Published in final edited form as:

Behav Genet. 2016 May ; 46(3): 416–430. doi:10.1007/s10519-016-9791-5.

A propensity scoring approach to characterizing the effects of maternal smoking during pregnancy on offspring's initial responses to cigarettes and alcohol

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Abstract

When examining the effects of prenatal exposure to maternal smoking during pregnancy (MSDP) on later offspring substance use, it is critical to consider familial environments confounded with MSDP. The purpose of this study was to examine the effect of MSDP on offspring's initial reactions to cigarettes and alcohol, which are indicators of future substance-use related problems. We tested these effects using two propensity score approaches (1) by controlling for confounding using the MSDP propensity score and 2) examining effects of MSDP across the MSDP risk distribution by grouping individuals into quantiles based on their MSDP propensity score. This study used data from 829 unrelated mothers with a reported lifetime history of smoking to determine the propensity for smoking only during their first trimester (MSDP-E) or throughout their entire pregnancy (MSDP-T). Propensity score analyses focused on the offspring (N=1616 female twins) of a large subset of these mothers. We examined the effects of levels of MSDP-E/T on offspring initial reactions to their first experiences with alcohol and cigarettes, across the distribution of liability for MSDP-E/T. MSDP-E/T emerged as significant predictors of offspring reactions to alcohol and cigarettes, but the effects were confounded by the familial liability for MSDP. Further, the unique MSDP effects that emerged were not uniform across the MSDP familial risk distribution. Our findings underscore the importance of properly accounting for

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Conflict of interest: All of the listed authors declare that they have no conflicts of interests.

Authorship: All authors collaborated to develop the study concept and design. L.C. B, R.H.P. and L.A.B. performed the data analysis and interpretation under the guidance of P.A.M., A.C.H. and V.S.K. L.C.B. drafted the paper, and V.S.K, R.H.P, P.A.M., and A.C.H. provided critical revisions. All authors approved the final version of the paper for submission.

correlated familial risk factors when examining the effects of MSDP on substance related outcomes.

Keywords

Prenatal exposure; nicotine; subjective drug responses; genetic; tobacco; substance use

Introduction

Smoking is the leading preventable cause of mortality in the US and considerable effort has been devoted to identifying those individuals at risk for regular smoking (Pomerleau et al. 1993). Initial reactions to substances, often broadly classified as “positive” and “negative,” are commonly thought to reflect the individual's subjective report of the pharmacological effect of a particular substance. A large body of evidence suggests that the intensity and quality of reactions to one's first substance use experiences are predictive of later problem use (Chen et al. 2003; DiFranza et al. 2004; O'Connor et al. 2005; Pomerleau et al. 1998; Riedel et al. 2003; Morean and Corbin 2008; Chung and Martin 2009). For example, several studies suggest that more intense initial reactions are predictive of future regular smoking regardless of whether they were positive or negative (Pomerleau et al. 1993; Pomerleau et al. 1998) and others suggest that only positive or pleasant initial reactions are indicators of future dependence (Chen et al. 2003; DiFranza et al. 2004; O'Connor et al. 2005; Riedel et al. 2003; Blitstein et al. 2003; Kozlowski and Harford 1976). Genetic studies support moderately high heritability for initial reactions to cigarettes (17-34%) and alcohol (31-56%) (Haberstick et al. 2011; Agrawal et al. 2014), suggesting that initial reactions are 1) an important indicator of future problem use and 2) a phenotype of strong interest to etiological studies of developmental genetic and environmental influences on addiction.

In addition, there have been a large number of animal and human studies that have reported the association between prenatal exposure to maternal smoking during pregnancy (MSDP) and harmful outcomes extending beyond the childhood years, including effects on offspring's later substance use during adolescence and adulthood (Cornelius et al. 2000; Kandel et al. 1994). Nicotine, one of the many harmful toxins present in tobacco smoke, is readily transferred to the fetus throughout pregnancy, where it binds to nicotinic acetylcholine receptors (nAChRs), thereby exerting an effect on fetal neurodevelopment (Hagino and Lee 1985). Neuronal nAChRs play an important role in neuronal migration and growth cone direction. Further, binding of nicotine to nAChRs has been shown to enhance the release of dopamine, norepinephrine, serotonin, γ -aminobutyric acid (GABA), and glutamate, in addition to acetylcholine, thereby affecting multiple neurotransmitter pathways with potential consequences on the programming of synaptic competence (Slotkin 1998). It is therefore possible that fetal exposure to nicotine and other components of cigarettes through MSDP would affect neuronal development and impact sensitivity to psychoactive substances during early drug use exposures, impacting risk for future use. Given the established role of initial reactions in increasing risk for continued and problem substance use, establishing a causal effect of MSDP on initial reactions would delineate an environmentally mediated risk pathway towards future dependence.

Importantly, while a large number of human studies have suggested that MSDP is a risk factor for adverse behavioral outcomes in the offspring, the association has not been without controversy (Ernst et al. 2001; Knopik 2009). Several genetically-informed studies have questioned the causal relation between MSDP and later externalizing outcomes, and have suggested that the observed increase in offspring substance use-related behaviors when mothers smoked during pregnancy are accounted for by unmeasured familial factors (genetic factors and/or exposure to household-level factors) (D'Onofrio et al. 2008; Langley et al. 2012; Lindblad and Hjern 2010; Skoglund et al. 2014; Thapar et al. 2009; Thapar and Rutter 2009; D'Onofrio et al. 2012; Kuja-Halkola et al. 2014). These familial risk factors include correlated prenatal factors (maternal alcohol consumption, stress, poor diet during pregnancy, exposure to toxins) and post-natal family factors (e.g. parental substance use, parental psychopathology, and socio-economic factors). In epidemiological studies, these correlates or confounders are typically either ignored or simply included as covariates in analyses. Family-based longitudinal designs can test the unique effects of MSDP more directly by looking at the effects of MSDP on later outcomes in offspring who have the same family risk profile. For example, in a large medical registry cohort study, siblings within the same nuclear family who were differentially exposed to MSDP did not differ in their risk for use or problem use of substances (D'Onofrio et al. 2012), suggesting that familial confounds associated with MSDP may account for any effects among MSDP and increased risk for substance use later in life. However, this discordant sibling design is not without its own limitations, including sample selection bias, limited phenotyping, and uneven distribution of confounders. Further, such methods involving matching individuals on family background, either statistically or through sample selection, have largely not been used to test for unique and unbiased effects of MSDP on adolescent substance use risk and behaviors (Heath et al. 2014), and have never been applied to test for an effect of MSDP on initial reactions to substances.

In order to account for these important familial confounding factors, we approached testing for a unique impact of MSDP on offspring's initial reactions to cigarettes and alcohol using propensity score analysis, a longstanding approach to statistically controlling for confounders and selection bias (Rosenbaum and Rubin 1983), albeit one rarely used in behavior genetics and in addiction research (Heath et al. 2014; Waldron et al. 2014). In the case of the current study, propensity scores are used to adjust the propensity for MSDP on a set of familial risk factors that are highly correlated with MSDP, such as maternal age, parental alcoholism, parental smoking outside of pregnancy, parental psychopathology, and socio-economic status. Hence, for a given propensity score, the set of familial risk factors will be similar for offspring of mothers who did and did not smoke during pregnancy. Having grouped individuals based on the propensity (due to pre-pregnancy familial factors) for MSDP, it is then possible to model the unique effect of exposure to MSDP on our outcome of interest, in this case, offspring's reactions to substances during their first use; and our confidence in the specificity of risks associated with levels of MSDP is greatly increased. Further, we can test for differential effects of MSDP on offspring initial reactions across levels of this probability risk distribution for MSDP by stratifying the distribution into quantiles and looking at effects within each level of risk (i.e. the first quantile of the distribution containing both MSDP exposed and MSDP unexposed offspring with the lowest

familial risk, the last quantile containing both MSDP exposed and MSDP unexposed offspring with the highest familial risk). Comparisons of individuals who have been matched across a specific range of probabilities has been used to successfully quantify and describe the effects of MSDP (across the MSDP liability distribution) on childhood behavior and externalizing outcomes related to substance use (Melchior et al. 2015; Boutwell et al. 2011; Palmer et al. 2016 [Current Issue]), but it has yet to be used to examine other adolescent substance related outcomes.

Thus, we sought to use propensity score methods to examine the effects of levels of MSDP on offspring's initial reactions to alcohol and cigarettes, which are an important predictor of future problem use. The specific goals were to (1) determine the effects of MSDP on offspring's initial reactions to alcohol and cigarettes across the entire risk propensity distribution for MSDP and (2) test whether the observed effects of MSDP are consistent among the lower and higher levels of risk across propensity distribution for MSDP. We assess the effects of levels of MSDP by identifying offspring of mothers who smoked only during the first trimester of their pregnancy [MSDP-Early (E)] and offspring of mothers who smoked throughout their pregnancy (MSDP-Throughout (T)). Notably, our comparison group consists of offspring of mothers who have a history of smoking, but who did not smoke during pregnancy, providing a relative index of the risk of smoking during pregnancy for mothers with a history of smoking. While this choice is expected to result in a smaller effect size than that of a comparison to offspring of “non-smoking” mothers, it is a more clinically meaningful comparison group (since it would be the rare case that a lifetime non-smoker would start smoking during pregnancy) and provides data on the impact of successfully avoiding and/or limiting offspring's smoke exposure during pregnancy (i.e., none, early part of pregnancy, versus throughout). A companion paper submitted for this same special issue uses a parallel modeling approach to quantifying the effect of MSDP on externalizing outcomes more broadly including risk for externalizing psychopathology and nicotine and alcohol dependence (Palmer et al. 2016 [Current Issue]).

Methods

Sample

Data were obtained from the Missouri Adolescent Female Twin Study cohort, a sample of female adolescent twin pairs and their parents participating in a longitudinal study of the development of alcohol problems and associated psychopathology in adolescent girls and women (MOAFTS; Heath et al. 2002). All twin pairs born in Missouri to Missouri-resident parents between July 1, 1975 and June 30, 1985, where both twins were still living, were identified from birth records. A cohort-sequential design was used with recruitment, over two years, of six-month cohorts of 13, 15, 17, and 19 year-olds. The third and fourth years of data collection added new cohorts of 11- and 13-year-old twins. Ascertainment of families began in January 1995 and continued through December 1998. Data for the current study are drawn from the baseline assessment and the 5 year follow-up (Wave 4). Verbal consent, or assent if minors, was obtained from all participants prior to their participation in each wave, as well as parental consent for the participation of their minor children in the study. All

procedures were approved by the Institutional Review Board at Washington University, St Louis.

The analyses described are limited to offspring [N= 1616 (42 singletons and 787 complete twin pairs) ages 12-23 (mean=15.52, standard deviation (SD) = 2.48)] from 829 families where mothers had a history of smoking and provided information on their smoking during their pregnancy. As described below, logistic regression modeling of MSDP behaviors in these mothers provided a propensity score for smoking during pregnancy (i.e., smoking during the first trimester of their pregnancy only (MSDP-E) or smoking throughout their entire pregnancy (MSDP-T) versus having a history of smoking, but not having smoked during pregnancy). Identified propensity scores for each family were assigned to both siblings as a family risk measure, and the effect of MSDP-E/T on offspring initial reactions was assessed using two propensity score analysis methods. Thirteen percent (N=212) of the sample classified themselves as minority and almost exclusively as African-American, reflecting the minority composition of the St. Louis, Missouri population.

Assessments

Comprehensive structured diagnostic telephone interviews were conducted with parents of the twins and with the twin pairs. Measures derive largely from the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA; Bucholz et al. 1994, Hesselbrock et al. 1999), a semi-structured interview developed for the Collaborative Study on the Genetics of Alcoholism (Begleiter and Reich 1995). The SSAGA has well-documented validity (Hesselbrock et al. 1999), with excellent retest and inter-rater reliability (Bucholz et al. 1994, Bucholz et al. 1995). Parents completed a telephone adaptation of the SSAGA-II—the DSM-IV update to the DSM-III-R-based SSAGA. Twins completed either the child or adolescent version of the SSAGA-II, also adapted for telephone administration. Mothers reported on their own smoking during pregnancy and the majority of family factors shared by both twins. Twins reported on their own histories of initial reactions to cigarettes and alcohol and a limited number of parental factors (e.g. paternal smoking).

Offspring factors

Initial reactions to cigarettes and alcohol—Twin self-report of initial subjective reactions to *cigarette smoking* were assessed at baseline using the following seven questions: “Did you enjoy smoking your first cigarettes?” and “While smoking your first cigarettes did you (a) cough, (b) feel dizzy, (c) get a headache, (d) feel your heart racing, (e) feel nauseated, or (f) like the taste? Initial subjective responses to *alcohol* were assessed using the following seven questions: “Did you enjoy your very first drink?” and “While drinking the first few times, did having just one (or two) full drink(s) of alcohol ever cause you to (a) flush, (b) feel dizzy or lightheaded, (c) feel very sleepy, (d) feel sick to your stomach, (e) have a headache, or (f) feel your heart beating inside your chest? Responses to these questions were coded as “Yes” (1) or “No” (0). Between 783-788 offspring with MSDP propensity score data who reported having initiated alcohol provided information on initial responses and between 750-752 twins who reported having initiated cigarette use provided information on initial reactions to cigarette use.

We reduced these items into dimensional factor scores, which provide an indicator of shared variance across items, theoretically improving power to detect effects and reducing the number of tests. In addition, there is data to suggest that separate initial reactions items may differentially impact risk for later substance use problems. For example, pleasurable initial reactions to cigarettes may be more strongly predictive of future dependence (Blitstein et al. 2003). Thus, item level variance is also important to consider when examining etiological and risk pathways and may give us important information on effects of MSDP on various indicators of future problem use. For these reasons, in the current analyses, initial reaction items were considered at both an individual item level and at a dimensional level via factor analysis.

Maternal and familial factors

Maternal smoking during pregnancy (MSDP)—Of mothers who reported a history of smoking (more than a single cigarette lifetime), maternal smoking during pregnancy was first divided into three categories operationalized into a set of orthogonal contrast codes: 1) smoker, but did not smoke at all during pregnancy (No MSDP/Reference group), 2) smoking during the first trimester (MSDP-E) and smoking beyond the first trimester (MSDP-T). If a mother stopped smoking at a certain point in her pregnancy, her data was included in the appropriate category. For example, if she quit after 1 month of the pregnancy, she would be counted as having smoked during the first trimester, and if she quit after 5 months, she would be counted in the MSDP-T category.

Familial predictors of MSDP—Correlated risks that might separately increase the likelihood of MSDP or offspring initial reactions to substances were used as predictors to generate matched MSDP propensity scores. These ten variables were coded for use as follows: Race (Black vs. Other), lifetime paternal smoking (yes/no), maternal education (≤ 12 years (completed high school)/ < 12 years), paternal education ≤ 12 years (completed high school)/ < 12 years), three or more symptoms of paternal alcohol dependence, three or more symptoms of maternal alcohol dependence, and parents never lived together. Maternal age was dummy coded into categories < 20 , 21-25, 26-30, 31-35, and > 35 years of age. Maternal year of birth was dummy coded into < 1949 , 1950-1954, 1955-1959, > 1960 . Maternal nicotine dependence severity consisted of a 5 category scale based on FTND severity (None=0, Very Low=1-2, Low=3-4, Moderate=5-7, and High=8-10; Fagerström 1978).

Data Analysis

Propensity scores were derived using logistic regression models conducted in SAS [version 9.4] (SAS Institute Inc 2013)(see Propensity Score Derivation section below). Descriptive statistics and factor analyses were conducted in Mplus [version 7] (Muthén and Muthén 1998-2012). Factor models were fit using full information maximum likelihood estimation to account for missing data at the item level. The main research questions were examined using logistic regression (i.e., where MSDP-E/T were used to predict presence of initial reactions to alcohol and cigarettes while accounting for within family effects of sibling pairs). Models were fitted before and after accounting for individual differences in the propensity for MSDP (i.e., propensity scores; note that MSDP-E/T propensity scores are a

family-level variable and as such, are identical for members of the same family), which was based on the combined effect of the set of familial factors on MSDP-E/T. Finally, rather than assume that the effects of MSDP on initial reactions for alcohol and cigarettes are consistent across all levels of MSDP (i.e., fitting a model including an interaction term between MSDP and the propensity for MSDP), we used an agnostic approach to discover whether the observed MSDP effects are consistent across the distribution of familial risk for MSDP. This was achieved by fitting a separate set of models across stratified levels of risk for MSDP based on categorization of the propensity score distribution into quartiles.

Propensity Score Derivation—Propensity score analysis was used to examine the relationship between MSDP and offspring's initial reactions to alcohol and cigarettes. This approach was selected for these data because it provided a means to examine direct MSDP effects on initial reactions across the risk distribution for MSDP that is inferred from the set of familial risk factors for MSDP (Waldron et al. 2014; Boutwell et al. 2011; Boutwell and Beaver 2010; Knopik et al. 2005; Knopik et al. 2006). MSDP-E/T status was predicted using dummy coded versions of familial risk factors relevant in risk for MSDP (see Supplemental Tables SIa and SIb for parameter estimates for the MSDP-E and MSDP-T models using the complete set of dummy codes for all categories of the predictors, respectively). Missingness on each familial risk variable was accounted for by including a dummy variable category. Model fit was assessed using the receiver operating characteristic (ROC) curve (Zhang 2007; Swets 1986), where values closer to one indicated better separation of the smoking during pregnancy categories and values close to 0.5 indicated chance.

Stratification on Propensity Score—Stratification on the propensity score distribution is a common approach to agnostically organize subjects into mutually exclusive ranked subsets based on their propensity score (Austin 2011). When analyses are stratified on quintiles of the confounding variable(s) (Cochran 1968), this approach has been shown to limit approximately 90% of the bias of the confounders (as captured by the propensity score). Simulation studies have recommended stratification into quartiles or quintiles, noting that the Type 1 error rate improves with the number of stratifications at the cost of statistical power (Leon and Hedeker 2011). For the current study, stratification by quartile was designed to maximize statistical power for the within-quartile analyses to afford as much available power to detect an effect of MSDP. From the observed propensity scores, we created a four-category variable that each contained approximately 25% of the distribution (i.e., quartiles (Q1: 0-25%ile, Q2: 26-50%ile, Q3: 51-75%ile, and Q4: 76-100%ile)).

Propensity Score Analyses—Study hypotheses were tested both across and within each stratum/quartile. Analyses across quartiles utilized the propensity score as a covariate to adjust for the effect of MSDP-E/MSDP-T in the regression model. The benefit of examining effects within each quartile was that individuals within each stratum would be very similar with respect to the set of familial factors used to derive the propensity score, thus observed stratum-specific effects of MSDP would indicate whether there were discontinuities in the effects of MSDP-E/T across their respective risk distributions (i.e., whether the effect the same among those at low, intermediate, or high probability of MSDP). Two models were fitted to the data for each initial reactions outcome using logistic regression in Mplus. Both

models accounted for the fact that twins were clustered within families. Consequently, the computed standard errors were adjusted for the non-independent nature of the observations using robust Maximum Likelihood estimation. In the first model, Model I, each individual initial reaction item and the derived factors were predicted by MSDP-E/T while controlling for the age of the participants (i.e., three levels [11-14, 15-18, and 19+] dummy coded) (Knopik et al. 2005; Knopik et al. 2009). In Model II, each initial reactions outcome was predicted by MSDP-E/T while controlling for the propensity for MSDP-E/T and age. The effect of MSDP-E/T on initial reactions within each quartile was assessed by repeating Model I, but within each quartile.

Results

Structure of items assessing initial reactions to cigarettes and alcohol

Comparisons of one- and two-factor models of the relationship between the initial subjective response items indicated that the two-factor model provided the best fit to the data for both cigarettes and alcohol. See Supplementary Materials for a description of the factor model results and Supplementary Table SII for CFA loadings and model fit. For alcohol, the resulting two-factor solution had one factor consisting of flush, dizzy, and sleep, and a second factor consisting of stomach, headache, and heart racing in your chest. Pleasure did not load on either factor and was considered as a single item only. For cigarettes, results supported the presence of a Hedonic Factor 1 indicated by pleasurable sensations of enjoying one's first cigarettes and liking the taste of one's first cigarette. They also suggest the existence of a Somatic Factor 2, which includes physiological sensations such as headache, dizziness, and nausea. Cough was a stand-alone item that did not clearly load on either factor. Factor scores controlling for baseline age were extracted for both cigarettes and alcohol and saved for use in subsequent analyses.

Table I shows the prevalence of individual initial reactions items and mean level of the derived initial reactions factors for the sample of offspring, separately for all levels of MSDP. With regard to initial reactions to cigarettes, the majority of respondents reported cough, dizziness, and pleasure/“enjoying their first cigarette.” The item with the lowest prevalence was “liking the taste of cigarettes.” For alcohol, the majority of respondents reported pleasure/“enjoying their first drink” and dizziness. “Feeling your heart beating in your chest” was the lowest prevalence item.

Propensity for SDP in Mothers—Based on the logistic regression models using all 11 familial factors to predict MSDP, the area under the ROC curves was 0.71 for the model predicting MSDP-E, and 0.81 for the model predicting MSDP-T, indicating good discriminatory power (Swets 1986). Notably, different familial factors were associated with the risk for MSDP-E and MSDP-T. Maternal FTND severity and maternal level of education were associated with MSDP-E while paternal education, maternal education, paternal alcohol dependence severity, maternal FTND severity, and paternal smoking (see Supplemental Tables SIIa and SIIb).

Propensity for MSDP-E and MSDP-T in Offspring of Mothers Who Smoked During Pregnancy—As expected, the number of individuals who met the criteria for

exposure increased across quartiles for MSDP-E/T. This was complemented by the observation that differences, with respect to the familial factors, between individuals in different quartiles increased across the propensity distribution (i.e., greater differences between Q1 and Q4 compared to Q1 and Q2, and so on so forth; see Supplemental Tables SIIIa and SIIIb). Tables IIa and IIb provide an indication of the associations between the familial factors and MSDP-E and MSDP-T amongst the offspring used to test the main research question (note that these tables reflect more clinically relevant categorizations of the familial factors (described in Supplemental Tables SIIa and SIIb)). For example, overall, children with fathers with 3+ alcohol dependence symptoms were more likely to have had a mother who smoked during part of her pregnancy (odds-ratio (OR) = 1.68 [95% confidence interval (CI): 1.20, 2.35], $p = 0.011$) and throughout her pregnancy (OR = 1.99 [95% CI: 1.48, 2.69], $p < 0.001$). Tables IIa and IIb also indicate the high level of similarity, when looking within quartile, between our groups of MSDP exposed and non-MSDP exposed offspring for each of the ten familial factors, highlight the successful matching on confounding familial factors.

Effect of MSDP on Offspring Initial Reactions across the MSDP Risk

Distribution—Tests of the main research question using propensity scores to control for familial confounding are presented in Tables IIIa (for MSDP-E effects) and Table IIIb (for MSDP-T effects). Results from the first set of models (i.e., Model-I, which did not adjust for MSDP-E/T) suggested that when ignoring familial factors, MSDP-E increased the intensity of two initial reactions items [Dizziness for alcohol ($\beta=0.61$ [95% CI: 0.41, 0.91], $p < 0.05$) and Headache for smoking ($\beta=1.66$ [95% CI: 1.12, 2.45], $p < 0.05$)]. MSDP-T increased the intensity of several initial reactions items, including stomach sickness, headache, and heart beating for alcohol and headache, heart beating, nausea, and Somatic Factor 2 for Cigarette Smoking. However, the MSDP-E effects on initial reactions were attenuated when the model controlled for familial factors using the propensity scores (i.e., Table IIIa-Model-II). Several effects of MSDP-T on offspring initial reactions to alcohol remained significant in Model-II, which controlled for familial factors using the propensity scores, including stomach sickness, heart racing, and Factor 2, which includes stomach sickness, heart beating, and headache. In Model-II, propensity score (P-score) itself was a significant predictor over and above MSDP-E for dizziness during first cigarettes ($\beta=5.77$ [95% CI: 1.75, 19.09], $p < 0.05$) and over and above MSDP-T for Smoking factor 2 ($\beta=0.35$ [95% CI: 0.07, 0.58], $p < 0.01$) and several of its constituent items (dizziness: $\beta=2.59$ [95% CI: 1.32, 5.08], $p < 0.05$ and heart beating: ($\beta=2.80$ [95% CI: 1.25, 6.26], $p < 0.05$). Overall, these findings would suggest that, although familial risk factors account for some of the associations with MSDP and initial reactions, MSDP-T is independently associated with greater intensity of particular offspring initial reactions to alcohol and that the effect of MSDP on later offspring initial experiences with alcohol is dependent upon on a higher level of exposure during the pregnancy (i.e., using report of smoking throughout pregnancy as a proxy for tobacco exposure levels).

Effect of MSDP on Offspring Initial Reactions within each Strata of the MSDP

Risk Distribution—Further analysis of the MSDP-E and MSDP-T effects amongst the individuals that were matched on family background (i.e., within quartile; see Tables IIIa

and IIIB, respectively) showed that MSDP does not consistently predict the intensity of initial reactions across the MSDP risk distribution. Despite the lack of observed effects of smoking during only the first trimester (MSDP-E) on offspring initial reactions, MSDP-E was shown to increase the level of pleasure during first cigarettes ($\beta = 0.34$, [95% CI: 0.15, 0.81], $p = 0.05$), but only in the 76-100th percentile families which had the highest levels of other MSDP-related risk factors such as parental alcoholism and smoking outside of pregnancy. Differences within quartile with respect to smoking throughout pregnancy (MSDP-T versus no MSDP) also reached significance in several instances, primarily in the middle of the risk distribution. For example, MSDP-T increased the intensity of Alcohol Factor 2 and several of its constituent items (stomach sickness and heart beating) and two smoking items, headache and nausea, in the 26-50th percentile families and increased risk for flush during first drinks of alcohol in the 51-75%. Overall, these findings suggest that while the confounding due to familial factors is complex, there are direct effects of MSDP on offspring initial reactions. These effects, however, are not consistent across the strata of risk for MSDP.

Discussion

Using data from a population-based sample of female twins and their mothers, we examined the type and quality of initial reactions to alcohol and cigarettes as a function of the level of prenatal exposure MSDP (early in pregnancy or throughout pregnancy) and important familial confounders that may be driving effects of MSDP propensity score approaches. These are among the first analyses to examine the effects of exposure to MSDP on offspring's later responses to initiation with substances. By using propensity analysis, we were able to provide estimates of the role of prenatal MSDP exposure on offspring responses to their first experiences with substances – alcohol and cigarettes – both across the distribution of risk for MSDP and within particular levels of MSDP risk while controlling for familial factors. Our results suggest that familial factors confound associations with MSDP and many offspring initial reactions to cigarettes and alcohol. Despite this confounding, our findings suggest that MSDP throughout pregnancy, and to some extent MSDP during the first trimester only, may influence some offspring initial reactions to alcohol. Further, MSDP effects on offspring initial reactions to cigarettes and alcohol may not be consistent across all levels of the distribution of risk for MSDP.

Findings suggested that correlated familial risk factors were associated with increased risk for offspring initial reactions to alcohol and cigarettes and, had we failed to account for these, we would have overestimated the effects of MSDP on offspring initial reactions. However, MSDP throughout pregnancy (MSDP-T) did emerge as a unique risk factor for certain alcohol initial reaction outcomes, including Somatic Factor 2 and its constituent items of stomach sickness and heart beating. This suggested that longer more frequent exposure to MSDP may be more likely than first trimester only exposure to exert a direct effect on offspring initial reactions to alcohol. Further, effects of MSDP were not uniform across the MSDP risk distribution. Exposure to MSDP was an independent predictor of offspring's initial reactions to alcohol primarily in the middle risk quartiles (for reactions such as pleasure, stomach sickness, and flush) and no effects of MSDP on alcohol outcomes were seen in the lowest risk quartile. Thus, the unique effects of MSDP in our study

emerged primarily in the middle range of the risk distribution for other familial and genetic risks. An important caveat is that due to differences in N between the reference and MSDP-E/T groups at the lowest and highest quartiles, the greatest power to detect effects was also in the middle quartiles. We did see one effect of first trimester only exposure (MSDP-E) on more pleasurable initial reactions to smoking, but only in offspring in the highest risk quartile. Given that increased positive initial reactions and greater sensitivity to both cigarettes and alcohol has been associated with increased risk for heavier patterns of use and dependence (Chen et al. 2003; DiFranza et al. 2004; O'Connor et al. 2005; Riedel et al. 2003; Chung and Martin 2009), these findings suggest a risk pathway where prenatal exposure to MSDP may have a unique, albeit small, effect on early drug responses for certain individuals depending on their other familial risk factors. Additional studies are needed to understand which contextual and neurobiological factors may link exposure to MSDP and alterations in these initial drug experiences, particularly in order to replicate and understand findings suggesting there may be a specific effect on alcohol-related initial reactions.

Although our results suggested that the effects of MSDP on initial reactions can partially be accounted for by key familial confounders, propensity score matching of offspring's familial risk revealed that MSDP may have unique causal effects on initial cigarette and alcohol reactions for certain risk profiles. Propensity scores were included to minimize the impact of confounding variables and provide less biased estimates of the role of MSDP on initial reactions outcomes. Although independent effects were only shown for a handful of outcomes within particular quartiles, by matching individuals on risk propensity for MSDP, we effectively control for important confounding variables and any effect we see of MSDP on increasing risk for initial reaction outcomes can more reliably be interpreted as a direct or true effect of MSDP. Our findings are consistent with those of Fang et al. (2010), who found that propensity score matching revealed effects of MSDP at various points across the risk distribution on neonatal attention outcomes that traditional multiple regression analyses masked. Our propensity score matching approach allowed parsing of familial risk in this way and statistically controlled for important confounders that is often only approximated through complex family designs that ascertain and compare individuals within the same family who are exposed or not exposed (Knopik 2009; D'Onofrio et al. 2012; Knopik et al. in press).

An important extension of these findings is the opportunity to use propensity score matching to extend the classic twin gene-environment interaction model, while simultaneously controlling for gene-environmental correlation and confounding effects. Twins with and without prenatal MSDP exposure can be matched on confounding familial variables using propensity scores across families on genetic and environmental risk for MSDP and ranked in terms of likelihood of MSDP exposure in order to 1) estimate additive genetic, shared environment (C), and non-shared environmental (E) effects within and between MSDP risk exposure profiles and 2) examine whether genetic and environmental influences on initial reactions vary as a function of this important environmental exposure, i.e. across the spectrum of risk for MSDP. Although we did conduct these analyses on a preliminary basis, due to limited power in the current sample for such integrated $G \times E$ twin models, we were unable to include these in the current report. Future studies using larger samples can use

such models to test whether the heritability of initial reactions or other offspring outcomes may vary across the distribution of risk for MSDP, after controlling for this prenatal environmental exposure and statically matching on important familial confounds.

Methodological considerations

Several important limitations need to be considered when interpreting these results. First, our findings are based on retrospective self-report and errors in recalling the type and quality of initial reactions and/or the extent of smoking during pregnancy could have caused us to under or over- estimate the role of these factors. Although imperfect, our use of retrospective self-report on initial reactions is consistent with prior work in this area (Chen et al. 2003; DiFranza et al. 2004; Agrawal et al. 2014). Further, importantly, other studies within this sample have reported reliability and stability of maternal reporting about their pregnancies, including smoking (Pickett et al. 2009; Knopik et al. 2015 [Current Issue]; Reich et al. 2003). A study of smoking during pregnancy in adult Australian female twin pairs (Heath et al. 2003) also found good agreement between twin self-report and rating by her twin sister of her MSDP, suggesting only limited under-reporting of smoking during pregnancy. In addition, although we did achieve successful matching via stratification, our study did not measure all possible familial confounders that may have influenced our propensity score derivation. Thirdly, a strength of our study is that we used a more conservative control group than most prior work and compared levels of prenatal exposure (either none, first trimester only, or throughout) in offspring from mother's who had a history of smoking. Other work that employed propensity scores to examine the role of MSDP on later externalizing outcomes has included offspring of non-smokers in the comparison group, which would have increased our sample size (Boutwell and Beaver 2010). Arguably, our choice of reference group provides an even more stringent and clinically-meaningful test of the unique effects of MSDP; however, our results should be interpreted in the context of this design choice and future work can go further by comparing offspring that differ on level of MSDP and other relevant exposures.

Summary

Our findings are consistent with the broader literature that suggest that effects of MSDP on offspring substance use outcomes may largely be a result of familial and environmental variables that commonly co-occur with MSDP. However, our use of propensity score modeling allows a more refined examination and suggests that there may be potentially direct, albeit small, unique effects of MSDP on initial reactions to cigarettes and alcohol at certain points on the MSDP risk distribution, highlighting a potential risk pathway to problem use for particular individuals. In a companion paper in this same special issue, a parallel modeling strategy is used to quantify the effects of MSDP on broader externalizing outcomes including psychopathology and substance dependence, with consistent findings supporting propensity score approaches for revealing independent effects of MSDP on substance related risk (Palmer et al. 2016 [Current Issue]). Thus, by incorporating the propensity score methods illustrated here into the modeling strategy, we offer one potential method to better characterize the true impact of prenatal MSDP exposure on important developmental outcomes in observational studies by statistically accounting for confounding influences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments and Disclosures

The authors would like to acknowledge the families that have and continue to participate in the Missouri Adolescent Female Twin Study.

Financial Disclosures: This work supported by NIH grants: DA17671 (Knopik), AA07728 (Heath), AA09022 (Heath), AA11998 (Heath), HD049024 (Heath), AA017688 (Heath), AA021492 (Heath) and DA0027995 (Madden). Dr. Bidwell is supported by K23DA033302. Dr. Palmer is supported by K01 AA021113.

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Table I

Initial reactions descriptive information: Proportion of individuals endorsing items and Mean (SD) for the initial reactions factor scores across maternal smoking during pregnancy categories

Items	NO MSDP	MSDP-E	MSDP-T	Total item endorsement* (Total N=1616)
<i>Alcohol</i>				
Pleasure	178 (80%)	145 (79%)	252 (73%)	752
Flush	65 (29%)	59 (32%)	112 (32%)	752
Dizzy	109 (49%)	69 (38%)	149 (43%)	751
Sleepy	63 (28%)	65 (35%)	122 (36%)	752
Stomach	56 (25%)	59 (32%)	113 (33%)	752
Headache	34 (15%)	41 (22%)	76 (22%)	752
Heart	29 (13%)	28 (15%)	78 (23%)	750
<i>Cigarette Smoking</i>				
Pleasure	97 (43%)	70 (39%)	144 (38%)	788
Cough	150 (67%)	126 (68%)	276 (73%)	787
Dizzy	106 (47%)	87 (47%)	200 (53%)	785
Nausea	36 (16%)	38 (21%)	84 (22%)	786
Like taste	31 (14%)	33 (18%)	73 (19%)	787
Headache	49 (22%)	57 (31%)	124 (33%)	785
Heart	43 (20%)	39 (21%)	113 (30%)	783
<i>Quantitative outcomes</i>				
<i>Alcohol</i>				
Somatic Factor 1	0.68 (0.77)	0.68 (0.78)	0.75 (0.82)	N/A
Hedonic Factor 2	0.14 (0.65)	0.22 (0.69)	0.26 (0.76)	N/A
<i>Cigarette Smoking</i>				
Hedonic Factor 1	0.32 (0.51)	0.29 (0.52)	0.29 (0.55)	N/A
Somatic Factor 2	0.13 (0.64)	0.22 (0.71)	0.31 (0.71)	N/A

Table shows prevalence (N (% within MSDP group endorsement)) of each item (by substance) for No Maternal Smoking During Pregnancy (MSDP), Maternal Smoking During Pregnancy- Early (MSDP-E; first trimester only) and Maternal Smoking During Pregnancy-Throughout (MSDP-T; beyond the first trimester). Total item endorsement is shown to reflect the level of reporting on each variable in the entire sample of offspring. MSDP-E and MSDP-T use the same reference population (No MSDP). Cigarette smoking Factor 1 includes pleasure and enjoying taste during first cigarettes and Cigarette smoking Factor 2 includes feeling dizzy, headache, beating heart, and nausea during first cigarettes. Alcohol Factor 1 includes feeling flush, dizzy, and very sleepy during first drinks and Alcohol Factor 2 includes stomach sickness, headache, and heart beating during first drinks.

Table IIa

Prevalence (n [%]) of familial factors for MSDP-E by propensity quartile

Familial factors	Overall ^f		by Quartile ^f							
	No MSDP (N=514)	MSDP-E (N=414)	0-25 %ile		26-50 %ile		51-75 %ile		76-100 %ile	
			No MSDP (N=183)	MSDP-E (N=41)	No MSDP (N=150)	MSDP-E (N=89)	No MSDP (N=115)	MSDP-E (N=117)	No MSDP (N=66)	MSDP-E (N=167)
Race (Black)	65 (13%)	69 (17%)	12 (7%)	6 (15%)	17 (11%)	10 (11%)	18 (16%)	23 (20%)	18 (27%)	30 (18%)
Paternal Smoking	300 (58%)	234 (57%)	124 (69%)	18 (47%)	81 (56%)	41 (53%)	59 (56%)	73 (67%)	36 (69%)	102 (70%)
Maternal Education	>13	177 (43%) ^{***}	106 (59%)	29 (71%)	87 (58%)	46 (52%)	52 (45%)	59 (51%)	16 (24%)	43 (26%)
Paternal Education	>13	166 (40%)	91 (53%)	16 (39%)	62 (42%)	37 (44%)	52 (47%)	52 (44%)	20 (30%)	61 (39%)
Maternal FTND severity ^a :	0	134 (26%) [‡]	102 (60%) [‡]	20 (57%) [‡]	30 (20%)	18 (20%) [‡]	2 (2%)	8 (7%)	0 (0%)	0 (0%) [‡]
	1	154 (30%)	28 (17%) ^{**}	10 (29%)	61 (41%)	27 (30%)	49 (43%)	46 (39%)	16 (24%)	24 (14%)
	2	115 (22%)	31 (18%) ^{***}	2 (6%)	38 (25%)	36 (40%)	36 (32%)	39 (33%)	10 (15%)	18 (11%)
	3	79 (15%)	8 (5%) ^{***}	3 (9%)	15 (10%)	8 (9%)	22 (19%)	19 (16%)	34 (51%)	106 (63%)
	4	16 (3%)	0 (0%) ^{**}	0 (0%) [‡]	6 (4%)	0 (0%) [‡]	4 (4%)	5 (4%) [‡]	6 (9%)	19 (11%) [‡]
Paternal AD	3+ sx	97 (19%)	21 (11%) [*]	6 (15%)	22 (15%)	12 (13%)	26 (23%)	27 (23%)	28 (42%)	76 (46%)
Maternal AD	3+ sx	28 (5%)	4 (2%)	0 (0%) [‡]	10 (7%)	4 (4%)	12 (10%)	2 (2%)	2 (3%)	16 (10%)
Maternal Age ^b :	20	58 (11%)	20 (11%)	8 (20%)	8 (5%)	12 (13%)	14 (12%)	13 (11%)	16 (24%)	30 (18%)
	30	206 (40%)	80 (44%)	14 (34%)	66 (44%)	39 (44%)	40 (35%)	49 (42%)	20 (30%)	35 (21%) [*]
	35	79 (15%)	33 (18%)	10 (24%)	24 (16%)	12 (13%)	14 (12%)	24 (21%)	8 (12%)	12 (7%)
	>35	25 (5%)	13 (7%)	1 (2%)	10 (7%)	5 (6%)	2 (2%)	0 (0%) [‡]	0 (0%)	7 (4%) [‡]
Maternal Year of Birth ^c :	1949	114 (22%)	52 (28%)	9 (22%)	34 (23%)	18 (20%)	16 (14%)	20 (17%)	12 (18%)	28 (27%)
	1959	169 (33%)	47 (26%)	10 (24%)	39 (26%)	32 (36%)	47 (41%)	40 (34%)	36 (55%)	84 (50%)
	1960	74 (14%)	28 (15%)	10 (24%)	18 (12%)	12 (13%)	20 (17%)	12 (10%)	8 (12%)	33 (20%)
Parents Never Together		32 (6%)	12 (8%)	4 (11%)	6 (4%)	4 (5%)	8 (9%)	5 (4%)	6 (12%)	20 (15%)

Characteristics of individuals from mothers with (MSDP-T)/without (no-MSDP) a history of smoking during the first trimester for each quartile of the MSDP-T risk distribution. Notation: proportion and percentages reported are relative to the total sample size for the given category for “No MSDP” or MSDP-T

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symptom
= p<.05,
*
= p<.01
**
*** = p<.001
I = Logistic regressions performed on the overall sample or within quartile to examine relationship between MDSP and familial factors
d = Reference group for the multinomial logistic regression is FTND=1 for Overall, Q1, and Q2 but is FTND=4 for Q3 and Q4 due to low cell counts
b = Reference group for the multinomial logistic regression is maternal age 21-25
c = Reference group for the multinomial logistic regression is maternal year of birth 1950-1954
i = can't compute difference due to cell size 0
* = used as reference group.

Table IIb

Prevalence (n [%]) of familial factors within each quartile of the MSDP-T risk distribution by MSDP status.

Familial factors	Overall ^f		by Quartile ^f				51-75 %ile				76-100 %ile			
			0-25 %ile				26-50 %ile				MSDP-T (N=120)			
	No MSDP (N=514)	MSDP-T (N=688)	No MSDP (N=250)	MSDP-T (N=42)	No MSDP (N=158)	MSDP-T (N=28)	No MSDP (N=91)	MSDP-T (N=22)	No MSDP (N=70)	MSDP-T (N=239)	No MSDP (N=36)	MSDP-T (N=287)	No MSDP (N=36)	MSDP-T (N=287)
Race (Black)	65 (13%)	78 (11%)	29 (12%)	8 (19%)	22 (14%)	21 (18%)	22 (14%)	8 (19%)	10 (14%)	19 (8%)	4 (11%)	30 (10%)	4 (11%)	30 (10%)
Paternal Smoking	300 (58%)	483 (70%)	130 (55%)	20 (53%)	96 (66%)	77 (73%)	96 (66%)	20 (53%)	44 (67%)	153 (67%)	30 (94%)	233 (87%)	30 (94%)	233 (87%)
Maternal Education	>13	261 (51%)	132 (53%)	28 (67%)	91 (58%)	40 (33%)	91 (58%)	28 (67%)	32 (46%)	85 (36%)	6 (17%)	88 (31%)	6 (17%)	88 (31%)
Paternal Education	>13	225 (44%)	131 (52%)	24 (57%)	64 (43%)	48 (43%)	64 (43%)	24 (57%)	26 (40%)	86 (37%)	4 (12%)	47 (18%)	4 (12%)	47 (18%)
Maternal FTND severity ^a :	0	134 (26%)	128 (55%)	16 (38%)	6 (4%)	4 (3%)	6 (4%)	16 (38%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	1	154 (30%)	65 (9%)	104 (44%)	24 (57%)	33 (28%)	48 (31%)	24 (57%)	2 (3%)	8 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	2	115 (22%)	163 (24%)	2 (1%)	2 (5%)	93 (59%)	74 (62%)	2 (5%)	20 (29%)	63 (26%)	0 (0%)	24 (8%)	0 (0%)	24 (8%)
	3	79 (15%)	326 (47%)	0 (0%)	0 (0%)	9 (6%)	9 (8%)	0 (0%)	44 (63%)	146 (61%)	26 (72%)	171 (60%)	26 (72%)	171 (60%)
	4	16 (3%)	114 (17%)	0 (0%)	0 (0%)	2 (1%)	2 (1%)	0 (0%)	4 (6%)	22 (9%)	10 (28%)	92 (32%)	10 (28%)	92 (32%)
Paternal AD	3+ sx	97 (19%)	222 (32%)	27 (11%)	8 (19%)	40 (25%)	24 (20%)	8 (19%)	16 (23%)	52 (22%)	14 (39%)	138 (49%)	14 (39%)	138 (49%)
Maternal AD	3+ sx	28 (5%)	66 (10%)	2 (1%)	2 (5%)	16 (10%)	10 (8%)	2 (5%)	8 (11%)	21 (9%)	2 (6%)	33 (12%)	2 (6%)	33 (12%)
Maternal Age ^b :	20	58 (11%)	98 (14%)	21 (8%)	8 (19%)	25 (16%)	14 (12%)	8 (19%)	8 (11%)	38 (16%)	4 (11%)	38 (13%)	4 (11%)	38 (13%)
	30	206 (40%)	216 (31%)	114 (46%)	16 (38%)	58 (37%)	42 (35%)	16 (38%)	24 (34%)	84 (35%)	10 (28%)	74 (26%)	10 (28%)	74 (26%)
	35	79 (15%)	103 (15%)	41 (16%)	4 (10%)	26 (16%)	18 (15%)	4 (10%)	8 (11%)	38 (26%)	4 (11%)	43 (15%)	4 (11%)	43 (15%)
	>35	25 (5%)	42 (6%)	9 (4%)	2 (5%)	6 (4%)	18 (15%)	2 (5%)	4 (6%)	10 (4%)	6 (17%)	12 (4%)	6 (17%)	12 (4%)
	1949	152 (30%)	111 (16%)	52 (21%)	10 (24%)	52 (21%)	10 (24%)	10 (24%)	36 (23%)	34 (28%)	12 (17%)	57 (24%)	12 (17%)	57 (24%)
Maternal Year of Birth ^c :	1959	250 (49%)	134 (19%)	91 (36%)	14 (33%)	91 (36%)	14 (33%)	14 (33%)	50 (32%)	34 (28%)	18 (26%)	72 (30%)	18 (26%)	72 (30%)
	1960	95 (18%)	72 (10%)	27 (11%)	6 (14%)	27 (11%)	6 (14%)	6 (14%)	21 (13%)	16 (13%)	20 (29%)	44 (18%)	20 (29%)	44 (18%)
Parents Never Together		32 (6%)	69 (10%)	12 (5%)	2 (6%)	10 (8%)	6 (6%)	2 (6%)	8 (13%)	27 (13%)	2 (7%)	34 (14%)	2 (7%)	34 (14%)

Characteristics of individuals from mothers with (MSDP-Ty)without (no-MSDP) a history of smoking during the first trimester for each quartile of the MSDP-T risk distribution. Notation: proportion and percentages reported are relative to the total sample size for the given category for “No MSDP” or MSDP-T

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symptom
= p<05,
*
/ = Logistic regressions performed on the overall sample or within quartile to examine relationship between MDSP and familial factors

d = Reference group for the multinomial logistic regression is FTND=1 for Overall, Q1, and Q2 but is FTND=4 for Q3 and Q4 due to low cell counts

b = Reference group for the multinomial logistic regression is maternal age 21-25

c = Reference group for the multinomial logistic regression is maternal year of birth 1950-1954

i = can't compute difference due to cell size 0

* = used as reference group.

Table IIIa

Effect (β , 95% confidence interval) of MSDP-E on offspring initial reactions to alcohol and cigarettes

Phenotype	Model-I		Model-II		$\beta_{\text{MSDP-E}}$ by quartile				
	$\beta_{\text{MSDP-E}}$	$\beta_{\text{P-SCORE}}$	$\beta_{\text{MSDP-E}}$	$\beta_{\text{P-SCORE}}$	0-25%ile	26-50%ile	51-75%ile	76-100%ile	
Alcohol Initial Reactions									
Pleasure	0.94 [0.63, 1.41]		1.13 [0.74, 1.71]	0.25 [0.08, 0.82] ^a	0.56 [0.22, 1.40]	1.02 [0.40, 2.64]	2.86 [1.13, 7.27] ^a	0.89 [0.42, 1.88]	
Flush	1.18 [0.77, 1.82]		1.16 [0.76, 1.75]	1.10 [0.37, 3.29]	1.06 [0.33, 3.42]	1.36 [0.62, 2.95]	0.59 [0.27, 1.31]	2.29 [1.08, 4.82] ^a	
Dizzy	0.61 [0.41, 0.91] [*]		0.68 [0.46, 1.00] ^a	0.58 [0.20, 1.69]	0.58 [0.27, 1.28]	0.53 [0.24, 1.21]	0.67 [0.33, 1.35]	0.81 [0.38, 1.70]	
Sleepy	1.45 [0.98, 2.15]		1.47 [0.96, 2.26]	0.89 [0.27, 2.92]	1.97 [0.77, 5.04]	1.56 [0.62, 3.96]	1.39 [0.63, 3.05]	1.39 [0.61, 3.17]	
Stomach	1.35 [0.83, 1.87]		1.61 [1.05, 2.47] ^a	0.38 [0.12, 1.19]	2.02 [0.71, 5.73]	1.91 [0.79, 4.63]	1.11 [0.51, 2.40]	1.44 [0.70, 2.99]	
Headache	1.60 ^a [1.02, 2.51]		1.77 [1.07, 2.90] ^a	0.49 [0.13, 1.89]	2.17 [0.61, 7.64]	2.51 [0.99, 6.36]	1.61 [0.69, 3.74]	0.88 [0.39, 2.03]	
Heart	1.25 [0.77, 2.03]		1.41 [0.83, 2.40]	0.41 [0.10, 1.72]	2.33 [0.93, 5.84]	1.97 [0.77, 5.07]	0.83 [0.25, 2.72]	1.65 [0.50, 5.41]	
Factor 1	0.01 [-0.07, 0.09]		0.04 [-0.09, 0.17]	-0.19 [-0.60, 0.15]	0.01 [-0.14, 0.15]	0.07 [-0.08, 0.23]	-0.04 [-0.18, 0.10]	0.05 [-0.11, 0.21]	
Factor 2	0.05 [-0.03, 0.14]		0.11 [-0.02, 0.23]	-0.26 [-0.56, 0.06]	0.10 [-0.09, 0.28]	0.14 [-0.05, 0.32]	0.01 [-0.16, 0.17]	0.06 [-0.10, 0.21]	
Cigarette Smoking Initial Reactions									
Pleasure	0.78 [0.55, 1.12]		0.80 [0.55, 1.18]	0.85 [0.32, 2.29]	1.89 [0.89, 4.01]	0.96 [0.42, 2.17]	0.81 [0.42, 1.58]	0.34 [0.15, 0.81] [*]	
Cough	1.08 [0.74, 1.58]		1.05 [0.70, 1.58]	1.24 [0.42, 3.67]	1.54 [0.59, 4.01]	0.86 [0.37, 1.96]	0.97 [0.46, 2.06]	0.94 [0.40, 2.24]	
Dizzy	0.98 [0.67, 1.41]		0.75 [0.50, 1.14]	5.77 [1.75, 19.09] [*]	2.54 [1.02, 6.31] ^a	0.52 [0.21, 1.29]	1.24 [0.65, 2.39]	0.36 [0.14, 0.94] ^a	
Headache	1.66 [1.12, 2.45] [*]		1.52 [1.00, 2.30]	1.85 [0.57, 5.93]	3.04 [1.15, 8.04] ^a	0.68 [0.25, 1.87]	2.27 [0.99, 5.19]	1.39 [0.61, 3.15]	
Heart	1.13 [0.74, 1.74]		1.09 [0.64, 1.86]	1.27 [0.30, 5.37]	3.31 [1.08, 10.15] ^a	0.98 [0.36, 2.63]	1.97 [0.71, 5.42]	0.43 [0.17, 1.09]	
Nausea	1.32 [0.84, 2.08]		1.22 [0.73, 2.05]	1.72 [0.46, 6.42]	0.65 [0.10, 4.27]	2.23 [0.79, 6.28]	0.62 [0.24, 1.59]	1.12 [0.46, 2.71]	
Like Taste	1.33 [0.81, 2.16]		1.42 [0.83, 2.43]	0.62 [0.16, 2.34]	1.97 [0.53, 7.33]	1.46 [0.53, 4.02]	1.14 [0.48, 2.70]	1.30 [0.42, 4.07]	
Factor 1	-0.03 [-0.12, 0.06]		-0.02 [-0.12, 0.08]	-0.09 [-0.34, 0.17]	0.13 [-0.05, 0.30]	0.02 [-0.17, 0.22]	-0.03 [-0.20, 0.13]	-0.16 [-0.32, 0.01]	
Factor 2	0.06 [-0.02, 0.15]		0.03 [-0.10, 0.17]	0.35 [-0.02, 0.73]	0.18 [0.02, 0.35] ^a	-0.05 [-0.28, 0.17]	0.10 [-0.07, 0.26]	-0.06 [-0.24, 0.12]	

Table showing the level of initial reactions to alcohol and cigarettes in off-spring of mothers who smoke during pregnancy (versus no MSDP-E) before (Model I, unadjusted regression coefficients) and after (Model II, adjusted regression coefficients) controlling for propensity for MSDP-E, as well as the effect of MSDP-E within each quartile of the MSDP-E risk distribution. Cigarette smoking Hedonic Factor 1 includes pleasure and enjoying taste during first cigarettes and Cigarette smoking Somatic Factor 2 includes feeling dizzy, headache, beating heart, and nausea during first cigarettes. Alcohol Somatic Factor 1 includes feeling flush, dizzy, and very sleepy during first drinks and Alcohol Somatic Factor 2 includes stomach sickness, headache, and heart beating during first drinks. Notations

50>d=
*
01>d=
p
100>d=***
10>d=**
through vary N, N = q

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Table IIIb
Effect (β , 95% confidence interval) of MSDP-T on offspring initial reactions to alcohol and cigarettes

Phenotype	Model-I		Model-II		$\beta_{\text{MSDP-T}}$ by quartile				
	$\beta_{\text{MSDP-T}}$	β	$\beta_{\text{MSDP-T}}$	β	P-SCORE	0-25%ile	26-50%ile	51-75%ile	76-100%ile
Alcohol Initial Reactions									
Pleasure	0.68 [0.49, 0.96] ^a	0.71 [0.46, 1.09]	0.71 [0.46, 1.09]	0.91 [0.45, 1.86]		0.51 [0.15, 1.71]	0.42 [0.21, 0.86] [*]	0.55 [0.24, 1.28]	1.62 [0.76, 3.47]
Flush	1.15 [0.82, 1.60]	1.21 [0.80, 1.83]	1.21 [0.80, 1.83]	0.85 [0.43, 1.68]		1.59 [0.47, 5.38]	1.63 [0.82, 3.23]	0.45 [0.23, 0.87] [*]	2.43 [0.83, 7.11]
Dizzy	0.79 [0.57, 1.07]	0.85 [0.57, 1.27]	0.85 [0.57, 1.27]	0.79 [0.41, 1.51]		0.93 [0.33, 2.62]	0.91 [0.45, 1.82]	0.58 [0.30, 1.12]	1.12 [0.41, 3.10]
Sleepy	1.36 [0.97, 1.89]	1.50 [1.00, 2.26]	1.50 [1.00, 2.26]	0.74 [0.38, 1.44]		0.70 [0.27, 1.83]	1.88 [0.94, 3.79]	1.43 [0.58, 3.53]	1.14 [0.52, 2.54]
Stomach	1.48 [1.06, 2.07] [*]	1.74 [1.14, 2.64] [*]	1.74 [1.14, 2.64] [*]	0.64 [0.33, 1.23]		1.31 [0.49, 3.54]	4.60 [2.28, 9.30] [*]	0.86 [0.47, 1.58]	1.22 [0.48, 3.15]
Headache	1.59 [1.09, 2.32] [*]	1.67 [1.03, 2.72] ^a	1.67 [1.03, 2.72] ^a	0.85 [0.40, 1.82]		2.02 [0.55, 7.44]	1.95 [0.86, 4.44]	0.79 [0.38, 1.67]	2.16 [0.64, 7.32]
Heart	2.02 [1.33, 3.05] ^{**}	2.12 [1.20, 3.77] [*]	2.12 [1.20, 3.77] [*]	0.86 [0.35, 2.12]		3.03 [0.95, 9.69]	2.49 [0.94, 6.55]	1.14 [0.50, 2.65]	2.67 [0.47, 15.32]
Factor 1	0.03 [-0.03, 0.10]	0.09 [-0.05, 0.23]	0.09 [-0.05, 0.23]	-0.11 [-0.46, 0.12]		0.05 [-0.11, 0.21]	0.13 [-0.03, 0.28]	-0.08 [-0.21, 0.05]	0.07 [-0.06, 0.20]
Factor 2	0.08 [0.01, 0.15] ^a	0.16 [0.02, 0.29] [*]	0.16 [0.02, 0.29] [*]	-0.12 [-0.38, 0.09]		0.11 [-0.07, 0.29]	0.20 [0.03, 0.36] [*]	-0.06 [-0.18, 0.07]	0.09 [-0.05, 0.23]
Smoking Initial Reactions									
Pleasure	0.80 [0.59, 1.08]	0.78 [0.52, 1.18]	0.78 [0.52, 1.18]	1.05 [0.53, 2.07]		1.33 [0.47, 3.77]	0.57 [0.29, 1.11]	0.60 [0.31, 1.15]	0.29 [-0.66, 1.25]
Cough	1.31 [0.94, 1.82]	0.99 [0.65, 1.50]	0.99 [0.65, 1.50]	2.19 [1.12, 4.26] ^a		2.32 [0.63, 8.60]	1.30 [0.67, 2.52]	0.52 [0.23, 1.19]	0.41 [0.12, 1.38]
Dizzy	1.27 [0.94, 1.73]	0.91 [0.61, 1.34]	0.91 [0.61, 1.34]	2.59 [1.32, 5.08] [*]		2.32 [0.84, 6.43]	0.91 [0.52, 1.59]	0.63 [0.30, 1.34]	0.48 [0.15, 1.54]
Headache	1.75 [1.25, 2.45] ^{**}	1.27 [0.81, 1.98]	1.27 [0.81, 1.98]	2.56 [1.13, 5.80] ^a		2.78 [0.98, 7.92]	2.83 [1.19, 6.75] [*]	0.56 [0.29, 1.08]	1.22 [0.50, 2.95]
Heart	1.76 [1.24, 2.49] ^{**}	1.24 [0.78, 1.95]	1.24 [0.78, 1.95]	2.80 [1.25, 6.26] [*]		3.29 [1.09, 9.92] ^a	1.25 [0.62, 2.50]	1.13 [0.50, 2.56]	0.77 [0.29, 2.04]
Nausea	1.58 [1.09, 2.29] [*]	1.60 [1.00, 2.54] ^a	1.60 [1.00, 2.54] ^a	0.97 [0.46, 2.08]		2.10 [0.95, 4.66]	3.31 [1.46, 7.51] [*]	0.76 [0.36, 1.61]	4.48 [0.80, 25.08]
Like Taste	1.50 [0.99, 2.26]	1.47 [0.89, 2.44]	1.47 [0.89, 2.44]	1.05 [0.44, 2.49]		1.14 [0.28, 4.62]	1.89 [0.83, 4.31]	1.19 [0.56, 2.52]	0.90 [0.33, 2.50]
Factor 1	-0.03 [-0.10, 0.06]	-0.03 [-0.13, 0.08]	-0.03 [-0.13, 0.08]	-0.01 [-0.23, 0.17]		0.02 [-0.19, 0.22]	-0.08 [-0.24, 0.09]	-0.07 [-0.19, 0.06]	0.03 [-0.09, 0.14]
Factor 2	0.13 [0.06, 0.20] ^{***}	0.07 [-0.07, 0.20]	0.07 [-0.07, 0.20]	0.35 [0.07, 0.58] ^{**}		0.21 [-0.01, 0.42]	0.13 [-0.01, 0.27]	-0.09 [-0.24, 0.05]	<0.01 [-0.11, 0.12]

Table showing the level of initial reactions to alcohol and cigarettes in offspring of mothers who smoke during pregnancy (versus no MSDP-T) before (Model I) and after controlling for propensity for MSDP-T (Model II), as well as the effect of MSDP-T within each quartile of the MSDP-E risk distribution. Cigarette smoking Hedonic Factor 1 includes pleasure and enjoying taste during first cigarettes and Cigarette smoking Somatic Factor 2 includes feeling dizzy, headache, beating heart, and nausea during first cigarettes. Alcohol Somatic Factor 1 includes feeling flush, dizzy, and very sleepy during first drinks and Alcohol Somatic Factor 2 includes stomach sickness, headache, and heart beating during first drinks. Notations:

'100'>d=

10>d=
**
50>d=
*
p<10
=b
q = N's vary by group

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