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Special Issue Article

The roles of familial transmission and smoking during pregnancy on executive function skills: A sibling-comparison study

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Abstract

This research examines maternal smoking during pregnancy and risk for poorer executive function in siblings discordant for exposure. Data ($N = 173$ families) were drawn from the Missouri Mothers and Their Children study, a sample, identified using birth records (years 1998–2005), in which mothers changed smoking behavior between two pregnancies (Child 1 [older sibling]: $M_{age} = 12.99$; Child 2 [younger sibling]: $M_{age} = 10.19$). A sibling comparison approach was used, providing a robust test for the association between maternal smoking during pregnancy and different aspects of executive function in early-mid adolescence. Results suggested within-family (i.e., *potentially* causal) associations between maternal smoking during pregnancy and one working memory task (visual working memory) and one response inhibition task (color-word interference), with increased exposure associated with decreased performance. Maternal smoking during pregnancy was not associated with stop-signal reaction time, cognitive flexibility/set-shifting, or auditory working memory. Initial within-family associations between maternal smoking during pregnancy and visual working memory as well as color-word interference were fully attenuated in a model including child and familial covariates. These findings indicate that exposure to maternal smoking during pregnancy may be associated with poorer performance on some, but not all skills assessed; however, familial transmission of risk for low executive function appears more important.

Keywords: executive function; family studies; smoking during pregnancy

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Introduction

EF is an umbrella term that involves a series of cognitive processes essential for intentional, goal-directed behaviors (Anderson, 2002; Gioia et al., 2001; Rabinovici et al., 2015). Processes of EF include anticipation, planning, behavior initiation, self-regulation, mental flexibility, deployment of attention, and utilization of feedback (Anderson, 2002). These processes have been further categorized into three subdomains of EF: (1) inhibition control (also known as response inhibition), which allows individuals to cognitively inhibit information and behavioral responses that are unrelated to the current task; (2) set-shifting (also called cognitive flexibility), which is the function of flexibly shifting attention between multiple tasks (Shields et al., 2015); and (3) working memory, which enables individuals to integrate new information into existing information networks.

EF develops throughout childhood and adolescence (Anderson, 2002), and maturation of brain regions, such as prefrontal cortex and inferior parietal regions, set the foundation of EF development (Bennett et al., 2013; Grattan & Eslinger, 1991). Consequently, both function and dysfunction of executive processes depend on factors that can alter the structure and functioning of related brain regions. These factors include, but are not limited to, genetic influences and exposures (such as maternal smoking during pregnancy) that might perturb various neurotransmitter systems in the brain (Barnes et al., 2011).

Etiology of individual differences in executive function

Individual differences in quantitative measures of EF are strongly driven by familial and genetic differences and many clinical outcomes marked by executive deficits are highly heritable (e.g., ADHD, dyslexia). Twin studies suggest a heritable latent (common) factor that affects all EF subdomains and accounts for 99% of the variance common to all three skills (Friedman et al., 2008). Specific EF skills (i.e., inhibition, set-shifting, and working memory) also generally show moderate heritability, with ranges between 25 and 81% depending on assessment, age, and sex of the sample (e.g., Anokhin et al., 2010; Coolidge et al., 2000; Friedman et al., 2008; Gustavson et al., 2022; Li & Roberts, 2017); noting, however, that reports of heritability

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of EF skills in toddlers are mixed (e.g., Leve et al., 2013). While there have been several genome-wide association studies (GWAS) of EF, few have identified any genome-wide significant variants. Wendel et al. (2021) identified nine genome-wide significant SNPs on chromosome 5 that may be associated with performance on a set-shifting task, though these results have yet to be replicated (Wendel et al., 2021). Thus, EF is likely highly polygenic, with few and weak specific genetic variants directly related to any phenotype (Chang et al., 2020).

Beyond familial and genetic etiological risk for EF skills, Friedman et al. (2018) note that EF skills remain sensitive to unique environmental influences. As noted above, investigations into the potential for other causal pathways have also identified variables such as neurological disorders, traumatic brain injury, brain structural differences, and differences in brain neurotransmitter levels, which help the brain maintain focus and control (e.g., Barnes et al., 2011; Bennett et al., 2013; Grattan & Eslinger, 1991). Maternal smoking during pregnancy has been identified as one exposure with associated teratological effects on brain development and related mechanisms that adversely affect EF (England et al., 2017).

Maternal smoking during pregnancy

Maternal smoking during pregnancy has been associated with numerous offspring outcomes, such as low birth weight (Knopik et al., 2016b), disruptive behavior problems (Ekblad et al., 2020a, 2020b), neurodevelopmental disorders such as ADHD (Buck et al., 2021; Knopik et al., 2016a; Micalizzi et al., 2018), reading and language performance (Micalizzi et al., 2021), and academic difficulties (Martin & Dombrowski, 2008). Despite its well-documented risks, maternal smoking during pregnancy remains prevalent, with roughly 7% of women reporting use during the prenatal period (Azagba et al., 2020). Rates of use are higher in women aged 20–24 (9.9%) and in those with less education (12.2%) (Azagba et al., 2020).

There are multiple reviews on the mode of action of prenatal smoke exposure from both the animal and human model perspective (e.g., Buck et al., 2021; Ernst et al., 2001; Slikker Jr et al., 2005). Maternal smoking during pregnancy alters neuronal differentiation, results in lower proportions of neurons in the developing dorsolateral prefrontal cortex, and is associated with reduced brain volume. Maternal smoking during pregnancy may exert these influences, in part, through its interaction with several neurotransmitter systems in the brain that act as key mediators of the actions of neuronal differentiation, maturation, and morphology. More specifically, maternal smoking during pregnancy has been associated with altered nicotinic acetylcholine receptor (nAChR) receptor patterns in both placental tissue of smoking mothers and in brains of children exposed to maternal smoking during pregnancy (e.g., Falk et al., 2005; Lavezzi, 2018; Machaalani et al., 2014), decreased levels of norepinephrine (Oncken et al., 2003) and perturbations in the catecholaminergic system (Barnes et al., 2011; Buck et al., 2021). Taken together, maternal smoking during pregnancy may, during the critical developmental period of pregnancy, affect brain regions and neurotransmitter systems thought to be implicated in executive processes (Knopik et al., 2016a).

Association of maternal smoking during pregnancy and executive function

Maternal smoking during pregnancy appears to be a risk factor for EF abilities, given that prenatal smoke exposure has been found to alter the developing brain regions responsible for executive processes. Children exposed to maternal smoking during pregnancy are at higher risk of having thinner parahippocampal, middle frontal, and orbitofrontal cortices (Toro et al., 2008), and smaller cortical gray matter and parenchymal volumes (Rivkin et al., 2008). At present, however, evidence concerning the association between maternal smoking during pregnancy and EF has been mixed, and the inconsistency in findings might be both age and assessment dependent, as outlined below.

Maternal smoking during pregnancy is associated with lower EF scores in early childhood, with assessment tools ranging from parent-rated scales to cognitive ability tasks. In an ethnically-diverse sample in the United States, maternal smoking during pregnancy predicted poorer EF, assessed by the Nebraska Barnyard task and a Go/NoGo task, in 5-year-old children (Clark et al., 2016). Studies in international samples also found similar associations between maternal smoking during pregnancy and offspring EF scores, using the Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF) (Daseking et al., 2015) and the McCarthy Scales of Children's Abilities (MCSA) (MCSA: Julvez et al., 2007).

There is a paucity of research in adolescence. To our knowledge, only two studies to date have examined the relationship between maternal smoking during pregnancy and EF skills in adolescents and results are mixed. Maternal smoking during pregnancy was associated with poorer teacher-rated EF scores using the BRIEF (Rose-Jacobs et al., 2017); however, this association was not found in an earlier study with EF tested by a variety of tasks, such as the Stroop Test (Fried et al., 2003).

One major challenge when considering the association between maternal smoking during pregnancy and EF is, as exemplified in the narrative above, the sheer variety of EF assessments and subsequent approaches to calculate EF. Specifically, a summed score of all subdomains was a common EF outcome of interest. EF factor scores were also considered consistent with research suggesting that the developmental pattern of EF progresses from unity to diversity. More specifically, EF has been shown to be unitary as it emerges in early childhood (Wiebe et al., 2011) such that a single factor EF model best explains EF performance in middle childhood. However, diversity begins to emerge around age 13 (e.g., Xu et al., 2013). Further, the three subdomains of EF have been shown to be related to different brain regions and functioning mechanisms (Fiske & Holmboe, 2019), such that when these subdomains were considered separately, distinct associations have been suggested. For example, maternal smoking during pregnancy has been related to set-shifting and inhibition domains more robustly, rather than to the domain of working memory (Fried et al., 1998; Oh et al., 2020). Therefore, research examining the three subdomains of EF separately is warranted to provide clearer implications for the relationship between maternal smoking during pregnancy and EF. One further point that contributes to inconsistent findings in this area is the assessment of maternal smoking during pregnancy, which ranged from prospective report of amount of cigarette smoking during the 2nd and 3rd trimesters of pregnancy (Cornelius et al., 2001) to a retrospective binary question of yes/no (Thakur et al., 2012).

Association of maternal smoking during pregnancy and working memory

Working memory is an online information processing and manipulation system which can be separated into visual and auditory components (Mesulam, 2002). While perhaps related,

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working memory is different from memory and is usually considered an element of EF. Given its executive nature, working memory is important for successful inhibitory control (Pennington et al., 1996; Roberts Jr & Pennington, 1996) and, therefore, is considered central to outcomes such as ADHD. Working memory is critical for advanced cognitive tasks, including language comprehension, spatial thinking, learning, and reasoning (Shah & Miyake, 1996) and, by extension, academic performance (Giofre et al., 2017; Rogers et al., 2011).

Imaging studies have suggested that maternal smoking during pregnancy affects the structural maturation of the developing brain (Rivkin et al., 2008; Toro et al., 2008), including regions suggested to be related to working memory functioning. In children across multiple studies and countries, maternal smoking during pregnancy has been associated with deficits in various memory-related tasks, including (i) the Wide Range Assessment of Memory and Learning-Screening (WRAML-S), which requires learning a list of words and recreating geometric designs from memory (Cornelius et al., 2001), (ii) Listening Recall, Backwards Digit Recall, Verbal fluency and Unusual Uses task (Vandenbroucke et al., 2016), as well as (iii) the Self-Ordered Pointing Task (SOPT) and the Wide Range Assessment of Memory and Learning (WRAML: Thakur et al., 2012).

In adolescents and young adults, the relationship between maternal smoking during pregnancy and working memory is inconsistent. Adolescent tobacco smokers with exposure to maternal smoking during pregnancy experienced greater nicotine withdrawal-related deficits in both immediate and delayed visuospatial memory as assessed by the Brief Visuospatial Memory Test-Revised (BVMT-R: Jacobsen et al., 2006); although maternal smoking during pregnancy effects may be confounded with youth current smoking status. Another study found no effect of maternal smoking during pregnancy on short-term working memory, verbal working memory, and immediate and long-term memory for auditory/verbal material as assessed by the Wechsler Intelligence Scale for Children III (WISC-III) and the Stories Immediate, Stories Delayed, and Stories Recognition subtests of Children's Memory Scale (CMS: Kafouri et al., 2009). In addition, fMRI studies in adolescents and young adults reported that those exposed to maternal smoking during pregnancy displayed similar task performance to unexposed control participants in a N-Back working memory task; however, exposed children showed greater brain activation in the regions responsible for verbal working memory, memory maintenance, and inhibitory control suggesting that exposed and unexposed children may use different brain regions and approaches to succeed when engaged in working memory tasks (Bennett et al., 2013; Longo et al., 2013).

Besides the possible age-dependent effect of maternal smoking during pregnancy on working memory, the assessment of working memory may also matter. Specifically, the association between maternal smoking during pregnancy and visuospatial working memory has been more robust irrespective of assessment (Jacobsen et al., 2006; Thakur et al., 2012), whereas the association between maternal smoking during pregnancy and verbal working memory has been inconsistent across studies (Cornelius et al., 2001; Longo et al., 2013; Marcelle et al., 2020; Vandenbroucke et al., 2016).

Association of maternal smoking during pregnancy and set-shifting

In early childhood, no robust relationship between maternal smoking during pregnancy and set-shifting has been reported. In preschool aged children, mean ratings of set-shifting did not differ between mothers who smoked and mothers who abstained (Daseking et al., 2015; Wiebe et al., 2009).

In adolescents, similar to other EF components already discussed, there is a general trend of little to no association between maternal smoking during pregnancy and set-shifting; although results were mixed. Generally, maternal smoking during pregnancy was not associated with set-shifting in adolescents when assessed using a Trail Making Task (Cornelius et al., 2001; Fried & Watkinson, 2000) and the Mirsky's shift/be flexible factor (Fried & Watkinson, 2001). However, when set-shifting was assessed using the Wisconsin Card Sorting Task (WCST) or the Stroop task, results were more mixed. This suggests that the association between maternal smoking during pregnancy and set-shifting during adolescence may be task specific. More specifically, when set-shifting was assessed using the WCST, two studies found no association (Fried & Watkinson, 2001; Fried et al., 2003) whereas one study found a positive association such that children whose mothers smoked at any point during the pregnancy displayed more perseverative behavior on the WCST than children whose mothers did not smoke (Cornelius et al., 2001). When set-shifting was assessed using the Stroop task, two studies found no association (Cornelius et al., 2001; Fried et al., 2003) and one study found an association when maternal smoking during pregnancy was measured continuously as opposed to dichotomously (yes/no) (Cornelius et al., 2011).

Association of maternal smoking during pregnancy and inhibitory control

In children, maternal smoking during pregnancy is associated with poorer performance in inhibitory domains. Preschool children exposed to maternal smoking during pregnancy exhibited increased inhibitory deficits, as much as four times higher than non-exposed children, as measured by parent and teacher ratings on the BRIEF-Preschool Version (BRIEF-P, German version: Daseking et al., 2015). School-aged children exposed to maternal smoking during pregnancy also showed poorer inhibitory control on the Delay Frustration Task (Huijbregts et al., 2008) and the Stroop task (Cornelius et al., 2011). Imaging studies suggested similar findings with those exposed to maternal smoking during pregnancy making more errors when completing a Go/NoGo response-inhibition task (Bennett et al., 2009). Additionally, maternal smoking during pregnancy was associated with greater brain activation in exposed children, suggesting, as with working memory, that exposed and unexposed children may use different brain regions and approaches to succeed when engaged in response inhibition tasks (Bennett et al., 2009).

In emerging adults, a longitudinal imaging study suggested that those exposed to maternal smoking during pregnancy displayed similar task performance as the control group when assessed by a Go/NoGo task; however, maternal smoking during pregnancy exposure was associated with greater brain activation in the regions responsible for response inhibition (Longo et al., 2013). Similar to the EF subdomains of working memory and set-shifting, findings appear to be assessment specific. For example, reports of greater brain activation as a function of maternal smoking during pregnancy were not supported in other samples of emerging adults exposed to maternal smoking during pregnancy, who exhibited less brain activity in the areas responsible for response inhibition while doing an Erikson flanker/NoGo task (Holz et al., 2014).

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Maternal smoking during pregnancy-EF associations examined using genetically-informed designs

As noted above, EF displays familial transmission and has been shown to be highly heritable. Maternal smoking during pregnancy has also been shown to have genetic influences (Agrawal et al., 2008). Yet, few studies have examined the relationship between maternal smoking during pregnancy and EF while also accounting for genetic risk (Micalizzi & Knopik, 2018). In fact, in many epidemiological studies of the relationship between maternal smoking during pregnancy and EF, there is very limited, if any, inclusion of maternal and paternal covariates, which may contribute to overestimated associations.

Quasi-experimental designs, such as sibling comparison models and other genetically-informed approaches, test for the likely possibility that risk factors that co-occur with maternal smoking during pregnancy might better explain poor outcomes than a teratogenic effect of maternal smoking during pregnancy itself (Knopik, 2009). More specficially, the sibling comparison design allows for the association between maternal smoking during pregnancy and offspring outcome to be examined both within a family and between families. Results can strengthen our inferences about causality in associations of maternal smoking during pregnancy and offspring outcomes. The between-family association can be considered consistent with the historically standard comparison of looking at offspring of mothers who smoke during pregnancy relative to offspring of mothers who do not. This comparison does not control for influences that siblings share (i.e., genetic and familial effects) that might confound the maternal smoking during pregnancy-outcome association; however, it does allow replication of historical associations found in the literature. Conversely, a significant within-family association provides the strongest support for a causal influence of maternal smoking during pregnancy on an offspring outcome (e.g., child EF): i.e., the exposed sibling has larger EF skill deficits than the unexposed sibling. Because the design controls for mother- and family-level characteristics, and to a certain extent genetic influences, the within-family association is the strongest evidence that maternal smoking during pregnancy may be causally linked with the outcome. Note, however, it is not proof of causation. In the case of EF, women with EF deficits may be more likely to smoke during pregnancy and thus, may pass down both correlated genes and environmental influences that are associated with EF problems. This possibility might contribute to a non-causal association between maternal smoking during pregnancy and EF.

It is also the case that there are other confounding variables, such as secondhand smoke exposure or other risk factors, that may contribute to what appears to be a causal relationship between maternal smoking during pregnancy and EF, when in reality, the association is due to associated genes, behaviors, or contexts that influence both EF and maternal smoking during pregnancy. Utilizing an adopted-at-birth design, prenatal risk (as assessed by maternal substance use during pregnancy as well as pregnancy illness/complications) was associated with worse set-shifting scores as assessed by the shape Stroop task in children approximately 2 years in age (Leve et al., 2013). However, prenatal risk was nonsignificant in the presence of genetic influences within the model (Leve et al., 2013). A limitation of this particular adoption study was that maternal smoking during pregnancy was not specifically examined but rather included in the larger context of risk. Additionally, child and maternal covariates were limited.

Micalizzi et al. (2018) used the present sample (MO-MATCH) to examine the relationship between maternal smoking during pregnancy and one aspect of EF, inhibitory control, using a sibling-comparison design. As outlined above, this design can directly inform questions of the etiology (i.e., genetic and environmental influences) of individual differences in offspring outcomes and provide a rigorous test of potentially causal effects of maternal smoking during pregnancy on these outcomes. In that study, maternal smoking during pregnancy was associated with poorer inhibitory control (i.e., a significant within-family effect) as measured by the Delis Kaplan Executive Function System (DKEFS) Color Word Interference task; however, once measured familial confounding variables (i.e., child and maternal covariates) were accounted for, the effect did not hold, suggesting that familial transmission is a more important consideration in offspring inhibitory control (Micalizzi et al., 2018).

Present study

Given: (1) the paucity of maternal smoking during pregnancy-EF investigations that account for familial confounding; (2) the inconsistent nature of the existing literature focused on the relationship between maternal smoking during pregnancy and EF as reviewed above, and (3) the knowledge from animal studies that maternal smoking during pregnancy affects brain regions known to be involved in EF skills (see Buck et al., 2021 and Knopik, 2009 for reviews), the present study attempts to add clarity to existing research on the maternal smoking during pregnancy-EF relationship using a sibling comparison design of early to middle adolescents. The dataset used for the present examination was collected specifically to attempt to disentangle familial influences from maternal smoking during pregnancy-exposure influences on four key domains, where based on animal work and existing human work, we might expect to find true deficits: memory, executive function, reading/language, and ADHD. For the purposes of this current study, measures assessing set-shifting, working memory and inhibitory control will be considered. This study also capitalizes on data regarding sociodemographic characteristics (used as covariates in the present study) which have been shown to be associated with maternal smoking during pregnancy and child EF.

It was hypothesized, based on the existing literature summarized above, that maternal smoking during pregnancy would be associated with poorer EF skills (set-shifting, working memory, and inhibitory control), but that, due to the familial nature of EF skills, the sibling comparison design would yield attenuated associations between maternal smoking during pregnancy and EF skills. If these hypotheses are supported, it would suggest that confounding factors – i.e., genetic and environmental influences that siblings share (familial transmission) – play a more important role in predicting EF skills in children and adolescents. If, however, the maternal smoking during pregnancy-EF association persists in the sibling comparison models, it would be suggestive of a potential causal role of maternal smoking during pregnancy above and beyond familial transmission.

Methods

Participants and procedure

The MO-MATCH (Knopik et al., 2015) sample consists of 173 families ($N = 344$ total children) in which mothers smoked (or smoked more) during one pregnancy but did not smoke

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(or smoked less) in the other pregnancy. Birth records (years 1998–2005) were obtained from the Missouri Department of Health and Senior Services Bureau of Health Informatics and used to identify families ($N > 4{,}000$ identified) with two children for which birth records indicated discordant smoke exposure. Mothers ($N = 1{,}520$) were screened to determine eligibility to participate in the current study. Consistent with reports regarding accuracy and reliability of birth record data (e.g., Bradford et al., 2007; Stout et al., 2017), 27% agreed with the birth record and were deemed eligible for recruitment.

Following a maternal interview, ($M_{age\ at\ assessment} = 39.83$, SD = 5.62) where mothers reported on their pregnancies, mental health, and her children's behavior, families (and when possible, fathers $n = 96$ [$M_{age\ at\ assessment} = 44.04$, SD = 6.34]) completed in-depth neuropsychological assessments. Families in which fathers participated were not different from families in which fathers did not participate on any focal variable (Knopik et al., 2015). Assessments of both children occurred simultaneously in the laboratory when youth were age 7–16 years (Child 1 $M_{age} = 12.99$, SD = 1.94, 53% male; Child 2 $M_{age} = 10.19$, SD = 1.80, 51% male). A project coordinator and four research assistants with backgrounds in psychiatric nursing, psychology, behavioral science, or related fields were trained to administer laboratory assessments by a pediatric clinical neuropsychologist. The study was approved by the Institutional Review Boards of Purdue University, Rhode Island Hospital, Washington University and the State of Missouri Department of Health and Senior Services.

Parents were primarily White (96%, $n = 250$). Most mothers and fathers completed at least some college education (77.2 and 65%, respectively) and 83.3% were married at the time of Child 1's [older sibling] birth and 81.7% were married at Child 2's [younger sibling] birth. Mothers typically smoked (or smoked more) in the first pregnancy (64%). Few families received food stamps at the time of birth of Child 1 (9.74%) and Child 2 (13.73%).

Measures

Smoking during pregnancy

A modified version of the Missouri Assessment of Genetics Interview for Children–Parent on Child (Todd et al., 2003) was used to assess maternal smoking during pregnancy in each pregnancy. Any smoking during pregnancy was assessed as a discrete indicator specific to each trimester (0 = No, 1 = Yes), overall quantity of smoking during pregnancy (0= no smoking during pregnancy, 1 = 21 or less, 2 = 21–99, 3 = 100 + cigarettes), and the quantity of cigarettes smoked in each trimester (continuous variable from 0 to 98 cigarettes) were assessed. Using the above, a severity score was created that was specific to each child's exposure to smoking during pregnancy, where 1 = no maternal smoking during pregnancy, 2 = maternal smoking during pregnancy in the first trimester only, 1–10 cigarettes per day, 3 = maternal smoking during pregnancy in the first trimester only, 11–19 cigarettes per day, 4 = maternal smoking during pregnancy in the first trimester only, 20+ cigarettes per day, 5 = maternal smoking during pregnancy beyond the first trimester, 1–10 cigarettes per day (max of all trimesters), 6 = maternal smoking during pregnancy beyond the first trimester, 11–19 cigarettes per day (max of all trimesters), 7 = maternal smoking during pregnancy beyond the first trimester, 20+ cigarettes per day (max of all trimesters). The score was calculated as such because: a) literature suggests exposure in late pregnancy may be more harmful than earlier in pregnancy (e.g., Dwyer et al., 2009; Hebel et al., 1988); and b) many maternal smoking during pregnancy effects follow a dose-response pattern (e.g., Knopik et al., 2016b).[1]

Executive function

Inhibitory control

Two tasks were used to assess inhibitory control.

(1) The inhibition condition of the *Color-Word Interference Test* on the Delis-Kaplin Executive Function System (DKEFS; Delis et al., 2001a). This one variable was examined in an earlier report (Micalizzi et al., 2018). In the present study, we aimed to comprehensively examine all subdomains of executive function using two assessments per domain. Thus, we include it here for a complete description of all EF tasks administered in MO-MATCH and, due to the prior examination in Micalizzi et al. (2018), limit discussion of the results to summary form (Table 2) and text (full results in Supplementary Table 6). For DKEFS inhibitory control, participants were required to report the ink color of words that spelled a dissonant color word. For example, if the word *red* was printed in green ink, the correct response was "green" rather than "red." Two baseline conditions (naming of color patches and naming of words that denote colors printed in black ink) preceded 10 practice items. If participants required four corrections the task was discontinued. Test trials included 50 color words printed in dissonant ink colors. If three consecutive errors were made on test trials, participants were prompted to name the ink color once. Raw completion time in seconds (maximum 180 seconds) were normed (mean = 10, SD = 3) and corrected for the appropriate age group. Higher scaled scores indicate better performance.
(2) The *Logan Stop-signal Task* (SSRT; implemented in E-Prime; Verbruggen et al., 2008), requires the participant to react to a stimulus by either withholding their response (i.e., stop-signal) or actively responding (i.e., go-signal). Performance was determined by go-signal obedience. The response is considered inhibited if the go-signal was not obeyed, and not inhibited if the go-signal was obeyed (Matzke et al., 2017). Inhibitory control is measured by calculating the delay time between introduction of stimuli and reaction time (Logan & Cowan, 1984; Logan et al., 1984). Poor task performance, i.e., requiring more time to inhibit responses to stop-signals, indicates slower cognitive processes characterized by decreased accuracy and impulsive responding (Dimoska & Johnstone, 2008). SSRT has been shown to be relatively constant, at approximately 200 ms, in healthy adults across a number of different forms of movement, including typing, button-pressing, and eye movement (Logan, 1994).

Working memory

Two measures of working memory in the present study:

1. To assess auditory working memory, the WISC (Wechsler, 2003) *Digit Span Backward* subtest assessed children's ability to manipulate verbally-presented information while in short term memory storage. The task requires children to repeat strings of numbers that increase in length in reverse order following verbal presentation (one number per second) from

[1]Sensitivity analyses were conducted to evaluate the correspondence across various operationalizations of maternal smoking during pregnancy exposure. Correlations across quantifications were high and are reported in supplemental materials of Knopik et al. (2016a).

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the experimenter. Digit Span Backward Total Raw Score (the sum of item scores) was used in the current analyses.
2. Visual working memory was assessed via the *Spatial Span Backward* subtest of the WISC in children. Spatial span backward is considered the nonverbal analog to the digit span backward task (Teixeira et al., 2011). In parents, visual working memory is assessed via WMS-III Symbol Span (Wechsler, 1997).

Set-shifting/cognitive flexibility

In this study, we considered two measures of cognitive flexibility in order to capture (i) cognitive flexibility in the visual motor domain and (ii) cognitive flexibility in the verbal domain.

1. The DKEFS *Trail Making Test* (Delis et al., 2001b) consists of five conditions. Condition 1 is a visual search task requiring participants to scan a page and cross out circles containing a given number. Condition 2 is a number sequencing task, in which participants draw lines to connect numbers in sequential order. Condition 3 is identical to condition 2, except that participants connect letters rather than numbers. Condition 4 measures set-shifting ability as it requires participants to switch between connecting numbers and letters. Condition 5 is a motor speed task that requires participants to trace a dotted line that connects a series of open circles. The contrast score from the Number Letter Switching Score (Condition 4) minus the Combined Number and Letter Sequencing Score was used to assess set-shifting, or more specifically cognitive flexibility in the visual motor domain.
2. Cognitive flexibility in the verbal domain was assessed with the DKEFS *Verbal Fluency Test*, which consists of four conditions: Letter Fluency, Category Fluency, Category Switching, and Category Switching Accuracy. The contrast score between the Category-Switching subtest minus the Category Fluency score will provide us with an additional measure of verbal cognitive flexibility. This contrast score accounts for the more basic verbal fluency abilities in order to assess (higher order) cognitive flexibility.

Covariates

Maternal and familial characteristics that could confound the association of maternal smoking during pregnancy and EF were included as covariates. These were selected based on the literature (e.g., Camerota & Willoughby, 2020) and to be consistent with prior reports using this sample and approach (Ekblad et al., 2020; Knopik et al., 2015; Marceau et al., 2018; Micalizzi et al., 2018, 2021): maternal report of her marital status, food stamp usage, age, and education at birth of each child, child birth order, child sex, and second-hand smoke exposure during pregnancy (by the father). There is some debate in the field as to the utility of including IQ in models considering EF (Arffa, 2007). This debate is largely due to mixed findings on the association between IQ and aspects of EF, with some studies finding strong correlations (e.g., Colom et al., 2008) and others finding no associations (e.g., Welsh et al., 1991). In order to be consistent with prior work using MO-MATCH (Micalizzi et al., 2018, 2021) and in order to determine the relationship between maternal smoking during pregnancy and EF that is independent of IQ, both child and mother IQ (Wechsler et al., 2004; Wechsler, 2003) were controlled for in all analyses. Finally, the corresponding mother EF variables were included as covariates, with the only exception being the Logan Stop Task (i.e., SSRT) since that was not assessed in the parents. Because only approximately half of fathers completed the study, only maternal covariates were included in the models reported in this paper. Sensitivity analyses were used to probe (a) inclusion of father covariates and (b) exclusion of IQ given the aforementioned debate in the field are available upon request. For the second set of sensitivity models, removing IQ did not change the pattern of findings.

Analytic plan

Factor structure of EF variables

A parallel analysis (Horn, 1965) was conducted to evaluate the number of factors underlying the indicators of executive function using the *psych* package in R (Revelle, 2013). Parallel analysis is a method for determining the number of factors to retain from a factor analysis from random data simulation. The parallel analysis method involves the generation of a series of correlation matrices among random variables that correspond to the sample size and number of variables in the actual dataset. An average is obtained of the eigenvalues from the randomly generated data and compared to the eigenvalues of the actual data. The number of factors for the actual data that are greater than random eigenvalues obtained from the parallel analysis should be retained (Hayton et al., 2004).

Hierarchical linear models (HLM)

In MO-MATCH, siblings (level 1) are nested in families (level 2). Our sibling comparison approach (identical to the approach detailed in Knopik et al., 2016a, 2016b; Micalizzi et al., 2018, 2021) involved fitting a series of HLM to account for non-independence of data, as well as to assess the within- and between-family associations of maternal smoking during pregnancy and EF. Standard models (i.e., those that do not leverage the sibling comparison aspect of the data) were conducted to test hypothesis 1 (i.e., that increased exposure to maternal smoking during pregnancy would be associated with lower EF) in a way more directly comparable to findings from non-genetically informed samples in the literature.

The *standard models* compared children whose mothers smoked (or smoked more) during pregnancy to those whose mothers who did not smoke (or smoked less) on EF. This approach does not capitalize on the family structure/sibling comparison aspect of the data, but does adjust for the non-independence of observations. The standard model was run without (Zero-order; Model 1) and with (Covariate Adjusted; Model 2) covariates.

The *sibling comparison models* parsed the extent to which maternal smoking during pregnancy operates at a within-family (i.e., contributing to differences in EF in one sibling versus another, within families) and/or between-family level (i.e., contributing to differences in overall, average levels of siblings' EF across families). Two variables were computed to capture maternal smoking during pregnancy severity and covaried in the sibling-comparison models: a) the *family average maternal smoking during pregnancy score* (i.e., the average score for maternal smoking during pregnancy across both siblings) and b) *child-specific maternal smoking during pregnancy severity relative to family average* for each child (i.e., resulting value when the family average maternal smoking during pregnancy was subtracted from each child-specific maternal smoking during pregnancy severity score; or within-

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family centering). *Family average maternal smoking during pregnancy severity* is included as a covariate to control for the between-family association between maternal smoking during pregnancy severity and EF (i.e., the overall associations between maternal smoking during pregnancy and related familial factors on EF, comparing across families). The association between the *child-specific maternal smoking during pregnancy severity relative to family average* and EF assesses a potentially causal within-family effect of maternal smoking during pregnancy in that familial confounding is controlled by design. That is, this association compares across siblings within a family, and thus is a test of any unique association between maternal smoking during pregnancy and child specific outcomes *beyond* familial and genetic factors that siblings share. The child-specific relative to family average maternal smoking during pregnancyseverity score was entered as a level 1 predictor, whereas the family average maternal smoking during pregnancy severity score was entered as a level 2 predictor. The sibling comparison model was also run without (Zero-order; Model 3) and with (Covariate Adjusted; Model 4) covariates.

Results

Means and standard deviations for study variables are presented in Table 1. A summary of the main findings (beta-weights from the maternal smoking during pregnancy variables for all outcomes from the zero-order and covariate adjusted *sibling-comparison* models) is provided in Table 2. More detailed tables providing the full context of models (all parameter estimates, including covariates, variance estimates, and model fit statistics from the covariate-adjusted *standard* and *sibling-comparison* models) are presented in supplemental materials.

Factor analysis of EF variables

The correlations between the EF variables in the present study ranged from −0.12 to 0.27) and were largely non-significant. Those that were significant are modest in magnitude (e.g., $r_{\text{TRAILS-ColorWordInterf}} = 0.25$, $r_{\text{TRAILS-SpatialSpanBwd}} = 0.27$, $r_{\text{SSRT-SpatialSpanBwd}} = 0.19$, $r_{\text{DigitSpanBwd-ColorWordInterf}} = 0.19$). These results are consistent with findings that the DKEFS subscales show only low positive correlations—suggesting that the tasks measure unique aspects of EF with low overlap in variance (Swanson, 2005). Thus, one explanation for this pattern of findings is a function of the use of the DKEFS assessment. One other plausible explanation for the discrepant findings with the previously observed three-factor structure is publication bias (Karr et al. (2018).

Results from the parallel analysis revealed that the eigenvalues from the random data were larger than the eigenvalues from the factor analysis. In fact, the eigenvalue of a factor extracted from random data exceeded even the first factor extracted from these data. As such, results from the parallel analysis indicated that there was no meaningful factor solution underlying the EF variables and, thus, no information to extract. As a result, all variables were treated as separate dependent variables in the HLMs. Because the DKEFS Color Word Interference task was the focus of a previously published paper from our group (Micalizzi et al., 2018), we do not discuss detailed results in the present report and instead only mention a summary of those findings as well as an extension of those models for a complete picture of the EF variables used in this analysis.

Hierarchical models examining associations between maternal smoking during pregnancy and component EF skills

In our early- to middle-adolescent sample, in the *standard models* without covariates (Model 1), maternal smoking during pregnancy predicted poorer performance in visual working memory as measured by WISC Spatial Span Backward ($b = -0.14$, SE = 0.06, $p < 0.01$; Supplemental Table 5) and response inhibition as measured by the DKEFS Color-Word Interference task ($b = -0.18$, SE = 0.07, $p < 0.05$; see detailed parameter estimates and model fit statistics in Supplemental Table 6 and report by Micalizzi et al., 2018). However, neither maternal smoking during pregnancy association survived covariate adjustment (Model 2). In the adjusted *standard models* for visual working memory and response inhibition, consistent with familial transmission, the corresponding maternal executive function variables were also associated with child visual working memory and child response inhibition, respectively. Maternal smoking during pregnancy was not associated with SSRT, set-shifting (visual motor or verbal fluency variables), or auditory working memory (see Table 2 and corresponding Supplemental Tables).

The significant maternal smoking during pregnancy-EF associations from the standard model were fully attenuated in the sibling comparison models. In the *sibling comparison models* without covariates, there was a significant within-family association between maternal smoking during pregnancy and visual working memory (WISC Spatial Span Backward; $b = -0.13$, SE = 0.07, $p < 0.05$; Table 2 and Supplemental Table 5) and inhibitory control (DKEFS Color Word Interference; $b = -0.17$, SE = 0.07, $p < 0.05$; Table 2, see detailed parameter estimates and model fit statistics in Supplemental Table 6 and prior report by Micalizzi et al., 2018). By themselves, these results would suggest a potentially causal effect of maternal smoking during pregnancy on these EF component skills. However, for both variables, this relationship with maternal smoking during pregnancy did not remain significant once covariates were included in the model (Model 4), indicating that familial confounding is present for visual working memory and response inhibition. Similar to the *standard models*, child IQ and respective maternal executive function variables significantly predicted outcome.

As a way to investigate nuances of familial transmission, post hoc analyses of the covariate-adjusted sibling comparison models were examined. That is, for the two models in which there was an effect of the maternal EF variable (i.e., for visual working memory and response inhibition), we examined one submodel where the respective maternal EF variable was dropped from the full covariate-adjusted sibling comparison model (i.e., Model 4). For each phenotype, this submodel was compared to the full covariate-adjusted *sibling comparison* model (Model 4) to evaluate the intergenerational transmission of these two EF phenotypes after controlling for the other covariates and maternal smoking during pregnancy. Specifically, model comparisons were evaluated using χ^2 difference tests and Akaike's information criterion, with lower Akaike's representing better fitting models. For both EF variables, maternal EF could not be dropped from the model without a significant decrement in model fit. When considering visual working memory (WISC Spatial Span Backward), when maternal visual working memory was dropped from the covariate-adjusted sibling comparison model (-2LL = 1322.4, AIC = 1330.4 *vs.* -2LL = 1332.5; AIC = 1340.5), the change in χ^2 was significant ($\Delta\chi^2 = 10.1$, df = 1, $p < 0.002$). Similarly, for response inhibition, when maternal DKEFS Color-Word

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Table 1. Sample characteristics

	N	Mean	SD	*N*	Mean	SD
Study Variables		**Child 1[3]**			**Child 2[3]**	
Maternal Smoking During Pregnancy: severity score	173	3.95	2.05	167	2.04	1.77
Executive Function						
Inhibitory control (DKEFS CWI)[1]	165	9.98	3.14	164	10.44	2.58
Inhibitory control (SSRT)	125	299.11	77.51	115	302.15	56.62
Set-shifting – Visual Motor (DKEFS Trails)	166	9.75	2.75	165	9.38	3.24
Set-shifting – Verbal (DKEFS Verbal Fluency)	166	9.19	3.01	166	9.23	3.03
Working Memory – Auditory (WISC Digit Span Backward)	167	7.37	1.80	167	6.75	1.60
Working Memory – Visual (WISC Spatial Span Backward)	167	10.47	2.62	166	10.81	2.45
Child-specific covariates		**Child 1[3]**			**Child 2[3]**	
Maternal age at birth	155	26.55	5.46	160	29.22	5.66
Maternal education (in years) at birth	155	13.31	2.07	160	13.48	1.90
Second-hand smoke exposure by fathers	164	1.82	1.44	157	1.59	1.43
Family-level covariates		**Mother**			**Father[2]**	
Executive Function						
Inhibitory control (DKEFS CWI)[1]	167	10.20	2.73	95	10.35	2.90
Set-shifting – Visual Motor (DKEFS Trails)	166	10.98	2.10	96	10.36	2.73
Set-shifting – Verbal (DKEFS Verbal Fluency)	167	10.13	3.00	96	9.35	3.42
Working Memory – Auditory (WISC Digit Span Backward)	167	7.04	2.31	96	7.11	2.20
Working Memory – Visual (WMS Symbol Search)	167	9.61	2.40	96	8.98	2.34
	N	%		*N*	%	
Marital status (percent married) at birth	143	85%		145	85%	
Food stamp usage at birth	142	7%		142	11%	
Family Demographics (at assessment)	*N*	Mean	(SD)			
Maternal age	162	39.83	5.62			
Paternal age	80	44.04	6.34			
Child 1 age	173	12.99	1.95			
Child 2 age	170	10.19	1.80			
Child age difference	170	2.79	1.54			
	Maternal			**Paternal**		
	N	**%**		***N***	**%**	
Education						
Less than high school	7	4%		9	10%	
High school	30	18%		19	20%	
1–2 years college	50	30%		14	15%	
3–4 years college	46	27%		17	18%	
More than college	29	17%		21	22%	
Not reported	7	4%		14	15%	
Mothers' marital status						
Never married	6	4%				
Married	130	77%				
Separated	5	3%				
Divorced	26	15%				
Widowed	2	1%				

[1]Analyzed in Micalizzi et al. (2018) and reported here for completeness.
[2]Because fewer fathers completed the assessment, only maternal covariates were included in the models reported in this paper. Father covariates were explored in sensitivity analyses and the results are available on request.
[3]Child 1 = older sibling; Child 2 = younger sibling.

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Table 2. Summary of maternal smoking during prengnacy effects from *sibling-comparison* models

	Zero-order (Model 3) Sib Comparison without Covariates		Covariate-Adjusted (Model 4) Sib Comparison with Covariates	
	Within-family	Between-family	Within-family	Between-family
Outcome	β (SE)	β (SE)	β (SE)	β (SE)
Inhibitory control (DKEFS color-word interference – examined in Anonymous et al., 2018)	**−0.17 (0.07)***	−0.18 (0.16)	−0.02 (0.10)	−0.18 (0.17)
Inhibitory control (SSRT)	−0.93 (2.40)	−0.42 (4.27)	2.93 (3.26)	3.42 (4.79)
Set-shifting – Visual Motor (DKEFS Trails)	0.02 (0.08)	0.06 (0.17)	0.09 (0.10)	0.11 (0.16)
Set-shifting - Verbal (DKEFS Verbal Fluency)	−0.05 (0.09)	0.04 (0.17)	−0.08 (0.12)	−0.04 (0.20)
Working Memory – Auditory (Digit Span Backward)	0.04 (0.05)	−0.03 (0.10)	−0.02 (0.07)	−0.06 (0.11)
Working Memory – Visual (Spatial Span Backward)	**−0.13 (0.07)***	−0.25 (0.15)	−0.03 (0.09)	−0.17 (0.15)

Note. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$
Covariates included in the covariate adjusted models were maternal age, education, marital status, food stamp usage, SES, birth order, child sex, secondhand smoke exposure by fathers, and child IQ.
Individual models controlled for the parallel mother variable (e.g., we controlled for mother set-shifting when child set-shifting was the focal outcome).
See Supplemental Tables for full model results including covariate estimates.

Interference was dropped from the model, the change in χ^2 was significant ($\Delta\chi^2 = 11.6$, df = 1, $p < 0.001$). These post hoc analyses of response inhibition as measured by the DKEFS Color Word Interference were *not* examined in Micalizzi et al (2018), thus we provide additional details here. Fit statistics from covariate-adjusted sibling comparison model including the maternal EF variable from Micalizzi et al. (2018): -2LL = 1333.9, AIC = 1341.9 vs dropping maternal EF variable -2LL = 1345.5, AIC = 1353.5. These analyses suggest that, above other child and familial variables that siblings share, there is no potentially causal effect of maternal smoking during pregnancy on EF in our sample. Further, in line with the literature suggesting that EF is highly heritable, maternal EF is one of the most significant predictors of child visual working memory and response inhibition.

Discussion

Using a genetically-sensitive sibling-comparison design, this study examined the association between maternal smoking during pregnancy and EF skills. This sample was specifically designed with the intent to examine maternal smoking during pregnancy separately from other familial confounding variables. That is, the sibling-comparison approach partially controls for measured and unmeasured genetic and environmental influences, enabling a more rigorous test of the maternal smoking during pregnancy-EF relationship. Results revealed no association between maternal smoking during pregnancy and Stop-Signal Reaction Time (one measure of inhibitory control), DKEFS Trails (visual motor set-shifting), DKEFS Verbal Fluency (verbal set-shifting), and WISC Digit Span Backward (auditory working memory). For WISC Spatial Span Backward (visual working memory) and DKEFS Color-Word Interference (response inhibition/inhibitory control), initial results suggested a within-family association with maternal smoking during pregnancy, which is one step closer to indicating potentially causal effects of maternal smoking during pregnancy than provided in studies where familial confounds are not controlled by design. However, these initial within-family associations between maternal smoking during pregnancy and visual working memory and response inhibition were fully attenuated following covariate adjustment, making causal effects highly unlikely. Further, consistent with the reported high heritability of EF skills (e.g., Anokhin et al., 2010; Coolidge et al., 2000; Friedman et al., 2008; Gustavson et al., 2022; Li & Roberts, 2017), maternal EF significantly predicted offspring EF, above other familial variables that siblings share.

The current study provides additional insight into the maternal smoking during pregnancy-EF association. Epidemiological, non-genetic studies report mixed results with regard to the effects of maternal smoking during pregnancy on EF. When associations are found, the general pattern is increased maternal smoking during pregnancy exposure with poorer performance. However, as explicated earlier, there is considerable variability in these reports, such as developmental stage, measurement of maternal smoking during pregnancy, and assessment of EF. Further, there is often little to no consideration of parental EF skills and by extension, a lack of control for genetic and unmeasured environmental confounding. Maternal smoking during pregnancy, in humans, is correlated with a constellation of outcomes in mothers, and thus it may not be maternal smoking during pregnancy that is causing EF deficits in children, but rather the possibility that mothers who smoke during pregnancy also exhibit deficits in EF. Thus, children of mothers who smoke may present with EF deficits because maternal smoking during pregnancy and EF problems are both caused by common familial (genetic and environmental) influences. This nuance has not been comprehensively addressed to date.

We are aware of only three studies, one of which uses the current sample, that investigated the association between maternal smoking during pregnancy and EF skills using genetically-informed designs (Ellingson et al., 2014; Leve et al., 2013; Micalizzi et al., 2018). These studies examined three different skills. Ellingson et al. (2014) examined the relationship between maternal smoking during pregnancy and WISC Digit Span and found no within-family association of maternal smoking during pregnancy; however, it is unclear which Digit Span test (forward vs backward vs total) was used and thus which specific EF skill was tapped. Leve et al. (2013) used an adopted-at-birth design and found that a broad index of prenatal risk (which included maternal smoking during pregnancy) was associated with worse set-shifting; however, this prenatal effect was attenuated in the presence of genetic influences. Finally, Micalizzi et al. (2018) used the present sample (MO-MATCH) to examine the relationship between

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maternal smoking during pregnancy and inhibitory control as we discuss and summarize in this report. In all three quasi-experimental studies to date, the samples are of different ages, maternal smoking during pregnancy was measured differently, and a variety of EF-skills were examined.

EF is comprised of multiple component skills – response inhibition, cognitive flexibility/set-shifting, and working memory – each of which can also be measured such that different aspects of that skill are assessed (e.g., visual vs auditory working memory). Consistent with that complexity, our results reflect mixed findings in the relationship between maternal smoking during pregnancy and each component skill. One possibility as to why we see maternal smoking during pregnancy associated with some EF skills but not all may be due to the brain regions and neurotransmitter systems involved in these skills. As noted earlier in this report, research has identified brain regions involved in EF and there is evidence from animal models that these some of these same areas are impacted by maternal smoking during pregnancy. Further, imaging studies show that adolescents and adults exposed to maternal smoking during pregnancy draw on a wider variety of brain regions to complete working memory and response inhibition tasks, but not with set-shifting (Bennett et al., 2009; Longo et al., 2013). Thus, it seems within reason that we would see different patterns of findings with regard to different EF component skills.

The results presented should be interpreted within the context of the following limitations. First, our findings are dependent on our assessment of maternal smoking during pregnancy, which is collected via retrospective report. There is a growing literature supporting the use and reliability of retrospective report (Estabrook et al., 2016; Knopik et al., 2016a, 2016b) and we conducted additional verification of smoking behaviors during pregnancy to supplement maternal report (see Knopik et al., 2016b). Nonetheless, our results hinge on our assessment and operationalization of maternal smoking during pregnancy to accurately reflect the amount of maternal smoking during pregnancy exposure. Second, to the extent to which executive function skills are taught, children exposed to maternal smoking during pregnancy and who live in poorer neighborhoods and attend potentially less effective schools may be at particularly high risk for EF deficits. We are currently working with Census data to consider neighborhood disadvantage in our sample and will be able to explore this question in future work. Third, given the nature of data collection, this sample is necessarily a community sample which includes the full range of executive function skills as opposed to the most extreme deficits; such a clinical population might afford additional exploration into the maternal smoking during pregnancy-EF association. Fourth, while the statistical covariates included were carefully and purposefully selected, we could not measure or include all covariates that differ between siblings. There are likely confounds that were not considered here that influence the sibling comparison. For example, we have not examined reasons why these sibling pairs differ in their exposure to SDP. More specifically, why have these mothers changed their smoking behaviors from one pregnancy to another? These data were indeed collected as part of the larger project and will be used in future extensions of this work. Fifth, our methodological approach included a series of models that are hierarchical in nature and overlapping. These models included multiple EF outcomes and multiple tests per outcome. Thus, depending on the multiple testing correction strategy used (i.e., correcting for number of outcomes, number of tests, or number of outcomes*number of tests), some of our results may not survive correction. We thus suggest that results be interpreted using that lens and should be replicated. Finally, since fathers participated in about ~60% of families, we chose to report the maternal covariate models to capitalize on power. When we restrict to families where both parents participated, the pattern does remain consistent across all variables (results available upon request).

In summary, our findings are consistent with a very small number of genetically-informed studies indicating familial confounding for cognitive-related phenotypes. We expand on prior work however, with the inclusion of maternal EF covariates, which appear to be a more salient risk factor for child EF skills, particularly visual working memory and response inhibition. That said, maternal smoking during pregnancy may be one indicator of a constellation of risks for EF and should be assessed in diagnostic evaluation. As such, intervention and prevention efforts focused on factors that contribute to maternal smoking during pregnancy could be one pathway to reduce poor outcomes in children exposed to smoking during pregnancy.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S095457942200075X.

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Conflicts of interest. None.

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