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Maternal nicotine metabolism moderates the impact of maternal cigarette smoking on infant birth weight: A Collaborative Perinatal Project investigation

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Abstract

Background: Maternal cigarette smoking is an important modifiable risk factor for low birth weight in the US. We investigated the maternal nicotine metabolite ratio (NMR; trans-3'-hydroxycotinine/cotinine) – a genetically-informed biomarker of nicotine clearance – as a moderator of links between prenatal cigarette use and birth weight. We also explored the role of race in these associations.

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CONTRIBUTORS

LRS and RN designed the study and received funding for the project. LRS and NB conceived of the analysis and planned the bioassays. LRS led the writing of the manuscript with input from all others. GDP performed the statistical analysis. GDP and NJ assisted with manuscript drafting, interpretation of findings, and revisions. RN and SB contributed to manuscript revisions. LRS, RN, and SB supported data collection. All authors have reviewed, edited, and approved of the final manuscript.

CONFLICT OF INTEREST

RN receives funding from the Food and Drug Administration Center for Tobacco Products via contractual mechanisms with Westat and the National Institutes of Health.

NLB is a consultant to pharmaceutical companies that market or are developing smoking cessation medications, and has been an expert witness in litigation against tobacco companies.

The remaining authors have no biomedical financial interests or potential conflicts of interest.

Methods: Participants were 454 pregnant women (M_{age}=25 years; 11% Black) who smoked cigarettes and their 537 infants from the Collaborative Perinatal Project. Cigarettes smoked per day were assessed at each prenatal visit; maternal NMR was assayed from third trimester serum. Birth weight was obtained from medical records. Generalized estimating equations were used to evaluate associations between cigarette smoking, NMR, race, and birth weight.

Results: NMR moderated continuous associations between cigarettes per day over pregnancy and infant birth weight (p=.025). Among women who smoked at moderate levels (<15 cigarettes per day), those with slower NMR showed ~50–100 gram decrements in birth weight versus those with faster NMR., while there were no significant associations between NMR and birth weight among women who smoked 15+ cigarettes per day. Although effects of NMR on birthweight were similar for Black and white women, Black women showed significantly slower NMR (p<.001).

Conclusions: This is the first demonstration that the maternal nicotine metabolism phenotype moderates associations between maternal smoking during pregnancy and birth weight. Infants of women with slower nicotine metabolism – including disproportionate representation of Black women – may be at heightened risk for morbidity from maternal smoking.

Keywords

smoking; pregnancy; birth weight; nicotine metabolism; race; disparities

1. Introduction

More than seven percent of women continue to smoke cigarettes during pregnancy in the US, with even higher rates among disadvantaged women, including those who are younger, poorer, and less educated (Azagba et al., 2020; Drake et al., 2018; Kondracki, 2019). One of the most pervasive and consistent consequences of prenatal cigarette exposure is diminished fetal growth and low birth weight (defined as birth weight less than 2500 grams) (Pereira et al., 2017; U.S. Department of Health and Human Services, 2014). Offspring of women who smoke are at twofold increased risk for low birth weight and are 50–250 grams lighter than offspring of women who do not smoke – with evidence for a dose response relationship between cigarettes per day and birth weight (Gilman et al., 2008; Juárez & Merlo, 2013; Pereira et al., 2017). While evidence for links between prenatal cigarette exposure and growth restriction have been deemed sufficient by the Surgeon General to infer causality (U.S. Department of Health and Human Services, 2014), not all infants exposed to maternal smoking are born small. Yet, mechanisms and moderators of links between smoking during pregnancy and offspring growth restriction remain unclear.

Maternal metabolism of nicotine and combustion byproducts may affect the passage and impact of prenatal cigarette exposure on the fetus. An emerging literature has investigated polymorphic variation in xenobiotic metabolic genes encoding CYP1A1 and GSTT1 metabolic enzymes as moderators of links between prenatal smoking and low birth weight (Danileviciute et al., 2012; Delpisheh et al., 2009; Dessi et al., 2018; Infante-Rivard et al., 2006; Qu et al., 2020).The CYP1A1 enzyme catalyzes metabolism of polycyclic aromatic hydrocarbons in tobacco smoke, while metabolism of nicotine is primarily regulated by the CYP2A6 enzyme. The CYP2A6 enzyme mediates metabolism of an average of 80%

of nicotine into cotinine and exclusively metabolizes cotinine into trans-3'-hydroxycotinine (3HC) (Benowitz & Jacob, 1994; Dempsey et al., 2004; Hukkanen et al., 2005). CYP2A6 shows the greatest individual variability in activity of all CYP enzymes (Tyndale & Sellers, 2002); it is also responsible for metabolism of certain tobacco-specific nitrosamines (e.g. NNK—4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) (Hukkanen et al., 2005).

CYP2A6 enzyme activity is influenced by both genetic and environmental mechanisms (Hukkanen et al., 2005; Mwenifumbo & Tyndale, 2009). Approximately 40–60% of variability in nicotine metabolism is believed to be related to polymorphic variation in the *CYP2A6* gene (Benowitz et al., 2006). Non-invasive measurement of CYP2A6 activity and the nicotine metabolism phenotype is possible via measurement of nicotine's metabolites (Dempsey et al., 2004; Levi et al., 2007a, 2007b). The ratio of 3HC/cotinine—referred to as the nicotine metabolite ratio (NMR)--is relatively constant for an individual and has been validated as a phenotypic measurement of CY2A6 activity (Dempsey et al., 2004). CYP2A6 activity and NMR increase throughout pregnancy with highest activity in late pregnancy (Arger et al., 2019; Bowker et al., 2015; Dempsey et al., 2002; Taghavi et al., 2018a, 2018b) – likely due to increasing sex hormone levels across pregnancy.

1.1. The Present Study

Converging lines of evidence suggest: (a) involvement of nicotine in mediating the impact of smoking during pregnancy on birth weight; (b) involvement of xenobiotic metabolic genes--including *CYP* genes--in moderating links between maternal smoking and birth weight; and (c) that environmental factors, including hormonal changes of pregnancy, contribute to prenatal CYP2A6 activity. Nevertheless, we know of no studies that have investigated phenotypic variation in nicotine metabolism as a moderator of links between maternal smoking in pregnancy and birth weight. Thus, our primary aim is to investigate maternal NMR as a moderator of the well-established association between smoking in pregnancy and offspring birth weight. We capitalize on detailed prospective smoking and birth outcome data, and maternal prenatal biospecimens available from the Collaborative Perinatal Project.

In addition, based on (a) persistent racial disparities in birth weight (i.e., infants of Black women are born smaller than infants of white women (Martin et al., 2021)) and (b) racial differences in NMR and CYP2A6 enzyme activity (i.e., Black adults show slower NMR and decreased CYP2A6 activity vs. white adults (Benowitz et al., 1999; Perez-Stable et al., 1998), our secondary exploratory aim was to examine the influence of maternal race on associations between maternal smoking, maternal NMR, and birth weight.

2. Material and Methods

2.1 Participants and Sample Selection

The Collaborative Perinatal Project (CPP) was a multisite, population-based, prospective investigation focusing on perinatal factors affecting birth and child outcomes in the US. The CPP enrolled over 50,000 pregnant women through prenatal clinics at 12 university-affiliated medical centers from 1959–1966, then followed their offspring for 7 years after birth (Broman et al., 1985; Broman et al., 1987; Niswander & Gordon, 1972). Serum

samples for a subset of participants from the Providence and Boston CPP cohorts (N=1,103) were obtained for the present analyses. Included participants were Black or white women with singleton pregnancies, available prenatal serum, positive maternal report of cigarette smoking during pregnancy, serum cotinine values >10 ng/ml, and negative maternal report of any illicit drug use (i.e., heroin, marijuana). Participants in the final sample included 454 pregnant women and their 537 infants. Specifically, 373 women had one singleton pregnancy in the final sample, 79 women had 2 separate singleton pregnancies (79 sibling pairs), and 2 women had 3 separate singleton pregnancies (2 sibling trios).

2.2 Study Procedures

Pregnant women were enrolled into the CPP during routine prenatal care visits. Following enrollment, mothers completed multiple measures, including socio-demographic, medical information, and reports of cigarette smoking during pregnancy. Offspring birth characteristics were recorded by study examiners after delivery. Non-fasting maternal blood was collected at each prenatal visit and extracted serum samples were frozen and stored at the central storage repository (Bethesda, MD). Serum samples drawn 31–36 weeks following last menstrual period and at least 14 days prior to the infant's birth date were selected to allow for a relatively tight window within third trimester to examine cotinine levels and documented links between third trimester smoking and infant birth weight (Abraham et al., 2017; Bernstein et al., 2005).

2.3 Measures

2.3.1 Maternal Characteristics and Cigarette Use.—Maternal age, race/ethnicity, years of education, gravida, and parity (number of prior live births) were provided by participants during study prenatal visits. Study physicians assessed maternal cigarette smoking at each prenatal visit by asking participants if they were smoking and, if so, the number of cigarettes smoked per day (CPD). CPD was defined as the maximum number of CPD reported during the third trimester. Validity of CPP maternal smoking reports with serum cotinine levels has been shown to be excellent (kappas = 0.83–0.87) (Klebanoff et al., 1998; Stroud et al., 2014). To determine race/ethnicity, in the initial enrollment interview, women were asked the open-ended question, "What is your race?" which was then coded as White, Black, Asian, Hispanic, or Other. Because maternal and infant race were concordant in 99.45% (534/537) of the pregnancies, all analyses are based on maternal race.

2.3.2. Infant Characteristics.—Infant characteristics were recorded by a nurse observer at delivery including infant birth weight in grams and infant sex. Infant gestational age (GA) was calculated based on maternal report of last menstrual period.

2.3.3 Nicotine Metabolite Ratio (NMR)—is a validated phenotypic measurement of CY2A6 activity defined as the ratio of 3HC to cotinine (Dempsey et al., 2004), where higher NMR indicates faster nicotine metabolism. Cotinine and 3HC levels were assayed from maternal CPP serum samples using liquid chromatography–tandem mass spectrometry (LC-MS/MS) by the Clinical Pharmacology Laboratory at the University of California, San Francisco (Dempsey et al., 2004). Limit of quantitation was 0.2 ng/ml for both cotinine

and 3HC. For additional details regarding sample collection, storage, and analysis, refer to Stroud et al. (2007).

2.4 Statistical Analyses

A composite index of socio-economic status (SES) was derived from five components: maternal and paternal education (years), maternal and paternal occupation (manual, non-manual, unemployed), and household income (based on US poverty threshold at the time). Each component was assigned a percentile based on US Census values for 1960 and the mean value calculated, using methods developed by the US Census Bureau (Myrianthopoulos & French, 1968). A value of 50 therefore corresponds to the 50th percentile or mean SES of all US adults in 1960.

Generalized estimating equations (GEE) with Gaussian errors, identity link and a working independence correlation matrix with “mother” as the cluster id were used to account for familial dependence in evaluating associations between continuous CPD and birth weight. [The sample included N=373 sole singleton pregnancies, N=79 sibling pairs (women who had 2 separate singleton pregnancies in the analytic sample) and N=2 sibling trios (women who had 3 separate singleton pregnancies in the analytic sample).] Cluster-robust standard errors were used to assess precision of the estimates provided by *geeglm()* command of the *geepack* software package in R (Højsgaard et al., 2005). We initially entered relevant a priori covariates into the model: infant sex, GA, maternal SES. In the second step, main effects of continuous CPD, NMR, maternal race (Black vs. white), and all interaction terms were added to the model. In the third step, these interaction terms were tested in a hierarchical fashion and those not significant at the 5% level were dropped from the model. Significant interactions were probed via the Johnson-Neyman technique (Johnson & Neyman, 1936) explained in detail by Bauer and Curran (2005) in order to determine at what level along the continuous CPD variable interaction effects became significant.

3. Results

3.1 Sample Characteristics

The sample included 454 pregnant women (mean age=25, *SD*=6; 11% Black, 89% white) who reported prenatal smoking and their 537 infant offspring. Women had an average 10.8 (*SD*=2.1) years of education and average gravida of 2 (*SD*=2) births. Average socio-economic status on a U.S. population centile scale was 53 (*SD*=19). Average GA for infants (62.4% biological female) at delivery was 40.1 (*SD*=2.2) weeks with an average birth weight of 3186 (*SD*=476) grams. Participants reported an average of 20.7 CPD (*SD* = 10.2) over the entire pregnancy and 19.6 (*SD*=10.1) during the 3rd trimester. Mean maternal serum cotinine, 3HC, and NMR (3HC/cotinine) were: 111.9 ng/ml (*SD*=76.5); 60.2 ng/ml (*SD*=42.5); and 0.57 (*SD*=0.24), respectively.

3.2 Impact of Maternal Smoking, NMR, and Race on Infant Birth Weight

Models predicting birth weight are shown in Table 1. Infant sex was modelled as a binary variable with female sex as the reference group. Race was modelled as a binary variable with white as the reference group. CPD was standardized so that its regression coefficient

(β) captures the effect on birth weight of a full-sample inter-quartile range (IQR) increase from 10 to 20 CPD. Maternal NMR was centered and standardized so that its regression coefficient captures the effect on birth weight of an IQR increase from the 1st quartile among white women.

After inclusion of a priori covariates (maternal SES, infant sex, infant GA, sex*GA), effects of CPD, NMR, maternal race, and all 2- and 3-way interactions were evaluated in a hierarchical fashion. The CPD*NMR*Race (p=.80) and the NMR*Race (p=.91) interactions did not attain statistical significance and were dropped from the model. Statistically significant CPD*NMR (p=.025) and CPD*Race (p<.001) interactions were retained in the final model. Given the presence of these 2-way interactions, main effects could not be interpreted in isolation.

3.3 Interaction Probing: Maternal Smoking*Maternal NMR

Figure 1 documents the impact of decreases in maternal NMR on infant birth weight at differing continuous maternal CPD levels for infants of white and Black women. Specifically, the impact of maternal NMR on birth weight diminished as maternal CPD increased; the impact of maternal NMR was greatest at the lowest levels of maternal CPD. Although results are shown stratified by race, there are no differences in the impact of NMR on birth weight in Black versus white women.

Figure 2 shows NMR effects on birth weight across the entire 5–20 CPD range, accompanied by pointwise 95% confidence intervals. Although analyses for the CPD*NMR interaction above were based on continuous CPD, detailed interaction probing allows for investigation of the value of CPD at which the interaction becomes statistically significant/non-significant. As shown in Figure 2, the detailed interaction probing revealed that the impact of a 0.30 unit decrease in maternal NMR on decrements in birth weight was statistically significant for women who smoked less than 15 CPD, but was no longer significant in women who smoked 15 CPD or more. In particular, a decrease of 0.30 units in maternal NMR was associated with a 97.9 gram decrease in birth weight (p=.016) in women who smoked 5 CPD, a 72.3 gram decrease (p=.024) in women who smoked 10 CPD, a 46.6 gram decrease (p=.067) in women who smoked 15 CPD, but only a 20.9 gram decrease in birth weight (p=.365) in women who smoked 20 CPD.

3.4 Interaction Probing: Maternal Smoking*Race

Black women showed overall slower NMR than white women (Wilcoxon p<.0001; *Med*=0.39 vs. 0.57, respectively). Although IQR intervals for NMR for Black versus white women (0.29–0.55 vs. 0.43–0.73, respectively) were generally similar (0.26 vs. 0.30), NMR distributions differed by race, with Black NMR quartiles (.29, .39, .55) consistently lower than the corresponding white NMR quartiles (.43, .57, .73).

The impact of CPD increases on decrements in birth weight was more pronounced for infants of Black versus white women across race-specific NMR quartiles. In particular, identical half-pack (10 CPD) increases in maternal smoking were associated with drops in birthweight that varied from 29.7 grams (p=.192) to 53.6 grams (p=.005) to 81.0 grams (p=.002) in infants of white women and from 159.6 grams (p=.006) to 176.7 (p=.002) to

204.0 grams ($p<.001$) in infants of Black women, as maternal metabolism varied over its race-specific IQR range (1st to 2nd to 3rd quartiles).

4. Discussion

Cigarette smoking in pregnancy is an important modifiable risk factor for low birth weight in the US (Pereira et al., 2017; U.S. Department of Health and Human Services, 2014). However, not all infants born to women who smoke are born small. Further, despite critical implications for targeted interventions, there has been little progress in understanding variability in birth weight outcomes following exposure to cigarette smoking. Capitalizing on a large sample of cigarette-exposed pregnancies with available biospecimens, we found that maternal nicotine metabolism moderated associations between maternal cigarettes per day and infant birth weight. Specifically, among women who smoked at moderate levels, those with slower nicotine metabolism levels showed ~50–100 gram decrements in birth weight versus those with faster nicotine metabolism. To our knowledge, our study represents the first demonstration that phenotypic variation in maternal nicotine metabolism explains variability in the impact of maternal smoking on birth weight. Results showing that slower nicotine metabolism--presumably increasing nicotine exposure--is associated with lower birth weight support a role of nicotine (in addition to combustion byproducts) in impacting fetal growth. Our findings may have implications for elucidating the impact of electronic nicotine delivery products on fetal growth, and for developing personalized interventions to prevent decrements in birth weight in pregnant women who continue to smoke.

One of the strengths of the current study was the inclusion of women reporting a wide range of smoking levels. We found that although maternal nicotine metabolism significantly moderated continuous smoking-birth weight associations, moderating effects were significant only for women smoking less than 15 cigarettes per day, while we found no impact of nicotine metabolism for women smoking more than 15 cigarettes per day. Results suggest a particular impact of nicotine metabolism at more “moderate” rather than “heavy” levels of smoking. This observation is consistent with a dose-response for nicotine with a plateau of harmful effects at higher nicotine levels. Given that the majority of pregnant women currently smoke at “moderate” levels or lower (Kondracki, 2019; Pickett et al., 2005; Pickett et al., 2003), the impact of nicotine metabolism on birth weight may be even more important and pronounced in present times.

Our results also support a role of nicotine in impacting fetal growth. While mechanisms underlying the impact of maternal smoking on birth weight are not well understood, our results support a role for both nicotine and combustion byproducts in contributing to the effects of maternal smoking on offspring weight. Nicotine is the primary addictive component of cigarettes and a well-established developmental toxicant with known teratogenic effects on human fetuses (England et al., 2017). During pregnancy, nicotine and its primary metabolite (cotinine) from maternal circulation cross the placenta and enter fetal circulation (Berlin et al., 2010; Luck et al., 1985). Nicotine may mediate intrauterine vessel constriction leading to placental apoptosis and chronic fetal hypoxia (Lambers & Clark, 1996; Vogt Isaksen, 2004). Our findings complement prior human studies demonstrating dose response associations between maternal nicotine levels and birth weight (Bardy et

al., 1993; Ellard et al., 1996; Eskenazi et al., 1995; Kobayashi et al., 2019; Perkins et al., 1997; Wang et al., 1997). Our findings also complement and extend prior studies revealing moderation of smoking-birth weight associations by xenobiotic metabolism gene variants *CPY1A1* and *GSTT1* (Danileviciute et al., 2012; Delpisheh et al., 2009; Infante-Rivard et al., 2006; Qu et al., 2020; Wang et al., 2002), as well as a study revealing moderation of prenatal second-hand-smoke-exposure and birth size associations by *CYP2A*6 polymorphisms (Xie et al., 2015).

Results also have implications for further elucidating the impact and relative impact (versus combustible cigarettes) of electronic nicotine delivery systems (ENDS) on infant outcomes. Pregnant women are increasingly using new tobacco products such as electronic cigarettes or ENDS (Kurti et al., 2017; Liu et al., 2021; Liu et al., 2019; Rollins et al., 2020). Despite perceptions of increased safety of ENDS versus combustible cigarettes, prenatal ENDS use has also been associated with increased risk for low birth weight and small-for-gestational age births in several studies (Cardenas et al., 2020; Kim & Oancea, 2020; Regan et al., 2021; Regan & Pereira, 2021; Wang et al., 2020; but also see McDonnell et al., 2020) — paralleling effects of combustible cigarettes. Thus, it is possible that, similar to combustible cigarettes, maternal nicotine metabolism may also moderate effects of prenatal ENDS use on birth weight.

Low birth weight infants are at increased risk for adverse health outcomes spanning infancy (neonatal intensive care admittance, sudden infant death syndrome), childhood (learning disabilities, mental health symptoms), and adulthood (cardiovascular and mental disorders) (de Mendonca et al., 2020; Getahun et al., 2004; Loret de Mola et al., 2014; Markopoulou et al., 2019; Mathewson et al., 2017; Pascal et al., 2018; Watkins et al., 2016). Given our findings of decrements in birth weight in slow metabolizers, additional research could be conducted in order to determine if personalized interventions based on nicotine metabolism would be useful in pregnant women who smoke. For example, increased intensity of behavioral interventions and/or differential pharmacotherapies could be considered for slow metabolizers (Chamberlain et al., 2017). Initial studies have also supported customizing of pharmaceutical smoking cessation treatments based on nicotine metabolism level as a personalized-medicine approach in non-pregnant adults (Choi et al., 2021; Perez-Paramo & Lazarus, 2021; Siegel et al., 2020). Specifically, in some studies, slow metabolizers have been shown to benefit from transdermal nicotine therapies, while faster metabolizers benefit more from varenicline (Siegel et al., 2020). Translating a personalized medicine approach to pregnancy would require consideration of overall increases in nicotine metabolism for all pregnant women (Arger et al., 2019; Bowker et al., 2015; Dempsey et al., 2002; Taghavi et al., 2018a, 2018b) as well as differences in safety considerations for pharmaceutical treatments in pregnancy (American College of Obstetricians and Gynecologists, 2020; Choi et al., 2021; Claire et al., 2020; Patnode et al., 2021; Wells et al., 2018).

Future important directions for this research include: (a) determining the consistency of personalized treatment response by NMR level in *non-pregnant adults*—especially in racially/ethnically diverse samples (Chen et al., 2018); (b) developing cut-points for individual differences in NMR *during pregnancy* in the context of the overall increase in NMR in all pregnant women; (c) better understanding of the safety of smoking cessation

pharmacotherapy in pregnancy (Patnode et al., 2021); and (d) clinical trials to determine the impact of personalized smoking cessation pharmacotherapy *during pregnancy*. For instance, a recent observational study with propensity-score matching (Choi et al., 2021) revealed nearly 3X increased rates of smoking cessation in pregnant women who were dispensed varenicline versus a nicotine patch. Women of reproductive age who are planning to become pregnant also represent an intriguing group for future research in personalized smoking cessation treatment. Finally, ongoing research is needed to develop, test, and disseminate evidence-based and novel behavioral approaches for all pregnant women who continue to smoke (Chamberlain et al., 2017; Tappin et al., 2015). Although the effects of nicotine metabolism on birth weight were similar for infants of Black and white women, Black women showed significantly slower nicotine metabolism, and thus were more likely to show decrements in birth weight from cigarette smoking. Studies of non-pregnant adults have also shown that Black individuals have lower NMR and are more likely to have decreased CYP2A6 activity versus whites (Benowitz et al., 1999; Perez-Stable et al., 1998). Results extend prior research in pregnant women showing increased per cigarette cotinine levels in Black versus white pregnant women (English et al., 1994; Klebanoff et al., 1998). Slower nicotine metabolism potentially leading to greater infant morbidity (i.e., decrements in birth weight) in Black pregnant women who smoke highlights the importance of additional attention to smoking cessation efforts for this group. A secondary finding from this study was that dose response effects of prenatal cigarette smoking on birth weight were more pronounced for infants of Black women. Results complement a prior study showing more pronounced impact of prenatal smoking on birth weight for Black versus white pregnant women that was related to increases in per-cigarette maternal nicotine levels in Black women (English et al., 1994). Additional research related to prenatal smoking, racism and racial disparities, nicotine metabolism, and birth weight is needed to replicate and further elucidate these findings.

There are a number of notable strengths of the present study, including: (1) large sample of women who smoked throughout their pregnancy, (2) prospective assessment of maternal smoking at all prenatal visits, (3) decreased social sanctions against smoking during the period of data collection allowing for analysis of a wide range of smoking levels, and (4) availability of maternal serum allowing for biochemical verification of maternal smoking and investigation of the nicotine metabolism phenotype. However, it is important to highlight that data for the present study was collected from a nationally-representative, prenatal cohort enrolled between 1959 and 1966. Although we do not believe that our key finding of nicotine metabolism as a novel biological moderator of the smoking-birth weight association is related to the time period of data collection, we outline important considerations in interpreting results related to the social and racial/ethnic context of the US during this time period.

First, although the racial/ethnic composition of the sample was consistent with New England in the 1960s, our sample is composed of 89% white women with only 11% Black women. Studies conducted within larger samples of Black pregnant women are needed to better understand the interactions of racism, smoking, nicotine metabolism, and birth weight. Further, race and ethnicity were queried at the time of data collection using limited options/choices of racial/ethnic identities--differing from the much broader range of options for

racial/ethnic identities in modern samples. In addition, the racial/ethnic composition of the US and New England has shifted considerably since the 1960s. Critically, our study did not include racial/ethnic groups outside of Black and white women and their infants. Differences in prevalence of smoking in pregnancy have been documented across a broad range of ethnic groups, including among Latinx and Asian women; there is also recent evidence that associations between maternal smoking and birth weight may differ by race and ethnicity (Amyx et al., 2021; Fishman et al., 2018; Mine et al., 2017; Ng et al., 2019). Future studies are needed to determine if the current findings replicate in modern samples that include Latinx and Asian groups as well as other racial/ethnic groups.

Second, the prevalence of tertiary and postgraduate degrees among women has increased since the 1960s. Further, in modern samples, there is a high degree of association between smoking in pregnancy and education attainment (Azagba et al., 2020; Drake et al., 2018; Kondracki, 2019), whereas in the present study, smoking in pregnancy was not significantly associated with educational attainment or socio-economic status. In some ways, the present sample offers an intriguing opportunity to investigate the role of nicotine metabolism unconfounded by socio-economic status, whereas in current samples, it is more likely that maternal education would serve as a significant confound or moderator. Nonetheless, future analyses in modern samples are needed to determine the role of socio-economic status and educational attainment in associations between prenatal smoking, NMR, and birth weight.

Finally, prevalence and levels of smoking in pregnancy have also changed since the mid-20th century (Office on Smoking and Health, 2001). In the present CPP subsample, prevalence of maternal smoking was more than 50% versus 7–15% prevalence of maternal smoking in modern US samples (Azagba et al., 2020; Drake et al., 2018; Kondracki, 2019). Replication in present-day samples is needed in the context of current smoking prevalence. However, although smoking was more prevalent in the 1960s, the present analytic sample includes *only women who smoke*. We believe associations between smoking level, nicotine metabolism, and birth weight *among women who smoke* would be less likely to be influenced by the prevalence of smoking at the time of data collection. In addition, in the current sample, nearly half of the women who smoked reported smoking more than 15 cigarettes per day, whereas most women today smoke <15 cigarettes per day. However, our statistical analyses focused on the impact of maternal nicotine metabolism on continuous levels of cigarettes per day over pregnancy. Further, that effects of maternal nicotine metabolism were greatest for women smoking <15 cigarettes per day suggests that maternal nicotine metabolism may play an even stronger role in impacting offspring birth weight in present-day samples.

Findings from the present study reveal an impact of nicotine metabolism on decrements in *continuous* birth weight outcomes, with *suggestive implications* for increased likelihood of small-for-gestational-age and low birth weight infants in offspring of women who smoke who have slower nicotine metabolism. Prior studies of maternal smoking, xenobiotic metabolism gene variants, and birth outcomes have found similar effects for both continuous as well as categorical birth weight outcomes (Danileviciute et al., 2012; Delpisheh et al., 2009; Infante-Rivard et al., 2006; Qu et al., 2020; Wang et al., 2002). However, future studies of the impact of phenotypic variation in nicotine metabolism in studies

over-sampled for low birth weight and small-for-GA infants are needed to determine the impact and direction of effects of phenotypic variation in nicotine metabolism on high-risk clinical outcomes. Finally, additional metabolic pathways (e.g., metabolism of combustion byproducts) are clearly relevant to understanding variability in the impact of maternal smoking on birth weight and other birth outcomes. Future studies are needed to uncover additional pathways relevant to birth weight and other infant outcomes. Future studies could also investigate the role of maternal nicotine metabolism in moderating links between prenatal smoking and offspring neurodevelopmental outcomes.

4.1. Conclusions

Maternal smoking in pregnancy is causally related to offspring birth weight; however, information regarding specific mechanisms and moderators has been a critical knowledge gap in the field. Our results suggest that infants of mothers with slower nicotine metabolism – including disproportionate representation of Black women – may be at heightened risk for morbidity from maternal smoking. Development of personalized interventions for pregnant persons accounting for nicotine metabolism could offer potential to improve perinatal and offspring health outcomes.

AUTHOR DISCLOSURES

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HIGHLIGHTS

- Rate of nicotine metabolism moderates the impact of prenatal smoking on birth weight.
- In women who smoked at moderate levels, those with slower nicotine metabolism had smaller infants.
- Black women were more likely to have slower nicotine metabolism.
- Personalized interventions accounting for nicotine metabolism could be investigated.

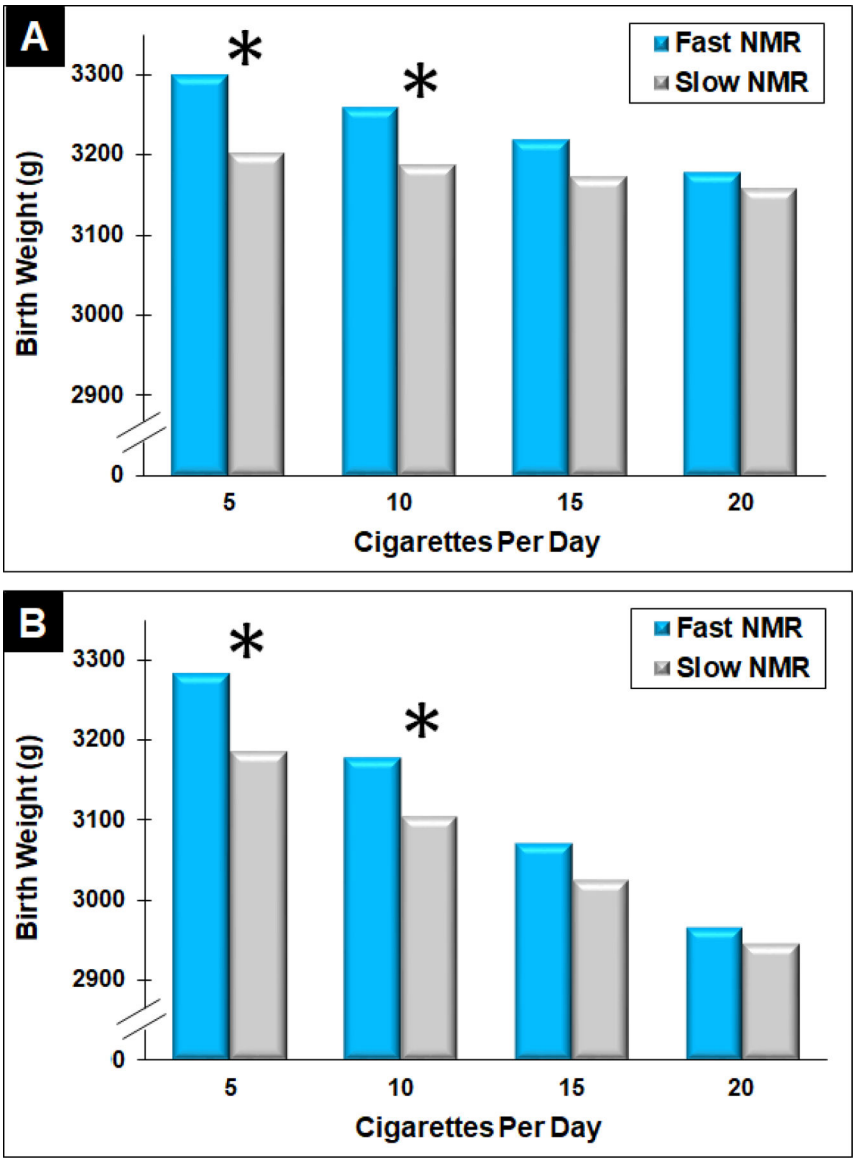

Figure 1.

Impact of maternal smoking and maternal nicotine metabolite ratio (NMR) on offspring birth weight in (A) white pregnant women and (B) Black pregnant women.

NOTE: NMR = Nicotine metabolite Ratio; Cigarettes per Day = Maximum cigarettes per day in 3rd trimester of pregnancy; Model-predicted infant birth weight at race-specific 3rd and 1st NMR quartiles (Fast and Slow NMR) shown by blue and grey bars respectively. * = $p < .05$

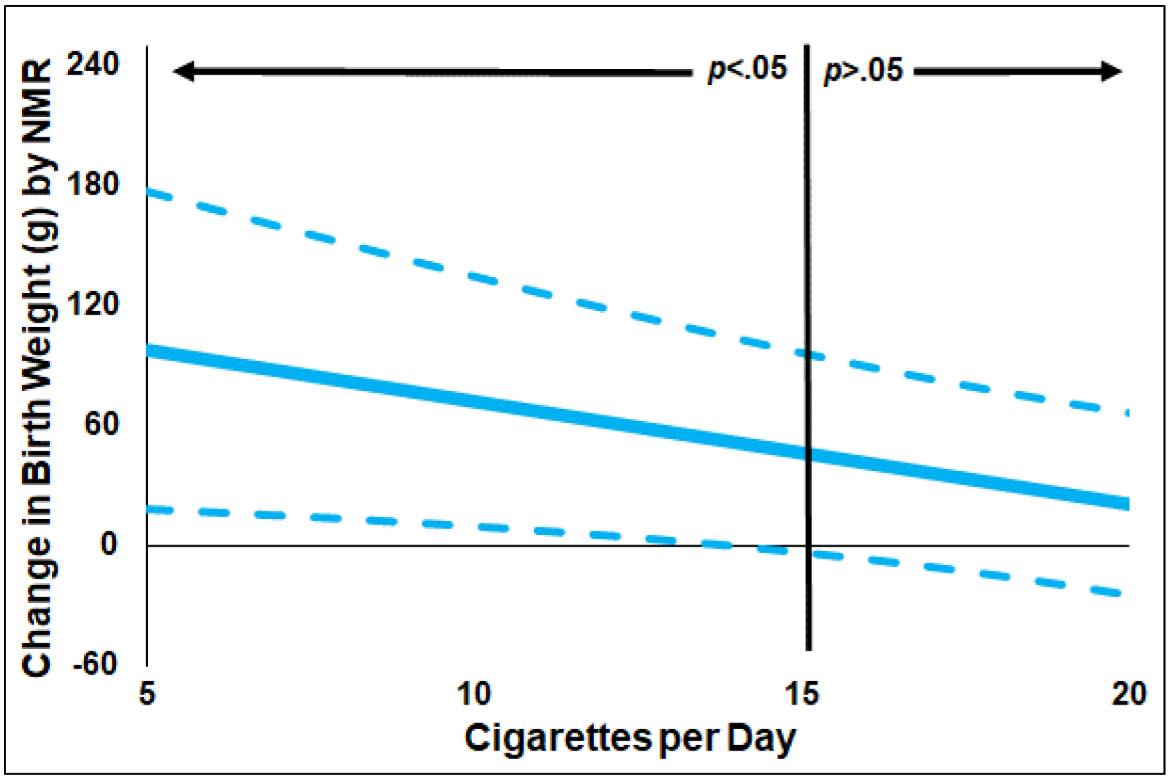

Figure 2.

Slower maternal nicotine metabolism (NMR) is associated with significant decrements in birth weight among women smoking <15 cigarettes per day, but not among those smoking 15+ cigarettes per day.

NOTE: NMR = Nicotine metabolite ratio; Cigarettes per day = Maximum cigarettes smoked per day in 3rd trimester of pregnancy. Solid blue line depicts the expected decrease in birth weight as a result of a full-sample IQR decrease in NMR (0.30). Dashed blue lines represent pointwise 95% upper and lower confidence limits.

Table 1.

Linear regression model of predictors of infant birth weight (n = 537)*

Variables	ß (grams)	S.E.	Z	*p*
Intercept	3188.5	37.6	84.81	<.001
Maternal SES	−48.1	45.7	−1.05	.293
Infant Sex (Male)	120.8	36.3	3.33	<.001
Infant GA	31.6	13.5	2.34	.019
Infant Sex * GA	108.0	20.2	5.35	<.001
Maternal Race (Black)	−50.7	87.3	−.58	.562
NMR	72.3	32.0	2.26	.024
CPD	−29.7	22.7	−1.30	.192
CPD * Maternal Race	−153.8	59.3	−2.59	<.001
CPD * NMR	−51.3	22.8	−2.25	.025

NOTES:

*Generalized estimating equations (GEE) with gaussian errors, identity link and a working independence correlation matrix were used to account for familial dependence in evaluating associations between maternal cigarettes per day and birth weight. Robust standard errors were used to assess precision of the estimates. Infant Sex (Male vs. Female = reference), Maternal Race (Black vs. White= reference), Infant GA = Gestational Age (centered at 40 weeks), Maternal socio-economic status (SES dichotomized at 1st sample quartile; Low vs. High = reference); CPD = maximum number of cigarettes per day in 3rd trimester (centered at 10, scaled by 10), NMR = maternal nicotine metabolite ratio (centered at .43, scaled by .30).