Immediate and Long-Term Effects of Maternal Smoking During Pregnancy on Newborn Functioning and Inhibitory Control

By

Rebecca Elise Gordon

B.A., University of California, Santa Cruz, 2014

Thesis

Submitted in partial fulfillment of the requirements for
Degree of Master of Science in the Department of Behavioral and Social Health Sciences

PROVIDENCE, RHODE ISLAND

MAY 2019

Signature Page

This thesis by Rebecca Elise Gordon is accepted in its present form by the Department of Behavioral and Social Sciences as satisfying the thesis requirements for the degree of Master of Science

Date: 5/7/19

Christopher Kahler, PhD, Advisor

Date: 5/7/19

Lauren Micalizzi, PhD, Co-Advisor & Reader

Approved by the Graduate Council

Date: _____

Andrew Campbell, PhD, Dean of the Graduate School

Curriculum Vitae

Rebecca Elise Gordon
Personal website: rebeccaefgordon.com
https://orcid.org/0000-0003-2296-4794

EDUCATION

March 2014 — Bachelor of Arts in Psychology
University of California, Santa Cruz

RESEARCH EXPERIENCE

2016 September – Present — Field: Alcohol and Addiction Studies
Principal Investigator: Christopher Kahler
"Positive Psychotherapy for Smoking Cessation Enhanced with Text Messaging: A Randomized Controlled Trial" NIH R01
Brown University School of Public Health, Providence, RI

2016 September – 2017 May — Field: HIV and Non-Communicable Disease Comorbidity
Principal Investigator: Patricia Cioe
"Cardiovascular Risk Perception and Wellness Perspectives in HIV-infected Adults" NIH K23
Brown University School of Public Health, Providence, RI

2016 June – December — Field: Alcohol and Addiction Studies
Principal Investigator: Molly Magill
"Technical, Relational, & Conditional Process Models of MI Efficacy: Meta-Analysis" NIAAA R21
Brown University School of Public Health, Providence, RI

2014 April – July — Field: Clinical Pediatric Psychiatry
Principal Investigator: Gemma Ochando Perales
Analysis of comorbidity between international adoption and ADHD in children and adolescents between the ages of 18 months and 18 years. Polytechnic and University Hospital La Fe, Valencia, Spain

2013 September – 2014 March — Field: Cognitive/Developmental Psychology
Principal Investigator: Maureen Callanan
Video and audio recorded data to study learning behaviors of children between the ages 3 and 14 and the mechanisms by which scientific knowledge is retained. University of California, Santa Cruz

AWARDS & ACCOLADES

2018 July — Conference Travel Award 2018 ($650)
Brown University Graduate School

2017 May	Merit-based Behavioral and Social Sciences Intervention Scholarship, Brown University
2014 November	Scholarship PAC "Programa Auxiliars de Conversa" Fundació Escola Cristiana de Catalunya, Barcelona, Spain
2014 April	'Estancia Por Estudios, Investigación De Extranjeros' Spanish Foreign Citizens' Specialized Training Program Scholarship University and Polytechnic La Fe Hospital, Valencia, Spain

PUBLICATIONS

4. Cioe, P. A., **Gordon, R. E.**, Williams, D. M., & Kahler, C. W. (2019). The effect of increased physical activity on symptom burden in older persons living with HIV. *AIDS care*, 1-7. https://doi.org/10.1080/09540121.2019.1601675

3. Kahler, C. W., Surace, A., **Gordon, R. E.**, Cioe, P. A., Spillane, N. S., Parks, A., ... & Brown, R. A. (2018). Positive psychotherapy for smoking cessation enhanced with text messaging: Protocol for a randomized controlled trial. *Contemporary clinical trials*, *71*, 146-153. https://doi.org/10.1016/j.cct.2018.06.013

2. Cioe, P. A., **Gordon, R. E.**, Guthrie, K. M., Freiberg, M. S., & Kahler, C. W. (2018). Perceived barriers to smoking cessation and perceptions of electronic cigarettes among persons living with HIV. *AIDS care*, *30*(11), 1469-1475. https://doi.org/10.1080/09540121.2018.1489103

1. Magill, M., Apodaca, T. R., Borsari, B., Gaume, J., Hoadley, A., **Gordon, R.**, … Moyers, T. (2017). A meta-analysis of motivational interviewing process: Technical, relational, and conditional process models of change. *Journal of consulting and clinical psychology*, *86*(2), 140–157. http://dx.doi.org/10.1037/ccp0000250

TRAINING SEMINARS COMPLETED

2018 November	"Student Leadership Institute 2018," Association of Schools and Programs of Public Health at APHA, San Diego, CA.
2018 Fall	"Teaching Certificate I in Critical Reflection and Inclusive Classrooms, Rhetorical Practice and Classroom, Communication, Learning Design, Engaged Learning." Hosted by the Harriet W. Sheridan Center for Teaching and Learning. Brown University, Providence, RI.
2018 June	PHP 101: Introduction to Public Health An Online Course Offered By The School Of Public Health At Brown University.
2017 July	"Social and Behavioral Research Best Practices for Clinical Research" Collaborative Institutional Training Initiative (CITI Program). Center for Alcohol and Addiction Studies. Brown University School of Public Health, Providence, RI.

Acknowledgements

I would like to express my sincere appreciation and gratitude for my thesis advisor, PI, professor, and mentor, Christopher Kahler, for his thoughtful and encouraging feedback at each step of this process. I would like to thank my co-advisor and reader, Lauren Micalizzi, for her comprehensive and supportive guidance, and providing me with the data and expert knowledge in a field I was passionate to learn more about. This work would not be possible without their patience and kind constructive feedback throughout conceptualizing, drafting, and many revisions. Thank you to Alejandro Damián Serrano for offering me reassurance and encouragement in the times when I needed it the most. I would also like to acknowledge my colleagues who concomitantly excel at their coursework and work full-time as research assistants: Erik Simpanen, Brianna Parlette, and Ariel Hoadley, who initially encouraged me to apply to the Master's program. Additionally, I would like to thank my family and friends: Ellen Gordon, Kris Kahn, Rachael Gordon, Juan Gramajo, Joaquin Nunez, Dylan Gaddes, Stephen Rong, and Augustine Kang for their continuous motivation and support.

Table of Contents

List of Figures

List of Tables

Abstract of Immediate and Long-Term Effects of Maternal Smoking During Pregnancy on Newborn Functioning and Inhibitory Control, by Rebecca Elise Gordon, ScM, Brown University, May 2019

Maternal smoking during pregnancy (MSDP) is associated with adverse outcomes in children including low birth weight, deficits in neurodevelopment, poorer academic achievement, and a spectrum of behavioral problems. Increased exposure to MSDP is linked to greater deficits in cognitive functioning in adolescence and decreased newborn physical health. Children exposed to MSDP also exhibit less efficient executive function (EF) abilities than non-exposed children, including inhibitory control (IC) problems. This study investigated the potential causal effects of MSDP on immediate newborn functioning, as well as on IC in adolescence. We applied a sibling comparison framework to evaluate within- and between-family effects of MSDP on: immediate (i.e., 5-minute APGAR scores) and long-term (i.e., IC) outcomes in siblings who were exposed to different levels of MSDP (N=173 families). We fit 5 hierarchical linear models to examine the effects of MSDP on each outcome. MSDP did not significantly predict newborn functioning or IC in adolescence. Further research is needed to examine the effects of MSDP on predictors of IC problems earlier in development to isolate potential targets for intervention. Further, more research is needed to explore the effects MSDP on different aspects of EF.

Keywords: Maternal smoking during pregnancy, inhibitory control, executive function

Immediate and Long-Term Effects of Maternal Smoking During Pregnancy on Newborn Functioning and Inhibitory Control

Maternal smoking during pregnancy (MSDP) is a prevalent environmental risk to the developing fetus and has been linked with poor immediate and long-term health outcomes across developmental stages (Gilman, Gardener, & Buka, 2008; Hebel, Fox, & Sexton, 1988; Knopik, Marceau, Bidwell, et al., 2016; Knopik, Marceau, Palmer, et al., 2016). The National Vital Statistics System-Natality (NVSS-N), the Centers for Disease Control and Prevention, Pregnancy Risk Assessment Monitoring System (PRAMS), and the National Center for Health Statistics (CDC/NCHS) report that 11.4% of pregnant women in the United States smoke during a portion of their pregnancy, and among those mothers, 8.8% of pregnant women continue to smoke throughout the last 3 months of pregnancy (PRAMS). Although national smoking rates have decreased, MSDP has continued to be pervasive and disproportionately affects younger minority women with low socioeconomic status (Curtin & Matthews, 2016).

MSDP is associated with adverse physical and neurocognitive outcomes both immediately after birth, as well as later in development. For example, MSDP is associated with premature birth status, low birthweight, and even neonatal mortality (Cnattingius, 2004; Knopik, Marceau, Palmer, et al., 2016). MSDP is also associated with immediate neurological deficits in infants and delays in cognitive functioning during and beyond childhood (Massey et al., 2015; Micalizzi & Knopik, 2018). Although there is evidence that MSDP is associated with deficits in cognitive abilities, recent systematic reviews found that the effect of MSDP on cognitive functioning and executive function (EF) in offspring is often partly or fully attenuated by control for maternal factors such as education,

socioeconomic status (SES), and psychosocial measures (Clifford, Lang, & Chen, 2012; Micalizzi & Knopik, 2018). The most influential aspects were environmental factors such as maternal IQ and education. Therefore, MSDP is unlikely to be the sole cause for cognitive and EF deficits in offspring, rather, a combination of genetic and environmental factors is more likely (Knopik, 2009).

Inhibitory Control

EF involves a set of higher-level cognitive skills that control and coordinate cognitive abilities and behaviors. Inhibitory control (IC, a component of EF, Miyake et al., 2000) involves the suppression of automatic responses to stimuli in order to focus attention on a relevant task or stimuli (Rothbart & Posner, 1985). Deficits in IC have been linked to low academic achievement, crime, externalizing behavioral problems (Gagne et al., 2018), ADHD, OCD, anxiety, mood disorders, and later addictive behaviors (Micalizzi et al., 2018). Low IC is often a marker of an underlying cognitive impairment and is frequently comorbid with other EF deficits. EF abilities vary across developmental stages and stabilize during adolescence (Anderson, 2002). Therefore, early adolescence is a distinctive period to evaluate individual differences in cognitive capabilities and potential sources of individual differences (e.g., MSDP).

The components of EF are highly heritable and individual capabilities vary due to a unique combination of environmental and genetic factors (Miyake et al., 2000; Friedman et al., 2008). Therefore, studies examining EF in MSDP-exposed children are often confounded because mothers who smoke during pregnancy may also pass genetic risk for poorer EF to their offspring. Individual differences in cognitive abilities are, in part, genetically influenced. However, genetic predisposition for cognitive deficits is

confounded by environmental exposures throughout development (Anokhin, Golosheykin, Grant, & Heath, 2017). In other words, cognitive abilities are likely not predetermined by heritability and are likely impacted by the prenatal environment.

Newborn Functioning –Apgar

Prenatal environmental effects on newborn health can be detected immediately after delivery by assessing newborn physiological functioning. A common marker of newborn functioning immediately after delivery is the Apgar score. The Apgar score is the most commonly used method to assess the newborn functioning, which involves ratings of five physiological signs: heart rate, respiration, muscle tone, irritability and color (American Academy of Pediatrics Committee on Fetus and Newborn & American College of Obstetricians and Gynecologists Committee on Obstetric Practice, 2015). It remains unclear if markers of newborn functioning are useful predictors of downstream cognitive problems. For example, some studies have associated low scores with poor adolescent educational achievement, neurodevelopmental disability in adulthood, and low intelligence quotients (IQ) (Ehrenstein et al., 2009; Odd et al., 2008). However, other studies have found that Apgar is not a significant predictor of individual neurological outcomes (Leinonen et al., 2018). These studies found that low Apgar scores can be a risk marker but are not a proxy for predicting neurodevelopmental outcomes. However, when low Apgar scores are detected, early intervention may prevent potential long-term cognitive outcomes for children (Tweed et al., 2016). Evidence suggests that there is a dose-response relationship between MSDP severity and depressed Apgar scores in infants of mothers who smoke more than 20 cigarettes per day (Garn, Johnston, Ridella, & Petzold, 1981; Kallen, 2001; Thorngren-Jerneck & Herbst, 2001). Predictors of developmental delays such as

birth weight can be assessed immediately after delivery and may mediate the effects of MSDP on further adverse outcomes (Knopik, Marceau, Palmer, et al., 2016). However, no existing research has investigated if Apgar scores mediate the effects of MSDP on EF. Understanding the emergence of EF deficits is a significant step toward identifying early markers for developmental problems and revealing their relationship with MSDP.

The current study seeks to examine the relationships between MSDP, immediate newborn functioning, and IC in adolescence (see Figure 1), with the goal of identifying if newborn health is a marker of long-term IC problems in MSDP-exposed youth. Data was drawn from the Missouri Mothers and Their Children study (Mo-MATCH; Knopik et al., 2015), a sibling comparison study of the effects of MSDP on youth outcomes. Methods that compare siblings differentially exposed to MSDP are robust at describing potentially causal effects of MSDP on offspring outcomes because they control for genetic confounding factors (i.e., children of mothers who smoke during pregnancy may inherit similar genetic risk for poorer IC) (Lahey & D'Onofrio, 2010). Sibling comparison designs control for maternal and familial confounding factors, such as SES characteristics associated with increased likelihood of MSDP (Knopik, 2009; Knopik et al., 2015).

In one previous study using the Mo-MATCH data, researchers examined the association between MSDP and adolescent IC as assessed with the inhibition condition of the Color-Word Interference Test on the Delis-Kaplin Executive Function System (Delis, Kaplan & Kramer, 2001a, 2001b) (Micalizzi et al., 2018). In this study, researchers implemented a sibling-comparison approach to control for genetic and environmental influences shared by siblings to examine the unique effect of MSDP exposure on adolescent IC. Their results indicated that when child and familial confounders were

considered, the association between MSDP and IC was not significant (Micalizzi et al., 2018).

The present study aimed to build upon this research in three ways. First, by evaluating the immediate effects of MSDP on newborn functioning (as measured with the Apgar score). Second, by evaluating the effects of MSDP on a different measure of IC (i.e., the Logan Stop Task, described below), to determine if the findings in Micalizzi et al. (2018) were replicated. Finally, if MSDP was linked to both newborn functioning and IC, we would conduct mediational analyses to determine if newborn functioning is a potential mechanism of the effects of MSDP on IC deficits.

Methods

Participants and Procedure

Data were obtained from Mo-MATCH (Knopik et al., 2015), a sibling-comparison study of children of mothers who changed her smoking behavior between pregnancies. The goal of Mo-MATCH was to investigate prenatal environmental influences on child attention problems, neuropsychological functioning, and substance use initiation. Eligible families were identified based on self-reported smoking habits in birth records (obtained from the Missouri Department of Health and Senior Services Bureau of Health Informatics). Over 4000 mothers were initially identified as changing smoking behaviors between two pregnancies during the years 1998–2005 and screening interviews were conducted with 1520 of these mothers in 2009. Of those screened, 27% confirmed birth record reports of their smoking during pregnancy and were invited to participate in the study. Families were excluded if: (a) mothers were unable to understand any part of informed consent; (b) English was not the primary language spoken in the home; (c)

children had a history of head trauma, neurological disorders, uncorrected visual or auditory impairments; or (d) mothers reported using nicotine replacement therapy during the pregnancy without any smoking exposure. Following consent, formal diagnostic interviews were completed with 173 families (334 pregnancies). Interviews were conducted when children were 7-16 years old (Child 1 (firstborn) Age: Mean=13.0 years, SD=1.9, 54.2% male; Child 2 (second born) Age: Mean = 10.2 years, SD=1.8, 51.5% male) (see Table 1).

Measures

Covariates. Potential confounders of the associations among MSDP, newborn functioning, and IC were determined *a priori* in accordance with previous sibling comparison studies of MSDP and child outcomes (D'Onofrio et al., 2012; Knopik, Marceau, Bidwell, et al., 2016; Micalizzi et al., 2018). These variables included: maternal age, marital status, education at the time of each child birth, qualification for food stamps at the time of each child birth, child birth order, sex, child IQ, and secondhand smoke exposure.

MSDP. Retrospective maternal report of MSDP was collected using a modified version of the Missouri Assessment of Genetics Interview for Children—Parent on Child (Todd et al., 2003). A categorical variable was created for MSDP exposure severity including number of cigarettes smoked per day and duration of smoking (i.e., during or beyond the first trimester). Severity of MSDP was calculated from maternal self-reported data for each child (Knopik, Marceau, Bidwell, et al., 2016):

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); and

7: smoked beyond first trimester, 20+ cigarettes per day (max of all trimesters).

IC. IC was assessed with the Logan stop-signal task (Logan & Cowan, 1984; Logan, Cowan, & Davis, 1984). The Logan stop-signal task requires the participant to react to a stimulus by either withholding their response (i.e., stop-signal) or actively responding (i.e., go-signal). Implemented in E-Prime (Verbruggen, Logan, & Stevens, 2008), performance was determined by go-signal obedience. The response is considered inhibited if the go-signal was not obeyed, and not inhibited if the go-signal was obeyed (Matzke, Love, & Heathcote, 2017). IC is measured by calculating the delay time between introduction of stimuli and reaction time (Logan & Cowan, 1984; Logan et al., 1984). The reaction time was measured in millisecond ranges of performance (0 to 150 milliseconds, 150 to 300 milliseconds, 300 to 450 milliseconds, > 450 milliseconds). Poor task performance (e.g., <300 milliseconds) indicates slower cognitive processes characterized by decreased accuracy and impulsive responding (Dimoska et al., 2003). In prior studies, the Logan stop-signal model has been implemented and combined with electroencephalogram (EEG) neuroimaging to demonstrate an association between delay period length, ADHD, and neurocognitive deficits (Dimoska, Johnstone, Barry, & Clarke, 2003; Swingler et al., 2018).

Newborn Functioning. Immediate newborn functioning was assessed with the Apgar score. Values range from 0-10, reflecting heart rate, respiration, reflex irritability, muscle tone, and color. The composite score is the sum of five scores, each ranging from 0 (e.g., for heart rate: absent heart rate) to 2 (e.g., >100 beats per minute heart rate) at 5-minutes post-delivery. A composite score below 3 can be an indicator of the need for resuscitation, a score of 4 to 6 is moderately abnormal, and 7 to 10 is normal.

Statistical Analyses

First, we ran correlational analyses for each individual child across all demographic variables separately by birth order (i.e., within firstborn children vs. within secondborn children) to determine if there are associations among birth order and the covariates assessed herein. Then, we used a sibling-comparison approach to examine the within-family (i.e., child-specific exposure) and between-family (i.e., overall family average exposure) effects of MSDP on newborn functioning and adolescent IC, see Knopik et al. (2016). Analyses were implemented by fitting a series of hierarchical linear models (HLM) using SAS PROC MIXED (Version 9.4; SAS Institute, 2014) to account for the non-independence of the data. This modeling approach involves fitting a series of five HLM (see Models 0-4 below).

a. **Model 0.** A null unconditional (intercept-only) model was fit to each outcome for comparison against the subsequent, more complex models (i.e., Models 1-4). This model was used as a baseline model to calculate and within-family and family-level variation, as well as to determine how much additional within-family (and potentially causal) variance each conditional model explained beyond the unconditional model.

b. **Models 1 and 2** were standard models which include an MSDP severity score that compares children whose mothers smoked [or smoked more] during pregnancy vs. those whose mothers did not smoke [or smoked less] as a predictor of newborn functioning and IC (independently). By examining the associations within the entire sample without capitalizing on the sibling-comparison aspect of the study (described below), the standard models are representative of how studies with non-sibling samples are modeled. Model 1 includes no covariates and Model 2 includes covariates (see Measures) to control for potential confounds.

c. **Models 3 and 4.** In order to evaluate within-family and family average effects of MSDP on newborn functioning and IC (and allow for a direct test of unique effects of MSDP on outcomes while controlling for genetic and environmental confounds; Ellingson et al., 2014), two sibling-comparison models were fit. Models 3 and 4 included two variables to capture MSDP severity: (1) a child-specific MSDP severity score relative to family average is calculated by subtracting the family average from the individual child score. That is, a child with no exposure would have a negative score and an exposed child would have a positive score; and (2) a between-family MSDP-severity score which pools within-family variation by averaging the MSDP exposure severity scores across siblings (i.e., reflects overall family average exposure). For example, the effect of the child-specific SDP severity relative to family average on IC assessed the potentially causal within-family effect of SDP on IC (comparing across siblings within a family, a test of any unique effect of SDP on child specific outcomes

beyond familial and genetic factors that siblings share). Model 3 examined the within-family and family average effects of MSDP on newborn functioning and IC in absence of covariates. Model 4 included covariates.

Results

Results from Preliminary Analyses

Results from the correlational analyses showed that birth order had a strong negative correlation with MSDP (r = -.45, p < .001), such that MSDP was nearly twice as high among firstborn than secondborn children ($t(329)$ = 1.93, p < .001) Therefore, to examine differences between MSDP and other demographic variables for the firstborn and secondborn child, we ran correlational analyses evaluating associations between all demographic variables separately for firstborn and secondborn children. Results from the correlation analyses revealed that MSDP was not significantly associated with Apgar scores or IC. The correlations among MSDP and some demographic variables were significantly different depending on birth order (see Table 2). For the firstborn child, MSDP was only significantly, positively correlated with mother's age (r = .23, p < .01), such that younger mothers of firstborn children smoked more during pregnancy than older mothers. For the secondborn child, MSDP was positively associated with food stamps (r = .17, p < .05) and secondhand smoke exposure (r = .36, p < .01), such that mothers with higher MSDP were qualified for food stamps and had higher secondhand smoke exposure. MSDP was negatively correlated with mother's education (r = -.21, p < .01) and IQ (r = -.20, p < .05), as such, mothers who smoked more had less education and their offspring had lower IQ. We found that the correlation between MSDP severity scores and mother's age was significantly different between firstborn (r = .23, p < .01) and secondborn (r = -

14., $p = .08$) children based on Fisher's z-test ($p < 0.0001$). Apgar was significantly positively correlated with IQ for both firstborn ($r = .16$, $p < .05$) and secondborn children ($r = .18$, $p < .05$), such that children with higher Apgar scores had higher IQ.

Hierarchical Linear Models

Effect of MSDP on infant functioning at 5-minutes post-delivery. In the standard models, (i.e., Models 1 and 2) higher severity of MSDP was not significantly associated with lower newborn functioning (see Table 3). In the sibling-comparison models (i.e., Models 3 and 4), neither the within-family or family average effect of MSDP were significant predictors of newborn functioning. However, between-family IQ was a significant predictor of newborn functioning when included as a covariate in the sibling-comparison Model 4, suggesting that, on average, families with higher IQ scores predicted high Apgar scores.

In order to examine how much of the total within-family variance each conditional model (i.e., Models 1-4) explained above and beyond the unconditional model (i.e., Model 0), we calculated the percentage of within-family variance (*unconditional* individual child-level variance–*conditional* [e.g., standard model with covariates] individual child-level variance)/*unconditional* individual child-level variance; Singer, 1998). In the standard model *without* covariates (i.e., Model 1), MSDP alone explained 7.14% of the variance for newborn functioning. When covariates were included, the standard model explained 8.13% of the variance, and IQ was a significant predictor of newborn functioning (i.e., Model 2). In the sibling-comparison model *without* covariates (i.e., Model 3), the two measures of MSDP (i.e., within-family and family average) together explained 4.26% of the variance. When covariates were included, the sibling-comparison model (i.e., Model 4) explained an

additional 10.77% of the total within-family variance beyond the unconditional model in newborn functioning.

Effect of MSDP on adolescent IC. In the standard models, (i.e., Models 1 and 2) higher severity of MSDP was not significantly associated with lower IC (see Table 4). In the standard model *with* covariates, there were no significant predictors of IC (i.e., Model 2). In the sibling-comparison models (i.e., Models 3 and 4), neither child-specific nor the family average MSDP was a significant predictor of IC. In the standard model *without* covariates, MSDP alone explained 3.62% of the variance for IC. In the sibling-comparison model *without* covariates, the MSDP effects explained 4.98% of the variance (see Table 4). The sibling-comparison model *with* covariates explained an additional 24.32% of the total within-family variation in IC. In this final model, birth order and child-specific mother's age were significant predictors of IC, suggesting that being born first, and a mother's youth may be protective factors against IC problems (see Figure 2).

Mediational Analyses. Because the HLM results revealed that there were no direct effects of MSDP on either newborn functioning or IC, mediational analyses were not conducted.

Discussion

In this manuscript, we report results from a study that assessed the association between effects of MSDP on both immediate (newborn functioning) and long-term (IC) outcomes in adolescence while controlling for potential genetic and environmental confounds. Results from the sibling-comparison modeling approach revealed that MSDP was not associated with either outcome. However, results from the correlational analyses shed additional light on the association between MSDP and child outcomes.

Overall, the correlation analyses between revealed that the firstborn child had higher rates of exposure to MSDP than the secondborn child and that younger mothers were more likely to smoke during pregnancy. These results highlight the importance of examining environmental factors such as mother's age and birth order which may increase the risk of poor outcomes. In the correlational analyses within first and secondborn children separately, IQ was negatively associated with MSDP (secondborn only), but IQ was positively correlated with Apgar, suggesting Apgar may, in fact, be associated with later IQ. Moreover, when the relationship between MSDP and newborn functioning (including child- and family- level covariates) was assessed (i.e., Model 4), the association between MSDP and IQ remained significant. This finding is consistent with literature which suggest that there is a dose response relationship between MSDP and cognitive abilities, such as IQ. Many studies have shown evidence of this association despite extensive adjustment for environmental factors and a range of other possible confounders (Clifford, Lang, & Chen, 2012).

To determine the specificity of effects from MSDP on IC, we examined the effects of MSDP using the stop-signal measure of IC. The goal of this was to determine if the null findings of MSDP on IC (as assessed with the inhibition condition of the Color-Word Interference Test) in Micalizzi et al. (2018) would be replicated, or if we would see a contrasting pattern with a different measure of IC. The authors of the prior study found that the initial MSDP-IC association was fully attenuated after controlling for confounding factors, and that co-occurring vulnerabilities were more likely significant predictors of poor IC than MSDP. In contrast with the present study, researchers in the prior study assessed adolescent IC using the Color-Word Interference Test, which measures selective attention

(Delis et al., 2001). The task requires inhibition of an automatic response (i.e., reading) to generate a conflicting response (i.e., naming the dissonant ink color). While both Stroop and Logan stop signal tasks measure inhibition through the ability to control a prepotent response to stimuli, evidence suggests that the two tasks vary and may be measuring different underlying constructs (Khng & Lee, 2014). This became evident when Khng & Lee (2014) found that performance on one inhibitory task does not predict performance on the other. However, when comparing the results of the present study and Micalizzi et al. (2018), results indicate that the Stroop task and Logan stop signal produced similar findings in this sample. That is, that direct adverse effects of MSDP were not observed on either measure of IC. Taken together, the findings across both studies indicate that IC deficits are more likely determined by environmental risk factors than MSDP.

The majority of studies that assess the stop signal reaction time (SSRT) calculate the difference in time between introduction of stimuli and reaction delay. While this model has been shown to be an effective means of estimating IC, the best method for calculating the deficit has been debated. In the present study, SSRT was calculated using the mean method (i.e., subtracting the mean of the stop signal delay from the mean reaction time). Other studies have used a different approach, such as the integration method, to estimate IC by subtracting the stop signal delay from the finishing time of the stop process (Verbruggen & Logan, 2009). Therefore, there may be inconsistent results when assessing SSRT using an alternate method.

A prior study which used the same sample utilized here found a significant effect of MSDP on low birth weight (Knopik et al., 2016). As such, we expected MSDP to have an effect on newborn functioning, a related newborn measure (Thorngren-Jerneck &

Herbst, 2001). However, we found no evidence for an effect of MSDP on newborn functioning as assessed with Apgar. The lack of effect from MSDP severity on Apgar contradicts studies where genetic confounders were uncontrolled and indicates that controlling for shared genetic factors attenuates the relationship (Kalen, 2001). Notwithstanding, results from the correlational analyses presented here suggest that the Apgar scale may be a useful risk marker for newborn physiological functioning and IQ in adolescence.

Limitations of the current study should be considered. First, retrospective smoking reports by mothers may not accurately represent MSDP severity due to recall bias. Inaccurate reporting may negatively bias the results, leading to apparent non-significant effects. Although there is evidence that retrospective report of smoking corresponds with other reporting methods (Knopik et al., 2016), the gold standard method for obtaining prenatal exposure is short-term retrospective reports using timeline follow back confirmed with a bio-marker (i.e., cotinine). However, this data was not available in Mo-MATCH. Future research may consider evaluating this question using prospective reports and biological data to corroborate the findings reported here. Second, there were missing values in the stop-signal task data, and thus it may not accurately capture the whole sample (for example, some families had a score for one child and not the other sibling). This reduced the sample sizes for the sibling-comparison analyses. Another limitation is that the Apgar can be inconsistently reported by medical staff and we are unable to validate the scores.

Our results show that IC is associated with environmental risk factors, such as mother's age and birth order (controlling for child age). This finding contributes to a substantial body of literature reflecting the importance of mother's age to EF, as has been

observed for other outcomes (D'Onofrio et al., 2012; Tearne, 2015). In summary, results indicate that MSDP was not associated with either newborn functioning or IC. However, significant effects of birth order and mother's age on IC, as well as newborn functioning on IQ were observed in correlational analyses, suggesting that these vulnerabilities may increase risk for poor cognitive functioning.

References

American Academy of Pediatrics Committee on Fetus and Newborn, & American College of Obstetricians and Gynecologists Committee on Obstetric Practice. (2015). The Apgar Score. *Pediatrics, 136*(4), 819-822. doi: 10.1542/peds.2015-2651

Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychol, 8*(2), 71-82. doi: 10.1076/chin.8.2.71.8724

Anokhin, A.P., Golosheykin, S., Grant, J.D., & Heath, A.C. (2017). Heritability of brain activity related to response inhibition: A longitudinal genetic study in adolescent twins. *Int J Psychophysiol, 115*, 112-124. doi: 10.1016/j.ijpsycho.2017.03.002

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. *Neurotoxicol Teratol, 34*(6), 560-570. doi: 10.1016/j.ntt.2012.09.004

Cnattingius, S. (2004). The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. *Nicotine Tob Res, 6 Suppl 2*(Suppl_2), S125-140. doi: 10.1080/14622200410001669187

Centers for Disease Control and Prevention. Pregnancy Risk Assessment Monitoring System (PRAMS). Available at: https://www.cdc.gov/prams/index.htm. Accessed September 13, 2018

Chen, R., Clifford, A., Lang, L., & Anstey, K. J. (2013). Is exposure to secondhand smoke associated with cognitive parameters of children and adolescents?-a systematic literature review. *Annals of epidemiology*, *23*(10), 652-661.

Curtin, S.C., & Matthews, T.J. (2016). Smoking Prevalence and Cessation Before and During Pregnancy: Data From the Birth Certificate, 2014. *Natl Vital Stat Rep, 65*(1), 1-14.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis–Kaplan Executive Function System (D-KEFS): Examiner's manual. San Antonio, TX: The Psychological Corporation.

D'Onofrio, B.M., Rickert, M.E., Langstrom, N., Donahue, K.L., Coyne, C.A., Larsson, H., . . . Lichtenstein, P. (2012). Familial confounding of the association between maternal smoking during pregnancy and offspring substance use and problems. *Arch Gen Psychiatry, 69*(11), 1140-1150. doi: 10.1001/archgenpsychiatry.2011.2107

D'Onofrio, B.M., Van Hulle, C.A., Waldman, I.D., Rodgers, J.L., Harden, K.P., Rathouz, P.J., & Lahey, B.B. (2008). Smoking during pregnancy and offspring externalizing problems: an exploration of genetic and environmental confounds. *Dev Psychopathol, 20*(1), 139-164. doi: 10.1017/S0954579408000072

Dimoska, A., Johnstone, S.J., Barry, R.J., & Clarke, A.R. (2003). Inhibitory motor control in children with attention-deficit/hyperactivity disorder: event-related potentials in the stop-signal paradigm. *Biol Psychiatry, 54*(12), 1345-1354.

Ehrenstein, V., Pedersen, L., Grijota, M., Nielsen, G.L., Rothman, K.J., & Sorensen, H.T. (2009). Association of Apgar score at five minutes with long-term neurologic disability and cognitive function in a prevalence study of Danish conscripts. *BMC Pregnancy Childbirth, 9*, 14. doi: 10.1186/1471-2393-9-14

Ellingson, J. M., Goodnight, J. A., Van Hulle, C. A., Waldman, I. D., & D'Onofrio, B. M. (2014). A sibling-comparison study of smoking during pregnancy and childhood psychological traits. *Behavior Genetics, 44,* 25–35. http://dx.doi.org/10.1007/s10519-013-9618-6

Friedman, N.P., Miyake, A., Young, S.E., DeFries, J.C., Corley, R.P., & Hewitt, J.K. (2008). Individual differences in executive functions are almost entirely genetic in origin. *Journal of Experimental Psychology: General, 137*(2), 201.

Gagne, J.R., Chang, C.N., Fang, H., Spann, C., & Kwok, O.M. (2018). A multimethod study of inhibitory control and behavioural problems in preschoolers. *Infant and Child Development*, e2115.

Gagne, J.R., & Saudino, K.J. (2016). The development of inhibitory control in early childhood: A twin study from 2-3 years. *Dev Psychol, 52*(3), 391-399. doi: 10.1037/dev0000090

Garn, S.M., Johnston, M., Ridella, S.A., & Petzold A. S. (1981). Effect of maternal cigarette smoking on Apgar scores. *American Journal of Diseases of Children, 135*(6), 503-506.

Gilman, S.E., Gardener, H., & Buka, S.L. (2008). Maternal smoking during pregnancy and children's cognitive and physical development: a causal risk factor? *Am J Epidemiol, 168*(5), 522-531. doi: 10.1093/aje/kwn175

Hebel, J.R., Fox, N.L., & Sexton, M. (1988). Dose-Response of Birth-Weight to Various Measures of Maternal Smoking during Pregnancy. *Journal of Clinical Epidemiology, 41*(5), 483-489. doi: Doi 10.1016/0895-4356(88)90050-9

KĀLLÉN, K. (2001). The impact of maternal smoking during pregnancy on delivery outcome. *European Journal of Public Health, 11*(3), 329-333. doi: 10.1093/eurpub/11.3.329 %J European Journal of Public Health

Khng, K.H., & Lee, K. (2014). The Relationship between Stroop and Stop-Signal Measures of Inhibition in Adolescents: Influences from Variations in Context and Measure Estimation. *Plos One, 9*(7), e101356.

Knopik, V.S. (2009). Maternal smoking during pregnancy and child outcomes: real or spurious effect? *Dev Neuropsychol, 34*(1), 1-36. doi: 10.1080/87565640802564366

Knopik, V.S., Heath, A.C., Marceau, K., Palmer, R.H., McGeary, J.E., Todorov, A., & Evans, A.S. (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

Knopik, V.S., Marceau, K., Bidwell, L.C., Palmer, R.H., Smith, T.F., Todorov, A., . . . Heath, A.C. (2016). Smoking during pregnancy and ADHD risk: A genetically informed, multiple-rater approach. *Am J Med Genet B Neuropsychiatr Genet, 171*(7), 971-981. doi: 10.1002/ajmg.b.32421

Knopik, V.S., Marceau, K., Palmer, R.H., Smith, T.F., & Heath, A.C. (2016). 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

Lahey, B.B., & D'Onofrio, B.M. (2010). All in the family: Comparing siblings to test causal hypotheses regarding environmental influences on behavior. *Current directions in psychological science, 19*(5), 319-323.

Leinonen, E., Gissler, M., Haataja, L., Rahkonen, P., Andersson, S., Metsäranta, M., & Rahkonen, L. (2018). Low Apgar scores at both one and five minutes are associated with long-term neurological morbidity. *Acta Paediatrica, 107*(6), 942-951.

Logan, G.D., & Cowan, W.B. (1984). On the Ability to Inhibit Thought and Action - a Theory of an Act of Control. *Psychological Review, 91*(3), 295-327. doi: Doi 10.1037/0033-295x.91.3.295

Logan, G.D., Cowan, W.B., & Davis, K.A. (1984). On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform, 10*(2), 276-291.

Massey, S.H., Bublitz, M.H., Magee, S.R., Salisbury, A., Niaura, R.S., Wakschlag, L.S., & Stroud, L.R. (2015). Maternal-fetal attachment differentiates patterns of prenatal smoking and exposure. *Addict Behav, 45*, 51-56. doi: 10.1016/j.addbeh.2015.01.028

Matzke, D., Love, J., & Heathcote, A. (2017). A Bayesian approach for estimating the probability of trigger failures in the stop-signal paradigm. *Behav Res Methods, 49*(1), 267-281. doi: 10.3758/s13428-015-0695-8

Micalizzi, L., & Knopik, V.S. (2018). Maternal smoking during pregnancy and offspring executive function: What do we know and what are the next steps? *Development and psychopathology, 30*(4), 1333-1354.

Micalizzi, L., Marceau, K., Brick, L.A., Palmer, R.H., Todorov, A.A., Heath, A.C., . . . Knopik, V.S. (2018). Inhibitory control in siblings discordant for exposure to maternal smoking during pregnancy. *Dev Psychol, 54*(2), 199-208. doi: 10.1037/dev0000423

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. Cognitive psychology, 41(1), 49-100.

Odd, D.E., Rasmussen, F., Gunnell, D., Lewis, G., & Whitelaw, A. (2008). A cohort study of low Apgar scores and cognitive outcomes. *Arch Dis Child Fetal Neonatal Ed, 93*(2), F115-120. doi: 10.1136/adc.2007.123745

Rothbart, M.K., & Posner, M.I. (1985). Temperament and the development of self-regulation *The neuropsychology of individual differences* (pp. 93-123): Springer.

SAS [computer program]. Version 9.4. Cary, NC: SAS Institute Inc; 2014.

Singer, J. D. (1998). Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. Journal of Educational and Behavioral Statistics, 23, 323–355. http://dx.doi.org/10.2307/1165280

Statistical Analysis System. (2014). SAS version 9.4.

Stroop, J.R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18*(6), 643-662. doi: DOI 10.1037/h0054651

Swingler, M.M., Isbell, E., Zeytinoglu, S., Calkins, S.D., & Leerkes, E.M. (2018). Maternal behavior predicts neural underpinnings of inhibitory control in preschoolers. *Dev Psychobiol, 60*(6), 692-706. doi: 10.1002/dev.21742

Tearne, J.E. (2015). Older maternal age and child behavioral and cognitive outcomes: a review of the literature. *Fertil Steril, 103*(6), 1381-1391. doi: 10.1016/j.fertnstert.2015.04.027

Thorngren-Jerneck, K., & Herbst, A. (2001). Low 5-minute Apgar score: a population-based register study of 1 million term births. *Obstetrics & Gynecology*, *98*(1), 65-70.

Todd, R.D., Joyner, C.A., Heath, A.C., Neuman, R.J., & Reich, W. (2003). Reliability and stability of a semistructured DSM-IV interview designed for family studies. *J Am Acad Child Adolesc Psychiatry, 42*(12), 1460-1468. doi: 10.1097/00004583-200312000-00013

Tweed, E.J., Mackay, D.F., Nelson, S.M., Cooper, S.A., & Pell, J.P. (2016). Five-minute Apgar score and educational outcomes: retrospective cohort study of 751,369 children. *Arch Dis Child Fetal Neonatal Ed, 101*(2), F121-126. doi: 10.1136/archdischild-2015-308483

Verbruggen, F., & Logan, G.D. (2009). Models of response inhibition in the stop-signal and stop-change paradigms. *Neurosci Biobehav Rev, 33*(5), 647-661. doi: 10.1016/j.neubiorev.2008.08.014

Verbruggen, F., Logan, G.D., & Stevens, M.A. (2008). STOP-IT: Windows executable software for the stop-signal paradigm. *Behav Res Methods, 40*(2), 479-483.

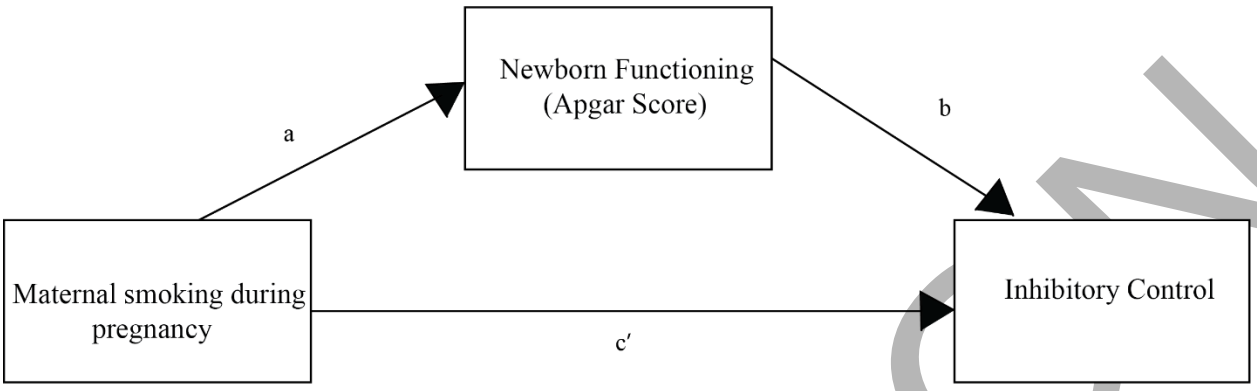

Figure 1. Theoretical Framework. Causal model of 5-minute newborn functioning mediating the relationship between MSDP on IC.

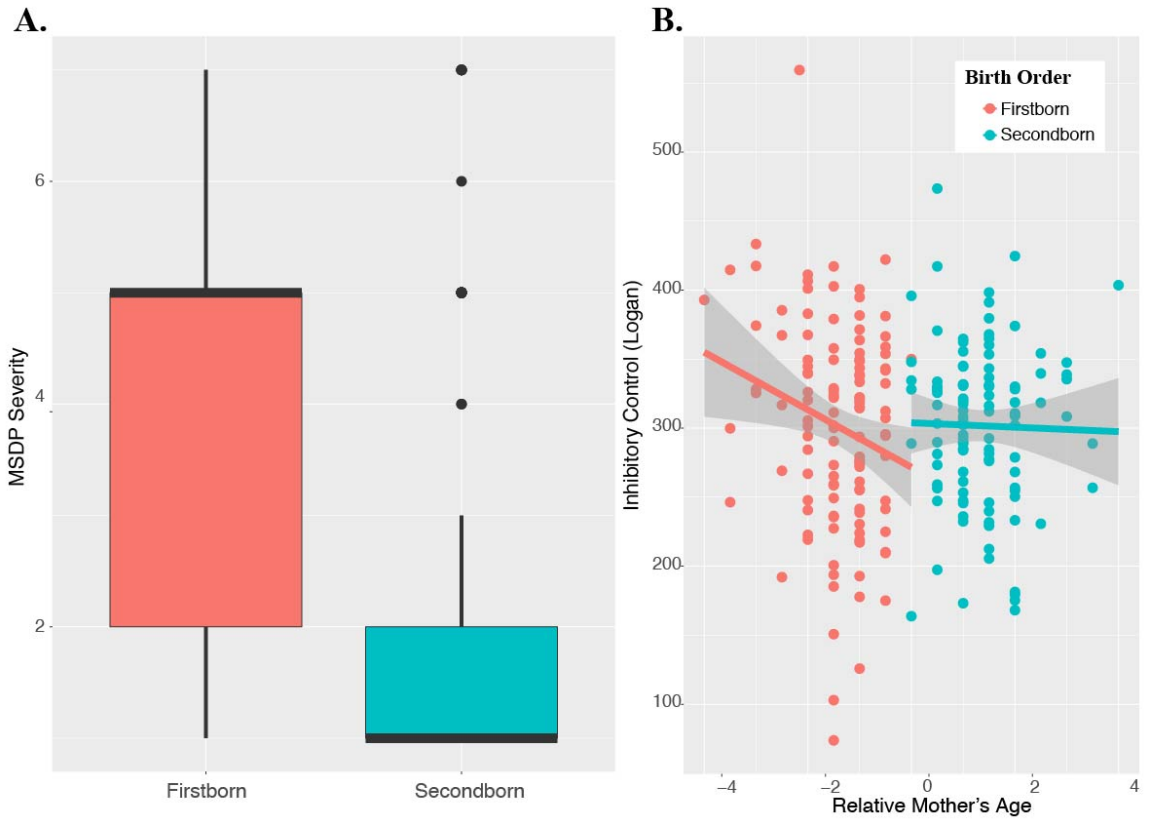

Figure 2. A. Boxplot showing the differences in MSDP severity for first and second born children. B. Scatterplot showing the linear relationships between IC and child-specific mothers age (relative to the average age at both deliveries) for first and second born children and the confidence intervals around the linear models.

Table 1. Sample Characteristics

Study variables	Child 1 (N=166)		Child 2 (N=165)	
	N	**%**	**N**	**%**
Male	90	54.2	85	51.5
	Mean	**SD**	**Mean**	**SD**
Child age at assessment	13.0	1.9	10.2	1.8
Child IQ	100.1	12.6	100.0	12.5
5-minute Apgar	8.9	0.67	8.9	0.52
	N	**Mean** **SD**	*N*	**Mean** **SD**
Maternal smoking during pregnancy severity score	166	3.9 2.0	165	2.1 1.8
Inhibitory control score (SSRT)	126	301 74.8	114	300.4 60.5
	Mean	**SD**	**Mean**	**SD**
Mother's age at birth	26.6	5.5	29.2	5.7
	N **%**		*N* **%**	
Marital status (percent married at birth)	131 85%		132 83%	
Food Stamps (percent qualified at birth)	14 8%		20 12%	
	N	**%**		
Maternal Education				
Less than high school	7	4%		
High school	30	18%		
1–2 years college	50	30%		
3–4 years college	46	27%		
More than college	29	17%		
Not reported	7	4%		
Mothers' marital status				
Never	6	4%		
Married	130	77%		
Separated	5	3%		
Divorced	26	15%		
Widowed	2	1%		

Note. Total Ns vary due to randomly missing data. Maternal Smoking During Pregnancy Severity ranges from 1 to 7; Inhibitory control score ranged from 73.81 to 559.44.

Table 2. Correlations among study variables by child.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1. IC	1	-0.01	0.01	0.14	-0.06	-0.1	0.11	-0.07	-0.14	.01
2. MSDP	-0.04	1	0.03	-0.21**	-0.14	-0.04	0.17*	0.36**	0.02	-0.20*
3. Apgar 5-min	-0.04	0.11	1	0.04	-0.01	-0.01	0.08	-0.05	0.16	0.18*
4. Mother EDU	0.04	0.14	-0.03	1	0.53**	0.26**	-0.31**	-0.23**	-0.03	0.32**
5. Mother Age	-0.05	0.23**	-0.09	0.47**	1	0.32**	-0.27**	-0.29**	0.1	0.20*
6. Marital Status r_{pb}	-0.02	0.06	0.01	0.18*	0.23**	1	-0.37**	0.04	0.09	0.19*
7. Food Stamps r_{pb}	-0.03	-0.06	0.09	-0.14	-0.13*	-0.21**	1	0.13	-0.16	-0.15
8. SHSE	0.06	0.09	0.18*	-0.05	-0.08	0.09	0.06	1	0.08	-0.19*
9. Sex	-0.05	0.11	0.05*	-0.13	-0.07	-0.11	0.13	0.19*	1	-0.09
10. IQ	0.13	0.01	0.16*	0.30**	0.11	0.15	-0.05	-0.02*	0.03	1

Note. Child 1 correlations are below the diagonal; child 2 correlations are above the diagonal. IC=Inhibitory control; MSDP=maternal smoking during pregnancy; EDU= education; SHSE=second-hand smoke exposure; Marital status: 0 = Not Married, 1 = Married. r_{pb} = point-biserial correlation coefficients. $^{**}p<.01$; $^{*}p<.05$

Table 3. Parameter estimates (95% confidence intervals) and variances in Apgar 5-minutes post-delivery

	Model				
	Unconditional	Standard without covariates	Standard with covariates	Sibling-comparison without covariates	Sibling-comparison with covariates
Intercept	8.92 (8.86, 8.99)**	8.89 (8.78, 9.00)**	8.17 (7.43, 8.91)**	8.82 (8.61, 9.03)**	7.99 (7.19, 8.81)**
MSDP					
MSDP		0.01 (-0.02, 0.04)	0.01 (-0.03, 0.05)	-0.001 (-0.04, 0.03)	-0.001 (-0.05, 0.05)
MSDP (FA)				0.03 (-0.03, 0.10)	0.03 (-0.04, 0.10)
Controls					
Birth Order			0.09 (-0.07, 0.25)		0.17 (-0.15, 0.49)
Mother education			-0.01 (-0.04, 0.04)		-0.03 (-0.14, 0.08)
Mother education (FA)					-0.003 (-0.05, 0.04)
Mother age			-0.01 (-0.02, 0.01)		-0.03 (-0.13, 0.05)
Mother age (FA)					-0.006 (-0.02, 0.01)
Mother marital status			-0.01 (-0.21, 0.21)		-0.02 (-0.24, 0.20)
Food stamps			0.21 (-0.03, 0.46)		0.34 (-0.14, 0.82)
Food stamps (FA)					0.20 (-0.09, 0.50)
Second-hand smoke exposure			0.01 (-0.04, 0.06)		0.03 (-0.07, 0.13)
Second-hand smoke exposure (FA)					0.02 (-0.04, 0.08)
IQ			0.01 (0.002, 0.01)***		0.003 (-0.01, 0.01)
IQ (FA)					0.01 (0.003, 0.02)**
Sex			-0.04 (-0.18, 0.09)		0.02 (-0.13, 0.17)
Sex (FA)					-0.01 (-0.15, 0.12)
Variance					
Between-Family level	.013	.007	.005	.034**	.030**
Individual-level	0.33**	0.31**	0.30**	0.34	0.37**
% Within-family variance explained beyond unconditional model		7.14%	8.13%	4.26%	10.77%

Note. MSDP= maternal smoking during pregnancy; Birth Order: 1 = firstborn, 2 = secondborn; Marital status: 0 = Not Married, 1 = Married; CS= child-specific; FA= family average. *p<.05; **p<.01.

Table 4. Parameter estimates (95% confidence intervals) and variances in IC

	Model				
	Unconditional	Standard without covariates	Standard with covariates	Sibling-comparison without covariates	Sibling-comparison with covariates
Intercept	300.74 (292.03, 309.44) **	302.91(287.41, 318.41) **	258.92 (149.06, 368.77) **	301.57 (273.84, 329.29) **	295.97 (180.56, 411.37) **
MSDP					
MSDP		-0.66 (-4.70, 3.39)	0.95 (-4.38, 6.28)	-0.57 (-5.31, 4.17)	1.50 (-5.15, 8.15)
MSDP (FA)				0.06 (-8.57, 8.68)	1.95 (-8.00, 11.90)
Controls					
Birth Order			7.88 (-14.85, 30.61)		60.94 (18.26, 103.61)**
Mother education			4.14 (-1.80, 10.08)		7.49 (-6.05, 21.04)
Mother education (FA)					3.19 (-3.42, 9.80)
Mother age			-1.30 (-3.27, 0.67)		-20.18 (-32.35, -8.02)**
Mother age (FA)					-0.50 (-2.54, 1.55)
Mother marital status			-10.00 (-38.65, 18.64)		-10.01 (-39.09, 19.07)
Food stamps			3.46 (-29.07, 35.98)		20.04 (-44.16, 84.24)
Food stamps (FA)					-4.06 (-41.50, 33.38)
Second-hand smoke exposure			1.57 (-5.49, 8.63)		2.27 (-11.30, 15.84)
Second-hand smoke exposure (FA)					1.02 (-7.22, 9.27)
IQ			.27 (-0.56, 1.10)		1.55 (-0.05, 3.16)
IQ (FA)					-0.07 (-1.04, 0.88)
Sex			-8.65 (-28.34, 11.04)		5.41 (-15.77, 26.58)
Sex (FA)					-9.59 (-29.60, 10.42)
Variance					
Between-Family level	0	-39.37	-296.12	39.31	88.81
Individual-level	4654.71**	4823.18**	4333.13**	4423.11**	3522.69**
% Within-family variance explained beyond unconditional model		3.62%	6.91%	4.98%	24.32%

Note. MSDP= maternal smoking during pregnancy; Birth Order: 1 = firstborn, 2 = secondborn; Marital status: 0 = Not Married, 1 = Married; CS= child-specific; FA= family average. *p<.05; **p<.01.