Prenatal Exposure Effects on Early Adolescent Substance Use: Preliminary Evidence From a Genetically Informed Bayesian Approach

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ABSTRACT. Objective: Given the controversy surrounding the question of whether there are direct or causal effects of exposure to maternal smoking during pregnancy (SDP) on offspring outcomes such as substance use during the adolescent years, we sought to test, on a preliminary basis, within- and between-family associations of SDP and initiation of substance use early in adolescence (by age 15 years) using a discordant sibling design. **Method:** We used a sibling-comparison approach in a sample of 173 families drawn from the state of Missouri, wherein mothers were discordant for smoking behaviors between two different pregnancies, to test for associations of SDP and initiation of substance use in a younger adolescent cohort. The discordant sibling-comparison approach allows for disentangling familial effects from

direct effects of SDP through the purposeful collection of data from siblings within the same family with differential exposure. **Results:** There were no between- or within-family effects of SDP on initiation of any type of substance use (alcohol, marijuana, smoking, and other drug classes), suggesting that SDP does not exert a direct effect on substance use in early adolescence. **Conclusions:** Preliminary findings did not support an association of SDP and initiation of substance use in this younger adolescent sample. Studies such as this one can help build a body of evidence to explain whether associations of SDP and adolescent outcomes reflect a direct effect of SPD or may instead be attributable to familial confounders that are controlled in the discordant sibling design. (*J. Stud. Alcohol Drugs*, 78, 789–794, 2017)

DESPITE CONSISTENT EVIDENCE suggesting that smoking during pregnancy (SDP) is deleterious to the fetus (Kuja-Halkola et al., 2014; Shah & Bracken, 2000), 12.3% of women in the United States report SDP (Tong et al., 2013). Exposure to SDP has been associated with later behavioral problems in offspring, including substance use, in both adolescence (Joya et al., 2014; Knopik et al., 2009) and adulthood (Ekblad et al., 2010; O’Callaghan et al., 2009). Although there is some evidence for a direct effect of SDP exposure on offspring substance use (Ernst et al., 2001; Shea & Steiner, 2008), other research suggests instead an indirect effect via correlated genetic and environmental factors, such as transmission of genetic risk and being raised in an environment including parental substance use outside of pregnancy (Knopik, 2009).

To explore whether the link between SDP and substance use is potentially causal or attributable to family-level confounds, a number of genetically informed study designs, such as twin studies and sibling case-crossover designs, have been leveraged. Notably, a study leveraging data from families in the United States and Sweden found that maternal SDP predicted offspring substance use in adolescence; however, when differentially exposed siblings were compared, the association was no longer significant (D’Onofrio et al., 2012). This pattern of results suggested that observed effects between SDP and offspring substance use/problems was driven by familial factors rather than SDP exposure per se (D’Onofrio et al., 2012).

Given the importance of early onset of substance use (by age 15 years) as an indicator of increased risk for the

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subsequent development of a range of use-related problems and substance use disorders (Bonomo et al., 2004; Hingson & Zha, 2009; Hingson et al., 2006) as well as the paucity of genetically informed studies in this domain, we sought to test and replicate these prior findings in early adolescent substance use using quasi-experimental family data.

Present study

We used a sibling case-crossover design to investigate the relationship between SDP and substance use initiation in young adolescents within a family study of sibling pairs who were discordant for SDP (i.e., mothers reported changing their smoking behaviors during subsequent pregnancies). Our goal was to provide a preliminary test of whether there are direct effects of SDP on substance initiation by age 15 years, a phenotypic indicator of substance use severity and later problem use. Based on prior work using similar designs to test the effects of SDP on externalizing outcomes, we hypothesized no evidence of direct effects of SDP on initiation of substance use in young adolescents.

Method

Participants and procedure

Data were from the Missouri Mothers and Their Children study (MO-MATCH) (Knopik et al., 2015). Families in which mothers changed smoking behavior between two pregnancies were identified using birth records (years 1998–2005) obtained from the Missouri Department of Health and Senior Services Bureau of Health Informatics. Of the more than 4,000 potential families flagged via birth records, 1,520 were screened, and informed consent and formal interviews were completed with 173 families in which the maternal report agreed with the birth record that the mother had changed her smoking behavior between two pregnancies. Further details and exclusion criteria are described elsewhere (Knopik et al., 2015). The study was approved by the Institutional Review Boards of Rhode Island Hospital, Washington University, and the State of Missouri Department of Health and Senior Services. Mothers completed a diagnostic interview about their pregnancies (including life events surrounding pregnancy) as well as about each child (including mental health and behavioral history), and children provided reports of their own substance use behaviors. Youth were 7–15 years old (Child 1 [older sibling] age: $M = 12.99$, $SD = 1.95$, 53% male; Child 2 [younger sibling] age: $M = 10.19$, $SD = 1.80$, 51% male). Parents were primarily White (96%, $n = 250$). See Table 1 and Knopik et al. (2015) for further sample details.

Measures

Smoking during pregnancy. Maternal reports of SDP were obtained using a modified version of the Missouri

Assessment of Genetics Interview for Children–Parent on Child (Todd et al., 2003). Any SDP was assessed on discrete indicators (0 = *no*, 1 = *yes*) of SDP across each pregnancy as a whole and specific to each trimester. Overall quantity smoked during pregnancy was assessed on an ordinal scale (0 = *no smoking during pregnancy*, 1 = *21 or fewer cigarettes*, 2 = *22–99 cigarettes*, 3 = *≥100 cigarettes*) and via mothers' estimates of the number of cigarettes smoked in each trimester (a continuous variable ranging from 0 to 98 cigarettes smoked across trimesters). From these data, we created a single SDP severity score for each child (Knopik et al., 2016a), as follows: 1 (*did not smoke during pregnancy*), 2 (*smoked during first trimester only, 1–10 cigarettes/day*), 3 (*smoked during first trimester only, 11–19 cigarettes/day*), 4 (*smoked during first trimester only, ≥20 cigarettes/day*), 5 (*smoked beyond first trimester, 1–10 cigarettes/day [maximum of all trimesters]*), 6 (*smoked beyond first trimester, 11–19 cigarettes/day [maximum of all trimesters]*), 7 (*smoked beyond first trimester, ≥20 cigarettes/day [maximum of all trimesters]*).

Adolescent substance use. The revised Drug Use Screening Inventory is a widely used self-report questionnaire designed to quantify the use of a range of substances, including alcohol, cigarettes, marijuana, and several classes of illegal and prescription drugs (Kirisci et al., 1994, 1995; Tarter & Kirisci, 2001; Tarter et al., 1992). To capture any substance use involvement and maximize power in this young sample, the current study used a phenotypic definition that involved offspring endorsement (yes/no) of experience with any substance. Although broad, substance use involvement by age 15 years is an established phenotypic marker for future problematic use (Bonomo et al., 2004; Hingson & Zha, 2009; Hingson et al., 2006). Thus, if familial or direct SDP effects are found, it would provide compelling evidence of an etiological pathway toward a future substance use disorder.

Covariates. Covariates were chosen to be consistent with other genetically informed studies of the SDP–adolescent substance use relationship and are detailed in a prior report (Knopik et al., 2015). Potentially confounding maternal and family characteristics were maternal report of marital status, maternal age, maternal education at birth of each child, child birth order, child sex, secondhand smoke exposure during pregnancy (by the father), qualification for food stamps (yes/no) at the time of delivery collected from the birth record, and maternal and paternal substance use outside of pregnancy. For maternal and paternal substance use, the number of lifetime substance use diagnoses was used to index the severity of substance use problems.

Statistical analysis

The sibling comparison approach consists of a series of hierarchical models to assess the within- and between-family association of SDP and substance use while accounting for

TABLE 1. Sample characteristics: Child- and family-level variables

Variable	Offspring 1 (<i>n</i> = 173)			Offspring 2 (<i>n</i> = 170)		
	Total <i>n</i>	<i>M</i> or % endorsed	(<i>SD</i>)	Total <i>n</i>	<i>M</i> or % endorsed	(<i>SD</i>)
Study variables						
SDP severity	173	3.95	(2.05)	169	2.04	(1.78)
Any substance use	164	26.8%	—	162	11.7%	—
Initiation						
Alcohol use		16.5%	—		4.9%	—
Tobacco use		7.9%	—		3.1%	—
Marijuana use		7.3%	—		1.2%	—
Other drug use		12.8%	—		4.3%	—
Individual-level covariates						
Maternal age at birth	162	26.48	(5.55)	164	29.20	(5.74)
Maternal education, years, at birth	162	13.28	(2.12)	164	13.48	(1.96)
Secondhand smoke exposure by fathers	171	1.84	(1.44)	161	1.15	(1.43)
Marital status, married, at birth	162	83.3%	—	164	81.7%	—
Food stamp usage at birth	154	9.7%	—	153	13.7%	—
Child sex, male	173	47.4%		170	48.8%	
Family-level covariates	Maternal		Paternal			
	<i>n</i>	%	<i>n</i>	%		
No. of substance use diagnoses						
0	35	21%	24	26%		
1	70	41%	37	39%		
2	46	27%	18	19%		
3	17	10%	15	16%		
4	1	1%	0	0%		
Family demographics	<i>n</i>	<i>M</i>	(<i>SD</i>)			
Maternal age	162	39.83	(5.62)			
Paternal age	80	44.04	(6.34)			
Child 1 age	173	12.99	(1.95)			
Child 2 age	170	10.190	(1.80)			

Notes: SDP = smoking during pregnancy. No. = number. (We focus on maternal report of SDP severity [a] because prior reports have suggested that maternal report of SDP [absence/presence and quantity/severity] has more predictive validity than do paternal and birth-record-reported SDP, [b] because the severity of SDP including SDP later in pregnancy imparts additional risk above and beyond the absence/presence of SDP, and [c] to be consistent with our prior work using this and other samples).

the non-independent nature of family data. Given our small, multilevel sample with nonnormal outcome, we used Bayesian estimation with a probit link to account for the binary nature of the substance use indicator. Bayesian estimation has been shown to correct the tendency for maximum likelihood methods to underestimate variance and covariance parameters in small samples and do a better job of modeling uncertainty in random coefficients estimates (Hamaker & Klugkist, 2011; Heck & Thomas, 2015; Hox et al., 2012; van de Schoot et al., 2015). Further, Markov chain Monte Carlo (MCMC) methods can be used to estimate models that are problematic or inefficient with maximum likelihood, such as two-level models with random slopes for observed categorical variables (Muthén & Asparouhov, 2012). As such, our approach was designed to maximize the ability to detect significant effects as well as to provide a preliminary source for which to draw informative priors for future Bayesian estimation studies. All analyses were conducted in Mplus Version 7 (Muthén & Muthén, 2015). Because of a lack of

previous research from which to draw informative priors, non-informative priors with means of zero and large variances were used for structural parameters. For the variance of the random intercept and slope parameters, an inverse gamma distribution was used for priors with shape and scale parameters equal to 0.001 (Asparouhov & Muthén, 2010). Two MCMC chains with 10,000 iterations and thinning every 300th iteration (to reduce autocorrelation) were used. Potential scale reduction values close to one were considered evidence of convergence (Gelman et al., 2004; Gelman & Rubin, 1992).

Two models were used to examine between- and within-family predictors of variation in substance use.

Model 1. Offspring-specific SDP was tested to determine whether children whose mothers smoked (or smoked more) during pregnancy compared with children whose mothers did not smoke (or smoked less) significantly influenced offspring substance use. This model examines SDP-offspring substance use associations in the entire sample and is represen-

TABLE 2. Model results for the effects of prenatal SDP exposure on offspring substance use

Variable	Unconditional model (UM) Estimate ^a [95% CI]	SDP-only model Estimate ^a [95% CI]	Model 1 Estimate ^a [95% CI]	Model 2 Estimate ^a [95% CI]
Intercept	0.19 [0.15, 0.24]*	0.12 [0.05, 0.18]*	0.44 [0.05, 0.82]*	0.15 [-0.24, 0.59]
SDP				
Offspring specific (OS)	—	0.03 [0.01, 0.05]*	0.01 [-0.02, 0.03]	—
Family average (FA)	—	—	—	<0.01 [-0.11, 0.10]
OS relative to FA	—	—	—	-0.07 [-0.18, 0.03]
Level 1: Covariates				
Child birth order	—	—	-0.12 [-0.22, -0.03]*	-0.13 [-0.29, 0.05]
Mother married	—	—	0.02 [-0.12, 0.16]	<0.01 [-0.14, 0.13]
Sex (OS)	—	—	-0.04 [-0.12, 0.05]	-0.02 [-0.13, 0.09]
Sex (FA)	—	—	—	-0.03 [-0.15, 0.10]
Mother education (OS)	—	—	-0.01 [-0.04, 0.02]	<0.01 [-0.07, 0.06]
Mother education (FA)	—	—	—	-0.01 [-0.04, 0.02]
Food stamps (OS)	—	—	-0.02 [-0.18, 0.12]	0.20 [-0.08, 0.47]
Food stamps (FA)	—	—	—	-0.05 [-0.24, 0.14]
Mother age (OS)	—	—	<0.01 [-0.01, 0.01]	-0.03 [-0.08, 0.03]
Mother age (FA)	—	—	—	<0.01 [-0.01, 0.01]
Father SDP (OS)	—	—	<0.01 [-0.03, 0.03]	0.01 [-0.05, 0.06]
Father SDP (FA)	—	—	—	-0.01 [-0.05, 0.03]
Level 2: Covariates				
Mother substance use	—	—	0.02 [-0.03, 0.07]	0.01 [-0.04, 0.06]
Father substance use	—	—	0.02 [-0.04, 0.08]	0.02 [-0.04, 0.08]
Variance ^b				
Individual-level variance	0.14 [0.11, 0.17]*	0.12 [0.09, 0.14]*	0.11 [0.09, 0.14]*	0.12 [0.10, 0.15]*
Family-level variance	0.02 [<0.01, 0.05]*	0.01 [<0.01, 0.03]*	0.01 [<0.01, 0.04]*	0.01 [<0.00, 0.03]*
Slope SDP variance	—	<0.01 [<0.01, <0.01]*	<0.01 [<0.01, <0.01]*	<0.01 [<0.01, 0.01]*
Intraclass correlation	0.10 [0.01, 0.28]*	0.07 [0.01, 0.25]*	0.09 [0.01, 0.29]*	0.04 [0.01, 0.22]*
% within-family variance explained beyond UM	—	14%	21%	14%

Notes: Covariates included in Models 1 and 2: Offspring-level covariates were child birth order, child sex, marital status, maternal education at birth of each child, whether the family was on food stamps at the time of child birth, mother age at the birth of each child, second-hand smoke exposure by the father during pregnancy; family-level covariates were maternal substance use and paternal substance use. Birth order was significantly (and negatively) correlated with age in this sample ($r = -.87$), which leads to a multicollinearity problem when modeling these data. Thus, birth order was included as a covariate rather than age given that (a) mothers usually smoked in the first pregnancy (64%) but not the second and (b) birth order was generally more highly associated with substance use measures than was age (Knopik et al., 2016; Marceau et al., 2016). CI = Bayesian credibility interval; SDP = smoking during pregnancy (maternal reported). ^aPoint estimates are the median of the posterior distribution; ^bsignificance tests for variance terms are presented, but it is noted that variance estimates are bounded at zero; therefore this does not mean that each family has the same mean but, instead, indicates that the clustering of the children within families does not help explain any of the overall variability.

*One tailed $p < .05$ (for positive estimates, p is the proportion of the posterior distribution that is below zero; for negative estimates, p is the proportion of the posterior distribution that is above zero).

tative of how SDP effects and associated familial confounds are typically modeled in non-sibling-based samples, without capitalizing on the family structure (or sibling comparison aspect) of the data, but adjusting for the non-independent observations of siblings nested within families. Relevant offspring-specific and family-level covariates are summarized in Table 2.

Model 2. In this sibling-comparison approach (Model 2), we specifically examined within-family associations of SDP and offspring substance use, allowing for a direct test of unique SDP exposure effects on offspring behavior while controlling for genetic and environmental variables that siblings share, as well as the between-family analog to traditional research (Model 1). The average score for SDP was computed across both siblings to obtain a family-average SDP severity value. This value was subtracted from each offspring-specific score to represent an offspring-

specific relative to family-average SDP severity as a predictor of substance use. Thus, hypothetically, a score of zero represents situations in which the mother smoked the exact same amount for both pregnancies, whereas a positive value would indicate that the mother smoked (or smoked more) for that particular child. The effect of the family-average SDP severity assessed the between-family effect of SDP severity on substance use (i.e., the overall effects of SDP and related familial factors on substance use outcomes, comparing across families). The effect of the offspring-specific SDP severity relative to family average assessed the direct within-family effect of SDP on offspring substance use (comparing across siblings within a family, a test of any unique effect of SDP on offspring-specific outcomes over and above familial and genetic factors that siblings share). Thus, Model 2 includes both the offspring-specific and family-average values as well

as family-centered offspring-specific covariates (child sex, maternal education, family on food stamps, mother's age, secondhand smoke exposure during pregnancy).

For each model, the intraclass correlation (ICC) determined the ratio of between-family variation relative to the total variation. The proportion of within-family variance explained by each conditional model relative to the unconditional model was also computed ([unconditional individual offspring-level variance – conditional {e.g., Model 1} individual offspring-level variance] / unconditional individual offspring-level variance) to provide an effect size for each model.

Results

As summarized in Table 2, the unconditional model evidenced small, but significant family-level variance and a significant individual-level variance (ICC = 0.10). When offspring-specific SDP was entered as a predictor with no additional covariates, it significantly predicted substance use. However, when familial covariates were included, the effect became nonsignificant. Child birth order was the only significant control variable in Model 1, but this effect was not found in Model 2. No other control variables were significantly related to substance use. Model 1 explained the largest amount of within-family variance above and beyond the unconditional model (21%) compared with the SDP-only predictor model (14%) and Model 2 (14%), indicating that this model had the largest overall effect. The ICC was reduced to 0.09 for Model 1 and 0.04 for Model 2, indicating that, although the main effects were nonsignificant, the addition of predictors reduced the within-family correlation in substance use. Importantly, these results were consistent in secondary models with alternative definitions of SDP, such as a binary yes/no indicator and a sum score across all trimesters.

Discussion

We used a sibling case-crossover design, wherein mothers smoked during one pregnancy but not the other, to assess the association between SDP and substance use initiation in early adolescence. Our analyses leverage the advantages of the discordant sibling sample, which controls for familial confounds and Bayesian modeling approaches, allowing us to obtain maximum power and precision in a smaller sample with a nonnormally distributed dependent variable. These preliminary findings suggest that SDP is not a significant predictor of offspring substance use. Further, models that controlled for child- and family-level confounders explained additional variance in initiation of substance use over and above an unconditional model that does not provide such controls. Together, findings suggest that unique/direct effects of SDP on substance use initiation are not present at this

developmental stage after controlling for shared genetic and familial influences.

Our study is limited by the younger age of the sample and the number of adolescents engaged in substance use. This, in addition to no previous literature from which to draw informative priors, leads to the possibility that we may have limited power to estimate within- or between-family effects of SDP on offspring substance use. Van de Schoot and colleagues (2015) explain that Bayesian analyses with informative priors can lead to more reliable results with higher power. The complex study design of our current study precludes a large sample; however, results from this study are, nonetheless, an important contribution to the literature and may serve as a source of prior information for future studies. In addition, although we have shown that retrospective reporting of SDP in this study appears reliable and accurate (Knopik et al., 2016b), our results are reliant on the ability of the SDP assessment to correctly reflect the amount of SDP exposure. Finally, our SDP severity measure assumes that smoking beyond the first trimester is more extreme than smoking only in the first trimester. Although this is supported via the preclinical and human literatures (e.g., Dwyer et al., 2009; Hebel et al., 1988), we also conducted sensitivity analyses to test this assumption, and our findings were consistent across different methods of defining SDP across the pregnancy (results available on request). Despite these limitations, our study is consistent with prior quasi-experimental work suggesting there is no direct effect of SDP on early initiation of substance use outcomes in a large sample of older adolescents (D'Onofrio et al., 2012). Given the increased risk of poor outcomes for early initiators, rigorous testing of the etiological processes involved in adolescent substance use proneness across different samples and developmental stages is crucial to advance developmental psychopathology theory and identify those who ultimately stand to benefit most from maternal and youth substance use prevention efforts.

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