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Effects of Maternal Smoking during Pregnancy on Offspring Externalizing Problems: Contextual Effects in a Sample of Female Twins

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Abstract

Studies of maternal smoking during pregnancy (MSDP) suggest increased risk for cognitive impairment and psychiatric outcomes. However, it is uncertain whether these associations are the direct result of MSDP or related to confounding familial variables associated with MSDP. The current study employed propensity score analysis to examine the effects of MSDP on offspring EXT using data from a large sample of 979 unrelated mothers. Logistic regression models were used to determine the propensity that the offspring of these mothers were likely to be exposed to MSDP (i.e., smoked during only the first trimester (MSDP-EARLY[E]) or smoked throughout their pregnancy (MSDP-THROUGHOUT[T])) given known familial confounders. Analyses focused on the effect of MSDP-E/T on the EXT behavior in offspring of these mothers (N=1616) were conducted across the distribution of liability for MSDP-E/T and at different levels of risk for MSDP-E/T. MSDP-E/T was associated with offspring EXT problems, but the effects were partly confounded by the familial liability for MSDP. Further, the observed effects were not consistent across all levels of the MSDP risk distribution. These findings suggest a direct association between MSDP and offspring EXT behaviors, and that varied associations observed across studies may be

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the result of differences in the level of familial confounders that also have an effect on offspring EXT.

Keywords

ADHD; conduct disorder; alcohol dependence; tobacco dependence; smoking during pregnancy; nicotine; pregnancy

Introduction

According to the Centers for Disease Control and Prevention, maternal smoking during pregnancy (MSDP) is a prevalent, albeit preventable, risk factor for negative outcomes in children of mothers who smoke during part or all of their pregnancy. MSDP is associated with complications during pregnancy, e.g., reduced placental blood flow (Larsen, Clausen et al. 2002) and low birth weight (Hegaard, Kjaergaard et al. 2006; Ward, Lewis et al. 2007; Varvarigou, Fouzas et al. 2010), as well as neurocognitive deficits (Daseking, Petermann et al. 2015) and externalizing problems (EXT), including attention deficit hyperactivity disorder (ADHD) (Han, Kwon et al. 2015), alcohol/nicotine dependence (D'Onofrio, Van Hulle et al. 2008; Rydell, Cnattingius et al. 2012; Zhou, Rosenthal et al. 2014) and conduct disorder (Slotkin 2013). Unfortunately, it is unclear whether the observed associations between MSDP and childhood EXT problems are the direct effect of tobacco exposure *in utero* or the result of inherited familial factors (i.e., genetic and environmental) related to both EXT (in general) and MSDP. In other words, does MSDP pose a significant risk for EXT, over and above familial factors that also influence the likelihood of developing externalizing problems? For instance, recent findings suggest limited effects of MSDP on adult tobacco use in the context of genetic and familial influences (Rydell, Granath et al. 2014). Further, MSDP effects on EXT (e.g. ADHD) are attenuated once familial influences (e.g., paternal alcoholism (Knopik, Heath et al. 2006; Thapar, Rice et al. 2009; Skoglund, Chen et al. 2014)) are taken into account, suggesting that the realization of the "true" association between MSDP and offspring EXT is dependent upon our ability to appropriately control for shared familial influences (i.e., genetic and shared family environmental factors). Overall, it remains unclear whether the effect of MSDP on future EXT is a consequence of inherited risk factors for these same EXT problems or other associated disorders, or whether tobacco exposure *in utero* results in unique effects that increase risk for EXT in conjunction with or beyond the effects transmitted by one's parents.

The mechanisms by which prenatal tobacco exposure affects the above mentioned neuropsychological and psychiatric outcomes are hypothesized to be the result of the teratogenic properties of the components of commercial tobacco products (predominantly cigarettes). MSDP has been shown to result in altered fetal blood flow and protein metabolism, as well as a proliferation of compounds that lead to fetal hypoxic stress (Hutter, Kingdom et al. 2010). Studies of the effects of nicotine exposure on neurotransmitters suggest that nicotine exposure *in utero* leads to marked neurodevelopmental alterations. Specifically, the alteration of receptor and neurotransmitter levels (e.g., increases in hippocampal muscarinic receptors and $\alpha 4\beta 2$ nicotinic acetylcholine receptor [in the occipital

cortex] levels (Yanai, Pick et al. 1992)) (Roy, Seidler et al. 2002; Slotkin 2004; Slotkin, Tate et al. 2006). Many of these same neurotransmitters are hypothesized to contribute to individual differences in EXT (DeYoung, Peterson et al. 2006; Hohmann, Becker et al. 2009; Stadler, Poustka et al. 2010; Caldwell, Armstrong et al. 2015). These common mechanisms may be the link between MSDP and EXT; however, additional research is needed to confirm this hypothesis.

The mixed effects across studies linking MSDP to offspring EXT behaviors are partly due to methodological differences. As previously mentioned, the conflicting evidence of an effect of MSDP on EXT may be the result of a lack of inclusion of confounders that affect the risk for MSDP and EXT. For instance, mothers who smoke during pregnancy have been shown to differ on a number of factors, including personality traits, maternal education, parental alcohol use/alcoholism, and preterm delivery, to name a few (Ramsay and Reynolds 2000; Linnet, Dalsgaard et al. 2003; Knopik, Sparrow et al. 2005). Two notable studies that have clearly demonstrated familial confounding of the effects of MSDP on EXT behaviors include an early report by Knopik et al. (2006) and a report by D'Onofrio et. al. (2008). Knopik et al., (2006) utilized the children-of-twins design to study maternal alcohol use disorder, MSDP and ADHD, while D'Onofrio et al., (2008) examined the effects of MSDP on EXT behaviors in a sample of females and their children. Both studies indicated an effect of MSDP on EXT problems, as well as an attenuation of the effects of MSDP when maternal/familial characteristics were included in the statistical model as control variables. Another notable finding to come from these studies was the observation that independent/direct effects of MSDP are dependent upon the nature of the sample used in the comparison (i.e., whether the comparison of MSDP effects occurs between (1) siblings or (2) unrelated individuals) and the specific EXT behavior under study. This was most evident in the report by D'Onofrio et al. (2008), which showed that the inclusion of confounding variables (as covariates) in the model predicting EXT using MSDP resulted in the attenuation of the observed effect of MSDP on attention deficit hyperactivity, oppositional defiance, and conduct problems among unrelated individuals. However, when the analyses were limited to siblings who differed in prenatal nicotine exposure, independent effects of MSDP were only observed for attention deficit hyperactivity problems. This pattern of results was later replicated in a study of the effects of MSDP on offspring substance use and problems, although all observed effects between MSDP and offspring substance use and problems appeared to be entirely driven by familial background factors (D'Onofrio, Rickert et al. 2012).

Given the mixed findings across prior studies and EXT behaviors (Knopik 2009), the current study sought to provide additional evidence of the direct effects of MSDP on externalizing behaviors. Quasi-experimental research designs, such as the Children-of-Twins (CoT) (D'Onofrio, Turkheimer et al. 2003) and sibling comparison (Frisell, Oberg et al. 2012) methods, are useful for accounting for environmental and genetic confounds when estimating the causal effect of parental measures on child outcomes. However, in the absence of such designs, as is the case with most observational studies, alternative methods, such as propensity scores (Rosenbaum and Rubin 1983; Austin 2011) can be used to account for similarities with respect to a large number of potential confounders. Our review of the literature identified three studies that have utilized propensity methods (i.e., matching,

stratification, or covariate adjustment using the propensity score) to account for familial confounds while examining the effects of MSDP in situations where sibling comparison or the children-of-twins design methods were unavailable. In an early report by Boutwell and Beaver (2010), MSDP (coded as 0=non-smoker, 1=smoker) was not associated with a composite measure of childhood externalizing behaviors (N~3300) after matching individuals on propensity for SDP using confounds that included: maternal and paternal antisocial behavior, substance abuse, and depression, to name a few. Similarly, another study by Boutwell et al. (2011) (using a separate sample and 11 confounding variables), showed that MSDP (coded as 'exposure to any cigarette smoke in utero,' with 0 = 'mother did not smoke while pregnant' and 1='mother did smoke while pregnant') was not associated with childhood externalizing (defined as a factor score based on 50 items indexing impulsivity, attention span, self-regulation, and aggression). In the most recent study by Melchior et al. (2015), which used the EDEN Mother-Child Cohort Study, smoking during pregnancy (in particular, smoking throughout pregnancy) was observed to be positively associated high symptoms of hyperactivity/inattention in five year old children. Notably, these findings were present before and after accounting for parental smoking outside of the pregnancy, children's characteristics (e.g., birth weight), maternal characteristics (e.g., maternal depression), and family characteristics (e.g., parental separation) (Melchior, Hersi et al. 2015). Compared to previous studies using the CoT and sibling-comparison approaches, it would appear that MSDP is unrelated to EXT; however, the aforementioned propensity score studies were limited to EXT in children (i.e., up to 4 years of age across both studies by Boutwell and colleagues) and used a broad measure of EXT. Since the direct effect of MSDP on offspring EXT has been shown to (1) have a dose-response relationship and (2) vary as a function of the behavior in question, the current study examined the effects of MSDP on five separate indices of EXT using a sample of adolescent twins for which the set of familial risk factors predicting MSDP and offspring-psychopathology will not largely differ between twins. Further, we assess the relative effect of MSDP by identifying mothers who smoked only during the first trimester of their pregnancy and mothers who smoked throughout their pregnancy. Notably, comparisons are made with offspring of mothers who have a history of smoking, but who did not smoke during pregnancy. This latter point represents a difference between this current work and that of others using propensity scores to address this question (i.e., (Boutwell and Beaver 2010; Boutwell, Beaver et al. 2011; Melchior, Hersi et al. 2015)) and is salient to the interpretation of the findings, as it provides a relative index of the risk of smoking during pregnancy for mothers with a history of smoking. While the effect size of such an estimate is undoubtedly expected to be much smaller than that of a comparison to offspring of "non-smoking" mothers, it has direct clinical implications as it provides an accurate representation of the gains of successfully avoiding and/or limiting offspring exposure during pregnancy (i.e., none, early part of pregnancy, versus throughout) among women who are regular smokers.

Overall, the specific goals of the current article were to (1) determine the effects of MSDP on EXT across all levels of the distribution of risk for MSDP and (2) explore whether the observed effects of MSDP are consistent across each level of the distribution of risk for MSDP. In doing so, the present study builds upon our understanding of the neuropsychological effects of MSDP by evaluating the assumption that the MSDP effect is

consistent across all levels of the risk distribution. We hypothesize that, given enough time for offspring of mothers who smoke during pregnancy to manifest their externalizing tendencies, MSDP will increase severity across all externalizing behaviors with larger effects amongst offspring of mothers who smoked throughout their pregnancy (see Bidwell et al. (*in the current issue*) for similar hypotheses in regards to MSDP effects on initial reactions to alcohol and tobacco exposure).

Methods

Participants

Data were obtained from the Missouri Adolescent Female Twin Study (MOAFTS) (Heath, Madden et al. 1999; Heath, Howells et al. 2002). Briefly, MOAFTS twins were identified from birth records (between July 1, 1975 – June 30, 1985). Twins were recruited using a cohort-sequential sampling method with the ages of the initial cohorts being 13, 15, 17, and 19 years old. These twins and their families were recontacted for involvement in all subsequent waves of recruitment. Data utilized come from the initial and fourth waves of assessment. The analyses described are limited to twins (N=1616; 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.

Measures

Phenotypes assessed in the study were obtained from the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA) (Bucholz, Cadoret et al. 1994; Hesselbrock, Easton et al. 1999). Parents were asked to provide information about themselves and each twin using a telephone-adapted version of the SSAGA-II (the DSM-IV version of the DSM-IIIR-based SSAGA). Twins provided information using either the child or adolescent versions of the telephone-adapted SSAGA-II.

Smoking During Pregnancy—Maternal smoking during pregnancy (MSDP) was assessed as “smoking during *none, part,* or *all* of the pregnancy”. MSDP was operationalized as a set of orthogonal contrast codes with “regular smoker, but did not smoke during pregnancy” as the reference group (referred to as “No MSDP”) and the comparative groups being “regular smoker who smoked during the 1st trimester” (MSDP-EARLY (E)) and “regular smoker who smoked throughout their entire pregnancy” (MSDP-THROUGHOUT (T)).

Familial Risk Factors for MSDP—Ten variables were available. These variables were dummy coded and included as covariates in the analyses to derive the family-level propensity score for MSDP-E/T. Familial variables included race (African American (AA)/not AA) and parents never together. Specific maternal variables included, maternal alcohol dependence, maternal education (above/below high school), maternal age (was dummy coded into categories <20, 21–25, 26–30, 31–35, and >35 years of age), maternal year of birth (dummy coded into <1949dummy coded into <1950–1954–1955–1959, >1960), and maternal Fagerstrom Test for Nicotine Dependence (FTND) severity (on a 0–4 scale). Paternal variables included paternal education (above/below high school), paternal

smoking (twin report of lifetime smoking by the father [obtained at the fourth MOAFTS wave of assessment]), and three or more alcohol dependence symptoms.

Twin EXT Behaviors—Mothers provided data for each member of the twin pair on DSM-IV ADHD symptoms (individually scored for each sub-type (inattention (ADHD-IN) and hyperactivity/impulsivity (ADHD-HI), and DSM-IV alcohol and tobacco dependence symptoms (coded as symptom counts). Twins reported on their own symptoms of DSM-IV conduct disorder (CD) (see (Knopik, Heath et al. 2009)). All EXT behavior symptoms were assessed using the SSAGA. Based on prior studies using these data, as well as the suggestion that measures of symptom counts should be used rather than categorical diagnoses (Levy, Hay et al. 1997), analyses focused on log-transformed symptom counts for each measure [log(x+1)] (i.e., to improve approximation to a normal distribution) (see (Knopik, Sparrow et al. 2005; Knopik, Heath et al. 2009)).

Statistical Analyses

Propensity score analysis was conducted in SAS [version 9.4] (SAS) and descriptive analyses were conducted in Mplus [version 7] (Muthén and Muthén (1998–2012)). The main research questions were examined using multiple regression models (i.e., where MSDP-E/T were used to predict EXT 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 EXT 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 into quartiles (see below).

Propensity Score Derivation—Propensity score analysis was used to examine the relationship between MSDP and EXT behaviors. This approach was selected for these data because it provided a means to examine direct MSDP effects on EXT across the risk distribution for MSDP that is inferred from the set of familial risk factors for MSDP (Boutwell and Beaver 2010; Boutwell, Beaver et al. 2011; Waldron, Vaughan et al. 2014). We derived the probability of MSDP-E and MSDP-T from logistic regression models conducted on data from unrelated mothers (N=979 families) who provided information on their smoking behavior during their pregnancies (see Supplemental Tables S1a and S1b, respectively). MSDP-E/T status was predicted using dummy coded versions of the familial risk factors (see Supplemental Table S1a and S1b 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, where values closer to one indicated better separation of the smoking during pregnancy categories. Analyses described below were limited to the

offspring of a subset of these mothers for whom complete descriptive information on each offspring was available (N=829 families).

Stratification on Propensity Score—Stratification on the propensity score distribution is a common approach to dividing subjects into mutually exclusive subsets based on their propensity score (Austin 2011). When analyses are stratified on quantiles 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 quantile was designed to maximize statistical power for the within-quantile analyses, such that there was over 80% power to detect a moderate-strong effect of MSDP-E/T on each EXT outcome. 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 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 was the same among those at low, intermediate, or high probability of MSDP). Two models were fitted to the data for each EXT outcome using Poisson 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 EXT behavior was 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 consistent with prior work (Knopik, Sparrow et al. 2005; Knopik, Heath et al. 2009)). In Model II, each EXT behavior was predicted by MSDP-E/T while controlling for the propensity for MSDP-E/T and age. The effect of MSDP-E/T on EXT within each quartile was assessed by repeating Model I, but within each quartile.

Results

Propensity for SDP in Mothers

Based on the logistic regression models using all 10 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. 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 1a and 1b).

Propensity for MSDP-E and MSDP-T in Offspring of Mothers Who Smoked During Pregnancy

Amongst the 1616 subjects with maternal reports of MSDP, 26% (N=414) reported smoking in the 1st trimester (MSDP-E) compared to 43% (N=688) who reported smoking throughout their pregnancy (MSDP-T); 514 mothers reported no MSDP. As expected, the number of individuals who met the criteria for MSDP-E/T 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 S2a and S2b). Tables 1a and 1b provide an indication of the associations between the familial factors and MSDP-E and MSDP-T amongst the 1616 offspring (from the 829 families) used to test the main research question (note that these tables reflect more clinically relevant categorizations of the familial factors (described in Supplemental Tables S1a and S1b)). 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 1a and 1b also indicate the high level of similarity between offspring exposed and non-exposed to SDP for each of the ten familial factors within quartile, confirming that, by analytical design, offspring within each quartile are similar with respect to each familial factor. Table 2 shows the mean level of each EXT behavior, separately for all levels of MSDP.

Effect of MSDP on Offspring EXT across the MSDP Risk Distribution

Tests of the main research question using propensity scores to control for familial confounding are presented in Tables 3a (for MSDP-E effects) and Table 3b (for MSDP-T effects). Results from the first set of models (i.e., Model-I) suggested that when ignoring familial factors, MSDP-E and MSDP-T was associated with increased levels of EXT (i.e., CD and ADHD; effects on alcohol (AD) and nicotine dependence (ND) were limited). For example, MSDP-E increased ADHD inattention (β=0.95 [95% CI: 0.48, 1.41], $p < 0.001$), hyperactivity problems ($\beta = 0.68$ [95% CI: 0.14, 1.21], $p = 0.038$ and conduct problems ($\beta = 0.45$ [95% CI: 0.17, 0.72], $p = 0.008$). However, when the model was expanded to account for familial confounders (i.e., Model-II), MSDP-E effects on ADHD-inattention and hyperactivity/impulsivity were significantly attenuated (Table 3a-Model-II; $\beta_{ADHD\text{-}IN:\text{MSDP-E}} = 0.32$ [95% CI: −0.74, 1.39], $p = 0.619$ and $\beta_{ADHD\text{-}HI:\text{MSDP-E}} = 0.18$ [95% CI: −0.38, 0.75], $p = 0.592$), but MSDP-E effects on CD were only modestly attenuated, suggesting a direct effect of MSDP-E on offspring CD (Table 3a-Model-IIl $\beta_{CD:\text{MSDP-E}} = 0.43$ [0.10, 0.76], $p = 0.032$). The effects of MSDP-T on offspring EXT showed a similar pattern of results. For example, in the models ignoring familial confounders, smoking throughout pregnancy was shown to increase the levels of ADHD-hyperactivity/impulsivity and conduct problems (Table 3b-Model-I), but all of these effects (with the exception of ADHD inattention (Table 3b-Model-II; $\beta_{ADHD\text{-}IN:\text{MSDP-T}} = 0.85$

[0.27, 1.44], $p = 0.017$)) were attenuated when the model accounted for familial factors using propensity scores (Table 3b-Model-II). However, the MSDP-T effect on offspring ADHD-inattention problems remained significant in Model-II, suggesting an independent effect of MSDP-T. Overall, these findings would suggests that MSDP is independently associated with offspring EXT, however, the observation of effect on a specific EXT behavior appears to be dependent upon the level of exposure during the pregnancy (i.e., using early vs. throughout as a proxy for tobacco exposure levels).

Effect of MSDP on Offspring EXT 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 3a and 3b, respectively) showed MSDP does not consistently predict higher externalizing problems across the MSDP risk distribution. Despite the lack of observed effects of smoking during only the first trimester on offspring ADHD-inattention problems, MSDP-E was shown to increase the level of ADHD ($\beta = 0.85$, [95% CI: 0.38, 1.32], $p = 0.003$) and CD ($\beta = 0.67$, [95% CI: 0.16, 1.17], $p = 0.028$) problems in the 0–25th percentile families. MSDP-E was also shown to increase the level of ADHD hyperactivity/impulsivity problems in 51–75th and 76–100th percentile families. Despite the lack of effects of MSDP-E/T on AD and ND across the MSDP risk distribution, effects of MSDP-E on AD and ND reached significance in the 76–100th percentile families. Differences within quartile with respect to smoking throughout pregnancy (versus not SDP) also reached significance in several instances. For example, MSDP-T increased the level of ADHD inattention problems in the 0–25th percentile families, CD in the 26–50th and 51–75th percentile families, but decreased the levels of AD in the 0–25th percentile families, which had offspring from families with the lowest rates of familial AD and ND. Overall, these findings suggest that while the confounding due to familial factors is complex, there are direct effects of MSDP on offspring EXT.

Discussion

The present findings provide additional evidence for the role of MSDP in offspring externalizing behaviors, confirming that while some effects are robust to a wide range of confounding variables, there is a potential for spurious associations due to the combination of familial factors in the subjects under study, and how said factors are incorporated in the statistical model. Specifically, we demonstrated the impact of two levels of MSDP on externalizing behaviors before and after controlling for familial demographic and psychopathological background. Notably, our review of the literature indicated that this is the first study of its kind to examine the independent effects of MSDP after grouping individuals with respect to their risk for exposure to MSDP based on a set of known familial factors. The major findings from this study include:

1. Parental factors, such as alcohol dependence, nicotine dependence, and low education levels, increase the risk for maternal smoking during the first trimester and beyond the first trimester.
2. MSDP-E and MSDP-T are directly associated with some, but not all offspring EXT problems.

3. Parental factors confound the association between MSDP and offspring externalizing behaviors.

4. The effect of MSDP on offspring EXT does not appear to be consistent across all levels of the distribution of risk for MSDP.

The results of this study are in agreement with previous research (Roza, Verhulst et al. 2009) that suggests independent effects of MSDP, and that MSDP effects are confounded by parental characteristics. Had we failed to account for these familial relationships, our results would have overestimated the effects of MSDP. Controlling for familial confounding using the propensity score resulted in a significant reduction of the observed univariate effects of MSDP on EXT; however, this was not the case for all MSDP-EXT relationships. Notably, offspring ADHD-IN, CD, and nicotine dependence were influenced by MSDP after accounting for the effects of confounders using the propensity scores; however, these effects (or lack thereof) were not consistent across all levels of the MSDP risk distribution. Given the lack of *a priori* evidence for the nature of the joint effects of MSDP and familial indicators of MSDP on offspring externalizing, we capitalized on the dimensionality reduction properties of propensity scores to group individuals by their percentile rank on the MSDP propensity scores. In doing so, we were able to take these analyses a step further by examining whether the observed MSDP effects were consistent across the four quartiles of each MSDP risk distribution. A caveat of this approach is that the observed MSDP effects within strata may be sensitive to the number of strata chosen. For the current analyses, we maximized statistical power by separating the MSDP-risk distribution into quartiles when testing the effect of MSDP on offspring EXT. Individuals within each quartile were very similar (with respect to familial risk factors), and there were marked differences between quartiles (see Methods and Supplemental Material). The observed differences in the effects of MSDP-E and MSDP-T on offspring EXT between quartiles is suggestive of a dose-response effect of MSDP that is still confounded with familial factors. This would indicate that there exist combinations of familial factors that jointly influence the risk for SDP and offspring externalizing problems.

Independent effects of MSDP on offspring ADHD-IN and CD across the MSDP risk distribution, as well as significant independent effects of MSDP on EXT within quartiles of the MSDP risk distribution are novel findings that suggest that MSDP is directly associated with offspring EXT. While there are some differences between the current study and recent SDP studies using a PSA approach, differences in findings between studies might be attributed to differences in the specific propensity score approach used (e.g., propensity score matching versus stratification on the propensity scores using quantiles) and the nature of the sample. The current study utilized propensity scores to construct a 4-level categorical variable that contained approximately 25% of the distribution for each propensity score (i.e., MSDP-E and MSDP-T). The current study sample is also quite unique in respect to many other SDP studies. The current analyses are limited to families of female smokers with or without a history of MSDP. As such, the propensity distributions were based on comparisons between mothers with a history of smoking, thereby providing MSDP effects that were less likely to be inflated by the likelihood of smoking. In both papers by Boutwell and colleagues, subjects were “matched on the probability for smoking during pregnancy by

balancing groups on conditional probability used to estimate propensity scores" (Boutwell, Beaver et al. 2011). Their analyses compared the effect of MSDP in the unmatched and matched samples. Further, the reference group of Boutwell and colleagues' papers included offspring of non-smokers. Limiting the current analyses to only offspring of mothers who are regular smokers is a major strength of the current study, as it limits parameter bias that may be introduced by including offspring of non-smokers in the reference group. More specifically, while offspring of non-smokers would have increased our study sample size, adding them to the reference group for MSDP-E and MSDP-T may have confounded the effect of smoking during pregnancy with the likelihood of mothers being regular smokers. Thus by conditioning the current analyses on 'regularly smoking' mothers, we are able to provide estimates that are specific to MSDP. That being said, readers should be cognizant of the fact that the current findings reflect the effects of MSDP amongst mothers who smoke regularly. While our findings differed from the previous Boutwell papers, the MSDP-T effects were similar to recent findings by Melchior et al. (2015). Although Melchior et al.'s (2015) study used (a) mothers who were non-smokers and (b) a dichotomous phenotype to indicate hyperactivity/inattention problems, we also evidenced a positive association between smoking throughout pregnancy and offspring ADHD inattention problems after controlling for familial confounders, thereby providing additional evidence for a direct effect of MSDP effect on ADHD. While not all EXT behaviors appear to be influenced by MSDP, additional research is needed to extend this approach to different levels of tobacco exposure during pregnancy (i.e., using a quantitative measure (see limitation section below)).

Overall, these results suggest a direct association between MSDP and offspring EXT. However, some limitations of the study need to be considered when making inferences from these findings. First, it is important to acknowledge that there are limitations of the propensity score approach, in particular, the inclusion of characteristics related to both childhood externalizing problems and maternal smoking during pregnancy. While the "true" propensity score for MSDP is unknown, we did our best to approximate it by employing ten familial characteristics to capture as many underlying factors that could confound the relationship between MSDP and offspring EXT. That said, the current scores do not correct for biases from unmeasured confounders. For instance, the current findings may not generalize well to a recent report by D'Onofrio et al., (2012) who utilized a slightly different set of familial covariates to adjust for confounding. Their factors included measures, such as "maternal intellectual abilities", "maternal criminal conviction", and "binge drinking", which may balance individuals differently, in terms of risk for MSDP. Despite the difference in the set of confounding factors, both the D'Onofrio et al. (2012) study and the current study had a demonstrable ability to account for differences in risk for MSDP. Despite differences in the selection of confounders, these findings do provide improved estimates of MSDP effects over models that ignore confounding. Second, the selection of the number of quartiles was driven by maximizing power for the MSDP analyses within strata. Although individuals within each quartile were highly similar, different stratification choices would result in different groupings. The choice of quartile versus quintiles is dependent upon the factors/predictors used in the model and sample size. Historically, stratification on quintiles has been the preferred stratification approach as it eliminates nearly 90% of the bias due to confounders, but simulation studies have found support for using quartiles, which provides

more power and still eliminates bias, though to a slightly lesser degree (Leon and Hedecker, 2011). The current sample size afforded less than 80% power to test the MSDP effect within quintiles. As such, we utilized quartiles. Additional studies using larger samples are needed to determine if these effects are consistent across quintiles. Third, our analyses utilized a broad measure of a retrospectively reported maternal smoking during pregnancy. While previous studies support the reliability and utility of retrospective reporting of pregnancy variables by mothers (Heath, Knopik et al. 2003; Reich, Todd et al. 2003; Christensen, Tobiassen et al. 2004; Pickett, Kasza et al. 2009; Knopik, Marceau et al. (*current issue*)), readers should be aware that the sensitivity of the MSDP variable (i.e., its ability to reflect the amount of tobacco exposure by the offspring *in utero*) has been shown to be an important factor in the observation of MSDP effects. In an earlier report by Boutwell et al. (2011), broadly defined MSDP was not associated with offspring externalizing behavioral problems, however, a continuous measure of MSDP (i.e., the number of cigarette packs smoked per day) was associated with childhood externalizing, such that more packs smoked per day resulted in higher scores on the externalizing problem scale (among matched subjects). The current study is also not without some degree of inaccuracy in the MSDP variables, as they are all based on retrospective report. Though it should be noted that in other Missouri twin studies (Heath, Knopik et al. 2003; Reich, Todd et al. 2003) and Missouri family studies (Knopik et al., current issue) we have observed high reliability and stability of maternal reporting, suggesting that they are likely to be suitable for studying adverse “parent behavior”-“child outcome” associations. Overall, the current study findings may not generalize to other studies utilizing alternative measures of MSDP. Despite differences in assessment of MSDP, future analyses that incorporate familial confounders will provide enhanced insight into the effects of MSDP on offspring EXT behaviors. Fourth, the current study focused only on female twins, which might also explain differences when compared to other research studies that might have included males. While this limits the generalizability of the findings to males, the observation of effects of MSDP on EXT behavior at different portions of the MSDP distribution, might explain the mixed findings between MSDP and EXT between males and females. Although stratification of MSDP effect by gender are rarely studied, previous investigations have suggested a preponderance of antisocial behaviors, such as conduct and delinquency problems in males of mothers who smoke during pregnancy (see (Wakschlag, Pickett et al. 2002) for a review); however, similar effects between genders have also been observed (Maughan, Taylor et al. 2004). Likewise, a recent study of the effects of MSDP on ADHD found no differences in the MSDP effect between genders (Silva, Colvin et al. 2014). To the extent that the current findings hold true for males, variation in the MSDP effect on offspring EXT between genders may be a function of differences in combinatorial risk due to familial confounds. Finally, the size of the current study was insufficient to provide enough power to explore gene-environment interaction effects on offspring EXT within the identified propensity quartiles. Despite the lack of power in the current study, within-strata biometrical ACE/ADE models would control for gene-environment correlation effects that often confound gene-by-environment interaction twin studies using observational data.

In summary, while these results are tentative and in need of replication, they suggest that despite familial background effects, limiting fetal tobacco exposure among pregnant mothers

will reduce the severity of offspring externalizing behaviors. The current findings provide new information, which suggests that the hypothesis that the teratogenic properties of cigarettes impair the psychological well-being of offspring of mothers who smoke during pregnancy is too broad. Further, the hypothesis should be redefined to also consider the moderating role of familial factors. Notwithstanding the possible limitations of the set of familial factors used in the current study, these findings align with MSDP studies that suggest a causal effect of MSDP on offspring outcomes. For example, in this same special issue, Bidwell and colleagues (Bidwell, Palmer et al. (*current issue*)) use the same sample and approach to examine MSDP effects on initial reaction endophenotypes for alcohol and nicotine dependence risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1a

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

Familial factors		Overall[1]		by Quartile[1]							
				0–25 %ile		26–50 %ile		51–75 %ile		76–100 %ile	
		No MSDP (N=514)	MSDP-E (N=414)	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	261 (51%)	177 (43%) *	106 (59%)	29 (71%)	87 (58%)	46 (52%)	52 (45%)	59 (51%)	16 (24%)	43 (26%)
Paternal Education	>13	225 (44%)	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%)‡	46 (11%)‡	102 (60%)	20 (57%)‡	30 (20%)	18 (20%)‡	2 (2%)	8 (7%)	0 (0%)	0 (0%)†
	1	154 (30%)	107 (26%) **	28 (17%)	10 (29%)	61 (41%)	27 (30%)	49 (43%)	46 (39%)	16 (24%)	24 (14%)
	2	115 (22%)	95 (23%) **	31 (18%)	2 (6%)	38 (25%)	36 (40%)	36 (32%)	39 (33%)	10 (15%)	18 (11%)
	3	79 (15%)	136 (33%) ***	8 (5%)	3 (9%)	15 (10%)	8 (9%)	22 (19%)	19 (16%)	34 (51%)	106 (63%)
	4	16 (3%)	24 (6%) **	0 (0%)	0 (0%)†	6 (4%)	0 (0%)†	4 (4%)	5 (4%)‡	6 (9%)	19 (11%)‡
Paternal AD	3+ sx	97 (19%)	121 (29%) *	21 (11%)	6 (15%)	22 (15%)	12 (13%)	26 (23%)	27 (23%)	28 (42%)	76 (46%)
Maternal AD	3+ sx	28 (5%)	22 (5%)	4 (2%)	0 (0%)†	10 (7%)	4 (4%)	12 (10%)	2 (2%)	2 (3%)	16 (10%)
Maternal Age[b]:	≤20	58 (11%)	63 (15%)	20 (11%)	8 (20%)	8 (5%)	12 (13%)	14 (12%)	13 (11%)	16 (24%)	30 (18%)
	≤30	206 (40%)	137 (33%)	80 (44%)	14 (34%)	66 (44%)	39 (44%)	40 (35%)	49 (42%)	20 (30%)	35 (21%) *
	≤35	79 (15%)	58 (14%)	33 (18%)	10 (24%)	24 (16%)	12 (13%)	14 (12%)	24 (21%)	8 (12%)	12 (7%)
	>35	25 (5%)	13 (3%)	13 (7%)	1 (2%)	10 (7%)	5 (6%)	2 (2%)	0 (0%)†	0 (0%)	7 (4%)†
Maternal Year of Birth[c]:	≤1949	114 (22%)	75 (18%)	52 (28%)	9 (22%)	34 (23%)	18 (20%)	16 (14%)	20 (17%)	12 (18%)	28 (27%)
	≤1959	169 (33%)	166 (40%)	47 (26%)	10 (24%)	39 (26%)	32 (36%)	47 (41%)	40 (34%)	36 (55%)	84 (50%)
	≥1960	74 (14%)	67 (16%)	28 (15%)	10 (24%)	18 (12%)	12 (13%)	20 (17%)	12 (10%)	8 (12%)	33 (20%)
Parents Never Together		32 (6%)	33 (8%)	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;

*** p<.001;

** p < .01;

* p<05; sx = symptom;

1 Logistic regressions performed on the overall sample or within quartile to examine relationship between MDSP and familial factors;

a 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;

† can't compute difference due to cell size 0;

≠ used as reference group.

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Table 1b

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

Familial factors		Overall[1]		by Quartile[1]							
				0–25 %ile		26–50 %ile		51–75 %ile		76–100 %ile	
		No MSDP (N=514)	MSDP-T (N=688)	No MSDP (N=250)	MSDP-T (N=42)	No MSDP (N=158)	MSDP-T (N=120)	No MSDP (N=70)	MSDP-T (N=239)	No MSDP (N=36)	MSDP-T (N=287)
Race (Black)		65 (13%)	78 (11%)	29 (12%)	8 (19%)	22 (14%)	21 (18%)	10 (14%)	19 (8%)	4 (11%)	30 (10%)
Paternal Smoking		300 (58%)	483 (70%) ***	130 (55%)	20 (53%)	96 (66%)	77 (73%)	44 (67%)	153 (67%)	30 (94%)	233 (87%)
Maternal Education	>13	261 (51%)	241 (35%) ***	132 (53%)	28 (67%)	91 (58%)	40 (33%) **	32 (46%)	85 (36%)	6 (17%)	88 (31%)
Paternal Education	>13	225 (44%)	205 (30%) ***	131 (52%)	24 (57%)	64 (43%)	48 (43%)	26 (40%)	86 (37%)	4 (12%)	47 (18%)
Maternal FTND severity[a]:	0	134 (26%)	20 (3%) ‡	128 (55%)	16 (38%) ‡	6 (4%)	4 (3%) ‡	0 (0%)	0 (0%) †	0 (0%)	0 (0%) †
	1	154 (30%)	65 (9%) **	104 (44%)	24 (57%)	48 (31%)	33 (28%)	2 (3%)	8 (3%)	0 (0%)	0 (0%) †
	2	115 (22%)	163 (24%) ***	2 (1%)	2 (5%)	93 (59%)	74 (62%)	20 (29%)	63 (26%)	0 (0%)	24 (8%) †
	3	79 (15%)	326 (47%) ***	0 (0%)	0 (0%) †	9 (6%)	9 (8%)	44 (63%)	146 (61%)	26 (72%)	171 (60%)
	4	16 (3%)	114 (17%) ***	0 (0%)	0 (0%) †	2 (1%)	0 (0%) †	4 (6%)	22 (9%) ‡	10 (28%)	92 (32%) ‡
Paternal AD	3+ sx	97 (19%)	222 (32%) ***	27 (11%)	8 (19%)	40 (25%)	24 (20%)	16 (23%)	52 (22%)	14 (39%)	138 (49%)
Maternal AD	3+ sx	28 (5%)	66 (10%) *	2 (1%)	2 (5%)	16 (10%)	10 (8%)	8 (11%)	21 (9%)	2 (6%)	33 (12%)
Maternal Age[b]:	≤20	58 (11%)	98 (14%)	21 (8%)	8 (19%)	25 (16%)	14 (12%)	8 (11%)	38 (16%)	4 (11%)	38 (13%)
	≤30	206 (40%)	216 (31%) *	114 (46%)	16 (38%)	58 (37%)	42 (35%)	24 (34%)	84 (35%)	10 (28%)	74 (26%)
	≤35	79 (15%)	103 (15%)	41 (16%)	4 (10%)	26 (16%)	18 (15%)	8 (11%)	38 (26%)	4 (11%)	43 (15%)
	>35	25 (5%)	42 (6%)	9 (4%)	2 (5%)	6 (4%)	18 (15%)	4 (6%)	10 (4%)	6 (17%)	12 (4%)
Maternal Year of Birth[c]:	≤1949	152 (30%)	111 (16%)	52 (21%)	10 (24%)	52 (21%)	10 (24%)	36 (23%)	34 (28%)	12 (17%)	57 (24%)
	≤1959	250 (49%)	134 (19%)	91 (36%)	14 (33%)	91 (36%)	14 (33%)	50 (32%)	34 (28%)	18 (26%)	72 (30%)
	≥1960	95 (18%)	72 (10%)	27 (11%)	6 (14%)	27 (11%)	6 (14%)	21 (13%)	16 (13%)	20 (29%)	44 (18%)
Parents Never Together		32 (6%)	69 (10%)	12 (5%)	2 (6%)	10 (8%)	6 (6%)	8 (13%)	27 (13%)	2 (7%)	34 (14%)

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;

*** p<.001;

** p < .01;

* p<05; sx = symptom;

1 Logistic regressions performed on the overall sample or within quartile to examine relationship between MDSP and familial factors;

a 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;

† can't compute difference due to cell size 0;

≠ used as reference group.

Table 2

Description of raw (untransformed) externalizing behaviors by maternal smoking during pregnancy

	No MSDP (N=514)		MSDP-E (N=414)		MSDP-T (N=688)	
Items	**N**	**MEAN (STD)**	**N**	**MEAN (STD)**	**N**	**MEAN (STD)**
ADHD-IN	510	1.62 (2.40)	412	1.79 (2.44)	681	2.15 (2.71)
ADHD-HI	512	1.22 (2.05)	410	1.44 (1.99)	679	1.70 (2.32)
CD	463	0.78 (1.23)	365	1.11 (1.51)	608	1.08 (1.47)
AD	463	0.81 (1.26)	355	0.96 (1.41)	613	0.77 (1.16)
ND	463	1.02 (1.64)	357	1.20 (1.51)	612	1.41 (1.90)

Table showing the mean levels of symptoms in the entire sample and by subjects utilized in each of the propensity score analyses. Recall that MSDP-E and MSDP-T utilize the same reference population (i.e., 'No MSDP'). Abbreviations: AD - alcohol dependence, ADHD-IN - ADHD inattention, ADHD-HI - ADHD hyperactivity/impulsivity, CD - conduct disorder, ND - nicotine dependence, STD - standard deviation.

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Table 3a

Effect (β [95% confidence interval]) of MSDP-E on offspring externalizing behavior

	Model-I	Model-II		$\beta_{MSDP\text{-}Eb}$ by quartile			
Phenotype	$\beta_{MSDP\text{-}E}$	$\beta_{MSDP\text{-}E}$	$\beta_{P\text{-}SCORE}$	**0–25%ile**	**26–50%ile**	**51–75%ile**	**76–100%ile**
ADHD IN	0.95 [0.48,1.41]***	0.32 [−0.74,1.39]	0.81 [0.08,1.55]^{a}	0.85 [0.38, 1.32]**	−0.36 [−1.29, 0.57]	0.28 [−0.35, 0.91]	−0.54 [−1.41, 0.33]
ADHD HI	0.68 [0.14,1.21]*	0.18 [−0.38,0.75]	0.78 [0.38,1.17]**	0.63 [0.09, 1.18]a	0.70 [0.31, 1.09]*	−0.39 [−1.34, 0.56]	−0.74 [−1.17, −0.32]**
CD	0.45 [0.17,0.72]**	0.43 [0.10,0.76]*	0.05 [−0.30,0.41]	0.67 [0.16, 1.17]*	0.24 [−0.04, 0.51]	0.31 [−0.25, 0.88]	0.19 [−0.93, 1.31]
AD	0.50 [−0.03,1.03]	0.48 [−0.06,1.02]	0.06 [−0.65,0.76]	0.01 [−0.96, 0.97]	−0.29 [−1.08, 0.50]	0.63 [−0.04, 1.29]	0.68 [0.29, 1.08]**
ND	0.38 [−0.13,0.47]	0.32 [−0.27.0.91]	0.15 [−0.47,0.77]	0.65 [−0.12, 1.41]	−0.22 [−1.01, 0.57]	0.11 [−0.56, 0.77]	0.98 [0.69, 1.27]***

Table showing the severity of externalizing behaviors in off-spring mothers who smoke during pregnancy (versus no MSDP-E) before (Model I) and after controlling for propensity for MSDP-E(Model II), as well as the effect of MSDP-E within each quartile of the MSDP-E risk distribution. Abbreviations: AD - alcohol dependence, ADHD-IN - ADHD inattention, ADHD-HI - ADHD hyperactivity/ impulsivity, CD - conduct disorder, ND - nicotine dependence.

Notations:

^{a}p<.10,

^{b}N's vary by group,

*p<.05,

**p<.01,

***p<.001.

Table 3b

Effect (β [95% confidence interval]) of MSDP-T on offspring externalizing behavior

	Model-I	Model-II		β_{MSDP-T} by quartile			
Phenotype	**β_{MSDP-T}**	**β_{MSDP-T}**	**$\beta_{P-SCORE}$**	**0–25%ile**	**26–50%ile**	**51–75%ile**	**76–100%ile**
ADHD IN	1.00 [0.93,1.07] **	0.85 [0.27,1.44] *	0.21 [−0.57,1.00]	0.96 [0.66, 1.25] ***	0.79 [−0.38, 1.96]	0.92 [0.13, 1.71] *a*	.87 [−2.19, 0.46]
ADHD HI	0.93 0.74,1.12] ***	0.20 [−0.21,0.61]	0.83 [0.51,1.15] ***	0.40 [−1.29, 2.09]	<0.01 [−1.20, 1.20]	0.23 [−1.29, 1.75]	0.62 [−0.44, 1.67]
CD	0.44 [0.21,0.67] **	0.34 [0.05,0.63] *a*	0.16 [−0.16,0.49]	−0.28 [−0.81, 0.26]	0.66 [0.19, 1.12] *	0.43 [0.16, 0.70] **	−0.16 [−1.14, 0.81]
AD	−0.31 [0.85,0.22]	−0.52 [−1.11,0.06]	0.37 [−0.29,1.03]	−0.87 [−1.34, −0.37] **	−0.30 [−0.84, 0.23]	−0.30 [−1.09, 0.49]	−0.03 [−1.03, 0.96]
ND	0.67 [0.37,0.97]	0.22 [−0.21,0.65]	0.61 [0.23,1.00] **	−0.63 [−1.25, −<0.01] *a*	0.49 [−<0.01, 0.97]	0.07 [−2.00, 2.14]	0.39 [−0.65, 1.43]

Table showing the severity of externalizing behaviors in off-spring 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-T risk distribution. Abbreviations: AD - alcohol dependence, ADHD-IN - ADHD inattention, ADHD-HI - ADHD hyperactivity/ impulsivity, CD - conduct disorder, ND - nicotine dependence.

Notations:

a p<.10,

b N's vary by group,

* p<.05,

** p<.01,

*** p<.001.