

ABSTRACT

Title of dissertation: THE PREVALENCE OF MATERNAL SMOKING
INTENSITY STATUS IN EARLY AND LATE
PREGNANCY AND ITS ASSOCIATION WITH EARLY
MORBIDITY IN SINGLETON TERM BIRTHS IN THE
UNITED STATES, 2016

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Relatively little is known about how maternal cigarette smoking influences the health of infants delivered at term. This study was based on the 2016 United States Natality File of live births (N= 3,956,112). The first aim was to examine the prevalence and patterns of smoking in the three months before and during pregnancy and the distribution of smoking intensity in early (1st and 2nd trimester) and late (3rd trimester) pregnancy across race/ethnicity, age, and educational attainment of mothers with all births and with singleton term births (37-41 completed weeks gestation) in the United States in 2016. The second aim was to compare the odds of low birthweight (LBW), low 5-minute Apgar score, and neonatal intensive care unit (NICU) transfer/admission in term singletons with changing maternal smoking status in early and late pregnancy indicating a potential

prenatal exposure effect. The third aim was to test and identify the role of low birthweight, as a potential mediator, in the association with maternal smoking status and NICU transfer/admission of a newborn delivered at term. The prevalence of smoking in the three months before pregnancy was 9.42% among all mothers and 9.20% among mothers of term singletons, and high intensity smoking was the highest in the first trimester among non-Hispanic White women, 20-24 years of age, and less educated women for all births and for singleton term births. High intensity smoking in early and late pregnancy was associated with a greater risk of LBW (aOR 3.33; 95% CI: 3.23, 3.44), low 5-min Apgar score (aOR 1.46; 95% CI: 0.88, 2.44), and NICU transfer/admission (aOR 1.62; 95% CI: 1.58, 1.67) in term neonates. The odds ratios of the natural direct and natural indirect effects of NICU transfer/admission were aOR 1.52 (95% CI: 1.47, 1.57) vs. aOR 1.07 (95% CI: 1.07, 1.09) and the proportion mediated through LBW (18.3%) indicated partial mediation. This study has important implications for clinical practice, public health policy and research, and it is particularly timely because of an information gap on the health of infants delivered at term with LBW to mothers who continue smoking at high intensity during pregnancy.

THE PREVALENCE OF MATERNAL SMOKING INTENSITY STATUS
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WITH EARLY MORBIDITY IN SINGLETON TERM BIRTHS
IN THE UNITED STATES, 2016

By

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“Every individual matters. Every individual has a role to play. Every individual makes a difference” - Jane Goodall, an English primatologist and anthropologist

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LIST OF ABBREVIATIONS

AAP: American Academy of Pediatrics

ACOG: American College of Obstetricians and Gynecologists

AGA: Appropriate for Gestational Age **AMA:** American Medical Association

aOR: Adjusted Odds Ratio **AS:** Apgar score **BMI:** Body Mass Index

BRFSS: Behavioral Risk Factor Surveillance System

CDC: Centers for Disease Control and Prevention **CI:** Confidence interval

DAG: Directed Acyclic Graph **DNA:** Deoxyribonucleic acid

E-cig: Electronic cigarette or e-cigarette **ET:** Early term

FDA: Food and Drug Administration **FGR:** Fetal growth restriction

GED: General Educational Development **GWG:** Gestational weight gain

HE: High intensity smoking in early pregnancy

HL: High intensity smoking in late pregnancy **IOM:** Institute of Medicine

IUGR: Intrauterine growth restriction

JAMA: Journal of the American Medical Association

LBW: Low birthweight **LE:** Low intensity smoking in early pregnancy

LL: Low intensity smoking in late pregnancy **LMP:** Last menstrual period

NCHS: National Center for Health Statistics

NHANES: National Health and Nutrition Examination Survey

NHIS: National Health Interview Survey **NICU:** Neonatal Intensive Care Unit

NNS: National Natality Surveys **NVSS:** National Vital Statistics System

OE: Obstetric Estimate **OR:** Odds ratio

PRAMS: Pregnancy Risk Assessment Monitoring System

PTB: Preterm birth **RR:** Relative risk **SD:** Standard deviation

SES: Socioeconomic score (education, employment, household income and assets)

SGA: Small for Gestational Age **TB:** Term birth **UK:** United Kingdom

UN: United Nations **USDA:** United States Department of Agriculture.

USDHEW: United States Department of Health, Education, and Welfare.

USDHHS: U.S. Department of Health and Human Services

US OMB: United States Office of Management and Budget

WHO: World Health Organization

WIC: Special Supplemental Nutrition Program for Women, Infants, and Children

Chapter I: INTRODUCTION AND OUTLINE OF THE STUDY

This chapter presents an overview of the dissertation, conceptual definitions, research specific aims and objectives, and the outline of the dissertation by individual chapters.

Overview

Pregnancy offers an opportunity to quit smoking cigarettes, but smoking cessation is an ongoing challenge. Although the prevalence rate of smoking in pregnancy in the United States during the past few decades has decreased, it remains unacceptably high. National reports indicate that nearly one-third of reproductive age women (18-44) are daily smokers, 11% of women smoke in the 3 months prior to pregnancy and 24% quit before becoming pregnant.¹ Women who smoke in pregnancy have the largest proportion of infants born with low birthweight (LBW) (<2,500g or 5lbs 8oz).^{2,3} In 2016, in the US, the rate of LBW rose to 8.16% from 8.07% in 2015.⁴ Low birthweight (LBW) has a significant public health importance because it strongly correlates with poor health postnatally and in the long-term.

A disproportionate number of infants delivered preterm (<37 weeks gestation) have LBW and suffer health complications related to short gestational age that is associated with high morbidity, mortality,⁵⁻¹¹ and cost.¹²⁻¹⁴ Recent studies have documented short and long-term health complications among infants born late preterm (34-36 weeks gestation) and early term births (38-39 weeks gestation) compared with being born full term (39 and 40 completed weeks gestation).¹⁵⁻²⁰ Late preterm and early term infants constitute largest gestational groups of newborns with LBW that substantially contribute

to disease burden.^{13,21,22} Relatively little is known about the health of infants delivered at term (37-41 completed weeks gestation), because only a few prospective population-based studies have been conducted in term neonates.²³⁻²⁵

Maternal smoking is known to adversely influence *in utero* fetal growth linking to intrauterine growth restriction (IUGR) and LBW in newborns of any gestational age.^{23,25,30-32} Newborns delivered at term that were prenatally exposed to smoking, while considered developmentally mature, may experience greater risk of health complications than healthy newborns. In general, respiratory morbidity has low incidence in newborns of term pregnancy and has received less attention in research,²⁶⁻²⁹ but it may be potentially fatal in low birthweight neonates.^{7,33-38} In surviving infants, expenses associated with the neonatal intensive care unit (NICU) in the immediate postnatal period and hospital costs within the first few months of life have been high.^{12-14,39} The association between maternal smoking, as a risk factor for LBW, low Apgar score and NICU transfer/admission among infants born at term, have not been fully explored in studies. Early diagnosis of fetal growth restriction in mothers, who smoked in pregnancy, is important, because it enables adequate monitoring high risk gestation and fetal health status in preparation for delivery.

To address these gaps, this study begins by first analyzing the current prevalence rate and smoking patterns by maternal characteristics, among all mothers with births and with singleton term births in the United States in 2016. Additionally, seven mutually exclusive maternal smoking status categories were created, based on combined measures of timing (by trimester) and intensity (the number of cigarettes/day) of smoking, to explore prenatal exposure in early and late pregnancy more thoroughly. Next, this study

examines prevalence rate of newborn morbidity in the association with maternal smoking status in early and late pregnancy and maternal and infant characteristics, using morbidity indicators of low birthweight (< 2,500g), low 5-minute Apgar score (< 7), and NICU transfer/admission. Finally, low birthweight (LBW) is tested in mediation analyses to explain its contribution to NICU transfer/admission in association with maternal smoking status.

Conceptual Definitions

The birth of a newborn is an event that implies a transition of a fetus to extrauterine life and may occur at any gestational age. Live birth is defined by the World Health Organization (WHO), the United Nations (UN) and the National Center for Health Statistics (NCHS) as “the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life such as heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles, whether the umbilical cord has been cut or the placenta is attached.”⁴⁰ A singleton term birth is delivering one live infant and occurs between 37 weeks 0 days and 41 weeks 6 days gestation, and may include early term birth between 37 weeks 0 days and 38 weeks 6 days gestation and late term birth between 39 weeks 0 days and 41 weeks 6 days gestation.⁴¹ Intrauterine growth restriction (IUGR) or fetal growth restriction is an in utero fetal developmental adaptation to minimize growth in response to various harmful stimuli^{42,43} and is defined in research as birth weight less than the 5th and 10th percentile for gestational age.⁴⁴

Newborn health characteristics include birth weight and Apgar score. Both measures are obtained and documented within a few minutes after delivery, and birth weight

represents intrauterine fetal growth and depends on the duration of pregnancy,⁵ and Apgar score describes newborn vitality at birth.²¹⁰ Low birthweight (LBW) (<2,500g) (a proxy for fetal growth restriction), low 5-minute Apgar score (<7 on a scale of 10) and NICU admission are newborn morbidity indicators clinically assessed and recorded.⁴⁵

Research Specific Aims and Objectives

This dissertation is organized by three specific aims that are sequentially connected to each other:

- Specific aim 1 is to examine the prevalence and patterns of smoking in the three months before and during pregnancy and the distribution of maternal smoking status in early (first and second trimester) and late (third trimester) pregnancy across race/ethnicity, age, and educational attainment among all mothers with all births and with singleton term births (37-41 completed weeks gestation) in the United States in 2016. I hypothesize that the prevalence of smoking is higher in the three months prior to and during the three trimesters of pregnancy among non-Hispanic White, younger, and less educated women, and that the distribution of high intensity smoking is higher in early than in late pregnancy.
- Specific aim 2 is to examine the distribution of maternal smoking status in early and late pregnancy across maternal and infant characteristics and the prevalence of neonatal morbidity assessed by indicators of low birthweight (LBW) (<2,500g), low 5-min Apgar score (<7) and NICU transfer/admission. I postulate that the association of maternal smoking status with infant morbidity will be strongest for high intensity smokers in early and late pregnancy, attributed to a higher magnitude of prenatal exposure.

- Specific aim 3 is to examine low birthweight (LBW) in the term neonate as a potential mediator in the association with maternal smoking status and NICU transfer/admission. LBW is a proxy for fetal growth restriction and an indicator of neonatal morbidity, and can be a precipitating factor for NICU transfer/admission. I hypothesize that low birthweight is a potential mediator in the association with maternal smoking status and it can explain its contribution to NICU transfer/admission in neonates at term.

To explore these aims, this cross-sectional study uses the 2016 Natality File of Live Births (N= 3,956,112); 2016 is the first year that all 50 states and the District of Columbia fully implemented the revised version of the 2003 U.S. Standard Certificate of Live Birth.⁴⁶ I conducted three sets of analyses in this study. First, I estimated the prevalence and frequencies of smoking in the three months before and during pregnancy across maternal race/ethnicity, age and educational attainment, distributed among all births and among singleton term births. Next, I estimated the rate of newborn morbidity at term using indicators of low birthweight <2,500g, low 5-minute Apgar score, and NICU transfer/admission, accounting for maternal smoking status in early and late pregnancy, and the odds ratios of each morbidity indicator in association with each maternal smoking status category were also calculated. Finally, in mediation analyses, I tested a percentage of the total effect, in the association with NICU transfer/admission, attributable to low birthweight (LBW) in term neonates prenatally exposed to maternal smoking.

Dissertation Outline

There are five chapters in this dissertation. Chapter I (Introduction) provides an overview of the study, research specific aims and objectives, and dissertation outline. The next chapters are arranged by three specific aims. Chapter II presents a review of the selected literature on trends in cigarette smoking and the epidemiology of current smoking in pregnancy, and the impact of tobacco control policies on smoking reduction and cessation, and the birth certificate as a data source on smoking (Aim 1); on prevalence rate and major determinants of low birthweight (LBW) in newborns, focusing on studies using LBW (<2,500g), low Apgar score and NICU transfer/admission as measures (Aim 2); reviewing studies investigating low birthweight in term neonates as a potential mediator in the association with maternal smoking status and NICU admission (Aim 3). Chapter III covers an explanation of methods used in analyses to achieve each specific aim, including descriptive tabulation, logistic regression and mediation analyses. Chapter IV reports on the study results presented in tables and figures. This dissertation ends with Chapter V which includes a discussion of important findings and conclusions in connection with specific aims, the strengths and limitations of this study, study implications for policy and practice, and suggestions for future research.

Chapter II: REVIEW OF SELECTED LITERATURE

In this chapter, the selected literature will be reviewed in subchapters arranged by specific aims.

SPECIFIC AIM 1: To review selected literature on historical trends in smoking and epidemiology of current cigarette smoking during pregnancy, an impact of tobacco control policies on smoking reduction and cessation, and birth certificate as a data source on smoking.

HISTORICAL TRENDS IN CIGARETTE SMOKING

Smoking Among the General Population of Women

The prevalence of smoking among women in the United States grew years before the US Surgeon General's Report on the harmful effects of nicotine on health was published in 1964.⁴⁷ In the early 1900s, cigarette smoking was not a frequent behavior among women because of social disapproval. The rate of smoking among women continued to rise, likely influenced by aggressive marketing of tobacco products to women, which began in the 1920s, as advertisers linked smoking with images of desirability and attraction.^{48,49} In the general population, early smoking behavior followed a pattern described by Rogers in his theory of diffusion of innovation, on how and why new ideas spread through communities.⁵⁰ First adopted by high status social groups, cigarette smoking quickly spread to the rest of the population. Although age at initiation was likely to be later in women than in men, as social acceptance of smoking grew, per capita

cigarette consumption among women between 1924 and 1935 more than tripled (6% to 20%)^{51,52} and increased from 6% in 1924 to 34% in 1965.⁵³ In the 1950's, women were not included in prospective epidemiologic studies because the mortality rate from lung cancer among women remained low. Moreover, no nationally representative surveys of individual smoking habits were conducted before 1955 and early evidence on the rate of smoking was based on consumer preference surveys conducted mostly for commercial purposes.⁵⁴ Even the majority of physicians smoked⁵⁵ and various tobacco products were advertised in medical journals.^{56,57} Ultimately, in 1953, the Journal of the American Medical Association (JAMA) stopped accepting cigarette advertisements and the American Medical Association (AMA) prohibited tobacco companies from exhibiting tobacco products at medical conventions.⁵⁵

The peak of the smoking epidemic lasted into the 1960s and 1970s and tobacco consumption began to decline in every sociodemographic category. Disparities in cigarette smoking by race/ethnicity, age, educational level and socioeconomic status have widened.^{50,57} In the 1960's, smoking initiation rates were higher among White young adults than among Black young adults, and White adolescents were more likely to persist in smoking becoming dependent on nicotine more than Black adolescents.⁵⁸ Women of higher educational level (college graduates) and occupational status started turning away from smoking earlier and in larger numbers, than women in less advantaged circumstances.^{59,60} Less educated women (< 12 years of education) were five times as likely to smoke and one-fourth less likely to quit than college educated women.⁵⁹ As of 2006, smoking prevalence among adult women in the United States was 18% overall and 22% among reproductive age women (18–44).⁶¹ Between 2013 and 2014, twenty out of

every 100 reproductive age women were current smokers and some smoked cigarettes in combination with using other forms of tobacco products.⁶²

Smoking among Pregnant Women

Smoking during pregnancy mirrored smoking among the general population of women in terms of rates and downward trends, but then began to shift among different sociodemographic subgroups of pregnant women. A national population-based study using data from the 1967-1980 National Natality Surveys (NNS), a follow-back survey sample of 1967 live birth certificates of US residents from the National Center for Health Statistics, reported a smoking rate of 40% among White pregnant women and 33% among Black pregnant women.⁶³ Between 1968 and 1979, smoking among teenage mothers increased from 19% to 26% and contributed to an increase in the overall incidence of low birthweight among less educated groups of women.⁶³ Another population-based cohort study linking 1979–1983 birth and death certificates (360,000 births, 2,500 fetal deaths, and 3,800 infant deaths) for Missouri residents, estimated the overall rate of smoking in pregnancy at 30%. The study concluded that fetal and infant deaths would have been reduced by nearly 10% if all pregnant women stopped smoking.⁶⁴ Analyses from the 1987-1996 standard US birth certificate data indicated a 16% decline in the prevalence of smoking among pregnant women.⁶⁵ Between 1990 and 1999, the percentage of women who smoked during pregnancy started declining each year, and about 12.3% of women who gave birth in 1999 smoked during pregnancy.⁶⁶ While declines in smoking were observed for most racial/ethnic groups of women in their twenties and older, non-Hispanic White women and women who had not completed high school had the highest smoking rates during pregnancy.⁶⁶

EPIDEMIOLOGY OF CURRENT SMOKING IN PREGNANCY

Prevalence and Trends of Smoking in Pregnancy

The prevalence of smoking among pregnant women has been changing worldwide. According to 2014/2015 National Health statistics data from the United Kingdom (UK), the rate of cigarette smoking during pregnancy was 11.4%.⁶⁷ In Australia⁶⁸ and in Canada⁶⁹ smoking rates in pregnancy were nearly the same as in the United States (i.e., about 9%).^{1,70} While the smoking rate among pregnant women in the US is considerably lower compared to countries such as Ireland (38.4%), Uruguay (29.7%), and Bulgaria (29.4%), the rate remains higher than the global average rate of 1.7%.⁷¹

Trend analyses in the US over the past two decades demonstrate that the prevalence of smoking during pregnancy varies substantially across race/ethnicity, age, and educational levels. A steady decline in the overall smoking rate from 19.5% in 1989 to 11.4% in 1999 was observed in most racial/ethnic groups including non-Hispanic Whites, non-Hispanic Blacks, Hispanics, and Asians or Pacific Islanders.⁶⁶ Between 1990 and 2000, 47.5% of non-Hispanic White women, 23.8% of non-Hispanic Black women, and 5.6% of Hispanic women, aged 20 and older, smoked during pregnancy and 31% of non-Hispanic White women and 14% -15% of Hispanic and non-Hispanic Black women reported smoking half a pack of cigarettes/day or more.⁷² Non-Hispanic Black women were less likely to smoke before pregnancy than non-Hispanic White women and more likely to quit during pregnancy and after delivery.⁷³ Hispanic women in lower education groups were half as likely to smoke as their non-Hispanic White counterparts, but with

higher levels of and education, they were likely to smoke at high intensity and persist in smoking during pregnancy.⁷⁴

In 2000 about 25% of women aged 18–24 and 23% of women aged 25–44 years old smoked; however, the decline from 26% in 1974 to 10% in 2000 was most evident among educated women, with a bachelor's degree or higher.⁵¹ Typically, increasing educational levels have been associated with decreasing smoking prevalence.^{75,76} Nearly 25.5% women with less than high school education had the highest smoking rates, whereas only 2.0% of college-educated women reported smoking.⁷²

The rate of cigarette smoking declined in the general population from 20.9% in 2005 to 18.1% in 2012, particularly among 18-24 year old adults.⁷⁷ Between 2013-2015, according to data from the Wave 1 and Wave 2 of the Population Assessment of Tobacco and Health Study (N = 7,814) of pregnant women aged 18-44, the overall smoking rate was 13.8% and about half (58%) of women quit smoking during pregnancy.⁷⁸ Non-Hispanic White women (15.5%) had a higher rate of smoking in the three months before pregnancy, compared with Hispanic (3.1%) and non-Hispanic Asian women (1.2%).¹ In 2016, among 9.4% of all women who reported smoking in the three months before pregnancy, 25.0% quit before pregnancy, 7.2% of women smoked at some point during pregnancy, nearly 7.0% of women smoked in the first trimester, 6.0% in the second, and 5.7% in the third trimester of pregnancy.⁴ Among women who smoked at some point during pregnancy, 10.5% were non-Hispanic White women, 6.0% were non-Hispanic Black and 1.8% of women were Hispanic. Smoking rates in pregnancy were highest among 20–24 year old women (10.7%) and among women younger than 20 years (8.5%), compared to 35+ year old women (4.4%).⁴ Women with less than 12 years of

education had a smoking rate as high as 21%, compared with college graduates (10%).⁷⁹

One of the goals of Healthy People 2020 is to increase abstinence from cigarette smoking in pregnancy by 10% to a target of 98.6%.⁸⁰

Other Factors Associated with Smoking in Pregnancy

In an extensive systematic literature review of population-based studies, Schneider and Schutz⁸¹ identified young, unmarried, and women with no prenatal care as those who were most likely to smoke during pregnancy. In prior studies, younger age at onset of pregnancy has been correlated with smoking during pregnancy^{82,83} and unmarried women had a higher smoking rate (20.6%) than married women (8%).⁷² The association between smoking and parity was examined, but the results have been inconclusive.^{73,84} About 16% of women with unintended pregnancies and 18% with unwanted pregnancies smoked during pregnancy⁸⁵ and did not attend prenatal care.⁸⁶ These findings are consistent with other studies on prenatal care use reporting that if prenatal care is delayed, medical advice to stop smoking would also be delayed.⁸⁷⁻⁸⁹ Compared to other groups of women, the smoking rate was higher (13.7%) in 2014 among women who initiated prenatal care late, in the third trimester, or had no prenatal care.¹ Family, friends and living with a partner who smokes may strongly influence overall smoking and hinder smoking cessation during pregnancy.^{81,90} Disparities among non-Hispanic White, young and less educated women remain and cannot be explained by individual socioeconomic status, mental health issues or health inequity.⁹¹

VARIABILITY IN SMOKING PATTERNS AND CESSATION EFFORTS IN PREGNANCY

Variability in Smoking Patterns

Women are becoming increasingly aware of the harmful effects of smoking and many are changing their smoking habits during pregnancy. Fluctuation in smoking patterns described by daily or non-daily smoking, different number of cigarettes smoked each day, as well as short-term changes in duration of smoking are becoming more common during pregnancy.⁹² Researchers seek to understand the consistency of maternal smoking and the way timing and intensity of smoking affect fetal exposure and newborn outcomes.^{6,93–97} While the number of cigarettes smoked per day contributes to the increased risk of fetal growth restriction and lower birth weight, there is inconsistent evidence on how low versus high intensity smoking can impact each trimester of pregnancy with exposure effects. Only a few studies examine time- and intensity-related smoking exposure effects in association with birth weight in preterm or term neonates,^{25,30,98,99} and certainly do not consider measures of timing and intensity in combination. Lieberman et al.²⁵ indicated that exposure to cigarette smoking in late pregnancy, regardless of intensity, had a greater effect on LBW in newborns than exposure early in pregnancy. A 2005 study by Bernstein et al.⁹⁸ that followed 160 women in prenatal clinics found a linear relationship between numbers of cigarettes smoked in the third trimester of pregnancy and decreased newborn birth weight. Another prospective cohort study of pregnant women (n=2,504) supported the previously accepted evidence on smoking throughout pregnancy and low birthweight in newborns, but indicated that women who succeeded quitting prior to 15 weeks of gestation were at no greater risk of delivering LBW infant than non-smokers.⁹⁹

Smoking Cessation Efforts

While existing research indicates that a proportion of pregnant women quit smoking spontaneously ($> 30\%$) upon pregnancy recognition or shortly thereafter, a complete cessation of smoking during pregnancy continues to be a challenge. Women who have been long term smokers cannot quit successfully and usually continue smoking at high intensity during pregnancy.^{52,61,100} According to studies based on data from the Pregnancy Risk Assessment and Monitoring System (PRAMS) in ten US states ($n=115,000$), nearly 55% of women who smoked three months before pregnancy quit smoking some time during pregnancy, 10% of women smoked during the last trimester,¹⁰¹ and quit rates in the first trimester were about 50%.¹⁰⁰ For comparison, in a Canadian study ($n=1,134$), the odds of smoking were 2.4 times higher (OR 2.4; 95% CI: 1.5-3.8) after pregnancy recognition among women under 25 years of age, compared to women 25 years and older,⁶⁹ and women with less education were less likely to quit during pregnancy than other groups of women. A prenatal smoking cessation study ($n=360$) by Benjamin-Garner et al. demonstrated that women who quit smoking in pregnancy had a 299 g increase in newborn birth weight ($p = .021$) and those who reduced smoking from heavy to light smoking had a 199 g increase in birth weight, compared with women who continued smoking at high intensity.³⁰ These studies suggest that smoking patterns during pregnancy and fetal exposures exhibit a great deal of variability. Currently, some pregnant women who attempt to quit are using electronic cigarettes (e-cigarettes or e-cigs) in place of regular tobacco cigarettes. While long-term effects of e-cigs in pregnancy have not yet been established, studies indicate that exposure to nicotine using e-cigs may be similar to regular cigarettes and depends on the frequency of use and a dose-level of a cartridge.¹⁰²

IMPACT OF TOBACCO CONTROL POLICIES ON SMOKING REDUCTION AND CESSATION

Tobacco control policies initiated in the US in 1980s were strongly supported by epidemiological evidence on harmful effects of smoking on health. The policies included widespread public media campaigns to raise awareness, restrictions of tobacco marketing, increased taxes and cost of tobacco products, and increasing the minimum age to 21 for purchase of tobacco products.¹⁰³ The National Tobacco Control Program, created by the CDC's Office on Smoking and Health in 1999, encouraged national efforts to reduce tobacco-related diseases and deaths and provided funding and technical support to health departments across the country.¹⁰³ Ten years later, the Food and Drug Administration (FDA) through the Family Smoking Prevention and Tobacco Control Act (2009), began nationwide regulatory policies directed at production, distribution, and marketing of tobacco products.¹⁰⁴

So far, according to the 2015 Behavioral Risk Factor Surveillance System (BRFSS) report, tobacco control policies in the general population show different effects on smoking prevalence rates among states ranging from 9.1% in Utah to 25.9% in Kentucky.¹⁰⁵ Two earlier population-based studies from the National Health and Nutrition Examination Survey (NHANES) data found decreasing rates of smoking in some participating states in response to tobacco control policy, confirmed with cotinine levels,^{106,107} and one later study reported no significant decrease in smoking in the general population since the introduction of smoke-free policies.¹⁰⁸

Impact of Tobacco Control Policies on Smoking in Pregnancy

The public health benefits of nicotine reduction and/or cessation during pregnancy are enormous in terms of costs and long-term health effects. The expenses of newborn delivery, initial neonatal intensive care unit (NICU) admission and readmissions for persistence of morbidity are high.^{14,39} Studies find that effective smoking cessation interventions targeting reproductive age and pregnant women could reduce these costs.¹⁰⁹ While tobacco control policies implemented at the population-level (e.g., increase in taxes, prohibiting smoking in public places) might have positively affected pregnant women, too little research has been directed specifically towards investigating an impact on pregnancy outcomes. There are only two cross-sectional studies that investigated changes in smoking habits during pregnancy in relation to tobacco control policies. Both studies, conducted in 2014 and based on the 2000–2010 Natality files from 28 states and the District of Columbia, indicated that the cigarette tax increase had the strongest association with improved birth outcomes among non-Hispanic White and non-Hispanic Black women without a high school degree.^{110,111}

BIRTH CERTIFICATE AS A DATA SOURCE ON SMOKING

The US Standard Certificate of Live Birth is a federally mandated system to register all live births in each state and the District of Columbia (DC).^{112,113} The first national US birth registration area was established in 1915 and consisted of 10 states and the District of Columbia (DC). By 1933 the rest of states were included in the system, with Alaska and Hawaii joining the system once they were granted statehood.¹¹⁴ The National Vital Statistics System in cooperation with the National Center for Health Statistics (NCHS) and the US states gather data from all birth certificates annually into the Natality File,

allowing public access to deidentified information and providing representativeness of data used in research.¹¹⁴ During the 20th century, the birth certificate had 11 revisions to improve reporting and data collection,¹¹⁵ and the 1989 version has been gradually replaced with the 2003 revised version.

As of January 2016, fully revised version of the Natality file contains all births registered in the United States⁴⁶ and some newly available information on the average number of cigarettes (or packs) smoked per day during the three months before pregnancy and in each trimester of pregnancy, usage and month of initiation of prenatal care, source of payment for the delivery, participation in the Women, Infants, and Children Supplemental Food Program (WIC) during pregnancy, and neonatal intensive care unit (NICU) admission.^{116,117} Race and Hispanic origin are reported independently, based on 1997 Office of Management and Budget (OMB) standards¹¹⁸ i.e. non-Hispanic single-race White, non-Hispanic single-race Black or African American, non-Hispanic single-race American Indian or Alaska Native (AIAN), non-Hispanic single-race Asian, and non-Hispanic single-race Native Hawaiian or Other Pacific Islander (NHOPI). A recent study by Thoma et al.¹¹⁹ provides an excellent review of the national vital statistics birth certificate data highlighting key concerns for the analysis and interpretation of estimates while using these data in research.

Data Quality and Validation

Self-reports on smoking during pregnancy have generally been perceived as inaccurate, underreported and likely affected by social desirability bias. About a quarter of pregnant women may not disclose their current smoking status related in part to social stigma.¹²⁰

The information on smoking collected from mothers on birth certificates showed moderate to high agreement with a similar self-reported information from the Pregnancy Risk Assessment Monitoring System (PRAMS) data, and slightly less agreement when compared with medical records.^{121,122} The third trimester prenatal smoking reported on the birth certificate also appeared to be highly correlated with newborn cotinine levels.¹²³

Cotinine is a main product of nicotine metabolism and accepted biochemical marker (biomarker) and a gold standard measure of current cigarette use.¹⁰⁷ It has a specificity (true negative rate or percentage of nonsmokers classified as non-smokers) and sensitivity (true positive rate or percentage of smokers classified as smokers) of over 95% when tested in urine, plasma, saliva or hair. However, a cut-off point for cotinine level in plasma or saliva of 15 ng/ml, to distinguish current smokers from non-smokers, were established over 20 years ago and might have changed since then.¹²⁴ Cotinine level depends on individual smoking behavior and on nicotine metabolism that is affected by race and pregnancy status.¹⁰⁷ Accelerated nicotine metabolism in pregnancy¹²⁵ and lower nicotine clearance in Black smokers¹²⁶ may result in differences in cotinine levels. Fluctuation in smoking during pregnancy may cause cotinine levels to be low or undetectable, at times.^{127,128} England et al., in a large multicenter randomized study (n=4,289 total women enrolled, n=508 were self-reported smokers and n=771 were self-reported quitters) found that some self-reported active pregnant smokers tested for cotinine levels were misclassified as quitters.¹²⁹ Studies by Pickett et al.¹²⁸ and George et al.¹³⁰ found plasma cotinine level to be highly correlated with self-reported number of cigarettes smoked at any given time during pregnancy. The percentage of records with

missing information on smoking during any trimester of pregnancy was small (0.5%) on the birth certificate, ranging from 0.1% (New York) to 4.4% (West Virginia).⁷⁰

SPECIFIC AIM 2: To review selected literature on prevalence of low birthweight (LBW), major determinants and precursors of LBW, short-and long-term health effects of LBW, and LBW (<2,500g), low 5-min. Apgar score, and NICU transfer/admission, as morbidity indicators in term neonates.

PREVALENCE OF LOW BIRTHWEIGHT

Low birthweight (LBW) is defined by the World Health Organization (WHO)¹³¹ as newborn weight of less than 2,500 grams (5 pounds 8 ounces) and is a public health concern because of the increased health risks for mothers and infants and socioeconomic burden.^{132,133} The prevalence of LBW in resource-limited countries reaches 20%, compared to up to 10% in developed countries.¹³²

In the United States, between the mid-1980s and 2006, the overall rate of infants born LBW continued to rise from 6.8% in 1983 to 8.3% in 2006, and the percentage of infants born LBW (< 2,500 g) increased 19% since 1990 and mostly included moderately LBW (1,500–2,499 g) infants.¹³⁴ Among singleton term births (>37 weeks gestation) the prevalence rate of LBW rose 10% and average birth weight decreased from 3,441 to 3,389 grams.¹³⁵ Similar trends were observed in Canada,¹³⁶ in the United Kingdom,¹³⁷ Scandinavian countries,¹³⁸ and Japan.¹³⁹ From 1990 through 2006, the prevalence of LBW (<2,500 g) in the US increased nearly 20% (8.26%), and then decreased to 7.99%

in 2012.¹⁴⁰ Birth weight among term births has decreased especially after 1999.¹³⁵ Between 2015 and 2017, the LBW rate rose each year (8.07%, 8.17%, and 8.28%, respectively) and the rate of singleton LBW rose from 6.34% in 2015 to 6.56% in 2017.¹⁴¹ In 2011, 15 per 1000 term newborns in the U.S. were born small-for-gestational-age (SGA), a 29.9 % increase since 2002.¹⁴² In 2017, the overall rates of LBW were highest among non-Hispanic Black (13.89%), compared to non-Hispanic White (7.00%), and Hispanic (7.43%) infants. Rates of LBW differed across states, ranging from 6.6% in Iowa and Washington to 8.1 % in New York, Connecticut and Oklahoma, and 11.6% in Mississippi, 10.7% in Louisiana, and 10.3% in Alabama.¹⁴¹ Low birthweight, after preterm birth, is the second leading cause of perinatal mortality in the United States.¹¹ Even though overall infant deaths from prematurity and low birthweight declined 8% between 2005 and 2014, infants of non-Hispanic Black mothers have higher mortality rates than infants of other major racial/ethnic groups of mothers.¹⁴³

MAJOR DETERMINANTS OF LOW BIRTHWEIGHT

The etiology of low birthweight is multifactorial and maternal, fetal and placental risk factors jointly influence the process of fetal growth and newborn birth weight. Among the commonly studied maternal risk factors are nutrition, low pre-pregnancy body weight, lifestyle behaviors (smoking, drugs and alcohol use), young or advanced age at giving birth, low socioeconomic status, previous pregnancy with intrauterine growth restriction (IUGR), nulliparity (i.e. never given birth to a child), multiparity (i.e. given birth to one or more children) and a short inter-pregnancy interval.^{32,131,144}

Nutrition and Low Pre-pregnancy Weight

Inadequate nutrition and low pre-pregnancy body mass index (BMI) are the main risk factors for reduced fetal growth and LBW in developing countries.¹⁴⁵ Maternal low pre-pregnancy BMI (i.e. underweight before pregnancy) has been independently associated with having LBW infants,^{146,147} and the effect of smoking during pregnancy on low birthweight remained in both underweight and normal weight women.¹⁴⁸

Young and Advanced Maternal Age

Infants of the youngest mothers experience almost twice the rates of preterm delivery (21.3%) and low birthweight (12.6%).¹⁴⁹ The findings from a California study 2005-2014 (N=5,267,519) indicate that young maternal age is a significant risk factor for LBW, regardless of maternal race and ethnicity or education level.¹⁵⁰ Older maternal age was also examined and found to be an independent risk factor for intrauterine growth restriction (IUGR) and small-for-gestational age (SGA) newborns.¹⁵¹ Non-Hispanic Black mothers (35-54 years old) had a 2.4-fold greater risk of delivering infants with LBW than non-Hispanic White mothers of the same age.¹⁵⁰ Whereas some authors argued that in older mothers preexisting medical conditions, obstetrical history, and social characteristics might have confounded the study results.^{152,153}

Nulliparity, Multiparity and Previous IUGR Pregnancy

Nulliparity (i.e. never given birth to a child), multiparity (i.e. given birth to one or more children), and previous birth to an IUGR infant are well recognized predictors of LBW, with the lowest birth weights recorded among infants born to the first time mothers.¹⁵⁴

The recurrence of a growth-restricted neonate in a subsequent pregnancy, in association

with behavioral risk factors (e.g. smoking and underweight) and maternal health (e.g. hypertensive disease, diabetes or renal disease), may be as high as 20.1% to 28.7% .¹⁵⁵

Inter-Pregnancy Interval

Evidence has not been conclusive on the length of inter-pregnancy interval in association with LBW. One study observed the strongest association for preterm birth with inter-pregnancy interval shorter than 6 months (adjusted OR 1.83, 95% CI 1.65-2.03),¹⁵⁶ in contrast, another study demonstrated much weaker effects on the odds of low birthweight in offspring; however, studies differed by design used in analyses (i.e. within mother vs traditional between mother analysis).¹⁵⁷

Sociodemographic status

Socioeconomic disparities in birth outcomes are prevalent and have been studied extensively at both the individual and the community level.^{158,159} The association between low socioeconomic status (SES) and LBW in neonates delivered preterm has been strong,¹⁵⁹ but few studies have considered exploring the association between low SES and the risk of delivering a LBW infant at term.

Lifestyle Factors

Smoking is the strongest maternal lifestyle-related and modifiable risk factor for the increased risk of LBW.^{160–162} The evidence of LBW in association with other maternal risk factors such as caffeine, alcohol and drug use or with multi-substance use is mounting.¹⁶²

MAJOR PRECURSORS OF LOW BIRTHWEIGHT, FETAL GROWTH AND PRETERM BIRTH

Major precursors of low birthweight include slow intrauterine fetal growth and premature delivery, and both may occur simultaneously.¹⁶³

Intrauterine Fetal Growth

About 5% of all pregnancies, either preterm or at term,¹⁶⁴ are affected with a pathological intrauterine fetal growth restriction (IUGR) resulting in small-for-gestational age (SGA) newborns with low birthweight.¹⁶⁵ IUGR is an estimated fetal weight of less than the 10th percentile for gestational age; not taking into account genetically determined fetal growth in a small-for-gestational age (SGA) newborn.¹⁶⁵

A study of 7,642 singleton pregnancies from Denmark, in which data were obtained from ultrasound measurements at 11-14 weeks (fetal crown-rump length and biparietal diameter) and at 17-21 weeks (biparietal diameter), revealed that slow growth of the fetal biparietal diameter between the first and second trimesters of pregnancy was a strong predictor of poor fetal growth including death before the 34 weeks gestation.¹⁶⁶

Preterm birth

Short duration of gestation marked with preterm birth is an important predictor of low birthweight (LBW) and infants born preterm may also be affected with IUGR.¹⁶³ The overall rate of preterm birth (<37 weeks gestation) rose from 9.63% in 2015 to 9.85% in 2016 and to 9.93% in 2017, and for singleton births only the rate increased from 7.82% in 2015 to 8.02% in 2016 and to 8.13 % in 2017.¹⁴¹ In a direct association with gestational

age, infants may have very low birthweight (VLBW) (<1500g), extremely low birthweight (<1000g) or an appropriate weight for gestational age (AGA).¹⁶⁷

LATE PRETERM AND EARLY TERM BIRTHS

Over the past two decades, a proportion of infants delivered late preterm (previously referred as “near term”) (defined as 34-36 weeks gestation) and early term (37-38 weeks gestation) with low birthweight (LBW) has increased by almost 50%.^{168,169} Research has documented vulnerabilities in infants born prior to full-term (39-40 completed weeks gestation) and of normal size and birthweight (>2,500g).^{9,17-19,21,22,170,171}

A population-based study, using Massachusetts birth and death certificate data (1998–2003) (n=26,170 late preterm and n=377,638 term infants), demonstrated that morbidity rates nearly doubled for each additional gestational week before 38 weeks.¹⁷¹ Infants born late-preterm were seven times more likely to have morbidities than infants at term (22% vs 3%).¹⁷¹ The number of hospitalizations for respiratory problems during the first year of life doubled in moderately preterm infants (32–36 weeks’ gestation)⁹ and the mortality rate was up to three times higher, compared with infants born at term.¹⁷³

It became evident that gestational age represents a continuum from less to more mature rather than just “preterm” and “term”¹⁷² and infants are at an increased risk of morbidity and dying throughout the neonatal period and postnatally.^{18,174–179} In different subgroups of term births, newborn health may also differ by a week or two of gestation.^{183–186} Therefore, to demonstrate these differences, term birth (37-41 completed weeks gestation) has been defined more precisely as early term (37–38 weeks gestation), full term (38-39 weeks gestation), and late term (40-41-week gestation).⁴¹

Currently, early term infants outnumber late preterm infants by 3 to 1 in the United States (27.6% vs 8.7% of all births in 2009)^{18,181,182} and in 2006, the mortality rate for early term infants (37-38 weeks gestation) was higher in non-Hispanic Black infants (2.2/1000), compared to non- Hispanic White (1.6/1000) and Hispanic (1.5/1000) early term infants.¹⁸⁰ Based on this research, previous authors have proposed that the last 3 weeks of gestation may represent a critical period in fetal growth and maturation of organ systems in preparation for birth.¹⁸⁷

SHORT- AND LONG-TERM HEALTH EFFECTS OF LOW BIRTHWEIGHT

Existing literature converges on the notion that neonatal morbidity and mortality increase with decreasing gestational age and birthweight. The most often investigated short-term health sequelae in association with LBW are respiratory disorders in infants and children,^{16,174} cerebral palsy and death in the first year of life,¹⁸⁸ neurodevelopmental delay,^{189,190} neurobehavioral and cognitive disorders,¹⁹¹ and attention deficit disorders in children.¹⁹² Implications of LBW in infants, who were growth restricted in utero, have been found extending into adulthood and linking to a higher incidence of hypertension, coronary artery disease and stroke,^{193,194} chronic obstructive pulmonary disease,¹⁹⁵ obesity and type-2 diabetes,¹⁷⁷ and depression.¹⁷⁸

MORBIDITY INDICATORS IN INFANTS AT TERM PRENATALLY EXPOSED TO SMOKING

Research has consistently supported smoking during pregnancy as a risk factor for adverse newborn outcomes using low birthweight, low Apgar score and NICU transfer or admission as morbidity indicators in assessment of newborn health status at birth.

Low Birthweight

Low birthweight (LBW) is the strongest single risk factor for perinatal, neonatal and infant mortality at any gestational age.¹⁸⁶ Low birthweight in term singletons (37- 41 completed weeks gestation) (term-LBW) is weight less than 2,500g (or 5lbs 8 oz.).^{41,196} It is expected that longer gestation is likely to increase infant maturity and birth weight, and infants delivered at term have always been considered fully grown and typically healthy.¹⁸⁰ While, the majority of infants with LBW are born preterm (<37 weeks gestation), a proportion of infants born at term (>37 weeks gestation) have LBW. Compared to infants born at term of normal weight, term infants with LBW have low Apgar scores,¹⁹⁷ higher rates of respiratory disorders and NICU admissions,^{172,174,198,199} longer durations of hospital stay,^{21,179} and higher re-hospitalization rates during the postnatal period.^{12-14,36,39,200,201}

Numerous review articles show that tobacco exposure at different levels of intensity and in different stages of pregnancy can influence fetal growth causing different severity of neonatal morbidity apparent at birth and later in life.²⁰²⁻²⁰⁴ Research articles demonstrate that decreasing birth weight is related to timing and intensity of smoking during pregnancy, and a reduction in birth weight correlates with the impairment in fetal growth²⁰⁶ and coincides with the maximum growth of the fetus during the third trimester.^{25,98,99,205} The average reduction in birth weight was 200 to 377 g, compared to

non-smokers, and larger reduction was seen among heavy maternal smokers²⁰⁷ and smoking during the third trimester.⁹³ A study from Sweden, of infants with known smoking exposure in early pregnancy (n= 1,413,811), demonstrated increased odds ratios for adverse outcomes of smoking less than 10 cigarettes/day (OR 1.39; 95% CI:1.37-1.41) and more than 10 cigarettes/day (OR 1.65; 95% CI:1.62-1.68), including preterm birth, IUGR, low Apgar score, stillbirths and neonatal deaths.²⁰⁸ In a retrospective cohort based on the birth certificate data (1990-2002) of 78,397 term live births in Kansas City, Missouri, the overall LBW rate was 3.3% and smoking was a major risk factor (OR 2.3; 95% CI: 2.0-2.4).¹⁶¹ A population-based prospective study (n=9,778) of pregnant women indicated that smoking before pregnancy, at any intensity, had no influence on newborn birth weight; however, smoking more than 9 cigarettes/day was associated with significant increase in the odds of LBW (aOR 3.39; 95% CI: 1.45, 7.91).⁹⁶

Low Apgar score

The Apgar score (AS) measures clinical health status of a newborn soon after birth and is recorded on every birth certificate. Developed over 60 years ago (in 1953) by an anesthesiologist Dr. Virginia Apgar, the Apgar score was initially intended to identify neonates in need of immediate cardiopulmonary resuscitation.^{210,211} “The score” has been used and interpreted by medical personnel with various levels of training all over the world. The Apgar scoring system forms the acronym APGAR describing five basic newborn health characteristics (parameters): appearance, pulse, grimace, activity, and respiration. Each parameter has an assigned score of 0, 1, or 2 for a total score of 10. The Apgar score (AS) is obtained at 1 and 5 minutes after birth and may be repeated at 5-minute intervals if newborn health status remains unstable.²¹⁰ Typically, a 5-minute

score of < 7 can identify neonates in need of ventilation and possible NICU transfer/admission.^{212,213} Risk factors for a low AS include gestational length, fetal growth abnormality, congenital malformations, and general maternal health.^{208,214}

In a Russian birth registry study (n=44,486), Kharkova et al.¹⁹⁹ demonstrated a dose-response relationship between the number of cigarettes smoked per day during pregnancy and a 5-minute AS of <7, with increasing odds of a lower score associated with a higher number of cigarettes smoked per day (i.e., 1-5 cigarettes/day (aOR 1.35, 95% CI:0.87, 2.08) ; 5-10 cigarettes/day (aOR 1.83, 95% CI: 1.23, 2.73); and ≥ 11 cigarettes/day (aOR 2.06, 95% CI: 1.10, 3.89).¹⁹⁹ In another study, while maternal smoking was associated with higher rates of a low AS (<7), compared to non-smokers (4.8 vs 8.1 % respectively; p = 0.003), smoking was found not to be an independent predictor of low 5-min AS.²¹⁵ A large retrospective analysis found the infant mortality rate to be 24.4% if the 5-min AS was < 7, compared to 0.02% if the AS was ≥ 7 .²¹² These findings were consistent with an earlier study that showed a 5-min Apgar score of ≤ 3 to be strongly related to the incidence of respiratory disorders (47.1%) and an increased risk of mortality,²⁷ and with a recent study that assessed high-risk neonates in a resuscitation training program in Illinois using AS.²¹⁶ The Apgar score has been used to study associations with short- and long-term clinical²¹⁷ and educational outcomes in children at the population level.²¹⁸ A low 5-min AS was associated with slight cognitive impairment, as measured by academic achievement at 16 years of age.²¹⁹

NICU Transfer/Admission

A rapid recognition of any change in newborn health status (e.g. low 5-min Apgar score) during the first few “golden minutes” of life and referral to specialized care in the NICU will increase chances for survival.^{213,220} A population-based cohort study (n=1,164,953) found a positive association between continued maternal smoking after the first trimester and an increased risk of NICU admission (aOR 1.27, 95% CI: 1.25, 1.30), compared to smoking in the first trimester only (aOR 1.19, 95% CI: 1.15, 1.24).²²⁴ Transient tachypnea of the newborn is the most common respiratory disorder of newborns delivered at term,^{38,221} but infants of mothers who smoked in pregnancy may have symptoms of severe respiratory distress syndrome³⁸ or suffer nicotine withdrawal.²²² In a sample of term singletons (n=65,000) admitted to the NICU, the most common diagnoses were transient tachypnea of the newborn (36.4%), meconium aspiration syndrome (31.0%) and respiratory distress syndrome (19.4%), which were often severe, as reflected by a high incidence of associated complications and a mortality rate of 3.9%.²²³ Low birthweight is a dominant risk factor in neonatal respiratory morbidities that account for a large portion of neonatal deaths in the United States.²²⁶ Growth restricted infants spend a significantly increased time in the NICU and on mechanical ventilation, compared to age-matched normal size control infants, and rates of respiratory distress syndrome and bronchopulmonary dysplasia are highly increased.²²⁵ These data suggest that morbidities in growth restricted infants born with LBW can substantially contribute to high health care utilization and overall disease burden.^{13,21,22} Admission rates to the NICU during 2007-2012 increased overall from 64.0 to 77.9 per 1000 live births (RR 1.22; 95% CI, 1.21-1.22; $p < .001$) and for all birth weight categories.²²⁷ Between 2009 and 2010, 50.4% of infants admitted to the NICU were term infants (37-41 weeks

gestation), more than 85% were singleton births, 46.9% of infants were born at 37-38 weeks, and 44.2% were born at 39-41 weeks gestation. An average length of stay was 13.2 days, ranging from 4.9 days among infants born at 39-41 weeks to 46.2 days among infants <32 weeks gestation.²²⁸ Infants admitted to the NICU as newborns had higher rates of hospital readmission during the neonatal period and in the first year of life than other healthy infants.¹³ Evidence shows that availability of regionalized higher level of care and optimal distribution of NICU services, including neonatal transport, improves newborn outcomes, quality of care and costs.²²⁹⁻²³¹

BIOLOGICAL MECHANISMS OF SMOKING EFFECTS

Tobacco smoke consists of a mixture of over 4,000 potentially toxic chemicals distributed between the particulate and gaseous phases of combustion products. Smokers take in an average of 1–1.5 mg of nicotine per cigarette²³² and nicotine is a main addictive and toxic agent recognized as reproductive toxicant.^{232,233} The exact mechanisms by which nicotine produces adverse fetal growth effects are not known. It is likely that nicotine can directly reach the fetus from maternal circulation, crossing the placental barrier,^{265,266} and acting indirectly, nicotine can damage the placenta, induce constriction of placental blood vessels, increase oxidative stress and inflammation, and ultimately reduce oxygen and nutrient transport to the fetus.²³⁵ Cotinine, a nicotine metabolic product, has been detected in amniotic fluid in the first half of pregnancy²³⁶ and throughout pregnancy in placental tissues, umbilical cord blood, and in maternal saliva, blood and urine.^{206,235}

Fetal growth and development begin with the period of embryogenesis and organogenesis in early pregnancy.²³⁷ Several lines of experimental and clinical evidence suggest that the timing and the extent of exposure in early stage of pregnancy can activate major fetal growth pathophysiology.^{206,234,238,239} A period toward the end of the first trimester, at the onset of placental development and beginning of maternal-placental-fetal unit circulation, appears to be the most sensitive (vulnerable) gestational period when smoking exposure can initiate fetal growth restriction resulting in low birthweight in newborns.^{237,240} Smoking influence on birth weight, manifested as a slower growth between the first and the second trimester, has been supported by ultrasound examination.¹⁶⁶ Grounded in the principles of evolutionary biology and in the developmental origins of health and disease, the placenta and the fetus have the potential to adapt to the adverse intrauterine environment through *in utero* “programming”.^{241,242} Findings from both animal and human studies provide plausible evidence that fetal lung²⁴³ and brain development²⁴⁴ can be adversely affected by smoking in early pregnancy. Recent evidence has emerged regarding the potential impact of prenatal smoking exposure on metabolic and cardiovascular diseases likely to be mediated by epigenetic mechanisms.^{245,246}

SPECIFIC AIM 3: To review selected literature on mediation as a statistical tool and to identify if any prior studies have investigated low birthweight as a potential mediator in the association with maternal smoking status and morbidity in a term neonate.

MEDIATION ANALYSIS AS A STATISTICAL TOOL

Mediation modeling has been widely used in epidemiological research to disentangle the effects of the association between an exposure and an outcome through intermediate causal mechanisms. More than three decades ago, Baron and Kenny²⁴⁷ proposed a framework on how to decompose a total effect of the exposure-outcome association into indirect and direct effects via the intermediate variable (mediator) under a certain set of assumptions, and how to test mediation involving a series of regressions.

In fact, an expanding scope of current mediation methods involves striving to unscramble the “black box” issue, to define mechanisms and to understand causal inferences.^{248–254} Efforts have been made to clarify the underlying assumptions and the construct of confounding to make causal mediation modeling and interpretation of causal effects useful in research.^{255–257} MacKinnon (2008) upholds that a mediator influenced by the exposure can produce indirect effects with the exposure and the outcome and a measurable change follows when variables are affected reciprocally.²⁵⁷ The goal of mediation analysis is to appreciate what proportion of the total effect, decomposed into direct and indirect effects, may be attributed to the potential mediator, eventually revealing possible causal mechanisms. Complete mediation^{247,258} implies a complete elimination of the exposure-outcome effect (direct effect) with inclusion of the mediator. Partial mediation^{247,258} occurs when the mediator partially describes the effect, which has been reduced, and may provide valuable information on alternative mechanisms involved in the association of interest.

LOW BIRTHWEIGHT IN A NEONATE AT TERM AS A MEDIATOR

Low birthweight (LBW) (<2,500g) in an infant delivered at term has been selected as a potential mediator in the association with maternal smoking status and NICU transfer/admission. Research indicates that infants with LBW delivered at term suffer morbidities apparent at birth, have higher rates of NICU admission, higher utilization of the emergency department and re-hospitalization during the first year of life, compared to non-LBW infants.^{21,36} Health complications commonly diagnosed at birth in LBW infants may continue throughout childhood and into adulthood,^{16,174,177,188–192,194,195,198,199,259–263} Although infants delivered at term (>37 weeks gestation) consist the largest group of newborns, compared to a smaller high-risk group of infants born preterm (<37 weeks gestation), few studies have been conducted that focus on health of infants at term who require immediate NICU admission.

So far, little is known about how LBW may influence immediate health status in term neonates. While researchers argued that birth weight may not be on the causal pathway to infant mortality,^{270,271} the role of LBW in morbidity of term neonates exposed to prenatal smoking^{5,25,45,93,98,164,208,215,264,265} is likely to be exposed. Only three studies have previously used birth weight as a potential mediator, and none of them considered LBW in term newborns in association with NICU transfer/admission. A study by Gold et al., using data from the 1998–2002 California Birth Cohort (n= 2,600,000 births), conducted a retrospective cohort analysis on the role of prematurity (< 37 weeks gestation) and low birth weight (<2,500 g), as a potential mediating risk factor.²⁷² The authors found birth weight to be a useful potential mediator to help understand higher rates of stillbirth in mixed race couples in comparison with same race couples. A more

recent study by Geraci & Mattei,²⁷³ based on the 2001-2005 NCHS file of live births (n=11,590,581) and infant deaths (n=57,245) of White singletons, used birth weight as a mediator to explain the association with maternal smoking and sudden infant death syndrome (SIDS). The study concluded that the indirect effect of smoking on the increased risk of SIDS was not mediated by changes in the birthweight distribution, but through pathways other than birthweight.²⁷³ A study by Gage et al.²⁷¹ investigated racial disparities in infant mortality in the US, and confirmed the hypothesis that birth weight was not on the causal pathway to infant mortality among “normal” births, but it could play a role among “compromised” births. Mediation is an important tool in exploring the association between the exposure and the outcome in testing hypotheses to elucidate etiologic mechanisms. Yet, there is limited research and a lack of studies that choose low birthweight, as a mediator, to explain its role in the association with morbidity and NICU transfer/admission in neonates delivered at term.

Chapter Summary-Literature review

This review of the literature indicates that smoking remains prevalent among pregnant women in the United States and continual monitoring is necessary for trends in smoking before and during pregnancy, including any changes in prevalence rates and patterns based on variability among the most vulnerable groups of women. Too little attention has been paid in research to the effects of tobacco control policies among pregnant women in relation to neonatal outcomes, particularly in states with the highest prevalence of smoking among reproductive age women. Maternal smoking disrupts normal fetal growth influencing newborn, child and adult health. Relations between low birthweight, low Apgar score and newborn morbidity are mainly based on clinical reports of preterm

and very preterm births, and there is a gap of information on the health of infants that are not born preterm. More attention is needed in research on the significance of prenatal smoking exposure in term neonates in association with short- and long-term health sequelae. This literature review reveals that there is limited research on low birthweight in term neonates, which is an important contributor to neonatal morbidity, health care cost and economic burden. A few available studies offer support for using LBW as a mediator in exploring etiologic mechanisms on adverse newborn outcomes in the association with maternal risk factors.

Chapter III: METHODS

This chapter is arranged by three specific aims and explains the design and methods of statistical analysis used in this dissertation to investigate the prevalence of maternal smoking and its association with morbidity in singleton term births.

DATA SOURCE

The data source for this dissertation was the 2016 Natality File of Live Births (N= 3,956,112) produced by the National Center for Health Statistics (NCHS) and representing 100% of births registered to all United States residents.^{46,116} As of January 2016, all 50 states and the District of Columbia implemented the 2003 revised version of the U.S. standard birth certificate, thus improving its content and making the data nationally representative. The 2003 revision of birth certificate expanded information on the average number of cigarettes (or packs) smoked per day during the three months before pregnancy and during each trimester of pregnancy. The new items in the revised version included maternal usage and month of initiation of prenatal care, highest educational degree attained, method of delivery, pre-pregnancy weight, participation in the Women, Infants, and Children Special Supplemental Nutrition Program (WIC) during pregnancy, height and weight at delivery for calculation of body mass index (BMI), principal source of payment for delivery.¹¹⁶ The use of such a broad dataset provided an opportunity for this dissertation to investigate the prevalence of smoking before and during pregnancy in the subpopulations and its association with newborn outcomes.

This study received an exemption from the University of Maryland Institutional Review Board (IRB).

DATA VALIDATION AND MISSING DATA

Studies validating the quality of data on the 2003 birth certificate in selected states provide evidence that most of the maternal demographic data and basic infant characteristics (e.g., birth weight, sex) are accurately collected and reported on birth certificates.^{274,275} Data quality was high on pregnancy risk factors (e.g., tobacco use, diabetes), on prenatal care utilization and infant health outcomes, when compared with information abstracted from hospital medical records.^{274,275} A low rate of missing information was found on demographic and health variables (e.g., mode of delivery, birth weight), and underreporting included a few other health data items.²⁷⁶ The total percentage of records with missing information on smoking during any trimester of pregnancy was 0.5%.⁷⁰ According to the Quarterly Provisional Estimates, Technical Notes (Quarter 1, 2016) published by the Centers for Disease Control and Prevention (CDC), a relatively low rate of missing values related to estimates of reproductive health has been identified in the 2016 revised birth certificate.²⁷⁷

Handling Missing Data

In this study, the listwise deletion technique,²⁷⁸ known as complete case analysis, was employed in sensitivity analysis for handling missing data. This approach involved using the IF-statement (conditional statement) and the DELETE statement in SAS version 9.4 (SAS Institute Inc., Cary, NC). The frequencies for each missing variable and its sub-

categories and the percentage of missing observations per each study variable and mean $\pm$ standard deviation (SD) were reported in Table 1.

ANALYTIC SAMPLE

The analytic sample in this study consisted of the entire Natality File of Live Births (N=3,956,112) registered in the United States in 2016 (Appendix B, Figure 1). The dataset was reduced by missing observations (N=384,270) leaving N=3,571,842 records for analysis in Specific aim 1. The sample of N=3,571,842 was subsequently restricted to singleton term births (37-41 completed weeks gestation) and reduced by multiple births and births <37 and >42 weeks gestation (N=395,869), leaving N=3,175,973 (88.91%) records for analyses in Specific aims 1, 2 and 3. (Appendix B, Figure 1) The reason for restricting the sample to singleton term births was to examine them separately from preterm and post-term births, because gestational age may be confounding the effects of prenatal smoking exposure across trimesters resulting in morbidity of different severity level.²⁷⁹ The effects of exposure may also vary for multiple births and for other newborn growth pathologies with different risk morbidity profile.²⁸⁰ In addition, a small group of women (N=2,973) who smoked at high and low intensity in late pregnancy (third trimester only) were not included in a separate smoking status category.

SPECIFIC AIM 1: To examine the prevalence and patterns of cigarette smoking in the three months before and during pregnancy across maternal race/ethnicity, age, and educational attainment and the distribution of smoking exposure in early (first and second

trimester) and late (third trimester) pregnancy among all births and among singleton term births (37-41 completed weeks gestation) in the United States in 2016.

STUDY POPULATION AND STUDY SAMPLE

The analytic sample in Specific aim 1 included the entire 2016 Natality File of Live Births (N=3,956,112) reduced by missing observations (N=384,270) leaving N=3,571,842 records for analyses of all births, and a sample restricted to singleton term births (37-41 completed weeks gestation), after excluding multiple births and births of <37 and >42 weeks gestation (N=395,869), leaving N=3,175,973 (88.91%) records for analyses of singleton term births (Appendix B, Figure 1). Because the file included the complete population of U.S. births, statistical sample weights were not needed to assure data representativeness.

STUDY DESIGN

This cross-sectional study was conducted to examine the prevalence and patterns of maternal smoking before and during pregnancy across maternal race/ethnicity, age, and educational attainment and the distribution of smoking exposure in early (first and second trimester) and late (third trimester) pregnancy among all births and among singleton term births (37-41 completed weeks gestation) in the United States in 2016.

MEASUREMENTS

Pregnancy is commonly divided into three trimesters (stages): the first trimester (months 1-3- or 1-13-weeks' gestation), the second trimester (months 4-6 months or 14-27 weeks

gestation), and the third trimester (months 7 to delivery or 28 + weeks gestation).²⁸¹

Pre-pregnancy is defined as the period during the three months before pregnancy.¹

Births in this study included all live births reported on the 2016 US standard birth certificate and occurring at any gestational age.⁴⁶ Singleton term birth was a delivery of only one infant between 37 and 41 completed weeks gestation.^{41,19641,196} The revised birth certificate uses the obstetric estimate as the standard primary measure of gestational age that combines the date of last menstrual period (LMP) and ultrasound (US) measurements (OE).²⁸² This estimate has been shown to have greater validity than the LMP-based measure alone when compared with medical records.²⁸³

Maternal demographic characteristics were self-reported on the birth certificate including race, ethnicity, age, and educational attainment.⁴⁶ In this study, race and ethnicity were classified based on the 1997 US Office of Management and Budget (OMB) classification standards¹¹⁸ and the leading categories in the US included non-Hispanic White race (White women), non-Hispanic Black race (Black women), Hispanic ethnicity (Hispanic women), and other race/ethnicity groups were non-Hispanic Asian (Asian women) and non-Hispanic American Indian/Alaska Native women.^{4,284}

Maternal age was categorized as less than 20, 20-24, 25-29, 30-34, and 35 years old or older; and maternal education was categorized as less than high school, high school graduate/GED (General Educational Development), some college or associate degree, and bachelor's degree or higher.

Smoking Status

Maternal smoking status was identified on the standard birth certificate by the number of cigarettes smoked daily.^{1,46} Women were considered smokers if they reported smoking at least one cigarette/day and were classified as non-smoking only if they reported no cigarette use during any trimester. Consistent smokers smoked in the first trimester only, in the first and second trimesters only, or in all three trimesters, and inconsistent smokers reported smoking in the first and in the third trimester only but denied smoking in the second trimester, and who reported smoking in the second trimester only, in the second and the third trimester, or in the third trimester only. Timing of smoking was assessed in the three months before pregnancy and in each trimester of pregnancy, in which smoking was reported, and intensity was assessed by the number of cigarettes smoked per day and categorized as low intensity (1-9 cigarettes/day) and high intensity (≥ 10 cigarettes/day).

Quality of Self-reported Smoking Data

While self-reports are a simple and practical way to obtain information on smoking, they may be misclassified due to reporting bias.²⁸⁵ About a quarter of pregnant women do not disclose smoking throughout pregnancy, related in part to social stigma.^{120,122} It was assumed that women who reported smoking were active smokers because nonsmokers would be less likely to report active smoking in pregnancy.^{107,286}

PRENATAL EXPOSURE STATUS

Prenatal exposure status in this study was examined accounting for the variability in patterns of timing and intensity of maternal smoking.^{128,287} To examine the extent of potential prenatal smoking exposure more thoroughly, the standard methodology was advanced in this study by creating a set of seven mutually exclusive maternal smoking

intensity categories, based on combined measures of timing and intensity of smoking across trimesters: (1) *Quitter-1*: low intensity smoking in early pregnancy only (only low intensity smoking in the first or second trimester, none in the third trimester); (2) *Quitter-2*: high intensity smoking in early pregnancy only (any high intensity smoking in the first or second trimester, none in the third trimester); (3) *Maintainer-1*: low intensity smoking in early (only low intensity smoking in the first or second trimester) and low intensity smoking in late pregnancy (the third trimester); (4) *Maintainer-2*: high intensity smoking in early (any high intensity smoking in the first or second trimester) and high intensity smoking in late pregnancy (the third trimester); (5) *Reducer*: high intensity smoking in early (any high intensity smoking in the first or second trimester) and low intensity smoking in late pregnancy (the third trimester); (6) *Increaser*: low intensity smoking in early (only low intensity smoking in the first or second trimester) and high intensity smoking in late pregnancy (the third trimester); (7) *Nonsmoker* (No smoking in any trimester during pregnancy, reference) (Table 4).

STATISTICAL ANALYSES

The analyses in this section described the prevalence of smoking before pregnancy and in early (the first and second trimester) and late (the third trimester) pregnancy by maternal demographic characteristics, among all births and among singleton term births in the United States in 2016. Descriptive cross-tabulations for all births were presented in Figures 2-4 and reported in a contingency table (Table 2), and for singleton term births in Figures 5-7, and in Table 3. The distribution of smoking exposure in early and late pregnancy among all births in 2016 was shown in Table 5, and among singleton term births in Table 6. The Chi-square test of Independence (Pearson Chi-Square test) was

used to assess differences in significance in the relationships between categories of variables. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

SPECIFIC AIM 2: To examine potential prenatal exposure among term singletons (37-41 completed weeks gestation) across maternal and infant characteristics in early (first and second trimester) and late (third trimester) pregnancy and the odds of low birthweight (<2,500 g), low 5-minute Apgar score (<7), and NICU transfer/admission in the association with maternal smoking status.

STUDY POPULATION AND STUDY SAMPLE

In this section of the study, the analytic sample (N=3,175,973) was restricted to singleton term births (37-41 completed weeks gestation) (Appendix B, Figure 1).

STUDY DESIGN

This cross-sectional study examined the association between maternal smoking status, as an exposure and low birthweight (<2,500 g), low 5-minute Apgar score (<7), and neonatal intensive care unit (NICU) transfer/admission, as newborn morbidity indicators and three independent outcomes.

MEASUREMENTS

Exposure Variable

The exposure variable was cigarette smoking during pregnancy classified into seven mutually exclusive maternal smoking intensity status categories across early (first and second trimester) and late (third trimester) pregnancy, as described in Specific aim 1 and presented in Table 4.

Outcome Variables

The three binary variables: low birthweight (LBW) <2,500g (or 5 pounds, 8 ounces), 5-minute Apgar score < 7, and NICU transfer/admission, were statistically independent outcomes and newborn morbidity indicators.

Definitions

Birth weight is reported on the birth certificate in grams ranging from 227 to 8165 grams.¹ Birth weight < 2,500 grams (or 5 pounds, 8 ounces)¹³¹ is considered abnormal in term neonates and is a proxy of fetal growth restriction and a measure of neonatal morbidity.²⁸⁸ The Apgar score (AS) is a tool used for a rapid clinical assessment of the newborn at 1 minute and at 5 minutes after birth and is recorded on every birth certificate.²⁸⁹ Apgar score < 7, on a scale of 0-10, measured at 5-minutes after birth is considered abnormal.²⁸⁹ The Neonatal Intensive Care Unit (NICU) is a facility or hospital unit staffed and equipped to provide specialized care to premature and sick newborns.^{290,291} The National Vital Statistics System in the US defines NICU transport//transfer and admission as two distinct variables,^{46,292} which in this study were combined into one binary (hybrid) variable to represent NICU transfer/admission.

Other Covariates

Several covariates were selected from the birth certificate for cross-tabulation based on established association with maternal smoking and/or an association with neonatal morbidity.^{32,293,294} Maternal race/ethnicity categories were: non-Hispanic White (referent), non-Hispanic Black, Hispanic and other, which included Asian, American Indian/Alaska Native, Native Hawaiian, Pacific Islander or mixed race; maternal age at delivery was categorized as less than 20, 20-24, 25-29 (referent), 30-34, or 35 and more years old; maternal educational attainment was defined as less than high school, high school/GED only (referent), some college/associate degree, or bachelor's degree and higher; marital status was categorized as married or unmarried (referent); parity was categorized as multipara (previously delivered ≥ 1 child) or nullipara (never gave birth) (referent); source of payment was categorized as private insurance (referent), enrollment in Medicaid or other (self-pay, Indian Health Service, Champus/Tricare, or government insurance); gestational weight gain (GWG) represented a combination of pre-pregnancy body mass index (BMI) and pregnancy weight gain, based on the Institute of Medicine (IOM) guidelines and was classified as: below recommendations- BMI <18.5 and weight gain <28 -40 lbs., met recommendations-BMI 18.5 to 24.9 and weight gain 25-35 lbs.(referent), or exceed recommendations-BMI ≥ 25 and wt. gain ≥ 11 lbs.;²⁹⁵ mode of delivery categories included spontaneous vaginal (referent), cesarean or other forms of delivery (i.e. forceps or vacuum); WIC (Women, Infants, and Children Special Supplemental Nutrition Program) offered for household incomes below 185% of the federal poverty line) participation categories were Yes or No (referent),²⁹⁶ information on prenatal care attendance was obtained from the birth certificate based on the recorded trimester in which prenatal care began and was categorized in this study as early prenatal

care- if initiated in the first trimester, or late/no prenatal care- if initiated in the second or the third trimester (referent); pre-pregnancy (in the three months before pregnancy) smoking obtained from the birth certificate was categorized as Yes or No (referent); and infant sex categories were male or female (referent).¹¹¹

STATISTICAL ANALYSES

In this study, I examined the distribution of maternal smoking intensity status categories in early and late pregnancy by maternal and infant characteristics among singleton term births, and the prevalence of low birthweight (<2,500g), low 5-minute Apgar score (<7) and NICU transfer/admission across maternal smoking intensity status and maternal and infant characteristics. Descriptive cross-tabulations were performed, and the results were displayed in two contingency tables (Table 7 and Table 8). The Chi-Square test of Independence (Pearson Chi-Square test) was used to assess significance in the relationship between variables and across variables, and level of significance was set at $p < 0.05$. Next, I quantified the unadjusted and adjusted odds ratios of each neonatal morbidity indicator (i.e. low birthweight, low 5-min Apgar score, and NICU transfer/admission) in association with each maternal smoking intensity category (nonsmokers as referent) in six separate logistic regression models (3 unadjusted and 3 adjusted) (Table 9). All data analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

SELECTING AND CONTROLLING FOR CONFOUNDING VARIABLES

Directed Acyclic Graph (DAG)

A directed acyclic graph (DAG) was used in this study to select observed and unmeasured confounders that could influence both the exposure and the outcome.²⁹⁷ The theory applied to DAGs has been described extensively by Rothman, Greenland, Pearl & Robins, Hernan and others.^{298–300} DAGs are directed graphs because arrows indicate direct effects between two variables (nodes), and they are acyclic because they do not form a closed loop between variables. Mothers who smoke can have co-occurring risk factors that constitute unmeasured confounders in association with infant health.^{301,302} The birth certificate does not include all variables that may influence maternal smoking and newborn birth weight and morbidity, thus identifying potential confounding factors may be a challenge.

The following selected observed covariates were adjusted in the binary logistic regression models: maternal race/ethnicity, age at giving birth, educational attainment, marital status, parity, source of payment at the time of delivery, and month prenatal care began. The selected potential unmeasured confounders included: maternal stress/anxiety,^{266,303} depression,^{304,305} alcohol consumption,³⁰⁶ drug use,^{307,308} and partner's smoking status³⁰⁹ were considered in the calculation of the E-value³¹⁰ (Figure 10).

MULTIPLE LOGISTIC REGRESSION ANALYSES

Multiple logistic regression analyses estimated the unadjusted and adjusted odds ratios for low birthweight (<2,500g), low 5-min Apgar score (<7) and NICU transfer/admission in association with each maternal smoking intensity status category, compared with nonsmokers (referent).

The three outcome variables (dependent variables, Y) were binary. In particular, for the i th birth, let $\Pr(Y_i=1) = \pi_i$ and $\Pr(Y_i = 0) = 1 - \pi_i$. Then, $E[Y_i] = \pi_i$ in $Y_i = \pi_i + \varepsilon_i$ is represented by a logistic curve:

$$\pi_i = \frac{\exp(X_i'\beta)}{1 + \exp(X_i'\beta)}.$$

where, X_i denotes predictors and β parameters in the model. Using the logit function, the natural log (ln) of the odds $\frac{\pi_i}{1 - \pi_i}$, the logistic regression may be written as:

$$\ln\left[\frac{\pi_i}{1 - \pi_i}\right] = X_i'\beta + \varepsilon_i$$

Given appropriate data on Y_i and X_i , SAS version 9.4 was used to obtain maximum likelihood estimates of the underlying parameters β in the model. The exponentiation of estimated parameters was obtained by running logistic regression yielding odds ratios (OR) of interest in this study.

For example, estimated model, $\ln\left(\frac{\hat{\pi}}{1 - \hat{\pi}}\right) = b_0 + b_1X$, yields $OR = e^{b_1}$ or $\ln(OR) = b_1$.

Interpretation of OR takes advantage of the fact that OR reflects the relative odds when X increases by one unit, *e.g.*, from X_0 to X_0+1 . If $X = X_0$, the estimated odds is:

$$\frac{\hat{\pi}_{X_0}}{1 - \hat{\pi}_{X_0}} = e^{b_0 + b_1X_0}.$$

On the other hand, if X increases by one unit to $X = X_o + 1$, the estimated odds will

become:
$$\frac{\hat{\pi}_{X_o+1}}{1 - \hat{\pi}_{X_o+1}} = e^{b_0 + b_1 X_o + 1}.$$

Therefore, the OR is estimated and interpreted by noting that:

$$OR = \frac{\frac{\hat{\pi}_{X_o}}{1 - \hat{\pi}_{X_o}}}{\frac{\hat{\pi}_{X_o+1}}{1 - \hat{\pi}_{X_o+1}}}$$

or, the fact that this reduces to $OR = e^{b_1}$.

The six logistic regression models (3 unadjusted and 3 adjusted) estimated unadjusted (OR) and adjusted odds ratios (aOR) for low birthweight, low 5-min Apgar and NICU transfer/admission in the association with maternal smoking intensity status in early and late pregnancy (nonsmokers as referent) (Table 9).

(1) Unadjusted logistic regression models:

Let Y_i represent the binary outcome ($Y = 1$ if there is low birthweight, low 5-min Apgar score or NICU transfer/admission, and $Y = 0$ if there is normal birth weight, normal Apgar score, or no NICU transfer/admission), and X_i to represent the exposure (maternal smoking intensity status).

We have

$$P(Y_i = 1) = \pi_i = \frac{\exp(\beta_0 + \beta_1 X_i)}{1 + \exp(\beta_0 + \beta_1 X_i)}$$

or

$$\text{Logit } [P(Y_i=1)] = \beta_0 + \beta_1 X_i$$

The exposure variable of interest was X_1 = maternal smoking intensity status. The outcome variable was $Y=1$ if there is low birthweight, low 5-min Apgar score or NICU transfer/admission, and $Y=0$ if there is normal birth weight, normal Apgar score, or no NICU transfer/admission.

(2) Adjusted logistic regression models:

$$\text{Logit } [pr(Y=1)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_6 + \beta_7 X_7$$

The exposure variable of interest was X_1 = maternal smoking status. The outcome variables were: $Y=1$ if there is low birthweight, low Apgar score or NICU transfer/admission, and $Y=0$ if there is normal birthweight, normal 5-min Apgar score, or no NICU transfer/admission. Observed confounding variables included in the adjusted models were: X_1 = race/ethnicity; X_2 =age; X_3 =education; X_4 =marital status; X_5 =parity; X_6 = source of payment; X_7 =prenatal care attendance. Statistical level of significance was set at $p < 0.05$. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

E-VALUE APPROACH FOR UNMEASURED CONFOUNDING

A new method for assessing unmeasured confounding in observational studies, known as the E-value, has recently been introduced by VanderWeele and Ding,³¹⁰ and was used in this study as an alternative approach to sensitivity analysis.

The following formulas were used:

(1) E-value for an estimate:

$$E - Value = RR + \sqrt{\{RR(RR - 1)\}}$$

(2) E-value for lower limit of the confidence interval (LL CI):

$$LL + \sqrt{\{LL(LL - 1)\}}$$

where, RR- is risk ratio; LL- lower limit of the confidence interval (CI).

The E-value approach quantified the strength of association (on the risk ratio scale) that potential unmeasured confounders have with both the exposure and the outcome, conditional on observed confounders, without making assumptions.³¹¹ For example, a large E-value indicates that strong unmeasured confounding is needed to explain away the effect estimates of the association, and a small E-value indicates that little unmeasured confounding would be needed to justify these effects, given observed confounders.³¹²

SPECIFIC AIM 3: To examine low birthweight in the term neonate as a potential mediator in the association between maternal smoking status and NICU transfer/admission.

STUDY POPULATION AND STUDY SAMPLE

In Specific aim 3, like in Specific aim 2, the analytic sample of N=3,175,973 was restricted to singleton term births (37-41 completed weeks gestation) (Figure 1).

STUDY DESIGN AND STUDY VARIABLES

Study Design

Mediation models were built proposing that an exposure variable influences an intermediate variable (a mediator) which in turn influences the outcome variable.²⁵⁷

Study Variables

Exposure variable

The exposure variable in this study was maternal smoking status, as described in Specific aims 1 and 2.

Outcome variable

The outcome was NICU transfer/admission in term singleton, a binary variable classified as Yes=1 or No=0, representing neonatal morbidity.

Mediator (intermediate) variable

Low birthweight (LBW) in a singleton term neonate, a binary variable classified as Yes if < 2,500g or No if > 2,500g, was a proposed mediator in the association between maternal smoking intensity status (exposure) and NICU transfer/admission (outcome) to explain its role in the association

SELECTING AND CONTROLLING FOR CONFOUNDING VARIABLES (DAG)

As in Specific aim 2, the following observed covariates were selected using a DAG and were included in mediation models: maternal race/ethnicity, age and education, marital

status, parity, source of payment, and prenatal care attendance. The following potential unmeasured confounders in the exposure-mediator, mediator-outcome and exposure-outcome relationship were also selected by means of a DAG and used in the E-value approach: anxiety/stress, depression, alcohol consumption and drug use, and partner's smoking status (Figure 13)

MEDIATION MODELING AND ANALYSES

Mediation Relationships and Mediation Hypothesis

Acknowledging the evidence established in Specific aim 2, low birthweight is an important marker of fetal growth and a newborn morbidity indicator that can precipitate NICU transfer/admission. Intervention research is often faced with the challenge of decomposing the effect of an exposure into different causal pathways working through distinct mediator variables, to understand the mechanisms of relationships or to suggest possible interventions. In this analysis, I want to investigate the contribution of LBW in term neonates to NICU transfer/admission in association with maternal smoking status. I hypothesize that LBW is a potential mediator in the association between maternal smoking status and newborn morbidity requiring NICU transfer/admission.

Mediation Models and Analysis

In a simple mediation model, the following pathways are considered: (1) the total effect of the exposure on the outcome (path c); (2) the direct effect between the exposure and the outcome, after controlling for the mediator (path c'); (3) the indirect effect (or mediated effect) between the exposure (maternal smoking intensity status) and the

potential mediator (LBW) (path a); (4) the indirect effect between the potential mediator (LBW) and the outcome (NICU transfer/admission) (path b)³¹³ (Figure 11).

In contrast to the traditional mediation method proposed by Baron and Kenny,²⁴⁷ this study follows a newer technique that emphasizes the counterfactual approach.^{313–316}

The counterfactual approach allows decomposition of the total effect into a natural direct effect of the exposure on the outcome and a natural indirect effect operating through a mediator. The natural direct and indirect effects were used in this study because they are more appropriate for effect decomposition in the counterfactual framework.³¹⁷ Four assumptions are required to identify natural direct and indirect effects: (1) no unmeasured treatment-outcome confounding, (2) no unmeasured mediator-outcome confounding, (3) no unmeasured treatment-mediator confounding, and (4) no mediator-outcome confounding affected by the exposure.³¹³

In mediation analysis, focusing on the mediator-outcome (LBW-NICU admission) association, two models are used that include observed confounder variables: fitted model for low birthweight (M) and fitted model for NICU transfer/admission (Y).

(1) Fitted model for low birthweight (M), conditional on smoking status (A) and a set of confounders (C):

$$\log [Pr (M = 1 | A = a, C = c)] = \beta_0 + \beta_1 A + \beta_2 C$$

(2) Fitted model for NICU transfer/admission (Y), conditional on smoking status (A), low birthweight (M), a smoking status-low birthweight interaction (A x M) and a set of confounders (C) is as follows:

$$\log [Pr (Y = I \mid A = a, M = m, C = c)] = \theta_0 + \theta_1 X + \theta_2 M + \theta_3 (A \times M) + \theta_4 C$$

For the binary mediator and outcome in this study, the following formulas were used to estimate the odds ratio (OR_{NDE}) of the natural direct effect, and the odds ratio (OR_{NIE}) of the natural indirect effects. Let a^* represent the exposure's reference level, then:

$$\log \{OR_{NDE}\} = \{\theta_1 + \theta_3(\beta_0 + \beta_1 a^* + \beta_2 c + \theta_2 \sigma^2)\} (a - a^*) + 0.5 \theta_3 \sigma^2 (a^2 - a^{*2})$$

$$\log \{OR_{NIE}\} = (\theta_2 \beta_1 + \theta_3 \beta_1 a) (a - a^*)$$

where, a is exposure level 1, a^* is exposure level 0, σ^2 is the variance of the error term in the regression for the mediator, β and θ are regression coefficients, and c is a confounder. The odds ratio (OR_{NDE}) of the average natural direct effect and odds ratio (OR_{NIE}) of the average natural indirect effects, for a binary mediator and outcome in association with confounder variables were estimated using the formulas below.³¹³

$$OR^{NDE} = \frac{\exp(\theta_1 a) \{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2 c)\}}{\exp(\theta_1 a^*) \{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2 c)\}}$$

$$OR^{NIE} = \frac{\{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c)\} \{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a + \beta_2 c)\}}{\{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c)\} \{1 + \exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2 c)\}}$$

where, β and θ –are regression coefficients, C and c –confounders, a –exposure level 1, a^* –exposure level 0, exp –exponential function

The total effect is the overall effect of exposure (smoking status) on the outcome (NICU transfer/admission). The natural direct effect explains how much an outcome (NICU transfer/admission) would vary if the exposure (smoking status) were set at level $a=1$

against the level $a^*=0$, but for every exposure (maternal smoking status category), the mediator (LBW) was fixed at the level it would have been without the exposure. The natural indirect effect explains the average change of an outcome (NICU transfer/admission) if the exposure (smoking status) was held constant at the level of $a=1$, but the mediator (LBW) was altered to a level it would accept if $a^*=0$ to the level it would accept if $a=1$.³¹³ Because this study involves binary outcomes, the effects are calculated on the odds ratio scale.³¹⁸ The natural direct, indirect and total effects are estimated using the PROC CAUSALMED procedure³¹⁹ that has now been offered in SAS version 9.4 (TS1M5) and presented in Table 10.

Ultimately, mediation analyses will determine the proportion of the total effect of the highest maternal smoking category (exposure) on the NICU transfer/admission (outcome) while acting through the mediator (LBW).

E-VALUE APPROACH FOR UNMEASURED CONFOUNDING

The E-value is an alternative approach to sensitivity analysis to report the presence of unmeasured confounding, which avoids making assumptions, given observed confounding. As in Specific aim 2, the same formula is used to calculate the E-value for the total effect.

Chapter Summary-Methods

The dataset and the methods of statistical analysis used in this study provided adequate tools and a proper framework for an in-depth investigation of the prevalence of maternal

smoking and its association with morbidity in singleton term births. First, it was possible to examine the prevalence and patterns of cigarette smoking in the three months before and during pregnancy across maternal race/ethnicity, age, and educational attainment in the United States in 2016, and the distribution of maternal smoking status in early (first and second trimester) and late (third trimester) pregnancy among all births and among singleton term births (37-41 completed weeks gestation). Second, the data and methods used in this study allowed a thorough investigation of the association between multiple categories of maternal smoking status in early and late pregnancy and the odds of low birthweight (LBW) (<2,500g), low 5-minute Apgar score (<7), and NICU transfer/admission, as morbidity indicators in singleton term neonates (37-41 completed weeks gestation). Finally, the data and the methods were successfully used to examine the contribution of low birthweight in a term neonate to NICU transfer/admission in the association with the highest maternal smoking intensity status category.

Chapter IV: RESULTS

In this chapter, the findings of the statistical analyses conducted in this study are reported in subchapters arranged by three specific aims.

MISSING DATA

Listwise deletion, known as complete case analysis²⁷⁸ was a technique employed in this study for handling missing data on selected variables using the DELETE statement in SAS version 9.4. Missing values on variables selected in this study including frequencies for each study variable and its sub-categories, the percentage of missing observations and mean $\pm$ SD are displayed in Table 1 (Appendix A). There were overall 384,270 (9.7%) missing observations in this study population that involved at least one or more missing covariates in the dataset. Less than 2% of observations were missing for education, prenatal care, and WIC participation and less than 1% were missing for maternal race/ethnicity, parity, source of payment, route and method of delivery, gestational weight gain, NICU transfer/admission, birthweight, Apgar score, gestational age, and number of cigarettes smoked/day. There were no missing observations for maternal age, marital status, and infant sex. A small group of women (N=2,973) who smoked at high and low intensity in late pregnancy (third trimester only) were not included in a separate smoking intensity category.

SPECIFIC AIM 1: To report the prevalence of cigarette smoking in the three months before pregnancy and during pregnancy by intensity level and the distribution of maternal smoking status in early and late pregnancy across maternal race/ethnicity, age, and educational attainment, among all births and among singleton term births (37-41 completed weeks gestation) in the United States in 2016.

Prevalence of Maternal Smoking before and during Pregnancy by Intensity Level, All Births, 2016

The estimates of the prevalence and patterns of smoking in the three months before pregnancy and during pregnancy (by trimester) across low and high intensity categories and by maternal characteristics for all births are displayed in Table 2 and Figures 2-4 and for singleton term births are displayed in Table 3 and Figures 5-7.

Among all births in 2016, nearly 9.42% of women reported smoking in the three months before pregnancy. During pregnancy, the highest rate of smoking was in the first trimester (6.98%), followed by second (5.93%) and third (5.62%) trimesters (Table 2). Non-Hispanic White women were more likely to smoke before pregnancy (13.36%), in the first (10.13%), in the second (8.75%), and in the third trimester (8.34%), compared with other racial/ethnic groups. Non-Hispanic White women also had the highest rate of high intensity smoking before pregnancy (9.75%), in the first (6.49%), the second (5.00%) and in the third trimester (4.25%), compared with other racial/ethnic groups (Table 2 and Figure 2). As depicted in Figure 3, smoking was more prevalent among women 20-24 years old before pregnancy (14.25%), in the first trimester (10.49%), in the second (8.74%) and in the third trimester (8.24%), and women in this age group were more likely to smoke at high intensity before pregnancy (9.33%), in the first (5.90%), in

the second (4.30%), and in the third trimester (3.54%), compared with women of other age groups (Table 2 and Figure 3). Women with a high school education/GED were more likely to smoke in the three months before pregnancy (15.11%), but women with less than high school education smoked more in the first (12.55%), the second (11.24%), and in the third trimester (10.81%), both at high and low intensity, than other women in the same category (Table 2 and Figure 4). While women with only a high school education/GED were more likely to smoke at a higher intensity before pregnancy (10.33%), women with less than a high school education smoked at a higher intensity in the first (7.62%), the second (6.13%), and in the third trimester (5.30%), compared to other women in the same group (Table 2 and Figure 4).

Distribution of Smoking Status in Early and Late Pregnancy by Maternal Characteristics, All Births, 2016

The distribution of smoking intensity status in early (first and second trimester) and in late (third trimester) pregnancy for all births among women who smoked is displayed in Table 5 and Figure 8 (pie chart).

Most women (65%) continued smoking in early and in late pregnancy (*Maintainer*) and smoked more at high (36.90%) than at low intensity (28.13%) level. Among women who quit smoking by the third trimester (21%) (*Quitter*), 7.33% smoked at a high and 13.19% at low intensity in early pregnancy. About 14.10% of women reduced smoking from high intensity in early pregnancy to low intensity in late pregnancy (*Reducer*), and 0.34% of women increased their smoking level from low intensity in early pregnancy to high intensity in late pregnancy (*Increaser*).

Non-Hispanic White women were more likely to be high intensity smokers in early and in late pregnancy (41.3%), low intensity smokers in early and in late pregnancy (24.8%), and also high intensity in early and low intensity smokers in late pregnancy (15.1%). In comparison, non-Hispanic Black women, Hispanic, and women of other race/ethnicity were more likely to smoke at low intensity in early and late pregnancy (44.3%, 35.5%, and 33.5%, respectively), followed by either low intensity only in early pregnancy (19.3%, 24.1%, and 18.2%, respectively) or high intensity in early and late pregnancy (20.6, 20.4, and 26.6%, respectively).

Women who were 35+ years old smoked at high intensity in early and late pregnancy (41.7 %). Conversely, women less than 20 years old were more likely to smoke at low intensity (30.3%) in early and late pregnancy, followed by high intensity only in early pregnancy (9.0%), but increased their smoking from low intensity in early to high intensity in late pregnancy (0.44%).

Finally, 41.4% of women with less than a high school education were high intensity smokers in early and in late pregnancy, 29.4% were low intensity smokers, and 0.35% of women were low intensity smokers in early pregnancy and high intensity smokers in late pregnancy. In comparison, women with bachelor's degree were either low intensity smokers in early pregnancy only (24.2%) or high intensity smokers in early pregnancy only (11.5%).

**Differences in the Prevalence and the Distribution of Maternal Smoking Status
between All Births and Singleton Term Births, United States, 2016**

Minimal differences were observed in the prevalence rates and the distribution of smoking in early (first and second trimester) and in late (third trimester) pregnancy across maternal characteristics, among all births and singleton term births in the United States in 2016. In the three months before pregnancy, the rates of smoking among mothers with singleton term births were 9.20% vs 9.42% for all births, and the rates of high intensity smoking for singleton term births were 6.13% vs 6.29% for all births. The rates of high intensity smoking during the first, second and third trimesters of pregnancy were slightly higher for all births (4.10%, 3.10% and 2.60%, respectively) than for singleton term births (3.95%, 3.0% and 2.50%, respectively) (Table 2 and Table 3; Figures 2-7). Minimal differences were also observed in maternal smoking status in early and late pregnancy among all births and among singleton term births. For comparison, the percentage and number values on smoking distribution among all births and singleton term births are shown in Table 5 and Table 6. In general, smoking patterns were consistent for mothers among all births and for singleton term births. Minor variations could be attributed to differences in health risks due to exclusion of preterm births from the singleton term birth sample.

SPECIFIC AIM 2: To present the results of the distribution of maternal smoking status in early (first and second trimester) and late (third trimester) pregnancy and the odds ratios of newborn morbidity (i.e. low birthweight (LBW), low 5-minute Apgar score (<7), and NICU transfer/admission) among term singletons.

Distribution of Maternal and Infant Characteristics across Smoking Status Categories in Early and Late Pregnancy, Singleton Term Births, 2016

The distribution of maternal and infant characteristics across smoking intensity status categories in early (first and second trimester) and late (third trimester) among term singletons is shown in Table 7.

In the analyzed subset of N=3,175,973 mothers with singleton term births 2,961,873 (93.26%) mothers reported not smoking and 214,100 (6.74%) mothers reported smoking during pregnancy. Compared to non-smokers, mothers, who smoked, were more likely to be non-Hispanic White (77.8%), younger (25-29 years old) (33.00%) and had a high school diploma/GED (41.80%). They were also more likely to be unmarried (72.0%), multiparas (69.50%), enrolled in Medicaid (73.88%), have exceeded IOM recommendations for gestational weight gain (49.30%), participated in WIC (62.40%), and attended early prenatal care (66.10%). The results were statistically significant at $p < .05$, likely because of the large sample size.

The distribution of maternal race/ethnicity was similar among low intensity smoking in early pregnancy only (*Quitter-1*), low intensity smoking in early and late pregnancy (*Maintainer-1*) and high intensity smoking in early and in late pregnancy (*Maintainer-2*), and high intensity smoking in early pregnancy (*Quitter-2*), high intensity smoking in early and low in late pregnancy (*Reducer*), and low intensity smoking in early and high in late pregnancy (*Increaser*) categories were also similar in distribution. Likewise, the distribution of maternal age categories was comparable among low intensity smoking in early pregnancy only (*Quitter-1*) and high intensity in early and high intensity in late

pregnancy (*Maintainer-2*), and also high intensity smoking in early pregnancy (*Quitter-2*), low intensity smoking in early and late pregnancy (*Maintainer-1*), high intensity smoking in early and low in late pregnancy (*Reducer*), and low intensity smoking in early and high in late pregnancy (*Increaser*) were similar in distribution (Table 7). The distribution of maternal educational attainment was similar for high intensity smoking in early and high intensity smoking in late pregnancy (*Maintainer-2*), and low intensity smoking in early pregnancy only (*Quitter-1*). Correspondingly, low intensity smoking in early and late pregnancy (*Maintainer-1*), high intensity smoking in early pregnancy (*Quitter-2*), high intensity smoking in early and low in late pregnancy (*Reducer*), and low intensity smoking in early and high in late pregnancy (*Increaser*) had similar distribution.

The distribution of infant characteristics was similar among maternal smoking intensity status categories, except for low intensity in early and high intensity smoking in late pregnancy (*Increaser*), which was higher for female than for male infants (Table 7). All results were statistically significant at $p < .05$.

Neonatal Morbidity Rates across Maternal and Infant Characteristics and Maternal Smoking Status in Early and Late Pregnancy

The prevalence rates of morbidity among term singletons (37-41 completed weeks gestation) across maternal characteristics and smoking status categories are displayed in Table 8. The prevalence rate of low birthweight (LBW) was the lowest for maternal non-smokers (2.2%). The prevalence of LBW increased for women who smoked either at low intensity in early pregnancy only (3.6%) (*Quitter-1*) or at high intensity in early pregnancy only (3.6%) (*Quitter-2*), but did not smoke in the third trimester, and among

women who smoked throughout pregnancy, either at low (5.4%) (*Maintainer-1*) or at high intensity (6.6%) (*Maintainer-2*). Between these two groups were women who smoked at high intensity in early pregnancy, but reduced their smoking to low intensity level in the last trimester (5.7%) (*Reducer*). Finally, the prevalence of LBW was 4.1% for the small number of women who increased their smoking from low intensity in early pregnancy to high intensity in the last trimester (*Increaser*) (Table 8).

The prevalence of low 5-min Apgar score (<7) was lowest for non-smokers (1.2%). The prevalence increased for women who smoked either low intensity (1.6%) (*Quitter-1*) or high intensity in early pregnancy only (1.8%) (*Quitter-2*). The prevalence was similar among women who smoked either at low intensity (*Maintainer-1*) or at high intensity in early and late pregnancy (1.5%) (*Maintainer-2*) and among women who smoked at high intensity in early pregnancy but reduced to low intensity smoking in the last trimester (1.5%) (*Reducer*). Lastly, the rate of low 5-min Apgar score (<7) was 2.0% among women who increased their smoking from low intensity in early pregnancy to high intensity in the last trimester (*Increaser*) (Table 8).

Finally, the rate of NICU transfer/admission was lowest for maternal non-smokers (4.3%). The prevalence increased moderately for women who smoked either low intensity (5.2%) (*Quitter-1*) or high intensity in early pregnancy only (5.8%) (*Quitter-2*), and slightly increased among women who smoked throughout pregnancy, either at low intensity (6.0%) (*Maintainer-1*) or at high intensity (6.7%) (*Maintainer-2*). Between these two groups were women who smoked high intensity in early pregnancy, but reduced their smoking level to low intensity in the last trimester (6.2%) (*Reducer*). The prevalence of NICU transfer/admission decreased further to 5.8 % among the small group

of women who increased their smoking from low intensity level in early pregnancy to high intensity level in late pregnancy (*Increaser*) (Table 8).

Neonatal Morbidity across Selected Covariates

The prevalence rates of low birthweight (LBW), low 5-min Apgar score and NICU transfer/admission across selected covariates are displayed in Table 8.

The rate of low birthweight (LBW) was highest for non-Hispanic Black women, young age (<20 years old), for women with less than a high school education, unmarried, nulliparous, women enrolled in Medicaid, who participated in WIC, who were below IOM GWG recommendations, had a cesarean delivery, had late or no prenatal care, were pre-pregnancy smokers, and women who delivered a female infant.

The rate of low 5- min Apgar score was highest among non-Hispanic Black women, young age (<20 years old) and women with high school/GED, unmarried, nulliparous, participated in WIC, had late or no prenatal care, were pre-pregnancy smokers, and delivered a male infant.

Finally, the prevalence rate of NICU transfer/admission was highest for non-Hispanic Black women, young age (<20 years old) and women with less than high school education, unmarried, nulliparous, women enrolled in Medicaid, who participated in WIC, had late or no prenatal care, were pre-pregnancy smokers, and delivered a male infant.

Odds Ratios of Neonatal Morbidity in Association with Maternal Smoking Status in Early and Late Pregnancy

The unadjusted and adjusted odds ratios of low birthweight (LBW), low 5-min Apgar score and NICU admission in association with maternal smoking intensity status in early and late pregnancy are displayed in Table 9.

Overall, maternal smoking at high intensity in early pregnancy was associated with the highest magnitude of LBW in a term neonate, even if the mother quit smoking or reduced her smoking intensity in the third trimester. Women who smoked at high intensity early in pregnancy and then quit (*Quitter-2*) had 60% higher odds of delivering a LBW infant (aOR 1.61; 95% CI: 1.47, 1.75) and women who smoked at low intensity in early pregnancy and then quit (*Quitter-1*) had 46% higher odds (aOR 1.46; 95% CI: 1.37, 1.55), compared with non-smokers. The odds of delivering a LBW neonate at term were also high for mothers who continued smoking from early into late pregnancy (*Maintainer*) and more for high intensity smokers in early pregnancy than for low intensity smokers, compared to non-smokers. Women who smoked at high intensity throughout pregnancy had tripled their odds of delivering a LBW neonate at term (*Maintainer-2*) (aOR 3.33; 95% CI: 3.23, 3.44), and the odds were slightly lower when women reduced smoking from high intensity in early pregnancy to low intensity in late pregnancy (*Reducer*) (aOR 2.71; 95% CI: 2.57, 2.84). In contrast, smoking at low intensity throughout the three trimesters of pregnancy (*Maintainer-1*) had a two-fold increase in the odds of LBW at term (aOR 2.31; 95% CI: 2.23, 2.40) and the magnitude of the association was lower, compared to high intensity smoking in early pregnancy. Finally, women who smoked at low intensity level in early pregnancy and then increased to high intensity level in late pregnancy (*Increaser*) were 1.83 times more likely to give

birth to an infant with LBW at term (aOR 1.83; 95% CI: 1.28, 2.63), compared with nonsmokers.

The association with Apgar score was found to be lower across all smoking status categories and less variation was present related to smoking in early pregnancy. The odds of delivering a neonate at term with low 5-min Apgar score were higher if woman reduced her smoking from high intensity level in early pregnancy to low intensity in late pregnancy (*Reducer*) (aOR 1.14; 95% CI: 1.04, 1.25), and the odds slightly increased for low intensity smokers in early pregnancy only (*Quitter-1*) (aOR 1.16; 95% CI: 1.06, 1.28) and for low intensity smokers from early to late pregnancy (*Maintainer-1*) (aOR 1.17; 95% CI: 1.10, 1.25). The highest odds (46%) of having a newborn with low 5-min Apgar score were among women who smoked at low intensity in early pregnancy and then increased their smoking to high intensity in late pregnancy (*Increaser*) (aOR 1.46; 95% CI: 0.88, 2.44); however, the association was not statistically significant. The odds of having a newborn with low 5-min. Apgar score were somewhat higher (26%) if women smoked at high intensity in early pregnancy only (*Quitter-2*) (aOR 1.26; 95% CI: 1.12, 1.42), compared to nonsmokers (Table 9). Finally, women who smoked at high intensity in early and in late pregnancy (*Maintainer-2*) had 23% higher odds of delivering a neonate with low Apgar score (aOR 1.23; 95% CI: 1.16, 1.30), compared with nonsmokers (Table 9).

Lastly, the odds of a term LBW neonate being transferred or admitted to the NICU were slightly higher (12%) for women who smoked at low intensity in early pregnancy only (*Quitter-1*) (aOR 1.12; 95% CI: 1.07, 1.19) and at high intensity in early pregnancy only (*Quitter-2*) (aOR 1.28, 95% CI: 1.19, 1.37); however, the odds increased

significantly (62%) for women who continued smoking at high intensity from early to late pregnancy (*Maintainer-2*) (aOR 1.62; 95% CI: 1.58, 1.67). Similarly, the odds were somewhat lower if women reduced their smoking from high intensity level in early pregnancy to low intensity level in late pregnancy (*Reducer*) (aOR 1.43; 95% CI: 1.37, 1.50). However, women who continued smoking at low intensity level from early to late pregnancy (*Maintainer-1*) had 38% higher odds of a neonate being transferred/admitted to the NICU (aOR 1.38; 95% CI: 1.33, 1.43). Lastly, women who increased their smoking from low intensity in early pregnancy to high intensity in late pregnancy (*Increaser*) had 33% higher odds of an infant being transferred/admitted to the NICU (aOR 1.33; 95% CI: 0.98, 1.81) (Table 9).

The inference regarding effects of prenatal smoking exposure in early and late pregnancy can be made by comparing the adjusted odds ratios of LBW, low 5-min Apgar score and NICU transfer/admission in relation to each maternal smoking status category in early and late pregnancy (Table 9).

E-VALUE APPROACH FOR UNMEASURED CONFOUNDING

The strength of the association attributed to potential unmeasured confounders with the exposure (maternal smoking status) and the three independent outcomes (i.e. low birthweight, low 5-min Apgar score and NICU transfer/admission) was assessed for the highest odds of each outcome using the E-value as an alternative approach to sensitivity analysis, given observed confounding, that avoids making assumptions.^{310,312} The calculations of the E-value for the highest aOR of maternal smoking status of each independent newborn outcome were performed as follows:

(1) Low birthweight (LBW) in association with maternal smoking at high intensity in early and high intensity in late pregnancy (*Maintainer-2*) (Table 9):

- The observed aOR = 3.33

$$\text{E-value for aOR}=3.33 + \sqrt{\{3.33 (3.33 - 1)\}}=6.12$$

- The observed lower limit of confidence interval (CI) = 3.23

$$\text{E-value for CI}= 3.23 + \sqrt{\{3.23 (3.23 - 1)\}}=5.91$$

(2) Low 5-min Apgar score in association with maternal smoking at low intensity in early and at high intensity in late pregnancy (*Increaser*) (Table 9):

- The observed aOR = 1.46

$$\text{E-value for aOR}=1.46 + \sqrt{\{1.46 (1.46 - 1)\}}=2.28$$

- The observed lower limit of the confidence interval CI=0.88

$$\text{E-value for CI}=1$$

(3) NICU transfer/admission in the association with maternal smoking at high intensity in early and high intensity in late pregnancy (*Maintainer-2*) (Table 9):

- The observed aOR = 1.62

$$\text{E-value for aOR}=1.62 + \sqrt{\{1.62 (1.62 - 1)\}}=2.62$$

- The observed lower limit of confidence interval CI=1.58

$$\text{E-value for CI}= 1.58 + \sqrt{\{1.58 (1.58 - 1)\}}= 2.54$$

Because the three outcomes in this study are rare (i.e. <5% prevalence), it is assumed that a corresponding odds ratios (OR) approximate the relative risk (RR).^{310,312} Also, as a statistically conservative strategy, the upper limit of the confidence interval for the E-value is not commonly calculated (Peng Ding, PhD, email communication, January 2019).

Among the three outcomes, the E-value was highest for low birthweight (LBW) (6.12), followed by NICU transfer/admission (2.62) and low 5- min Apgar score (2.28). This implies that for LBW the highest magnitude of the estimate of the association with an unmeasured confounder would be needed to explain away the exposure-outcome relationship, given an observed confounder. While, for low 5-min Apgar score and for NICU transfer/admission the E-values were somewhat lower (2.28 and 2.62, respectively), a lower magnitude of the estimate of association with an unmeasured confounder will be required to explain away the exposure-outcome relationship, given an observed confounder. The lower limit of confidence interval (CI) could be moved to include the null for the unmeasured confounders associated with each exposure-outcome by the odds ratios of 5.9, 1, and 2.5-fold, respectively, above and beyond the measured confounders, but weaker confounding could not do so.

SPECIFIC AIM 3: To present the results of the mediation analyses using low birthweight (LBW) in term neonates as a potential mediator in the association with maternal smoking status and NICU transfer/admission.

MEDIATION EFFECTS AND MEDIATION PROPORTION

The results of mediation analyses are displayed in Table 10 (Appendix A). Among all smoking status categories, the effects on NICU transfer/admission were highest for mothers who smoked at high intensity in early and late pregnancy (*Maintainer-2*) and the adjusted odds ratios of the total effect, the natural direct effect and the natural indirect were aOR 1.62 (95% CI: 1.58, 1.67), aOR 1.52 (95% CI: 1.47, 1.57), and aOR 1.07 (95% CI: 1.07, 1.09), respectively. The proportion mediated was 18.3% (95% CI: 15.99, 20.54) for high intensity smokers in early and late pregnancy, compared with nonsmokers. For mothers who smoked at low intensity in early pregnancy only (*Quitter-1*), the odds of the total effect of an infant being admitted to the NICU were aOR 1.12 (95% CI: 1.07, 1.19), the odds of the natural direct effect were aOR 1.11 (95% CI: 1.05, 1.17) and for the natural indirect effect, the odds were aOR 1.02 (95% CI: 1.01, 1.02); the proportion mediated was 14.8% (95% CI: 7.15, 22.54). Among mothers who smoked at high intensity in early pregnancy only (*Quitter-2*) the effects were somewhat higher, the odds of the total effect were aOR 1.28 (95% CI: 1.19, 1.37), the odds of the natural direct effect were aOR 1.25 (95% CI: 1.16, 1.33) and the odds of the natural indirect effect were aOR 1.03 (95% CI: 1.02, 1.04); the proportion mediated was 14.4% (95% CI: 8.61, 20.14). For women who continued smoking at low intensity from early to late pregnancy (*Maintainer-1*), the odds of the total effect on an infant being admitted to NICU were aOR 1.38 (95% CI: 1.33, 1.43), the odds of the natural direct effect were aOR 1.32 (95% CI: 1.27, 1.37), and the odds of the natural indirect effect were aOR 1.05 (95% CI: 1.04, 1.06); the proportion mediated was 16.7% (95% CI: 13.74, 19.60). Also, among women who increased their smoking from low intensity in early pregnancy to

high intensity in late pregnancy (*Increasers*), the odds of the total effect on NICU transfer/admission of an infant delivered at term were aOR 1.33 (95% CI: 0.98, 1.81), the odds of the natural direct effect were aOR 1.29 (95% CI: 0.89, 1.69), and the odds of the natural indirect effect were aOR 1.03 (95% CI: 0.97, 1.09); the proportion mediated was 13.3% (95% CI: -10.05, 36.56). Finally, the effect on NICU transfer/admission was somewhat lower among women who reduced their smoking from high intensity in early pregnancy to low intensity in late pregnancy (*Reducer*). The odds of the total effect were aOR 1.43 (95% CI: 1.37, 1.50), the odds of the natural direct effect were aOR 1.37 (95% CI: 1.31, 1.44) and the odds of the natural indirect effect were aOR 1.05 (95% CI: 1.04, 1.06); the proportion mediated was 14.9% (95% CI: 11.12, 18.72).

These findings imply that LBW is a partial mediator in the association because nearly 18.3% of the effect of high intensity maternal smoking in early and late pregnancy on the NICU transfer/admission among term neonates was attributed to LBW.

E-VALUE APPROACH FOR UNMEASURED CONFOUNDING

In this section, as in Specific aim 2, DAGs informed about the number of selected observed and unmeasured confounders in the association between the exposure (i.e. maternal smoking status) and the outcome (i.e. NICU transfer/admission), based on prior knowledge and biological plausibility (Figure 13). As in Specific aim 2, the E-value approach was used as an alternative to sensitivity analysis to report the presence of unmeasured confounding in the association, given observed confounders.^{310,312} The E-value was calculated for the aORs of the high intensity smoking category in early and in late pregnancy (*Maintainer-2*), because it had the highest estimates, among other

smoking status categories, in the association with the NICU transfer/admission (Table 10).

The E value was calculated using the following formula:

- The observed aOR = 1.62

$$\text{E-value for aOR}=1.62 + \sqrt{\{1.62 (1.62 - 1)\}} = 2.62$$

- The observed lower limit of confidence interval CI=1.58

$$\text{E-value for CI}= 1.58 + \sqrt{\{1.58 (1.58 - 1)\}} = 2.54$$

The E-value calculation (2.62) implies that less unmeasured confounding in the exposure-outcome association is needed to explain away the effect of observed confounding, with the mediator held constant. The lower limit of confidence interval (CI) could be moved to include the null for an unmeasured confounder associated with the exposure-outcome by an odds ratio of 2.54 above and beyond the measured confounders, but weaker confounding could not do so.

Chapter Summary-Results

Among women in the United States in 2016, the prevalence of cigarette smoking before pregnancy was 9.42% and the highest rate of smoking was in the first trimester (6.98%) of pregnancy. White women, young and less educated women had the highest overall rate of smoking during pregnancy. The strongest predictor of the risk of newborn morbidity was exposure to high intensity maternal smoking in early pregnancy. Low birthweight (LBW) is a partial mediator because it contributed almost one-fifth (18.3%)

of the effect of high intensity maternal smoking in early and late pregnancy to NICU transfer/admission among term neonates.

Chapter V: DISCUSSION AND CONCLUSIONS

There is substantial evidence documenting harmful effects of cigarette smoking during pregnancy, yet at least half of pregnant women smoke risking the health of their unborn children. This study was designed to estimate the prevalence and patterns of smoking before and during pregnancy in the United States in 2016, to identify differences in prevalence and distribution of maternal smoking status among all births and singleton term births, to examine prenatal exposure status in early and late pregnancy in association with immediate morbidity, and to explore the contribution of LBW to NICU admission among term infants (>37 weeks gestation) prenatally exposed to maternal smoking.

While numerous studies support short and long-term health effects in infants born preterm, these data show a similar disease risk occurring among low birthweight infants delivered at term. Gestational age alone cannot explain low birthweight (LBW) and physiological immaturity in term neonates, if not accounting for risk factors (e.g. smoking) that influence fetal growth in the first half of pregnancy.¹⁶⁶ There are multiple fetal, placental and maternal risk factors associated with LBW^{29,266–269} and the severity of infant morbidity may depend on multiple correlated risk factors. One comparative advantage of studying the population of infants at term is that confounding by gestational age does not need to be considered in assessment of the effects of exposure. There is limited research on the significance of LBW in term neonates as an important contributor to neonatal morbidity at birth, related high health care costs and economic burden throughout the life time.

To my knowledge, this is the first population-based study to examine prenatal exposure status, measured by combined timing and intensity of smoking, in association with an increased likelihood of delivering a LBW infant at term with low 5-min Apgar score and being transferred/admitted to the NICU.

This chapter begins with a summary and interpretation of the study findings in comparison with similar studies, by specific aims, followed by strengths and limitations, discussion on significance and implications of the findings, future directions for research and practice, and final conclusions.

SUMMARY OF THE STUDY RESULTS (By Specific Aims)

Summary of findings from Specific Aim 1 compared with similar studies

This study analysis indicates that nearly one in ten women (9.42%) smoked during the three months before pregnancy and about three quarters of these women continued smoking in the first trimester (6.98% overall) (Table 2). These findings are consistent with an earlier report based on 2014 US birth certificate data, representing 95% of all births, showing the highest rate of smoking in the first trimester (8.2%), followed by the second (7.0%), and by the third trimester (6.6%).¹

Substantial disparities in smoking patterns in different trimesters were observed across maternal race, age, educational attainment and intensity level. Non-Hispanic White women were more likely to be high intensity smokers throughout pregnancy and were more likely to increase their smoking intensity in late pregnancy (i.e. in the third

trimester) than other racial/ethnic groups of women (Table 2). Most women in this study smoked at high intensity (>10 cigs/day) in early pregnancy, but with advancing pregnancy, women were likely to smoke at low intensity (i.e. 3.10% of high intensity vs. 2.83% of low intensity smoking in the 2nd trimester). Hispanic women, women 20-24 years old, and women with a bachelor's degree or higher had the highest overall reduction in smoking throughout pregnancy (Table 2), which is in accordance with studies by Perez-Stable et al.⁷⁴ and Detjen et al.³²⁰ Women 30 years old and over were more likely to smoke at high intensity in the third trimester, which was also reported in a study by Mohsin & Bauman³²¹ and mentioned in the literature review. This is in line with previous research showing that pregnant women try to quit or reduce their smoking intensity because of concern about the health of their pregnancy,^{100,322} while commonly reported barriers to quitting included craving for a cigarette, stress, and being around people who smoke.⁹⁰ Three studies that biochemically validated self-reported spontaneous quitting in early pregnancy found considerable over-reporting (10-20%) of cessation.³²³ Less educated women were more likely to smoke during their entire pregnancy, while older women and women with a bachelor's degree or higher were usually low intensity smokers in the second and third trimesters, as reflected in other US population studies.^{70,75,100}

To account for fluctuation in smoking patterns across trimesters and to assess prenatal exposure status more thoroughly along the continuum of pregnancy, this study created a set of maternal smoking intensity status categories (Table 4), based on combination of intensity levels (high or low) and timing of smoking in early (first and second trimester) and in late (third trimester) pregnancy. Almost 7% (6.96%) of women in this study

smoked both in early and in late pregnancy, which was slightly lower (8.4%) than the anytime smoking rate reported in 2014.¹ The largest group of women who smoked during pregnancy (36.91%, or 2.57% of all pregnant women) consisted of high intensity smokers in early and in late pregnancy (*Maintainer-2*), and the second largest group (28.13%, or 1.96% of all pregnant women) included low intensity maternal smokers in early and in late pregnancy (*Maintainer-1*). The majority of quitters in early pregnancy (*Quitter-1*) were low intensity smokers (13.33% of all maternal smokers) which included non-Hispanic White, 20-24-year-old, unmarried women, multiparas, women with high school/GED or some college education, and women who reported having early prenatal care, which is consistent with other reports.^{275,324} At the same time, Hispanic women and women less than 20 years old were more likely to be low and high intensity early pregnancy smokers (*Quitter-1 and Quitter-2*), and they were more likely to quit, compared with other age and ethnic groups.

These results indicate that most women who smoked during pregnancy (65.04%, or 4.52% of all pregnant women) continued smoking throughout pregnancy at consistent rates (Table 5). The differences in smoking distribution in early and late pregnancy among all births and singleton term births were found to be minimal.

Summary of Findings from Specific Aim 2 Compared with Similar Studies

This study adds to research on smoking during pregnancy examining associations with several different covariates (maternal and infant characteristics). Multiparas (women who previously gave birth two or more times) and who smoked during pregnancy were more likely to be high intensity smokers (76.82% of smokers) in early pregnancy and low

intensity smokers (70.43% of smokers) in late pregnancy, compared with nulliparas (women who never previously gave birth). These findings have limited support by the results from a cross-sectional study from Iceland (n=1,111) showing that 60% of multiparous women smoked during early pregnancy.³²⁵ Because the US and Icelandic populations differ, no inferences could be drawn from this prior study.

In this study, women who exceeded the Institute of Medicine (IOM) recommended guidelines for gestational weight gain (GWG) were more likely to be low intensity (59.96%) and high intensity (60.97%) smokers in early pregnancy only (*Quitter-1 and Quitter 2*), compared with women who were at or below the recommendation guidelines. These results are in accordance with an intervention study among pregnant women (n=357) who quit smoking in early (<54 days before delivery) or in late (>54 days before delivery) pregnancy and gained adequate or excessive weight, compared with women who continued smoking throughout pregnancy (57.9% vs. 28.9%).³²⁶

This study adds to the literature on smoking among women who are recipients of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). This study shows lower rates of smoking for Hispanic women, 20–24-year-old women and women with less than 12 years of education, unmarried women, women enrolled in Medicaid and women participating in WIC, which is compatible with prior studies.^{100,324,327} However, women who were enrolled in Medicaid and participated in WIC were more likely to smoke at higher intensity than other groups of women. These results reinforce findings from other studies mentioned in the literature review³²⁸ suggesting that WIC participants are a suitable target population for smoking cessation interventions.

In the current study, delivering a female infant was associated with low intensity smoking in early pregnancy and high intensity smoking in late pregnancy, which is somewhat consistent with Koshy et al.⁹⁰ (n=8960) who reported an increased risk of delivering a female infant (aOR 1.41, 95% CI: 1.12, 1.92; p<0.001) to mothers who were heavy smokers (>10 cigarettes/day). The reasons for this sex-specific association are unclear.

A few prior studies explored prenatal exposure status based on reported variability in maternal smoking patterns during pregnancy^{92,95,329–331} The findings from only a handful of available studies that include infants delivered at term demonstrate the harmful effects of prenatal tobacco exposure on newborn outcomes.^{6,25,34,94,174,199,215,217,332,333} Strong scientific evidence indicates that maternal smoking contributes to fetal growth restriction and LBW in newborns, regardless of gestational age.^{164,334,335} This study adds new insights on term gestation to fill the gaps in research on the morbidity of infants at term that were prenatally exposed to maternal smoking.

Infants exposed to high intensity maternal smoking in early and late pregnancy were at higher risk of low birthweight (<2,500g), low 5 min Apgar score (<7), and NICU transfer/admission compared to non-smokers (Table 9), which was somewhat consistent with a study from Finland described in the literature review.²²⁴ The rate of newborns transferred/admitted to the NICU varied by maternal smoking intensity status, ranging from 5.19% for low intensity smokers, who quit in early pregnancy, to 6.70% for high intensity smokers who continued smoking throughout pregnancy, as opposed to nonsmokers (4.29%). In comparison, high intensity quitters in early pregnancy were more likely to have an infant with low 5-min Apgar score than non-smokers, which is in

agreement with findings in other studies.^{6,94,215} In contrast, low intensity smoking in early and high intensity smoking in late pregnancy was insignificantly associated with higher odds of a low 5-min Apgar score, possibly due to a small sample size in that category and decreased statistical power. This is also fairly consistent with a study from Russia showing that reducing smoking intensity during pregnancy, relative to its level before pregnancy, was associated with a higher risk of low 5-min Apgar score (aOR 1.10, 95% CI: 0.91, 1.34) in infants delivered at term.¹⁹⁹ These findings provide a potential explanation on how high intensity smoking (measured by the number of cigarettes smoked per day per trimester) in early pregnancy, compared to lighter smoking or no smoking at all, results in greater prenatal exposure leading to newborn morbidity apparent at birth.

A novelty in this study was using the E-value approach in place of sensitivity analysis to report a relationship with potential unmeasured confounders in the association between exposure and outcome.^{310–312} As explained in the Methods section, the E-value is a tool for quantifying the strength of association (on the risk ratio scale) that an unmeasured confounder has with both the exposure and the outcome to negate the observed exposure-outcome association. In contrast to standard methods for sensitivity analysis commonly used in observational studies, the E-value uses a simple formula in calculations, requires no prior assumptions, is based on the lowest possible risk ratio (RR) of 1, and is applied to the bounds of a 95% CI. There are no prior research studies for comparison that used the E-value approach.

Summary of Findings from Aim 3 Compared with Similar Studies

This is the first nationally-based study exploring the role of low birthweight in term neonates as an intermediate variable in the association between maternal smoking status and NICU transfer/admission. Prior research demonstrated that low birthweight (LBW) could be a marker of fetal growth and a risk factor of newborn morbidity, but there are no published studies exploring maternal smoking as a risk factor in early morbidity in LBW neonates delivered at term. In addition, this study proposed LBW, as a mediator, to provide an understanding of poorly known mechanisms of increased rates of NICU transfer/admissions among LBW term neonates. This has not been previously reported in the literature.

In this study, LBW was a partial mediator implying that almost one fifth (18.3%) of NICU transfer/admissions among neonates at term exposed to high intensity maternal smoking may be attributed to LBW, and the proportion mediated was lower (roughly 14%) for maternal quitters and reducers. Low birthweight may not be the primary mechanism through which maternal smoking status exerts its effect on NICU transfer/admission in term neonates and the risk may occur through other pathways or processes independent of LBW.³³⁶ These findings are somewhat consistent with a mediation analysis by Geraci and Mattei,²⁷³ but Gold et al.²⁷² maintained that LBW and prematurity could almost fully explain an increased risk of infant mortality. However, unlike studies by Geraci and Mattei and Gold et al., this study examines the effect of low birthweight on infant morbidity, not mortality, and uses a sample restricted to term births allowing the mediated effects to be investigated independent of gestational age. Lastly, this study suggests that it is biologically plausible that prenatal exposure from high intensity smoking in early pregnancy can adversely influence fetal growth and induce

LBW that results in morbidities in a neonate at term, which was not apparent in previous research.

STRENGTHS AND LIMITATIONS

This study benefited from several strengths. The main strength was availability of the United States National Vital Statistics 2016 Natality File (N= 3,956,112) of all births in 50 states and the District of Columbia that implemented the revised version of the 2003 United States standard certificate of live birth.^{46,112} More detailed information on timing and intensity of smoking before and during pregnancy was included in the fully revised version of the 2016 Natality file making this study possible. This study estimates on prevalence and patterns of maternal smoking among all births and singleton term births (37-41 completed weeks gestation) are considered generalizable to the entire United States population. To examine the effect of potential prenatal smoking exposure more thoroughly and to make inferences regarding the increased risk of neonatal morbidity, this study created seven mutually exclusive maternal smoking intensity status categories, based on combined measures of timing and intensity of smoking in early (1st and 2nd trimester) and in late (3rd trimester) pregnancy (Table 4). Regression adjustment for observed confounding variables was used to decrease bias and to improve precision of estimates, and the strength of an association with potential unmeasured confounders was reported as the E-value.³¹²

This study has a few inherent limitations resulting from its cross-sectional design. The self-reported data on smoking obtained from the birth certificate could introduce recall or selection bias²⁸⁵ and the presence of measurement error³¹⁷ cannot be ruled out. The

possibility of residual confounding also exists, because information on some variables (e.g. maternal medical conditions, paternal smoking status, and secondhand smoke) was not available in the dataset, and the presence of unobserved mediators³³⁷ is hard to identify. Using dichotomous variables in this study may lead to a loss of a portion of an effect in estimates and statistical significance in the association of interest.³³⁸ The cross-sectional design cannot account for time sequence among exposure, mediator and outcome variables in the mediation analysis. Overall, 9.70% missing observations in this study involved at least one or more missing covariates. A small group of women (1.19%) who did not smoke in the first and second trimesters, but smoked at low or high intensity in the third trimester only, were not assigned to a separate maternal smoking intensity status category. Moreover, this study did not consider in analyses different categories of birth weight (e.g. 1,500g, 2,000g, and 2,490g) and did not stratify term births into early term (37-38 completed weeks gestation), full term (39-40 completed weeks gestation) and late term (41 weeks 6 days gestation) to determine their proportional contributions to newborn morbidity.

SIGNIFICANCE AND IMPLICATIONS

This study has significant implications for clinical practice, public health policy and research. First, this is the first nationally-based study that provided important data on recent prevalence of smoking in the three months before and during pregnancy among pregnant women in the United States in 2016. The evidence presented in this study helped identify differences between demographic groups of women e.g. who were recent quitters or reducers and had a greater readiness to quit during transition into pregnancy, and maintainers who continued to smoke at high intensity. These groups of women may

benefit from more intensive cessation interventions. Second, morbidity among infants born at term with low birthweight to mothers who smoke during pregnancy has been an overlooked problem in research. Increased risk of low birthweight is more likely not only when compared to infants of nonsmoking mothers, but also when compared to infants of mothers who quit in a specific period during pregnancy. An important implication of this study derives from creating a set of maternal smoking intensity status categories in early and late pregnancy to account for variability in smoking patterns and to establish prenatal exposure status more accurately. I also examined different maternal smoking status categories on the increased risk of low birthweight (LBW) (<2,500g), low 5-min Apgar score (<7) and NICU transfer/admission among term neonates in the immediate birth period. These types of specific exposure-effect relationships have not been considered in prior studies. Low birthweight (LBW) predicts survival in the immediate birth period better than any other newborn characteristic²⁷⁰ and it is an important contributor to newborn long-term morbidity. Overall, 50% of special care nursery admissions following delivery have been among term neonates (37-41 weeks gestation).²²⁸ This study determined in mediation analyses that almost one fifth of NICU transfer/admissions among tobacco-exposed neonates at term may be attributed to LBW, opening opportunities for future research on other newborn morbidity indicators (e.g. Apgar score) that have not been fully explored among infants delivered at term. Estimated initial hospital costs for infants in the US can reach \$6 billion a year (average 13 days stay in the NICU for a LBW infant vs. 2 days for a healthy newborn),¹² and persistence of morbidity accounts for additional costs related to hospital readmissions, particularly within the first year of life.^{13,21} This evidence has implications for

understanding the burden to families and the society of caring for these newborns in the short and long-term.

FUTURE DIRECTIONS FOR RESEARCH

This study raises several opportunities for future research. Continued monitoring of trends in prevalence of smoking before and during pregnancy is necessary, including any changes in smoking patterns that also reflect neonatal health outcomes over time.

Considering lack of studies, more attention is needed in research on the significance of prenatal smoking exposure on morbidities across the whole spectrum of term births (i.e. early term, full term and late term births). Prenatal smoking exposure and placental insufficiency predict the severity of IUGR and pulmonary, neurological and cardiovascular morbidities at birth and in the long-term. It would be interesting to extend the current study to other maternal risk factors (e.g. alcohol and drug use, medications) and consider using biochemical markers to improve prenatal detection and early treatment of growth restriction. Finally, studying the outcomes of term-LBW infants remains critical for enhancing clinical care, planning long-term support and for advancing our understanding of the life-course consequences of low birthweight.

CONCLUSIONS

In contrast to studies focusing on outcomes in premature infants, this is the first population-based study that adds to the knowledge on the elevated risks of morbidity among neonates delivered at term to mothers who smoke during pregnancy. This study is the first to report an increased risk of low birthweight (LBW) (<2,500g), low 5-min Apgar and NICU transfer/admission in infants at term in association with maternal

smoking exposure status and the first to use LBW in mediation analyses to explain almost one fifth of NICU transfer/admissions among term-LBW newborns exposed to maternal smoking prenatally. Based on this evidence, it can be a strong argument for targeting reproductive age and pregnant women, who are non-Hispanic White, young and less educated, in cessation interventions and to convince them to quit smoking early in pregnancy to improve health outcomes of future generations. The findings of this study will raise awareness among practitioners to the fact that infants delivered at term with LBW to women who smoked in pregnancy require immediate assistance and NICU placement to improve survival and future attention to health complications that extend beyond the neonatal period.

APPENDIX A. TABLES

Table 1. Missing values on selected variables: Frequencies for each variable, its sub-categories and the percentage of missing observations per each study variable including mean $\pm$ SD

VARIABLES	N (%)
Maternal Race/ethnicity	
Non-Hispanic White	1,896,363 (53.09)
Non-Hispanic Black	490,914 (13.74)
Hispanic	843,564 (23.62)
Other race/ethnicity	341,001 (9.55)
<i>Missing</i>	<i>36,466 (0.90)</i>
Maternal Age (mean $\pm$ SD)	28.69 $\pm$ 5.79
<i>Missing</i>	<i>0 (0)</i>
Maternal Education	
Less than high school	482,503 (13.51)
High School/GED	890,648 (24.94)
Some college/Assoc.	1,042,518 (29.19)
Bachelor's or higher	1,156,173 (32.37)
<i>Missing</i>	<i>51,721 (1.27)</i>
Marital Status	
Unmarried	1,402,372 (39.26)
Married	2,169,470 (60.74)
<i>Missing</i>	<i>0 (0)</i>
Parity	
Nullipara	1,368,124 (38.30)
Multipara	2,203,718 (61.70)
<i>Missing</i>	<i>15,958 (0.38)</i>

Source of Payment

Medicaid	1,504,722 (42.13)
Private Insurance	1,781,461 (49.88)
Other payment	285,659 (7.99)
<i>Missing</i>	<i>24,640 (0.60)</i>

Route & Method of Delivery

Spontaneous	2,318,408 (64.91)
Cesarean	1,141,592 (31.96)
Other delivery	111,842 (3.13)
<i>Missing</i>	<i>2640 (0.07)</i>

Gestational Weight Gain, lbs. (mean $\pm$ SD) 30.00 $\pm$ 15.06

Pre-pregnancy BMI (mean $\pm$ SD) 26.79 $\pm$ 6.60

IOM GWG Recommendations

Below	764,387 (21.40)
Met	1,117,626 (31.29)
Exceeded	1,689,829 (47.31)
<i>Missing</i>	<i>20,073 (0.54)</i>

Prenatal care

Early	2,465,518 (77.63)
Late/no care	710,445 (22.37)
<i>Missing</i>	<i>72,508 (1.99)</i>

WIC Participation

No	2,165,310 (60.62)
Yes	1,406,532 (39.38)
<i>Missing</i>	<i>49,731 (1.21)</i>

Infant Sex

Female	1,745,698 (48.87)
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Male	1,826,144 (51.13)
<i>Missing</i>	<i>0 (0)</i>
NICU transfer/admission	
No	3,259,510 (91.26)
Yes	312,332 (8.74)
<i>Missing</i>	<i>7,300 (0.07)</i>
Birth weight, grams (mean ±SD)	3,276±582.15
<i>Missing</i>	<i>4,543 (0.12)</i>
Apgar Score, 5-minute (mean ±SD)	8.79±0.79
<i>Missing</i>	<i>16,088 (0.40)</i>
Gestational age, weeks (mean ±SD)	38.52±2.03
<i>Missing</i>	<i>3,513 (0.08)</i>
Average number of cigarettes smoked/day	
Pre-pregnancy (mean ±SD)	13±9.94
<i>Missing</i>	<i>19,350 (0.49)</i>
1 st trimester (mean ±SD)	11±8.18
<i>Missing</i>	<i>19,719 (0.51)</i>
2 nd trimester (mean ±SD)	9±7.34
<i>Missing</i>	<i>19,985 (0.50)</i>
3 rd trimester (mean ±SD)	9±7.26
<i>Missing</i>	<i>20,035 (0.50)</i>

SD-standard deviation

Table 2. Prevalence of smoking in the three months before and during pregnancy (by trimester) by low and high intensity and across maternal race/ethnicity, age and educational attainment, **all births**, United States, 2016

Maternal Characteristics	N (%)	Three months before pregnancy low intensity smoking	Three months before pregnancy high intensity smoking	First trimester low intensity smoking	First trimester high intensity smoking	Second trimester low intensity smoking	Second trimester high intensity smoking	Third trimester low intensity smoking	Third trimester high intensity smoking
Total N (%)	3,571,842 (100)	111,638 (3.13)	224,626 (6.29)	102,892 (2.88)	146,359 (4.10)	101,088 (2.83)	110,689 (3.10)	107,125 (3.00)	93,698 (2.62)
Race/ethnicity									
Non-Hispanic White	1,896,363 (53.09)	68,471 (3.61)	184,977 (9.75)	69,100 (3.64)	123,104 (6.49)	71,150 (3.75)	94,809 (5.00)	77,575 (4.09)	80,640 (4.25)
Non-Hispanic Black	490,194 (13.74)	21,074 (4.29)	17,349 (3.53)	17,835 (3.63)	10,303 (2.10)	16,026 (3.26)	7,124 (1.45)	15,630 (3.18)	6,016 (1.23)
Hispanic	843,564 (23.62)	13,155 (1.56)	10,730 (1.27)	8,409 (1.00)	5,799 (0.69)	6,937 (0.82)	3,770 (0.45)	6,786 (0.80)	3,009 (0.36)
Other race/ethnicity ^a	341,001 (9.55)	8,938 (2.62)	11,570 (3.39)	7,548 (2.21)	7,153 (2.10)	6,975 (2.05)	4,986 (1.46)	7,134 (2.09)	4,033 (1.18)
Age (years)									
<20	191,026 (5.35)	8,578 (4.49)	13,840 (7.25)	7,809 (4.09)	8,083 (4.23)	7,115 (3.72)	5,466 (2.86)	7,306 (3.82)	4,394 (2.30)

20-24	727,695 (20.37)	35,787 (4.92)	67,904 (9.33)	33,402 (4.59)	42,937 (5.90)	32,341 (4.44)	31,324 (4.30)	34,181 (4.70)	25,793 (3.54)
25-29	1,044,485 (29.24)	35,210 (3.37)	73,897 (7.07)	32,912 (3.15)	49,211 (4.71)	32,816 (3.14)	37,920 (3.63)	35,036 (3.35)	32,270 (3.09)
30-34	1,007,923 (28.22)	21,582 (2.14)	46,326 (4.60)	19,350 (1.92)	30,819 (3.06)	19,484 (1.93)	23,972 (2.38)	20,717 (2.06)	20,749 (2.06)
35+	600,713 (16.82)	10,481 (1.74)	22,659 (3.77)	9,419 (1.57)	15,309 (2.55)	9,332 (1.55)	12,007 (2.00)	9,885 (1.65)	10,492 (1.75)
Education									
Less than high school	482,503 (13.51)	22,532 (4.67)	49,012 (10.16)	23,779 (4.93)	36,756 (7.62)	24,668 (5.11)	29,564 (6.13)	26,601 (5.51)	25,575 (5.30)
High School/GED ^b	890,648 (24.94)	42,608 (4.78)	92,037 (10.33)	41,953 (4.71)	61,833 (6.94)	41,987 (4.71)	47,333 (5.31)	44,596 (5.01)	40,139 (4.51)
Some college/Assoc.	1,042,518 (29.19)	37,797 (3.63)	73,365 (7.04)	32,672 (3.13)	43,645 (4.19)	30,967 (2.97)	31,131 (2.99)	32,511 (3.12)	25,748 (2.47)
Bachelor's or higher	1,156,173 (32.37)	8,701 (0.75)	10,212 (0.88)	4,488 (0.39)	4,125 (0.36)	3,466 (0.30)	2,661 (0.23)	3,417 (0.30)	2,236 (0.19)

Low intensity smoking <10 cigs/day/trimester; High intensity smoking ≥10 cigs/day/trimester; ^a Other race/ethnicity: Asian, American Indian/Alaska Native, Native Hawaiian, Pacific Islander or mixed race; ^b GED-general educational development; All comparisons are statistically significant at $P \leq .05$ for the χ^2 statistic corresponding to each smoking group and maternal characteristic in this table

Table 3. Prevalence of smoking in the three months before and during pregnancy (by trimester) by low and high intensity and across maternal race/ethnicity, age and educational attainment, **singleton term births** (37-41 completed weeks gestation), United States, 2016

Maternal Characteristics	N (%)	Three months before pregnancy Low intensity smoking	Three months before pregnancy High intensity smoking	First trimester Low intensity smoking	First trimester High intensity smoking	Second trimester Low intensity smoking	Second trimester High intensity smoking	Third trimester Low intensity smoking	Third trimester High intensity smoking
Total N (%)	3,175,973 (100)	97,378 (3.07)	194,773 (6.13)	89,060 (2.80)	125,559 (3.95)	87,117 (2.74)	94,549 (2.98)	92,728 (2.92)	80,092 (2.52)
Race/ethnicity									
Non-Hispanic White	1696310 (53.41)	60,730 (3.58)	161,571 (9.52)	60,862 (3.59)	106,358 (6.27)	62,312 (3.67)	81,523 (4.81)	68,067 (4.01)	69,431 (4.09)
Non-Hispanic Black	417,863 (13.16)	17,303 (4.14)	14,002 (3.35)	14,446 (3.46)	8,195 (1.96)	12,902 (3.09)	5,654 (1.35)	12,670 (3.03)	4,774 (1.14)
Hispanic	756374 (23.82)	11,517 (1.52)	9,259 (1.22)	7,209 (0.95)	4,928 (0.65)	5,914 (0.78)	3,143 (0.42)	5,819 (0.77)	2,486 (0.33)
Other race/ethnicity ^a	305,426 (9.62)	7,828 (2.56)	9,941 (3.25)	6,543 (2.14)	6,078 (1.99)	5,989 (1.96)	4,229 (1.38)	6,172 (2.02)	3,401 (1.11)
Age (years)									
<20	170,816 (5.38)	7,650 (4.48)	12,340 (7.22)	6,925 (4.05)	7,172 (4.20)	6,305 (3.69)	4,831 (2.83)	6,547 (3.83)	3,867 (2.26)

20-24	654,101 (20.60)	31,788 (4.86)	60,296 (9.22)	29,524 (4.51)	37,838 (5.78)	28,560 (4.37)	27,468 (4.20)	30,302 (4.63)	22,625 (3.46)
25-29	937,529 (29.52)	30,798 (3.29)	64,449 (6.87)	28,551 (3.05)	42,475 (4.53)	28,324 (3.02)	32,641 (3.48)	30,403 (3.24)	27,761 (2.96)
30-34	895,814 (28.21)	18,423 (2.06)	39,195 (4.38)	16,342 (1.82)	25,724 (2.87)	16,308 (1.82)	19,969 (2.23)	17,378 (1.94)	17,335 (1.94)
35+	517,713 (16.30)	8,719 (1.68)	18,493 (3.57)	7,718 (1.49)	12,350 (2.39)	7,620 (1.47)	9,640 (1.86)	8,098 (1.56)	8,504 (1.64)
Education									
Less than high school	425,842 (13.41)	19,222 (4.53)	41,839 (9.83)	20,232 (4.75)	31,186 (7.32)	20,974 (4.93)	24,974 (5.86)	22,797 (5.35)	21,575 (5.07)
High School/GED ^b	789,304 (24.85)	37,119 (4.69)	80,305 (10.17)	36,435 (4.62)	53,374 (6.76)	36,377 (4.61)	40,639 (5.15)	38,797 (4.92)	34,456 (4.37)
Some college/Assoc.	925,407 (29.14)	33,268 (3.59)	63,769 (6.89)	28,469 (3.08)	37,456 (4.05)	26,765 (2.89)	26,645 (2.88)	28,165 (3.04)	22,130 (2.39)
Bachelor's or higher	1,035,420 (32.60)	7,769 (0.75)	8,860 (0.86)	3,924 (0.38)	3,543 (0.34)	3,001 (0.29)	2,291 (0.22)	2,969 (0.29)	1,931 (0.19)

Low intensity smoking <10 cigs/day/trimester; High intensity smoking ≥10 cigs/day/trimester; ^a Other race/ethnicity: Asian, American Indian/Alaska Native, Native Hawaiian, Pacific Islander or mixed race; ^b GED-general educational development; All comparisons are statistically significant at $P \leq .05$ for the χ^2 statistic corresponding to each smoking group and maternal characteristic in this table

Table 4. Maternal smoking intensity status categories in early and late pregnancy

	Quitter-1	Quitter-2	Maintainer-1	Maintainer-2	Reducer	Increaser	Reference
Early Pregnancy	Low intensity	High intensity	Low intensity	High intensity	Low intensity	Low intensity	Nonsmoker
Late Pregnancy	None	None	Low intensity	High intensity	High intensity	High intensity	Nonsmoker

Early pregnancy: 1st and 2nd trimester; Late pregnancy: 3rd trimester; Low intensity smoking <10
cigs/day/trimester; High intensity smoking $\geq$ 10 cigs/day/trimester

Table 5. Distribution of smoking intensity status categories in early and late pregnancy stratified by maternal race/ethnicity, age, and educational attainment, among **all births**, United States, 2016

Maternal Characteristics	TOTAL	QUITTER-1	QUITTER-2	MAINTAINER-1	MAINTAINER-2	REDUCER	INCREASER
	Smoking in Early and Late pregnancy N (%)	Low intensity smoking in Early pregnancy only	High intensity smoking in Early pregnancy only	Low intensity smoking in Early and Low intensity smoking in Late pregnancy	High intensity smoking in Early and High intensity smoking in Late pregnancy	High intensity smoking in Early and Low intensity smoking in Late pregnancy	Low intensity smoking in Early and High intensity smoking in Late pregnancy
Total N (%)	248,510 (100)	32,781 (13.19)	18,206 (7.33)	69,903 (28.13)	91,718 (36.91)	35,048 (14.10)	854 (0.34)
Race/ethnicity							
Non-Hispanic White	191,281 (76.97)	21,201 (11.08)	14,146 (7.40)	47,384 (24.77)	79,057 (41.33)	28,808 (15.06)	685 (0.36)
Non-Hispanic Black	28,330 (11.40)	5,471 (19.31)	1,717 (6.06)	12,556 (44.32)	5,842 (20.62)	2,658 (9.38)	86 (0.30)
Hispanic	14,236 (5.73)	3,441 (24.17)	1,245 (8.75)	5,058 (35.53)	2,915 (20.48)	1,540 (10.82)	37 (0.26)
Other race/ethnicity ^a	14,663 (5.90)	2,668 (18.20)	1,098 (7.49)	4,905 (33.45)	3,904 (26.62)	2,042 (13.93)	46 (0.31)
Age (years)							

<20	15,906 (6.40)	3,035 (19.08)	1,438 (9.04)	4,824 (30.33)	4,243 (26.66)	2,296 (14.43)	70 (0.44)
20-24	76,124 (30.63)	11,298 (14.84)	5,865 (7.70)	22,034 (28.94)	25,206 (33.11)	11,435 (15.02)	286 (0.38)
25-29	81,900 (32.96)	10,076 (12.30)	5,578 (6.81)	22,746 (27.77)	31,653 (38.65)	11,589 (14.15)	258 (0.32)
30-34	49,935 (20.09)	5,632 (11.28)	3,511 (7.03)	13,666 (27.37)	20,334 (40.72)	6,639 (13.30)	153 (0.31)
35+	24,645 (9.92)	2,740 (11.12)	1,814 (7.36)	6,633 (26.91)	10,282 (41.72)	3,089 (12.53)	87 (0.35)
Education							
Less than HS	60,543 (24.36)	5,931 (9.80)	3,275 (5.41)	17,773 (29.36)	25,073 (41.41)	8,279 (13.67)	212 (0.35)
High School/GED ^b	103,421 (41.62)	12,750 (12.33)	7,249 (7.01)	29,004 (28.04)	39,309 (38.00)	14,744 (14.26)	365 (0.35)
Some college	75,964 (30.57)	12,027 (15.83)	6,693 (8.81)	20,678 (27.22)	25,168 (33.13)	11,145 (14.67)	253 (0.33)
Bachelor's +	8,582 (3.45)	2,073 (24.15)	989 (11.52)	2,448 (28.52)	2,168 (25.26)	880 (10.25)	24 (0.28)

Early pregnancy: 1st and 2nd trimester; Late pregnancy: 3rd trimester; Low intensity smoking <10 cigs/day/trimester; High intensity smoking ≥10 cigs/day/trimester; ^a Other race/ethnicity: Asian, American Indian/Alaska Native, Native Hawaiian, Pacific Islander or mixed race; ^b GED-general educational development; All comparisons are statistically significant at $P \leq .05$ for the χ^2 statistic corresponding to each smoking group and maternal characteristic in this table

Table 6. Distribution of maternal smoking intensity status categories in early and late pregnancy stratified by maternal race/ethnicity, age, and educational attainment, among **singleton term births** (37-41 completed weeks gestation), United States, 2016

Maternal Characteristics	TOTAL	QUITTER-1	QUITTER-2	MAINTAINER-1	MAINTAINER-2	REDUCER	INCREASER
	Smoking in Early and Late Pregnancy N (%)	Low intensity smoking in Early pregnancy only	High intensity smoking in Early pregnancy only	Low intensity smoking in Early and Low intensity smoking in Late pregnancy	High intensity smoking in Early and High intensity smoking in Late pregnancy	High intensity smoking in Early and Low intensity smoking in Late pregnancy	Low intensity smoking in Early and High intensity smoking in Late pregnancy
Total N (%)	214,100	28,541 (13.33)	15,684 (7.33)	60,333 (28.18)	78,338 (36.59)	30,441 (14.22)	763 (0.36)
Race/ethnicity							
Non-Hispanic White	166,521 (77.78)	18,808 (11.29)	12,274 (7.37)	41,621 (24.99)	68,017 (40.85)	25,186 (15.12)	615 (0.37)
Non-Hispanic Black	22,800 (10.65)	4,417 (19.37)	1,364 (5.98)	10,175 (44.63)	4,630 (20.31)	2,142 (9.39)	72 (0.32)
Hispanic	12,170 (5.68)	3,002 (24.67)	1,087 (8.93)	4,294 (35.28)	2,402 (19.74)	1,351 (11.10)	34 (0.28)
Other race/ethnicity ^a	12,609 (5.89)	2,314 (18.35)	959 (7.61)	4,243 (33.65)	3,289 (26.08)	1,762 (13.97)	42 (0.33)
Age (years)							

<20	14,117 (6.59)	2,689 (19.05)	1,264 (8.95)	4,277 (30.30)	3,727 (26.40)	2,095 (14.84)	65 (0.46)
20-24	67,180 (31.38)	9,980 (14.86)	5,195 (7.73)	19,473 (28.99)	22,089 (32.88)	10,181 (15.15)	262 (0.39)
25-29	70,852 (33.09)	8,817 (12.44)	4,825 (6.81)	19,667 (27.76)	27,216 (38.41)	10,103 (14.26)	224 (0.32)
30-34	41,915 (19.58)	4,826 (11.51)	2,946 (7.03)	11,469 (27.36)	16,987 (40.53)	5,554 (13.25)	133 (0.32)
35+	20,036 (9.36)	2,229 (11.12)	1,454 (7.26)	5,447 (27.19)	8,319 (41.52)	2,508 (12.52)	79 (0.39)
Education							
Less than HS	51,457 (24.03)	5,058 (9.83)	2,775 (5.39)	15,099 (29.34)	21,125 (41.05)	7,210 (14.01)	190 (0.37)
High School/GED ^b	89,507 (41.81)	11,136 (12.44)	6,288 (7.03)	25,140 (28.09)	33,733 (37.69)	12,888 (14.40)	322 (0.36)
Some college	65,680 (30.68)	10,523 (16.02)	5,771 (8.79)	17,958 (27.34)	21,608 (32.90)	9,591 (14.60)	229 (0.35)
Bachelor's +	7,456 (3.48)	1,824 (24.46)	850 (11.40)	2,136 (28.65)	1,872 (25.11)	752 (10.09)	22 (0.30)

Early pregnancy: 1st and 2nd trimester; Late pregnancy: 3rd trimester; Low intensity smoking <10 cigs/day/trimester; High intensity smoking ≥10 cigs/day/trimester; ^a Other race/ethnicity: Asian, American Indian/Alaska Native, Native Hawaiian, Pacific Islander or mixed race; ^b GED-general educational development; All comparisons are statistically significant at $P \leq .05$ for the χ^2 statistic corresponding to each smoking group and maternal characteristic in this table.

Table 7. Distribution of maternal and infant characteristics across smoking intensity status categories in early and late pregnancy, singleton term births (37-41 completed weeks gestation), United States, 2016

	REFERENCE	TOTAL	QUITTER-1	QUITTER-2	MAINTAINER-1	MAINTAINER-2	REDUCER	INCREASER
Maternal and Infant Characteristics	Non-smoker N (%)	Smoking in Early and Late pregnancy N (%)	Low intensity smoking in Early pregnancy only	High intensity smoking in Early pregnancy only	Low intensity smoking in Early and Low intensity smoking in Late pregnancy	High intensity smoking in Early and High intensity smoking in Late pregnancy	High intensity smoking in Early and Low intensity smoking in Late pregnancy	Low intensity smoking in Early and High intensity smoking in Late pregnancy
Total N	2,961,873	214,100	28,541	15,684	60,333	78,338	30,441	763
Race/ethnicity								
Non-Hispanic White	1,529,789 (51.65)	166,521 (77.78)	18,808 (65.90)	12,274 (78.26)	41,621 (68.99)	68,017 (86.83)	25,186 (82.74)	615 (80.60)
Non-Hispanic Black	395,063 (13.34)	22,800 (10.65)	4,417 (15.48)	1,364 (8.70)	10,175 (16.86)	4,630 (5.91)	2,142 (7.04)	72 (9.44)
Hispanic	744,204 (25.13)	12,170 (5.68)	3,002 (10.52)	1,087 (6.93)	4,294 (7.12)	2,402 (3.07)	1,351 (4.44)	34 (4.46)
Other race/ethnicity ^a	292,817 (9.89)	12,609 (5.89)	2,314 (8.11)	959 (6.11)	4,243 (7.03)	3,289 (4.20)	1,762 (5.79)	42 (5.50)
Age (years)								
<20	156,699 (5.29)	14,117 (6.59)	2,689 (9.42)	1,264 (8.06)	4,277 (7.09)	3,727 (4.76)	2,095 (6.88)	65 (8.52)

20-24	586,921 (19.82)	67,180 (31.38)	9,980 (34.97)	5,195 (33.12)	19,473 (32.28)	22,089 (28.20)	10,181 (33.45)	262 (34.34)
25-29	866,677 (29.26)	70,852 (33.09)	8,817 (30.89)	4,825 (30.76)	19,667 (32.60)	27,216 (34.74)	10,103 (33.19)	224 (29.36)
30-34	853,899 (28.83)	41,915 (19.58)	4,826 (16.91)	2,946 (18.78)	11,469 (19.00)	16,987 (21.68)	5,554 (18.25)	133 (17.43)
35+	497,677 (16.80)	20,036 (9.36)	2,229 (7.81)	1,454 (9.27)	5,447 (9.03)	8,319 (10.62)	2,508 (8.24)	79 (10.35)
Education								
Less than high school	374,385 (12.64)	51,457 (24.03)	5,058 (17.72)	2,775 (17.69)	15,099 (25.03)	21,125 (26.97)	7,210 (23.69)	190 (24.90)
High School/GED ^b	699,797 (23.63)	89,507 (41.81)	11,136 (39.01)	6,288 (40.09)	2,5140 (41.67)	33,733 (43.06)	12,888 (42.34)	322 (42.20)
Some college/Assoc.	859,727 (29.03)	65,680 (30.68)	10,523 (36.86)	5,771 (36.80)	17,958 (29.76)	21,608 (27.58)	9,591 (31.51)	229 (30.01)
Bachelor's or higher	1,027,964 (34.71)	7,456 (3.48)	1,824 (6.39)	850 (5.42)	2,136 (3.54)	1,872 (2.39)	752 (2.47)	22 (2.88)
Marital Status								
Married	1,880,847 (63.50)	59,944 (28.00)	7,887 (27.63)	4,461 (28.44)	15,809 (26.20)	23,703 (30.26)	7,857 (25.81)	227 (29.75)
Unmarried	1,081,026 (36.50)	154,156 (72.00)	20,654 (72.37)	11,223 (71.56)	44,524 (73.80)	54,635 (69.74)	22,584 (74.19)	536 (70.25)
Parity								

Nullipara	1,799,331 (60.75)	65,298 (30.50)	12,516 (43.85)	6,689 (42.65)	17,842 (29.57)	18,155 (23.18)	9,829 (32.29)	267 (34.99)
Multipara	1,162,542 (39.25)	148,802 (69.50)	16,025 (56.15)	8,995 (57.35)	42,491 (70.43)	60,183 (76.82)	20,612 (67.71)	496 (65.01)
Form of Payment								
Private Insurance	1,545,751 (52.19)	45,900 (21.44)	8,453 (29.62)	4,663 (29.73)	12,717 (21.08)	14,008 (17.88)	5,889 (19.35)	170 (22.28)
Medicaid	1,170,159 (39.51)	158,179 (73.88)	18,628 (65.27)	10,175 (64.88)	44,907 (74.43)	60,739 (77.53)	23,171 (76.12)	559 (73.26)
Other form of payment ^c	245,963 (8.30)	10,021 (4.68)	1,460 (5.11)	846 (5.39)	2,709 (4.49)	3,591 (4.59)	1,381 (4.53)	34 (4.46)
IOM GWG Guidelines ^d								
Below	60,744 (20.51)	51,356 (23.99)	4,622 (16.19)	2,484 (15.84)	14,829 (24.58)	22,130 (28.25)	7,105 (23.34)	186 (24.38)
Met	950,092 (32.08)	57,211 (26.72)	6,807 (23.85)	3,638 (32.20)	16,433 (27.24)	21,901 (27.96)	8,250 (27.10)	182 (23.85)
Exceeded	1,404,337 (47.41)	105,533 (49.29)	17,112 (59.96)	9,562 (60.97)	29,071 (48.18)	34,307 (43.79)	15,086 (49.56)	395 (51.77)
Delivery Method								
Spontaneous	1,999,139 (67.50)	140,281 (65.52)	18,830 (65.98)	10,086 (64.31)	39,980 (66.27)	50,768 (64.81)	20,124 (66.11)	493 (64.61)
Cesarean	864,846 (29.20)	66,923 (31.26)	8,681 (30.42)	5,029 (32.06)	18,557 (30.76)	25,166 (32.12)	9,249 (30.38)	241 (31.59)

Other delivery ^e	97,888 (3.30)	6,896 (3.22)	1,030 (3.60)	569 (3.63)	1,796 (2.97)	2,404 (3.07)	1,068 (3.51)	29 (3.80)
WIC Participation ^f								
No	1,848,603 (62.41)	80,408 (37.56)	12,076 (42.31)	6,647 (42.38)	22,508 (37.31)	28,202 (36.00)	10,723 (35.23)	252 (33.03)
Yes	1,113,270 (37.59)	133,692 (62.44)	16,465 (57.69)	9,037 (57.62)	37,825 (62.69)	50,136 (64.00)	19,718 (64.77)	511 (66.97)
Prenatal Care^g								
Early	2,323,923 (78.46)	141,595 (66.13)	20,018 (70.14)	10,718 (68.34)	40,033 (66.35)	50,889 (64.96)	19,368 (63.62)	569 (74.57)
Late/no care	637,950 (21.54)	72,505 (33.87)	8,523 (29.86)	4,966 (31.66)	20,300 (33.65)	27,449 (35.04)	11,073 (36.38)	194 (25.43)
Pre-pregnancy Smoking								
No	2,881,042 (97.27)	2,780 (1.30)	1,181 (4.14)	639 (4.07)	546 (0.90)	258 (0.33)	135 (0.44)	21 (2.75)
Yes	80,831 (2.73)	211,320 (98.70)	27,360 (95.86)	15,045 (95.93)	59,787 (99.10)	78,080 (99.67)	30,306 (99.56)	742 (97.25)
Infant Sex								
Male	1,508,561 (50.93)	108,942 (50.88)	14,309 (50.13)	7,987 (50.92)	30,792 (51.04)	40,050 (51.12)	15,436 (50.71)	368 (48.23)
Female	1,453,312 (49.07)	105,158 (49.12)	14,232 (49.87)	7,697 (49.08)	29,541 (48.96)	38,288 (48.88)	15,005 (49.29)	395 (51.77)

Early pregnancy: 1st and 2nd trimester; Late pregnancy: 3rd trimester; Low intensity smoking <10 cigs/day/trimester; High intensity smoking ≥ 10 cigs/day/trimester; LE- low intensity smoking in early pregnancy; HE- high intensity smoking in early pregnancy; LL- low intensity smoking in late pregnancy; HL-high intensity smoking in late pregnancy; ^a Other race/ethnicity includes non-Hispanic Asian, non-Hispanic American Indian Alaska Native, non-Hispanic Native Hawaiian or other Pacific Islander or mixed race; ^b GED- general educational development; ^c Other form of payment-self-pay, Indian Health Service, CHAMPUS/TRICARE, other government; ^d Institute of Medicine (IOM) guidelines for gestational weight gain (GWG) based on BMI (body mass index): below BMI <18.5 and wt. gain <28-40 lbs., met BMI 18.5 to 24.9 and wt. gain 25-35 lbs., or exceeded BMI ≥ 25 and wt. gain ≥ 11 lbs.; ^e Other mode of delivery: forceps or vacuum; ^f WIC-Special Supplement Nutrition Program for Women, Infants, and Children; ^g Prenatal care: early-initiated in the 1st trimester or late/no prenatal care- initiated in the 2nd or 3rd trimester. All comparisons are statistically significant at $P < .05$ for the χ^2 statistic corresponding to each smoking group and maternal characteristic in this table.

Table 8. Prevalence of low birthweight, low 5-min. Apgar score, and NICU admission stratified by maternal smoking intensity status and by maternal and infant characteristics, singleton term births (37-41 completed weeks gestation), United States, 2016

Maternal Smoking Status	Total N=3,175,973 (100%)	Low Birthweight N=76,327 (2.40%)	Low 5-min Apgar N=37,633 (1.18%)	NICU admission N=140,301 (4.42%)
Nonsmoker	2,961,873 (93.26)	64,563 (2.18)	34,292 (1.16)	127,116 (4.29)
Quitter-1 (LE)	28,541 (0.90)	1,019 (3.57)	464 (1.63)	1,480 (5.19)
Quitter-2 (HE)	15,684 (0.49)	568 (3.62)	277 (1.77)	912 (5.81)
Maintainer-1(LE+LL)	60,333 (1.90)	3,254 (5.39)	922 (1.53)	3,608 (5.98)
Maintainer-2 (HE+HL)	78,338 (2.47)	5,150 (6.57)	1,200 (1.53)	5,250 (6.70)
Reducer HE+LL	30,441 (0.96)	1,742 (5.72)	463 (1.52)	1,891 (6.21)
Increaser LE+HL	763 (0.02)	31 (4.06)	15 (1.97)	44 (5.77)
Maternal and Infant Characteristics				
Race/ethnicity				
Non-Hispanic White	1,696,310 (53.41)	32,417 (1.91)	21,223 (1.25)	71,461 (4.21)
Non-Hispanic Black	417,863 (13.16)	18,733 (4.48)	6,956 (1.66)	21,944 (5.25)
Hispanic	756,374 (23.82)	16,367 (2.16)	6,360 (0.84)	32,721 (4.33)
Other race/ethnicity ^a	305,426 (9.62)	8,810 (2.88)	3,094 (1.01)	14,175 (4.64)
Maternal Age (years)				
<20	170,816 (5.38)	6,228 (3.65)	2,931 (1.72)	8,377 (4.90)

20-24	654,101 (20.60)	19,048 (2.91)	8,932 (1.37)	29,068 (4.44)
25-29	937,529 (29.52)	21,236 (2.27)	10,815 (1.15)	40,491 (4.32)
30-34	895,814 (28.21)	17,810 (1.99)	9,216 (1.03)	37,724 (4.21)
35+	517,713 (16.30)	12,005 (2.32)	5,739 (1.11)	24,641 (4.76)

Education

Less than high school	425,842 (13.41)	14,048 (3.30)	5,064 (1.19)	19,775 (4.64)
High School/GED ^b	789,304 (24.85)	23,012 (2.92)	10,087 (1.28)	36,332 (4.60)
Some college/Assoc.	925,407 (29.14)	21,538 (2.33)	11,828 (1.28)	42,347 (4.58)
Bachelor's or higher	1,035,420 (32.60)	17,729 (1.71)	10,654 (1.03)	41,847 (4.04)

Marital Status

Married	1,940,791 (61.11)	36,130 (1.86)	20,526 (1.06)	77,612 (4.00)
Unmarried	1,235,182 (38.89)	40,197 (3.25)	17,107 (1.38)	62,689 (5.08)

Parity

Nullipara	1,227,840 (38.66)	37,095 (3.02)	21,160 (1.72)	71,551 (5.83)
Multipara	1,948,133 (61.34)	39,232 (2.01)	16,473 (0.85)	68,750 (3.53)

Form of Payment

Private Insurance	1,591,651 (50.12)	29,326 (1.84)	17,609 (1.11)	65,521 (4.12)
Medicaid	1,328,338 (41.82)	41,310 (3.11)	16,753 (1.26)	64,624 (4.87)
Other form of payment ^c	255,984 (8.06)	5,691 (2.22)	3,271 (1.28)	10,156 (3.97)

IOM GWG Guidelines ^d				
Below	658,800 (20.74)	28,422 (4.31)	7,021 (1.07)	27,879 (4.23)
Met	1,007,303 (31.72)	24,448 (2.43)	10,723 (1.06)	40,419 (4.01)
Exceeded	1,509,870 (47.54)	23,457 (1.55)	19,889 (1.32)	72,003 (4.77)
Delivery Method				
Spontaneous	2,139,420 (67.36)	47,775 (2.23)	19,585 (0.92)	69,503 (3.25)
Cesarean	931,769 (29.34)	26,207 (2.81)	15,469 (1.66)	63,604 (6.83)
Other mode of delivery ^e	104,784 (3.30)	2,345 (2.24)	2,579 (2.46)	7,194 (6.87)
WIC Participation ^f				
No	1,929,011 (60.74)	38,905 (2.02)	21,749 (1.13)	81,566 (4.23)
Yes	1,246,962 (39.26)	37,422 (3.00)	15,884 (1.27)	58,735 (4.71)
Prenatal Care ^g				
Early	2,465,518 (77.63)	54,814 (2.22)	28,472 (1.15)	104,100 (4.22)
Late/no care	710,445 (22.37)	21,513 (3.03)	9,161 (1.29)	36,201 (5.10)
Pre-pregnancy Smoking				
No	2,883,822 (90.80)	62,648 (2.17)	33,087 (1.15)	123,225 (4.27)
Yes	292,151 (9.20)	13,679 (4.68)	4,546 (1.56)	17,076 (5.84)
Infant Sex				
Male	1,617,503 (50.93)	30,161 (1.86)	21,138 (1.31)	79,242 (4.90)

Female	1,558,470 (49.07)	46,166 (2.96)	16,495 (1.06)	61,059 (3.92)
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Early pregnancy: 1st and 2nd trimester; Late pregnancy: 3rd trimester; Low intensity smoking <10 cigs/day/trimester; High intensity smoking ≥ 10 cigs/day/trimester; LE- low intensity smoking in early pregnancy; HE- high intensity smoking in early pregnancy; LL-low intensity smoking in late pregnancy; HL-high intensity smoking in late pregnancy; ^a Other race/ethnicity includes non-Hispanic Asian, non-Hispanic American Indian Alaska Native, non-Hispanic Native Hawaiian or other Pacific Islander or mixed race; ^b GED-general educational development; ^c Other form of payment-self-pay, Indian Health Service, CHAMPUS/TRICARE, other government; ^d Institute of Medicine (IOM) guidelines for gestational weight gain (GWG) based on BMI (body mass index): below-BMI <18.5 and wt. gain <28-40 lbs., met-BMI 18.5 to 24.9 and wt. gain 25-35 lbs., or exceeded- BMI ≥ 25 and wt. gain ≥ 11 lbs.; ^e Other mode of delivery: forceps or vacuum; ^f WIC-Special Supplement Nutrition Program for Women, Infants, and Children; ^g Prenatal care: early-initiated in the 1st trimester or late/no prenatal care- initiated in the 2nd or 3rd trimester. All comparisons are statistically significant at $P < .05$ for the χ^2 statistic corresponding to each smoking group and maternal characteristic in this table.

Table 9. The odds of low birthweight, low 5-min. Apgar score and NICU admission across maternal smoking intensity status categories in early and late pregnancy, term singletons (37-41 completed weeks gestation), United States, 2016

MATERNAL SMOKING STATUS	TOTAL N=3,175,973 (100%)	Low birthweight N=76,327 (2.40%)		Low 5-min Apgar N=37,633 (1.18%)		NICU admission N=140,301 (4.42%)	
		Model 1 Crude OR, (95% CI)	Model 2 Adjusted aOR, (95% CI)	Model 1 Crude OR, (95% CI)	Model 2 Adjusted aOR, (95% CI)	Model 1 Crude aOR, (95% CI)	Model 2 Adjusted aOR, (95% CI)
Non-smoker (ref.)	2,961,873 (93.26)	1	1	1	1	1	1
Quitter-1 (LE, None)	28,541 (0.90)	1.66 (1.56, 1.77)	1.46 (1.37, 1.55)	1.41 (1.29, 1.55)	1.16 (1.06, 1.28)	1.22 (1.16, 1.28)	1.12 (1.07, 1.19)
Quitter-2 (HE, None)	15,684 (0.49)	1.68 (1.55, 1.83)	1.61 (1.47, 1.75)	1.54 (1.36, 1.73)	1.26 (1.12, 1.42)	1.37 (1.28, 1.47)	1.28 (1.19, 1.37)
Increaser (LE, HL)	763 (0.02)	1.90 (1.33, 2.72)	1.83 (1.28, 2.63)	1.71 (1.03, 2.86)	1.46 (0.88, 2.44)	1.36 (1.01, 1.85)	1.33 (0.98, 1.81)
Maintainer-1 (LE, LL)	60,333 (1.90)	2.56 (2.47, 2.65)	2.31 (2.23, 2.40)	1.32 (1.24, 1.41)	1.17 (1.10, 1.25)	1.42 (1.37, 1.47)	1.38 (1.33, 1.43)
Reducer (HE, LL)	30,441 (0.96)	2.72 (2.59, 2.86)	2.71 (2.57, 2.84)	1.32 (1.20, 1.44)	1.14 (1.04, 1.25)	1.48 (1.41, 1.55)	1.43 (1.37, 1.50)
Maintainer-2 (HE, HL)	78,338 (2.47)	3.16 (3.07, 3.25)	3.33 (3.23, 3.44)	1.33 (1.25, 1.41)	1.23 (1.16, 1.30)	1.60 (1.56, 1.65)	1.62 (1.58, 1.67)

Early pregnancy: 1st and 2nd trimesters; Late pregnancy: 3rd trimester; Low intensity smoking: ≤9 cigarettes/trimester/day, High intensity smoking: ≥10 cigarettes/trimester/day; LE -low intensity smoking in early pregnancy; HE-high intensity smoking in early pregnancy; LL-

low intensity smoking in late pregnancy; HL-high intensity smoking in late pregnancy; aOR-adjusted odds ratio; Low Birthweight < 2,500g; Low 5-min Apgar < 7. Adjustment for: race/ethnicity, age, education, marital status, parity, source of payment, and prenatal care.

Table 10. Estimates of the natural direct and indirect effects and total effect of the association between maternal smoking status in early and late pregnancy (exposure), low birthweight (mediator) and NICU transfer/admission (outcome), and the proportion mediated through low birthweight, singleton term births (37-41 completed weeks gestation), United States, 2016

Adjusted Odds Ratios (aORs)							
Smoking Status	Natural Direct Effect		Natural Indirect Effect		Total Effect		Proportion Mediated Through Low Birthweight
	aOR _{NDE}	95% CI	aOR _{NIE}	95% CI	aOR	95% CI	% (95% CI)
Quitter-1 (LE)	1.11	1.05,1.17	1.02	1.01, 1.02	1.12	1.07, 1.19	14.8 (7.15, 22.54)
Quitter-2 (HE)	1.25	1.16, 1.33	1.03	1.02, 1.04	1.28	1.19, 1.37	14.4 (8.61, 20.14)
Increaser (LE, HL)	1.29	0.89, 1.69	1.03	0.97, 1.09	1.33	0.98, 1.81	13.3 (-10.05, 36.56)
Maintainer-1 (LE, LL)	1.32	1.27, 1.37	1.05	1.04, 1.06	1.38	1.33, 1.43	16.7 (13.74, 19.60)
Reducer (HE, LL)	1.37	1.31, 1.44	1.05	1.04, 1.06	1.43	1.37, 1.50	14.9 (11.12, 18.72)
Maintainer-2 (HE, HL)	1.52	1.47, 1.57	1.07	1.07, 1.09	1.62	1.58, 1.67	18.3 (15.99, 20.54)

CI- confidence interval; aOR-adjusted odds ratio; NDE-natural direct effect ; NIE-natural indirect effect; LE- low intensity smoking in early pregnancy; HE-high smoking in early pregnancy; LL- low intensity smoking in late pregnancy; HL-high intensity smoking in late pregnancy; Adjusted for: maternal race/ethnicity, age, education, marital status, parity, source of payment, and prenatal care; Proportion mediated estimated as: NIE excess relative risk/total excess relative risk x 100%

APPENDIX B. FIGURES

Figure 1. Flow diagram of the study population based on the 2016 Natality File of Live Births; United States Standard Birth Certificate; National Vital Statistics System

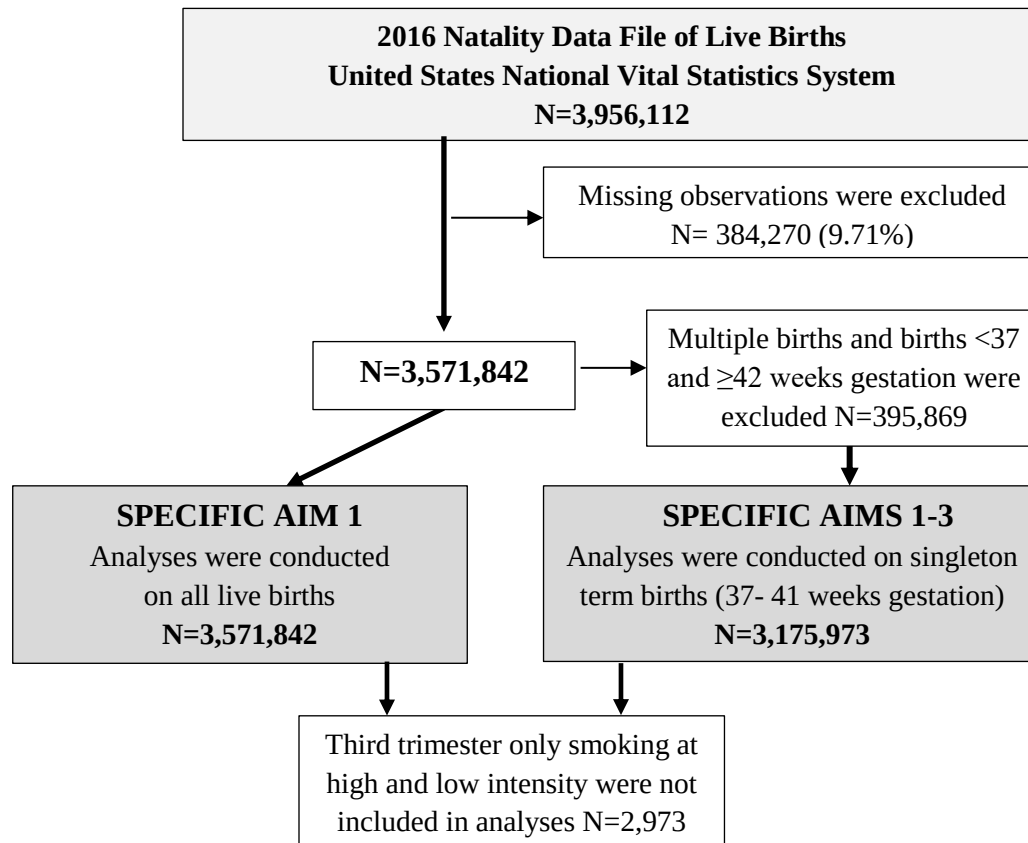


Figure 2. Smoking prevalence in the three months before and during pregnancy (by trimester) across intensity categories and maternal race/ethnicity, **all births**, United States, 2016

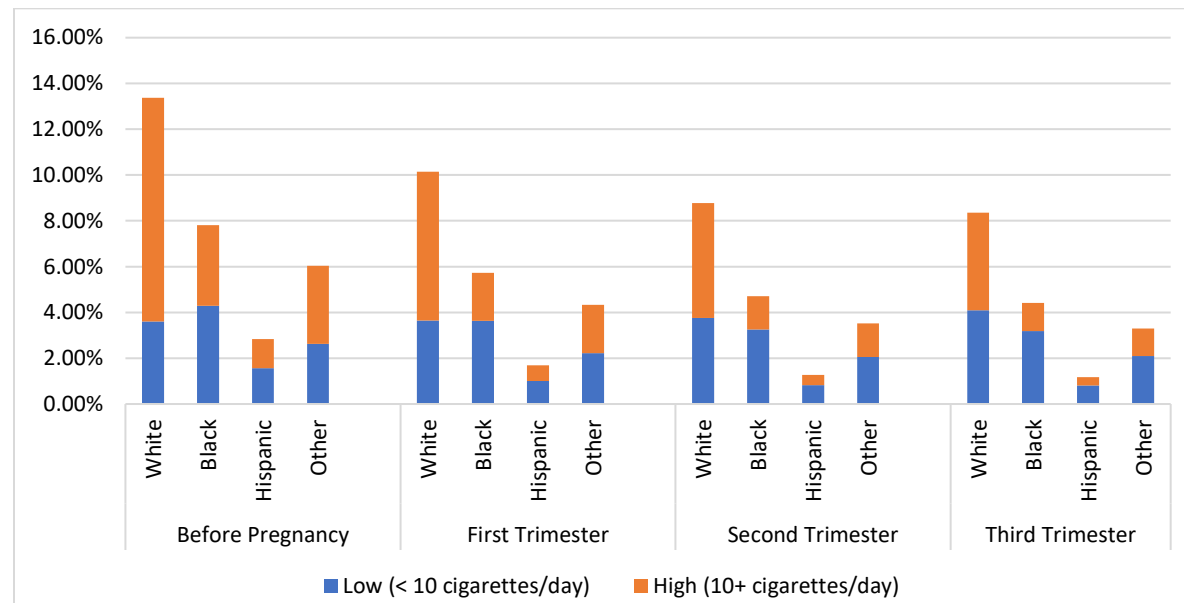


Figure 3. Smoking prevalence in the three months before and during pregnancy (by trimester) across intensity categories and maternal age, **all births**, United States, 2016

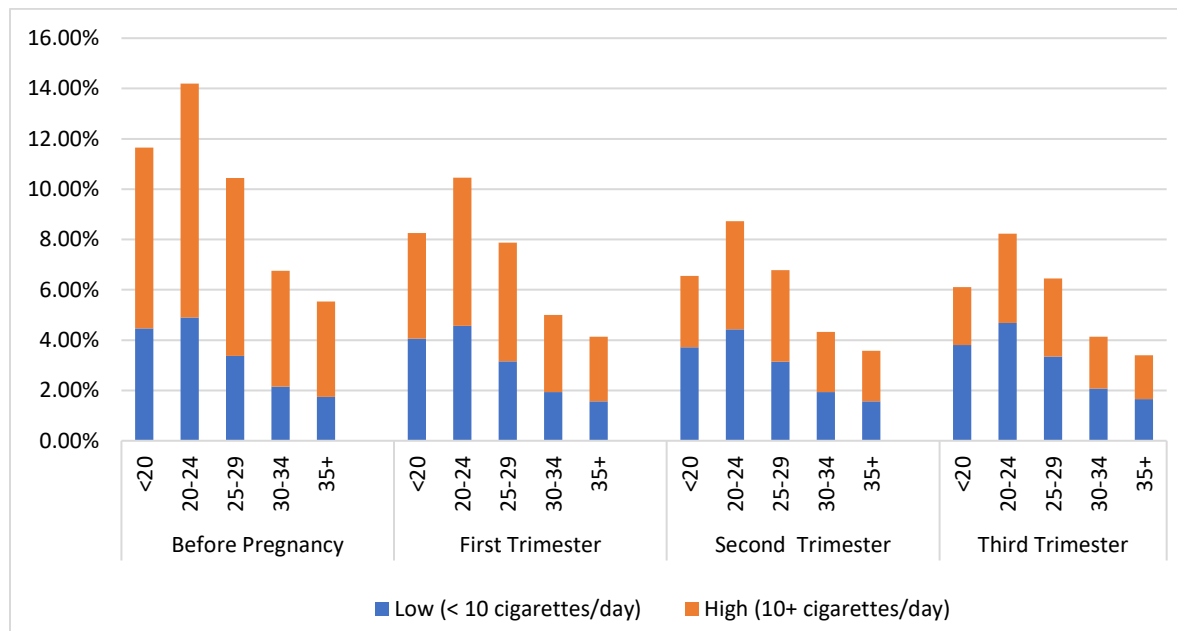


Figure 4. Smoking prevalence in the three months before and during pregnancy (by trimester) across intensity categories and maternal educational attainment, **all births**, United States, 2016

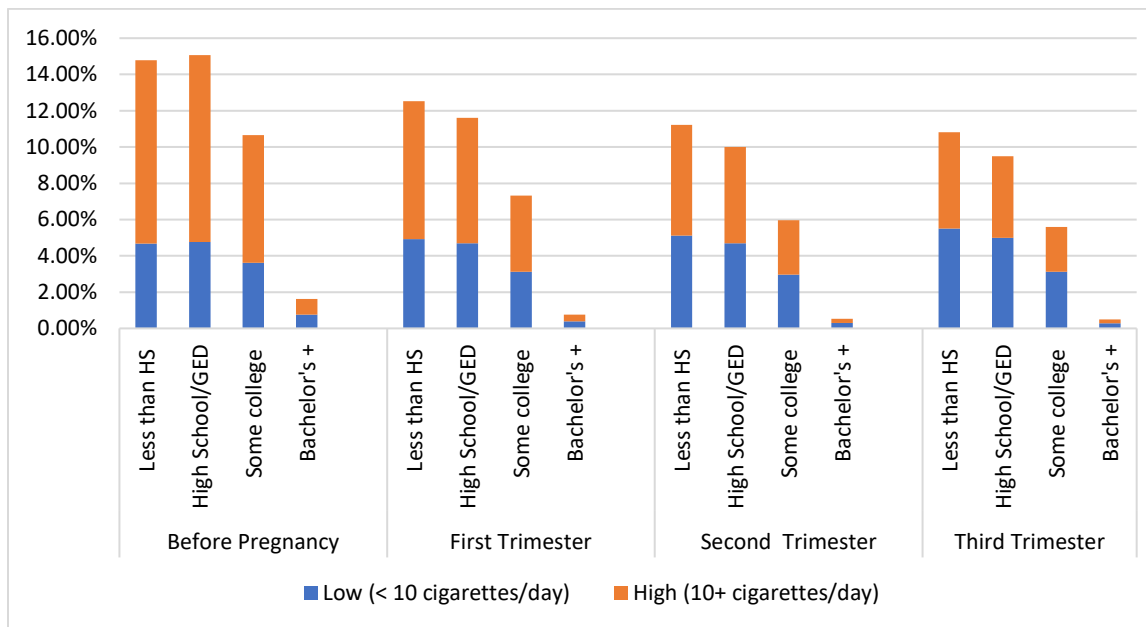


Figure 5. Smoking prevalence in the three months before and during pregnancy (by trimester) across intensity categories and maternal race/ethnicity, **singleton term births** (37-41 completed weeks gestation), United States, 2016

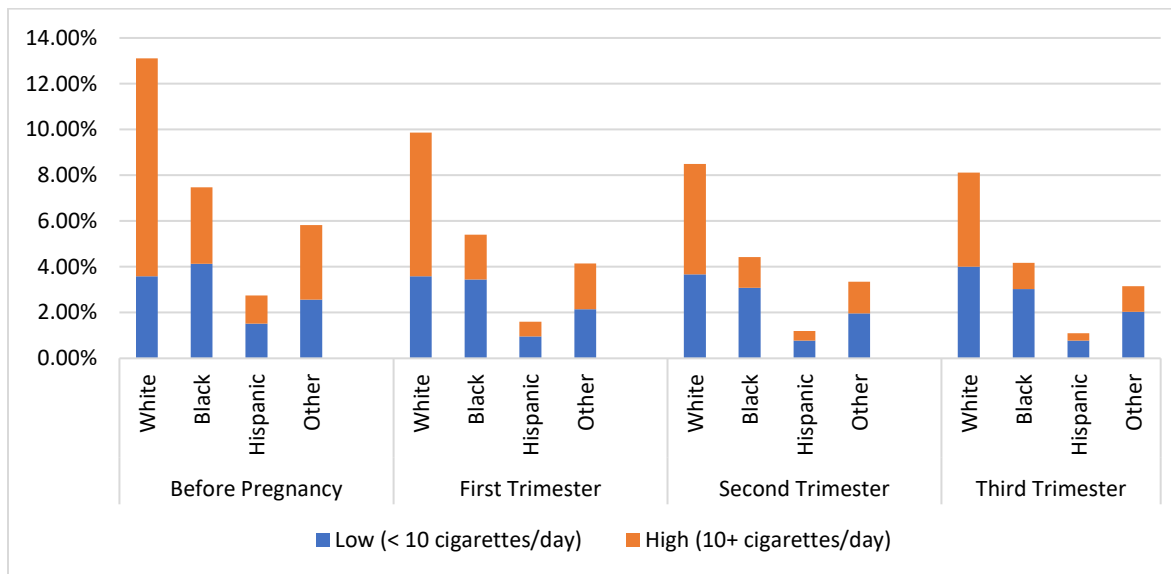


Figure 6. Smoking prevalence in the three months before and during pregnancy (by trimester) across intensity categories and maternal age, **singleton term births** (37-41 completed weeks gestation), United States, 2016

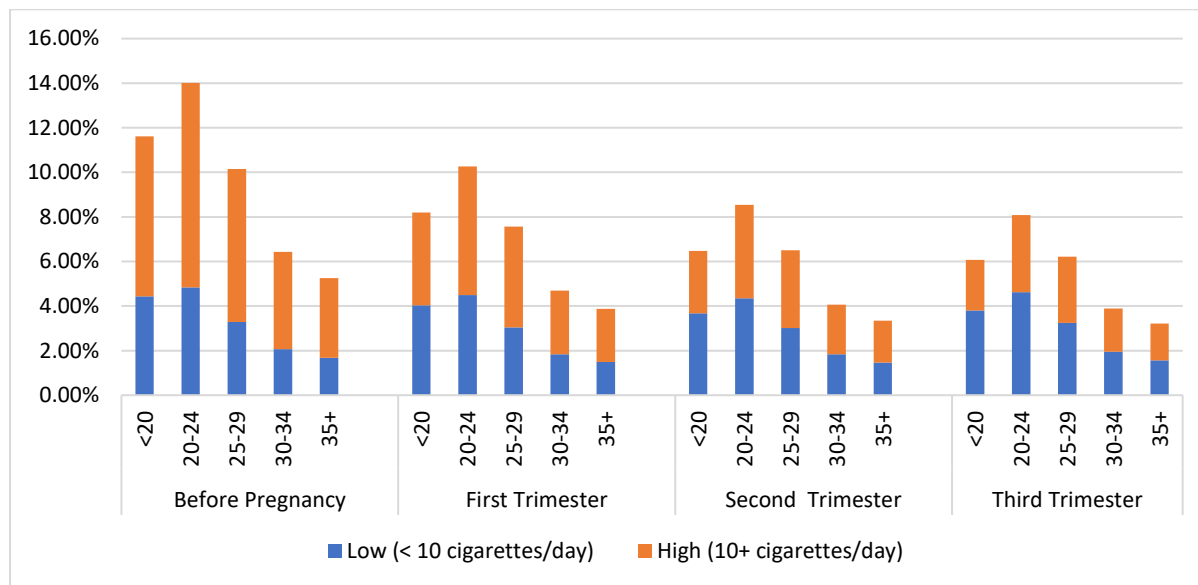


Figure 7. Smoking prevalence in the three months before and during pregnancy (by trimester) across intensity categories and maternal educational attainment, **singleton term births** (37-41 completed weeks gestation), United States, 2016

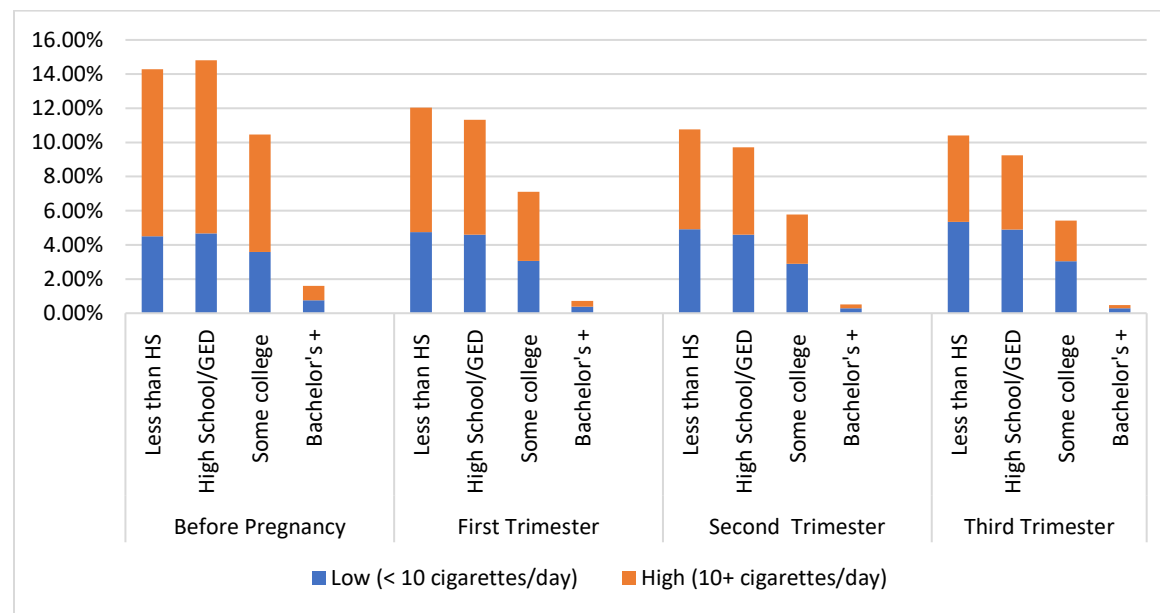


Figure 8. Distribution of maternal smoking patterns by intensity categories in early (first and second trimester) and late (third trimester) pregnancy among **all births**, United States, 2016

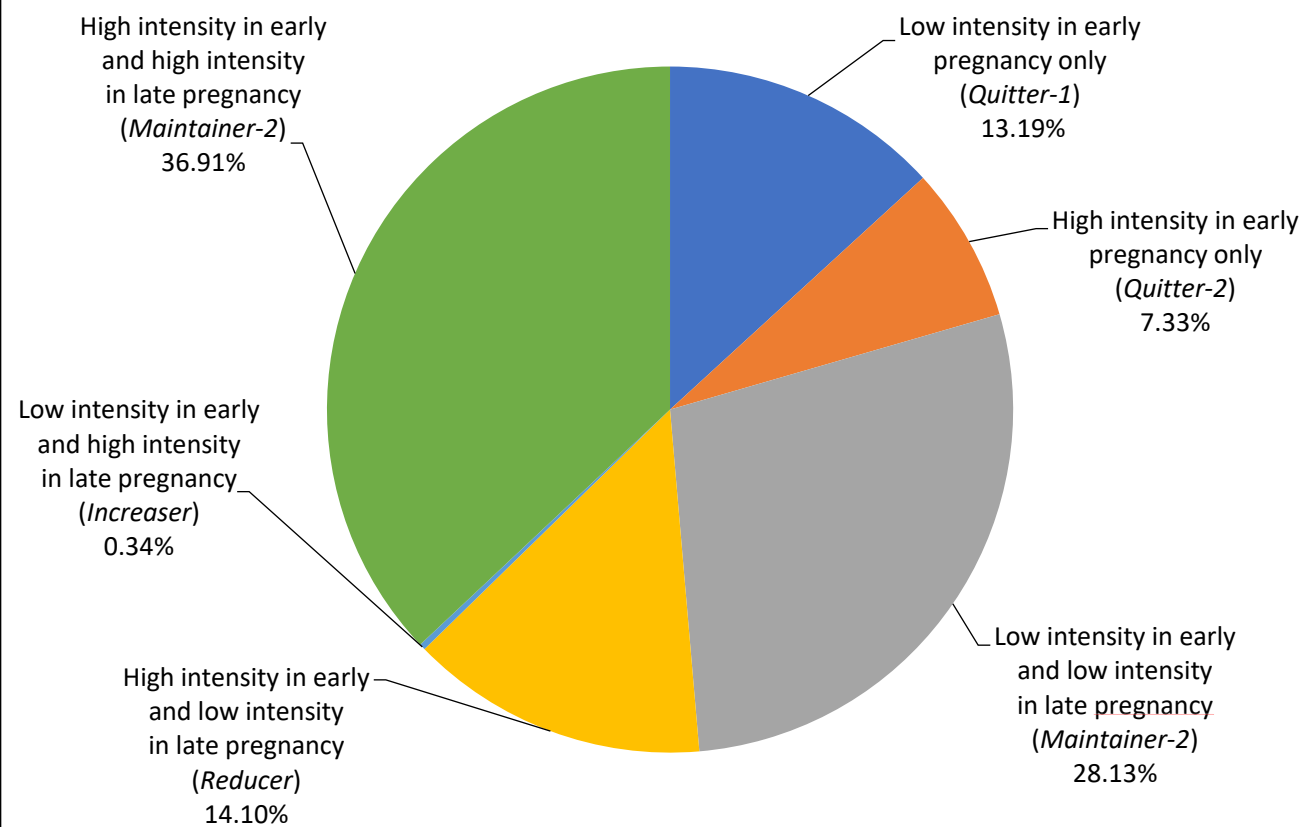


Figure 9. Conceptual diagram for the association between exposure (maternal smoking status, X) and outcome (neonatal morbidity, Y) with observed (O) and unmeasured confounders (U)

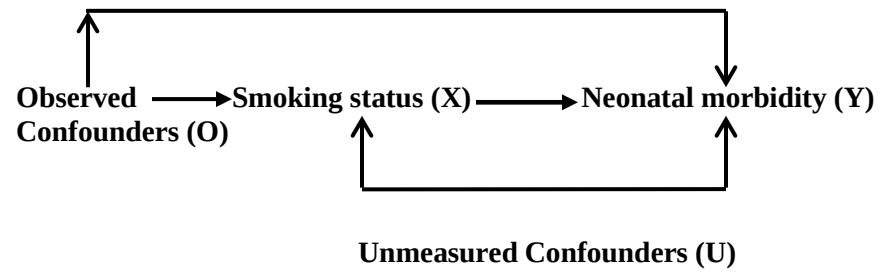


Figure 10. Directed acyclic graph (DAG) is showing observed (solid lines) and unmeasured confounders (in boxes and dashed lines) in the association with maternal smoking status (X) and neonatal morbidity (Y). Unmeasured confounders were considered in the E-value calculation

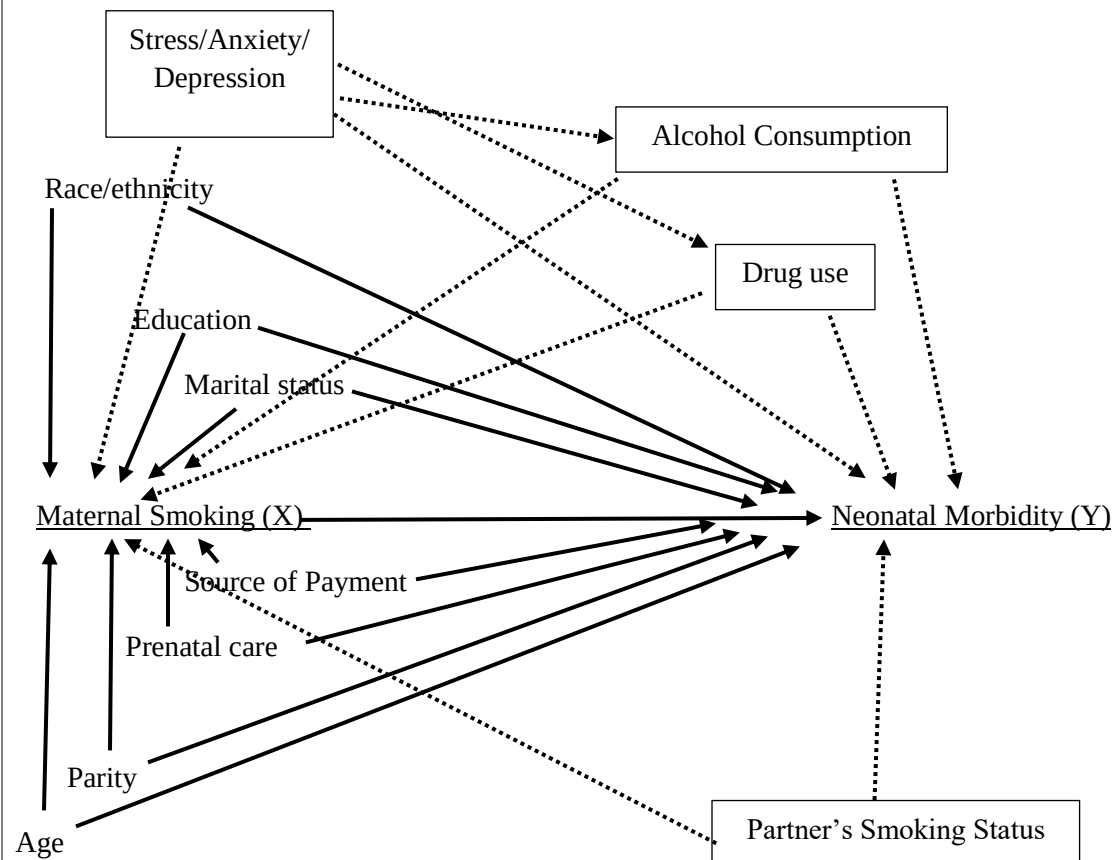
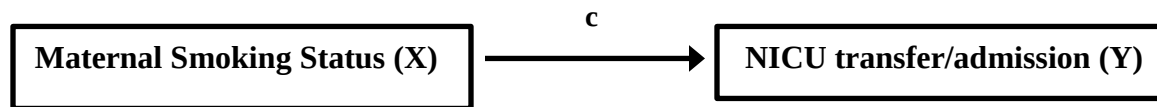


Figure 11. Hypothesized simple unmediated (A) and mediated (B) models for the relationship between maternal smoking status (X), NICU transfer/admission (Y) and infant low birthweight (M); a and b- natural indirect effects; c'-natural direct effect; c- total effect

A) Hypothesized Unmediated Model



B) Hypothesized Simple Mediated Model

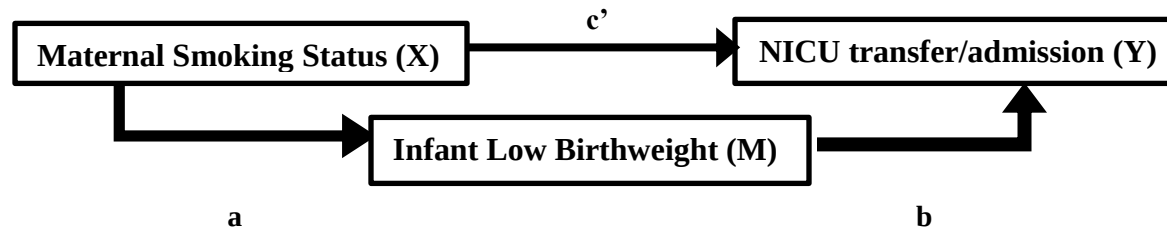


Figure 12. Conceptual diagram of the mediated model for exposure-outcome (X-Y), exposure-mediator (X-M), and mediator-outcome (M-Y) associations with observed (O) and unmeasured (U) confounders (O); LBW-low birthweight; dashed arrows indicate the natural indirect effects

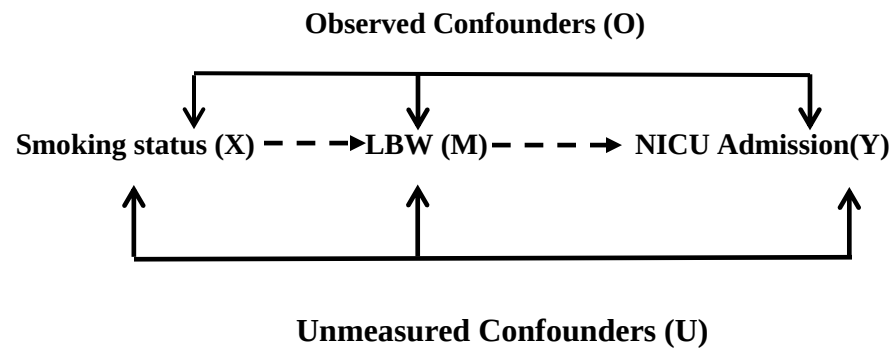
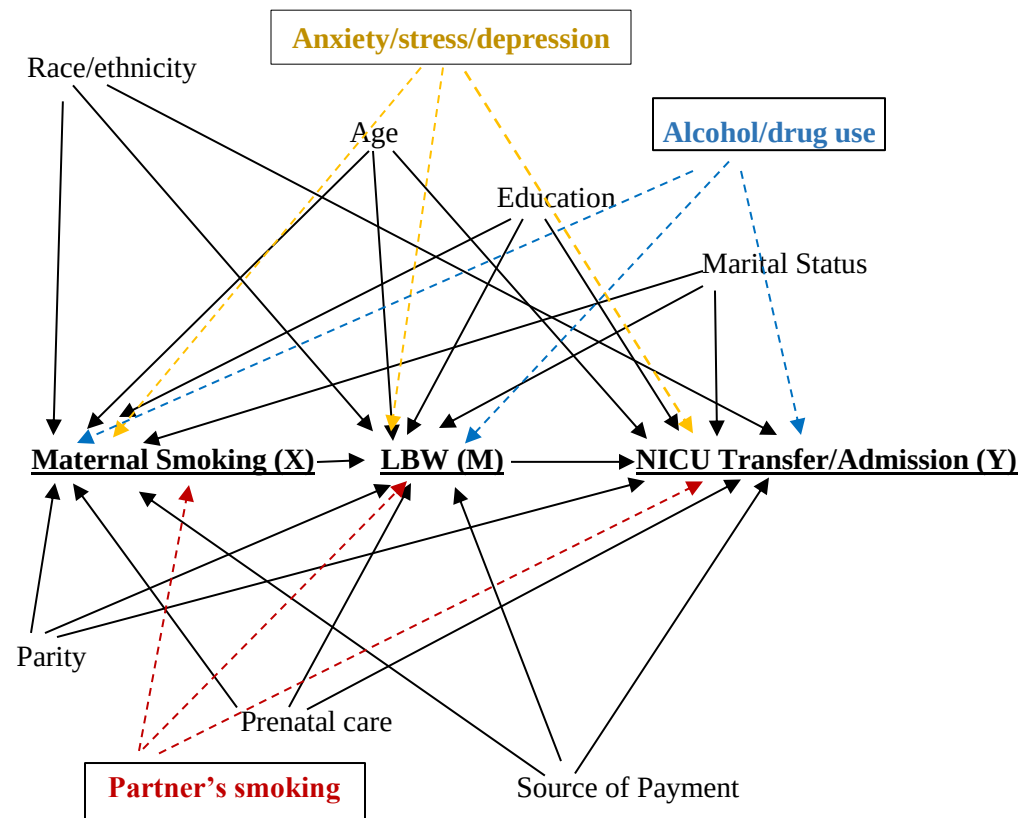


Figure 13. Directed acyclic graph (DAG) is showing observed (solid lines) and unmeasured confounders (in boxes and dashed lines) in the relationship between maternal smoking status (X), low birthweight (LBW) (M), and NICU transfer/admission (Y). Unmeasured confounders were considered in the E-value calculation



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