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Intrauterine exposure to tobacco and executive functioning in high school

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Abstract

Background—Executive functioning (EF), an umbrella construct encompassing gradual maturation of cognitive organization/management processes, is important to success in multiple settings including high school. Intrauterine tobacco exposure (IUTE) correlates with negative cognitive/behavioral outcomes, but little is known about its association with adolescent EF and information from real-life contexts is sparse. We evaluated the impact of IUTE on teacher-reported observations of EF in urban high school students controlling for covariates including other intrauterine and adolescent substance exposures.

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Methods—A prospective low-income birth cohort (51% male; 89% African American/Caribbean) was followed through late adolescence (16–18 years old). At birth, intrauterine exposures to cocaine and other substances (52% cocaine, 52% tobacco, 26% marijuana, 26% alcohol) were identified by meconium and/or urine assays, and/or maternal self-report. High school teachers knowledgeable about the student and unaware of study aims were asked to complete the Behavior Rating Inventory of Executive Functioning-Teacher Form (BRIEF-TF) annually.

Results—Teachers completed at least one BRIEF-TF for 131 adolescents. Multivariable analyses included controls for: demographics; intrauterine cocaine, marijuana, and alcohol exposures; early childhood exposures to lead; and violence exposure from school-age to adolescence. IUTE was associated with less optimal BRIEF-TF Behavioral Regulation scores ($p < 0.05$). Other intrauterine substance exposures did not predict less optimal BRIEF-TF scores, nor did exposures to violence, lead, nor adolescents' own substance use.

Conclusions—IUTE is associated with offspring's less optimal EF. Prenatal counseling should emphasize abstinence from tobacco, as well as alcohol and illegal substances.

Keywords

Intrauterine tobacco exposure; Executive functioning; High school students; Teacher behavior rating of executive; functioning

1. Introduction

Approximately 12% of pregnant U.S. women in 2008 reported smoking tobacco during the third trimester, despite increased long-term health risks for themselves and offspring (Tong et al., 2013). Executive functioning (EF) encompasses a set of higher-level neurocognitive functions (e.g., working memory, inhibitory control, organization, and planning) necessary for independent, purposeful, goal-directed day-to-day activity. Intrauterine tobacco exposure (IUTE) has been associated with less optimal performance on measures of children's neurocognitive abilities (Fried et al., 2003) including working memory (Fried and Watkinson, 2001), attention, emotion and behavioral regulation (Cornelius et al., 2012; Wiebe et al., 2014) and aggression/other anti-social behaviors in older children and adolescents (Huizink and Mulder, 2006; Wakschlag et al., 2011). Few studies specifically examine IUTE effects on executive functioning (EF) during adolescence (Clifford et al., 2012). EF encompasses a set of higher-level neurocognitive functions (e.g., working memory, inhibitory control, organization, and planning) necessary for independent, purposeful, goal-directed day-to-day activity including helping to manage competing performance demands (Alvarez and Emory, 2006; Lezak et al., 2012).

Prior studies evaluating IUTE effects on neurobehavioral outcomes usually focus on individualized, laboratory-based assessments rather than measures of functioning in real-life contexts where environmental stimuli may influence individuals' behavior (Chaytor et al., 2006; Clifford et al., 2012). Context is known to be an important factor influencing EF (Williams et al., 2009). For example, success in high school requires constant adaptation to variable, unpredictable conditions, but it is not known whether adolescents with versus

without IUTE show observable EF differences in this “real world”, rather than a controlled laboratory environment (Diamantopoulou et al., 2007).

Regardless of setting, studies of specific effects of any single intrauterine substance exposure also must evaluate potential environmental, demographic and biologic covariates, particularly other intrauterine substance exposures and adolescents' own substance use (Fried et al., 2003; Richardson et al., 2013; Rose-Jacobs et al., 2011). As evident in substance-exposure literature, outcomes may be influenced by specific samples, ages tested, assessments used, and covariates included (Clifford et al., 2012; Piper and Corbett, 2012). Potential covariates based on published literature should be evaluated to avoid misinterpretation of results. For example, in low-income, urban populations, environmental exposure to second-hand tobacco smoke (Cornelius and Day, 2009), lead (Min et al., 2009), and violence (Frank et al., 2011; Perkins and Graham-Bermann, 2012) may influence EF.

The present study goal is to evaluate possible associations between IUTE and EF reported by participants' high school teachers. We hypothesize that after controlling for contextual variables including demographics, childhood blood lead levels, childhood and adolescent exposure to violence, other intrauterine substance exposures, and the adolescent's own substance use, IUTE will be negatively associated with high school teachers' ratings of students' classroom EF.

2. Methods

2.1. Sample

Participants were high school students from low-income, urban backgrounds enrolled in a prospective, longitudinal birth cohort study evaluating potential developmental sequelae of intrauterine exposure to cocaine and other substances. As previously reported (Frank et al., 1999), participants were recruited (1990–1993) postpartum at an urban hospital serving a large Medicaid population. Inclusion criteria were: gestational age ≥ 36 weeks, no level III NICU care, no diagnosed Fetal Alcohol Syndrome or HIV infection; mother's English fluency, age ≥ 18 year, and no documented use during index pregnancy of opiates, benzodiazepines, amphetamines, phencyclidine, barbiturates or hallucinogens (Mirochnick et al., 1991). Exclusion criteria included known major risk factors (e.g., preterm birth, adolescent mother, genetic syndromes) that might confound the effects of intrauterine substance exposures. The Institutional Review Board of Boston City Hospital/Boston University Medical Center approved the study. A Certificate of Confidentiality was obtained.

2.2. Intrauterine substance exposure classification

Research staff interviewed postpartum mothers about cocaine, alcohol, marijuana, cigarette, and other illicit drug use during pregnancy via an adaptation of the Addiction Severity Index (ASI) (McLellan et al., 1992). At that time, cotinine assays (to measure gestational tobacco exposure) were prohibitively expensive and there were no biological markers for gestational alcohol exposure. For analytic purposes, we created a 3-level intrauterine tobacco exposure variable (none = no cigarettes during pregnancy, lighter (< 10 cigarettes/day on average, and

heavier (≥ 10 cigarettes/day.). We categorized prenatal alcohol use as none, lighter (< 0.5 average drinks/day), and heavier (≥ 0.5 drinks/day).

Urine samples were analyzed for benzoylecgonine, opiates, amphetamines, benzodiazepines and cannabinoids by radioimmunoassay using commercial kits (Abuscreen RIA, Roche Diagnostics Systems, Inc., Montclair, N.J.). Meconium specimens were analyzed by radioimmunoassay for the cocaine metabolite benzoylecgonine, metabolites of opiates, amphetamines, benzodiazepines, and cannabinoids (Mirochnick et al., 1991; Ostrea et al., 1989). We classified IUCE exposure as “unexposed”, “lighter”, or “heavier” based on composite information derived from maternal self-report, mother or infant urine, and/or the meconium assays (Tronick et al., 1996). Identification of intrauterine marijuana exposure was based on a composite index of the urine assays, meconium assay, and maternal self-report and categorized as “unexposed”, “lighter” or “heavier.” (Frank et al., 2011).

2.3. Procedures

Primary caregivers and their child/adolescent completed multiple follow-up evaluations at a developmental laboratory between the target child's birth and late adolescence. At follow-up visits, research assistants masked to the target child's intrauterine exposure status interviewed caregivers regarding family demographics, psychosocial variables, and cigarette smoking among household contacts. Another research assistant masked to the intrauterine exposures and previous assessments administered the developmental and behavioral protocol assessments to target children/adolescents.

2.3.1. Age groups and problematic substance use determination—During three adolescent visits, early (ages 12–14.4 years), middle (14.5–16.4 years), and late (16.5–18 years), adolescents reported their own substance use history using an auditory computer-assisted self-interview (ACASI). Questions about cocaine, marijuana, alcohol, tobacco, and other substance use were taken from the U.S. Center for Disease Control (2005) Youth Risk Behavior Surveillance System and the Wisconsin Youth Risk Behavior Surveillance middle and high school questionnaires (Eaton et al., 2006). Adolescents voluntarily provided urine samples at each visit to screen for legal and illegal substances (Frank et al., 2011). Urine samples were tested by the United States Drug Testing Laboratories, Inc., using the No-Excuse Urine Panel that has a limit of detection panel using enzyme multiplied immunoassay technique at the lowest validated concentrations achieved. Gas chromatography–mass spectrometry confirmations were used for some drug classes: cannabinoids, opiates, amphetamines and cocaine metabolites. Enzyme-linked immunosorbent assay technique was used for cotinine. The No-Excuse Urine test level gives a detection window of up to a week for most drugs, and even longer for marijuana. We classified adolescents as currently substance-positive if they self-reported use of alcohol, marijuana, and other substances excluding tobacco experimentation during the past 30 days or if their urine assay was positive. We classified adolescents reporting substance use prior to the past 30 days and with negative urine assay as “ever” having used a particular substance. To maintain adequate cell sizes for statistical analyses, adolescents' own cigarette or cocaine use each were categorized as two-level variables, “never” and “ever”. Problematic substance use was identified by a composite of ACASI substance use answers, and/or urine

assays encompassing the DSM-IV indication of tolerance, abuse, and dependence on alcohol, marijuana, and tobacco and any use of cocaine, glue or opiates during adolescence (Frank et al., 2014).

2.3.2. Measures—The primary outcome for these analyses, the BRIEF-TF (Behavior Rating Inventory of Executive Functioning-Teacher Form), is a standardized 86 item three-point scale (Never, Sometimes, Often) teacher-reported questionnaire developed to rate observations of student classroom EF-related behavioral tendencies (Gioia et al., 2000; Toplak et al., 2008). The BRIEF-TF consists of eight subscales summarized as two indexes measuring day-to-day functioning. Behavioral Regulation (sub-scales: Inhibit, Shift, Emotional Control) represents abilities to shift attention between different tasks, efficiently adapt to changing situations, and use inhibitory control to modulate strong or automatic behavioral/emotional responses. Meta-cognition (subscales: Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor) represents higher-order thinking enabling understanding, analysis, and control of one's cognitive processes in order to manage performance (Gioia et al., 2000). Indexes are scored as T-scores ($M = 50$, $SD = 10$), with higher scores reflecting less optimal functioning (Gioia et al., 2000).

With caregivers' permission, we mailed the BRIEF-TF to high school homeroom or Language Arts teachers who knew the student and asked teachers to complete and return the questionnaire. Teachers were unaware of the students' participation in the longitudinal study and study goals.

2.3.3. Covariates—Candidate covariates were identified *a priori* based on theoretical or empirical importance to the independent (IUTE) or dependent (BRIEF-TF) variables and were assessed at intake and/or at each subsequent visit via medical record review, caregiver interview, or direct caregiver or child assessment. Candidate variables included: intrauterine cocaine, marijuana, and alcohol exposures; maternal age and educational level at participant's birth; maternal country of birth (U.S. vs other), primiparous vs other; infant sex, gestational age, birth weight z score for gestational age; neonatal head circumference; log of maximum blood lead prior to age 4, exposure to violence since age 8, adolescent's IQ, household tobacco use (see details below); adolescent's age at each BRIEF-TF assessment; number of caregiver changes prior to late adolescence; any adolescent problem substance use or initiation of substance use by age 16.

Blood lead values prior to age four were obtained via medical record review. Thirty lead values were missing and multiply imputed in 10 data sets based on sex, IUSE, and the youth's birth mother's age, education, and race/ethnicity with the single chain MCMC method using PROC MI in SAS.

At the early adolescent visit, IQ was measured using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). If missing, the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 1991) from age 11 (5 cases), or the WASI measured at the middle adolescent follow-up (7 cases) were substituted because IQ scores for groups of middle school-aged children and older are considered relatively stable (Watkins and Smith, 2013).

Exposure to violence was measured face-to-face during 8.5, 9.5 and 11-year protocol points using the Violence Exposure Scale for Children-Revised (VEX-R) (Fox and Leavitt, 1995), a 21-item, cartoon-based 4-point Likert scale for recording different types of violence experienced/observed (e.g., being yelled at, beaten up, or stabbed with a knife) and frequency of occurrence (0 = never, 1 = once, 2 = a few times, 3 = lots of times). During adolescent laboratory protocol points, we removed the cartoons and questions related to spanking, modified questions to be time-specific (during past year or ever), and administered the instrument via Audio Computer-Assisted Self-Interview (AC-ASI). There is no standard method of VEX-R scoring (Frank et al., 2011; Brandt et al., 2005). Addressing the non-interval scaling and skewed total VEX-R total scores, as in our previous publications, (Rose-Jacobs 2011), we created quartiles, ranking each youth's score at each protocol point and subdividing scores into approximately equal groups (highest indicating greater violence exposure) at each age, allowing for time-dependent analysis. We then created a variable reflecting whether the respondent was “ever in the highest quartile of violence exposure” versus “always in the lower three violence exposure quartiles” up to the age of each BRIEF-TF. Missing continuous VEX-R total scores were multiply imputed at each time point based on: child's sex, mother U.S. or foreign born; current caregiver (birth mother, kinship caregiver, non-kinship caregiver); caregiver's education, and caregiver's report of experience of violence or child's witness to violence earlier in childhood. Imputation of at least one evaluation point was performed for 101 participants, including 94 who had at least one time point missing and 7 who were missing VEX-R scores at all time points.

Second-hand smoke exposure was derived from caregiver interviews obtained at each protocol point between 8 years through late adolescence. Caregivers reported the number of household members who smoked cigarettes. Responses were summed across all visits and dichotomized such that ever living with at least one cigarette smoker was considered having second-hand smoke exposure.

2.3.4. Data analyses—While IUTE was the primary independent variable, levels of intrauterine cocaine, alcohol, and marijuana exposure were also evaluated as predictors in each analysis because other intrauterine substance exposures have been postulated or found to be correlated with EF (Frank et al., 2002; Fried et al., 2003; Rose-Jacobs et al., 2012). All unadjusted and adjusted analyses of association with BRIEF-TF outcomes were conducted using generalized estimating equations (GEE) models with an exchangeable working correlation to account for multiple BRIEF-TF reports per participant. In unadjusted analyses, we first evaluated each intrauterine exposure with each BRIEF-TF index T-score. We then adjusted the relationship between levels of each intrauterine exposure and each index T-score for salient covariates using GEE linear models for correlated observations.

Based on previous literature, exposures to cocaine, alcohol, marijuana, childhood lead, and exposure to violence were included. Additional covariates were included in the final models if they altered estimates of association of the IUTE or other intrauterine exposure variables with any BRIEF-TF dependent variable by more than 10% in adjusted versus unadjusted models (Mickey and Greenland, 1989). Final covariates included: each of the other intrauterine substance exposures; maternal demographics (maternal age, race/ethnicity, education, and whether mother was U.S. born; child's sex, birth weight z-score for

gestational age; adolescent age at time of BRIEF-TF assessment; highest level of lead exposure up to age four, adolescent IQ and exposure to violence.

We then evaluated the following potential independent predictors of the BRIEF-TF indexes and potential interactions with IUTE: Childhood exposure to second-hand smoke; adolescents' own substance use (any drug use except tobacco experimentation by the age at BRIEF-TF assessment); and any adolescent problematic substance use during adolescence (Frank et al., 2014). Second-hand smoke exposure and adolescent's own substance use or problematic use were tested as possible independent predictors and in interaction with IUTE. These did not alter the relationship between intrauterine exposures and BRIEF-TF scores and were not included in the final models.

As secondary analyses, we also examined associations with findings of clinical concern on the BRIEF-TF (t-scores ≥ 70 , representing 2.0 standard deviation units above the standardized mean) (Gioia et al., 2000) in GEE logistic regression models.

SAS version 9.3 was used in all data management and statistical analyses. Results were deemed statistically significant using two-tailed tests, where $p < 0.05$.

3. Results

We received a total of 247 independent BRIEF-TF assessments on 131 adolescents with enough items completed to compute in the standardized manner (Gioia, 2000) at least one of the two BRIEF-TF primary indexes (244 Behavioral Regulation and 241 Metacognition) for each assessment. Bivariate analyses revealed no significant differences on key biological and social demographic variables (child's birth weight, head circumference, or length, sex, maternal age or ethnicity, IUSE status) between those in the current sample and those in the original sample but lost to follow-up.

3.1. Sample characteristics

Final sample descriptive statistics by IUTE level can be found in Table 1. There were significant group differences ($p < 0.05$) in maternal: race/ethnicity and African-American versus not; US versus other country of birth; age at delivery; education; and use of cocaine, marijuana, and/or alcohol during pregnancy. In addition, there were significant group differences on child: sex; birth weight in grams, and as a z-score of birth weight for gestational age; and on exposure to violence. There were no significant differences by IUTE for IQ, lead exposure, or adolescent problem substance use.

3.2. Unadjusted analyses

Sample mean and standard deviation for Behavioral Regulation T-score was 68.1 (20.4) with 44% in the clinical range (greater than or equal to 70); Metacognition T-Score 69.6 (16.9) with 49% in the clinical range. There were significant overall differences in bivariate Behavioral Regulation analyses ($p = 0.007$), tobacco unexposed group mean was 63.3 (17.3) and was significantly more optimal than the lighter IUTE [73.0 (21.5), $p = 0.005$]; and heavier IUTE [72.6 (23.1), $p = 0.02$]. More than half (56%) of the lighter and 48% of the heavier exposure groups were above the clinical cutoff (less optimal), as compared to 36%

of the unexposed group (chi-square = 7.46, $p = 0.02$). Mean Metacognition T-scores were not significantly different across IUTE groups [unexposed: $M = 68.2$ (17.0); lighter $M = 71.4$ (14.5); heavier: $M = 70.4$ (19.0), $p = 0.26$]. There were no significant IUTE Metacognition T-score differences in the percentage above versus below the clinical cutoff (unexposed: 46%, lighter exposure: 59%, heavier exposure: 47%; chi-square 3.05, $p = 0.22$).

In unadjusted analyses, IUTE was a significant predictor of higher Behavioral Regulation T-scores ($\beta = 10.4$, $p = 0.005$ for lighter exposure, and $\beta = 9.89$, $p = 0.017$ for heavier exposure). IUTE was not a significant predictor of Metacognition T-scores. There were no significant associations between intrauterine cocaine or alcohol exposure and BRIEF-TF Index T-scores. In contrast, heavier intrauterine marijuana exposure was significantly associated with more optimal Behavioral Regulation ($\beta = -9.39$, $p = 0.03$) and Metacognition Index ($\beta = -7.75$, $p = 0.02$) T-scores, compared to unexposed adolescents.

3.3. Multivariable analyses

Table 2 identifies final multivariable analyses evaluating IUSE covariate adjusted associations with BRIEF-TF Behavioral Regulation and Metacognition T-scores. Only IUTE and heavier intrauterine marijuana exposure compared to unexposed differed for the Behavioral Regulation Index. IUTE was significantly associated with less optimal Behavioral Regulation T-scores [lighter exposure: 9.8 (2.0, 17.5), $p = 0.01$, heavier exposure 9.1 (1.7, 16.4), $p = 0.02$]. Heavier in-trauterine marijuana was significantly associated with more optimal Behavioral Regulation T-scores [-11.6 (-20.8 , -2.5), $p = 0.01$]. While IUTE was not significantly associated with Metacognition, heavier intrauterine marijuana exposure [-11.9 (-19.9 , -3.9), $p = 0.003$] was associated with more optimal scores.

In secondary multivariable analyses associated with dichotomized scores, lighter versus no IUTE [OR = 3.3 (1.4, 7.9), $p = 0.008$], history of violence exposure [OR = 1.8 (1.0, 3.3), $p = 0.04$], and younger age at the time of the BRIEF assessment [OR = 0.9 (0.7, 1.0), $p = 0.05$] were associated with clinical risk Behavioral Regulation Index scores. On the Metacognition Index, lighter versus no IUTE [OR = 2.4 (1.0, 5.6), $p = 0.05$], and male versus female sex [OR = 3.2 (1.8, -5.6), $p < 0.0001$] were associated with clinical risk range scores. Heavier intrauterine marijuana versus no exposure was associated with significantly less Metacognition clinical risk [OR = 0.3 (0.2, 0.9), $p = 0.04$].

Table 3 shows BRIEF-TF adjusted mean scores (rather than adjusted regression coefficients in the previous table) resulting from the multi-variable models controlling for intrauterine substance and lead exposures, violence exposure, sex, birth weight, IQ, mothers' country of birth, and age at BRIEF-TF assessment.

4. Discussion

This study evaluated effects of intrauterine tobacco exposure (IUTE) and other substance exposures, controlling for relevant covariates, on high school students' executive functioning (EF) as documented by their teachers in a naturalistic setting using the BRIEF-TF. Lighter or heavier vs no IUTE was associated with greater risk for less optimal Behavioral Regulation when scored as a continuous variable and was associated with both Behavioral Regulation

and Metacognition Index scores when using a clinical cut-off range consistent with clinically recognized EF dysfunction. Particularly concerning is that for adolescents exposed to less than half a pack of cigarettes/day, the odds of having scores in the EF dysfunction range were more than three times greater for Behavioral Regulation and more than two times greater for Metacognition. Other recent research reported EF impact of IUTE on offspring EF in laboratory settings including varieties of assessments and participant samples (Bennett et al., 2013; Daseking et al., 2015; Fried et al., 2003; Piper and Corbett, 2012) and neurodevelopment (Cornelius and Day, 2009), as well as internalizing and externalizing behaviors (Linnet et al., 2003; Sithisarn et al., 2012). These results are consistent with other analyses examining IUTE and response inhibition, attention, impulsivity (Boucher et al., 2014).

Minnes et al. (2014) evaluated caregiver (not teacher-reported) continuous BRIEF T-scores and reported multivariable intrauterine cocaine effects on Metacognition for 12-year-old girls, not boys. IUTE was the only other intrauterine substance with independent effects on the caregiver-reported BRIEF, and that was for a single subscale (Monitoring) of Metacognition but not Behavioral Regulation subscales.

In contrast with prior findings by this research group (Rose-Jacobs et al., 2011) and others (Fried et al., 2006; Squeglia et al., 2009; Tapert et al., 2002), the present study found that concurrent adolescent substance use was not related to EF ratings. This difference may be due to two reasons. First, prior studies employed performance-based measures of specific facets of EF (e.g., cognitive flexibility and visual-motor processing) in a laboratory setting, whereas the present study examined teachers' global behavioral ratings of adolescents' EF in a high school setting. Second, it is possible that higher risk adolescents – those using more substances or experiencing more problematic substance use – may have dropped out of high school and would not have teacher-reported BRIEF-TF.

In contrast to our expectations, intrauterine marijuana exposure was independently associated with more optimal estimates of both BRIEF-TF indexes. Prior studies reported detrimental effects of intrauterine marijuana exposure on laboratory-based neurocognitive measures of EF in predominantly white, middle class Canadian youth however their intrauterine marijuana and IUTE effects were associated with separate neurocognitive facets (Fried et al., 2001, 2003; Smith et al., 2016). Others have reported that marijuana, in combination with other substance use, may be neuroprotective, or not exacerbate other substances' neurotoxicity (Gonzalez et al., 2004; Squeglia et al., 2009). Explanations for our unexpected marijuana finding remain uncertain and further research into the relationship between intrauterine marijuana exposure and later EF in at-risk populations is required.

4.1. Strengths and limitations

This study evaluated EF in a low-income urban African-American population using teacher observations of day-to-day EF in a naturalistic high school setting by teachers unaware of study goals rather than in a one-to-one laboratory setting. Methodologically, future studies of IUTE and EF, should consider evaluation of participant functioning over a range of epochs within naturalistic as well as laboratory settings. Additionally, this study is one of few to simultaneously evaluate IUTE with a range of other intrauterine substance exposures

and adolescents' own substance use while also controlling for a variety of personal and environmental factors.

Our study also has limitations. First, the present findings may not generalize to high school students born preterm or living in more economically privileged or rural settings. Secondly, while the BRIEF-TF measures students' EF as perceived by classroom teachers who know the students, all behavioral reports by parents, teachers, other observers, or self-reports are beset by unmeasurable biases including possible racial biases in this predominantly African-American sample attending under-financed, under-performing urban schools. Bias of this nature may partially explain the high percentage of BRIEF-TF clinical range scores in this sample. Adolescents who dropped out of high school and potentially might have had less optimal scores, could not be included in the analyses. Nonetheless, the adjusted mean BRIEF-TF scores in all groups with or without IUTE (Table 3) were higher than published norms. BRIEF-TF scoring might reflect negative teacher expectations; however, because we did not inform teachers of the purpose of the request to fill out the forms, any bias would not have been associated with study aims. Unknown biases might have affected the variability of scores in our sample, making it more difficult to identify sample differences. Lastly, while we were able to significantly detect the effects of IUTE, our sample of 131 adolescents may have limited statistical power to detect smaller effects of other substances.

5. Conclusions

An important clinical and public health implication of our study is the identification of negative effects of intrauterine exposure to tobacco, one of the most common substances used during pregnancy and legal for adult use. These effects were present even after controlling for the effects of licit and illicit intrauterine substances including cocaine, marijuana, and alcohol. The potentially protective effect of marijuana should be evaluated as legalization of marijuana continues to spread. Although the danger of prenatal tobacco is well known, these findings bolster the imperative for evidence-based, tobacco smoking cessation programs for all individuals to be funded, particularly targeting women of child-bearing age and pregnant women.

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References

- Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol Rev.* 2006; 16:17–42. [PubMed: 16794878]
- Bennett DS, Mohamed FB, Carmody DP, Malik M, Faro SH, Lewis M. Prenatal tobacco exposure predicts differential brain function during working memory in early adolescence: a preliminary investigation. *Brain Imaging Behav.* 2013; 7:49–59. [PubMed: 22820891]

- Boucher O, Jacobson JL, Burden MJ, Dewailly E, Jacobson SW, Muckle G. Prenatal tobacco exposure and response inhibition in school-aged children: an event-related potential study. *Neurotoxicol Teratol.* 2014; 44:81–88. [PubMed: 24946039]
- Brandt R, Ward CL, Dawes A, Flisher AJ. Epidemiological measurement of children's and adolescents' exposure to community violence: working with the current state of the science. *Clin Child Fam Psychol Rev.* 2005; 8:327–342. [PubMed: 16362258]
- Chaytor N, Schmitter-Edgecombe M, Burr R. Improving the ecological validity of executive functioning assessment. *Arch Clin Neuropsychol.* 2006; 21:217–227. [PubMed: 16554143]
- Clifford A, Lang L, Chen R. Effects of maternal cigarette smoking during pregnancy on cognitive parameters of children and young adults: a literature review. *Neurotoxicol Teratol.* 2012; 34:560–570. [PubMed: 23022448]
- Cornelius MD, Day NL. Developmental consequences of prenatal tobacco exposure. *Curr Opin Neurol.* 2009; 22:121–125. [PubMed: 19532034]
- Cornelius MD, Goldschmidt L, De Genna NM, Larkby C. Long-term effects of prenatal cigarette smoke exposure on behavior dysregulation among 14-year-old offspring of teenage mothers. *Matern Child Health J.* 2012; 16:694–705. [PubMed: 21380771]
- Daseking M, Petermann F, Tischler T, Waldmann H. Smoking during pregnancy is a risk factor for executive function deficits in preschool-aged children. *Geburtshilfe und Frauenheilkunde.* 2015; 75:64–71. [PubMed: 25684788]
- Diamantopoulou S, Rydell AM, Thorell LB, Bohlin G. Impact of executive functioning and symptoms of attention deficit hyperactivity disorder on children's peer relations and school performance. *Dev Neuropsychol.* 2007; 32:521–542. [PubMed: 17650992]
- Eaton DK, Kann L, Kinchen S, Ross J, Hawkins J, Harris WA, Lowry R, McManus T, Chyen D, Shanklin S. Youth risk behavior surveillance—United States, 2005. *J Sch Health.* 2006; 76:353–372. [PubMed: 16918870]
- Fox, NA., Leavitt, LA. The Violence Exposure Scale for Children – Revised. University of Maryland; College Park, MD: 1995.
- Frank DA, McCarten KM, Robson CD, Mirochnick M, Cabral H, Park H, Zuckerman B. Level of in utero cocaine exposure and neonatal ultrasound findings. *Pediatrics.* 1999; 104:1101–1105. [PubMed: 10545554]
- Frank DA, Rose-Jacobs R, Beeghly M, Augustyn M, Bellinger D, Cabral H, Heeren T. Level of prenatal cocaine exposure and scores on the Bayley Scales of Infant Development: modifying effects of caregiver, early intervention, and birth weight. *Pediatrics.* 2002; 110:1143–1152. [PubMed: 12456912]
- Frank DA, Rose-Jacobs R, Crooks D, Cabral HJ, Gerteis J, Hacker KA, Martin B, Weinstein ZB, Heeren T. Adolescent initiation of licit and illicit substance use: impact of intrauterine exposures and post-natal exposure to violence. *Neurotoxicol Teratol.* 2011; 33:100–109. [PubMed: 20600847]
- Frank DA, Kuranz S, Appugliese D, Cabral H, Chen C, Crooks D, Heeren T, Liebschutz J, Richardson M, Rose-Jacobs R. Problematic substance use in urban adolescents: role of intrauterine exposures to cocaine and marijuana and postnatal environment. *Drug Alcohol Depend.* 2014; 142:181–190. [PubMed: 24999059]
- Fried PA, Watkinson B. Differential effects on facets of attention in adolescents prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol.* 2001; 23:421–430. [PubMed: 11711244]
- Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol.* 2003; 25:427–436. [PubMed: 12798960]
- Fried PA, Watkinson B, Gray R. Neurocognitive consequences of cigarette smoking in young adults—A comparison with pre-drug performance. *Neurotoxicol Teratol.* 2006; 28:517–525. [PubMed: 16904287]
- Gioia GA, Isquith PK, Guy SC, Kenworthy L. Behavior rating inventory of executive function. *Child Neuropsychol.* 2000; 6:235–238. [PubMed: 11419452]

- Gonzalez R, Rippeth JD, Carey CL, Heaton RK, Moore DJ, Schweinsburg BC, Cherner M, Grant I. Neurocognitive performance of methamphetamine users discordant for history of marijuana exposure. *Drug Alcohol Depend.* 2004; 76:181–190. [PubMed: 15488342]
- Huizink AC, Mulder EJJ. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. *Neurosci Biobehav Rev.* 2006; 30:24–41. [PubMed: 16095697]
- Lezak, MD., Howieson, DB., Bigler, ED., Tranel, D. *Neuropsychological Assessment.* fifth. University Press; Oxford: 2012.
- Linnet KM, Dalsgaard S, Obel C, Wisborg K, Henriksen TB, Rodriguez A, Kotimaa A, Moilanen I, Thomsen PH, Olsen J. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am J Psychiatry.* 2003; 160:1028–1040. [PubMed: 12777257]
- McLellan A, Kushner H, Metzger D, Peters R, Smith I, Grissom H, Pettinati M. Fourth edition of the addiction severity index. *J Subst Abuse Treat.* 1992; 9:199–213. [PubMed: 1334156]
- Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol.* 1989; 129:125–137. [PubMed: 2910056]
- Min MO, Singer LT, Kirchner HL, Minnes S, Short E, Hussain Z, Nelson S. Cognitive development and low-level lead exposure in poly-drug exposed children. *Neurotoxicol Teratol.* 2009; 31:225–231. [PubMed: 19345261]
- Minnes S, Singer LT, Min MO, Lang AM, Ben-Harush A, Short E, Wu M. Comparison of 12-year-old children with prenatal exposure to cocaine and non-exposed controls on caregiver ratings of executive function. *J Youth Adolesc.* 2014; 43:53–69. [PubMed: 23423839]
- Mirochnick M, Meyer J, Cole J, Herren T, Zuckerman B. Circulating catecholamine concentrations in cocaine-exposed neonates: a pilot study. *Pediatrics.* 1991; 88:481–485. [PubMed: 1909023]
- Ostrea EM, Brady MJ, Parks PM, Asenio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. *J Pediatr.* 1989; 155:474–477.
- Perkins S, Graham-Bermann S. Violence exposure and the development of school-related functioning: mental health, neurocognition, and learning. *Aggress Violent Behav.* 2012; 17:89–98. [PubMed: 22837647]
- Piper BJ, Corbett SM. Executive function profile in the offspring of women that smoked during pregnancy. *Nicotine Tob Res.* 2012; 14:191–199. [PubMed: 22039071]
- Richardson GA, Larkby C, Goldschmidt L, Day NL. Adolescent initiation of drug use: effects of prenatal cocaine exposure. *J Am Acad Child Adolesc Psychiatry.* 2013; 52:37–46. [PubMed: 23265632]
- Rose-Jacobs R, Soenksen S, Appugliese DP, Cabral HJ, Richardson MA, Beeghly M, Heeren TC, Frank DA. Early adolescent executive functioning, intrauterine exposures and own drug use. *Neurotoxicol Teratol.* 2011; 33:379–392. [PubMed: 21371553]
- Rose-Jacobs R, Augustyn M, Beeghly M, Martin B, Cabral HJ, Heeren TC, Richardson MA, Frank DA. Intrauterine substance exposures and Wechsler Individual Achievement Test-II scores at 11 years of age. *Vulnerable Child Youth Stud.* 2012; 7:186–197.
- Sithisarn T, Granger DT, Bada HS. Consequences of prenatal substance use. *Int J Adolesc Med Health.* 2012; 24:105–112. [PubMed: 22909919]
- Smith, AM., Mioduszeowski, O., Hatchard, T., Byron-Alhassan, A., Fall, C., Fried, PA. Prenatal marijuana exposure impacts executive functioning into young adulthood: an fMRI study. *Neurotoxicol Teratol.* 2016. <http://dx.doi.org/10.1016/j.ntt.2016.05.010>
- Squeglia LM, Jacobus J, Tapert SF. The influence of substance use on adolescent brain development. *Clin EEG Neurosci.* 2009; 40:31–38. [PubMed: 19278130]
- Tapert SF, Baratta MV, Abrantes AM, Brown SA. Attention dysfunction predicts substance involvement in community youths. *J Am Acad Child Adolesc Psychiatry.* 2002; 41:680–686. [PubMed: 12049442]
- Tong VT, Dietz PM, Morrow B, D'Angelo DV, Farr SL, Rockhill KM, England LJ. Trends in smoking before, during, and after pregnancy—pregnancy risk assessment monitoring system, United States, 40 Sites, 2000–2010. *MMWR Surveill Summ.* 2013; 62:1–19.

- Toplak ME, Bucciarelli SM, Jain U, Tannock R. Executive functions: performance-based measures and the behavior rating inventory of executive function (BRIEF) in adolescents with attention deficit/hyperactivity disorder (ADHD). *Child Neuropsychol.* 2008; 15:53–72.
- Tronick EZ, Frank DA, Cabral H, Mirochnick M, Zuckerman B. Late dose-response effects of prenatal cocaine exposure on newborn neurobehavioral performance. *Pediatrics.* 1996; 98:76–83. [PubMed: 8668416]
- Wakschlag LS, Henry DB, Blair RJR, Dukic V, Burns J, Pickett KE. Unpacking the association: individual differences in the relation of prenatal exposure to cigarettes and disruptive behavior phenotypes. *Neurotoxicol Teratol.* 2011; 33:145–154. [PubMed: 21256429]
- Watkins MW, Smith LG. Long-term stability of the Wechsler Intelligence Scale for Children-Fourth edition. *Psychol Assess.* 2013; 25:477–483.
- Wechsler, D. Wechsler Abbreviated Scale of Intelligence. Psychological Corporation; San Antonio, TX: 1999.
- Wechsler, D. WISC-III: Wechsler Intelligence Scale for Children. Psychological Corporation; San Antonio, TX: 1991.
- Wiebe SA, Fang H, Johnson C, James KE, Espy KA. Determining the impact of prenatal tobacco exposure on self-regulation at 6 months. *Dev Psychol.* 2014; 50:1746. [PubMed: 24512173]
- Williams PG, Suchy Y, Rau HK. Individual differences in executive functioning: implications for stress regulation. *Ann Behav Med.* 2009; 37:126–140. [PubMed: 19381748]

Table 1

Descriptive Statistics by Level of IUTE (247 observations on 131 adolescents and their mothers).

Intrauterine Tobacco Exposure				
Variables Mean $\pm$ SD or n (%)	No IUTE (n = 63)	IUTE<1/2 pack/day (n = 33)	IUTE > 1/2 pack/day (N = 35)	p-value
Maternal Variables				
Race/Ethnicity				0.005
White	5 (7.94)	2 (6.06)	3 (8.57)	
African-American	43 (68.25)	29 (87.88)	30 (85.71)	
African/Caribbean (not U.S. born)	14 (22.22)	1 (3.03)	0 (0)	
Hispanic	1 (1.59)	0 (0)	1 (2.86)	
Other	0 (0)	1 (3.03)	1 (2.86)	
US born	49 (77.78)	31 (93.94)	34 (97.14)	0.01
Age at delivery	25.02 $\pm$ 5.46	27.78 $\pm$ 4.87	28.25 $\pm$ 4.99	0.001
Years education	11.67 $\pm$ 1.37	11.91 $\pm$ 1.53	11.06 $\pm$ 1.08	0.008
Health insurance				0.26
Public	49 (77.78)	24 (72.73)	29 (82.86)	
Private	5 (7.94)	0 (0)	1 (2.86)	
Other	9 (14.29)	9 (27.27)	5 (14.29)	
Intrauterine Exposures				
Cocaine				< 0.0001
Unexposed	47 (74.6)	6 (18.18)	9 (25.71)	
Lighter	14 (22.22)	17 (51.52)	17 (48.57)	
Heavier	2 (3.17)	10 (30.3)	9 (25.71)	
Marijuana				0.05
Unexposed	54 (85.71)	21 (63.64)	22 (62.86)	
Lighter	5 (7.94)	7 (21.21)	7 (20.00)	
Heavier	4 (6.35)	5 (15.15)	6 (17.14)	
Alcohol				< 0.0001
None	60 (95.24)	15 (45.45)	22 (62.86)	
1 < 0.5 drink/day	3 (4.76)	13 (39.39)	10 (28.57)	
2 0.5 drink/day	0 (0)	5 (15.15)	3 (8.57)	
Child Birth Variables				
Sex: Female	30 (47.62)	16 (48.48)	17 (48.57)	0.99
Birth weight (grams)	3325.02 $\pm$ 519.04	2979.85 $\pm$ 314.87	3010.86 $\pm$ 465.29	0.0005
Birth weight for gestational age z score	- 0.12 $\pm$ 0.98	- 0.87 $\pm$ 0.64	- 0.62 $\pm$ 0.91	0.0003
Child and Adolescent Variables				
Average age across BRIEF-TF exams (yrs) *	15.20 $\pm$ 1.81	14.84 $\pm$ 1.68	15.19 $\pm$ 1.86	0.36
Age at first BRIEF-TF exam (yrs)	14.10 $\pm$ 1.58	13.52 $\pm$ 2.84	14.43 $\pm$ 1.88	0.46
IQ	94.44 $\pm$ 12.9	91.15 $\pm$ 11.54	89.51 $\pm$ 13.67	0.18
Ever in 4th quartile of VEX (ages 8–18) [missing imputed], yes	71%	70%	59%	0.04

Intrauterine Tobacco Exposure				
Variables Mean $\pm$ SD or n (%)	No IUTE (n = 63)	IUTE<1/2 pack/day (n = 33)	IUTE > 1/2 pack/day (N = 35)	p-value
Maximum lead Value [missing imputed]	8.97 $\pm$ 0.63	10.18 $\pm$ 1.33	9.39 $\pm$ 0.88	0.73
Log of maximum lead Value [missing imputed]	2.07 $\pm$ 0.07	2.14 $\pm$ 0.12	2.12 $\pm$ 0.09	0.73
Adolescent alcohol, marijuana, tobacco, or other drug (hallucinogens or sedatives) problem use (abuse/dependence/tolerance), or cocaine, glue or opioid use	13 (21)	6 (18)	6 (17)	0.90

* Numbers in this table generally reflect one observation per child (except average across BRIEF-TF). Categorical variables: N (%); Continuous variables: Mean $\pm$ SD.

Table 2

Multivariable Linear Models Examining Association of BRIEF-TF T Scores with Independent Variables of Interest* (247 observations on 131 adolescents and their mothers).

	Behavioral Regulation T-Score		Metacognition T-score	
	Beta estimate (95% CI*)	p-value	Beta estimate (95% CI*)	p-value
Intrauterine Tobacco Exposure				
< ½ pack per day vs. unexposed	9.75 (2.00, 17.50)	0.01	2.46 (−3.93, 8.85)	0.45
½ pack per day vs. unexposed	9.07 (1.70, 16.44)	0.02	4.06 (−2.08, 10.19)	0.19
Intrauterine Cocaine Exposure				
Heavier vs. unexposed	−2.89 (−12.17, 6.38)	0.54	4.43 (−3.25, 12.11)	0.26
Lighter vs. unexposed	0.16 (−6.44, 6.77)	0.96	4.85 (−0.65, 10.36)	0.08
Intrauterine Alcohol Exposure				
< ½ drink per day vs. unexposed	1.41 (−6.03, 8.86)	0.71	0.30 (−5.85, 6.46)	0.92
½ drink per day vs. unexposed	−7.69 (−22.15, 6.78)	0.30	3.58 (−8.21, 15.37)	0.55
Intrauterine Marijuana Exposure				
Heavier vs. unexposed	−11.68 (−20.88, −2.48)	0.01	−11.92 (−19.91, −3.93)	0.003
Lighter vs. unexposed	−3.64 (−10.95, 3.68)	0.33	−2.32 (−8.39, 3.75)	0.45
Maternal Variables				
African-American vs. not	−5.03 (−14.31, 4.2)	0.29	−6.81 (−14.50, 0.87)	0.08
US born	2.88 (−8.43, 14.19)	0.62	−5.46 (−14.87, 3.95)	0.26
Age at delivery	0.15 (−0.40, 0.69)	0.60	−0.13 (−0.58, 0.33)	0.58
Years education	−1.07 (−3.17, 1.03)	0.32	−0.03 (−1.79, 1.73)	0.97
Child/Adolescent Variables				
Sex, female	−0.43 (−5.48, 4.62)	0.87	9.90 (5.65, 14.14)	0.001
Birth weight z-score	−1.04 (−3.90, 1.82)	0.48	0.56 (−1.81, 2.93)	0.64
Log of maximum lead value	3.67 (−2.11, 9.45)	0.21	1.37 (−3.28, 6.01)	0.56
History of exposure to violence (VEX) – ever in highest sample quartile	−4.37 (−10.43, 1.69)	0.16	−2.38 (−8.12, 3.36)	0.41
Age-at BRIEF-TF	−0.79 (−2.12, 0.54)	0.24	−0.09 (−1.21, 1.04)	0.88
Adolescent IQ (WASI)	−0.06 (−0.28, 0.16)	0.60	−0.09 (−0.28, 0.09)	0.32

* controlled for intrauterine substance exposures, violence exposure, sex, birth weight, IQ, mothers' country of birth, age at BRIEF-TF assessment, and lead exposure.

Table 3

BRIEF-TF T-Scores by Intrauterine Tobacco Exposure^{*}. (n = 247 observations on 131 adolescents and their mothers)

	Adjusted Mean (SE) [*]	p-value (vs. unexposed)
Behavioral Regulation		
Unexposed	55.24 (4.30)	–
< 1/2 pack per day	64.08 (4.25)	0.01
1/2 pack per day	63.28 (5.10)	0.02
Metacognition (N.S.)		
Unexposed	66.78 (3.13)	–
< 1/2 pack per day	69.73 (2.77)	0.45
1/2 pack per day	70.31 (3.63)	0.19

^{*} Controlled for: intrauterine substance exposures, violence exposure, sex, birth weight, IQ, mothers' country of birth, age at BRIEF-TF assessment, and lead exposure.