HHS Public Access

Author manuscript

Neurotoxicol Teratol. Author manuscript; available in PMC 2022 March 01.

Published in final edited form as:

Neurotoxicol Teratol. 2021 ; 84: 106961. doi:10.1016/j.ntt.2021.106961.

A sibling-comparison study of smoking during pregnancy and risk for reading-related problems

Lauren Micalizzi[a,*], **Kristine Marceau**[b], **Allison S. Evans**[c], **Leslie A. Brick**[d], **Rohan H. C. Palmer**[e], **Andrew C. Heath**[f], **Valerie S. Knopik**[b,f]

[a]Center for Alcohol and Addiction Studies, Brown University, Box G-S121-5 Providence, RI 02903

[b]Department of Human Development and Family Studies, Purdue University, 610 Purdue Mall, West Lafayette, IN 47906

[c]Concord Comprehensive Neuropsychological Services, 86 Baker Avenue Extension #301, Concord, MA 01742

[d]Department of Psychiatry and Human Behavior, Quantitative Sciences Program, Warren Alpert Medical School of Brown University, 345 Blackstone Blvd, Providence, RI 02906

[e]Behavioral Genetics of Addiction Laboratory, Department of Psychology, Emory University, 36 Eagle Row, Atlanta, GA 30322

[f]Midwest Alcoholism Research Center, Department of Psychiatry, Washington University School of Medicine, 660 S Euclid Ave, St. Louis, MO 63110

Abstract

This research examines the relationship between smoking during pregnancy (SDP) and risk for reading related problems in siblings discordant for exposure to SDP. 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 her smoking behavior between two pregnancies (Child 1 [older sibling]: M=12.99; Child 2 [younger sibling]: M=10.19). A sibling comparison approach was used, providing a robust test for the association between SDP and reading related outcomes in school-aged children. Results suggested within-family (i.e., *potentially* causal) associations between SDP and reading and language/comprehension factor scores, as well as between SDP and specific reading-related skills, including reading accuracy and receptive language, with increased exposure to SDP associated with decreased performance. SDP was not associated with spelling, reading rate, or receptive vocabulary. Initial within-family associations between SDP and word-letter identification, phonetic/decoding skills, and reading comprehension were fully attenuated following partial control for genetic and environmental confounding of the associations. These findings indicate that exposure to SDP is associated with poorer performance on some, but not all skills assessed.

[*]**Corresponding author at**: Box G-S121-5 Providence, RI 02912; lauren_micalizzi@brown.edu.

Conflicts: The authors have no conflicts of interest to report.

Keywords

Family studies; Reading; Language; Smoking during pregnancy

1. Introduction

Early reading problems may initiate a negative cascade of events that have broad implications for healthy development. For example, when compared with their typically developing and SES-matched counterparts, late talkers (i.e., toddlers with expressive language delay) scored lower on assessments of vocabulary, grammar, verbal memory, and reading comprehension in adolescence (Rescorla, 2005). Despite this, the prevalence of problems in reading-related skills remains relatively high, with approximately 5-17% of school aged children experiencing reading difficulties (Knopik, Neiderhiser, DeFries, & Plomin, 2017). In light of the developmental significance of reading problems, there is a need to better understand the sources of individual differences in these skills.

1.1 Etiology of Individual Differences in Reading-related Skills

Twin and other genetically-sensitive studies provide evidence for genetic and environmental contributions to individual differences in normative variation in reading-related skills (Astrom, Wadsworth, Olson, Willcutt, & DeFries, 2011; Byrne et al., 2013; Christopher et al., 2013; Harlaar, Spinath, Dale, & Plomin, 2005; Keenan, Betjemann, Wadsworth, DeFries, & Olson, 2006; Knopik et al., 2017; Little, Haughbrook, & Hart, 2017; Olson, Keenan, Byrne, & Samuelsson, 2014), as well as Dyslexia (Pennington & Olson, 2008), a dimensional disorder (Branum-Martin, Fletcher, & Stuebing, 2013; Spencer et al., 2014) that is characterized by difficulties learning to read and write (Snowling, Hulme & Nation, 2020). Environmental influences on reading-related outcomes that have been examined to date include, but are not limited to: the availability of educational resources within the home and school, familial structure and other socio-economic factors, neighborhood influence, quality and quantity of reading instruction in school, peer influences, bilingual reading, and print exposure (Grigorenko, 2001; Little, Haughbrook, & Hart, 2017; Olson et al., 2014). Further, children born to older mothers tend to perform better on reading assessments (e.g., Duncan, Lee, Rosales-Rueda, & Kalil, 2018). The focus on environmentally-based or -mediated causal pathways to reading problems is sensible given that reading is a learned skill that initially requires formal instruction (Olson et al., 2014); yet, research suggests that reading-related outcomes may be vulnerable to insult from the prenatal, as well as postnatal environment. For example, there is evidence that intrauterine exposure to maternal cigarette smoking during pregnancy (SDP) may contribute to problems in reading-related skills in SDP-exposed children (e.g., Eicher et al., 2013).

1.2 Maternal Smoking During Pregnancy and Offspring Development

Although national smoking rates have decreased, SDP remains pervasive. In their most recent report, the Centers for Disease Control and Prevention reported that 7.6% of women who gave birth in the United States reported SDP via the birth certificate (Drake, Dristol, & Matthews, 2018). Rates differed substantially by state (ranging from less than 5% in Arizona

to over 25% in West Virginia) and by age group. Specifically, rates were highest among pregnant women aged 20-24 (10.7%), followed by women 15-19 (8.5%), and 25-29 years old (8.2%; Drake et al., 2018). These rates are likely conservative given research suggesting that birth record data tend to under-report the true nature of SDP (Feng et al., 2013; Knopik et al., 2015). Associations between SDP and adverse birth and developmental outcomes are well documented (Knopik, 2009; Knopik et al., 2015). For example, exposure to SDP is associated with offspring behavior problems (D'Onofrio et al., 2008; Knopik et al., 2016a; Martin, Dombrowski, Mullis, Wisenbaker, & Huttunen, 2006; Ruisch, Dietrich, Glennon, Buitelaar, & Koekstra, 2018]), temperament (e.g., Martin et al., 2006), neurocognitive problems (e.g., Clifford et al., 2012) and academic problems (Martin & Dombrowski, 2008; Martin et al., 2006).

Prenatal SDP exposure may have teratological effects for altering fetal brain development or other biological mechanisms that adversely impact reading-related abilities. For example, SDP may insult brain regions that are known to be implicated in reading-related outcomes (England et al., 2017; Knopik et al., 2015). Animal and human studies (Slikker, Xu, Levin, & Slotkin, 2005) indicate that the mode of action of nicotine acts primarily through its action on nicotinic cholinergic receptors (nAChRs). This results in a cascade of events, encompassing brain structure alterations and cell death, and the consequences of this action extends to negative child behavioral and neural outcomes that directly reflect the effects of nicotine on the brain (Ernst, Moolchan, & Robinson, 2001). In humans, periods of high nAChR density have been found in frontal cortex, hippocampus, cerebellum, and brainstem during mid-gestation and neonatal periods. Differences in developmental profiles of receptor binding between species and strains suggest that genetic factors regulate maturation of nicotinic receptors and may explain interindividual differences in sensitivity to effects of prenatal nicotine. Another possibility is that SDP exerts its effects on reading-related skills through intermediary abilities such as audition. For example, children who are exposed to SDP often present for auditory problems (e.g.., have higher rates of middle ear effusions, process auditory information differently than nonexposed children; e.g., Kable, Coles, Lynch, & Carroll, 2009). Therefore, it may be the case that SDP is casually linked to auditory problems and that this mechanism explains the observed association between SDP and reading-related outcomes.

1.3 Maternal Smoking during Pregnancy and Child Reading-related Skills

Findings from studies of the association between SDP and reading-related outcomes are mixed. There is evidence that increased exposure to SDP is associated with lower speech and language abilities (e.g., Bauman et al., 2001; Eicher et al., 2013; Fried, Watkinson, & Siegel, 1997; Makin, Fried, & Watkinson, 1991; McCartney et al., 1994), lower reading (e.g., passage comprehension; Fried et al., 1997) and non-word reading scores (McCartney et al., 1994), poorer reading achievement (Butler & Goldstein, 1973; Davie, Butler, & Goldstein, 1972; Fogelman, 1980), and lower reading performance (Cho et al., 2013; Feng et al., 2013). Research suggests that associations between SDP and delayed or decreased reading skills (e.g., accuracy, comprehension) persist despite control for a range of confounding influences, including phonology, attendance in prenatal education classes, literacy-based interaction with the child, and maternal social class (Cho et al., 2013).

However, for other reading-related outcomes, their associations with SDP do not withstand covariate adjustment (Fergusson & Lloyd, 1991) and other reading outcomes (e.g., reading comprehension) have been found not to be associated with SDP (Kafouri et al., 2009).

Quasi-experimental studies (e.g., sibling comparison studies) reveal that for many neurodevelopmental outcomes, risk factors that co-occur with SDP better explain poorer outcomes than a teratogenic effect of SDP itself (e.g., Micalizzi et al., 2017). For example, women with reading problems may be more likely to exhibit SDP and may pass on correlated genes and environments to the child that are associated with reading problems, giving rise to a non-causal association between SDP and youth reading problems. Other confounding influences should also be considered. For example, SDP-reading associations may be confounded by other risk factors for poorer child outcomes (e.g., secondhand smoke exposure). Alternatively, SDP may appear to have a causal influence on reading-related outcomes but apparent associations may actually be due to associated genes and/or behaviors (e.g., impulse control) that influence both reading and SDP.

To our knowledge, only one study systematically assessed familial and prenatal/postnatal influences that co-occur with SDP in the study of reading-related outcomes (Peabody Individual Achievement Test Reading and Reading Recognition subtests; Ellingson, Goodnight, Van Hulle, Waldman, & D'Onofrio, 2014). Ellingson and colleagues examined the relations between SDP and multiple outcomes and reported that, after accounting for familial confounding, SDP was independently associated with decreases in reading recognition at 4-5 years of age, and surprisingly, on its trajectory—that is, SDP was associated with increased performance on reading recognition over time (Ellingson et al., 2014). Sibling comparison studies of the association between SDP and child outcomes can directly inform questions of the etiology (i.e., genetic and environmental influences) of individual differences in children's skills and provide a rigorous test of *potentially* causal effects of SDP on these outcomes.

In sum, reading relies on many component skills that must function both independently and in concert to support reading. To capture both the breadth and specificity of associations with SDP, research should evaluate both higher order factors of reading-related skills, as well as individual skills that support reading. It's understood that there is likely more clinical utility in understanding the association between SDP and individual tests, as knowledge of SDP exposure could help identify those at risk for specific problems (e.g., Dyslexia subtypes). This knowledge would allow for early identification and early treatment, which yields the best prognosis. However, considering the role of SDP in shared variance among reading measures is also useful from an etiological standpoint. The sources of individual differences in reading skills are both genetic and environmental in origin and the presence and robustness of the associations between SDP and reading-related outcomes to genetic and environmental confounding remains unresolved. Further, both non-genetic studies and the only quasi-experimental study to date yield mixed results with regard to associations between SDP and reading outcomes. The sibling-comparison design utilized in the present study enables a direct and rigorous test of the association between SDP and child reading related skills while partially controlling for genetic and environmental variables that siblings share (Ellingson et al., 2014; Knopik, 2009; Knopik, et al., 2016a). This novel approach has

not yet been applied to reading-related measures that capture both higher-order factors and component skills necessary for successful reading. As such, the goal of this study is to build on previous work by using a sibling-comparison analysis of the associations between SDP and reading-related outcomes.

1.4 Present Study

Given: (1) the paucity of studies that account for familial confounding; (2) the knowledge from animal studies that SDP affects brain regions known to be involved in reading-related skills; and (3) the preliminary findings from the one study to date that considers a quasi-experimental approach to the SDP-reading relation, the present study attempts to add clarity to existing research on the associations between SDP on reading-related outcomes by using carefully chosen measures in a purposefully designed and deeply-phenotyped dataset. This study also capitalizes on data regarding socio-economic characteristics (used as covariates in the present study) which have been shown to be associated with SDP and child reading outcomes (e.g., Little et al., 2017).

Based on the existing literature (e.g., Knopik et al., 2015), it was hypothesized that: (1) SDP would be associated with poorer performance on both higher order reading-related factors, as well as individual component reading-related skills—assessments that tap brain regions shown in basic science studies to be affected by prenatal nicotine exposure; and (2) sibling comparisons will show attenuated associations (i.e., partial or full attenuation of SDP parameters) suggesting confounding due to influences that siblings share (e.g., genetic effects). Embedded in hypothesis 2 is the investigation of the potentially causal effect of SDP on reading-related outcomes. That is, SDP associations with reading related outcomes that persist despite partial control for genetic and environmental confounding are suggestive of causal effects of SDP on the reading-related outcome.

2. Materials and Methods

2.1 Participants and Procedure

Data for the current study were drawn from the larger Missouri Mothers and Their Children study (MO-MATCH; Knopik et al., 2015). Families in which mothers apparently changed smoking behavior between two pregnancies (i.e., increased or decreased smoking across pregnancies or smoked during one pregnancy and did not smoke during the other pregnancy) were identified using birth records (years 1998-2005) obtained from the Missouri Department of Health and Senior Services Bureau of Health Informatics (N>4000 identified). Mothers were contacted to complete a screening interview (N=1520) in which we determined eligibility to participate in the current study. The objective of this interview was to corroborate the information listed in the birth records about her smoking behavior across two pregnancies. 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 into the current study (Knopik et al., 2016b). As was expected based on review of the birth records, most women changed their smoking behavior across pregnancies (i.e., increased or decreased her smoking behavior from child 1

to child 2). However, when interviewed (see below), 19 women indicated smoking the same magnitude across pregnancies. These women were retained in all analyses.

Exclusion criteria included: (1) mothers' failure to understand the elements of informed consent; (2) English not being the primary language spoken in the home; (3) children's history of head trauma, neurological disorders or uncorrected visual or auditory acuity deficits; and (4) mothers' use of nicotine substitutes in the 'non-smoking' pregnancy (i.e., the pregnancy in which they indicated not smoking or smoking less than the comparison pregnancy). 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.

After consent (N=173 families), mothers ($M_{age\ at\ assessment}$=39.83, SD=5.62) completed a diagnostic interview about their pregnancies (including life events surrounding pregnancy), diagnostic interviews about each child (including mental health and behavioral history), and both parents (when possible; fathers n=96 [$M_{age\ at\ assessment}$=44.04, SD=6.34]) provided information on their own mental health history. Families in which fathers participated were not different from families in which fathers did not participate on any focal variable (Knopik et al., 2015). 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.

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% at Child 2's [younger sibling] birth. Few families received food stamps at the time of birth of Child 1 (9.74%) and Child 2 (13.73%). 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). Mothers (64%) typically smoked (or smoked more) during the first pregnancy (see Knopik et al., 2015 for further detail on the sample).

2.2 Measures

2.2.1 SDP.—

Maternal report of SDP was obtained using a modified version of the Missouri Assessment of Genetics Interview for Children (MAGIC)–Parent on Child (Todd, Joyner, Heath, Neuman, & Reich, 2003). The following items were used to create an SDP severity score (described below) that encompassed information about *Any SDP* (0=No, 1=Yes) across each pregnancy as a whole, as well as specific to each trimester, and *overall SDP quantity* assessed via mothers' estimate of the number of cigarettes smoked in each trimester. Here, we focus on maternal report of SDP severity because prior reports suggest that: (1) maternal report of SDP (absence/presence and quantity/severity) has more predictive validity than paternal and birth record reported SDP (Knopik, Marceau, Palmer, Smith, & Heath, 2016b); (2) the severity of SDP including SDP later in pregnancy imparts additional risk above and beyond the absence/presence of SDP (e.g., Estabrook et al., 2015); and (3) in order to be consistent with prior work (e.g., Knopik et al., 2016a; Knopik et al., 2016b). A single *SDP severity* score ranging from 1-7 was created for each child based on the following information[1]:

1. : did not smoke during pregnancy
2. : smoked during first trimester only, 1-10 cigarettes per day
3. : smoked during first trimester only, 11-19 cigarettes per day
4. : smoked during first trimester only, 20+ cigarettes per day
5. : smoked beyond first trimester, 1-10 cigarettes per day (max of all trimesters)
6. : smoked beyond first trimester, 11-19 cigarettes per day (max of all trimesters)
7. : smoked beyond first trimester, 20+ cigarettes per day (max of all trimesters)

2.2.2 Reading Abilities.—Subscales from the Woodcock-Johnson III Tests of Achievement (WJ-III; Woodcock, McGrew, & Mather, 2001) were administered. Children's word identification skills were assessed via the *word-letter identification* subscale, which requires students to identify individual letters, and then read words of increasing difficulty in isolation. Children's abilities to apply phonetic/decoding skills to unfamiliar words was assessed via the *word attack* subscale. Initial items require the child to produce sounds for single letters, and subsequent items require children to pronounce nonsense words of increasing complexity. Thus, *word-letter identification,* and *word attack* assess basic reading in isolation/out of context. Children's abilities to correctly write orally presented words was assessed via the *spelling* subscale. Standardized scores were used for all subscales.

Reading accuracy, rate, and comprehension were assessed with the Gray Oral Reading Test, 4th Edition (GORT-4; Bryant, Shih, & Bryant, 2009). For the GORT, the child reads aloud increasingly complex passages and then, immediately following, answers questions about the text. The research assistant tracked reading accuracy and reading rate during the task. *Accuracy* assesses the numbers of errors and miscues. *Rate* assesses the speed of reading. Thus, *accuracy* and *rate* assessed applied reading skills in context. *Reading comprehension* was also assessed; after the participant read a passage, the research assistant asked a range of multiple-choice questions pertaining to the text, which were later scored. Standardized scores were used for all subscales.

Three common reading composite scores were also derived based on the assessment manuals. The *basic reading skills* cluster score was calculated by summing the standard scores from the Woodcock-Johnson *word-letter identification* and *word attack* subtests (Mather & Woodcock, 2001). *Fluency* is the sum of GORT accuracy and rate. The *oral reading quotient* (ORQ) was derived by summing the scaled scores for GORT fluency (i.e., rate and accuracy) and GORT reading comprehension and converting that sum score into the ORQ (based on Appendix C, Table C.1; Bryant, Shih, & Bryant, 2009). The ORQ provides an overall index of the child's ability to read orally. Findings for these reading composite scores are reported in supplemental materials.

[1]Sensitivity analyses were conducted to evaluate the correspondence across various operationalizations of SDP exposure. Correlations across quantifications were high and are reported in footnote 1 of Knopik et al (2016a). We re-ran all of the models using the four new scores described in Knopik et al. Our findings appear robust to different methods of assessing SDP; results are available upon request.

2.2.3 Receptive Vocabulary and Language.—Receptive vocabulary was assessed via the Peabody Picture Vocabulary Test –Third Edition (PPVT-III; Dunn & Dunn, 1997). The participant was required to point to a named picture when given several possible options. Receptive language was assessed via the Clinical Evaluation of Language Fundamentals CELF-4; (Semel, Wiig, & Secord, 1995), where youth choose two related words and describe their relation. Standardized scores on the PPVT and CELF were used. We are not able to calculate sample alphas because our database only included raw and scaled scores for the reading assessments. However, all measures reported above have excellent psychometric properties; coefficient alphas range from .91-.98. More detailed information is reported in Table 4 of Knopik et al. (2015).

2.2.4 Covariates.—Maternal and family characteristics that could confound the association of SDP and neuropsychological functioning included maternal report of her marital status, age, and education at birth of each child, child birth order, child sex, and second-hand smoke exposure during pregnancy (by the father). Birth order was significantly negatively correlated with age in this sample ($r = -.87$), which leads to a multicollinearity problem when modeling these data. Birth order was included as a covariate rather than age given that: (1) mothers usually smoked in the first pregnancy (64%); and (2) age is accounted for in the standardization of the measures.

Child and mother IQ at the time of assessment were also controlled for in all analyses. For child IQ, a sum of scaled scores was created for the following WISC IV-Integrated (Wechsler, 2003; Wechsler et al., 2004) subtests: Similarities, Vocabulary, Matrix Reasoning, Symbol Search, and Arithmetic. For parent IQ, a sum of scaled WAIS-III (Wechsler, 1997) scores was created for: Vocabulary, Block Design, Matrix Reasoning, Digit Span, and Information. This approach to calculating an estimated full-scale IQ (FSIQ) follows protocols presented in the WISC-IV and WAIS-III administration manuals (Wechsler, 2003; Wechsler et al., 2004; Wechsler, 1997) as well as that originally proposed by Tellegen and Briggs (1967). The combination of these 5 subtests for the WISC-IV and the WAIS-III have demonstrated reliability coefficients of .95 and .96 for child and parent scores, respectively, as well as validity coefficients of .95 and .93 (Wechsler, 2003; Wechsler et al., 2004; Wechsler, 1997).

Finally, for each child outcome, a measure indexing the same skill in the mother was included in the model. That is, parallel maternal scores to the focal child outcome under study were used as covariates in each model. The maternal covariates utilized for each model are outlined as follows: for child WJ-III subscales, the maternal scores on the same subscales were included as covariates (e.g., mother spelling was covaried when child spelling was the dependent variable). For the GORT subscales, the corresponding mother scores from the Comprehension subtests of the Nelson-Denny Reading Test, a widely-used measure of adult reading comprehension (Brown, Fishco, & Hanna, 1993) that requires participants to read passages and respond to multiple choice questions that assess comprehension were included as covariates. For the CELF and PPVT, mothers' scores on the WAIS-III vocabulary subtest was used as a covariate. Because only approximately half of fathers completed the study, only maternal covariates were included in the models reported in this paper. Inclusion of father covariates was explored in sensitivity analyses.

2.3 Statistical Analysis

There is theoretical and epidemiological utility in evaluating the association between SDP and higher-order factors of reading-related skills, as well as clinical utility in the study of the association between SDP and component reading-related skills. For this reason, we first evaluated the factor structure of the child reading-related skills measures using a rigorous exploratory/confirmatory factor analytic approach. We then ran the series of hierarchical linear models HLM; (described below) using the extracted factor scores. Subsequently, we fit the series of HLM for each component reading-related skill.

2.3.1 Exploratory and Confirmatory Factor Analysis.—One child from each family was randomly assigned to one of two groups and an independent-samples t-test was conducted to ensure that SDP exposure was not biased to one group. An exploratory factor analysis (EFA) was then conducted using half of the sample to evaluate the factor structure of the measures of child reading-related skills. The criteria used to determine the number of factors to extract included evaluation of the scree plot, Eigenvalues (i.e., >1), total percent variance explained, as well as an evaluation of the conceptual meaningfulness of the factors extracted. The results from the EFA were then confirmed in a confirmatory factor analysis (CFA) using the second half of the child sample, and again in a CFA using the full sample. Factor scores were extracted and utilized as dependent variables in the HLM.

2.3.2 Hierarchical Linear Models.—To probe the associations between SDP and the reading-related skills, we first fit the series of models for each of the factor scores, and then fit models examining each of the measures of component skills (i.e., word-letter identification, phonetic/decoding skills, spelling, accuracy, rate, comprehension, receptive vocabulary, and receptive language). Our sibling comparison approach included a series of HLM to account for non-independence of data, as well as to assess the within- and between-family associations of SDP and reading-related skills, identical to the approach detailed in Knopik et al., 2016a, 2016b. In order to test hypothesis 1 (i.e., that increased exposure to SDP would be associated with lower component reading and receptive language skills), standard models (i.e., those that do not leverage the sibling comparison aspect of the data) were conducted.

The *standard* model compared children whose mothers smoked (or smoked more) during pregnancy to those whose mothers who did not smoke (or smoked less) on reading-related skills, controlling for covariates. This model examines SDP-reading associations in the entire sample and is representative of how SDP effects and associated familial confounds are typically modeled in non-sibling-based samples, without capitalizing on the family structure (or sibling comparison aspect) of the data, but adjusting for the non-independent observations of siblings nested within families. The *standard* model was run without (e.g., Zero-order) and with (e.g., Covariate Adjusted) covariates. The *standard* models provide a direct test of hypothesis 1. The standard model is specified by Equation 1 (using reading as a proxy for the factor scores as well as all specific reading-related component scores tested):

$$Reading_{ij} = \beta_{0i} + \beta_{1i}(SDP_{ij}) + \beta_{2i\ldots}\beta_{8i}(covariates) + e_{ij}$$
$$\beta_{0i} = \gamma_{00} + u_{0j} \quad (1)$$
$$\beta_{1i} = \gamma_{10} + u_{1j}$$

where $reading_i$ was individual i's reading score, nested in family j. The SDP parameter (using the child-specific SDP values described above) was modeled at level 1 (the child level). Thus, readings was modeled as a function of child-specific coefficients β_{0i} (intercept level of the reading score), β_{1i} (association of SDP severity and the reading score), and e_{ij} a series of residuals (one per child in each family). Additionally, child sex (β_{2i}), child birth order (β_{3i}), mother education (β_{4i}), maternal age (β_{5i}), marital status (β_{6i}), prenatal second-hand smoke exposure (by fathers) (β_{7i}), and the corresponding maternal covariate (β_{8i}) were included as covariates. Random effects were not included on the level 1 covariates. Child-specific coefficients β_{0i} and β_{1i} were, in turn, modeled where γ_{00} and γ_{10} were sample means for the intercept and SDP association with the reading score, respectively. u_{0i} was the variation in intercepts between families, and u_{1i} was the individual child-level variation within families for SDP.

To test hypothesis 2 (i.e., that the SDP parameters included in the standard models would be fully or partially attenuated due to familial confounding), the *sibling-comparison* model parsed apart the extent to which SDP operates at a within-family (i.e., contributing to differences in reading-related skills in one sibling versus another, within families) and/or between-family level (i.e., contributing to differences in overall, average levels of siblings' reading-related skills across families). Two variables were used to capture SDP severity in the *sibling-comparison* models. First, *family-average SDP severity* for each family was the average score for SDP severity (across both siblings). *Family average SDP severity* is included as a covariate to control for the between-family association between SDP severity and reading skills (i.e. the overall associations between SDP and related familial factors on reading skills, comparing across families). Second, *child-specific SDP severity relative to family average* for each child was the resulting value when the *family average SDP* was subtracted from each child-specific SDP severity score (i.e., the SDP severity scores used in the *standard* models)[2]. This within-family centering resulted in a score of zero if mothers smoked the exact same amount for both pregnancies, a positive score for the sibling for whom mothers smoked, or smoked more, and a negative score for the sibling for whom mothers did not smoke, or smoked less. The association between the *child-specific SDP severity relative to family average* and reading-related skills assesses a the potentially causal within-family effect of SDP (comparing across siblings within a family, a test of any unique association between SDP and child specific outcomes over and above familial and genetic factors that siblings share). *Family average* and *child-specific relative to family average* scores were created and included as covariates that varied across children for inclusion in the *sibling-comparison* models. The child-specific relative to family average SDP severity score was entered as a level 1 predictor, whereas the family average SDP severity score was

[2]We calculated a separate variable, within-mother differential smoking severity across pregnancies (i.e., the absolute value of the child 1 SDP severity score minus child 2 SDP severity score) to provide additional information about differential smoke exposure. This variable is distinct from the child-specific SDP severity score used in analyses. The descriptive statistics for this variable are provided in supplemental materials.

entered as a level 2 predictor (specified in Equation 2; using reading as a proxy for the factor scores as well as all specific reading-related component scores tested):

$$\begin{gathered} Reading_{ij} = \beta_{0i} + \beta_{1i}\left(Child - specific\ SDP_{ij}\right) + \beta_{2i\ldots}\beta_{8i}(covariates) + e_{ij} \\ \beta_{0i} = \gamma_{00} + \gamma_{01}(family\ average\ SDP_j) + u_{0j} \\ \beta_{1i} = \gamma_{10} + u_{1j} \end{gathered} \quad (2)$$

Again, $reading_{ij}$ was modeled as a function of person-specific coefficients β_{0i} (intercept level of reading score), β_{1i} (linear relationship of SDP severity, this time using the child-specific relative to the family average SDP severity score, and the reading score), and e_{ij} a series of residuals. Person-specific coefficients β_{0i} and β_{1i} were, in turn, modeled where γ_{00} and γ_{10} were sample means for the intercept and SDP severity association with reading score, respectively. Additionally, γ_{01} was included to capture the level 2 (family level) parameter of family average SDP severity on the reading score. As in Model 1, u_{0i} was the variation in intercepts between families, and u_{1i} was the individual child-level variation within families for the child-specific relative to family average SDP severity parameter. The covariates were included in the same way as described in Model 1, with the exception that covariates that differed non-systematically for siblings 1 and 2 (mother age at childbirth, education, secondhand smoke exposure, child sex) were separated into child-specific relative to family average and family average components in the same way that SDP was (described above). Thus, both the within- and between-family effects of covariates were controlled (with separate variables). Within-family covariates were also centered within-family. Marital status did not differ for any participants, and thus was not separated into within- and between-family components.

2.3.3 Covariates for the Factor Score Models.—

As discussed above, parallel maternal variables were covaried in the HLMs for specific reading-component skills. For the models in which the child factor scores were the dependent variables, the parallel mother variables were standardized and aggregate averages were calculated to covary in the HLM. We were not able to utilize the same EFA/CFA approach in mothers due to sample size limitations (i.e., the sample of mothers is half of the sample of children) and because we did not have parallel mother variables for all child variables (e.g., WAIS vocabulary was a covariate for both child receptive language and child receptive vocabulary). As a sensitivity check for our use of the aggregate mother variables as covariates, we conducted a Principal Component Analysis (PCA) using the mother reading-related variables. The PCA revealed that a single component solution best described the data. These first principal component scores for mothers were extracted and covaried in the HLMs. The pattern of findings using this PCA covariate approach was identical to those presented here using the more conceptually relevant standardized aggregate approach (results available upon request).

3. Results

Means and standard deviations for study variables are presented in Table 1. A summary of the main findings (beta-weights from the SDP 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.

3.1 Exploratory and Confirmatory Factor Analyses

The magnitude of prenatal smoke exposure was not significantly different between the two halves of the sample (t[340] = .12, p = .90) indicating that the random assignment of one child to each half of the sample was successful (i.e., the groups were not biased with regard to SDP). Model fit and parameter estimates for the split-half EFA and CFA are presented in Supplemental Table 1. EFA with promax rotation utilizing data from half of the sample (n = 168) revealed that a correlated 2-factor solution best fit the data (model fit statistics: chi-square[χ2] = 53.75 (df = 13), p < .001; RMSEA = 0.14). Rate, accuracy, world-letter identification, phonetic/decoding, and spelling loaded in the first factor ("reading"). Receptive vocabulary, receptive language, and comprehension loaded on the second factor ("language/comprehension"). The 2-factor solution was confirmed with a CFA using oblique rotation in the second half of the sample (n = 165; model fit statistics: χ2 = 94.93(df = 19), p < .001; RMSEA = .16 [.13-.19]; CFI = .906), and again with the full sample N = 333; model fit statistics: χ2 = 131.739(df = 19), p < .001; RMSEA = .13 [.11-.16]; CFI = .930. Based on confirmation of a correlated 2-factor solution in the CFA, factor scores from this solution were extracted to be utilized as dependent variables in the HLMs.

3.2 Models Evaluating Associations between SDP and the Reading and Language/Comprehension Factor scores

Consistent with hypothesis 1, in the *standard* models without covariates, SDP was associated with both the reading factor score (b = −0.06, SE = .02, p < .01; Supplemental Table 2) and the language/comprehension factor score (b = −.06, SE = .02, p < .01; Supplemental Table 3). The associations between SDP and the reading factor score (b = −.05, SE = .02, p < .05) and the language/comprehension factor score (b = −.04, SE = .02, p < .05) withstood covariate adjustment. In the *sibling comparison* models, there were significant within-family associations between SDP and the reading factor score (b = −.05, SE = .02, p <.05) and SDP and the language/comprehension factor score (b = −.06, SE = .02, p < .01). Both the association between SDP and the reading factor score (b = −.06, SE = .03, p <.05) and SDP and the language/comprehension factor score (b = −.06, SE = .02, p < .01) withstood covariate adjustment.

3.3 Models Evaluating Associations between SDP and Component Reading Skills

Consistent with hypothesis 1, in the *standard* models without covariates, SDP predicted poorer word-letter identification (b = −.78, SE = .25, p < .01; supplemental Table 4, phonetic/decoding skills (b = −.95, SE = .24, p < .001; supplemental Table 5), accuracy (b = −.14, SE = .07, p < .05; supplemental Table 6), comprehension (b = −.19, SE = .07, p < .01; supplemental Table 7), and receptive language (b = −.16, SE = .05, p < .01; supplemental Table 8). SDP was not associated with spelling (b = −.37, SE = .20, p = .20; supplemental Table 9), rate (b = −.11, SE = .07 p = .11; supplemental Table 10), or receptive vocabulary (b = −.15, SE = .28, p = .60; supplemental Table 11). Only the associations between SDP and phonetic/decoding skills (b = −.82, SE= .28, p <. 01) and SDP and accuracy (b = −.18, SE= .08, p <. 05) survived covariate adjustment in the *standard* model with covariates

Consistent with hypothesis 2, most significant parameters from the standard models were fully or partially attenuated in the *sibling comparison* models. In the *sibling comparison* model without covariates, there were significant within-family associations between SDP and: word-letter identification ($b = -.74$, SE = .27 $p < .01$), phonetic/decoding skills ($b = -.90$, SE = .26 $p < .001$), comprehension ($b = -.21$, $SE = .08$, $p < .05$) and receptive language ($b = -.17$, SE = .06 $p < .01$). Only the within-family association between SDP and receptive language ($b = -.16$, SE = .07 $p < .05$) survived covariate adjustment. The within-family association between SDP and accuracy became significant when covariates were included in the model ($b = -.24$, SE = .02 $p < .05$).

3.3 Sensitivity Analyses

Two sets of sensitivity analyses were conducted to verify the robustness of the findings reported above. First, we explored the role of alcohol use. Alcohol use was uncommon in this sample; mothers drank twice per month or greater in only 13 of 344 pregnancies. Nonetheless, as a sensitivity check, all analyses were re-rerun excluding these pregnancies and the pattern of findings did not change. Second, we evaluated if the inclusion of father covariates would impact the results. Because fathers participated in only approximately half of the families, the findings reported herein are from models that include the corresponding mother covariates (e.g., mother reading accuracy was included as a covariate when assessing child reading accuracy as the primary outcome). To evaluate if findings were corroborated in the subset of families (n=96) in which both mothers and fathers participated, all models that include covariates were re-run including both mother and father covariates (see Supplemental Tables). In the *sibling comparison* model including both mother and father covariates, the within-family association with SDP was fully attenuated when father covariates were included for the reading and language/comprehension factor scores, reading accuracy, and receptive language. When father covariates were included, there were significant within-family associations between SDP and phonetic/decoding skills.

4. Discussion

The goal of this study was to leverage the sibling-comparison design to conduct a genetically-sensitive study of the association between SDP and reading-related skills. The sibling-comparison approach partially controls for both measured and unmeasured genetic and environmental influences, enabling a methodologically rigorous evaluation. The findings revealed a within-family association between SDP and both the reading and language/comprehension factor scores, as well as between SDP and reading accuracy and SDP and receptive language, suggesting potentially causal effects of SDP. However, for other phenotypes, within-family effects were ruled out; initial within-family associations between SDP and word-letter identification, phonetic/decoding and reading comprehension were fully attenuated following covariate adjustment. SDP was not associated with spelling, oral reading rate, or receptive vocabulary.

4.1 SDP and Reading-related Outcomes

The current findings provide some clarity to studies of the association between SDP and reading-related outcomes. Existing findings are mixed, but phenotypic (i.e., non-genetic)

studies of SDP and reading-related outcomes have found associations between increased exposure to SDP and decreased reading skills/performance. However, as has been observed for other neurocognitive outcomes in SDP-exposed youth (e.g., inhibitory control; Micalizzi et al., 2017), concluding ostensibly direct effects of SDP on reading outcomes in these prior studies may be incorrect given the lack of control for genetic and other unmeasured environmental confounding. That is, children of mothers who smoke may present with reading problems either because reading problems are caused by SDP, or because SDP exposure and reading problems are both caused by common familial (genetic and environmental) influences. This notion is supported by decades of twin studies demonstrating that there is genetic transmission of risk for reading problems (Little et al., 2017). However, this has not been comprehensively addressed empirically using quasi-experimental designs that can be applied to evaluate familial confounding.

To our knowledge only one study has examined the association between SDP and child reading skills using a quasi-experimental design (Ellingson et al., 2014). There was a significant within-family association between SDP and the intercept and trajectory of reading recognition in 4- to 5-year-old children as measured by the Peabody Individual Achievement Test, suggesting a potentially causal effect of SDP but in the opposite direction than would be hypothesized (i.e., SDP led to better reading scores over time). In the current study, there was an initial association observed among within-family SDP and word-letter identification, but this association was fully attenuated following control for confounding influences. These conflicting findings may be due to the fact that the Woodcock Johnson subtests are more valid tests of reading problems than the Peabody Individual Achievement Test (Caskey, 1985) and because there is low overlap among the tests in diagnosing comprehension difficulties (Keenan & Meenan, 2014). Another explanation may be developmental; the children in Ellingson et al., 2014 were younger than the children included in the present study and SDP may be differentially associated with reading outcomes across age.

Research suggests that genetic influences on print exposure (a variable considered by some to be a purely environmental measure) are correlated with genetic influences on reading fluency, suggesting that observed genetic effects on individual differences in child reading skills may, in part, reflect gene-environment correlations (i.e., literacy environments reflect genetic variation that are associated with individual differences in reading skills [Harlaar, Deater-Deckard, Thompson, DeThorne, & Petrill, 2011]). Reading-related problems are, in part, genetically influenced, therefore, prenatal exposure to SDP may interact with genetic predisposition for reading problems by way of gene-environment interplay (Cho et al., 2013). The sibling comparison design can be used to strengthen causal inferences regarding environmental risks by ruling out specific forms of confounding, including confounding by gene-environment correlation (D'Onofrio, Class, Lahey, & Larsson, 2014; D'Onofrio, Lahey, Turkheimer, & Lichtenstein, 2013; Kendler, 2017). Results from the present study suggest that increased SDP exposure is a potentially causal environmental risk leading to decreased performance in oral reading accuracy and receptive language, as well as on the reading and language/comprehension factor scores, after methodological control of influences that siblings share, including gene-environment confounding. While the initial within-family association between of SDP and reading accuracy was not significant in the sibling

comparison model without covariates, the within-family association became significant only after covariates were included in the model. While this is suggestive of a potentially causal effect, replication is needed.

Reading is a complex behavior comprised of multiple component skills. Our pattern of results exemplifies this complexity in that there were not consistent patterns observed in the relationship between SDP and each of the component measures of reading-related skills. SDP was associated with both the reading and language/comprehension factor scores, indicating that the variance that is common to these groups of measures was associated with SDP exposure in the expected direction, such that increased exposure was associated with decreased performance. One potential explanation as to why we see significant associations between some but not all measures may be due to the brain regions involved in these skills. Research has identified specific brain regions involved in speech production and language comprehension and additional evidence that these same regions are also impacted by exposure to SDP. For example, there is a cerebellar deficit in Dyslexia (Nicolson et al., 2001; Norton et al., 2014) which suggests that differences in locus of cerebellar impairment may account for subtypes of Dyslexia and possibly other developmental disorders, which would also have implications for different types of treatments. Notably, exposure to SDP is linked to decreased cerebellar volumes in offspring (Ekblad et al., 2010) and therefore knowing SDP exposure could help identify those at risk for Dyslexia subtypes, an in turn, would allow for early identification and early treatment, which yields the best prognosis. As such, it is reasonable, if not expected, that we would see different patterns of findings with regard to associations between SDP and component reading skills.

Environmental explanations for associations between SDP and reading should be considered in conjunction with biologically based explanations. Reading skills are not perfectly genetically correlated (e.g., Petrill, Deater-Deckard, Thompson, De Thorne, & Schatschneider, 2006), and there are common and unique environmental influences found for reading skills (e.g., Olson et al., 2011). While the sibling-comparison design utilized here controls for environmental influences that children share, there are likely environmental factors that vary across pregnancies (e.g., stressors). These aspects of the environment may influence or be influenced by SDP, and these factors may also be related to reading. Future research may consider investigating these pregnancy-specific environmental factors to facilitate a more complete understanding of the role that exposure to SDP plays in child reading problems.

Another consideration is that SDP may be associated with reading and language outcomes via problems with auditory functioning. Previous research indicates that SDP is associated with auditory problems (e.g., Kable et al., 2009) and audition is integral to reading and language abilities (e.g., Key et al., 2007). Auditory problems were an exclusion criterion for participation in Mo-MATCH. Therefore, it does not appear to be the case that significant associations with SDP were due to auditory problems in this sample.

4.2 Implications for Reading Disorders and Practical Application

Knowledge that SDP is linked to a host of reading-related deficits (albeit, of small effect size) may be relevant for neuropsychologists, evaluators, and interventionists during the

diagnostic process. Diagnosing reading disorders is a complex process that requires not only a thorough evaluation of the student's reading skills (broadly defined), but also requires an evaluation of their intellectual ability, a review of their educational history and exposure to reading intervention, and an understanding of possible family contributors. Knowledge of a history of SDP or other parental substance use may be a potential indicator of an amalgam of risks that can be used to help with identifying which struggling readers (even those as young as preschool, kindergarten, first grade) should receive early intervention services to thwart the emergence of more severe Dyslexic or other reading-related symptoms.

4.4 Limitations

The following limitations should be noted. First, although retrospective report of SDP appears to be reliable and accurate in this and other samples (Estabrook et al., 2015; Knopik et al., 2016a; Knopik et al., 2016b), these results hinge on maternal retrospective report to accurately reflect the amount of SDP exposure. Second, a lower proportion of minority families participated in the study than would be expected by the composition of the catchment area. This is particularly relevant to the study of reading skills, as children who attend less effective schools (often in higher poverty areas) are more likely to experience reading difficulties resulting from the lack of proper instruction. Children who are both exposed to SDP and receive lower quality education may be at particularly high risk for reading problems. A related point is that only 27% of mothers agreed with the birth record report of SDP and were deemed eligible for recruitment into this study. Birth records are known for accuracy issues (e.g., Salemi et al., 2017), thus we conducted additional verification of smoking behaviors during pregnancy (see Knopik et al., 2016b). Nonetheless, predicating recruitment on agreement with the birth record may have resulted in a non-representative sample or presented sample bias in SDP relative to the population.

Third, the methodological decision to assess a community sample permitted us to capture associations between SDP and the full range of reading abilities. However, we did not obtain full diagnostic information about reading and language diagnoses. Future research may prioritize recruitment of children with the most extreme presentations of reading and language problems. Fourth, these data are drawn from a larger study of the association between SDP exposure and child behavioral and neurocognitive outcomes; to reduce participant burden we did not administer the full WJ-III which prevented us from exploring all available composites. Fifth, although measured statistical confounds were carefully selected due to their hypothesized relations with reading outcomes and/or SDP, it was not possible to measure all possible variables that differ across siblings that may influence the sibling comparison. Finally, we report the findings from the mother covariate only models to capitalize on power by not restricting inclusion to only families in which fathers were involved. Future studies should aim to identify and measure relevant father-specific confounds that may play a role in child reading skills.

4.5 Conclusion

Despite these limitations, the current findings provide specificity to existing research seeking to clarify the relationship between SDP and child reading-related skills by providing rigorous tests of the associations between SDP on these outcomes. There were within-family

associations (i.e., potentially causal effects) between SDP and reading and language/comprehension factor scores, as well as SDP and reading accuracy and receptive language, but these results should be replicated. These findings add to the accumulating evidence for familial confounding of the association between SDP and many neurocognitive phenotypes, yet they also provide evidence for associations between SDP and poorer performance on some reading related outcomes that persist despite partial control for genetic and environmental confounding. SDP may be one indicator of an amalgam of risks for reading-related problems and should be assessed in diagnostic evaluation for reading related problems. Additionally, these findings indicate that future research should identify and target factors motivating smoking behavior change across pregnancies to potentially reduce poorer outcomes in SDP-exposed children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This work supported by NIH grants: R01 DA023134 (Knopik), K01 DA17671 (Knopik), K01 DA048135 (Micalizzi), K01 DA039288 (Marceau), R37 AA07728 (Heath), R01 AA09022 (Heath), P60 AA11998 (Heath), R01 HD049024 (Heath), K05 AA017688 (Heath), R01 AA021492 (Heath), R01 DA042742 (Palmer) and L30 TR001045 (Palmer).

References

Astrom RL, Wadsworth SJ, Olson RK, Willcutt EG, & DeFries JC (2011). DeFries–Fulker analysis of longitudinal reading performance data from twin pairs ascertained for reading difficulties and from their non-twin siblings. Behavior Genetics, 41(5), 660–667. doi:10.1007/s10519-011-9445-6 [PubMed: 21259040]

Bauman KE, Flewelling RL, & LaPrelle J (1991). Parental cigarette smoking and cognitive performance of children. Health Psychology, 10(4), 282–288. doi:10.1037/0278-6133.10.4.282 [PubMed: 1915215]

Brown JI, Fishco VV, & Hanna G (1993). Nelson-Denny Reading Test (Forms G and H). Chicago, IL: Riverside.

Bryant BR, Shih M, & Bryant DP (2009). The Gray Oral Reading Test—Fourth Edition (GORT-4). In Practitioner's guide to assessing intelligence and achievement, (pp. 417–447). Hoboken, NJ, US: John Wiley & Sons Inc.

Butler NR, & Goldstein H (1973). Smoking in pregnancy and subsequent child development. British Medical Journal, 4(5892), 573. doi:10.1136/bmj.4.5892.573 [PubMed: 4758516]

Byrne B, Wadsworth SJ, Boehme K, Talk AC, Coventry WL, Olson RK, … Corley R (2013). Multivariate genetic analysis of learning and early reading development. Scientific studies of reading: The official journal of the Society for the Scientific Study of Reading, 17(3), 224–242. doi:10.1080/10888438.2011.654298

Caskey WE (1985). The use of the Peabody Individual Achievement Test and the Woodcock Reading Mastery Tests in the diagnosis of a learning disability in reading: A caveat. Diagnostique, 11(1), 14–20. doi:10.1177/073724778501100103

Cho K, Frijters JC, Zhang H, Miller LL, & Gruen JR (2013). Prenatal exposure to nicotine and impaired reading performance. The Journal of Pediatrics, 162(4), 713–718.e712. Doi: 10.1016/j.jpeds.2012.09.041 [PubMed: 23122624]

Christopher ME, Hulslander J, Byrne B, Samuelsson S, Keenan JM, Pennington BF, … Olson RK (2013). Modeling the etiology of individual differences in early reading development: Evidence for

strong genetic influences. Scientific Studies of Reading, 17(5), 350–368. doi:10.1080/10888438.2012.729119 [PubMed: 24489459]

Clifford A, Lang L, & Chen R (2012). Effects of maternal cigarette smoking during pregnancy on cognitive parameters of children and young adults: A literature review. Neurotoxicology and Teratology, 34(6), 560–570. Doi: 10.1016/j.ntt.2012.09.004 [PubMed: 23022448]

D'Onofrio BM, Class QA, Lahey BB, & Larsson H (2014). Testing the developmental origins of health and disease hypothesis for psychopathology using family-based quasi-experimental designs. Child Dev Perspect, 8(3), 151–157. doi:10.1111/cdep.12078 [PubMed: 25364377]

D'Onofrio BM, Lahey BB, Turkheimer E, & Lichtenstein P (2013). Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. Am J Public Health, 103 Suppl 1, S46–55. doi:10.2105/ajph.2013.301252 [PubMed: 23927516]

D'Onofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Harden KP, Rathouz PJ, & Lahey BB (2008). Smoking during pregnancy and offspring externalizing problems: An exploration of genetic and environmental confounds. Development and Psychopathology, 20, 139–164. doi: 10.1017/S0954579408000072 [PubMed: 18211732]

Davie R, Butler NR, & Goldstein H (1972). From birth to seven: the second report of the National Child Development Study (1958 cohort). Harlow, London: Longman/National Children's Bureau.

Drake P, Driscoll AK, & Mathews TJ (2018). Cigarette smoking during pregnancy: United States, 2016.

Duncan GJ, Lee KTH, Rosales-Rueda M, & Kalil A (2018). Maternal age and child development. Demography, 55(6), 2229–2255. Doi: /10.1007/s13524-018-0730-3 [PubMed: 30387046]

Dunn L, & Dunn L (1997). Peabody Picture Vocabulary Test—Third Edition (PPVT-III). Circle Pines, MN: American Guidance Service.

Eichler EE, Flint J, Gibson G, Kong A, Leal SM, Moore JH, & Nadeau JH (2010). Missing heritability and strategies for finding the underlying causes of complex disease. Nature Reviews Genetics, 11(6), 446–450.

Eicher JD, Powers NR, Cho K, Miller LL, Mueller KL, Ring SM, … Gruen JR (2013). Associations of prenatal nicotine exposure and the dopamine related genes ANKK1 and DRD2 to verbal language. PLOS ONE, 8(5), e63762. doi:10.1371/journal.pone.0063762 [PubMed: 23691092]

Ellingson J, Goodnight J, Van Hulle C, Waldman I, & D'Onofrio B (2014). A Sibling-comparison study of smoking during pregnancy and childhood psychological traits. Behav Genet, 44(1), 25–35. doi:10.1007/s10519-013-9618-6 [PubMed: 24085497]

England LJ, Aagaard K, Bloch M, Conway K, Cosgrove K, Grana R, … & Lanphear B (2017). Developmental toxicity of nicotine: A transdisciplinary synthesis and implications for emerging tobacco products. Neuroscience & Biobehavioral Reviews, 72, 176–189. doi:10.1016/j.neubiorev.2016.11.013 [PubMed: 27890689]

Ernst M, Moolchan ET, Robinson ML (2001). Behavioral and neural consequences of prenatal exposure to nicotine. J Am Acad Child Adolesc Psychiatry, 40, 630–641. doi:10.1097/00004583-200106000-00007 [PubMed: 11392340]

Estabrook R, Massey SH, Clark CA, Burns JL, Mustanski BS, Cook EH, … Wakschlag LS (2015). Separating family-level and direct exposure effects of smoking during pregnancy on offspring externalizing symptoms: Bridging the behavior genetic and behavior teratologic divide. Behav Genet. doi:10.1007/s10519-015-9762-2

Feng J, Kramer MR, Dever BV, Dunlop AL, Williams B, & Jain L (2013). Maternal Smoking During Pregnancy and Failure of the Georgia First Grade Criterion-Referenced Competency Test. Paediatr Perinat Epidemiol, 27(3), 275–282. doi:10.1111/ppe.12044 [PubMed: 23574416]

Fergusson DM, & Lloyd M (1991). Smoking during pregnancy and its effects on child cognitive ability from the ages of 8 to 12 years. Paediatr Perinat Epidemiol, 5(2), 189–200. doi:10.1111/j.1365-3016.1991.tb00700.x [PubMed: 2052481]

Fogelman KEN (1980). Smoking in pregnancy and subsequent development of the child. Child: Care, Health and Development, 6(4), 233–249. doi:10.1111/j.1365-2214.1980.tb00154.x

Fried PA, Watkinson B, & Siegel LS (1997). Reading and language in 9- to 12-year-olds prenatally exposed to cigarettes and marijuana. Neurotoxicology and Teratology, 19(3), 171–183. doi:10.1016/S0892-0362(97)00015-9 [PubMed: 9200137]

Grigorenko EL (2001). Developmental Dyslexia: An Update on Genes, Brains, and Environments. The Journal of Child Psychology and Psychiatry and Allied Disciplines, 42(1), 91–125. doi:10.1017/S0021963001006564

Harlaar N, Deater-Deckard K, Thompson LA, DeThorne LS, & Petrill SA (2011). Associations between reading achievement and independent reading in early elementary school: A genetically informative cross-lagged study. Child Development, 82(6), 2123–2137. doi:10.1111/j.1467-8624.2011.01658.x [PubMed: 22026450]

Harlaar N, Spinath FM, Dale PS, & Plomin R (2005). Genetic influences on early word recognition abilities and disabilities: A study of 7-year-old twins. Journal of Child Psychology and Psychiatry, 46(4), 373–384. doi:10.1111/j.1469-7610.2004.00358.x [PubMed: 15819646]

Harlaar N, Trzaskowski M, Dale PS, & Plomin R (2014). Word reading fluency: Role of genome-wide single-nucleotide polymorphisms in developmental stability and correlations with print exposure. Child Development, 85(3), 1190–1205. doi:10.1111/cdev.12207 [PubMed: 24392801]

Kable JA, Coles CD, Lynch ME, & Carroll J (2009). The impact of maternal smoking on fast auditory brainstem responses. Neurotoxicology & Teratology, 31(4), 216–224. Doi: 10.1016/j.ntt.2009.02.002 [PubMed: 19224709]

Kafouri S, Leonard G, Perron M, Richer L, Séguin JR, Veillette S, … Paus T (2009). Maternal cigarette smoking during pregnancy and cognitive performance in adolescence. International Journal of Epidemiology, 38(1), 158–172. doi:10.1093/ije/dyn250 [PubMed: 19039007]

Kaiser HF (1960). The application of electronic computers to factor analysis. Educational and Psychological Measurement, 20, 141–151.

Keenan JM, Betjemann RS, Wadsworth SJ, DeFries JC, & Olson RK (2006). Genetic and environmental influences on reading and listening comprehension. Journal of Research in Reading, 29(1), 75–91. doi:10.1111/j.1467-9817.2006.00293.x

Keenan JM, & Meenan CE (2014). Test differences in diagnosing reading comprehension deficits. J of Learning Disabil., 47(2), 125–135. doi:10.1177/0022219412439326

Kendler KS (2017). Causal inference in psychiatric epidemiology. JAMA Psychiatry, 74(6), 561–562. doi:10.1001/jamapsychiatry.2017.0502 [PubMed: 28467524]

Key AP, Ferguson M, Molfese DL, Peach K, Lehman C, & Molfese VJ (2007). Smoking during pregnancy affects speech-processing ability in newborn infants. Environ Health Perspect, 115(4), 623–629. doi:10.1289/ehp.9521 [PubMed: 17450234]

Knopik VS (2009). Maternal smoking during pregnancy and child outcomes: Real or spurious effect? Developmental Neuropsychology, 34(1), 1–36. doi:10.1080/87565640802564366 [PubMed: 19142764]

Knopik VS, Heath AC, Marceau K, Palmer RH, McGeary JE, Todorov A, & Schettini Evans A (2015). Missouri Mothers and Their Children: A family study of the effects of genetics and the prenatal environment. Twin Res Hum Genet, 18(5), 485–496. doi: 10.1017/thg.2015.46 [PubMed: 26220592]

Knopik VS, Marceau K, Bidwell LC, Palmer RHC, Smith TF, Todorov A, … Heath AC (2016a). Smoking during pregnancy and ADHD risk: A genetically informed, multiple-rater approach. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 171(7), 971–981. doi:10.1002/ajmg.b.32421

Knopik VS, Marceau K, Palmer RH, Smith TF, & Heath AC (2016b). Maternal smoking during pregnancy and offspring birth weight: A genetically-informed approach comparing multiple raters. Behav Genet, 46(3), 353–364. doi:10.1007/s10519-015-9750-6 [PubMed: 26494459]

Knopik VS, Neiderhiser JM, DeFries JC, & Plomin R (2017). Behavioral Genetics (Vol. 7th Edition). New York: Worth Publishers.

Little CW, Haughbrook R, & Hart SA (2017). Cross-study differences in the etiology of reading comprehension: A meta-analytical review of twin studies. Behavior Genetics, 47(1), 52–76. doi:10.1007/s10519-016-9810-6 [PubMed: 27630039]

Ludwig KU, Schumacher J, Schulte-Körne G, König IR, Warnke A, Plume E, … Hoffmann P (2008). Investigation of the DCDC2 intron 2 deletion/compound short tandem repeat polymorphism in a large German dyslexia sample. Psychiatric Genetics, 18(6), 310–312. doi:10.1097/YPG.0b013e3283063a78 [PubMed: 19018237]

Makin J, Fried PA, & Watkinson B (1991). A comparison of active and passive smoking during pregnancy: Long term effects. Neurotoxicology and Teratology, 13, 5–12. doi:10.1016/0892-0362(91)90021-N [PubMed: 2046627]

Martin RP & Dombrowski SC (2008). Prenatal Exposures: Psychological and Educational Consequences for Children. New York: Springer Science.

Martin RP, Dombrowski SC, Mullis C, Wisenbaker J, Huttunen MO (2006). Smoking during pregnancy: Association with childhood temperament, behavior, and academic performance, Journal of Pediatric Psychology, 31(5), 490–500, doi:10.1093/jpepsy/jsj041 [PubMed: 16002482]

Mather N, & Woodcock RW (2001). Woodcock-Johnson III Tests of Achievement Examiner's Manual. Itasca, IL: Riverside Publishing Company.

McCartney JS, Fried PA, & Watkinson B (1994). Central auditory processing in school-age children prenatally exposed to cigarette smoke. Neurotoxicology and Teratology, 16(3), 269–276. doi: 10.1016/0892-0362(94)90048-5 [PubMed: 7935260]

Micalizzi L, Marceau K, Brick LA, Palmer RH, Todorov AA, Heath AC, … Knopik VS (2017). Inhibitory control in siblings discordant for exposure to maternal smoking during pregnancy. Developmental Psychology, 54(2), 199–208. doi:10.1037/dev0000423 [PubMed: 29058937]

Olson RK, Keenan JM, Byrne B, & Samuelsson S (2014). Why do children differ in their development of reading and related skills? Scientific Studies of Reading, 18(1), 38–54. doi:10.1080/10888438.2013.800521 [PubMed: 25104901]

Olson RK, Keenan JM, Byrne B, Samuelsson S, Coventry WL, Corley R, Wadsworth SJ, Willcutt EG, Defries JC, Pennington BF, & Hulslander J (2011). Genetic and environmental influences on vocabulary and reading development. Scientific studies of reading: The official journal of the Society for the Scientific Study of Reading, 15(1), 26–46. 10.1007/s11145-006-9018-x

Pennington BF, & Olson RK (2008). Genetics of Dyslexia. In Snowling MJ and Hulme C. (Eds), The Science of Reading: A Handbook, doi:10.1002/9780470757642.ch24

Peterson RL, & Pennington BF (2015). Developmental Dyslexia. Annual Review of Clinical Psychology, 11(1), 283–307. doi:10.1146/annurev-clinpsy-032814-112842

Petrill SA, Deater-Deckard K, Thompson LA, De Thorne LS, & Schatschneider C (2006). Reading Skills in Early Readers: Genetic and Shared Environmental Influences. Journal of Learning Disabilities, 39(1), 48–55. Doi: 10.1177/00222194060390010501 [PubMed: 16512082]

Rescorla L (2005). Age 13 language and reading outcomes in late-talking toddlers. Journal of Speech, Language, and Hearing Research, 48(2), 459–471.

Ruisch IH, Dietrich A, Glennon JC, Buitelaar JK, Hoekstra PJ (2018). Maternal substance use during pregnancy and offspring conduct problems: A meta-analysis. Neurosci Biobehav Rev, 84, 325–36. [PubMed: 28847489]

Salemi JL, Tanner JP, Sampat DP, Rutkowski RE, Anjohrin SB, Marshall J, & Kirby RS (2017). Evaluation of the Sensitivity and Accuracy of Birth Defects Indicators on the 2003 Revision of the U.S. Birth Certificate: Has Data Quality Improved? Paediatric and Perinatal Epidemiology, 31(1), 67–75. 10.1111/ppe.12326 [PubMed: 27859434]

Semel E, Wiig EH, & Secord WA (1995). Clinical evaluation of language fundamentals: Third edition examiner's manual. San Antonio, TX: The Psychological Corporation.

Slikker W Jr., Xu ZA, Levin ED, & Slotkin TA (2005). Mode of action: Disruption of brain cell replication, second messenger, and neurotransmitter systems during development leading to cognitive dysfunction–Developmental toxicity of nicotine. Crit Rev of Toxicology, 35, 703–711. doi:10.1146/annurev.psych.60.110707.163548

Taylor J, Roehrig AD, Soden Hensler B, Connor CM, & Schatschneider C (2010). Teacher quality moderates the genetic effects on early reading. Science, 328(5977), 512–514. doi: 10.1126/science.1186149 [PubMed: 20413504]

Tellegen A, & Briggs PF (1967). Old wine in new skins: Grouping Wechsler subtests into new scales. Journal of Consulting and Clinical Psychology, 31, 499–506.

Todd RD, Joyner CA, Heath AC, Neuman RJ, & Reich W (2003). Reliability and Stability of a Semi structured DSM-IV Interview Designed for Family Studies. Journal of the American Academy of Child & Adolescent Psychiatry, 42(12), 1460–1468. doi:10.1097/00004583-200312000-00013 [PubMed: 14627881]

Toro R, Leonard G, Lerner JV, Lerner RM, Perron M, Pike GB, … & Paus T (2008). Prenatal exposure to maternal cigarette smoking and the adolescent cerebral cortex. Neuropsychopharmacology, 33(5), 1019–1027. [PubMed: 17609681]

Wechsler D (1997). Wechsler Adult Intelligence Scale (3rd ed.), San Antonio, TX: The Psychological Corporation.

Wechsler D (2003). Wechsler Intelligence Scale for Children (4th ed.), San Antonio, TX: The Psychological Corporation.

Wechsler D, Kaplan E, Fein D, Kramer J, Morris R, Delis D, … Maerlender A (2004). Wechsler Intelligence Scale for Children (4th ed.), Integrated. San Antonio, TX: Harcourt Assessment.

Woodcock RW, McGrew KS, & Mather N (2001). Woodcock Johnson (3rd ed.), (WJ III). Rolling Meadows, IL: Riverside Publishing Company.

Young AI (2019) Solving the missing heritability problem. PLoS Genet 15(6): e1008222. Doi: 10.1371/journal.pgen.1008222 [PubMed: 31233496]

Highlights

- Smoking during pregnancy (SDP) was associated with some, but not all aspects of reading.
- There is familial confounding of the association between SDP and some aspects of reading.
- SDP may be one indicator of an amalgam of risks for reading-related problems.
- SDP should be assessed in diagnostic evaluation for reading-related problems.

Table 1.

Sample Characteristics

	N	Mean	SD	*N*	Mean	SD
Study Variables		**SDP+**[1]			**SDP−**	
SDP severity	150	4.85	1.60	150	1.20	0.57
Reading						
Word-letter identification	144	101.01	11.75	146	104.11	11.42
Phonetic/decoding skills	144	100.84	10.90	146	104.25	10.05
Spelling	144	103.62	14.54	145	104.50	13.54
Accuracy	143	8.78	3.11	144	9.19	3.23
Comprehension	143	10.04	2.66	144	10.94	3.24
Rate	143	9.84	3.11	144	10.17	2.99
Language						
Receptive vocabulary	144	106.34	13.06	147	106.88	12.79
Receptive language	144	10.30	2.54	146	10.92	2.59
Child-specific covariates		SDP+			SDP−	
Maternal age at birth	143	27.34	5.38	143	29.12	5.89
Maternal education (in years) at birth	143	13.39	2.15	143	13.64	1.94
Second-hand smoke exposure by fathers	145	1.81	1.44	144	1.11	1.42
Family-level covariates		**Mother**			**Father**[2]	
Reading						
Word letter identification	167	102.78	7.89	96	101.25	9.73
Phonetic/decoding	167	102.02	8.76	96	100.94	10.73
Spelling	167	106.62	8.10	96	101.41	11.12
Reading rate	167	199.28	17.51	96	192.27	23.62
Comprehension	167	213.87	23.04	96	199.33	27.56
Language						
WAIS Vocabulary	167	10.74	2.68	96	9.81	3.08

[1]Means for study variables and child-specific covariates are presented for families in which the magnitude of smoke exposure differed across pregnancies. SDP+ refers to children that had (more) SDP exposure, while SDP− refers to children that had (less) SDP exposure. Data from 19 families that had equivalent SDP exposure were excluded from the SDP+ and SDP− calculations.

[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 reported in supplemental tables and summarized in the main text.

Table 2.

Summary of effects from *sibling-comparison* models

Outcome	Zero-order		Covariate Adjusted	
	Within-family β (SE)	Between-family β (SE)	Within-family β (SE)	Between-family β (SE)
Factor Scores				
Reading	**−.05 * (.02)**	−.09 (.06)	**−.06 * (.03)**	−.04 (.05)
Language/Comprehension	**−.06 ** (.02)**	−.02 (.06)	**−.06 ** (.02)**	−.02 (.04)
Component Skills				
Reading				
Word letter identification	**−0.74 ** (.27)**	−0.93 (.72)	−0.49 (.34)	−0.71 (.62)
Phonetic/decoding	**−0.90 *** (.26)**	−1.23 (.62)	−0.64 (.35)	−1.09 * (.55)
Spelling	−0.29 (.30)	−1.25 (.92)	−0.52 (.36)	−0.59 (.81)
Accuracy	−0.11 (.08)	−0.31 (.19)	**−0.24 * (.10)**	−0.14 (.18)
Comprehension	**−0.21 * (.08)**	<0.001 (.17)	−0.11 (.10)	0.03 (.16)
Rate	−0.09 (.07)	−0.19 (.19)	−0.08 (.09)	−0.06 (.17)
Language				
Receptive vocabulary	−0.29 (.30)	0.77 (.83)	−0.42 (.33)	0.43 (.55)
Receptive language	**−0.17 ** (.06)**	−0.12 (.17)	**−0.16 * (.07)**	−0.10 (.12)

Note.

*** $p<.001$

** $p<.01$

* $p<.05$

Bolded estimates are significant within-family parameters, indicating potentially casual associations between SDP and each of these outcomes.

Covariates included in the covariate adjusted models were maternal age, education, marital status, SES, birth order, child sex, secondhand smoke exposure by fathers, maternal and child IQ.

Individual models controlled for the parallel mother variable (e.g., we controlled for mother spelling when child spelling was the focal outcome).

See Supplemental Tables for full model results including covariate estimates.