	0.70 (0.09, 5.39)	0.65 (0.09, 4.74)
Total	1.24 (0.88, 1.73)	1.26 (0.90, 1.75)
Daily use to marijuana dependence		
Between	1.11 (0.75, 1.65)	1.15 (0.77, 1.71)
Within	1.21 (0.18, 8.09)	1.23 (0.18, 8.46)
Ratio	0.92 (0.13, 6.71)	0.93 (0.12, 6.93)
Total	1.12 (0.77, 1.63)	1.15 (0.79, 1.69)

Adjusted models control for number of pregnancies and offspring sex.

Between indicates between-mother effects; within, within-mother effects; ratio, ratio of between-mother to within-mother effects; total, total effects; GEE, generalized estimating equation; OR, odds ratio; CI, confidence interval.