Missouri Mothers and Their Children: A family study of the effects of genetics and the prenatal environment

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Abstract

The Missouri Mothers and Their Children Study was specifically designed to critically investigate prenatal environmental influences on child attention problems and associated learning and cognitive deficits. The project began as a pilot study in 2004 and was formally launched in 2008. Participants in the study were initially identified via the Department of Vital Statistics birth record database. Interview and lab-based data were obtained from (1) mothers of Missouri-born children (born 1998–2005), who smoked during one pregnancy but not during another pregnancy, (2) biological fathers when available, and (3) the children [i.e., full sibling pairs discordant for exposure to maternal smoking during pregnancy (SDP)]. This within-mother, between-pregnancy contrast provides the best possible methodological control for many stable maternal and familial confounding factors (e.g., heritable and socio-demographic characteristics of the mother that predict increased probability of SDP). It also controls for differences between mothers who do and do not smoke during pregnancy, and their partners, that might otherwise artifactually create, or alternatively mask, associations between SDP and child outcomes. Such a design will therefore provide opportunities to determine less biased effect sizes while also allowing us to investigate (on a preliminary basis) the possible contribution of paternal or other second-hand smoke exposure during the pre-, peri- and postnatal periods to offspring outcome. This protocol has developed a cohort that can be followed longitudinally through periods typically associated with increased externalizing symptoms and substance use initiation.

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Keywords

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In the United States, maternal smoking during pregnancy (SDP) continues to be a major public health concern. Rates of SDP vary by individual state, but on average, 12.3% of women report smoking during pregnancy (Tong et al., 2013). Despite a large literature suggesting undesirable outcomes in children exposed to SDP and warnings encouraging women to stop smoking while pregnant, the decrease in prevalence of SDP during recent years has been non-significant (13.3% in 2000 to 12.3% in 2010; Tong et al., 2013). SDP is associated with multiple adverse birth related outcomes, such as preterm delivery (Castles, et al., 1999; Shah & Bracken, 2000), increased risk for spontaneous abortion (Castles, Adams, Melvin, Kelsch, & Boulton, 1999), and lower birth weight (e.g., Kuja-Halkola et al., 2014; Benjamin-Garner et al., 2014; Marceau et al., under review; Knopik et al., under review). It has also been associated with prenatal ischemia-hypoxia (see Smith et al., under review), respiratory disease (Cook & Strachan, 1999), cancer later in life (Doherty, Grabowski, Hoffman, Ng, & Zelikoff, 2009), and a host of neurodevelopmental and behavioral outcomes (see Knopik, 2009 for a review). Findings also suggest that there are a variety of placental complications linked to prenatal exposure to cigarette smoke (e.g., alterations to the development and function of the placenta; Einarson & Riordan, 2009), which could effectively translate into a number of sequelae (e.g., intrauterine growth retardation and later behavioral problems; Huizink and Mulder, 2006; Knopik, 2009; Joya et al., 2014).

Until fairly recently, studies of the effects of SDP did not take into account more precise measurement of parental characteristics or genetic/familial influences that might also contribute to the SDP-outcome relationship. Some early attempts to do this included modeling maternal and paternal psychopathology in twin studies (e.g., Knopik et al., 2005; Maughan et al., 2004; Thapar et al 2003) and children of twin studies (D'Onofrio et al., 2003; Knopik et al., 2006). The twin design can offer considerable knowledge in the genetic etiology of, not only outcomes of interest (e.g., ADHD), but also risk factors (e.g., SDP; see Agrawal et al., 2008 for genetic etiology of SDP; D'Onofrio et al, 2003, 2008). It can also determine whether genetic effects differ in two environments; however, twin models may only partially control for how genetic factors may impact outcomes, since they assume that the specified environments represent 'true' or 'pure' environmental risk factors which are free from genetic influences (i.e., that there is no gene-environment correlation; Caspi, Taylor, Moffitt & Plomin, 2000; D'Onofrio et al., 2003; Purcell & Koenen, 2005). Further, the prenatal environment is an obligatory shared environment in the twin design (i.e., differential exposure between members of the twin pair is challenging, if not impossible, to determine). Classical twin studies, even those that add explicit measures of the environment, are also not able to delineate the actions involved in intergenerational processes (D'Onofrio et al., 2003). Twin studies that have examined the association of SDP and behavioral outcomes suggest that, once genetic and environmental risks were controlled for, the effects of SDP on conduct disorder were reduced (Maughan et al., 2004;); however, despite this reduction for conduct problems, SDP explained a small but significant amount of the

variance above and beyond genetic effects on ADHD (e.g., Thapar et al., 2003; Knopik et al., 2005).

The Children-of-Twins (COT) design, which has also been used to investigate SDP-outcome associations, can begin to elucidate the role that specific environments (such as prenatal exposure) play in the etiology of psychological and behavioral phenomena (D'Onofrio et al., 2003), while studying intergenerational associations with fewer assumptions than the twin-family design. In the case of prenatal exposure, it allows one to begin to disentangle genetic, prenatal exposure, and other environmental effects on offspring outcomes. It also offers the additional advantage of including offspring sibling pairs that may differ in their amounts and/or timing of prenatal exposure (Knopik, 2009). However, there are relatively few COT datasets and even fewer that include detailed assessment of SDP. Results from COT designs addressing the SDP-outcome association yielded a pattern of results consistent MSDP having an independent effect on offspring birth weight (D'Onofrio et al., 2003) and ADHD (Knopik et al., 2006) even after controlling for potential confounders (e.g., genetic transmission, other environmental factors, and other covariates).

The ability to begin to disentangle genetic and environmental intergenerational transmission in the domain of SDP is critical for understanding the magnitude of risk that SDP carries as this can have real implications for future research, intervention, and prevention efforts. It is unlikely that a single design will provide the answers to the complicated nature of the association between SDP and subsequent outcomes, given methodological limitations and the risk factor under consideration (SDP which, in twin offspring, will not differ). Thus, as a general call to the field, Knopik (2009) suggested the importance of a comprehensive approach to studying SDP effects, while also acknowledging the role of genetic influences. D'Onofrio et al (2013) later called this a "comprehensive family-based quasi-experimental approach." The case-crossover design (or within-mother between-pregnancy design used in MO-MATCH) is an example of one such approach, which examines siblings discordant for prenatal exposure to SDP. A strength of the case-crossover design is that associations of SDP with a child outcome can be examined both within a family and between families, and results can strengthen our inferences about causality in associations of SDP and child 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 SDP-outcome association; however, it does allow replication of historical associations found in the literature. Conversely, the strongest support for a causal influence of SDP on a child outcome (e.g., child ADHD) occurs when there is a within-family association: the exposed sibling has more ADHD symptoms 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 SDP may be causally linked with the outcome.

At the time that MO-MATCH was considered for funding and ultimately funded, there were only two studies that considered relatives differentially exposed to prenatal smoking (Lambe et al., 2006; D'Onofrio et al., 2008). These studies drew their samples from larger projects

that were not necessarily designed to examine SDP, but which had useful data with which to examine these associations. Results suggested that for school performance (Lambe et al., 2006) and conduct problems (D'Onofrio et al., 2008), the observed associations between these outcomes and SDP might not be causal. However, findings for ADHD problems, as measured by the Child Behavior Checklist (CBCL, Achenbach, 1978), were less clear (D'Onofrio et al., 2008). Their comparison of siblings who differed in SDP exposure showed a small but significant effect of SDP on ADHD problems, a finding consistent with Knopik et al. (2006), who used a children-of-twins approach.

Over the course of this data collection effort, there has been a surge of interest in the prenatal environment (e.g., Knopik et al., 2009; Rice et al., 2009; Thapar et al., 2009; D'Onofrio et al., 2010; D'Onofrio et al., 2013; Gaysina et al., 2013; Kuja-Halkola et al., 2014; see also upcoming Special Issue of *Behavior Genetics* on the prenatal environment). The majority of studies to date have used phenotypes pulled from medical records and national databases. These sources are incredibly useful and offer large sample sizes, but there is a need for purposefully designed deep-phenotyping that will allow for more nuanced questions to address the complex nature of the SDP-outcome association. With purposefully designed studies we can begin to address questions concerning *why* mothers change their behaviors between pregnancies, a question that, as of yet, has not been available in larger registry based datasets. More detailed phenotyping allows researchers to approach these questions from angles that are not supported with the larger medical records based dataset. As one example, incorporating an extensive laboratory-based neuropsychological testing battery offers the potential advantage that laboratory-based measures may be relatively free from bias, whereas checklists, rating scales, and structured interviews can be influenced by a number of factors (Nichols & Waschbusch, 2004). It also affords the investigation of multiple aspects of the ADHD-related behavior spectrum. For instance, research has suggested that children with ADHD exhibit impairments in executive function and processing speed in real-world activities as well as in neuropsychological testing and that cognitive deficits detected by standardized neuropsychological testing are related to performance difficulties in real-world activities (e.g., Lawrence et al., 2004). Further, youth exhibit different types of ADHD-related behaviors in the classroom than at home. This observation lends credence to the collection of both parent and teacher reported symptoms, each of which are considered valid and provide important insights into how and when children experience ADHD-related impairments (e.g., Lahey et al., 1994).

Overview of the Current Study

The Missouri Mothers and Their Children study (MO-MATCH) study is an ongoing data collection collaboration between Rhode Island Hospital/Brown University and Washington University, St. Louis MO. The Institutional Review Boards of Rhode Island Hospital, Washington University, and the State of Missouri Department of Health and Senior Services approved the study. MO-MATCH started as a pilot project in 2004 to determine the feasibility of locating, contacting, and interviewing a specific group of mothers of Missouri-born children. These mothers had, according to birth records, reported smoking during one pregnancy but not during another pregnancy. This within-mother, between-pregnancy design (or sibling comparison design) provides the best possible methodological control for many

stable maternal and familial confounding factors (e.g., heritable and sociodemographic characteristics of the mother that predict increased probability of SDP). The design also controls for differences between mothers who do and do not smoke during pregnancy; differences that might otherwise artifactually create, or alternatively mask, an association between SDP and child outcomes. The overarching goals of this project are: (1) to critically investigate prenatal environmental influences on child attention problems and associated learning and cognitive deficits, and (2) to provide a foundation for later characterization of the molecular epidemiology of effects of SDP and offspring attention, learning, and cognition.

Study Hypotheses and Aims

There were three primary aims for this study. Aim 1 was a procedural aim to enroll and interview a new sample of mothers, identified via birth records, and to confirm full sibling pairs discordant for maternal SDP. Following maternal diagnostic telephone interview about each child (assessing pregnancy and life events surrounding pregnancy, early life exposures, and child behavior), these families completed in-depth neuropsychological lab assessment of children and parents (including general cognitive ability, memory, reading, receptive language, executive function). Full sib-ship will be verified via DNA from samples collected on parents and discordant sibling pairs. DNA has currently been isolated and will be stored for future informed molecular analyses. Aim 2 was to assess the effects of SDP on offspring neurocognitive outcomes (especially memory, executive function, lexicon, and reading), capitalizing on the unique within-mother, between-pregnancy comparison. The first hypothesis of Aim 2 was that, when genetic and familial effects are not modeled, SDP will be associated with significant childhood deficits in tests (particularly memory, executive function, receptive language, and reading) which tap brain regions shown in basic science studies to be affected by prenatal nicotine exposure. The second hypothesis of Aim 2 was that sibling comparisons will show attenuated associations, suggesting partial confounding due to influences that siblings share. Aim 3 was to assess the effects of SDP on ADHD, as measured by multiple assessments (see Table 2) and multiple reporters (parent and teacher). We hypothesized that (a) significantly greater ADHD symptoms will be found in children who have been exposed to SDP when considering the standard between-mother comparison; and (b) within-mother between-pregnancy (or sibling comparison) will suggest, at least for maternal reported ADHD variables, partial confounding due to effects that siblings share.

Recruitment Methods

The literature on smoking during pregnancy heavily guided our decision making process for recruitment, and the target age range of the offspring in our design was a large deciding factor for our entire recruitment and assessment protocol. Given that ADHD is a clinically significant condition with very clear public health implications, and that neuropsychological alterations, such as executive function, memory, reading, and language, found in school-age populations, are also of public health concern due to the consequences and special services involved, we chose our target offspring age range as 8–15 years of age. Our justification for this age range is as follows: (i) the uncertainty of findings in infants/toddlers (see Knopik, 2009 for a review) provide a rationale for our focus on an older age group, where apparent

deficits are seen more robustly; (ii) our research team has considerable experience with assessment administration, clinical treatment, and research with children of the proposed age range; (iii) two of our primary outcomes of interest, ADHD and reading, can be adequately studied in this age group (i.e., DSM-IV ADHD criteria suggest that children exhibit behaviors before the age of 7 years, thus they will be through the period of risk for first symptom onset by the time they enter our study; most standard and validated reading assessments are designed for children with a minimum age of 8 years); and (iv) the proposed sampling scheme will develop a cohort which, in the future, can be followed longitudinally through periods of increased externalizing symptoms and substance use initiation, abuse, and dependence.

Families were identified using birth records obtained from the Missouri Department of Health and Senior Services Bureau of Health Informatics. Birth Records (BR) in Missouri, for birth years 1998–2005 (to target children aged 8–15 at the time of testing over the project period), were examined for mothers who changed smoking behavior between two pregnancies. Over 4000 mothers were identified. In order to locate and track these families, our research team had permission to use birth records, drivers license records, marriage, and divorce records to assist in locating the best possible contact information for each potential family. These records were supplemented using commercial databases.

Candidate mothers were sent a letter, prior to attempts to contact that family by telephone, to introduce them to the study and to tell them that they would be contacted for a brief (10 minute) screening interview to determine eligibility. The letter stressed voluntary participation and included a phone number at which families choosing not to participate, or those having concerns or questions, could contact project staff. Attempts were then made to reach the biological mother of the children. Once contacted, the voluntary nature of the study was again explained, and the mother was also told that she could choose not to answer any or all of the questions.

After 1520 initial screening interviews to verify the primary inclusion criteria obtained through the BR (i.e., mom smoked during one pregnancy but not the other), only 27% of mothers agreed via screening with the BR (the majority [57%] reported smoking during both pregnancies, and 16% reported not smoking for both pregnancies). Once BR information was verified, additional exclusionary criteria were assessed. Families were excluded at this point if: (1) mothers failed to understand the elements of informed consent, (2) English was not the primary language spoken in the home, (3) if the children had a history of head trauma, neurological disorders or uncorrected visual or auditory acuity deficits. Additional criteria that precluded participation: (4) the children did not have the same biological father (as based on maternal report at this point in the protocol), (5) the mother did not have custody of the children, and (6) if one of the children was deceased. Based on evidence (e.g., Morales-Suarez-Varela et al., 2006) suggesting that offspring of nonsmokers who used nicotine substitutes (NRT) during pregnancy are at increased risk for congenital malformations, mothers who report using nicotine substitutes in the 'nonsmoking' pregnancy were also excluded.

Once initial eligibility (i.e., mother smoked during one pregnancy but not during another) was confirmed through the screening interview (N=413) brief information about the study was given with opportunity to answer questions, and the mother was invited to complete a diagnostic interview. One hundred and seventeen women declined to participate in the study, after the screening interview, and mothers (N=70) were excluded due to the additional eligibility criteria (criteria 4–6) listed above. If the mother agreed to participate, a respondent booklet containing consent documents and a 10-page packet containing a brochure about future genetic research was mailed to the participant and her family, and an appointment was made for a consent interview (to take place before the diagnostic interview) in which these materials were reviewed with the participants. Once verbal consent was obtained, the maternal telephone diagnostic interviews could take place. At the time that data collection ended for the current project, 173 mothers had consented and completed the entire protocol.

Once the mother was recruited, permission was sought from the mother to contact the birth father. The mother was asked about the birth father's identity (which could confirm BR information if it was recorded), information about how to locate the birth father, and any potential concerns. Birth fathers were only included if the mother agreed to providing contact information and released his information to the study. We recruited 54% of fathers from our 173 families (N=94). Biological paternity will be confirmed via DNA.

In addition to maternal diagnostic interviews in which mothers provide information about their pregnancies and their children's behavior, mothers, fathers (when available) and children travelled to our research offices to complete in-person family laboratory neuropsychological testing. Prior to starting the lab-based session, consent forms for the lab-based session and saliva sample were reviewed and participant understanding was confirmed by project staff. Consent forms (and assent forms for children) were then signed. Mothers also signed a release providing the names of their children's teachers so that project staff could contact teachers to complete questionnaires regarding certain child behaviors. At the completion of the laboratory assessment, the session was concluded and participants were debriefed.

Sample

Mother-reported data was available on 344 pregnancies and father-reported data was available on 181 pregnancies. Demographic information regarding parent age, child age, education and marital status are provided in Table 1. The mean age of mothers and fathers at the time of interview was 39.83 years (standard deviation (SD) = 5.62) and 44.04 years (SD = 6.34), respectively. Parents were primarily of Caucasian ancestry (96%, n=250; three individuals refused to provide ancestral information). In a comparison to census data for the state of Missouri (census.missouri.edu), the MO-MATCH sample appears consistent with the demographics of the state in terms of marriage rates (75% census vs 77% MO-MATCH). MO-MATCH parents show slightly lower rates of stopping at a high school education (31.6% census vs 18–20% MO-MATCH) and completing at least 'some graduate school' (26.2% census vs 17–22% MO-MATCH), but are consistent with rates of completing 'some college.' The MO-MATCH sample appears to have lower rates of children and families

served by food stamps (20–30% in the state of Missouri and 11% in MO-MATCH). MO-MATCH shows higher rates of tobacco usage than state averages, which is expected given the nature of sample selection. Additional sample characteristics are shown in Table 2.

Of the 173 participating families, 94 fathers provided data. We examined possible differences between families where fathers did vs. did not participate using Wilcoxon-Mann-Whitney tests (e.g., non-parametric analog to independent samples t-tests) on demographic and study variables. Specifically, we tested for differences where fathers did vs. did not participate for marital status, maternal age, maternal employment status, maternal education, age difference between siblings, the most prevalent maternal diagnoses: nicotine dependence and alcohol abuse, and child 1 and child 2' age, sex, birth weight, smoking during pregnancy severity, and ADHD symptoms (a total of 17 tests). There were only 2 differences (fewer than expected by chance): in mothers' age and marital status. The remainder of demographic variables and all study variables did not differ for families where fathers did vs. did not participate, $\chi^2 < 2.91$, $p > .05$. Mothers were slightly older in families where fathers participated (M = 38.17, SD = 5.66) than in families where fathers did not participate (M = 41.18, SD = 5.36), $\chi^2 = 25.09$, $p < .05$. Second, families where fathers participated were more likely to have a "married" status, whereas families with fathers who did not participate had a higher proportion of "divorced" status, $\chi^2 = 12.89$, $p < .05$ (Families where fathers participated: married = 95.45%, never married = 2.27%, divorced = 2.27%; families where fathers did not participate: married = 54.67%, never married = 6.67%, divorced = 30.67%, separated = 5.33%, widowed = 2.67%).

Assessment

This MO-MATCH protocol was carefully chosen to be standard and comprehensive, while also targeting behavioral/cognitive deficits linked to brain regions that have been proposed to be negatively affected by prenatal nicotine exposure. To select phenotypes, we relied on both basic science (i.e., animal) models as well as human studies to identify phenotypes that are suggested to be influenced by maternal SDP. Animal studies (see Knopik, 2009 for a review) have shown a clear effect of prenatal nicotine on offspring behavior. Several studies indicate that chronic prenatal nicotine exposure in rats and mice results in increased receptor density of fetal and neonatal cerebral nicotine acetylcholine receptors (nAChRs; for example, Slotkin, 1998; Van de Kamp & Collins, 1994). Upregulation of the nAChRs during development is conclusive evidence that the cell has experienced chronic nicotinic stimulation. The long-term effects of this up-regulation remain unclear (Ernst et al., 2001); although the proposed mode of action suggests that this stimulation results in premature onset of cell differentiation, at the expense of replication, leading to (i) brain cell death, (ii) structural changes in regional brain areas, and (iii) altered neurotransmitter systems (i.e., norepinephrine, dopamine, and serotonin; Slikker et al., 2005). Such alterations could translate to deficits in later learning, memory, behavior, and development. Differences in developmental profiles of receptor binding between species and strains suggest that genetic factors regulate the maturation of the nicotinic receptor (Van de Kamp & Collins, 1994). These genetic factors may explain interindividual differences in sensitivity to the effects of in utero exposure to nicotine (Ernst et al., 2001).

However, the rat, mouse, and other model organism brains are very different from the human brain. Moreover, model organism studies tend to focus only on prenatal nicotine (and can be very controlled in their exposures), whereas in human studies, the fetus is exposed to over 4000 chemicals in the average cigarette, including a large amount of other toxic components, such as carbon monoxide, ammonia, nitrogen oxide, lead, and other metals (Huizink & Mulder, 2006). Human studies have been somewhat variable, particularly in studies examining behavioral outcomes (see Knopik, 2009 for a review); however, some of the most robust associations reported tend to be in the externalizing spectrum (i.e., ADHD and Conduct Disorder). Further, at the time that this project began, there were only a few genetically-informed studies considering the role of SDP in child and adolescent behavior, but the ones that were published focused on ADHD and related disruptive behavior. Considered together, animal studies provided a clear biological pathway for possible prenatal nicotine associations with learning and behavior, and human studies tend to converge on an association between SDP and externalizing behaviors (before considering genetic effects). We applied this information to aid in the selection of the primary phenotypes under investigation and the covariates that would be included.

The MO-MATCH assessment includes questionnaires (parent-report and teacher-report), maternal telephone diagnostic interviews, in-person interviews, an extensive neuropsychological testing battery, and collection of DNA. Birth record data for both children are also available as they are the initial means of finding potential participants. The interviews were semi-structured diagnostic interviews, which allowed project staff to establish rapport with mothers, and computer assisted personal interviews that were completed privately by mothers and fathers to facilitate confidentiality and honest responses. The incorporation of detailed phenotypic parental assessment (interview and lab-based) increases our ability to identify the potential confounding effects of heritable and socio-demographic characteristics, that may create false-positive findings in between-family comparisons. Most studies do not control for the fact that prenatal exposures may be correlated with parental behaviors that could also act as important risk factors that are in turn transmitted to their offspring. A listing of the measures administered is presented in Table 3. Reliability information for key measures is presented in Table 4 and supporting literature identifying the major domains for which SDP effects have been reported is shown in Table 5.

Of primary importance to the study aims, both the semi-structured telephone diagnostic interview (Missouri Assessment of Genetics Interview for Children – Parent on Child [MAGIC-Parent on Child]; Todd et al., 2003) and the personal computerized interviews completed by mothers and fathers (MAGIC-Adult on Self; Todd et al., 2003) assess detailed assessment of SDP. The MAGIC-Adult on Self also includes questions regarding tobacco exposure during and after pregnancy, and assesses tobacco use by mother, father or significant other, and any other person living in the household such as a relative or older sibling, during and after pregnancy into the first five years of the child's life. The questions ask about specific time periods, including overall pregnancy, first, second and third trimester, first six months of child's life, second six months of child's life, and second through fifth years of life. The total number of smokers in the home during these periods is also assessed. The protocol includes maternal and teacher report of child externalizing

behavior (e.g., ADHD), lab-based assessment of major domains of child cognition, lexicon, memory, executive function, fine motor, and reading, complimentary lab-based assessment of these domains in parents, as well as assessment of parental psychopathology.

The protocol also includes assessment of environmental risks through which parental psychopathology and related prenatal, and possibly perinatal, substance use are hypothesized to impact child outcome, within-family risks (prenatal substance use, prenatal care); and between-family environmental risks (socio-demographic disadvantage). While this protocol has been carefully selected to be comprehensive, we focus this project on four key domains where we expect, based on basic animal work and existing human work, to find true deficits: memory, executive function, reading/lexicon, and ADHD (see Table 5 for domains and supporting literature).

Retrospective report of SDP

The first paper using MO-MATCH data (Knopik et al., under review) examined rates of agreement across birth record report of SDP, retrospective maternal report of SDP, and retrospective paternal report of SDP. Specifically, we compared reports for any SDP during pregnancy and for quantity of cigarettes smoked across each pregnancy. We then compared rates of agreement for changes in SDP behavior from one pregnancy to another. This is a key first step, as results will inform every subsequent model fitted to these data. Once predictive utility of various reports of SDP was determined, we then fit a sibling comparison model to examine the association between SDP and birth weight. This approach controls for genetic and familial influences that make the siblings similar and provides a test of whether SDP has an independent effect on birth weight once effects that siblings share are taken into account. Results showed high agreement between reporters and support the utility of retrospective report of SDP. Further, we replicated a causal association between SDP and birth weight, wherein SDP results in reduced birth weight even when accounting for genetic and familial confounding factors via a sibling comparison approach.

Plans for Future Research

Composite indices for each domain (see Table 4) will be constructed in order to pursue hypothesis testing. Further, in instances where we have multiple reporters, we will create composites consistent with the gold-standard in the clinical literature. When the associations between measures (for the same construct) are low-to-moderate, we will forego composites and analyze measures separately. The rich data collection allows for many avenues of further research. For example, in addition to the primary aims of this project, we will explore reasons why these sibling pairs differ in their exposure to SDP. More specifically, we investigate why these mothers changed their smoking behaviors from one pregnancy to another. Our assessment protocol included questions related to stressors and complications surrounding pregnancy that will aid our efforts in this domain. Another additional area of research will allow us to begin to explore the effects of maternal passive exposure to environmental tobacco exposure (ETS) during pregnancy, child's postnatal exposure to ETS, and possible contributions of paternal or household smoking in the pre-, peri- and postnatal periods to offspring outcome.

Conclusion

The MO-MATCH study, while still in the early stages of data analysis, has the potential to be an important and distinctive asset to the field of prenatal exposure. Not only is this study among the first *specifically designed* US-based family studies (i.e., not a convenience sample pulled from a larger study designed for other purposes) to leverage the sibling comparison approach to prenatal smoke exposure, but it is also positioned to begin to characterize the molecular epidemiology of effects of SDP, both genetic and epigenetic, on carefully selected phenotypes such as offspring attention, learning, and cognition. Further, not only can this study begin to disentangle SDP effects from genetic/familial effects, it can also begin to achieve an accurate assessment of the magnitude of the association between SDP, ADHD, and neuropsychological outcomes. This more refined effect size is of great public health significance because this information could help clarify what are and are not potential causes of ADHD and other neuropsychological deficits seen in school-aged children, findings that can inform treatment providers and prevention efforts concerning how to treat the public health concern of SDP. The future of the MO-MATCH study may include tracking the sample into high school and early adulthood with assessments of additional behavior problems and substance use as well as additional assessments of neighborhood constructs. As an invaluable complement to larger samples with less detailed phenotypic assessment, we are confident that the MO-MATCH data will provide a valuable scientific resource in the years ahead.

Acknowledgments

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Table 1

Sample Demographics (*N = 341 pregnancies from 173 families*)

	Mean	**(SD)**	**Min**	**Max**
Maternal age	39.83	(5.62)	29	54
Paternal age	44.04	(6.34)	33	60
Child 1 age	12.99	(1.95)	9	16
Child 2 age	10.19	(1.80)	7	14
Child age difference	2.79	(1.54)	1	7
# living in home	4.92	(1.40)	3	12

Mothers' Marital status	**N**	**%**
Never married	6	4%
Married	130	77%
Separated	5	3%
Divorced	26	15%
Widowed	2	1%

Education	**Maternal**		**Paternal**	
	N	**%**	**N**	**%**
Less than HS	7	4%	9	10%
HS	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%
Food Stamp Use	22	11%		

Total N's vary because of randomly missing data

Table 2

Sample Characteristics

	Child 1		Child 2	
	Mean	**(SD)**	**Mean**	**(SD)**
Child Symptoms from Diagnostic Interview (MAGIC-Parent[*])				
Lifetime ADHD inattentive (of 9)	2.68	(3.20)	2.32	(3.17)
Lifetime ADHD hyperactive/impulsive (of 9)	1.42	(2.26)	1.82	(2.45)
Lifetime ADHD total symptoms (of 18)	4.10	(4.87)	4.14	(5.11)
Oppositional Defiant (of 8)	1.52	(1.66)	1.42	(1.65)
Conduct Disorder (of 15)	0.38	(0.89)	0.32	(0.92)
ADHD symptoms from normative checklist (SWAN[*])				
Inattention (of 9)	2.84	(2.74)	3.27	(3.06)
Hyperactive/impulsive (of 9)	1.52	(2.11)	2.63	(2.91)
Total (of 18)	4.36	(4.24)	5.90	(5.50)

	Maternal		Paternal	
Parent Psychopathology Diagnosis (absence/presence)[^]	**N**	**%**	**N**	**%**
Nicotine Abuse	16	9%	14	15%
Nicotine Dependence	104	62%	37	39%
Alcohol Abuse	76	45%	50	53%
Alcohol Dependence	20	12%	17	18%
Marijuana Abuse	1	< 1%	0	
Marijuana Dependence	0		0	
Conduct Disorder	1	<1%	1	1%
Present Oppositional Defiant Disorder (ODD)	2	1%	0	
Past ODD	3	2%	0	
Lifetime ADHD inattentive	5	3%	2	2
Lifetime ADHD hyperactive/impulsive	1	< 1%	3	3%
Lifetime ADHD combined type	3	2%	2	2%
Past Depressive Episode	68	40%	1	1%
Present Depressive Episode	8	5%	0	5
Generalized Anxiety	12	7%	0	

[*] MAGIC: Missouri Assessment of Genetics Interview for Children-Parent Interview; SWAN: Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder and Normal Behavior Scale

[^] From MAGIC-Adult on Self interview

Table 3

Summary of core assessments

Instrument(s)	Method	Rater/Ratee
Parental psychopathology/cognition		
DSM-IV alcohol abuse/dependence, smoking & tobacco dependence, illicit drug use & dependence, depression and anxiety disorders, antisocial behavior, childhood ADHD, childhood conduct disorder, including family history — MAGIC-Adult on Self (Todd et al, 2003) interview	L	M/M, M/F
General Cognitive Ability — Wechsler Adult Intelligence Scale (Wechsler, 1991)	L	O/M, O/F
Prenatal and peri-natal environment		
Pregnancy/birth history (including preterm birth and birth weight) — MAGIC-Parent (Todd et al., 2003)	I	M
Prenatal and perinatal exposure to toxins — MAGIC-Parent & Adult on Self (Todd et al., 2003);	I	M, F
Marital/partner/family relationship & life events surrounding pregnancy		
Marital/partner/sib conflict and life events surr. preg. — MAGIC-Parent & Adult on Self (Todd et al., 2003)	L	M/M-F, F/M-F
Child behavior/disorder/cognition		
General Cognitive Ability — Full Scale IQ - Wechsler Intelligence Scale for Children (Short Form) (Wechsler, 2003; Wechsler et al., 2004)	L	O/C
Receptive Language — Peabody Picture Vocabulary Test-III (PPVT-III) (Dunn & Dunn, 1997)	L	O/C
CELF-IV: Word Classes-Receptive (Semel, Wiig, & Secord, 2003)	L	O/C
Reading Ability — Word Attack – Woodcock Johnson-III (Woodcock, McGrew, & Mather, 2001)	L	O/C, O/M, O/F
Letter Word Identification – Woodcock Johnson-III (Woodcock, McGrew, & Mather, 2001)	L	O/C, O/M, O/F
Spelling – Woodcock Johnson-III (Woodcock, McGrew, & Mather, 2001)	L	O/C, O/M, O/F
GORT-IV – measures reading rate, accuracy, and comprehension (Weiderholt & Brytant, 2001)	L	O/C
Nelson-Denny Rdg Test (Brown, Fishco, & Hanna, 1993)	L	O/M, O/F
Auditory and Visual Memory — Digits Forward & Spatial Span Forward– Wechsler Intelligence Scale for Children (Wechsler et al., 2004) or WAIS in parents (Wechsler, 1991)	L	O/C, O/M, O/F
Story Memory and Faces Memory – Children's Memory Scale (Cohen, 1992)	L	O/C
Logical Memory and Faces Memory – Wechsler Memory Scale III (Wechsler, 1997)	L	O/M, O/F
Executive Function — Logan Stop Task (Logan, 1994)	L	O/C
Trail Making Test – Delis Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001)	L	O/C, O/M, O/F
Verbal Fluency – Delis Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001);	L	O/C, O/M, O/F
Color-Word Interference – Delis Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001)	L	O/C, O/M, O/M

Instrument(s)	Method	Rater/Ratee
Digits Backward & Spatial Span Backward – Wechsler Intelligence Scale for Children (Wechsler et al., 2005) or WAIS and WMS-III in parents (Wechsler, 1991; 1997)	L	O/C, O/M, O/F
ADHD/Externalizing behavior		
MAGIC-Parent (Todd et al., 2003) – maternal report	I	M/C
Child Behavior Checklist 6–18 (CBCL 6–18; Achenbach 1991a) and Achenbach Teacher Report Form (TRF; Achenbach, 1991b)	Q	M/C, T/C
Conners Rating Scale – Parent and Teacher (Conners et al., 1998a, 1998b)	Q	M/C, T/C
Strengths and Weaknesses of ADHD and Normal behavior (SWAN, Swanson et al., 2006)	Q	M/C
Fine motor		
Grooved Peg Board (Klove, 1963; Trites, 1977)	L	O/C
Substance use/initiation		
Substance Use domain - Youth ver. Drug Use Screening Inventory- Rev (DUSI-R; Tarter, 1990; Tarter et al., 1994)	L	C/C
Sociodemographic/contextual		
Family and neighborhood SES		
Hollingshead (1975) & geocoding	I	M

Note. I = Maternal Interview; Q = Questionnaire; L = Lab; M = Mother; F = Father; C = Child; O = Observer, T = Teacher ; MAGIC = Missouri Assessment for Genetics Interview for Children; GORT-IV = Gray Oral Reading Test – Fourth edition.

Table 4

Published reliability data for key constructs in the assessment protocol

Child development/disorder	Measure	coefficient alpha (internal consistency)	short-term test-retest	inter-rater reliability
General Cognitive Ability	WISC-IV-INT Full Scale IQ	.97	.93	
Receptive language	PPVT-III	.92–.98	.90	
	CELF-4 Word Classes-Receptive	.82	.83–.91	
Auditory and visual memory	WISC-IV-INT Digit Span Fwd and Spatial Span Fwd	.87	.83	
	CMS Stories	.80		
	CMS Faces	.80		
Executive Functioning	DKEFS Trail Making	.57–.79		
	DKEFS Verbal Fluency	.68–.81		
	DKEFS Color-Word Interference	.62–.70		
	Logon Stop Task	.90		
	WISC-IV-INT Digit Span Backward and Spatial Span Backward.	.87	.83	
Fine Motor	Grooved Peg Board		.86	
Reading	WJ-III Letter Word Identification	.94		
	WJ-III Word Attack	.87		
	WJ-III Spelling	.95		
	GORT-4	.91–.97	.78–.95	
	Nelson Denny	.88–.95		
ADHD/Externalizing behavior	MAGIC ADHD present			.97
	MAGIC ADHD past			.96
	MAGIC endorsement of 18 Criterion A symptoms			.97
	Conners Parent	.83–.91		
	Conners Teachers	.88–.94		
	CBCL combined for males and females	.84	.89	
	CBCL for mother-father report on females			.65–.69
	CBCL for mother-father report on males			.72–.75
	CBCL TRF	.72–.95		

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Note. WISC-IV-INT: Wechsler Intelligence Scale for Children (Short Form); PPVT-III: Peabody Picture Vocabulary Test-III; CELF-4: Clinical Evaluation of Language CMS: Children's Memory Scale; DKEFS: Delis Kaplan Executive Function System; Logan: Logan Stop Task; Fundamentals-Fourth Edition; WJ-III: Woodcock Johnson-III; GORT: Gray Oral Reading Test – Fourth edition; CBCL: Child Behavior Checklist; TRF: Teacher's Report Form

Table 5

Measure-linked domains, component key constructs and empirical basis for testing.

Key Child outcomes	Child outcome measured by:	Empirical basis for testing
Auditory Memory	1. Digit Span fwd (WISC) 2. Story memory (CMS)	Fried et al (1992a; 1992b) McCartney et al (1994) Roy et al. (2002)
Visual Memory	1. Faces memory (CMS) 2. Spatial Span Fwd (WISC)	Cornelius et al (2001) Roy et al. (2002)
Executive Function (EF)	1. Cognitive flexibility (DKEFS) 2. Verbal Fluency (DKEFS) 3. Interference Cntrl (DKEFS)	Willcutt et al (2000) Arnsten (1998) Cabeza & Nyberg (1997)
	4. Response Inhibition (Logan)	Fried et al (1992a; 1992b)
	5. Working Memory: Digit Span Bkwd (WISC) 6. Working Memory: Spatial Span Bkwd (WISC)	Fried et al (1992a; 1992b) McCartney et al (1994) Roy et al. (2002)
Reading & Receptive language	1. Receptive vocab (PPVT-III) 2. Receptive lang (CELF-4)	Makin et al (1991) Fried et al (1992a; 1992b) Bauman et al (1991) McCartney et al (1994)
	3. Single-word reading (WJ-III) 4. Nonword reading (WJ-III) 5. Reading compreh (GORT) 6. Reading Fluency (GORT)	Bauman et al (1991) McCartney et al (1994) Fried et al. (1997)
Attention Deficit Hyperactive Didorder (ADHD)	1. DSM-IV symptom ct or dx 2. Conners' Rating Form 3. Achenbach series: CBCL/TRF 4. SWAN	Fried et al (1992a; 1992b) D'Onofrio et al (2008)

WISC: Wechsler Intelligence Scale for Children (Short Form); CMS: Children's Memory Scale; DKEFS: Delis Kaplan Executive Function System; Logan: Logan Stop Task; PPVT-III: Peabody Picture Vocabulary Test-III; CELF-4: Clinical Evaluation of Language Fundamentals-Fourth Edition; WJ-III: Woodcock Johnson-III; GORT: Gray Oral Reading Test – Fourth edition; CBCL: Child Behavior Checklist; TRF: Teacher's Report Form; SWAN: Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder and Normal Behavior Scale