Racial disparities in fetal growth restriction in the United States: the effect of adequacy of prenatal care

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ABSTRACT

Background: Race/ethnicity is associated with intrauterine growth restriction (IUGR) and small-for-gestational age (SGA). We evaluated the extent to which this association is mediated by adequacy of prenatal care (PNC).

Methods: A retrospective cohort study was conducted using the National Center for Health Statistics Natality Files for the years 2011-2017. A mediation analysis was conducted using log-binomial regression to decompose the total effect of race/ethnicity on IUGR and SGA into an effect of race/ethnicity mediated through PNC adequacy ("indirect effect") and not mediated through PNC adequacy ("direct effect"). The indirect effect of race/ethnicity mediated through PNC adequacy was expressed as a percentage.

Results: Among 23,118,656 singleton live births, 54.5% were White non-Hispanic, 14.0% were Black non-Hispanic, 24.3% were Hispanic, and 7.3% were Other. The excess risk of IUGR among Black, Hispanic and Other women compared with White women was partly mediated by PNC adequacy: 13% of the effect of Black race on IUGR was attributable to PNC inadequacy, 12% in Hispanic women, and 10% in Other women. The percentage of excess risk of SGA that was mediated was 7% in Black women, 6% in Hispanic women, and 5% in Other women.

Conclusions: Our findings suggest that PNC adequacy partly mediates the association between race/ethnicity and fetal growth restriction. Given the population effect of this association, public health initiatives targeting PNC access and usage among racialized pregnant mothers could have an important effect on reducing the risk of fetal growth restriction.

RÉSUMÉ

Contexte: La race est associée au retard de croissance intra-utérin (RCIU) et au petit poids pour l'âge gestationnel (SGA). Nous avons évalué dans quelle mesure cette association est influencée par la qualité des soins prénataux (SPN).

Méthodes: Une étude de cohorte rétrospective a été réalisée à l'aide des dossiers de naissance du National Center for Health Statistics des années 2011-2017. Une analyse de médiation a été effectuée avec une régression binomiale logarithmique pour décomposer l'effet total de la race sur le RCIU et le SGA en un effet de race médié par des SPN adéquats (« effet indirect ») et un effet non-médié par des SNP adéquats (« effet direct »). L'effet indirect de race médié par une qualité de SPN adéquats a été exprimé en pourcentage.

Résultats: Parmi les 23,118,656 naissances uniques vivantes, 54.5% étaient identifiées comme caucasiennes non-hispaniques, 14.0% étaient noires non-hispaniques, 24.3% étaient hispaniques and 7.3% étaient classées comme « autres ». L'excès de risque de RCIU parmi les femmes noires, hispaniques et « autres » lorsque comparé aux femmes caucasiennes était partiellement médié par des SPN adéquats: 13% de l'effet de la race noire sur le RCIU était attribuable aux SPN inadéquats, 12% chez les femmes hispaniques et 10% chez dans la catégorie « autre ». Le pourcent d'excès de risque du SGA médié était 7% chez les femmes noires, 6% chez les hispaniques et 5% chez les femmes « autres ».

Conclusion: Nos trouvailles suggèrent que les SPN adéquats médient partiellement l'association entre la race et le retard de croissance intra-utérin. Compte tenu des effets populationnels de cette association, des initiatives de santé publique visant l'accès aux SPN

pour les femmes racialisées enceintes pourrait avoir un effet important dans la réduction du RCIU.

PREFACE

This thesis contains six chapters. In Chapter 1, I give a rationale for my research and outline the main objectives of the thesis. Chapter 2 is a literature review that summarizes the epidemiology of fetal growth restriction and the role of race/ethnicity and prenatal care. Chapter 3 describes the study methodology. In Chapter 4, the results are presented in the form of a manuscript that has been submitted to the *American Journal of Epidemiology.* Finally, the results are discussed in Chapter 5, with concluding remarks in Chapter 6. References are provided in Chapter 7.

This thesis has been prepared according to the guidelines for a "Manuscript-Based Thesis". The results are given in the following manuscript:

Nasiri, K., Moodie, E.E.M., & Abenhaim, H.A. (2019). To what extent is the association between race and fetal growth restriction explained by adequacy of prenatal care? A causal mediation analysis of a retrospective cohort. *American Journal of Epidemiology.* Submitted May, 2019.

CONTRIBUTION OF AUTHORS

The original research ideas and study design were conceived by Dr. Haim A. Abenhaim and Khalidha Nasiri. The study analysis was conceived by Dr. Haim A. Abenhaim, Dr. Erica E.M. Moodie, and Khalidha Nasiri.

All non-manuscript chapters of this thesis were written by Khalidha Nasiri and critically reviewed and revised by Dr Haim A. Abenhaim and Dr. Erica E.M. Moodie.

The manuscript (Chapter 4) was written by Khalidha Nasiri and critically reviewed and revised by Dr. Haim A. Abenhaim and Dr. Erica E.M. Moodie.

Valerie Akim a contribué à la révision du résumé en français.

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A special thank you to the Student Affairs team at the Department of Epidemiology, Biostatistics, and Occupational Health (EBOH): Katherine Hayden, Deirdre Lavery, and André Yves-Gagnon – a great team that is always looking out for students and helping us submit things on time even when we're a bit late.

I am so grateful to be a part of an amazing cohort of EBOH MSc students who come from all walks of life and who I am confident will all go on to do great things.

Lastly, I would like to express a deep gratitude to my family, including my Mom and my three siblings, who have given me unconditional support on my educational journey.

DEDICATION

I dedicate my thesis to Ayesha Riaz, my friend who passed away in February 2018 at an Ontario hospital due to childbirth complications and who left behind a beautiful baby boy. Here is to a future where no child has to grow up without their mother, and where no mother has to risk her life to give life.

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LIST OF ABBREVIATIONS/ACRONYMS

ACOG: American College of Obstetrics and Gynecology

CI: Confidence Interval

FGR: Fetal Growth Restriction

IUGR: Intrauterine Growth Restriction

LBW: Low Birth Weight

NCHS: National Center for Health Statistics

NVSS: National Vital Statistics System

PNC: Prenatal Care

R-GINDEX: Revised-Graduated Prenatal Care Utilization Index

RR: Risk Ratio

SGA: Small for Gestational Age

US: United States

WHO: World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Rationale

In the United States (U.S.), racial disparities in birth outcomes are well established, with Black non-Hispanic women consistently experiencing the worst outcomes (1,2). Fetal growth restriction, which refers to a fetus that is not fulfilling its growth potential (3), is one of many outcomes for which racial disparities persist (4). Fetal growth restriction can be prevented or managed through access to routine prenatal care (PNC) (3). The World Health Organization (WHO)'s (5) *Every Woman, Every Child* vision calls for a "world where every pregnant woman and newborn receives quality care throughout the pregnancy … period". PNC is important because it provides a platform for health promotion, screening and diagnosis, and disease prevention (5). Racial disparities in PNC access and utilization exist (6), making PNC a natural subject of study with respect to the etiological mechanism of the association between race/ethnicity and fetal growth restriction.

1.2 Objectives

This thesis will investigate the role that PNC adequacy plays in the association between race/ethnicity and fetal growth restriction in the U.S. The first objective is to describe the association between race/ethnicity and PNC adequacy. The second objective is to investigate the extent to which the association between race/ethnicity and fetal growth restriction is explained by PNC adequacy using a novel statistical approach to mediation analysis.

CHAPTER 2: LITERATURE REVIEW

2.1 Fetal Growth Restriction

2.1.1 Definitions

Birth weight is an important indicator of infant and neonatal morbidity and mortality and is a function of gestational age and rate of fetal growth (7,8). Accordingly, birth weight should be considered with respect to gestational age. The terminology and definitions concerning the classification of fetuses and newborns who have not achieved normal weight per gestational age is inconsistent. According to the American College of Obstetrics and Gynecology (ACOG), fetal growth restriction describes fetuses with a fetal weight that is less than the 10th percentile for its gestational age and is synonymous with the term intrauterine growth restriction (IUGR) (3). The term small for gestational age (SGA) refers to newborns whose birth weight is less than the 10th percentile for gestational age (3). SGA is commonly used as a proxy measure of IUGR; however, there are differences (9). IUGR usually corresponds with SGA but with additional evidence indicating abnormal growth (3). Conversely, SGA does not always correspond with IUGR. In this thesis, fetal growth restriction is used as a general term that encompasses both IUGR and SGA.

The above definitions do not take into account the individualized growth potential of each fetus, which may result in misdiagnosis and misclassification (10,11). References constructed from various populations and stratified by race/ethnicity, sex, and parity have been developed (12-16).

2.1.2 Prevalence, Etiology, and Risk Factors

Estimates of the prevalence of IUGR and SGA vary depending on the definition used. In addition, the U.S. does not track trends in fetal growth restriction or birthweight per gestational age. In 2017, 6.56% of singleton births in the U.S. were low birth weight (LBW), the highest LBW rate since 2006 (17).

IUGR and SGA neonates are at a high risk of several adverse outcomes, including infant mortality, developmental delays, and other postnatal complications (18-20). In adulthood, they are also at greater risk of developing cardiovascular disease, hypertension, and diabetes (21,22). The etiology of fetal growth restriction has an endocrine basis. Fetal growth depends on several hormones which promote the growth and development of the fetus (23). Several animal studies have established that endocrine changes during fetal development can be induced through maternal undernutrition, placental insufficiency, and glucocorticoid exposure (e.g., maternal stress) (23).

Risk factors for fetal growth restriction can be categorized into three areas: maternal, fetal, and placental (3). Maternal risk factors include maternal age, interpregnancy interval, substance abuse (e.g., tobacco use, alcohol consumption, illicit drug use such as cocaine and narcotics), parity, multiple gestation, previous SGA or IUGR newborn, severe gestational malnutrition, weight, teratogen exposure, medical conditions (e.g., pre-gestational diabetes, autoimmune diseases, preeclampsia), infectious diseases, and poor medical care during pregnancy (24-30). Fetal risk factors include chromosomal abnormalities, genetic syndromes, structural malformations (e.g., congenital heart disease), and congenital infections (31-36). Placental risk factors include placental disorders (e.g., abruption) and

umbilical cord abnormalities (37-42). Placental insufficiency caused by abnormal placentation is the most common pathology associated with fetal growth restriction (2,43).

2.1.3 Identification and Prevention

Prenatal care (PNC) refers to care that women receive throughout their pregnancy. PNC is a form of preventive care which has the goal of early detection and management of potential pregnancy and childbirth complications (44). The ACOG recommends that from as early as 24 weeks of gestation, pregnant women be screened for risk factors for fetal growth restriction, such as a prior history of a SGA or IUGR newborn. PNC also enables health care providers to identify modifiable risk factors, such as nutrition and smoking behaviors (3). The WHO's guidelines (5) on antenatal care for a positive pregnancy experience recommend dietary interventions such as diet counseling, nutrition education on daily energy and protein intake, and balanced energy and protein supplementation to reduce the risk of SGA and low birth weight neonates. Once identified, PNC involves determining the cause and severity, monitoring the growth-restricted fetus using ultrasonography, counseling the parents, and ascertaining the optimal time and route for childbirth which may involve antenatal corticosteroid administration (3).

2.2 Race/ethnicity and Fetal Growth Restriction

Racial/ethnic disparities in birth outcomes in the U.S. are well documented (1,2) and maternal race/ethnicity has been identified as a risk factor for fetal growth restriction (44). Previous research has shown that Black non-Hispanic women are most likely to experience fetal growth restriction compared to women of other races/ethnicities (14, 45-49). Other studies in the U.S. have shown that Black non-Hispanic women have a higher risk of low

birth weight (LBW) relative to White non-Hispanic women, followed by Asians and Hispanics (50-53). The 2017 LBW rate was higher among Black non-Hispanic women (13.89%) compared to all Hispanics (7.43%), White non-Hispanics (7.00%), American Indians or Alaskan Natives (8.25%), Asians (8.52%), and Native Hawaiians or Other Pacific Islanders (7.74%) (17). In a study on New York City women, Black, Hispanic, and Asian women were 1.5 times, 1.1 times, and 1.6 times as likely to have SGA newborns compared to White women (51).

To understand the racial patterns observed in the U.S., it is useful to view race/ethnicity as a social exposure that reflects ongoing features of the social, physical, and economic environment in the U.S., as opposed to a biological characteristic (4). From this viewpoint, risk factors associated with fetal growth restriction may be differentially distributed among certain racial groups. Further to this point, since race/ethnicity itself is not modifiable, factors that are downstream from race/ethnicity are potential targets for addressing disparities in fetal growth restriction. Herein I refer to race/ethnicity as simply 'race', with an understanding that White and Black backgrounds are considered races while Hispanic and several other backgrounds are considered ethnic characteristics.

2.3 Race/ethnicity and Prenatal Care

Routine PNC is key to identifying and managing potential pregnancy complications. Differential access to PNC has been proposed as one downstream factor by which racial disparities in birth outcomes occur (4,54). For example, in the U.S., Black non-Hispanic and Hispanic women have been identified as less likely to receive early PNC compared to White non-Hispanic women (54). Partridge et al. (6) reported that from 1995 to 2002, the

prevalence of inadequate PNC was highest in Black non-Hispanic women (18.4%), followed by Hispanic women (17.4%), Other non-Hispanic women (12.6%) and White non-Hispanic women (7.3%).

An interesting observation is that racial disparities in fetal growth restriction and other perinatal health outcomes have been documented in countries with universal health access, such as Canada, which has a single payer healthcare system, suggesting that the role of PNC in racial disparities in perinatal outcomes may be limited. However, we posit that in accordance with viewing race as a social exposure, the experience of, say Black race, in the U.S. will likely be different than the experience of the same in Canada. In such a way, the downstream effect of race on PNC could differ between the two countries. Quantifying the mediating role of PNC could offer insight into the effect of the unique experiences of race in the U.S. on PNC utilization and perinatal health outcomes.

Previous studies investigating the association between race and PNC have mainly used stepwise adjustment methods. In one study, after adjusting for a set of maternal behavioral constructs including PNC timing (maternal education, maternal pre-pregnancy body mass index, previous live births, Medicaid coverage, Women, Infants and Children food program participation, tobacco and alcohol use, physical abuse during pregnancy, and medical problems during pregnancy), the association between Black non-Hispanic race and preterm birth risk was only slightly attenuated (odds ratio from 1.67 to 1.61, reference group White non-Hispanic) (55). A similar pattern was observed for American Indian/Alaskan Native, Asian-Pacific Islanders, and Hispanics. Conversely, a second study found that after adjusting for PNC adequacy, the association between Black non-Hispanic

race and preterm birth risk was significantly attenuated (odds ratio from 1.335 to 1.173, reference group White non-Hispanic) and the association between U.S. born Mexicans reversed direction (odds ratio from 1.108 to 0.958) (56). However, the association for other races (Native American, Asian, and Other Hispanic) did not significantly change (56). A third study found that the association between race and SGA differed depending on whether women received any PNC or no PNC, which points to the presence of an interaction between race and PNC (57). These studies provide information on whether PNC is associated with race and birth outcomes, however, they do not quantify the role that adequate PNC plays in the etiology of racial disparities in fetal growth restriction. Furthermore, studies that aim to examine the relationship between race, PNC, and birth outcomes should verify and, if confirmed, account for the presence of a race-PNC interaction.

CHAPTER 3: STUDY METHODOLOGY

3.1 Data Source

This retrospective cohort study was conducted using the publicly available U.S. National Center for Health Statistics' (NCHS) Natality Files for the years 2011 to 2017 (58). Specifically, the "Birth Cohort" Data file was used. The U.S. Natality Files are compiled annually by the National Vital Statistics System (NVSS) in the U.S. and serve as the basis of official birth and death statistics (59). The NVSS is a decentralized, cooperative system comprised of 57 registration areas (the 50 U.S. states, the District of Columbia, New York City, and five territories) (60). Briefly, standardization in data collection is achieved through U.S. Standard Certificates and Reports and via the Vital Statistics Cooperative Program (60,61). Data from birth and fetal death certificates are transmitted by states to the NCHS, who then compile, anonymize, and disseminate them for public use. The datasets contain information on 100% of all registered births each year (i.e., approximately 4 million per year), a major advantage (59). Information on maternal sociodemographic characteristics, clinical characteristics, and characteristics of labor and delivery are available in the dataset. Detailed information on the NVSS' structure, programs, and data collection procedures can be found elsewhere (60).

3.2 Inclusion and Exclusion Criteria

All live deliveries between 2011 to 2017 inclusive were identified (n=27,670,554). Births at less than 20 weeks of gestation were considered miscarriages (i.e., not live births) and thus excluded (n=8,319). Non-singleton births were also excluded because of differences in fetal growth and gestational age patterns (n=956,955). Births without data on race (n=703,964;

2.6%), IUGR or SGA (15,034; 0.06%), or PNC adequacy (n=3,110,258; 11.6%) were excluded. Thus, the final cohort consisted of 23,118,656 (83.5%) deliveries.

3.3 Exposure Variable

Maternal race was self-reported via the "Mother's Worksheet" (62). The first question about race asks the mother to identify as Hispanic (i.e., Spanish/Hispanic/Latina) or non-Hispanic origin. If they identify as Hispanic origin, they are asked to further classify themselves as Mexican/Mexican American/Chicana, Puerto Rican, Cuban, or other (e.g., Spaniard, Salvadoran, Dominican, Colombian). If they identify as non-Hispanic, they are asked to classify themselves as White, Black/African American, American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Native Hawaiian, Guamanian or Chamorro, Samoan, Other Pacific Islander, and Other. Although women are given the option to select multiple races, the system imputes multiple race data to a single race according to the combination of races, Hispanic origin, sex, and age of the mother or father (62). This imputation is done by the NCHS.

The "mracehisp" code was used to classify race into four categories in this thesis, based on Hispanic origin: White non-Hispanic only, Black non-Hispanic, Hispanic, and Other non-Hispanic (American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, and Native Hawaiian), herein referred to as White, Black, Hispanic, and Other non-Hispanic. This classification system was selected to facilitate comparability of our findings with the literature.

3.4 Mediator Variable

The mediator of interest was PNC adequacy. The vital statistics data do not provide a direct measure of PNC adequacy. They provide information on the total number of PNC visits and the trimester of the first PNC visit. This information is obtained using the "Facility Worksheet" (61). For the Facility Worksheet, data are obtained from the mother's and infant's medical records. If the information is not available in the medical records, the PNC provider is contacted to obtain a copy of the record (61).

The Revised-Graduated Prenatal Care Utilization Index (R-GINDEX) was used to assign a PNC adequacy level (63). The R-GINDEX is based on the ACOG's recommendations for the number of recommended visits and timing of the first visit (64). The R-GINDEX uses information on gestational age (in weeks), total number of PNC visits, and trimester of PNC initiation to classify each woman into one of six major categories of PNC: no care, missing data on PNC, inadequate PNC, intermediate PNC, adequate PNC, and intensive PNC. For the purposes of analysis, PNC adequacy was operationalized as a dichotomous variable: the categories of adequate and intensive care were considered "adequate PNC", and the categories of "intermediate", "inadequate", and "no care" were considered "inadequate PNC". The SAS algorithm for the R-GINDEX is publicly available (65).

3.5 Outcome Variables

The outcomes of interest were IUGR and SGA. The Kramer et al. (12) sex-specific formula is used in this thesis to ascertain IUGR and SGA. IUGR was defined as birth weight below the 3rd percentile of the gestational age- and sex- specific reference and SGA was defined as birth weight between the 3rd and 10th percentile of the gestational age- and sex- specific reference (12).

3.6 Demographic and Clinical Variables

Maternal race was considered to be defined at conception/birth and to represent the composite of factors that make up the experience of being a certain race in the U.S. (66). From this perspective, only maternal age and calendar year were considered potential confounding variables. The following baseline characteristics were calculated for each racial group:

Maternal age. Self-reported as a continuous variable.

Marital status. Self-reported as married or unmarried.

Maternal education. Self-reported as the highest level of schooling completed at the time of delivery: 8th grade or less, 9th to 10th grade (no diploma), high school graduate or GED completed, some college but no degree, associate degree, Bachelor's degree, Master's degree, and Doctorate or Professional degree.

Number of prior live births. Obtained from medical records.

Smoking during pregnancy. Self-reported as the number of cigarettes or packs of cigarettes smoked on an average day during each of the following time periods: three months before pregnancy, first three months of pregnancy, second three months of pregnancy, and third trimester of pregnancy. If the mother reports smoking in any of the three trimesters of pregnancy, the NCHS classifies her as a smoker.

Body mass index. Weight and height are self-reported by the mother and were used to calculate body mass index.

Pre-pregnancy and/or gestational hypertension. Obtained from medical records.

Pre-pregnancy and/or gestational diabetes. Obtained from medical records.

3.7 Statistical Analysis

All analyses were conducted using RStudio v1.1.463 (RStudio Inc., Boston, MA) and SAS Studio v9.4 (SAS Institute Inc., Cary, NC).

3.7.1 Analysis: Objective 1

For the first objective (association between race and PNC adequacy), log-binomial regression was performed to obtain risk ratios (RRs). The outcome variable was PNC adequacy, a binary variable (adequate versus inadequate), and the exposure/predictor variable was maternal race, a categorical variable (White, Black, Hispanic, and Other non-Hispanic). White race and adequate PNC were used as the reference groups. All analyses were adjusted for maternal age as a continuous variable and calendar year as a dummy variable. The results for the adjusted regression model are reported in the manuscript in Chapter 4. The results for the crude (unadjusted) regression model can be found in Appendix I, Supplementary Table S1.

3.7.2 Analysis: Objective 2 – Mediation Analysis

For objective 2 (investigate the extent to which the association between race and fetal growth restriction is explained by PNC adequacy), we used a novel approach to mediation analysis developed by Valeri and VanderWeele (67) and described in detail by VanderWeele (68). What is particularly useful about this method is that it allows for the researcher to take into account potential exposure-mediator, i.e., race-PNC adequacy, interaction.

Mediation analyses were performed separately for IUGR and SGA using the publicly available SAS macro by Valeri and VanderWeele (67). All models were adjusted for maternal age and calendar year. For each outcome, two log-binomial regression models were fit: an outcome model and a mediator model. The outcome model included IUGR or SGA as the outcome, and race, PNC adequacy, and interaction terms for race and PNC adequacy as the predictors. The presence of an exposure-mediator interaction was confirmed in both outcome models ($P < 0.001$), thus the interaction terms were retained in the models. The outcome model was specified as follows:

$$\log(P[Y=1|\, a,m,c]) = \theta_0 + \theta_1 a_B + \theta_2 a_H + \theta_3 a_O + \theta_4 m + \theta_5 a_B m + \theta_6 a_H m + \theta_7 a_O m + \theta_8 c$$

where Y is the binary indicator of the outcome (IUGR or SGA) and P[Y=1| *a,m,c*] is the probability of the presence of the outcome conditional on the variables *a, m,* and c. The variables included are *a*, denoting the exposure (race) and the subscripts B, H, and O referring to Black, Hispanic, and Other non-Hispanic, respectively; *m*, denoting the mediator (PNC adequacy); and *c*, denoting the set of confounding variables. The term θ_0 represents the intercept; θ_1, θ_2, and θ_3 represent the coefficients for race (Black, Hispanic, and Other non-Hispanic, respectively); θ_4 represents the coefficient for PNC adequacy; θ_5 to θ_7 represent the interaction terms; and θ_8 represents the vector of coefficients for the confounders.

The mediator model had PNC adequacy as the outcome, and race as the exposure. The mediator model is as follows:

$$\log(P[M=1|\, a,c]) = \beta_0 + \beta_1 a_B + \beta_2 a_H + \beta_3 a_O + \beta_4 c$$

where M refers to the outcome (PNC adequacy), and *a* and *c* as above. The term β_0 represents the intercept; β_1 to β_3 represent the coefficients for race (Black, Hispanic, and Other non-Hispanic, respectively); and β_4 represents the vector of coefficients for the confounders.

Based on the above two regression models, the SAS algorithm by Valeri and VanderWeele (67,68) calculated the total effect, natural direct effect, and natural indirect effect on the RR scale along with their corresponding standard errors and 95% confidence intervals (CIs). Standard errors were computed using the delta method (69). The total effect is the product of the direct and indirect effects and represents the overall effect of race on IUGR and SGA. The natural indirect effect represents the effect of race on IUGR and SGA that is mediated through PNC adequacy, while the natural direct effect represents the effect of race on IUGR and SGA that is *not* mediated through PNC adequacy. The proportion mediated is the fraction of the total effect that is mediated by PNC adequacy and was expressed as a percentage.

3.8 Sensitivity Analyses

A series of sensitivity analyses were performed. First, because we conducted a complete case analysis, there was a potential for selection bias by excluding women with missing data on the exposure, mediator, or outcome. Due to the low proportion of missing values, we elected to use deterministic imputation to test several possible combinations for the missing data. This was done to observe whether our mediation analysis results would change. Because the highest proportion of missing values was for PNC adequacy (11.6%), we also compared demographic and obstetric characteristics between women who were

missing data on PNC adequacy and women who were not (Supplementary Table S2). Overall, both groups of women had similar characteristics. Of note, women without missing data were more likely to have higher education, gestational diabetes, and gestational hypertension.

A second sensitivity analysis was conducted to ensure our findings were robust to the possible effects of potential repeated pregnancies to the same woman throughout our study period of interest. In the NCHS Birth Cohort dataset, it is not possible to link potential repeated pregnancies to the same woman. This is important because the outcome of a previous pregnancy can have an effect on the decision of whether or when to become pregnant again and can alter health behaviors as well as the outcomes of future pregnancies (70).

As discussed in the manuscript, gestational age was mainly ascertained from the date of the last menstrual period (LMP). In 2014, the NCHS began using the obstetric estimate of gestational age as the default method for calculating gestational age. A third sensitivity analysis restricting the data to the years 2014 to 2017 for which obstetric estimate-based gestational age data were available showed that LMP-based estimates during this time period tended to overestimate the number of women at 39 weeks' gestation and greater compared to obstetric estimates.

3.9 Ethics

The institutional review board at Jewish General Hospital considered this study exempt from ethical approval because it based on publicly available data.

CHAPTER 4: STUDY RESULTS

4.1 PREFACE

The results of this thesis are presented in one manuscript:

Nasiri, K., Moodie, E.E.M., & Abenhaim, H.A. (2019). To what extent is the association between race and fetal growth restriction explained by adequacy of prenatal care? A causal mediation analysis of a retrospective cohort. *American Journal of Epidemiology.* Submitted May, 2019.

This manuscript has been targeted at an epidemiology-focused journal, the *American Journal of Epidemiology*. It addresses both objectives of the thesis. The journal that it has been submitted to uses a blinded format for submission thus author names and identifiable information are not included in the manuscript that follows.

An additional figure that is not in the manuscript is included in Appendix II as Supplementary Figure S1. This figure shows trends in the annual prevalence of IUGR and SGA by racial group.

4.2 MANUSCRIPT

To what extent is the association between race and fetal growth restriction explained by adequacy of prenatal care? A causal mediation analysis of a retrospective cohort

Word count:

Abstract: 199

Manuscript: 2800 (excluding references and tables/figures)

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; NCHS, National Center for Health Statistics; PNC, prenatal care; RR, risk ratio; SGA, small-for-gestational age

Running head: Race, Prenatal Care, and Fetal Growth Restriction

ABSTRACT

Race is associated with intrauterine growth restriction (IUGR) and small-for-gestational age (SGA). We evaluated the extent to which this association is mediated by adequacy of prenatal care (PNC). A retrospective cohort study was conducted using the National Center for Health Statistics Natality Files for the years 2011-2017. We performed mediation analyses using a statistical approach that allows for exposure-mediator interaction, and estimated natural direct effects, natural indirect effects, and proportions mediated. All effects were estimated as risk ratios. Among 23,118,656 singleton live births, the excess risk of IUGR among Black, Hispanic and Other women compared with White women was partly mediated by PNC adequacy: 13% of the effect of Black race on IUGR was attributable to PNC inadequacy, 12% in Hispanic women, and 10% in Other women. The percentage of excess risk of SGA that was mediated was 7% in Black women, 6% in Hispanic women, and 5% in Other women. Our findings suggest that PNC adequacy partly mediates the association between race and fetal growth restriction. Given the population effect of this association, public health initiatives targeting PNC access and usage among racialized pregnant mothers could have an important effect on reducing the risk of fetal growth restriction.

Keywords: fetal growth restriction, intrauterine growth restriction, mediation analysis, prenatal care, small for gestational age, racial disparity, retrospective cohort study

Racial disparities in birth outcomes persist in the United States, particularly in the Black non-Hispanic population. The infant mortality rate for Black non-Hispanic mothers is almost double that of the overall population rate (1-2). The preterm birth rate and incidence of low birthweight is also significantly higher in Black non-Hispanic population compared to White non-Hispanic mothers (1-3). Morbidities related to low birth weight, namely intrauterine growth restriction (IUGR) and small-for-gestational age (SGA), present major public health challenges due to their robust association with infant mortality (1) and conditions such as developmental delays (4). Thus, addressing racial gaps in IUGR and SGA are pertinent public health goals. Researchers have called for the investigation of etiological pathways that can explain why these racial disparities exist so that appropriate interventions can be implemented (1).

While the exact mechanism through which racial disparities in IUGR and SGA occur is unclear, prenatal care (PNC) access and utilization has been proposed as an important mechanism by which racial disparities in neonatal birth outcomes occur (5). The premise for this is that proper prenatal care can address modifiable risk factors for IUGR or SGA, such as poor nutrition during pregnancy (4). Despite the existing literature on the importance of PNC in preventing adverse birth outcomes, to our knowledge, no studies have quantified the effect of prenatal care use in the association between race and fetal growth restriction. Additionally, mediation methods need to be able to accommodate for the likely presence of an interaction between race and PNC adequacy (6). In the present study, using statistical approaches developed by Valeri and Vanderweele (7) which allow for exposure-mediator interactions, we evaluate the degree to which the association between race and fetal growth restriction is mediated by PNC adequacy.

METHODS

Data source and study design

A retrospective population-based cohort study was performed using all registered births in the United States between 2011 and 2017. Data was obtained from the 2011 to 2017 U.S. Natality files (Birth Cohort dataset) compiled annually by the Center for Disease Control and Prevention's National Center for Health Statistics (NCHS). The NCHS provides information on 100% of all registered births each year in the United States including information on maternal obstetrical risk factors, morbidities, and characteristics and complications of labor and delivery (8).

Population

We defined an initial cohort of all live deliveries that took place between 2011 and 2017 in the United States, Hawaii, and Alaska (*n*=27,670,554). Deliveries prior to 20 weeks' gestation were considered miscarriages and excluded from our cohort (*n*=8,319). Following common practice, we also excluded non-singleton deliveries due to differences in fetal growth and gestational age patterns (*n*=956,955). Deliveries which had incomplete data on the exposure (*n*=703,964), outcome (*n*=15,034), or mediator (*n*=3,110,258) were not included in the analysis, resulting in a final cohort of 23,118,656 deliveries which were analyzed. See flow chart in Figure 1.

Definitions of exposure, mediator, and outcome variables

There have been numerous discussions in the causal inference literature on the use of race as an exposure and the importance of having conceptual clarity on how race is defined. Vanderweele and Robinson 2015 (9) posit that due to the non-manipulable nature of race, it is impossible to define a counterfactual framework in which a

hypothetical intervention could be applied on race. To address this challenge, one of their propositions is to interpret the "effect of race" as the extent to which a racial inequality could be eliminated by intervening on a downstream risk factor that is manipulable. Thus, in our study, we considered maternal race to be defined at conception/birth and to represent the composite of factors that make up the experience of being a certain race in the U.S. Furthermore, we used causal mediation analysis to assess the magnitude of the disparity that would remain under an intervention on a modifiable mediator, PNC utilization (10). In accordance with such a framework that is premised upon counterfactual manipulability of the mediator, we move away from questions such as "what would a Black woman's birth outcome have been had they been White?" (9) to "what would a Black woman's birth outcome have been had they received the same level of prenatal care as a White woman?"

Race was self-reported by the mother and categorized as White non-Hispanic, Black non-Hispanic, Hispanic, and Other non-Hispanic (herein referred to as White, Black, Hispanic, and Other) based on the "mracehisp" code in the NCHS Birth Cohort files. Hispanic race includes Mexican, Puerto Rican, Cuban, Central and South American, and other Hispanic. Other non-Hispanic race includes American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, and Native Hawaiian.

The mediator of interest was adequacy of PNC utilization. It was defined by the Revised-Graduated Prenatal Care Utilization Index (R-GINDEX) (11) which has been shown to be robust to potential effect modification by gestational age on SGA when compared to other commonly used indices (12) and has comparable results for SGA compared to the other indices (13). The R-GINDEX makes use of three variables:

gestational age of the newborn (in weeks), trimester during which prenatal care began (calculated from the gestational age of the newborn, date of birth, and date of the first PNC visit), and the total number of PNC visits during pregnancy. It has five categories of PNC: "no care", "inadequate", "intermediate", "adequate", and "intensive". The "adequate care" category of the R-GINDEX reflects the American Congress of Gynecologists and Obstetricians' guidelines for the number of recommended visits and timing of first visit. For the purposes of our analysis, PNC adequacy was defined as a dichotomous variable: PNC classified as "adequate" and "intensive" was considered "adequate prenatal care", and PNC classified as "intermediate", "inadequate" or "none" was considered "inadequate prenatal care".

The neonatal birth outcomes of interest were IUGR and SGA. IUGR was defined as birth weight below the 3rd percentile, and SGA was defined as birth weight between the 3rd and 10th percentile. Sex-specific population-based references for birth weight for gestational age were based on Kramer et al. (14). Gestational age was derived from date of the last menstrual period (LMP), with or without ultrasound dating. Where the LMP-based estimate was inconsistent with the expected birthweight, the NCHS replaced it with either a clinical estimate of gestation or imputation (15-16).

Mediation analysis

Figure 2 shows the hypothesized mediation path model. We performed our analysis according to methods developed by Valeri and VanderWeele (7) and elaborated in VanderWeele 2015 (17) to decompose the total effect of race on IUGR and SGA into the effect of race mediated through PNC adequacy (natural indirect effect) and the effect of race not mediated through PNC adequacy (natural direct effect). The fraction of the total effect mediated by adequacy of prenatal care was expressed as a percentage. Log-

binomial regression was used to express effect measures as risk ratios (RRs). Standard errors for the indirect effect were computed using the delta method (17-18). We confirmed the presence of an interaction between race and PNC adequacy on the multiplicative scale ($P < 0.001$), therefore the mediation analysis incorporated an exposure-mediator interaction term.

All outcomes were binary and were modeled separately with "adequate prenatal care" and "White" used as the reference groups in all cases. Regression models controlled for the potential confounding effects of maternal age (as a continuous variable) and calendar year (coded as a dummy variable). All analyses were conducted using RStudio v1.1.463 (RStudio Inc., Boston, MA) and SAS Studio v9.4 (SAS Institute Inc., Cary, NC). The institutional review board at the authors' institution considered this study exempt from ethical approval because it is based on publicly available data.

Our analysis was conducted in three steps. First, we performed demographic and clinical descriptive statistics for the four racial groups. Second, adjusted risk ratios (aRRs) and corresponding 95% confidence intervals (CI) for associations between race and PNC adequacy were calculated using log-binomial regression. Third, mediation analyses were conducted.

Sensitivity analysis

We explored the robustness of our results to the potential selection bias introduced by excluding observations with missing data on the exposure, mediator, or outcome. We used deterministic imputation to test several possible combination of values for the missing data (see Web Appendix 1). As we were not able to link repeated births to the same woman during our study period, we conducted a sensitivity analysis

restricted to nulliparous women with singleton gestations from 2011 to 2017 to test the robustness of our findings to clustering effects (Web Appendix 2).

RESULTS

Of the 27,670,554 live births recorded in the United States during our 7-year study period, 23,118,656 (83.5%) met the study inclusion criteria. There were 909,635 cases of IUGR and 1,856,893 cases of SGA identified within our cohort, which constituted 3.9% and 8.0% of all pregnancies, respectively.

Demographic and clinical characteristics stratified by race are presented in Table 1. Within our cohort, 54.5% of mothers were White, 14.0% were Black, 24.3% were Hispanic, and 7.3% were Other. Black and Hispanic women were more likely to be under 25 years old and unmarried. Hispanic women were more likely to have less than a high school education, while White women were more likely to have completed higher education and smoke during pregnancy. Black women were most likely to have a BMI of 30 or above, have pre-pregnancy, and gestational hypertension. Other women were most likely to have gestational diabetes.

Table 2 shows the association between race and inadequate PNC. Relative to White mothers, Black mothers had an approximately 16% higher risk of inadequate prenatal care while Hispanic and Other mothers both had an approximately 14% higher risk.

Mediation analyses were conducted for IUGR and SGA separately. Results are shown in Table 3. Black, Hispanic, and Other maternal race was significantly associated with a higher risk of IUGR and SGA compared to White mothers, as indicated by the direct and total effects. PNC adequacy was a significant mediator of the race-IUGR and

race-SGA association, mediating between 5% to 13% of the increased risk of the outcome depending on the racial group (Table 3).

Our first sensitivity analysis showed that excluding observations with missing information on the exposure, mediator, or outcome had a minimal impact on our results and thus confirmed the robustness of our findings. Our second sensitivity analysis showed that the indirect effects and percent mediated are slightly attenuated among nulliparous women with singleton gestations, but overall confirmed the robustness of our findings.

DISCUSSION

In our retrospective population-based cohort study, we found that PNC adequacy partly mediates the association between race and IUGR and SGA. For Black and Hispanic mothers, adequacy of prenatal care mediated almost 15% of the association for IUGR. There are several mechanisms by which adequacy of prenatal care can act as a mediator between race and our birth outcomes of interest. Mediation models hypothesize that an exposure causes the mediator, which in turns causes the outcome variable (see Figure 2) (7). As shown by our results in Table 2, race and adequacy of prenatal care are directly associated. This is corroborated by several studies that show that non-White women are less likely to initiate prenatal care (19) and face several barriers to accessing prenatal care, such as wait time and appointment availability (20). Furthermore, perceived racism and discrimination can delay or inhibit women's decision to seek prenatal care (21).

With regards to the association between adequacy of prenatal care and IUGR or SGA, more frequent access and usage of prenatal care means timely intervention for at-risk women can occur. For example, women at risk of IUGR or SGA newborns can

receive dietary counselling (22), be recommended for restricted activity and work modification for mothers who work longer hours or night shifts (23), and receive diagnosis and management of hypertensive diseases of pregnancy (22). In their review of the best targets for prenatal care intervention to prevent low birth weight conditions including IUGR and SGA, Alexander and Korenbrot (22) found that psychosocial (e.g., interventions targeting behaviours such as smoking), medical (e.g., aimed at general medical conditions), and nutritional (e.g., targeting pre-pregnancy or gestational weight) approaches were most effective. However, whether these prenatal care interventions would be equally effective across racial groups is not known.

It remains that a majority of the observed racial differences in IUGR and SGA risk operate through pathways other than PNC utilization, as reflected by the small indirect effects in all of our analyses. Our study did not analyze other potential mediators, such as income, psychological factors such as stress and depression, attitudes towards healthcare providers, and work status during pregnancy, as these data are not available in the NCHS Birth Cohort files. It is plausible that adequacy of PNC utilization reflects factors such as income or insurance status. Importantly, then, one challenge for future studies is to disentangle other potential mediators from adequate PNC utilization. Unlike race, PNC utilization is a modifiable target for public health interventions that can potentially enable women at risk of delivering IUGR or SGA newborns to be identified and receive timely interventions.

Our study has a number of limitations. Misclassification of our exposure variable, self-reported maternal race, is a possibility due to the inherent complexities involved in classifying race, particularly in the case of mixed races. Furthermore, on U.S. birth certificates, when the race of the mother is not reported, the race of the father is

assigned to the mother. If the race of the father is not known either, maternal race is imputed. Imputation of maternal race in the NCHS Birth Cohort data occurs in approximately 6% of births annually. Any exposure misclassification is likely to be nondifferential with respect to our outcomes of interest, since it is highly probable that a diagnosis of IUGR or SGA would not affect how one classifies their race.

We ascertained IUGR and SGA using information on newborn birthweight, sex, and gestational age (14). In 2014, the NCHS changed the default method for calculating gestational age from the LMP-based method to the obstetric estimate (24), but LMP-based data continue to be available to enable trend analysis. In the present study, we used the pre-2014 default method in order to ensure a consistent measure of gestational age throughout our study period of interest, 2011 to 2017, although Callaghan and Dietz (16) note that the obstetric estimate may be superior for investigating fetal growth conditions.

Large administrative datasets have a natural potential for misclassification of data elements due to data entry errors, recall bias, and inconsistent reporting (25). The NCHS attempts to minimize this by using standardized coding specifications and implementing statistical quality checks on the data (26). Moreover, an additional limitation of using administrative dataset is that measures of variables that could influence PNC utilization, such as quality and content of PNC, were not available (22).

Strengths of our study include a cohort size of over 23 million live births, resulting in confidence interval estimates with high precision. Because the NCHS is a nationwide population database which forms the basis for official U.S. statistics, the data is generalizable. Additionally, our sensitivity analysis confirmed that even under a worst case scenario where data were more likely to be missing from individuals who were

Black, received inadequate care, and had an IUGR or SGA newborn, the proportion mediated would hardly change. Under a best case scenario where data were more likely to be missing from White mothers who received adequate care and did not have an IUGR or SGA newborn, the proportions mediated would decrease slightly but our qualitative conclusions would remain unchanged (Web Appendix 1). Although we were not able to adjust for the effects associated with repeated pregnancies to the same woman during the study period, our findings were replicated in a subpopulation of nulliparous women with singleton gestations from 2011 to 2017 (Web Appendix 2).

The importance of this study is predicated upon the use of mediation analysis. Mediation is defined as the "totality of processes that explain an observed relationship between exposure and disease" (27). Mediation analysis moves from simply identifying risk factors for adverse outcomes to investigating the specific mechanisms by which an exposure/risk factor is associated with an outcome. From a public health perspective, mediation analysis is extremely useful in evaluating the feasibility of implementing population-level interventions. In our study, we have observed that targeting inadequate PNC utilization among racialized mothers can potentially partly decrease the racial gap in fetal growth restriction.

Our findings reveal that adequacy of PNC utilization is a significant mediator in the causal pathway between race and IUGR and SGA. Adequate PNC utilization allows women at risk of delivering IUGR or SGA newborns to be identified and receive timely interventions such as nutrition counselling. Given that a majority of the association was not explained by our mediator of interest, we hope that this study serves as the basis for future research to further evaluate other mediators of the race-fetal growth restriction relationship.

Table 1. Demographic and Clinical Characteristics of 23,118,656 Singleton Deliveries by Race in the United States, 2011-2017

	White non-Hispanic (*n*=12,581,133) (%)	**Black non-Hispanic** (*n*=3,240,087) (%)	**Hispanic** (*n*=5,608,708) (%)	**Other** (*n*=1,688,728) (%)
Maternal Age				
<25	24.2	39.8	35.4	13.3
25-34	60.0	47.6	49.9	62.7
≥35	15.8	12.6	14.8	24.0
Married	70.4	29.3	45.9	76.8
Maternal Education				
0-8 years	1.3	1.6	10.8	2.6
9-12 years, no GED	6.6	14.5	21.1	6.8
9-12 years, yes GED	21.3	33.0	30.6	15.8
13-15 years	56.1	44.7	33.0	50.0
>16	14.3	5.4	3.3	23.5
Prior Live Births				
0	41.4	37.8	34.5	44.6
1	33.1	28.8	30.0	35.7
2 or more	25.3	32.9	35.3	19.5
Smoking During Pregnancy	11.2	6.2	1.8	2.7
BMI 30+	22.6	33.6	26.7	11.2
Pre-Pregnancy Hypertension	1.5	3.3	1.0	1.0
Gestational Hypertension	5.5	6.5	4.2	3.3
Pre-Pregnancy Diabetes	0.7	1.1	0.9	0.9
Gestational Diabetes	5.0	4.7	6.1	9.9

Table values are percentages rounded to one decimal, thus not all rows sum to 100%.

Table 2. Log-Binomial Regression Analysis Showing Risk of Inadequate Prenatal Care by Race in the United States, among the 2011-2017 Singleton Birth Cohort

	Inadequate Prenatal Care	
	N (%)	aRR (95% CI)[a,b]
White non-Hispanic	6,211,036 (49.4)	Reference
Black non-Hispanic	1,909,634 (58.9)	1.161 (1.159, 1.162)
Hispanic	3,226,232 (57.5)	1.142 (1.141, 1.143)
Other	918,908 (54.4)	1.138 (1.136, 1.140)

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval

[a]All aRRs were $P < 0.001$ and adjusted for maternal age and calendar year.

[b]Reference group for outcome is adequate prenatal care

Table 3. Analysis of the Mediating Effect of Adequacy of Prenatal Care in Racial Disparities in Fetal Growth Restriction among United States Singleton Deliveries, 2011-2017

	Black non-Hispanic aRR (95% CI)[b]	**Hispanic** aRR (95% CI)	**Other** aRR (95% CI)
IUGR			
N (%)[a]	211,822 (6.54)	206,635 (3.68)	82,006 (4.86)
Direct Effect	1.0941 (1.0920, 1.0962)	1.1983 (1.1937, 1.2029)	1.3137 (1.3061, 1.3214)
Indirect Effect	1.0129 (1.0127, 1.0130)	1.0219 (1.0215, 1.0222)	1.0268 (1.0260, 1.0277)
Total Effect	1.1082 (1.1051, 1.1104)	1.2245 (1.2198, 1.2292)	1.3490 (1.3412, 1.3567)
% Mediated	13.0	11.7	10.1
SGA			
N (%)	374,681 (11.56)	446,151 (7.95)	177,789 (10.53)
Direct Effect	1.1117 (1.1103, 1.1132)	1.2366 (1.2333, 1.2398)	1.3762 (1.3707, 1.3816)
Indirect Effect	1.0076 (1.0075, 1.0077)	1.0123 (1.0121, 1.0126)	1.0141 (1.0136, 1.0147)
Total Effect	1.1202 (1.1187, 1.1216)	1.2518 (1.2485, 1.2551)	1.3956 (1.3901, 1.4011)
% Mediated	7.0	6.0	4.9

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; IUGR, intrauterine growth restriction; SGA, small for gestational age

[a]N (%) for IUGR and SGA among White women (reference group) is 409,172 (3.25) and 858,272 (6.82), respectively

[b]All aRRs were $P < 0.001$ and adjusted for maternal age and calendar year.

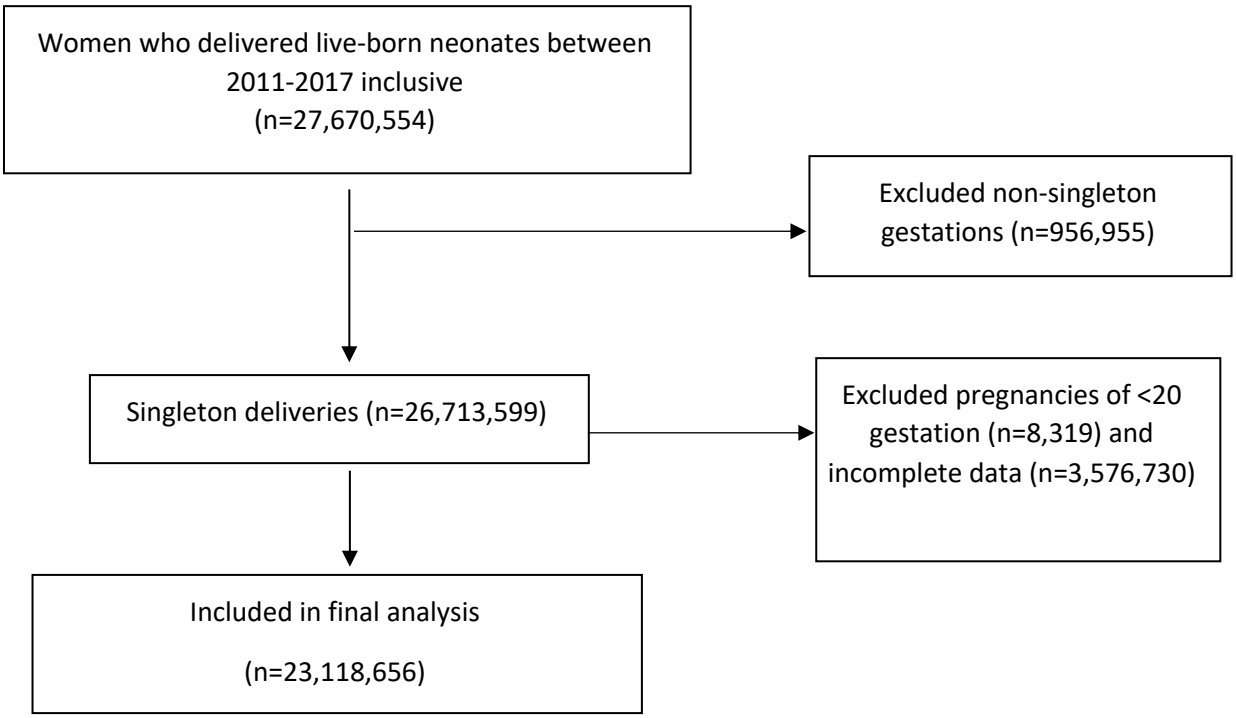

Figure 1. Study population flowchart

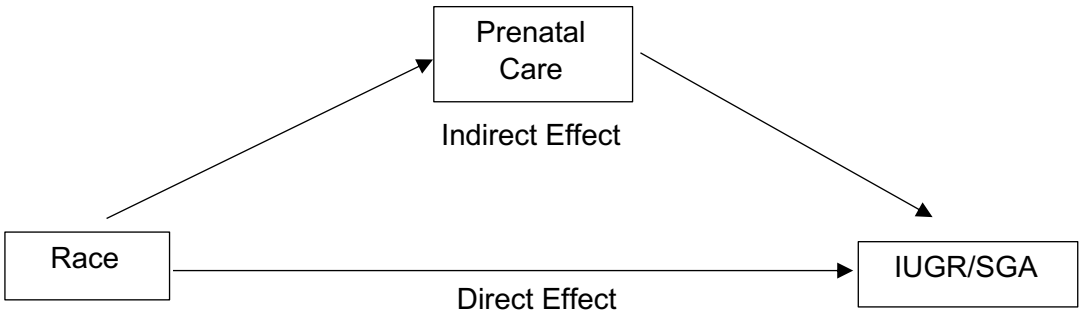

Figure 2. Model of the potential mediating effect of adequacy of prenatal care on the relationship between race and IUGR or SGA. The total effect of race includes the product of the direct and indirect effects.

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Web Appendix 1 - Sensitivity analysis: Impact of potential selection bias from excluding missing data

In our analysis, observations with missing data on the exposure (race), outcome (IUGR and SGA), or mediator (adequacy of prenatal care utilization) were excluded: 2.6% of deliveries had missing data on race, 0.06% had missing data on IUGR and SGA, and 11.6% had missing data on adequacy of prenatal care utilization. As a result, a total of 3,576,730 deliveries were excluded.

Deterministic imputation was used to assign values for the missing data based on three potential scenarios. For each scenario, we re-ran the mediation analysis to assess the impact of each scenario on our findings:

1) The first scenario assumed a "worst" case scenario where all observations missing data on the exposure (race) were Black non-Hispanic, missing data on the mediator (timing of prenatal care entry) were those with inadequate care, and missing data on the outcome were those who experienced the outcome,

2) The second scenario assumed an “intermediate” case scenario where all observations missing data on exposure (race) were Hispanic, and missing data on the mediator and outcome were treated in the same way as in scenario 1, and

3) The third scenario assumed a "best" case scenario where all observations missing data on the exposure (race) were White non-Hispanic, missing data on the mediator (adequacy of prenatal care) were those with adequate care, and missing data on the outcome were those who did not experience the outcome.

Supplementary tables 1, 2, and 3 below shows the results of each of the scenarios. The sensitivity analysis shows that the various scenarios slightly exaggerated or attenuated the % mediated, but overall, excluding the missing data did not introduce significant bias to our results.

Supplementary table 1. "Worst" Case Scenario

	Black non-Hispanic	**Hispanic**	**Other**
	RR (95% CI)	RR (95% CI)	RR (95% CI)
IUGR			
Direct Effect	1.0941 (1.0921, 1.0961)	1.1983 (1.1939, 1.2028)	1.3139 (1.3066, 1.3213)
Indirect Effect	1.0129 (1.0128, 1.0131)	1.0218 (1.0215, 1.0222)	1.0267 (1.0259, 1.0275)
Total Effect	1.1083 (1.1062, 1.1103)	1.2245 (1.2200, 1.2291)	1.3490 (1.3415, 1.3565)
% Mediated	13.1	11.7	10.0
SGA			
Direct Effect	1.1198 (1.1182, 1.1213)	1.2546 (1.2512, 1.2579)	1.4064 (1.4007, 1.4121)
Indirect Effect	1.0077 (1.0076, 1.0078)	1.0125 (1.0122, 1.0127)	1.0143 (1.0137, 1.0148)
Total Effect	1.1284 (1.1269, 1.1299)	1.2702 (1.2668, 1.2736)	1.4264 (1.4207, 1.4322)
% Mediated	6.7	5.8	4.7

Supplementary table 2. “Intermediate” Case Scenario

	Black non-Hispanic	**Hispanic**	**Other**
	RR (95% CI)	RR (95% CI)	RR (95% CI)
IUGR			
Direct Effect	1.0920 (1.0900, 1.0940)	1.1938 (1.1895, 1.1982)	1.3066 (1.2994, 1.3138)
Indirect Effect	1.0141 (1.0139, 1.0142)	1.0236 (1.0233, 1.0240)	1.0287 (1.0278, 1.0300)
Total Effect	1.1074 (1.0139, 1.0142)	1.2220 (1.2176, 1.2265)	1.3441 (1.3367, 1.3515)
% Mediated	14.3	12.7	10.9
SGA			
Direct Effect	1.1173 (1.1158, 1.1188)	1.2490 (1.2457, 1.2524)	1.3972 (1.3917, 1.4028)
Indirect Effect	1.0084 (1.0083, 1.0085)	1.0134 (1.0132, 1.0137)	1.0152 (1.0146, 1.0158)
Total Effect	1.1266 (1.1251, 1.1281)	1.2658 (1.2625, 1.2692)	1.4184 (1.4128, 1.4241)
% Mediated	7.4	6.3	5.1

Supplementary table 3. “Best” Case Scenario

	Black non-Hispanic	**Hispanic**	**Other**
	RR (95% CI)	RR (95% CI)	RR (95% CI)
IUGR			
Direct Effect	1.0949 (1.0929, 1.0970)	1.1996 (1.1952, 1.2040)	1.3150 (1.3078, 1.3224)
Indirect Effect	1.0080 (1.0078, 1.0081)	1.0133 (1.0129, 1.0136)	1.0159 (1.0151, 1.0166)
Total Effect	1.1037 (1.1016, 1.1057)	1.2155 (1.2110, 1.2200)	1.3359 (1.3285, 1.3433)
% Mediated	8.4	7.4	6.2
SGA			
Direct Effect	1.1176 (1.1161, 1.1191)	1.2495 (1.2461, 1.2528)	1.3973 (1.3917, 1.4029)
Indirect Effect	1.0056 (1.0055, 1.0057)	1.0092 (1.0090, 1.0095)	1.0110 (1.0104, 1.0115)
Total Effect	1.1239 (1.1224, 1.1254)	1.2610 (1.2576, 1.2644)	1.4126 (1.4069, 1.4182)
% Mediated	5.0	4.4	3.7

Web Appendix 2 - Sensitivity analysis: Restriction to 9,117,029 nulliparous women with singleton gestations, 2011-2017

An important consideration is that the outcome of a previous pregnancy can have an effect on the decision of whether or when to become pregnant again [1]. It can also change health behaviors, and impact the outcome of a future pregnancy [1]. In our analysis, we were not able to link successive pregnancies to the same woman during the study period. To ensure that findings are robust to the possible effects of repeated pregnancies, we conducted a sensitivity analysis restricted to nulliparous women with singleton gestations during our study period of interest, 2011 to 2017.

Results are shown in supplementary table 4 below. The sensitivity analysis shows that the various scenarios slightly exaggerated the direct effect and attenuated the indirect effects, thereby attenuating the % mediated. Overall, however, the effects and direction are consistent.

Supplementary table 4. Analysis of the Mediating Effect of Adequacy of Prenatal Care in Racial Disparities in Fetal Growth Restriction among Nulliparous Singleton Deliveries, 2011-2017

	Black non-Hispanic	**Hispanic**	**Other**
	RR (95% CI)	RR (95% CI)	RR (95% CI)
IUGR			
Direct Effect	1.1193 (1.1164, 1.1222)	1.2538 (1.2472, 1.2603)	1.4054 (1.3944, 1.4165)
Indirect Effect	1.0119 (1.0116, 1.0121)	1.0203 (1.0197, 1.0208)	1.0251 (1.0239, 1.0263)
Total Effect	1.1326 (1.1296, 1.1355)	1.2791 (1.2725, 1.2858)	1.4407 (1.4294, 1.4520)
% Mediated	10.0	9.1	8.0
SGA			
Direct Effect	1.1243 (1.1223, 1.1263)	1.2646 (1.2600, 1.2692)	1.4229 (1.4152, 1.4306)
Indirect Effect	1.0068 (1.0067, 1.0069)	1.0111 (1.0107, 1.0114)	1.0128 (1.0120, 1.0136)
Total Effect	1.1320 (1.1299, 1.1340)	1.2786 (1.2740, 1.2832)	1.4411 (1.4333, 1.4489)
% Mediated	5.8	5.0	4.1

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CHAPTER 5: DISCUSSION

5.1 Summary and Interpretation of Results

The manuscript comprising this thesis examined the question of the extent to which PNC adequacy explains the association between race and fetal growth restriction. The aims of this study were to 1) assess the association between race and PNC adequacy and 2) investigate the extent to which PNC adequacy mediates the relationship between race and fetal growth restriction (IUGR and SGA). To test these hypotheses, a retrospective cohort study was conducted from 2011 to 2017 using a dataset that is representative of the U.S. population of pregnant women.

The primary result of the first analysis was that race is associated with PNC adequacy, with the risk of inadequate PNC being highest for Black women relative to White women (aRR = 1.161, 95% CI 1.159, 1.162). The association was similar for Hispanics (aRR = 1.142, 95% CI 1.141, 1.143) and Other non-Hispanics (aRR = 1.138, 95% CI 1.136, 1.140). This is line with previous literature showing that non-White women are more likely to receive inadequate PNC relative to White women (6). Compared to the crude estimates (Supplementary Table S1), the adjusted estimates were slightly attenuated for Blacks and Hispanics and slightly exaggerated for Other non-Hispanics, however the conclusions remain the same. This confirms that there are differences in PNC utilization among racial groups in the U.S. The next question was whether these differences were significant enough to explain part of the association between race and fetal growth restriction.

The second analysis sought to quantify the extent to which PNC adequacy mediates the association between race and fetal growth restriction using mediation analysis. Results

showed that race was associated with both IUGR and SGA, as indicated by the total effect. The risk of IUGR and SGA was highest in Other non-Hispanic women relative to White women (IUGR: aRR = 1.3490, 95% CI 1.3412, 1.3567; SGA: aRR = 1.3956, 95% CI 1.3901, 1.4011), followed by Hispanics (IUGR: aRR = 1.2245, 95% CI 1.2198, 1.2292; SGA: aRR = 1.2518, 1.2485, 1.2551) and Blacks (IUGR: aRR = 1.1082, 95% CI 1.1051, 1.1104; SGA: aRR = 1.1202, 95% CI 1.1187, 1.1216). This was unexpected as most studies on race and fetal growth restriction suggest that White-Black differences are most significant (47,48). Frisbie et al. (49) reported that the odds ratio for IUGR risk in Blacks versus Whites was 1.4 (95% CI 1.2, 1.6) and for Mexican Americans was 0.9 (95% CI 0.7, 1.2). Our findings should encourage further research on other racial groups that could have higher risks of certain birth outcomes.

Our mediation analysis results showed that PNC adequacy mediates the association between race and fetal growth restriction. PNC adequacy was more important for IUGR, explaining 13.0%, 11.7%, and 10.1% of the White-Black, White-Hispanic, and White-Other disparity in IUGR, respectively. For SGA, PNC adequacy explained 7.0%, 6.0%, and 4.9% of the White-Black, White-Hispanic, and White-Other disparity, respectively. On a population level, these results highlight the important role that routine PNC plays in preventing and managing fetal growth restriction. Adequate PNC involves initiating PNC in a timely manner and achieving the recommended number of visits throughout pregnancy as per clinical guidelines (3). Through adequate PNC, women at risk of having growth-restricted fetuses can be identified, counseled, and their pregnancies managed to reduce the risk of adverse birth outcomes (3). However, it should be noted that evidence from randomized controlled trials have shown that pregnancy outcomes including LBW were not clinically

different between women who had a lower number of antenatal care visits compared to women receiving care according standard antenatal care models (82). Measures of PNC, such as the one used in this study, which incorporate the timing and number of visits but not necessarily quality and content of care, may be flawed since they do not capture important indicators of quality of care that impact the continuity and outcomes of care, such as respectful maternity care, social and emotional support, and effective communication (83).

Despite these caveats, for public health practice, this study identified a plausible mediator for intervening on racial gaps in fetal growth restriction. Differences in the risk of LBW have been identified between foreign-born and U.S.-born women of the same race (50,71), and the risk may differ between states as well. Thus, these findings should be confirmed in subpopulations within the U.S.

With regards to clinical practice, clinicians should be aware of the role of routine PNC and the implications on birth outcomes. For examples, clinicians could strive to encourage high-risk patients to return to follow up appointments and should foster a welcoming environment that facilitates open communication and non-judgement so that continuity of care can be achieved (72).

As noted in the manuscript, a majority of the race-fetal growth restriction disparity was not explained by our mediator of interest, PNC adequacy. This is unsurprising considering that there are several additional plausible mediators. One such mediator could be perceived racism and racial discrimination. Collins and colleagues (73) conducted a case-control study and found that Black women who scored high on lifetime exposure to interpersonal

racism were more likely to have delivered LBW infants compared to those who were not exposed. A literature review by Giurgescu et al. (74) reported a consistent association between perceived racial discrimination and LBW. Information on perceived racism or stressors related to racial discrimination were not available in the NCHS dataset. This is an avenue for future research to explore.

5.2 Strengths and Limitations

The main advantage of this project was the use of mediation analysis, a statistical method which enabled us to move from investigating the association of interest towards investigating the mechanism by which the association of interest could occur. One important motivation for mediation is when intervention on the primary exposure, in our case race, is not possible (68). By examining the portion of the association that operates through a mechanism of interest, we can obtain an idea of how effective it would be to intervene on the mediator. A second strength of our study is the large sample size (n=23,118,656) and representativeness of the dataset.

Aside from the limitations discussed in the manuscript, there are other limitations of our study that should be noted. One of the assumptions of causal mediation analysis is that all potential exposure-outcome and mediator-outcome confounders have been adjusted for (81). In the path diagram shown in Figure 2 of the manuscript, it is possible that there are common causes of PNC adequacy and IUGR/SGA, such as pre-pregnancy hypertension, that we have not accounted for in our analysis. These confounders, however, could be affected by race, therefore adjusting for them would result in collider bias (81). Were comprehensive data on potential mediator-outcome variables available, more complex

methodology such as inverse probability weighting mediation or g-computation could have been implemented (84,85); however, these approaches carry different modelling assumptions than those made here.

Schoendorf and Branum (75) emphasize the importance of using vital statistics data in informing clinical research, but highlight problems related to random underreporting of some clinical and obstetric variables. Furthermore, as noted previously, epidemiological estimates of IUGR and SGA vary based on the population reference used (76). There are many issues related to the choice of which reference population to use (9,11). While these were not reviewed in detail here and were not the subject of this thesis, it is important to acknowledge that the cutoffs for fetal growth restriction can vary depending on the standard used, making outcome misclassification a possibility in this study (77).

The R-GINDEX was used to ascertain PNC adequacy level. There are other indices available, such as the Adequacy of Prenatal Care Utilization Index (APNCU) index (78). Alexander and Kotelchuck (63) compared five PNC utilization indices and found that there were differences in the proportion of cases classified as adequate and inadequate care. It is possible that in the current study we have underestimated the number of inadequate care cases, since studies have reported that the R-GINDEX assigns a significantly lower proportion of cases to the "intensive" PNC utilization category compared to the APNCU (63, 79). Although the possibility of mediator misclassification cannot be ruled out, when used for SGA outcome models, the R-GINDEX has been shown to have similar results to other indices (80).

CHAPTER 6: CONCLUSION

From 2011 to 2017, the IUGR and SGA rate was highest in Black non-Hispanic women, followed by Other non-Hispanic, Hispanic, and White non-Hispanic women. Black non-Hispanic women were most likely to receive inadequate PNC, followed by Hispanic women, Other non-Hispanic women, and White non-Hispanic women. The magnitude of these differences in inadequate PNC was significant enough to explain part of the association between race and fetal growth restriction, with the percent mediated being highest for Black non-Hispanic women. However, a majority of the association was not explained by PNC adequacy.

This research demonstrates the utility of mediation analysis methods, which are useful in investigating causal mechanisms of exposure-outcome associations. In the case of the approach we have used, we were able to account for exposure-mediator interactions. There is great opportunity for utilizing this method to further investigate racial disparities in birth outcomes in the U.S. Increased collaboration between researchers, clinicians, and policymakers can help provide best targets for intervention to close the racial gap in birth outcomes.

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APPENDIX I

Supplementary Table S1. Crude Log-Binomial Regression Analysis Showing Risk of Inadequate Prenatal Care by Race in the United States, among the 2011-2017 Singleton Birth Cohort

	Inadequate Prenatal Care RR (95% CI)[a,b]
White non-Hispanic	Reference
Black non-Hispanic	1.1938 (1.1926, 1.1951)
Hispanic	1.1652 (1.1642, 1.1663)
Other	1.1022 (1.1005, 1.1039)

Abbreviations: RR, risk ratio; CI, confidence interval

[a]All RRs were $P < 0.001$

[b]Reference group for outcome is adequate prenatal care

Supplementary Table S2. Demographic and Clinical Characteristics of Women with and without Missing Data on Adequacy of Prenatal Care

	Not Missing Data (%)	**Missing Data** (%)
Race		
White non-Hispanic	54.5	46.2
Black non-Hispanic	14.0	18.3
Hispanic	24.3	20.8
Other	7.3	7.1
Maternal Age		
<25	28.4	32.1
25-34	55.9	53.0
≥35	15.7	14.9
Married	39.1	46.0
Maternal Education		
0-8 years	3.6	2.5
9-12 years, no GED	11.2	8.1
9-12 years, yes GED	24.7	14.3
13-15 years	48.3	19.6
>16	11.0	3.8
Prior Live Births		
0	39.5	38.5
1	31.9	29.9
2 or more	28.3	29.6
Smoking During Pregnancy	7.6	5.1
Pre-Pregnancy Hypertension	1.6	0.8
Gestational Hypertension	5.2	2.2
Pre-Pregnancy Diabetes	0.8	0.4
Gestational Diabetes	5.6	1.9

APPENDIX II

Supplementary Figure S1: Annual Prevalence of IUGR and SGA by Race in the United States, 2011-2017 Singleton Birth Cohort