ORIGINAL ARTICLE

Familial Confounding of the Association Between Maternal Smoking During Pregnancy and Offspring Substance Use and Problems

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Context: Previous epidemiological, animal, and human cognitive neuroscience research suggests that maternal smoking during pregnancy (SDP) causes increased risk of substance use/problems in offspring.

Objective: To determine the extent to which the association between SDP and offspring substance use/problems depends on confounded familial background factors by using a quasi-experimental design.

Design: We used 2 separate samples from the United States and Sweden. The analyses prospectively predicted multiple indices of substance use and problems while controlling for statistical covariates and comparing differentially exposed siblings to minimize confounding.

Setting: Offspring of a representative sample of women in the United States (sample 1) and the total Swedish population born during the period from January 1, 1983, to December 31, 1995 (sample 2).

Patients or Other Participants: Adolescent offspring of the women in the National Longitudinal Survey of Youth 1979 (n=6904) and all offspring born in Sweden during the 13-year period (n=1 187 360).

Main Outcome Measures: Self-reported adolescent alcohol, cigarette, and marijuana use and early onset (before 14 years of age) of each substance (sample 1) and substance-related convictions and hospitalizations for an alcohol- or other drug-related problem (sample 2).

Results: The same pattern emerged for each index of substance use/problems across the 2 samples. At the population level, maternal SDP predicted every measure of offspring substance use/problems in both samples, ranging from adolescent alcohol use (hazard ratio [HR]$_{moderate}$, 1.32 [95% CI, 1.22-1.43]; HR$_{high}$, 1.33 [1.17-1.53]) to a narcotics-related conviction (HR$_{moderate}$, 2.23 [2.14-2.31]; HR$_{high}$, 2.97 [2.86-3.09]). When comparing differentially exposed siblings to minimize genetic and environmental confounds, however, the association between SDP and each measure of substance use/problems was minimal and not statistically significant.

Conclusions: The association between maternal SDP and offspring substance use/problems is likely due to familial background factors, not a causal influence, because siblings have similar rates of substance use and problems regardless of their specific exposure to SDP.

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MATERNAL SMOKING DURING pregnancy (SDP) is associated with pregnancy-related problems and poor offspring functioning across a number of domains,[1-3] including increased risk for substance use and substance problems during adolescence and adulthood.[4] For instance, maternal SDP predicts greater use of cigarettes, alcohol, marijuana, and other illicit substances among the offspring during adolescence and early adulthood.[5-9] Offspring exposed to maternal SDP also are more likely to have substance problems.[7,10-15] Most epidemiological research has found robust statistical associations between SDP and substance use/problems in offspring when controlling for measured covariates,[4] which is consistent with a causal inference, although some studies suggest that these associations are accounted for by correlated risks.[12,13]

Animal studies and human cognitive neuroscience research have documented plausible neural pathways through which exposure to maternal SDP could cause offspring substance use/problems.[16,17] First, the hypothalamic-pituitary-adrenal axis, which has been implicated in drug-seeking behavior,[18] may be altered prenatally by SDP exposure through nicotine binding to acetylcholine receptors.[2] Second, the mesolimbic system, where drugs exert their reinforcing effects, has been implicated in animal models of prenatal drug exposure.[4,19] Third, the orbitofrontal cortex is involved in decision making and re-

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sponsiveness to drug-related stimuli,[20] and exposure to SDP has been correlated with decreased volume in this structure in adolescent humans.[8]

Numerous studies, however, indicate that maternal SDP frequently co-occurs with other environmental and genetic risks for offspring substance use and problems.[2,3] To provide strong tests of the causal inference, research designs that can rule out plausible alternative explanations are necessary.[21-23] Recent quasi-experimental studies (ie, studies using design features to exclude plausible alternative mechanisms) suggest that the association between maternal SDP and characteristics related to substance use and problems, such as child conduct problems,[24-26] attention-deficit/hyperactivity disorder,[27,28] lower intellectual abilities and academic achievement,[29-31] and adolescent and young-adult criminality,[32,33] are due to confounded background familial factors, not a causal influence of SDP.

Although these studies suggest that the association between maternal SDP and offspring substance use and problems may be confounded, considerable disagreement remains regarding the findings from previous quasi-experimental research. In particular, several researchers have suggested that the limitations of the quasi-experimental studies greatly hinder the generalizability of the results and that the existing quasi-experimental research does not negate "the numerous studies that have shown long-term adverse effects of prenatal nicotine exposure."[34(p1094)] Furthermore, to our knowledge, no published quasi-experimental studies have specifically predicted offspring substance use/problems from maternal SDP.

We tested the hypothesis that maternal SDP has a causal effect on numerous indices of subsequent offspring adolescent substance use/problems. To explicitly address concerns about the generalizability of the findings from previous sibling-comparison studies, the present study included prevalent behaviors, such as use of alcohol, tobacco, and marijuana during adolescence, and less common indices of substance problems, including early onset of use,[35-38] narcotics-related convictions, and hospitalization for substance-related problems. We used the following 2 methods to test for confounding factors: (1) controlling for measured covariates that were correlated with maternal SDP and (2) comparison of siblings within nuclear families who were differentially exposed to maternal SDP, a design that rules out some confounding factors, such as environmental and genetic factors that make siblings similar.[39,40] Data were drawn from 2 different studies and countries, which provided the opportunity to find converging evidence.

METHODS

US STUDY

Sample

The National Longitudinal Survey of Youth 1979 (NLSY79) was funded by the Bureau of Labor Statistics to study characteristics of individuals in the US workforce. A nationally representative household sample of 6111 male and female adolescents and young adults (aged 14-22 years) who were not in the military was selected for the NLSY79, using a complex survey design.[41] An additional 3652 African American and Hispanic youths were selected for the NLSY79 mother-generation sample to oversample from these ethnicity groups. The response rate for the initial NLSY79 assessment was approximately 90% of the eligible sample. Participants were interviewed annually from 1979 through 1994 and have been interviewed biennially since 1995. Retention rates for the NLSY79 during follow-up assessments were 90% or more during the first 16 waves and more than 80% in subsequent waves. To date, 4926 NLSY79 female subjects (1472 African American, 977 Hispanic, and 2477 non-Hispanic white and other ethnicities) have given birth. The sample included in the analyses consisted of 3168 mothers with 1 or more offspring at least 14 years of age.

Biennial assessments of the biological children of women in the NLSY79, referred to as the CNLSY study, began in 1986.[42] In 1986, at least 95% of the offspring of NLSY79 mothers underwent assessment with an average retention rate of approximately 90% in assessments occurring through 2008. In each wave, self-report questionnaires were administered to older children and adolescents based on the age of the offspring. Adolescents and young adults (aged 14-30 years) completed the Young-Adult Computer Assisted Personal Interview on academic, social, and emotional development during adolescence and the transition into adulthood. As of the 2008 wave of assessment, 11 506 offspring have been born to women in the NLSY79. We sequentially excluded offspring from the data set who were missing a maternal identification number (n=11) or an assessment of maternal SDP (n=1244), mostly because of an incorrect skip pattern in the assessment procedure in 1 wave,[24] or who were younger than 14 years (n=3347), resulting in a sample of 6904 offspring. Mean (SD) age of the offspring was 22.1 (4.9) years at the latest assessment (2008).

The NLSY79 provides sample weights, indicating the inverse of the probability of each participant being selected into the sample based on the clustered, unequal selection probability design. We applied these weights, which apply equally to all offspring of a given mother, to all analyses to better approximate population-based estimates. More details about the sample and measurement are available elsewhere.[43,44]

Risk Factors

In the first assessment wave of the CNLSY study after the birth of a child, mothers reported their SDP frequency on a 4-point ordinal scale of none, less than 1 pack/d, 1 to 2 packs/d, and more than 2 packs/d. Less than 1 pack/d was considered moderate use (1387 [20.1%]) and the highest 2 categories were combined to indicate high use (520 [7.5%]).

Demographic characteristics of the CNLSY sample are presented in **Table 1**. For each measure, individuals at higher risk or with missing values were compared with individuals at low risk using ordinal or binary scales. We used offspring sex and birth order, maternal age at childbearing, and maternal alcohol consumption during pregnancy[45] as measured offspring-specific covariates.

The study also included measured traits of the mothers and the families. Maternal adolescent antisocial behavior was based on maternal self-reports.[45] An index of low maternal intellectual abilities was based on a composite derived from the Armed Services Vocational Aptitude Battery given in 1980. Maternal education was based on the highest completed grade. Total family income was based on assessments when the mothers were 30 years of age. The mothers also completed a detailed assessment of lifetime history of alcohol problems in 1994. If a woman ever reported binge drinking or any history of alcohol abuse or dependence problems (from a 25-item

Table 1. Demographic Characteristics of Offspring and Families in the US NLSY79 Data Set

Variable	No. (%) of Subjects[a]
Offspring-specific covariates[b]	
Female sex[c]	3356 (48.6)
Birth order	
First[c]	3164 (45.8)
Second	2221 (32.2)
Third	1015 (14.7)
Fourth or higher	504 (7.3)
Maternal teenage childbearing	
No[c]	3856 (55.9)
Yes	2926 (42.4)
Missing	122 (1.8)
Frequency of maternal alcohol consumption during pregnancy	
Never[c]	4777 (69.2)
<1 time/mo	1015 (14.7)
1 time/mo	503 (7.3)
3-4 d/mo	277 (4.0)
1-2 d/wk	250 (3.6)
3-4 d/wk	43 (0.6)
Nearly every day or more	28 (0.4)
Missing	11 (0.2)
Maternal/familial covariates[d]	
Maternal adolescent antisocial behavior	
Low[c]	752 (23.7)
Medium low	714 (22.5)
Medium high	745 (23.5)
High	803 (25.3)
Missing	154 (4.9)
Maternal intellectual abilities	
Low	642 (20.3)
Medium low	775 (24.5)
Medium high	783 (24.7)
High[c]	842 (26.6)
Missing	126 (4.0)
Maternal educational attainment, y	
≤12[c]	1165 (36.8)
13-15	1000 (31.6)
≥16	1003 (31.7)
Family income	
Low	672 (21.2)
Medium low	697 (22.0)
Medium high	754 (23.8)
High[c]	793 (25.0)
Missing	252 (8.0)
Lifetime history of binge drinking	
No[c]	2655 (83.8)
Yes	513 (16.2)
Lifetime history of alcohol abuse/dependence problems	
No[c]	2564 (80.9)
Yes	502 (15.8)
Missing	102 (3.2)
Maternal adolescent substance use	
No[c]	2448 (77.3)
Yes	662 (20.9)
Missing	58 (1.8)
Family race/ethnicity	
White[c]	1536 (48.5)
African American	1005 (31.7)
Hispanic	627 (19.8)

Abbreviation: NLSY79, National Longitudinal Survey of Youth 1979.
[a] Percentages have been rounded and may not total 100.
[b] Based on 6904 offspring.
[c] Used as the reference group in the analyses.
[d] Based on 3168 unique mothers.

assessment), we considered her to be at higher risk of alcohol problems. The mothers also reported their use of any illicit substances during adolescence. The women's race/ethnicity was divided into the following 3 categories: white, African American, and Hispanic.

Offspring Outcomes

At each childhood assessment wave (ages 10-13 years), participants were asked, "Have you ever drunk alcohol, other than just a sip or two? (Do not include childhood sips that you might have had from an older person's drink.)" Participants responding yes were asked to report how old they were the first time they had "a glass of beer or wine or a drink of liquor, such as whiskey, gin, scotch, etc." At each young adult assessment wave (ages 14-30 years), participants were asked if they ever drank alcohol in the past 12 months and their age at their first alcoholic drink. If participants reported varying ages at their first drink across assessment waves, an average reported age at the first drink was calculated. Reported age at the first drink younger than 7 years was also coded as missing owing to low prevalence rates and concerns about reporting accuracy. Because the present analyses focused on adolescent alcohol use, we created an indicator of drinking before age 20 years. For offspring younger than 20 years, time-to-event information was based on their last age at assessment. Owing to missing values (233 [3.4%]), analyses were run with 6671 offspring. Kaplan-Meier estimates indicated that 87% of offspring used alcohol during adolescence. Because previous studies have shown that early onset of alcohol use (ie, before 14 years of age) is a strong predictor of subsequent alcohol problems,[35,36] we identified offspring who reported being younger than 14 years at their first drink (1470 [22.0%]) to index problematic use.

At each childhood and young adult assessment wave, participants were asked to report whether they had ever smoked a cigarette or used marijuana. Participants responding yes to each item were subsequently asked to report their age at their first use. We followed the same pattern as with the alcohol variables to create measures of cigarette and marijuana use. Kaplan-Meier estimates indicated that 58% tried cigarettes during adolescence (from a sample of 6620 offspring with valid information), and 22.7% had early cigarette use (n = 1501).[37] Kaplan-Meier estimates indicated that 53% had used marijuana during adolescence (from a sample of 6708 offspring), and 10.2% reported first marijuana use before age 14 years (n = 685).[38] The reported ages at onset for each substance use were quite reliable (correlations ranged from 0.89 to 0.97 based on multiple reports), and the estimates of drug use in the CNLSY are very consistent with the findings of recent epidemiological studies in the United States.[46] More details about the assessment are available elsewhere.[24]

SWEDISH STUDY

Sample

The analyses were based on all offspring born in Sweden from 1983 to 1995. All data were obtained by merging information available from the following 7 government-maintained population registers: (1) the Swedish Medical Birth Registry, kept by the National Board of Health and Welfare, included data on more than 99% of pregnancies in Sweden from 1973 onward[47,48]; (2) the Multi-generation Register, held by Statistics Sweden, contained information about biological and adoptive relationships for individuals living in Sweden since 1933[49]; (3) the National Crime Register, held by the National Council for Crime Prevention, included detailed information about all criminal convictions since 1973 for those 15 years or older[50]; (4) the Inpatient

Registry, held by the National Board of Health and Welfare, provided data on all hospital admissions for psychiatric disorders in Sweden since 1973[51]; (5) the Education Register, held by Statistics Sweden, contained information on highest level of completed formal education[52]; (6) the Cause of Death Register, held by the National Board of Health and Welfare, provided data on principal and contributing causes of death since 1958; and (7) the Migration Register, held by Statistics Sweden, supplied data on dates for migration into or out of Sweden.

From 1983 to 1995, data for 1 411 134 children were included in the Medical Birth Registry. Children who had serious malformations at birth (n = 57 555), were stillborn before or during delivery (n = 4669), were from multiple births (n = 30 967), died before 15 years of age (n = 4956), or emigrated from the country before age 15 years (n = 47 004) were sequentially dropped because they were not eligible for inclusion. Of the remaining 1 265 983 offspring, those who were missing data on SDP (n = 78 503), offspring sex (n = 36), or the identification number of their mother (n = 84) were sequentially excluded from the analyses. The resulting sample of 1 187 360 offspring represents 93.8% of the targeted population. The final sample includes offspring born to 743 673 different mothers; the siblings in our analyses share the same mother. More details about the sample and measurement are available elsewhere.[30,32]

Risk Factors

Maternal SDP was based on self-report of daily tobacco use at the first antenatal visit, which typically occurred during the first trimester, using the following responses: no smoking, 1 to 9 cigarettes/d (moderate SDP; 186 342 [15.7%]), or 10 or more cigarettes/d (high SDP; 114 351 [9.6%]). Previous studies indicate that the validity of this measure is high.[53] We converted SDP into 2 dummy codes to compare moderate and high levels of SDP with no smoking.

Demographic characteristics of the Swedish sample are presented in **Table 2**. Sex, birth parity, maternal and paternal ages at childbearing, and maternal cohabitation with the father at childbirth were offspring-specific risk factors included in the analyses. Low maternal and paternal levels of education (indexed by ≤1-2 years of upper secondary education), history of any criminal conviction, and history of ever being hospitalized for a substance-related problem were included as familial risk factors. We created dummy codes to compare high-risk groups and those with missing values (if present) with the low-risk groups.

Offspring Outcomes

The following 2 types of offspring substance-related criminality were modeled in the current study: (1) crimes committed by driving a motor vehicle under the influence of alcohol or another substance (driving under the influence), as defined by the Swedish Penal Code, and (2) narcotic drug offenses as defined by the Narcotic Drugs Criminal Act, which includes possession for personal use, supply, and manufacture. The time-to-event for these outcomes is based on the date of the first criminal act leading to a criminal conviction. In the present sample, 11 231 of the offspring had a driving-related criminal conviction and 16 790 had a drug-related conviction. Kaplan-Meier estimates indicated that by 25 years of age, 2% of the sample had at least 1 driving-related conviction and 3% had at least 1 narcotic drug offense.

We also used hospitalization for alcohol and drug problems to indicate substance-related problems. All substance-related hospitalizations in the current study were derived from inpatient records. We restricted our focus to events for which the primary diagnosis involved psychoactive substance use as defined by diagnostic codes from *International Classification of Diseases, Eighth Revision* (*ICD-8*), *ICD-9*, and *ICD-10*. The 3 categories of offspring substance-related outcomes modeled were (1) any primary or secondary diagnosis of alcohol-related hospitalization or any other nonnicotine substance misuse–related hospitalization; (2) only primary alcohol-related diagnosis (*ICD-8* and *ICD-9* code 303, *ICD-9* code 305A, and *ICD-10* code F10), (3) only primary drug-related diagnosis (excluding nicotine dependence; *ICD-8* and *ICD-9* code 304, *ICD-9* code 305X, and *ICD-10* codes F11-F16 and F18-F19). Estimated time-to-event and indicator were set to missing if the hospitaliza-

Table 2. Demographic Characteristics of Offspring and Families in the Swedish Data Set

Variable	No. (%) of Subjects[a]
Offspring-specific covariates[b]	
Female sex	578 721 (48.7)
Birth order	
First[c]	485 857 (40.9)
Second	427 318 (36.0)
Third	193 692 (16.3)
Fourth or more	80 493 (6.8)
Maternal age at childbirth, y	
<20	33 085 (2.8)
20 to <25	267 409 (22.5)
25 to <30[c]	445 367 (37.5)
30 to <35	302 946 (25.5)
≥35	138 553 (11.7)
Paternal age at childbirth, y	
<20	7843 (0.7)
20 to <25	135 851 (11.4)
25 to <30[c]	375 561 (31.6)
30 to <35	362 932 (30.6)
≥35	299 351 (25.2)
Missing	5822 (0.5)
Cohabitating at time of childbirth	
Yes[c]	1 073 686 (90.4)
No	59 781 (5.0)
Missing	53 893 (4.5)
Maternal covariates[d]	
Low educational level	
≤1 to 2 y of upper secondary education	88 034 (11.8)
>1 to 2 y of upper secondary education[c]	654 398 (88.0)
Missing	1241 (0.2)
Criminal conviction	
Any lifetime conviction	94 734 (12.7)
No history of conviction[c]	648 939 (87.3)
Substance-related hospitalization	
Any lifetime hospitalization	16 170 (2.2)
No history of hospitalization[c]	727 503 (97.8)
Paternal covariates[d]	
Low educational level	
≤1 to 2 y of upper secondary education	143 687 (19.3)
>1 to 2 y of upper secondary education[c]	591 499 (79.5)
Missing	8487 (1.1)
Criminal conviction	
Any lifetime conviction	318 624 (42.8)
No history of conviction[c]	420 086 (56.5)
Missing	4963 (0.7)
Substance-related hospitalization	
Any lifetime hospitalization	32 251 (4.3)
No history of hospitalization[c]	706 459 (95.0)
Missing	4963 (0.7)

[a] Percentages have been rounded and may not total 100.
[b] Based on 1 187 360 offspring.
[c] Used as the reference group in the analyses.
[d] Based on 743 673 unique mothers and traits of fathers of the first child of those women.

tion and diagnosis occurred before 12 years of age. In the present sample, we found 22 092 hospitalizations for alcohol or other drug problems (for which the *ICD* codes could be the primary or a secondary diagnosis), 14 850 hospitalizations for which alcohol was the primary diagnosis, and 5560 hospitalizations for which other drugs were the primary diagnosis. Kaplan-Meier estimates indicated that 3% had any substance-related hospitalization (primary or secondary), 2% had an alcohol-related (primary) hospitalization, and 1% had another drug-related (primary) hospitalization by 25 years of age.

Convictions for driving under the influence (odds ratio [OR], 9.95 [95% CI, 9.44-10.49]) and narcotic drug offenses (19.81 [19.07-20.58]) were highly associated with hospitalization for a problem with alcohol or another drug.

STATISTICAL ANALYSES

Three models were fit to each measure of substance use/problems in the NLSY79 and Swedish samples. We used 2 analytical models. First, we used Cox proportional hazards survival analysis models for all outcomes in which the outcome was right-censored (ie, not all of the offspring had lived through the risk period). For example, some of the offspring in the CNLSY study had not reached 20 years of age. Second, logistic regression models were used when the outcome was a dichotomous measure. All analyses used robust standard errors to account for the nested nature of the data (ie, cousins and siblings were nested within extended families).

For each outcome, model 1 (of 3) regressed substance use/problems on maternal SDP, offspring sex, and offspring birth order. This model provided an estimate of the increased risk associated with moderate and high SDP (compared with no SDP) in the entire population. Model 2 included all the offspring-specific and familial covariates in the model. This model provided the independent association between moderate and high SDP and offspring substance use/problems while statistically controlling for the measured covariates. Model 3, in contrast, introduced a fixed intercept term at the maternal level, thereby estimating the increased risk associated with moderate and high SDP while comparing differentially exposed siblings. These models effectively control for all factors that are shared by siblings, whether those factors are observed or not,[54] automatically accounting for all genetic and environmental factors that make siblings similar.[39,40] The CNLSY included 1364 differentially exposed offspring (those experiencing more or less SDP than their siblings) among 462 women. The Swedish study had 141 408 differentially exposed siblings from 60 056 women.

We also conducted a number of sensitivity analyses to examine whether the use of the sibling-comparison design with the 2 data sets resulted in findings consistent with previous quasi-experimental analyses that found an independent association between maternal SDP and offspring low birth weight (<2500 g).[1,3,24,26,55] We fit the 3 models predicting low birth weight in the United States (1318 in the entire sample of 10 251 offspring [12.9%] born to women in the NLSY79 sample) and the Swedish sample (39 827 in the entire sample of 1 187 360 offspring [3.4%]) while controlling for gestational age.

The institutional review board at Indiana University approved both studies.

RESULTS

US STUDY

Results of the 3 analytical models regarding effects of SDP on each outcome measure of substance use/problems are presented in **Table 3**. The corresponding hazard ratios (HRs) and ORs (with 95% CIs) for the US study are shown in **Figure 1**.

In model 1, moderate (HR, 1.32) and high maternal SDP (1.33) were associated with approximately a 30% increased odds of alcohol use during adolescence. In model 2, when measured covariates were included in the model, the estimates were somewhat attenuated, but moderate (HR, 1.20) and high maternal SDP (1.17) were still associated with approximately 20% increased risk. In model 3, in which differentially exposed siblings were compared, however, moderate (HR, 1.05) and high maternal SDP (1.16) did not predict adolescent alcohol use because the magnitude of the associations was greatly attenuated compared with the unadjusted associations, and the associations were not statistically significant. Similarly, for early alcohol use among offspring, maternal SDP ($OR_{moderate}$, 1.27; OR_{high}, 1.57) was a moderate predictor in model 1. The inclusion of measured covariates in model 2 slightly reduced the magnitude of the associations ($OR_{moderate}$, 1.10; OR_{high}, 1.30), but maternal SDP was not associated with early alcohol use in the fixed-effects model (model 3: $OR_{moderate}$, 0.84; OR_{high}, 1.02).

The same pattern of results emerged when predicting offspring cigarette use and early cigarette use. Finally, the results for models predicting adolescent marijuana use paralleled those for alcohol and cigarette use. Maternal SDP was strongly associated with offspring substance use/problems in model 1 and the association was attenuated in model 2, but maternal SDP did not predict early substance use/problems measures in model 3.

SWEDISH STUDY

The corresponding HRs and ORs (with 95% CIs) for the Swedish study are shown in **Figure 2**. Maternal SDP was strongly associated with substance-related driving convictions in Sweden (model 1 $HR_{moderate}$, 2.07; HR_{high}, 2.66). In model 2 (which included statistical covariates), maternal SDP remained a robust predictor ($HR_{moderate}$, 1.46; HR_{high}, 1.65), although the magnitude of the association was reduced. In model 3 (the fixed-effects model), in contrast, the associations were completely attenuated ($HR_{moderate}$, 0.97; HR_{high}, 1.12) and not statistically significant. The same pattern occurred when predicting a narcotics-related conviction.

The same pattern of associations was evident also for all the substance-related hospitalizations, which included all primary and secondary diagnoses of alcohol or other drug problems (excluding nicotine dependence), only primary alcohol problems, and only primary other drug problems (Table 3 and Figure 2).

SENSITIVITY ANALYSES

To examine the statistical power and other limitations (eg, measurement bias in SDP) of the sibling comparison approach (model 3), we applied the 3 analytical models to the prediction of low birth weight in both samples. In the US sample, moderate SDP (OR, 1.22 [95% CI, 1.01-1.47]) and high SDP (1.42 [1.09-1.84]) predicted low birth weight in model 1. In model 2, SDP still predicted low

Table 3. Parameter Estimates Quantifying the Effects of Maternal SDP on Offspring Substance Use/Problems in the US and Swedish Samples[a]

	β Value (SE)		
	Model 1	Model 2	Model 3
US Study			
Adolescent alcohol use[b]			
Moderate SDP	0.28 (0.04)[c]	0.19 (0.05)[c]	0.05 (0.10)
High SDP	0.29 (0.07)[c]	0.16 (0.07)[c]	0.15 (0.14)
Early alcohol use[d]			
Moderate SDP	0.24 (0.10)[c]	0.10 (0.10)	–0.17 (0.17)
High SDP	0.45 (0.12)[c]	0.27 (0.13)[c]	0.02 (0.25)
Adolescent cigarette use[b]			
Moderate SDP	0.43 (0.05)[c]	0.23 (0.06)[c]	0.14 (0.10)
High SDP	0.66 (0.07)[c]	0.39 (0.07)[c]	0.15 (0.15)
Early cigarette use[d]			
Moderate SDP	0.68 (0.09)[c]	0.45 (0.10)[c]	0.28 (0.17)
High SDP	1.03 (0.12)[c]	0.66 (0.12)[c]	0.07 (0.24)
Adolescent marijuana use[b]			
Moderate SDP	0.43 (0.06)[c]	0.23 (0.06)[c]	0.03 (0.11)
High SDP	0.52 (0.09)[c]	0.24 (0.09)[c]	–0.05 (0.16)
Early marijuana use[d]			
Moderate SDP	0.37 (0.13)[c]	0.18 (0.14)	–0.13 (0.22)
High SDP	0.71 (0.17)[c]	0.43 (0.18)[c]	–0.44 (0.33)
Swedish Study			
Substance-related driving conviction[b]			
Moderate SDP	0.73 (0.02)[c]	0.38 (0.02)[c]	–0.03 (0.10)
High SDP	0.98 (0.02)[c]	0.50 (0.03)[c]	0.11 (0.12)
Narcotics conviction[b]			
Moderate SDP	0.80 (0.02)[c]	0.43 (0.02)[c]	–0.05 (0.08)
High SDP	1.09 (0.02)[c]	0.55 (0.02)[c]	0.01 (0.09)
Substance-related hospitalization (primary or secondary diagnosis)[b]			
Moderate SDP	0.60 (0.02)[c]	0.35 (0.02)[c]	0.06 (0.06)
High SDP	0.82 (0.02)[c]	0.43 (0.02)[c]	0.02 (0.07)
Alcohol-related hospitalization (primary diagnosis)[b]			
Moderate SDP	0.54 (0.02)[c]	0.32 (0.02)[c]	0.12 (0.07)
High SDP	0.73 (0.02)[c]	0.40 (0.03)[c]	0.04 (0.08)
Other drug-related hospitalization (primary diagnosis)[b]			
Moderate SDP	0.82 (0.03)[c]	0.42 (0.04)[c]	0.02 (0.12)
High SDP	1.15 (0.03)[c]	0.56 (0.04)[c]	0.08 (0.14)

Abbreviation: SDP, smoking during pregnancy.

[a] Parameter estimates are log odds ratios or log hazard ratios. Hazard ratios and odds ratios (with their 95% CIs) for these parameters are presented in Figures 1 and 2. Complete results of the model fitting, including the estimates of the covariate effects, are available from the corresponding author upon request.

[b] Based on Cox proportional hazard survival models.

[c] $P < .05$.

[d] Based on logistic regression models.

birth weight ($OR_{moderate}$, 1.20 [95% CI, 1.00-1.44]; OR_{high}, 1.52 [1.17-1.97]). Finally, in the sibling comparisons (model 3), both ORs indicated higher risk of low birth weight, although the 95% CIs for moderate SDP included 1.00 ($OR_{moderate}$, 1.19 [95% CI, 0.75-1.91]; OR_{high}, 1.86 [1.01-3.41]). In the Swedish sample, in model 1, moderate SDP (OR, 1.71 [95% CI, 1.65-1.76]) and high SDP (OR, 2.09 [2.02-2.17]) predicted low birth weight. The associations persisted in model 2 ($OR_{moderate}$, 1.67 [95% CI, 1.62-1.73]; OR_{high}, 1.99 [1.91-2.07]). In model 3, SDP still predicted low birth weight ($OR_{moderate}$, 1.46 [95% CI, 1.26-1.69]; OR_{high}, 1.47 [1.24-1.74]).

COMMENT

We found converging evidence across samples and measures. Consistent with previous research, offspring exposed to maternal SDP were more likely to use and abuse substances during adolescence and young adulthood. The association between maternal SDP and offspring substance use was generally robust to the use of measured statistical covariates, also consistent with most previous research.[4] However, siblings within the same nuclear family who were differentially exposed to maternal SDP did not differ in their risk of substance use or abuse. As such, these results strongly suggest that familial confounds account for the increased risk of substance use/abuse among offspring exposed to maternal SDP. It is not possible to accept the null hypothesis regarding SDP, of course, but the present results are not consistent with a causal effect of SDP on offspring substance use outcomes.

These conclusions are strengthened by the internal and external validity of the present findings.[21] First, the study used a powerful design, the comparison of differentially

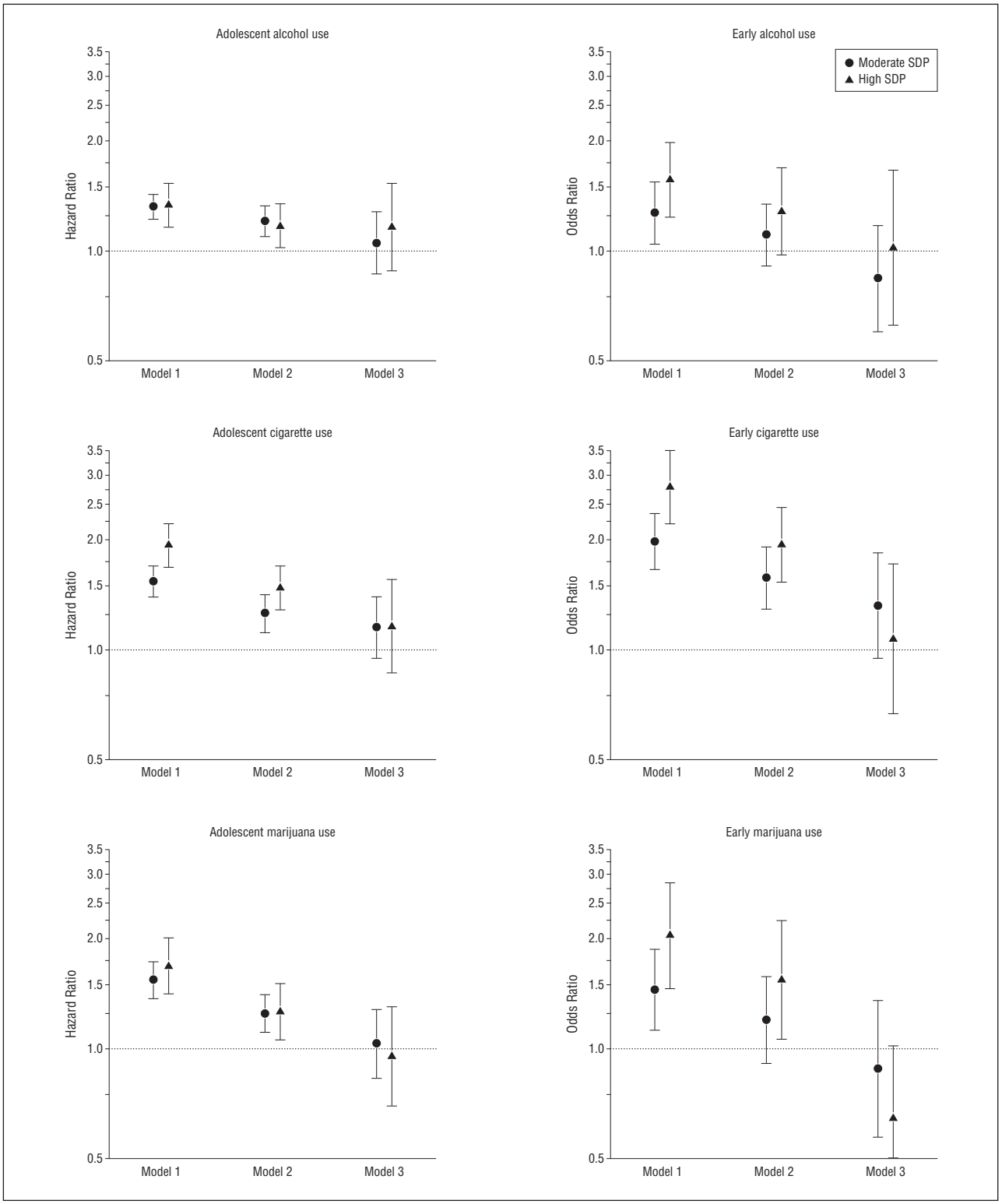

Figure 1. Hazard and odds ratio estimates for the association between maternal smoking during pregnancy (SDP) and offspring substance use/problems in the US sample. Whiskers represent 95% CIs. Point estimates for moderate and high SDP are compared with no SDP. Model 1 presents the unadjusted associations in the entire sample. Model 2 presents the associations in the sample controlling for statistical covariates. Model 3 presents the estimated associations fitting fixed-effects models at the maternal level, which compared differentially exposed siblings. The estimated hazard ratios for adolescent use of alcohol, cigarettes, and marijuana were based on Cox proportional hazard survival models with a sandwich estimator to account for familial clustering. The estimated odds ratios for early use of alcohol, cigarettes, and marijuana were based on logistic regression models with a sandwich estimator to account for familial clustering.

exposed siblings,[39,40] to control for unmeasured confounds that could account for the association between maternal SDP and offspring substance use/problems rather than solely relying on the use of measured covariates. Second, the results are based on multiple data sets, including a study of offspring of a representative sample of

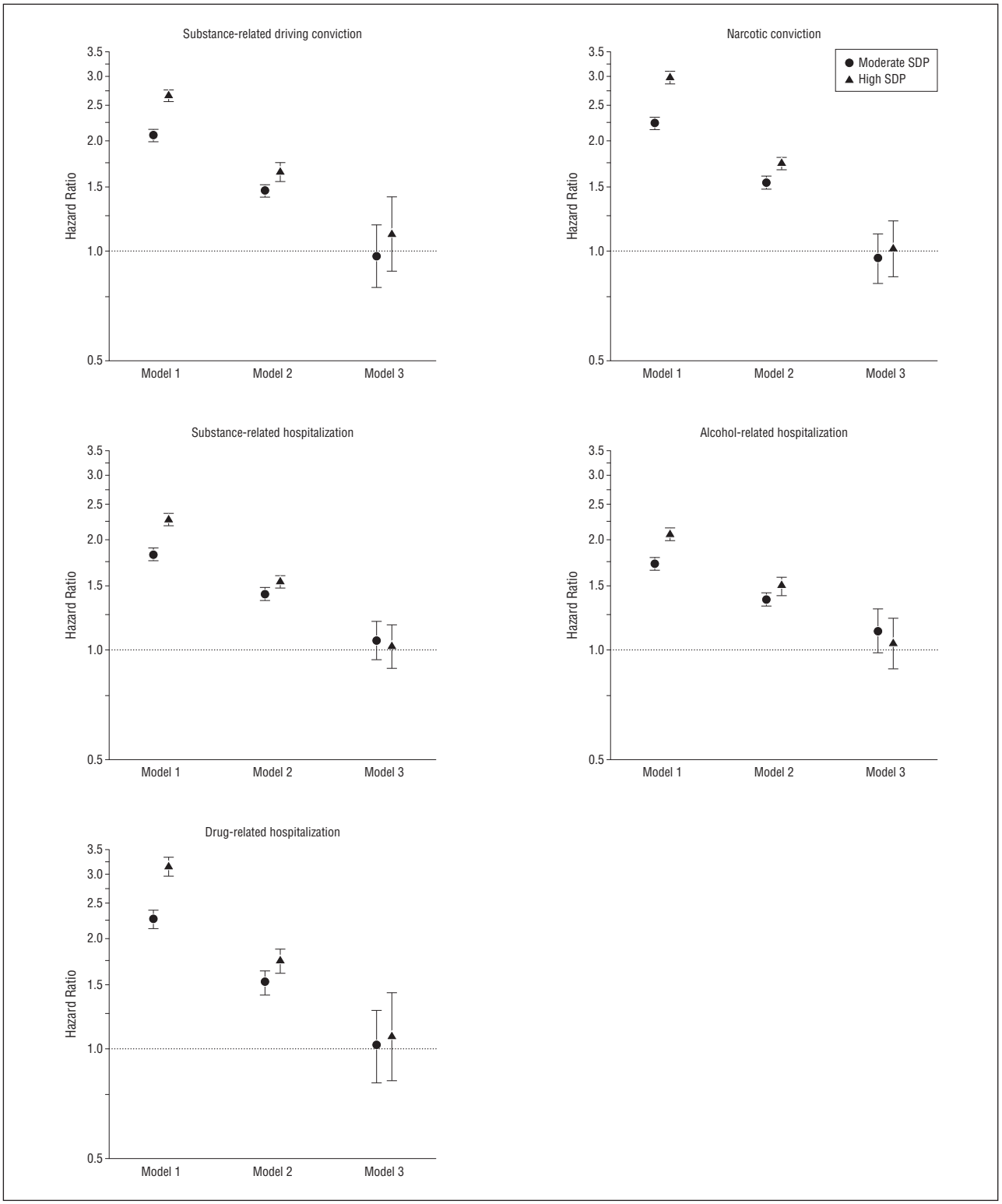

Figure 2. Hazard ratios for the association between maternal smoking during pregnancy (SDP) and offspring substance use/problems in the Swedish sample. Whiskers represent 95% CIs. Point estimates for moderate and high levels of SDP are compared with no SDP. Model 1 presents the unadjusted associations in the entire sample. Model 2 presents the associations in the sample controlling for statistical covariates. Model 3 presents the estimated associations fitting fixed-effects models at the maternal level, which compared differentially exposed siblings. All estimated hazard ratios are based on Cox proportional hazard survival models, which used a sandwich estimator to account for familial clustering.

women in the United States and a population-based study of all offspring born in Sweden during a 13-year period. These results, therefore, do not depend on using one particular sampling strategy and do not apply only to a sample with restricted demographic, racial, or ethnic characteristics. Third, the study addressed concerns regarding the generalizability of previous quasi-experimental research on maternal SDP[34] by using multiple indices of

substance use and problems. We used measures of substance use that (1) were quite common, such as adolescent alcohol, cigarette, and marijuana use; (2) indicated risk for substance-related problems (ie, early onset of use[35-38]); and (3) documented serious substance problems, including substance-related convictions and hospitalizations. Different methods (eg, self-ratings, register of criminal convictions, and clinical diagnoses) were also used to assess substance use/problems across the 2 samples. It is quite remarkable that the same pattern of results was found for each measure across the 2 samples.

A number of limitations should also be considered. Although we were able to replicate the same findings across measures and samples, the same outcomes were not measured in both samples. For instance, we do not have information on adolescent substance use or age at onset in the Swedish sample. The CNLSY study includes measures of alcohol and marijuana impairment for individuals meeting strict gateway criteria. However, the prevalence of each was too small to predict, and the assessments did not include usable information about age at onset of such problems. Furthermore, the present analyses of the CNLSY sample also were based on a subset of the offspring because not all offspring had reached adolescence. The present study used sample weights to address concerns about the generalizability of the results from the subset, and prevalence rates from this study are comparable to recent epidemiological studies in the United States.[46] In addition, a number of assumptions and limitations occur in the sibling-comparison design.[39,40] The statistical power to detect small effects is limited in the sibling-comparison designs, as with all fixed-effects models,[54] because the estimates rely on the subset of women who varied their smoking across pregnancies. As a result, the 95% CIs are relatively large around the estimates from the sibling-comparison models in the US sample, although the large Swedish sample allowed for more precise estimates. Family-based quasi-experimental studies also are sensitive to problems with poor measurement reliability in the predictor variable,[56] but previous research has shown that self-reported maternal SDP is reliable[57] and valid (eg, compared with serum cotinine levels).[58] Research in Sweden[59] and the United States[60] also suggests that the validity of self-reported SDP has not changed over time. Nevertheless, the study suggests that limitations of the present studies (eg, the limitations of self-reported SDP) and the assumptions in the sibling-comparison design may not lead to overly conservative estimates of maternal SDP because we replicated the well-established finding of a robust, independent association between maternal SDP and low birth weight in their offspring[1,3,24,26,55] in both samples.

Future studies also should explore the timing of maternal SDP across pregnancies[33] and test the generalizability of findings from women who vary their smoking over time.[32] Additional research must also seek to specify the exact familial confounds that increase risk for offspring substance use/problems because sibling comparison studies cannot identify those factors by themselves.[39,40] Additional quasi-experimental designs, such as the comparison of full and half siblings,[30] children of siblings and twins,[24,30,55,61] adopted individuals,[62] and offspring conceived through fertility treatments,[26] are necessary to answer such questions because the confounding factors make siblings within a nuclear family similar. The present studies had limited measures of confounding variables; for example, the CNLSY study did not include paternal characteristics, and neither study included measures of postnatal smoking exposure.[63] Future studies will need to include extensive measures of family functioning.

The present findings are consistent with a growing body of research on maternal SDP using quasi-experimental designs,[3] which strongly suggests that familial background factors are responsible for increased risk of childhood child conduct problems,[24-26] attention-deficit/hyperactivity disorder,[27,28] lower intellectual abilities and academic achievement,[29-31] suicidal behavior,[64] and adolescent and young adult criminality.[32,33] Certainly, the conclusions concerning substance use/problems drawn from the present study will need to be replicated in other studies, particularly other studies that (1) include precise measures of SDP, covarying environmental risks, and substance use/problems and (2) use design features to rule out plausible alternative processes.[21]

The recent quasi-experimental studies as a whole, nonetheless, have serious implications for several research areas and intervention efforts.[3,65] First, research needs to focus on the translation of findings regarding SDP from animal studies to human studies and vice versa, as is true in all areas of neuropsychiatric research.[66,67] Differences in pregnancies across species, such as factors influencing timing of gestation,[68] may limit the generalizability of animal studies of SDP. Second, researchers studying moderating factors, such as gene-environment interactions, must also be aware that maternal SDP may not be a causal environmental risk factor for offspring behavioral and substance use problems, which is necessary for correctly interpreting such studies.[69] Third, the results of our analyses predicting low birth weight and other quasi-experimental research on pregnancy and infancy-related problems[1,70] indicate that prevention and intervention efforts should continue to focus on reducing maternal SDP. The present results for offspring substance use/problems, in concert with other quasi-experimental studies,[3] however, suggest that solely reducing maternal SDP may not ameliorate offspring cognitive, social, behavioral, or drug problems. Rather, wraparound services[71] that address multiple familial risks associated with maternal SDP are necessary.

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