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Association between Environmental Tobacco Smoke Exposure Across the First Four Years of Life and Manifestation of Externalizing Behavior Problems in School-Aged Children

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Abstract

Background: Extensive literature in human and animal models has documented an association between maternal smoking during pregnancy and externalizing behavior in offspring. It remains unclear, however, the extent to which postnatal environmental smoke exposure is associated with behavioral development, particularly for children whose mothers did not smoke during pregnancy. The present study examined whether magnitude of exposure to environmental smoke across the first four years of life demonstrated a linear association with later externalizing symptoms.

Methods: Exposure was quantified through salivary cotinine measured when children were 6, 15, 24, and 48 months of age, providing a more accurate quantification of realized exposure than can be estimated from parental-report of cigarettes smoked. Data were available for n = 1,096 (50% male; 44% African American) children recruited for the Family Life Project, a study of child development in areas of rural poverty.

Results: Analyses indicate a linear association between cotinine and children's symptoms of hyperactivity and conduct problems. This association remained significant after controlling for family poverty level, parental education, parental history of ADHD, hostility, depression, caregiver IQ, and obstetric complications. Furthermore, this association was unchanged when excluding mothers who smoked during pregnancy from the model.

Conclusions: Findings are consistent with animal models demonstrating an effect of environmental exposure to nicotine on ongoing brain development in regions related to hyperactivity and impulsivity, and highlight the importance of mitigating children's exposure to environmental smoke, including sources that extend beyond the parents.

Extensive research has documented an association between maternal smoking during pregnancy and offspring externalizing psychopathology including hyperactivity (Keyes, Davey Smith, & Susser, 2014), aggression (Huijbregts, Seguin, Zoccolillo, Boivin, & Tremblay, 2007), anti-social behaviors (Gaysina et al., 2013), and criminal arrests (Murray, Irving, Farrington, Colman, & Bloxsom, 2010). Some research suggests that this association may be accounted for by shared genetic effects, owing to increased prevalence of antisocial behaviors among mothers who smoke during pregnancy (Button, Maughan, & McGuffin, 2007). In addition to potential mechanisms of heritability, multiple lines of evidence indicate that prenatal exposure to nicotine directly alters neural function in ways that likely affect offspring's behavioral outcomes (Tiesler & Heinrich, 2014). Furthermore, recent research has begun to extend this line of inquiry to the impact of environmental exposure in the early years of life, thus examining the cumulative effects of smoke exposure from sources beyond the mother. In addition to second-hand exposure to cigarette smoke, exposure to the nicotine residue that remains on surfaces with which children frequently interact (e.g. toys, floor, parents) exposes children to nicotine well beyond the cigarette's airborn phase (Matt et al., 2011). The current study utilizes measures of salivary cotinine (the metabolic byproduct of nictoine exposure) in children in order to quantify exposure with greater accuracy and precision than can be extracted from parental self-report (Ding et al., 2011), and to examine whether there is a dose-response association between postnatal exposure to enviornmental cigarette smoke and children's later attention and behavioral problems.

Addressing the issue of postnatal exposure has important implications for genetically informed studies seeking to disentangle the correlated risks of heritability and teratogen exposure. For instance, multiple studies have reported that associations between prenatal smoke exposure and neurobehavioral outcomes in offspring are not evidence when examining siblings whose mother changed smoking behavior between pregnancies such that one sibling was exposed prenatally and the other was not (D'Onofrio et al., 2008; Lundberg et al., 2009). Importantly, these studies examined only maternal self-report of smoking status during her pregnancy, and did not account for the possibility of postnatal exposure from the mother, or other adults. This may be especially problematic given the high failure rate of smoking cessation efforts, and evidence that women who quit smoking during pregnancy frequently relapse after pregnancy (Meernik & Goldstein, 2015). Thus more research is needed to understand how postnatal smoke exposure relates to externalizing behaviors in children.

True causality cannot be determined in humans due to the inability to randomly assign exposure, but experimental models in animals provide significant evidence of the effects of nicotine on the dopamine system (Smith, Dwoskin, & Pauly, 2010). Sustained exposure to nicotine during neurodevelopment has been shown to alter the expression of thousands of genes in dopamine-producing neurons (Keller, Dragomir, Yantao, Akay, & Akay, 2018), lead to reduced neuronal density in the medial prefrontal cortex (Aoyama et al., 2016), and result in a blunted dopamine response to nicotine exposure in adolescence (Kane, Fu, Matta, & Sharp, 2004). Dopamine systems have been widely implicated in the pathophysiology of externalizing problems (Gatzke-Kopp & Beauchaine, 2007b; Gatzke-Kopp, 2011; Gatzke-Kopp et al., 2009), and studies have reported that the developmental smoke exposure

demonstrates specificity in its association to externalizing, but not internalizing symptoms (Gatzke-Kopp & Beauchaine, 2007a; Tiesler & Heinrich, 2014).

Evidence that smoking during pregnancy increases the risks of physical health complications for both the child and the mother resulted in a robust public health effort to encourage women to quit smoking while pregnant. However, the focus on prenatal development as a limited stage of vulnerability may have been shortsighted. Unlike alcohol, which can only be inadvertently passed to the child through the placenta, cigarette smoke continues to permeate the child's environment after birth. Evidence from primate models indicates that many of the neurodevelopmental consequences of nicotine exposure are comparable regardless of whether exposure is induced across the pre- and post-natal period, or restricted to the postnatal period alone (Slotkin, Pinkerton, & Seidler, 2006), suggesting that more research is needed on the effects of exposure in early life.

Epidemiological studies indicate that environmental smoke exposure is fairly prevalent among children, with NHANES detecting cotinine in nearly half of the children studied (Environmental Protection Agency, 2015). However, most studies examining environmental exposure in children have taken a classification approach to dichotomize children as exposed or not, with less information available about the magnitude of exposure or the implications of dosage. Our lab recently examined cotinine levels in a sample of 1,096 children across the first four years of life, and found that at 6 months of age, only 24% of the sample had no, or very little measured cotinine, whereas 64% had levels indicative of moderate second-hand exposure, and 12% had levels of cotinine considered to indicate active smoking in adults (> 12ng/mL) (Gatzke-Kopp et al., 2018). The current study examines whether exposure dosage, measured as an average cotinine level across 4 assessments from ages 6 to 48 months, is associated with externalizing symptom severity in children at 1st grade.

Methods

Participants

The Family Life Project is a prospective longitudinal study of families residing in low-wealth counties in eastern North Carolina and central Pennsylvania. Complex sampling procedures were employed to ensure a representative sample while also oversampling for low-income families, and for African American families in North Carolina (see Willoughby et al., 2013 for details), resulting in the enrollment of n = 1,292 families. All study procedures were reviewed and approved by the University of North Carolina, Chapel Hill, IRB. The study sample includes children with at least one, and up to four (M = 3.31, SD = .83), valid cotinine measures and at least one valid parent- or teacher-report of externalizing symptoms (n = 1,096). Children with these data did not differ from those who did not meet inclusion criteria (n = 196) with respect to state of residence (p = 0.78), poverty status (p = 0.14), gender (p = 0.33), or primary caregiver education (p = 0.67). Children in the analytic sample were marginally more likely to be identified as African American (44% vs. 37%, p = 0.08).

Measures

Children's externalizing symptoms were assessed through multiple rating scales of hyperactivity/impulsivity and disruptive/antisocial behaviors. The primary caregiver completed ratings for their child during the 1st grade home visit, and consented for ratings to be provided by the teacher.

Hyperactivity/Impulsivity.—Both reporters completed the Disruptive Behavior Disorders Rating Scale (DBDRS; Pelham, Gnagy, Greenslade, & Milich, 1992; Erford, 1997) consisting of 18-items reflecting diagnostic criteria for attention-deficit/hyperactivity disorder, and the 5-item hyperactivity subscale of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). Descriptive data are reported in Table 1. Observed scores on both hyperactivity scales for both raters spanned the full possible range of symptom severity.

Conduct Problems: Both reporters completed the 5-item conduct problems subscale of the SDQ (Goodman, 1997). Primary caregiver completed the conduct problems portion of the DBDRS, consisting of 8 items assessing oppositional defiance and 9 items assessing conduct disorder behaviors, averaged together to create a composite score. Teachers also completed the Teacher Observation of Child Adaptation-Revised (TOCA-R; Werthamer-Larsson, Kellam, & Wheeler, 1991), which contained an additional 5 items assessing aggressive and oppositional behaviors (e.g. "breaks things on purpose") averaged to create a single score. Observed scores spanned the full possible range of symptom severity in parent-reported scales, and teacher-reported maximum scores were near the maximum possible range.

Environmental Smoke Exposure.—Exposure to cigarette smoke was quantified by assaying cotinine, the primary metabolic byproduct of nicotine, from children's saliva (as described in Granger et al., 2007), using a commercially available diagnostic immunoassay (US Food, Drug cleared, and Cosmetic Act §501(k); conforms with European health and safety requirements [CE Marked]) (Salimetrics, Carlsbad, CA). Unstimulated whole saliva was collected from children during home visits corresponding to 6, 15, 24, and 48 months of age. Full methodological details are reported in Gatzke-Kopp et al., 2018. Previous analyses confirm substantial variation in exposure severity within this sample, with evidence indicating that exposure severity was reasonably stable across time (Gatzke-Kopp et al., 2018). Because cotinine data is logarithmically scaled, a log transform was applied to each time point to normalize the distributions.

Information regarding prenatal exposure to smoking was collected at the intake visit when the child was approximately 2 months of age. Mothers were asked only whether they smoked during their pregnancy, with 23.4% of mothers indicating that they had.

Caregiver Education.—The highest level of education obtained by the time the child was 48 months of age was classified into one of 3 categories: did not complete high school (10%), graduated from high school but did not obtain a higher degree (69%), and completed a bachelor's degree or greater (21%). Two dummy codes were created indicating (1) whether

or not the caregiver completed high school and (2) whether or not the caregiver completed college. Having completed college was significantly correlated with lower cotinine when children were 6 months of age ($r = -.45$, $p < .001$), a comparable, but slightly smaller effect emerged for having completed high school ($r = -.29$, $p < .001$).

Income/Needs Ratio (INR).—Household poverty levels were defined by summing the income of all residents and dividing it by the federal poverty threshold (for each calendar year) for a given family size. Household income information was collected at the 6-month home visit and every home visit thereafter. The mean INR value across assessments ranged from 0 to 13.60, ($M = 2.13$, $SD = 2.55$). Across the first 4 years of the child's life, 23% of the families lived consistently below the poverty line (INR ≤ 1) and another 36% of the sample had an average value > 1.0 but ≤ 2.0 times the federal poverty limit. Lower INR was significantly correlated with higher cotinine values in children at 6 months of age ($r = -.41$, $p < .001$).

Parental History of ADHD.—A single item was asked to establish whether either the biological mother or father of the target child had a childhood history of ADHD (i.e., "Has a doctor or other medical professional ever told you [him/her] that you [s/he] have [has] attention-deficit disorder"). When the primary caregiver was not a biological parent of the target child, s/he answered the question with reference to the child's biological parents. Endorsement of this item was relatively low at 2.52% ($n = 27$) of mothers and 3.65% ($n = 39$) for fathers, which may be a reflection of the lower income status of participants who may have been less likely to have access to professional evaluations as children. A weak, but significant association emerged between higher cotinine levels in children at 6 months and paternal history of ADHD ($r = .13$, $p < .001$) as well as maternal history of ADHD ($r = .07$, $p < .05$).

Caregiver hostility and depression index.—The primary and secondary caregiver were assessed using items from the Brief Symptom Inventory (BSI; Derogatis, 1993) including a 6-item subscale assessing depression, and a 5-item subscale assessing hostility, both of which have demonstrated reliability and validity (Derogatis, 2000). Primary caregivers could have up to 4 valid measures from the 2-, 6-, 15-, and 24-month follow-ups ($M = 3.90$, $SD = .39$); secondary caregivers could have up to 3 measures from the 6-, 15-, and 24-month follow-ups ($M = 1.43$, $SD = 1.16$). Mean scores across available time points were calculated for primary caregivers ($\alpha = .79$ each for hostility, depression) and secondary caregivers ($\alpha = .73$ for hostility; $\alpha = .77$ for depression). Associations were somewhat stronger between child's 6-month cotinine values and maternal levels of hostility ($r = .26$, $p < .001$) and depression ($r = .24$, $p < .001$) than they were for secondary caregiver levels of hostility ($r = .15$, $p < .001$) and depression ($r = .15$, $p < .001$).

Caregiver IQ.—The primary caregiver was administered the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale, 3rd edition (Weschler, 1997) at the 48-month home visit and the average of the standardized scale scores was used as an approximate measure of caregiver's IQ. Lower IQ was significantly correlated with higher child cotinine at 6 months of age ($r = -.35$, $p < .001$).

Low Birth Weight and Pregnancy and Delivery Complications.—Biological mothers completed the pregnancy and delivery module of the Missouri Assessment of Genetics Interview for Children (MAGIC) at the intake home visit (Todd, Joyner, Heath, Neuman, & Reich, 2003). Infants reported to have weighed ≤ 2500 grams were designated low birth weight. Retrospective recall of events during pregnancy and delivery are reliable and stable within the first year post term (Reich, Todd, Joyner, Neuman, & Heath, 2003). There were very small, but significant, associations between higher child cotinine at 6 months and greater number of pregnancy/delivery complications ($r = .11$, $p < .01$) as well as greater likelihood of being classified as low birth weight ($r = .08$, $p < .05$).

Additional covariates included in the models consisted of demographic risk factors correlated with child cotinine levels at the 6 month assessment. Specifically, higher cotinine was associated with lower maternal age ($r = -.40$, $p < .001$), and an increased likelihood of the father not living in the child's home ($r = -.27$, $p < .001$). There was also an association with lower cotinine being observed among African American families ($r = .17$, $p < .001$). No association emerged with child sex ($r = .01$, $p > .05$).

Analytic Strategy

Analyses proceeded in four steps. First, a series of confirmatory factor analysis (CFA) models were used to represent children's aggregate exposure to cotinine, and to represent a cross-informant measure of externalizing behaviors (i.e., hyperactivity-impulsivity, inattention, and conduct problems). Model fit was evaluated following convention (i.e., statistical significance of likelihood ratio test statistics, Root Mean Square Error [RMSEA] ≤ 0.05, Comparative Fit Index [CFI] ≥ 0.95, and standardized root mean square residual [SRMR] < 0.08). Second, once acceptable model fit was achieved for cotinine exposure and externalizing symptoms separately, a combined model was estimated to determine the unadjusted, bivariate associations between cotinine, conduct, and ADHD latent variables. Third, the SEM was extended to include additional risk factors (potential confounders) to test the unique association between cotinine and externalizing outcomes. Fourth, the SEM was re-estimated excluding children whose mother reported smoking during pregnancy. All analyses were conducted in *Mplus* Version 8.1 (Muthen & Muthen, 1998–2017) and accounted for the complex sampling design (probability weights and stratification variables). Full information maximum likelihood (FIML), which uses all observed data in estimating parameters, was used to account for missing data (Graham, 2009).

Results

Descriptive statistics

Descriptive statistics, including bivariate correlations, for the study variables are shown in Table 1. Logged cotinine values across all four time points were highly correlated (rs = 0.68 – 0.78), suggesting that a single latent variable could adequately capture individual differences in early exposure. Additionally, moderate to high correlations were evident for caregiver and teacher reports of hyperactivity (rs = 0.44 – 0.88) and conduct problem (rs = 0.25 – 0.85); however, correlations were stronger within-informants than within-symptom domains, indicating shared reporter variance. Consistent with the study hypothesis, zero-

order correlations between cotinine and externalizing scales were significant for both hyperactivity (*r*s = .21 – .35) and conduct problems (*r*s = .15 – .28).

Measurement Models

A series of confirmatory factor analytic (CFA) models were estimated to summarize associations between the four assessments of cotinine, and caregiver- and teacher-reported hyperactivity and conduct problems at 1st grade. A 1-factor model for cotinine fit the data well, χ^2 (2) = 4.59, $p < .001$, CFI = .998, RMSEA = .03 (see Table 2). The factor loadings were strong in magnitude (λs = .81 – .89, *p*s < .001) and the latent variance was statistically significant (φ = 2.14, $p < .001$), which indicated significant interindividual differences in postnatal exposure.

A two-factor model that included multi-informant ratings of hyperactivity and conduct problems as separate factors fit the data poorly, χ^2 (19) = 2737.24, $p < .001$, CFI = .268, RMSEA = .36 (see Table 2), due to strong cross-construct, within-informant correlations. Following Podsakoff, MacKenize & Podsakoff (2012), a four-factor model that included two substantive (hyperactivity-impulsivity, conduct problems) and two informant (caregiver, teacher) factors was estimated. This model was parameterized such that each indicator cross-loaded on both substantive and informant factors, and only a single latent correlation (i.e., hyperactivity-impulsivity with conduct) was estimated. The caregiver and teacher informant factors represented nuisance variation and are not considered further. This four-factor model fit the observed data reasonably well, χ^2 (11) = 81.30, $p < .001$, CFI = .981, RMSEA = .08 (see Table 2). The factor loadings for hyperactivity-impulsivity (λs = .52 – .78, *p*s < .001) and conduct problems (λs = .23 – .76, *p*s < .001) were all moderate to strong. The latent variances were statistically significant for hyperactivity-impulsivity (φs = .16, $p < .001$) and conduct problems (φs = .50, $p < .001$), which indicated significant interindividual differences in behavioral outcomes. Hyperactivity-impulsivity was positively correlated with conduct problems (φ = .59, $p < .001$).

A combined cotinine and behavioral outcomes CFA model was estimated. This five-factor model fit the data well, χ^2 (43) = 142.78, $p < .001$, CFI = .983, RMSEA = .05 (see Table 2). Cumulative cotinine exposure was positively correlated with hyperactivity-impulsivity (φ = .40, $p < .001$) and conduct problems (φ = .26, $p < .001$).

Structural Models

A SEM regressed latent hyperactivity-impulsivity and conduct problems on the latent cotinine variable, as well as a range of covariates. The model fit the data well, χ^2 (187) = 511.42, $p < .001$, CFI = .954, RMSEA = .04. Even in the presence of 16 covariates, cotinine continued to be positively associated with increased levels of hyperactivity-impulsivity (β = .20, 95% confidence interval [95% CI] = 0.10 – 0.30, $p < .001$). In addition to cotinine, child sex (being male), higher levels of caregiver depression, and more pregnancy and delivery complications were also associated with higher levels of hyperactivity-impulsivity.

Similarly, after controlling for all covariates, cotinine continued to significantly predict conduct problems (β = .16, 95% CI = 0.06 – 0.26, $p < .01$). Greater severity of conduct

problems was also predicted by child sex (being male), higher levels of caregiver hostility, and lower caregiver IQ (see Table 3 for summary of all regression coefficients).

A model that included an interaction between child sex (being male) and cotinine was also estimated, but interaction terms were not statistically significant and therefore excluded from the final model.

Robustness Check.—Approximately one-quarter of the study sample had mothers who reported smoking during pregnancy (n = 840 vs. 1,096), and these children had higher levels of cotinine at each home visit compared to children whose mothers did not report smoking during pregnancy (*Cohen d*s = 1.08 – 1.24, all ps < .001). Hence, postnatal exposure was confounded with prenatal smoking. When re-estimating the full SEM model excluding children whose mother reported smoking during pregnancy, the impact of cotinine on hyperactivity-impulsivity (β = 0.22, 95% CI [0.11, 0.33], p<0.001) and conduct problems (β = 0.20, 95% CI [0.07, 0.33], p<0.01) remained unchanged.

Discussion

Substantial research in animals and humans has documented associations between prenatal smoke exposure and offspring externalizing behaviors, with relatively less research on the effects of postnatal exposure on ongoing neurodevelopment. The present study found that, even when controlling for a range of potential confounds including family history of ADHD, caregiver IQ, caregiver symptoms of psychopathology, economic adversity, and obstetric problems, children's cotinine levels were significantly associated with both hyperactivity and conduct problem dimensions of externalizing behavior. Furthermore, results were identical regardless of whether exposure also occurred prenatally, indicating that the postnatal period continues to be a vulnerable time for neurobehavioral development.

Attention to the effects of postnatal exposure is important given evidence that as many as 43% of women who successfully quit during pregnancy resume smoking by the time the child is 6 months old (Jones, Lewis, Parrott, Wormall, & Coleman, 2016). While failure rates for smoking cessation efforts are generally high, health information that is delivered in the context of promoting a healthy pregnancy may seem less critical to women after their child is born. Although there is a wealth of research on the dangers of environmental smoke for infants, the majority of the research focuses on the more proximal health risks such as respiratory problems and susceptibility to illness (DiFranza, Aligne, & Weitzman, 2004), which could lead to a false reassurance among parents whose children do not display these ailments.

Furthermore, parents may be focused primarily on their children's exposure to smoke, potentially overlooking the risks of surface residue routes of exposure. Previously reported results from the present sample illustrate that young children are capable of absorbing quantities of nicotine typically considered to be indicative of active smoking, and may be more vulnerable to exposure than older children (Gatzke-Kopp et al., 2018). Intervention programs aimed at educating smoking parents to reduce their children's exposure have found that providing mothers with information documenting the air quality in their homes is

effective in motivating greater efforts to reduce exposure (Wilson et al., 2013). Given research demonstrating that nicotine remains detectable in dust and surface residue up to six months after verified quitting (Matt et al., 2016), intervention efforts should consider providing parents with information about their infant's cotinine levels rather than air quality, helping to illuminate exposure from non-airborne sources.

Children's cotinine levels correlated with a range of sociodemographic factors associated with risk for externalizing problems including lower socioeconomic status, parental hostility and depression, and parental history of ADHD. It is important to note that these findings do not preclude a genetic mechanism underlying both the predisposition to smoke and externalizing symptoms, nor the possibility of genetic moderation of the effects of smoke exposure. For instance, research in animals demonstrates that variation in CHRNA5 gene, a genetic marker shown to be associated with propensity for smoking in humans (Liu et al., 2019), moderates the impact of prenatal nicotine exposure on self-administration of nicotine in adolescence (O'Neill et al., 2018). These findings suggest that one mechanism of shared genetic risk may be through an increase in susceptibility to environmental exposures.

Results from the present study also indicate that efforts to disentangle genetic and environmental pathways between developmental nicotine exposure and offspring externalizing behavior need to examine sources of exposure beyond the mother. Previous work has reported no differences in externalizing symptoms among siblings who differ with regard to their prenatal exposure via maternal smoking behavior, but this study did not account for other potential sources of exposure, such as the father or other relatives (D'Onofrio et al., 2008). In the present study, the strength of association between dosage of exposure and children's symptom severity was unchanged when examined only among participants whose mothers reported not smoking during pregnancy, suggesting that other sources of exposure (e.g. father, grandparent) represent the same degree of risk as mothers. The reliance on maternal report of prenatal smoking and of biological parents' history of ADHD, as well as the lack of information about other smokers in the home, are notable limitations in this study. Further research is needed to examine whether this effect is replicated when the source of exposure was not genetically related to the child (e.g. daycare worker), as well as cases in which exposure may be mediated through mothers' second-hand exposure in the workplace (Gatzke-Kopp & Beauchaine, 2007a).

Epidemiological studies have reported associations between exposure to second hand smoke and child externalizing behavior problems, even after controlling for prenatal exposure (Kabir et al., 2011; Twardella et al., 2010). The present study provides additional support for previous findings, which relied on parental report to classify exposure as low, medium, or high, by employing rigorous and sensitive assessments of biological exposure. In addition to providing a more precise quantification of exposure with which to examine dosage effects, this approach quantifies realized exposure without regard to source. Reliance on parental report of smoking behavior likely underestimates the potential contribution of other adults in the child's life and does not account for additional factors that affect the relation between parental smoking and child exposure such as smoking outside and home square footage.

Replication of the effect on children not exposed prenatally indicates that this association is not driven by the children with the highest levels of exposure. Although some research has reported a threshold effect whereby adverse outcomes emerge at exposure equivalent to approximately 10 cigarettes (half a pack) per day (e.g. Chen, Adhami, & Martins-Green, 2018), other studies have reported linear effects of dose in the range of 1 to 15 cigarettes per day (e.g. Albers et al., 2018). It is not possible to estimate a cigarette equivalent for the cotinine values observed in children because the realized exposure from one parental cigarette can vary dramatically as a function of the child's proximity to the parent while smoking. Given the lack of evidence for a safe level of exposure, parental education should focus on the goal of eliminating exposure. It is important to note, however, that these results do not imply a risk of transient irregular exposure, but rather that even low levels of exposure confer risk when sustained chronically over time.

Despite some evidence that the effects of nicotine on the brain are sexually dimorphic (Cross, Linker, & Leslie, 2017; Eiden et al., 2015), analyses in the current study provided no evidence of moderation by sex, suggesting that the effect of sustained environmental exposure affects both male and female children's propensity for hyperactivity and behavior problems similarly. Additional research is needed to determine whether sexually dimorphic effects emerge only for certain outcomes, are dependent on the timing of developmental exposure, or are dependent on the timing that the outcome behavior is assessed (e.g. post puberty).

Finally, it is important to note that the effects examined in this study were a function of the dosage of nicotine that children were exposed to, as quantified by the metabolic byproduct, cotinine. Experimental research confirms that nicotine is a behavioral teratogen, although research also indicates that additional toxicants present in tobacco cigarettes also impact developmental brain function (Hall et al., 2016; Slotkin et al., 2015). As such, additional research is needed to examine whether "cleaner" nicotine products such as vaping systems confer comparable risk to children's behavioral development. Furthermore, while nicotine exposure may alter dopaminergic brain development in ways that increase externalizing risk probabilistically, additional research is needed to understand factors that exacerbate or mitigate this pathway.

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- Children's cotinine levels across the first four years of life predict later externalizing symptoms, even among children whose mothers did not smoke during pregnancy.
- Findings have important implications for risks associated with postnatal exposure that extend beyond the well-documented respiratory and immunological consequences.
- Assessing cotinine directly from children captures exposure from sources that may extend beyond the parents, and accounts for factors that might exacerbate or mitigate children's exposure, such as whether parents smoke indoors.
- Findings have implications for policy, such as incorporating routine screening for cotinine as is commonly done for lead.
- Results provide important characterization of the timing and magnitude of environmental smoke exposure that can inform studies examining genetic pathways of the development of externalizing problems.

Table 1.

Weighted Descriptive Statistics

	1	2	3	4	5	6	7	8	9	10	11	12
1. Cotinine (6 months)	–											
2. Cotinine (15 months)	0.76***	–										
3. Cotinine (24 months)	0.73***	0.78***	–									
4. Cotinine (48 months)	0.68***	0.71***	0.73***	–								
5. DBD - ADHD (PC)	0.30***	0.29***	0.31***	0.34***	–							
6. DBD - ADHD (TCH)	0.21***	0.23***	0.22***	0.23***	0.44***	–						
7. SDQ - hyperactivity (TCH)	0.21***	0.23***	0.21***	0.24***	0.44***	0.88***	–					
8. SDQ - hyperactivity (PC)	0.32***	0.31***	0.33***	0.35***	0.81***	0.45***	0.48***	–				
9. SDQ - conduct (PC)	0.24***	0.24***	0.25***	0.28***	0.61***	0.29***	0.27***	0.58***	–			
10. SDQ - conduct (TCH)	0.16***	0.17***	0.16***	0.17***	0.35***	0.67***	0.60***	0.32***	0.34***	–		
11. DBD - Oppositional Defiant (PC)	0.17***	0.18***	0.19***	0.24***	0.58***	0.24***	0.22***	0.48***	0.69***	0.25***	–	
12. TOCA - Aggression (TCH)	0.15***	0.19***	0.16***	0.16***	0.33***	0.69***	0.63***	0.33***	0.31***	0.85***	0.25***	–
N	1010	860	846	911	1065	914	914	1067	1067	914	1058	916
Possible Range					0 – 3	0 – 3	0 – 2	0 – 2	0 – 2	0 – 2	0 – 3	1 – 6
Observed Range					0 – 3	0 – 3	0 – 2	0 – 2	0 – 2	0 – 1.8	0 – 3	1 – 5.8
M	0.31	0.37	0.29	−0.33	0.79	0.65	0.69	0.80	0.37	0.25	0.44	1.84
SD	1.73	1.71	1.74	1.69	0.63	0.75	0.65	0.55	0.39	0.39	0.48	0.95

Note: Cotinine was logged to account for skewness in the raw cotinine values; PC – primary caregiver report; TCH – teacher report; N – sample size; M – Mean; SD – Standard Deviation; DBD – disruptive behavior disorders questionnaire; SDQ – Strengths and Difficulties Questionnaire; TOCA - Teacher Observation of Child Adaptation-Revised questionnaire.

*** $p < .001$.

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Table 2.

Model Fit for Confirmatory Factor and Structural Equation Models

Model	Description	χ^2 (df)	CFI	RMSEA [90% CI]	SRMR
1	1 Factor CFA (Cotinine)	4.59 (2)	0.998	0.03 [0.00, 0.08]	0.007
2	2 Factor CFA (Hyperactivity, Conduct)	2737.24 (19)	0.268	0.36 [0.35, 0.37]	0.177
3	4 Factor CFA (Hyperactivity, Conduct, Parent, Teacher)	81.30 (11)	0.981	0.08 [0.06,0.09]	0.061
4	5 Factor CFA (Combine models 1 and 3)	142.78 (43)	0.983	0.05 [0.04, 0.05]	0.065
5	SEM (Extend model 4 to include covariates)	511.42 (187)	0.954	0.04 [0.04,0.04]	0.050
6	SEM (Repeat model 5 excluding prenatal smoking cases)	418.407 (187)	0.956	.04 [0.03, 0.04]	0.044

Note: All models N = 1096, except model 6 which is N = 840; all likelihood ratio tests have chi square test statistics of *ps* < .001. CFA - confirmatory factor analysis; SEM – structural equation model; CFI – Comparative Fit Index; RMSEA – Root Mean Squared Error of Approximation; SRMR – Standardized Root Mean Residual.

Table 3.

Standardized Regression Coefficient for Predictors of Hyperactivity and Conduct Problems in 1st Grade.

	Hyperactivity		Conduct Problems	
	β	[95% CI]	β	[95% CI]
Cotinine	0.20***	[.10, .30]	0.16**	[.06, .26]
Biological Dad in household	−0.03	[−.11, .06]	−0.01	[−.11, .09]
PC high school degree	−0.01	[−.08, .07]	−0.02	[−.12, .07]
PC college degree	−0.09	[−.17, .01]	0.01	[−.09, .10]
PC IQ estimate	−0.06	[−.15, .03]	−0.13**	[−.23, −.04]
PC depression	0.09	[−.01, .19]	0.01	[−.10, .12]
PC hostility	0.03	[−.08, .14]	0.20**	[.09, .31]
SC depression	0.15*	[.04, .26]	0.03	[−.10, .17]
SC hostility	−0.05	[−.16, .06]	0.03	[−.09, .15]
Biological mother history ADHD	−0.01	[−.10, .08]	−0.05	[−.13, .03]
Biological father history ADHD	0.07	[−.01, .16]	0.03	[−.08, .14]
PC age	−0.03	[−.11, .05]	−0.04	[−.13, .05]
Child sex (male)	0.23***	[.17, .30]	0.17***	[.09, .24]
Child race (African American)	0.04	[−.04, .11]	−0.05	[−.14, .04]
Income-to-needs ratio	0.07	[−.01, .15]	−0.02	[−.10, .07]
Child low birth weight	0.08	[.00, .15]	0.03	[−.05, .11]
Pregnancy and delivery complications	0.09*	[.01, .18]	0.07	[−.02, .15]

Note: N = 1096;

* $p < .05$,

** $p < .01$,

*** $p < .001$. 95% CI – 95% confidence interval; PC – primary caregiver; SC – secondary caregiver.