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Race, place, and scale: Residential segregation and racial disparities in very preterm birth

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Race, place, and scale: Residential segregation and racial disparities in very preterm birth

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An abstract of
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Abstract

Race, place, and scale: Residential segregation and racial disparities in very preterm birth

By Michael R. Kramer

Very preterm (VPT) birth (<32 weeks gestation) is a leading cause of infant mortality, accounting for one third of all infant deaths, and a significant portion of neurocognitive pediatric morbidity. In the US, black women experience triple the risk of VPT birth compared to non-Hispanic white women, accounting for 80% of the racial disparity in infant mortality. There is geographic variation in the magnitude of the racial disparity in VPT birth as a result of wide variation in the risk for black women across Metropolitan Statistical Areas (MSAs), with relatively little inter-MSA variation for white women. A small body of literature has suggested that residential segregation may be a determinant of racial disparities in health. Four questions motivate the exploration of the association between segregation and prematurity.

1. How should residential segregation be conceptualized and measured in epidemiologic research?
2. If segregation is associated with preterm birth, is the association similar for very and moderately preterm births?
3. Through what mechanisms might segregation influence VPT birth?
4. Does adjustment for segregation explain any of the geographic variation in VPT disparities?

Recently introduced spatial measures of residential segregation were validated against traditional Census-tract derived indices as predictors of commonly hypothesized health mediating variables including individual socioeconomic attainment and neighborhood socioeconomic environment. In each case spatial measures of isolation or dissimilarity outperformed Census-tract derived measures in explaining inter-MSA variation.

In analyses conducted at two scales (nationally comparing segregation in 231 MSAs, and locally comparing neighborhoods in the Atlanta MSA) spatial isolation segregation increased risk for very preterm births in black women, net of individual factors. Controlling for segregation reduced the inter-MSA variation in the racial disparity of VPT birth.

Although residential segregation was associated with risk for preterm birth in black women under various model specifications, joint control for measured risk factors only explained a portion of the racial disparity. Better understanding the mediating pathways between segregation and health may open opportunities for effective intervention to reduce disparities, but currently much of the excess risk experienced by black women remains unexplained.

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My interest in the world is on facilitating how individuals and families survive and thrive. I cannot adequately express how important my wife and children have been in making me stop work when I should and letting me keep working when I need to.

Finally I wish to honor the memory of Anoopa Sharma whose wise soul made a huge impact on me in her short stay in this world and in our lives.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF EQUATIONS

INTRODUCTION

Very preterm birth (birth before 32 weeks gestation) occurred in 20.3/1,000 live births in 2006.(1) Although relatively small in number, this population of births accounts for a third of all infant deaths, 67% of neonatal mortality, and is a significant contributor to the prevalence of pediatric neurocognitive morbidities such as cerebral palsy and mental retardation. Preterm births (a broader category including all births less than 37 weeks gestation) are also economically costly, with an estimated $26 billion per year price tag ($51,500 per preterm infant) for medical, rehabilitative and educational expenses.(2)

Yet the risk for preterm birth is not evenly shared by American women. Racial disparities in pregnancy outcomes such as low birth weight, fetal growth retardation, stillbirth, preterm birth, and infant mortality have persisted for decades. African American women experience 60% more preterm birth, and nearly three times more very preterm birth, when compared with non-Hispanic white women. Disparities in preterm birth risk also vary geographically. The rates of very preterm birth vary by region of the country and even from city to city. Notably, the amount of variation across metropolitan areas is three times greater for African American women as for white women, suggesting that some characteristic of area of residence impacts population risk.(3)

Intensive clinical and epidemiologic research has combined with ongoing bench science in an effort to better understand the causes of preterm birth, with an ultimate goal of identifying interventions which can improve the outcomes of pregnancies. While much knowledge has been gained, the causes of preterm birth remain largely a mystery, as do explanation for the racial disparity in its occurrence. Age, parity, poverty, education, cocaine

use, smoking, and marital status have all emerged as risk factors for preterm birth. Yet excess risks persist among college-educated black women married to college-educated black men, who are delivering their first- or second-born infant in their twenties or thirties, after having received prenatal care from the first trimester.(4) Growing evidence for the etiologic role of sexually transmitted as well as spontaneous genital tract infections particularly in very preterm births has raised hopes that an important and modifiable risk factor could be addressed. While trials treating infections during pregnancy have produced disappointing results, interest remains that much racial disparity in very preterm birth may be mediated through interactions of maternal stress, immune response, and genital tract infection.

The persistence of racial disparities after attempts to statistically control for known risk factors has lead some investigators to suggest the differences are genetic in nature. While there is likely a genetic component to preterm birth in general, it is not clear whether genetics explains the excess risk experienced by black women in the US. For example women of African descent who immigrate to the US from Africa, South America or the Caribbean experience risk intermediate between US born African Americans and US born whites. In addition, consistent evidence across all racial groups suggests that lower socioeconomic status as measured by low maternal education or poverty increases risk for preterm birth. Finally, the wide variation of very preterm birth risk for black women across US cities argues against a fully heritable explanation of excess risk. Together these observations suggest an important role for environment in explaining the gradient of risk for preterm birth.

Given the correlation in the United States of race, class, and some characteristics of social environment, interest has grown in the role of 'upstream' social determinants of preterm birth risk. These upstream risks, such as poverty concentration, housing quality, neighborhood

deterioration, access to health and social services, and racism may not be direct causes of the biologic processes that lead to preterm birth, but they could be broad processes which allot 'toxic' and protective exposures to women differentially with respect to race or class.

At the close of the nineteenth century W.E.B. DuBois observed neighborhood differences in black adult and infant mortality in Philadelphia (5). In the 1950's Dr. Alfred Yankauer observed that increasing residential segregation of blacks in New York City was associated with increasing risk for infant mortality. Although segregation received relatively little attention as a determinant of health in the subsequent decades, recent years have seen resurgence in interest and approaches to understanding the role of social environment in determining population disease patterns. Segregation has been characterized as a manifestation of institutional racism, and a process which sorts individuals into living environments on the basis of their race and income, and as such a fundamental cause of racial health disparities.(6) Whether segregation is a useful construct for better understanding racial disparities in preterm birth is unclear, but it serves as one potential exposure which could explain dramatic observed geographic and racial variation in risk.

DISSERTATION AIMS

This dissertation is motivated and organized around four questions.

1. How should residential segregation be conceptualized and measured for effective epidemiologic research?
2. If residential segregation is associated with preterm birth, is the association similar for very and moderately preterm birth categories?
3. Through what pathways and at what scale (e.g. neighborhood, metropolitan area) is the segregation-preterm birth association mediated?
4. Does segregation explain any of the geographic variation in racial disparities of very preterm birth?

The answers to these questions (to the extent that answers rather than more questions result) and the remainder of this dissertation are thus organized around seven separate manuscripts, three of which are published at the time of this writing, and four of which will be submitted. The previously referenced article on the geographic variation in very preterm birth for black but not white women (see Appendix 1) poses the crux of the question being asked: why does very preterm birth risk for black women vary so greatly, and by extension is residential segregation one explanation? The literature reviews in Chapters 1 and 2 were reformulated into a pair of review articles in Epidemiologic Reviews, 2009 (see Appendices 2 and 3), reviewing the current literature on determinants of racial disparities in prematurity, as well and evidence for residential segregation as a health relevant exposure. Chapter 3 is an overview of the methods used in the three studies composing the dissertation project.

Chapters 4-7 are stand-alone manuscripts describing the methods and results from the three studies; each offers a partial contribution to answering the primary dissertation questions. Chapter 4 presents results of a validation study introducing to the public health

literature a new class of spatial measures of segregation, and validating their performance against traditional Census-tract derived indices. Chapter 5 is the results of the national-scale study of segregation in 231 metropolitan areas, and the risk for very and moderately preterm birth in black and white residents of those MSA's. Chapter 6 also arises from the national-scale study and tests one specific hypothesis for the mediation of the segregation-preterm association: the weathering hypothesis. Chapter 7 presents results from a neighborhood-scaled study of racial composition in the Atlanta metropolitan area. Finally Chapter 8 is a conclusion and summary of the strengths, limitations, and contributions of this dissertation. Additional analyses which did not fit in one of the four results chapters are presented in additional appendices as indicated at the beginning of each chapter.

Chapter 1 UNDERSTANDING PRETERM BIRTH[1]

This chapter will review the background literature relevant for better understanding preterm birth in general, and racial disparities in the risk for preterm birth more specifically. A brief overview of the normal physiology of human parturition will be followed by current understandings of the physiology of premature parturition, including genetic hypotheses. Although this dissertation does not explicitly test any biologic mechanisms, each general dissertation question is placed in the context of plausible social and biologic pathways. Therefore the biologic background is germane to the dissertation.

Following this biologic groundwork, the population epidemiology of preterm birth will be reviewed. Particular attention will be paid to racial similarities and differences in risk, and previously observed determinants of preterm birth by race, as well as issues and evidence for a genetic explanation for racial differences.

Throughout this and subsequent chapters the term 'race' will be applied to distinguishing socially constructed categorizations commonly used in the United States in the latter two centuries. The focus of this dissertation is on comparisons between two groups, African Americans, hereafter referred to as blacks, and non-Hispanic whites, hereafter referred to as whites. Although race is commonly assumed to infer the continental ancestral history of an individual, it is nonetheless considered to more meaningfully describe the social and cultural experience of individuals.(7) In nearly all literature cited herein, self-reported race is used.

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[1] This chapter is summarized in a review article in Appendix 2

Except where noted, racial categories will be used to infer socially or historically meaningful groups, but will not infer distinct biologic categories.

PHYSIOLOGY OF NORMAL AND ABNORMAL PARTURITION

The primary focus of this dissertation is on the role of a social process (residential segregation) patterning population risk for a biologic outcome (preterm birth). Both as general background, and to build the hypothesized links between social processes and biologic outcomes, the normal and abnormal physiology of parturition will be reviewed. This will be indirectly relevant for the first three aims of this dissertation, and more directly relevant for the fourth.

NORMAL PHYSIOLOGY OF HUMAN PARTURITION

Human reproduction intrinsically links social processes with complex dynamic biologic systems resulting from eons of selective pressure, all with the biologic and social goal of success of future generations (although *success* might be differently defined from social and biologic stand points). Courting and mate selection, conceptional timing, hospitability of the uterine environment to implantation, and subsequent intra uterine milieu result from varying degrees of biologic programming, inherited characteristics, and social behaviors and experiences of the mother and father. In fact, humans alone among mammals are the only species who seek the assistance of others during delivery, making birth itself a social rather than a solitary occasion.(8) The full extent of adaptations of human reproduction is well beyond the scope of this paper. However a brief overview of current understandings of the determinants of normal gestational length and processes for normal parturition will be addressed.

Numerous factors could potentially influence gestational length in eutherian mammals (mammals with placentas) including maternal and fetal size, size of fetal brain and rate of brain

growth, and maternal pelvic anthropometry.(9) Physical anthropologists suggest that brain weight and development is the primary correlate for mammalian gestational length(10), yet for humans if this pattern were maintained, an average gestation of 18 months would be expected.(11) It is suggested that the halving of this expected gestational period to the mean observed length of 280 days is an evolutionarily constructed balancing of the mechanics of the bipedal human pelvis, with increased brain development: to maximize the adaptive benefits of both greater cortical mass and upright stature and mobility, only partial brain growth occurs in utero, with the remainder occurring during childhood.

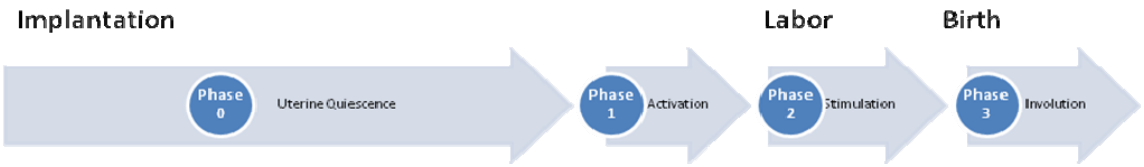
Yet intra uterine fetal development can only be truncated so far; birth in humans typically occurs with the fetal cranium at the maximum size permissible through the birth canal (as compared with other primates (8)), but basic fetal motor and pulmonary function must also be adequately developed for extra uterine life. The processes that determine when this balance has been met are only partly understood.

Early progenitors of the mechanisms of and triggers for parturition begin with blastocyst implantation into the receptive endometrium 6-7 days after fertilization. It is at this time that trophoblast differentiation begins. The trophoblast is extra-embryonic tissue which is responsible for implantation itself, and develops into the most prolific and various endocrine source in all of mammalian physiology.(12) The trophoblast differentiates and gives rise to the chorionic villi of the placenta and chorionic membrane, and invades the endometrial lining to forge the first steps of the maternal-fetal circulation. The amniotic membrane, which is also important for fetal protection and nutrition fuses with the chorionic membrane at 8-10 weeks post-fertilization (10-12 weeks gestational age) forming the amniochorionic fetal membranes which are critical in the pathway to parturition. At the time of implantation, the name of the

lining of the uterus changes from endometrium to decidua. As the embryo-fetus continues to grow, the amniotic sac expands to the limits of the uterus, and eventually the chorionic membrane is in intimate contact with the entire decidua vera (portion of the decidua without placental implantation) functionally isolating the uterine cavity from the outside world. This occurs in the middle of the second trimester, and may be relevant in later discussion of the timing of ascending genital tract infections in preterm birth.(13)

Although many questions remain about how the fetus, fetal membranes, decidua, placenta, and maternal systemic physiology interact to determine the timing of parturition, much is known. The process of parturition is commonly divided into stages (see Figure 1-1), with the bulk of pregnancy occupying Phase 0 or uterine quiescence.(14, 15)

Figure 1-1. Stages of parturition



Phase 0 – Uterine quiescence

For the best part of the duration of pregnancy (>95% of the 280 day gestation), multiple complex systems work in harmony for one goal: to retain the developing fetus in the confines of the uterus. This involves both control of maternal immune response to the presence of an invasive foreign body, as well as suppression of the uterine myometrium, essentially a muscular organ. The natural state of the smooth muscle of the uterus is to react to the presence of

mechanical and chemical stimulation by contracting, yet the period of quiescence is marked by near contractile paralysis, and firmness of the cervix.(12) This results from multiple processes, many of which increase intracellular myometrial cyclic adenosine phosphate (cAMP) thus inhibiting calcium release.(2, 12, 16) For example relaxin, prostacyclin (PGI_2), parathyroid hormone-related peptide (PTHrP), and nitric oxide (NO) may all have a suppressive effect on the myometrium via this mechanism. In addition progesterone (produced primarily in the chorion and placenta after 6 weeks gestation) steadily increases throughout pregnancy and plays a crucial (although mechanistically undefined) role in myometrial suppression.(12)

Phase 1 – Uterine activation

The transition from a quiescent to a receptive and activated myometrium is necessary in preparation for labor. Challis et al suggest that the timing and triggering of the activation in normal pregnancy is largely driven by the fetal genome.(16) The activation consists largely of development of sensitized receptors to uterine stimulators and increased gap junctions, which are connecting channels between myocytes allowing ionic and electrical communication and thus coordination of contraction. Two mechanisms may initiate the activation process: uterine stretch and endocrine stimuli from the fetal hypothalamic-pituitary-adrenal (HPA) axis.

Mechanical stretch of the fetal membranes and myometrial cells from the growing fetus and amniotic fluid may trigger the formation of connexin-43 which is a component of the gap junctions. Although the exact mechanism for this is unclear, experimental animal models as well as the observation that multiple gestation and polyhydramnios (excess amniotic fluid) result in preterm labor, suggest that uterine distention plays a role.(15, 17, 18)

Fetal endocrine activity appears to be intimately involved with the transition from quiescence to activation and subsequent stimulation in Phase 2. Corticotropin releasing

hormone (CRH) is a hormone and neurotransmitter normally synthesized by the hypothalamus in response to stress. However in phase 1, CRH production by the placenta is greater than either fetal or maternal hypothalamic sources.(19) CRH stimulates the fetal adrenal glands in the final weeks of gestation to produce large amounts of cortisol and androgen steroids which are converted to estrogen in the placenta. Unlike the negative feedback loop of CRH and cortisol in the hypothalamus, there appears to be a positive feedback loop with regards to cortisol and placental production of CRH.(20, 21) This acceleration of CRH and cortisol late in gestation is relevant because both cortisol and CRH may directly enhance myometrial contraction. Cortisol may also trigger prostaglandin synthesis from the membranes and myometrium.(12) Finally, the surge in fetal adrenal output of androgens which are aromatized into estrogen in the placenta shifts the ratio of estrogen to progesterone (also produced in increasing concentrations by the placenta throughout gestation) causing a functional progesterone withdrawal which both ripens the cervix and activates the myometrium.

Phase 2 – Uterine stimulation

Three events occur during phase 2: the previously firm and thick cervix softens, dilates and effaces; the uterus begins powerful, coordinated contractions in its upper segment while relaxing in the lower segment; and the decidua and fetal membranes are activated allowing separation of the membranes from the decidua, and weakening the tensile strength of the membranes themselves. CRH, estrogen, functional progesterone withdrawal, cytokines and prostaglandins all play a role in this rapid cascade.

Cervical ripening results largely from the effects of inflammatory cytokines and prostaglandins (produced from the fetal membranes) in degrading the collagen matrix, allowing

increased plasticity and remodeling. This plasticity is encouraged by pressure exerted by contraction on the fetus.

Coordinated uterine contractions are possible because of the activation and sensitization process that occurred during Phase 1. Oxytocin and prostaglandins play a critical role in directly stimulating the now activated and coordinated myometrium.

Finally, a family of degrading enzymes called matrix-degrading enzymes (MMP) are activated by an unknown trigger, and break down the fetal membranes and decidua, allowing membrane separation and rupture, and promoting apoptosis of cells in the amnion.(2)

Two pathways to term birth

In summary, normal human parturition results from a complex interplay of cellular and molecular processes. Much is unknown about the exact mechanism triggering the transitions from one phase to another. However, it is generally thought that normal parturition is a result of one of two pathways, independently or in combination: a growth pathway leading to uterine stretch or an endocrine pathway resulting from placental-fetal-HPA activation. It is clear that CRH is a primary driver in the timing and regulation of the cascade and it has been proposed that CRH marks a 'placental clock' that may be set early in gestation.(22, 23) The absolute CRH levels as well as the rate of CRH increase may both be relevant for triggering the transition through the phases. Another feature prominent in the pathways to parturition is the strong role for fetal, placental, and maternal involvement.

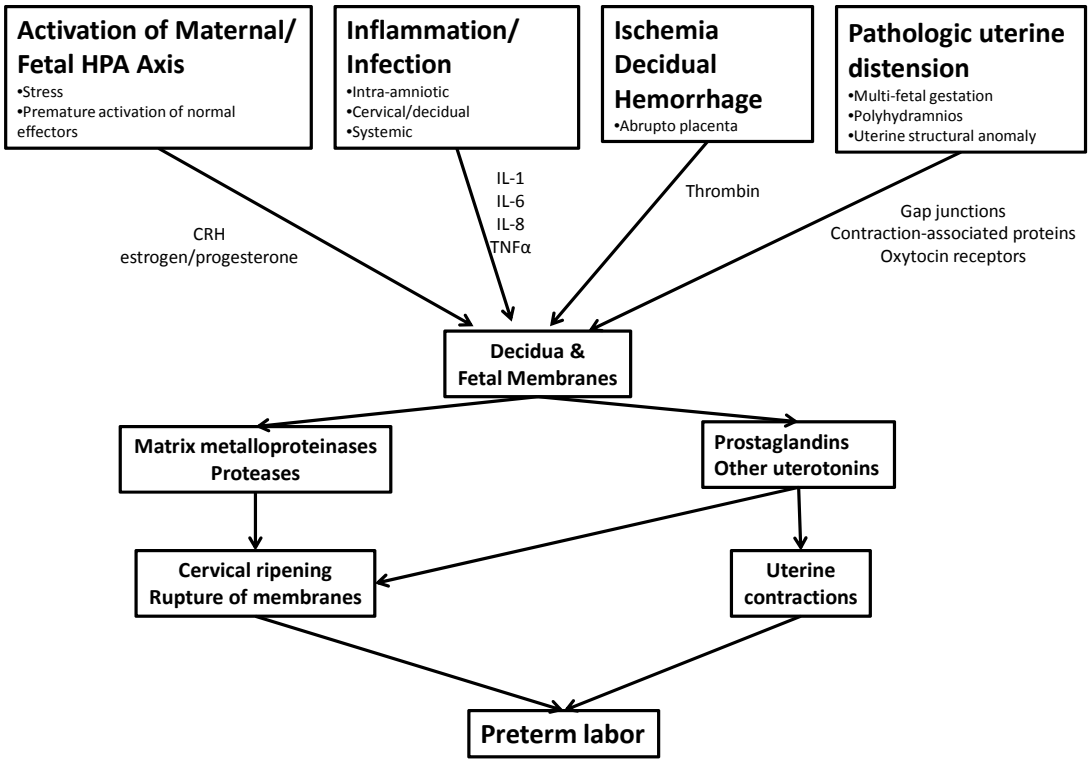
PHYSIOLOGY OF PREMATURE PARTURITION

Premature parturition will be defined in this section as the process resulting in birth before the physiologically optimal time for the fetus. While clinical and epidemiologic cut

points for the category of preterm birth will be discussed in a subsequent section, the focus here is on the general notion of a pathologically early triggering of the normal cascade of parturition. For this reason, most processes described here are related to spontaneous preterm birth, as opposed to indicated preterm birth, where maternal or fetal distress lead health care providers to induce labor or deliver via caesarean section. Two overlapping syndromes lead to spontaneous preterm birth: preterm premature rupture of membranes (PPROM) and spontaneous preterm labor. PPROM is rupture of the amniotic sac prior to contractions, and preterm labor begins with contractions, and rupture of the membranes follows. In clinical practice it can often be difficult to distinguish between the two syndromes.

Preterm birth has been described as a common syndrome, or result of various pathologic processes. This heterogeneity of cause for a final clinical outcome has complicated clinical and epidemiologic research. While there are perhaps more gaps in our understanding of the pathologic triggers for parturition than for the physiologic triggers, there are still some observable general patterns. Whereas there were two apparent pathways (which are likely inter-related) to normal parturition, there are four possible, broad pathways to premature parturition (Figure 1-2). The first two are aberrations of the normal process: pathologic uterine distension from multiple gestations or polyhydramnios and premature activation of the maternal-fetal HPA axis. The other two are irregularities in aspects of the normal milieu: infection and inflammation, and decidual hemorrhage or vasculopathy.(24) A brief overview follows of each pathway and its possible contribution to racial disparities in preterm birth.

Figure 1-2 Four common biologic pathways to preterm birth (Adapted from Behrman, 2007)(2)



Pathologic uterine distension

As previously discussed, uterine distention and stretch may trigger formation of important proteins such as connexin-43, which are required for gap junctions.(25) In addition pathologic stretch can upregulate oxytocin receptors, and stimulate prostaglandin production which can stimulate contractions and ripen the cervix.(26, 27) It is also likely that the uterine stretch pathway interacts with endocrine activation.

The two most likely causes of pathologic distension either do not vary by race, or vary in ways which are not explanatory of racial disparities. Polyhydramnios (excess amniotic fluid) is associated with fetal congenital anomalies, and occurs in approximately 1% of pregnancies.(12) In a large population based study in Alabama, polyhydramnios was more prevalent in white

women than in black women.(28) The more prevalent explanation for uterine distension is multiple gestations, which occur in about 34/1,000 live births, and have similar occurrence between black and white women.(29)

Activation of the maternal/fetal HPA axis

Increasing placental production of CRH throughout gestation leads to elevated fetal production of cortisol and steroids, as well as elevation of prostaglandins and proteases such as MMP, all of which lead to activation and stimulation phases of normal parturition. However significant evidence exists that this fetal-placental-maternal hypothalamic-pituitary-adrenal axis can be *prematurely* triggered resulting in preterm birth. The question of a neuroendocrine role in preterm parturition is raised by the observation that prospectively measured maternal serum CRH is elevated in women who subsequently deliver prematurely.(30, 31, 32) CRH could be coincidentally elevated as a result of another process, and thus not causal, however the in vitro evidence that elevated CRH can directly stimulate cytokines from the decidua and fetal membranes, as well as placenta, suggests that elevated CRH is a causal part of the cascade.(23, 33)

Population-based prospective cohorts have noted increases in both the absolute CRH and the trajectory of CRH increase as early as the mid second trimester in women who subsequently deliver preterm as compared with term deliveries.(23, 34, 35) The fact that observable differences in CRH levels are measurable weeks before delivery has raised the hypothesis that CRH is a marker of the 'placental clock' which is set early in gestation and determines length of gestation.(22, 36) Under this hypothesis, premature birth occurs either

from 'setting forward' the clock (as might be seen from an elevated baseline CRH), or 'speeding up the clock' (as might be seen with a steeper trajectory of CRH increase).

Two possible triggers for the premature activation of the HPA axis which have received attention are maternal psychosocial stress and infection or inflammation. In the non-pregnant state, CRH mediates physiologic responses to stress.(37) While the epidemiologic literature linking experiences of maternal stress to the occurrence of preterm birth will be discussed in a later section, it is worth noting here that measures of maternal psychosocial stress during pregnancy have been associated with elevated CRH and preterm delivery, suggesting that CRH plays a parallel role in pregnancy. Hobel, et al, report that maternal perceptions of stress at 18-20 weeks gestation explained a significant proportion of the difference in CRH at 28-30 weeks between women who subsequently delivered preterm rather than term.(38) Maternal stress has also been linked in pregnancy to elevated levels of several other components of the HPA axis, including ACTH, β-endorphin, and cortisol.(39)

While genital tract infection and inflammation is considered to have an independent effect on triggering preterm birth, it is has also been proposed that maternal stress mediates maternal immune status and susceptibility to infection via the HPA axis.(40, 41) Bacterial endo- and exotoxins may also trigger increased CRH production from the placenta.(13)

Observed racial differences in maternal median CRH have been reported, but with differing findings. Herrmann, et al, in a study of the effects of fasting during pregnancy, report an over representation of black women in the 'high CRH' group as compared with white women.(42) Holzman, et al , report differences in maternal CRH measured at 15-19 weeks gestation in a multi-racial nested case-control study.(43) Black women who delivered both term and preterm had lower median CRH compared with whites in either group, but within

each racial group, CRH was negatively associated with length of gestation, and in fact the association was stronger for black women than white women. Wadhwa also reports lower CRH and cortisol in black compared with white pregnant women, but notes elevated ACTH in black women at all gestational ages, and a lower gradient to CRH increase across gestational ages.(44) Investigators have hypothesized that if racial disparities in preterm operate through alteration of the HPA axis, it may not simply be the result of an elevated acute stress reaction, but rather an alteration in response to stress resulting from chronic exposure to high stress environments.(41, 45)

Infection and inflammation

Bacterial colonization or invasion of the pregnant uterus (infection of the membranes – chorioamnionitis; infection of the amniotic fluid – amnionitis; infection of the umbilical cord – funisitis), and the resulting host inflammatory response, can trigger several processes which may lead to premature birth. This pathway is considered particularly important because infection appears to be associated with 30-70% of preterm births, with an inverse association between prevalence of culture positive amniotic fluid or membranes and gestational age.(13, 46, 47) Because infant mortality and morbidity are also inversely associated with gestational age, infection may have a high attributable risk for the sequelae of preterm birth.

The presence of bacteria (and possibly viruses) anywhere within the uterus during pregnancy could lead to premature parturition through several pathways.(48, 49, 50) Bacterial endotoxins and exotoxins can stimulate increased formation of prostaglandins which increase proteases such as MMP, resulting in cervical ripening and rupture of membranes. They can also result in formation of pro-inflammatory cytokines such as interleukin-1, -6, and -8, (IL1, IL6, IL8) as well as tumor necrosis factor (TNF-α) which, via neutrophil infiltration can increase

MMP activity in the cervix and membranes. Finally, the fetus and placenta may respond to bacterial infection by increasing fetal hypothalamic and placental production of CRH, thus enlisting further pressure for uterine activation and stimulation. Chorioamnionitis is also associated with placental abruption, which is a cause of medically induced preterm birth.(51)

The source of most infecting organisms is assumed to be vaginal with ascent into the uterus. Organisms frequently isolated include *Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis*, and peptostreptococci and bacteroides species.(52, 53) There is evidence that uterine colonization occurs either preconceptionally(54), or during the first half of pregnancy (before the chorioamnion expands sufficiently to effectively seal off the uterus)(55, 56), thus offering a possible explanation for the inverse association between prevalence of histologic or clinical infection and gestational age.

Growing evidence of an association between maternal periodontal (gum) disease and the occurrence of preterm birth raises the question of whether infection is the culprit or rather a systemic inflammatory response to low grade chronic infectious agents.(57, 58)

Despite growing evidence for the role of infection, particularly in very premature births, there has been limited success of treatment. For example bacterial vaginosis (BV)—a non-invasive overgrowth of gram-negative and anaerobic bacteria in the vagina—has been widely observed to be associated with preterm birth, with an OR of 2.19 (95% CI 1.54-3.12) from a recent meta-analysis of 18 studies.(59) While BV is generally considered to be low-virulence and easily treatable, results from numerous randomized clinical trials of BV treatment have shown no reduction in preterm risk in treated compared to untreated women.(60) This is unlikely due to dose or route of treatment, as many combinations have been tried, but may be due to timing. If pre-conceptional or early pregnancy colonization of the uterus lead to 'setting

forward the placental clock' (via interaction between maternal and fetal immune responses), treatment of the clinical infection may simply be too late. While inter-pregnancy colonization with bacterial vaginosis may in fact be relevant in the pathogenesis of preterm birth, inter-conceptional antibiotics treatment has been no more effective than perinatal antibiotics in preventing preterm birth.(61)

It is probable that some portion of excess preterm birth among black women occur through the infection pathway. Bacterial vaginosis is 2-3 times more common in black woman as compared with white women, and this difference persists after control for risk factors for BV such as douching, smoking, and number of sexual partners.(62, 63, 64) In addition, the association between histologic chorioamnionitis (HCA) and very premature birth is stronger in black women than in white women. Andrews, et al identified 56% of black births less than 32 weeks gestation to have HCA, while only 39% of white births had evidence of chorioamnionitis.(65) Holzman, et al found that HCA was not associated with preterm birth before 35 weeks in white women, but accounted for half of such preterm births in black women.(66) Recently, Menon, et al demonstrated that TNF-α levels were significantly higher in black preterm birth compared to black controls, while TNF-α did not appear to be associated with preterm birth among white women.(67)

Decidual hemorrhage and ischemia

Vaginal bleeding during pregnancy has been long noted as a risk factor for preterm birth.(68, 69) Vaginal bleeding may be a clinical sign of underlying uteroplacental ischemia, vascular malformation, thrombosis, or hypoperfusion. Salafia found that 43% of placentas delivered at <32 weeks gestation showed histologic evidence of hemorrhage at the decidual-placental junction.(70) Arias reports similar prevalence, but also looked for histologic evidence

of infection and found that infection and hemorrhage or ischemia are largely distinct causes of preterm birth.(71) Hemorrhage could occur as a result of malformation or thrombosis of fetal or maternal arteries, resulting in uteroplacental ischemia, and thrombin production.(2) Thrombin then stimulates increased production of MMP, resulting in rupture of membranes and cervical ripening.(72, 73)

Hemorrhage and ischemia are also associated with other conditions which are risk factors for spontaneous and medically indicated preterm birth, such as preeclampsia (pregnancy induced hypertension and proteinuria which can lead to maternal seizures and death if the fetus is not delivered) and non-hypertensive placenta abruption (premature separation of the placenta from the uterus).(70, 74, 75) Fiscella argues that these conditions can be seen as part of a larger constellation of microvascular dysfunction related to maternal vascular health, hypertension, and dyslipidemia.(76) This hypothesis is supported by the observation that women who deliver preterm have elevated risk factors for cardiovascular disease (CVD) during pregnancy and higher incidence of CVD later in life.(77, 78) For example women with both an elevated C-reactive protein and dyslipidemia measured prior to 21 weeks gestation had a 6.4 fold increased odds for preterm birth before 34 weeks.(79) Whether this result is mediated through utero-placenta ischemia and thrombin, through an inflammatory response similar to the infection pathway, or a combination of the two is unclear.

The evidence for racial differences in preterm as a result of this pathway is mixed. Fiscella suggests that microvascular dysfunction is a primary component for the excess risk for preterm birth seen in black women.(76) Pre-eclampsia, and to a lesser degree placental abruption, are seen more frequently in black women than white women.(80, 81, 82, 83) However Goldenberg, et al, did not find a racial difference in the prevalence of diffuse decidual

leukocytoclastic necrosis of decidual base, a histologic finding associated with preeclampsia.(75)

Genetics Part I: genes and preterm birth in humans

Interest in a genetic role in preterm birth has been growing with recent advances such as sequencing of the human genome, and technologic improvements in high-throughput genetic methodologies. It is not infrequent for the presence of racial and ethnic disparities in preterm birth risk to be used as evidence of the existence of a genetic component.(84, 85) However this may be a premature convergence of two (possibly) separate questions: do genetic variations account for varying risk in preterm birth in humans and do genetic variations explain *excess* risk for preterm birth in African American as compared with non-Hispanic white women? To address these issues, this review of literature is divided into Genetics Part I and II. In this first section, evidence for genetic contribution to preterm birth in humans will be reviewed. After consideration of the other epidemiologic evidence for preterm birth generally, and racial disparities more specifically, the possible role of genetics in explaining excess black preterm birth will be reviewed in Part II.

Beyond racial and ethnic differences in preterm birth risk, observations of familial and intergenerational clustering of preterm birth, recurrent risk in the same woman, and twin studies have been noted as evidence for a genetic cause of preterm birth.

One of the strongest risk factors for preterm birth is a history of a previous preterm birth in the same woman. Overall a prior preterm birth confers a 2.5 fold increased risk for preterm in a subsequent pregnancy. (86) The risk of a subsequent preterm birth before 28

weeks was elevated 10-fold for women with *any* prior preterm birth and elevated 22-fold if the prior preterm birth had occurred prior to 28 weeks. This strong association with early preterm births raises questions of heritability, as well as the role of persistent subacute infection through the inter-pregnancy interval.

In addition to risk for preterm clustering within the individual woman, it also appears to have weak affinity for clustering within families. In a genealogic study of preterm birth in the Amish, Khoury reported that preterm birth of <37 weeks gestation was associated with an elevated inbreeding coefficient (measure of the probability that two genes were received from the same ancestor) for the mothers, but not for the infants or fathers.(87) A similar study in a Utah cohort found that any two randomly drawn pregnant women in the cohort were 23rd degree relatives, while any two women who delivered at <36 weeks gestation were on average 8th degree relatives.(88)

Three studies which used inter-generationally linked birth certificates looked at similar issues. Porter, et al, found that women who were themselves born before 37 weeks gestation, had a slightly elevated risk for preterm birth in their own pregnancy (OR 1.18, 95% CI 1.02-1.37).(89) The OR was 2.38 (95% CI 1.37-4.16) if the mother herself had been born prior to 30 weeks gestation. While Winkvist did not find an association between a mother's preterm birth status and that of her own pregnancies in a Swedish cohort, they did note elevated risk for preterm birth if the mother had been born small for gestational age (growth retarded), or if her sister had delivered preterm.(90) Finally, Wilcox, et al, found in a Norwegian linked cohort that women who were themselves born preterm had relative risk of 1.54 (95% CI 1.42-1.67) for preterm birth themselves.(91) In contrast, men born preterm had little to no association with

fathering an infant born preterm. Wilcox concludes those maternally inherited genes, as opposed to fetal or paternal, are the most relevant in determining propensity for preterm birth.

Twin studies have classically been used to try to tease apart the contributions of genetic and environmental sources of a disease state. Only two such studies have been conducted, one each in an Australian and Swedish cohort, with estimated heritability of preterm birth <37 weeks between 17% and 31%.(92, 93)

A shortcoming of the preceding literature is the inability to identify specific genetic traits or polymorphisms which are causally related to preterm birth. Candidate gene studies of individual single nucleotide polymorphisms (SNPs) and preterm birth have thus far provided mixed results with limited replication of the significant findings. To date no genome-wide scans have been conducted with regards to preterm birth, although this approach may be more fruitful, allowing consideration of more SNPs as well as the role for gene-gene interactions.(2, 94)

The strongest evidence to date for a genetic mechanism in preterm birth is for a polymorphism in the gene coding for the pro-inflammatory cytokine tumor necrosis factor alpha, TNF(-308A).(95) This polymorphism in either the fetus or the mother was associated with spontaneous preterm birth in some(96, 97) but not all(98) studies. Additionally there is evidence of a gene-environment interaction between TNF polymorphism and vaginal infections. Specifically, Macones, et al reported that TNF (-308A) conferred increased risk for preterm birth (OR 2.7, 95% CI 1.7-4.5), which was much stronger in the presence of clinically diagnosed bacterial vaginosis (OR 6.1, 95% CI 1.9-21.0).(99)

There has also been initial evidence for an association between preterm birth and IL1 receptor antagonist (IL1RA) (100), IL4 (101), IL6 (102). Further gene-environment interactions have been described between vaginal infections and preterm birth for IL1 (103), IL6 (104), and toll-like receptor 4 (TLR4) (105). Most studies to date have focused on the infectious pathway, and gene-environment interactions have similarly focused on infection. Future work with whole genome scans, gene-gene interactions, and other gene-environment interactions, and inclusion of proteomics have been proposed.(85, 106, 107) The recent Institute of Medicine report on preterm birth listed 124 physiologically plausible candidate genes for all of the common pathways to preterm birth.(2)

Genetics Part II: Race and preterm birth

Race, genetics, and health

It is not uncommon for the evidence described above of persistent racial difference in preterm birth risk in the US after control for known behavioral risk factors to be attributed to genetic predisposition.(84, 108) Whether this is in fact the case is currently unknown. However the already thorny problem of establishing causal links between genetic polymorphisms and disease phenotypes is made all the more troublesome when the question at hand concerns racial disparities. This is for two reasons. First, 'race' as we use it in this country is a historically and socially constructed categorization scheme (as opposed to scientifically created from biologically meaningful markers) that may not accurately proxy genetic ancestry. Secondly, related to the historical and social nature of the categorization scheme, 'racial' categories have strong correlations with a wide range of environmental factors which could associate with disease, making the complete control of these factors challenging at best in population research.

While few would argue that social categories of race are perfect markers of genetic ancestry, it is a frequently assumed starting point by many health researchers that 'race' correlates highly with genetic commonalities. However the strength of this correlation may be lower than commonly assumed (109). The Human Genome Project demonstrated that humans across the globe share 99.9% of their genetic information (110). When samples are taken from geographically diverse populations, neutral polymorphisms across the genome can be used to roughly categorize humans into 5 continental groups, with many individuals showing contribution from more than one group. Of the 0.1% of the genome that varies, 93-95% of all variance is attributable to within-group variance.(111) In other words, only 5-7% of the genetic variation in humans is attributable to continental groups, with the remainder occurring *within* each continental group. When considering the ancestral heritage of African Americans in the US, it appears that there is a wide spectrum of inheritance of African-specific genes. As a result of population admixture (inter-marriage between continental groups) African Americans carry a wide range of European and Native American ancestry. In one study African Americans from various US cities had an estimated European contribution ranging from 11-23%.(112) A cardiovascular health study of self-identified African Americans found a mean ancestral heritage of 76% African, 21% European, and 3% Native American.(113) These studies base the components of ancestry on the use of ancestry-informative markers, which are theoretically neutral polymorphisms spread throughout the genome. However it is unknown if medically relevant polymorphisms—which are more likely sensitive to selective pressures and population bottlenecks—would even track with these ancestral markers.(114)

Another complication of using race as a proxy for ancestral heritage in medical research is that, largely as a result of the very historical and social processes which create the current

categories of race, there are racial differences in a wide array of health-relevant social and environmental exposures.(115) This residual confounding by social characteristics can be a problem for any epidemiologic study, but may be insurmountable in attempts to tease apart social environment and genetic contribution to racial disparities in health.(116, 117)

Evidence for genetic source for racial disparities in preterm birth

These two issues raise validity concerns of misclassification, sample selection bias, and residual confounding by unmeasured or incompletely measured characteristics for many claims of inherited traits as an etiologic agent in excess black preterm birth. Nonetheless there is literature—with mixed findings—attempting to estimate the role of either broad racial differences in propensity for preterm birth, or the more specific transmission of risk-inducing polymorphisms that through differential prevalence, or gene-environment interaction, play a role in observed racial differences in risk.

As previously mentioned, it is commonly reported that the mean length of gestation (from first day of last menstrual period) is 280 days. However, some investigators hypothesize that black babies mature faster than white babies, and thus the entire gestational age curve is shifted to the left. Two studies in African American and Nigerian populations report mean gestational length of around 275 days.(118, 119) Patel, et al also report a shortening of the normal gestational length by about 1 week in black as opposed to white British mothers, and note higher prevalence of meconium staining of the amniotic fluid (cited as a sign of fetal maturity) in the black babies born before 37 weeks.(120) Savitz argues in a commentary on this study that it is challenging to distinguish the constitutionally quick-maturing baby from the pathologically preterm. (121) It remains unclear whether it is absolute gestational age (e.g. <37 or <32 weeks) or relative position in the distribution (e.g. <5th percentile) which is most

relevant for infant health. It has also been proposed that evidence of earlier maturation of black infants could result from maternal experiences of stress which could lead to acceleration of lung and gut maturity via cortisol and the HPA axis.(119) Kramer, et al, evaluate mortality risk in standardized birthweight-gestational age strata, and find that mortality is highest for blacks born to mothers who were themselves born in the US, followed by foreign-born black mothers, followed by whites.(122) They conclude that racial differences in growth patterns are more likely pathologic as opposed to normal physiologic variants. Regardless of whether the mean 'normal' gestational age differs across racial groups, it is unlikely that any births at the early extremes of gestational age (e.g. <32 weeks) occur as a result of normal adaptation, given the high mortality for all groups at this age.(121)

Nativity studies

Another way to broadly consider whether genetic versus environmental factors contribute to preterm birth is to use migration studies. If women of African ancestry are genetically prone to preterm birth, one would expect that this would be most pronounced in African women, and perhaps less so in Afro-Caribbean or African American women as generations have inter-married with Europeans, Native Americans, or others. In general, black women have higher risk than white women for preterm birth and low birth weight infants across all of these studies. However relative discrepancy varies widely depending on where the mother was born. A summary of these studies is presented in Table 1-1 below.

In two studies by David and Collins using vital records from Illinois, comparisons were made between US born blacks and Caribbean(123) or African(124) born blacks. In both cases foreign-born black women had low birth weight (<2500 grams) rates intermediate between

whites and US-born blacks. This trend was attenuated but still present for births below 1500 grams.

Fang, et al, were able to further tease apart the role of mother's region of origin by using vital statistics from New York City, where there is greater detail on maternal birth place. They report blacks born in the Southern and Northern US with the highest risk for preterm birth, LBW, and VLBW, Caribbean and South American born blacks below that, followed by African-born blacks (Figure 1-3).(125) For VLBW infants, the risk ratio for African-born blacks compared to whites was 2.3 (95% CI 1.9-2.6) while the RR for Southern US born blacks and whites was 4.3 (95% CI 3.9-4.6).

Figure 1-3. Pregnancy outcomes by maternal nativity (125)

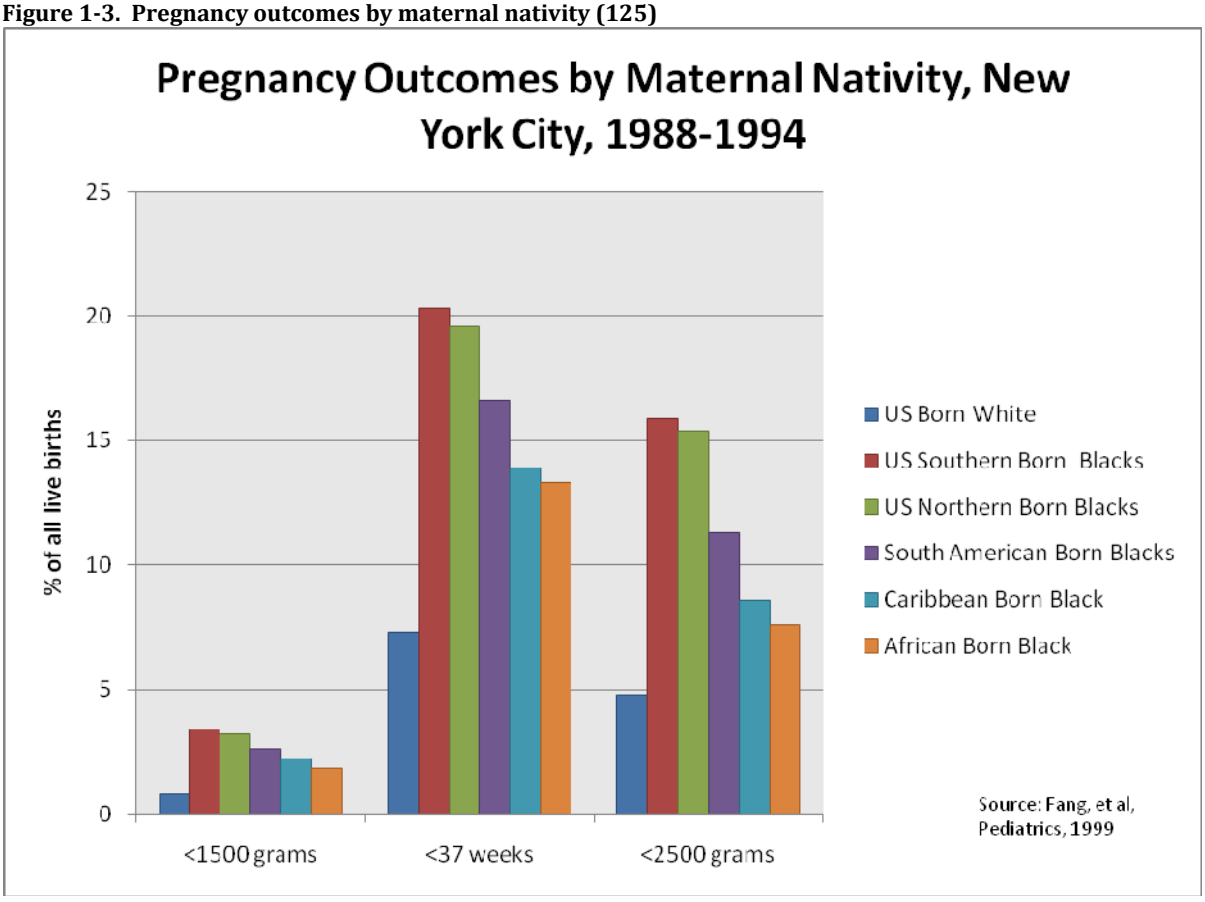


Table 1-1. Summary of maternal nativity and pregnancy outcomes (124, 125, 126, 127, 128, 129, 130)

Author and study information	Outcome	Population	Crude Percent	OR/RR	95% CI	Crude/ Adjusted
Aveyard (2002)	<37 wks	White	7.7	1.0		Adjusted
UK, 1994-97		African	8.0	1.0	(0.58-1.6)	
		Afro-Caribbean	10.8	1.2	(1.1-1.4)	
	<34 wks	White	2.5	1.0		Adjusted
		African	4.7	1.8	(0.9-3.4)	
		Afro-Caribbean	3.9	1.3	(1-1.6)	
	<28 wks	White	0.6	1.0		Adjusted
		African	2.4	4.0	(1.6-10.1)	
		Afro-Caribbean	0.1	1.3	(0.8-2.1)	
Collins (1997)	<1500 gms	European White	1.3	1.0		
London, 1987-1990		West Indian	2.9	2.1	(1.7-2.8)	
		African	2.2	1.8	(1.2-3.1)	
Bakeo (2006)	<1500 gms	UK - White	0.8	1.0		
UK, 1990-2001		Caribbean - Black	1.9	2.2	(2-2.4)	
		West Africa - Black	2.4	2.9	(2.7-3)	
David (1997)	1500-2500 gms	US Born White	3.6	1.0		Crude
Illinois, 1980-95		African Born Black	4.8	1.3	(1.1-1.6)	
		US Born Black	10.6	3.0	(2.8-3.1)	
	<1500 gms	US Born White	0.7	1.0		Crude
		African Born Black	2.3	3.2	(2.5-4.1)	
		US Born Black	2.6	3.5	(3.1-4)	
	1500-2500 gms	US Born White	3.1	1.0		Matched
		African Born Black	4.7	1.5	(1.2-2)	
		US Born Black	6.1	2.0	(1.5-2.5)	
	<1500 gms	US Born White	0.5	1.0		Matched
		African Born Black	2.2	4.1	(2.4-7)	
		US Born Black	2.4	4.5	(2.6-7.7)	
Harding (2004)	<2500 gms	White, UK born	4.7	1.0		
UK 1983-2000		Black Caribbean, UK born	9.1	1.9	(1.3-3)	

Author and study information	Outcome	Population	Crude Percent	OR/RR	95% CI	Crude/ Adjusted
		Black Caribbean, Migrant	5.5	1.2	(0.5-2.7)	
		Black African, UK born	8.0	1.7	(0.8-3.7)	
		Black African, migrant	6.3	1.3	(0.8-2.2)	
Harding (2006)	Small preterm	Portuguese White	1.5	1.0		
Portugal, 2001-2		Portuguese Born African	2.3	1.6	(0.8-3.1)	
		Foreign Born African	3.9	2.6	(1.7-4.1)	
Fang (1999)	<1500 grams	White	0.8	1.0		Crude
NY City, 1988-94		Black -Southern US born	3.4	4.3	(3.9-4.6)	
		Black -Northern born	3.2	4.0	(3.8-4.2)	
		Black -South American born	2.6	3.2	(2.9-3.7)	
		Black -Caribbean born	2.2	2.8	(2.6-2.9)	
		Black -African born	1.8	2.3	(1.9-2.6)	
	<37 wks	White	7.3			Crude
		Black -Southern US born	20.3	2.8	(2.7-2.9)	
		Black -Northern born	19.6	2.7	(2.6-2.7)	
		Black -South American born	16.6	2.3	(2.2-2.4)	
		Black -Carribbean born	13.9	1.9	(1.9-2)	
		Black -African born	13.3	1.8	(1.7-1.9)	
	<2500 grams	White	4.8			Crude
		Black -Southern US born	15.9	3.3	(3.1-3.4)	
		Black -Northern born	15.4	3.2	(3.1-3.3)	
		Black -South American born	11.3	2.4	(2.2-2.5)	
		Black -Carribbean	8.6	1.8	(1.7-1.9)	

Author and study information	Outcome	Population	Crude Percent	OR/RR	95% CI	Crude/ Adjusted
		born				
		Black -African born	7.6	1.6	(1.5-1.7)	
	<2500 grams	White				Adjusted
		Black -Southern US born		1.5	(1.4-1.7)	
		Black -Northern born		1.3	(1.2-1.4)	
		Black -South American born		1.2	(1.1-1.4)	
		Black -Carribbean born		1.0	(0.9-1)	
		Black -African born		0.9	(0.7-1)	

In a study of the inter-generational effects of immigration to the US on whites and blacks, Collins et al linked women giving birth in 1989-1991 to their own birth certificates from 1956-1975.(131) The women who gave birth in the 1956-1975 cohort were generation 1, their daughters were generation 2, and their grandchildren were generation 3. The authors note that while there was a slight improvement in mean birthweight from generation 2 to 3 if generation 1 (the grandmother) was US-born white, US-born black or foreign-born white, the expected generational improvement did not exist if the grandmother was a black immigrant. In fact for blacks alone, migration to the US resulted in a slight decrease in inter-generational birth weight.

Similar studies in the UK demonstrate that racial disparities also exist, but they tend to be of smaller magnitude than in the US. In separate studies by Collins and Bakeo, the rate of VLBW among black Caribbean women in the United Kingdom was about twice that of white English women, rather than the three-fold difference in the US.(127, 128) Aveyard, et al conducted a similar study with gestational age and report virtually no difference in <37 week gestation rates between white, African, and Afro-Caribbean women, and smaller disparities

than observed in the US for <34 weeks and <28 weeks, with the exception of African women <28 weeks who had a 4-fold elevated rate with a very wide confidence interval.(126)

When the low birth weight (<2500 grams) rate of British-born blacks were compared to black immigrants to England, and to whites, UK-born Caribbean blacks had an elevated risk compared to whites (OR 1.9, 95% CI 1.3-3), but foreign-born Caribbean blacks and both UK-born and immigrant black African women had elevated but not significant OR's compared to whites .(129) Portuguese-born blacks had lower rates of being small and preterm (defined as being in the residual of the birthweight distribution using the Wilcox-Russell method (132, 133)) than African-born blacks, suggesting migration is beneficial in this setting.(130) In fact there was no significant disparity between Portuguese-born blacks and whites in this study.

Candidate gene studies

A newer avenue of research into possible inherited propensity for excess preterm birth risk among African American women uses candidate gene association studies. There are at least two primary ways through which genetics could cause an observed racial disparity in preterm birth: an etiologically relevant polymorphism or group of polymorphisms is differentially prevalent by race, or a polymorphism that has constant prevalence by race interacts with an environmental factor which varies by race. There are a small numbers of studies which support either mechanism.

The TNF-α polymorphism (TNF (-308A)) has been demonstrated in several studies to be associated with preterm birth and PPROM in both black and white populations (see Genetics I review). However both the prevalence of the polymorphism and its apparent effect on preterm birth appear to be similar by race.(104, 134) While Macones claims there is an increased risk for preterm birth in black women carrying the polymorphism, they also

demonstrate the effect modification by the presence of bacterial vaginosis, but do not simultaneously consider both race and BV.(99) Given the significantly higher prevalence of BV among black women (generally and in their study) it is possible that the elevated effect of 'race' is the same effect seen for BV.

Findings for IL6 are mixed. Engel et al report that one polymorphism (IL6 (-274)) is associated with increased risk equally in black and white women, but is *less* prevalent in black women.(104) However the authors do note a gene-environment interaction between minor allele and race, with black women having both bacterial vaginosis and the polymorphism experiencing a 4.4 elevated odds ratio (05% CI 1.2-16.4). Velez et al also report racial difference in allele prevalence of the IL6 and IL6-receptor gene.(135) They subsequently note that one SNP in the IL6R gene was significantly different in black cases and controls. Simhan et al found that a polymorphism of the IL6 promoter region was protective against preterm birth and was completely absent in black women, but there were only 46 black women in the study.(102) Finally, Menon, et al report that amniotic fluid levels of IL6 were higher in births <37 weeks compared to those 37 or greater weeks for white women, but levels were similar for black women.(136)

Wang et al report that a functional SNP in the promoter regions for SERPINH1—a gene involved in collagen production, and thus theoretically involved in tensile strength of fetal membranes—is associated with PPROM in a case-control study of black women (OR 3.2, 95% CI 1.5-7.2).(137) Using prevalence estimates from a different database, they suggest that the allele is more prevalent in women of African ancestry than white women. However there were no white women enrolled in their preterm study.

To date there has been no well-designed study of adequate size that has demonstrated that a difference in minor allele frequency accounts for a portion of the excess preterm birth risk observed in African American women.

SUMMARY: PHYSIOLOGY OF NORMAL AND ABNORMAL PARTURITION

The normal human gestation lasts 280 days on average. The transition from intrauterine to extra-uterine life occurs as a result of complex interactions between fetal and maternal biochemical pathways, and is triggered by uterine stretch, and increased placental production of CRH, each of which trigger further cascade of prostaglandins and cytokines which stimulate coordinated contractions, and production of proteases (MMPs) which weaken the fetal membranes and soften the cervix.

All evidence to date suggests that premature or pathologic initiation of the parturition cascade can result from one of four inter-linked pathways: pathologic uterine distension, premature activation of the maternal-fetal-placental HPA axis, intrauterine infection and inflammation, and vascular dysfunction resulting in hemorrhage and ischemia. Each of these pathways represents a different 'trigger' but all result in a common final pathway of MMP production, weakening of membranes, and cervical softening.

There is also evidence that there may be racial differences in the prevalence of each of the four pathways, with infection and HPA activation as likely candidates for excess early preterm birth in black women, and a possible role for the vascular path as well.

Evidence for specific genetic mechanisms in the etiology of preterm birth is in its infancy, but quickly growing. This area is troubled by issues common to many explorations into specific mechanistic genetic hypotheses, including replicability of findings, quality of study

design for population inference, bioinformatic challenges of high-dimensional data, and rapidly changing measurement capabilities.(107) Nonetheless it seems clear that at a least a portion of the occurrence of preterm birth can be attributed to genetic predisposition.

EPIDEMIOLOGY OF PRETERM BIRTH

This section will review the measurement, categorization, population trends and identified risk factors for preterm birth.

MEASUREMENT AND CLASSIFICATION OF PRETERM BIRTH IN POPULATION RESEARCH

Population research into causes and consequences of preterm birth are complicated by a variety of overlapping, but not exchangeable categorizations systems. Three systems considered here are categorizations based on clinical presentation, pregnancy outcome, or gestational length. While each system serves a purpose, if not fully understood one categorization scheme could result in spurious findings or lack of findings.

Categorization by clinical presentation

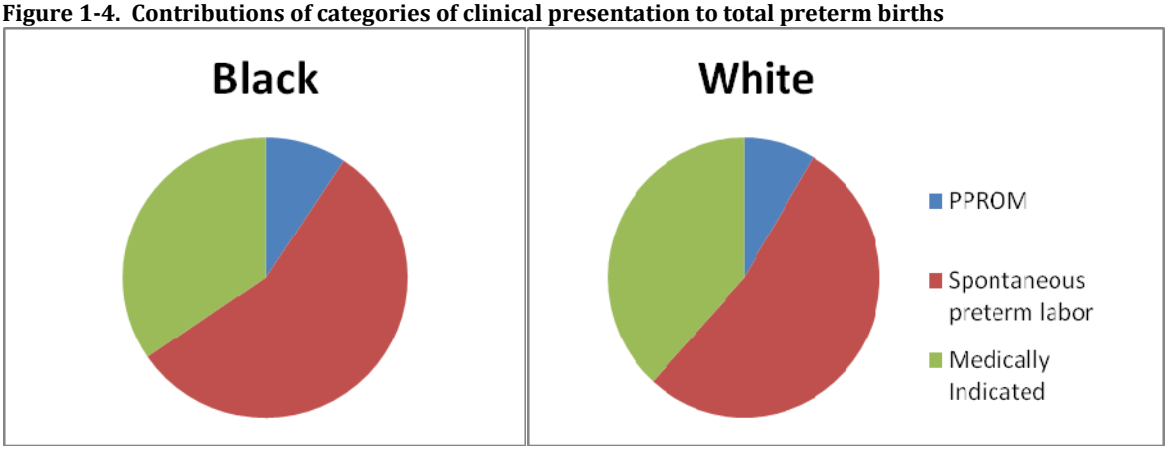
Preterm birth is typically divided into three clinical presentations. Preterm premature rupture of membranes (PPROM) refers to a spontaneous rupture of fetal membranes *before* the onset of clinical labor. Preterm labor leading to preterm birth occurs when contractions precede rupture of the fetal membranes. Because clinically it is often difficult to establish timing of membrane rupture in relation to initiation of early labor, PPROM and spontaneous preterm labor are frequently combined into a group called 'spontaneous preterm birth' which is then distinguished from the third clinical presentation, medically indicated preterm birth. Medically indicated preterm is an iatrogenic response to maternal or fetal distress, such as severe preeclampsia, placental abruption, or severe fetal growth retardation. Estimates of the relative prevalence of these clinical subtypes vary across time and population, but range from

8.5%-51.2% for PPROM, 27.9%-65.4% for spontaneous labor, and 20%-38.3% for medically indicated preterm.(138) Ananth, et al estimate that in the US in 2000, 69% of all preterm births were spontaneous, and 31% were medically indicated.(139) While the absolute rates for each subtype vary by race (see Table 1-2), the relative contribution of each subtype to the total percentage of preterm birth is relative similar between black and white women in the US (see Figure 1-4).

Table 1-2. Preterm birth rates and perinatal mortality rates by clinical subtype, US, 2000(138)

Preterm birth clinical subtypes[1]	PTB rate[2]	Perinatal mortality rate[3]
White women		
All preterm birth	9.4	36.2
PPROM	0.8	42.6
Spontaneous preterm labor	5	29.3
Medically Indicated	3.6	44.4
Black women		
All preterm birth	16.2	47.4
PPROM	1.5	70.9
Spontaneous preterm labor	9.1	41.1
Medically Indicated	5.6	51.4
[1] Preterm birth <37 weeks gestation		
[2] Per 1,000 live births		
[3] Per 1,000 live singleton birth		
Adapted from Ananth, et al, 2006		

Figure 1-4. Contributions of categories of clinical presentation to total preterm births



While these clinical subtypes do not overlap exactly with hypothesized causal pathways to preterm birth, there are some generalizations that can be made. It has been argued that 50-80% of medically indicated preterm births are in response to causes related to placental-fetal ischemia.(140, 141) Uterine distention, infection and stress may more commonly result in spontaneous preterm birth (either PPROM or spontaneous preterm labor).(142) However others argue that the similarities in risk factors for indicated and spontaneous preterm birth are such that investigators should consider both pooled and stratified analyses.(143)

Categorization by pregnancy outcome

Three clinical presentations of adverse pregnancy outcomes have important overlap, and important differences, and are thus worth a brief review (see Figure 1-5 and Figure 1-6). Intrauterine growth retardation (IUGR), low birth weight (LBW), and preterm birth (PTB) are not final health endpoints, but rather intermediate markers of elevated risk for mortality and morbidity. Birthweight is the oldest measure of pregnancy outcome in population research and has often been assumed to tell us about 'prematurity' or fetal fitness for extra-uterine life. However it has been strongly argued that birthweight can mislead investigators in clinical and

epidemiologic research because a) it is not causally associated with either mortality or morbidity, and thus is a poor proxy (and perhaps a confounder) in etiologic research(144); and b) categorizations such as low birth weight (typically operationalized as birthweight <2500 grams) create a mixture of genetically small but healthy babies, babies with growth retardation despite adequate time in utero, and babies with normal growth parameters, but inadequate time in utero.(145) In population distributions of birth weights, Wilcox has argued that population means are less predictive of mortality than the proportion of a given population in the extreme left tail of the distribution. This residual population, he argues, can be conceived as a meaningfully different group of babies who have suffered insults which are causally associated with subsequent mortality and morbidity.(146)

While growth retardation and prematurity overlap and may share etiologic pathways, they are nonetheless distinct. Growth retardation is conceptually a departure from an individual fetus' growth potential. This could mean that a statistically normal weight infant born at term could nonetheless have suffered an insult which disrupted his/her growth potential. IUGR is usually operationalized as an infant born at less than the 5^{th} or 10^{th} percentile birthweight for gestational age week. An IUGR baby could be born at term, or could be born prematurely, but not all preterm infants are growth retarded. This dissertation will use the metric of gestational age as the endpoint of interest.

Figure 1-5. Overlapping categories of pregnancy outcomes: Preterm, low birthweight and IUGR (Adapted from weight for age reference tables in Oken, 2003)(147)

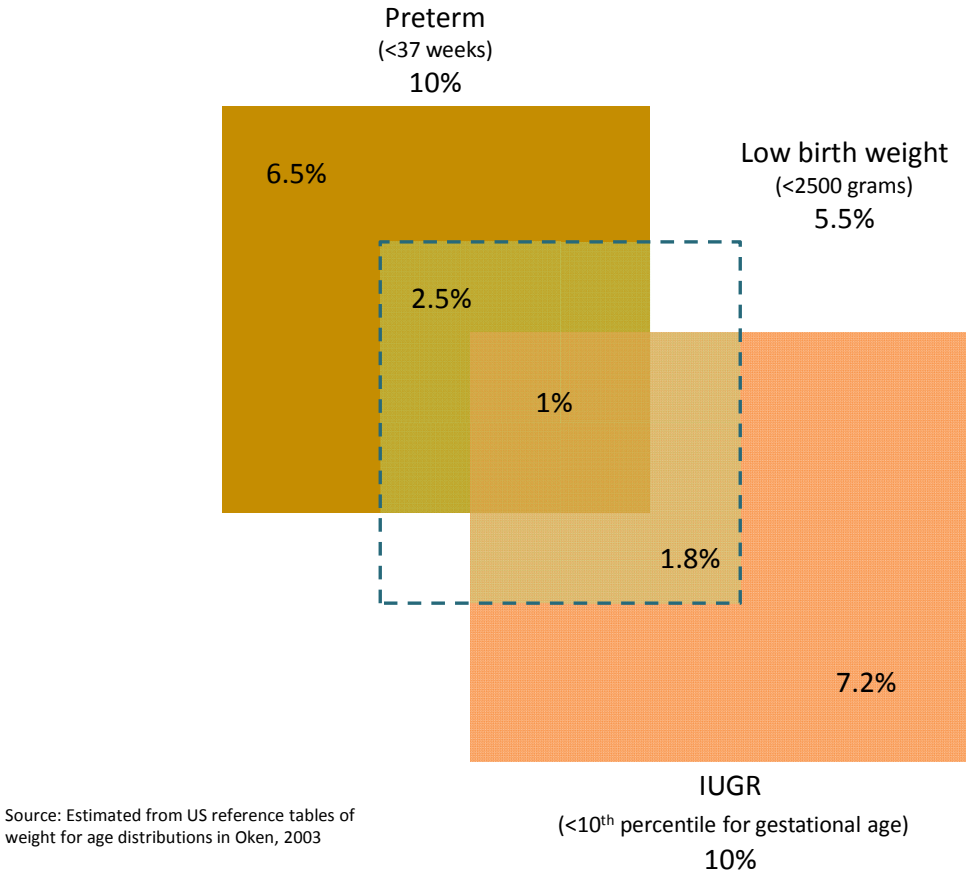
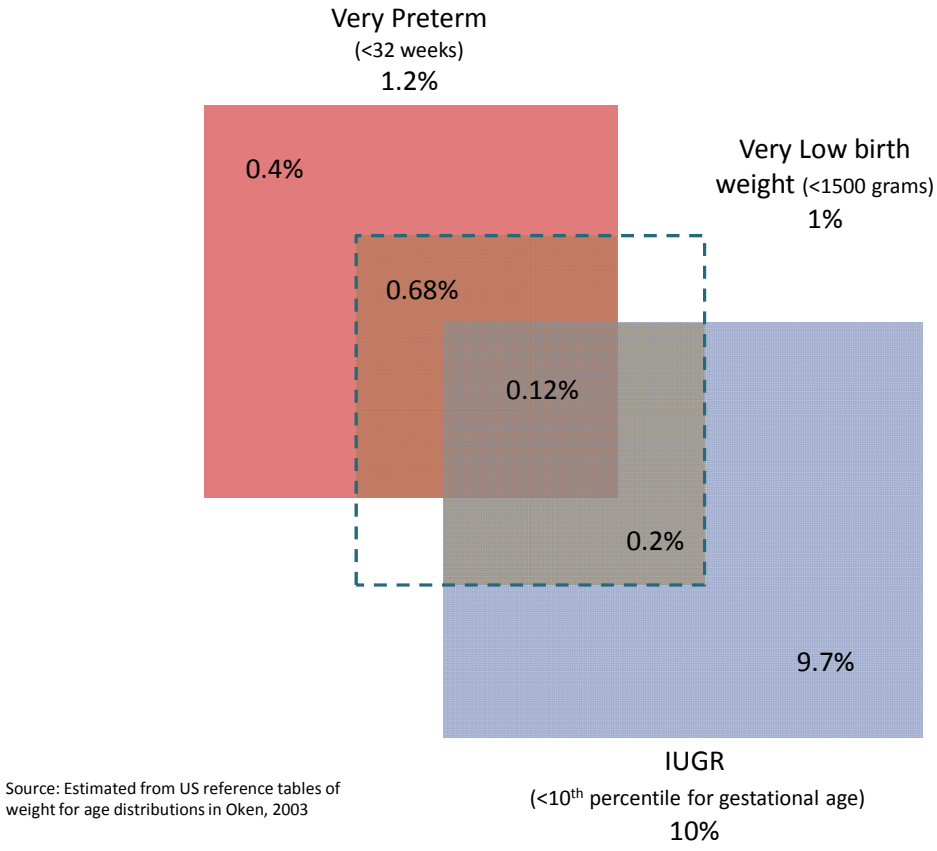


Figure 1-6. Overlapping pregnancy outcomes: very preterm, very low birthweight and IUGR (Adapted from weight for age reference tables in Oken, 2003)(147)

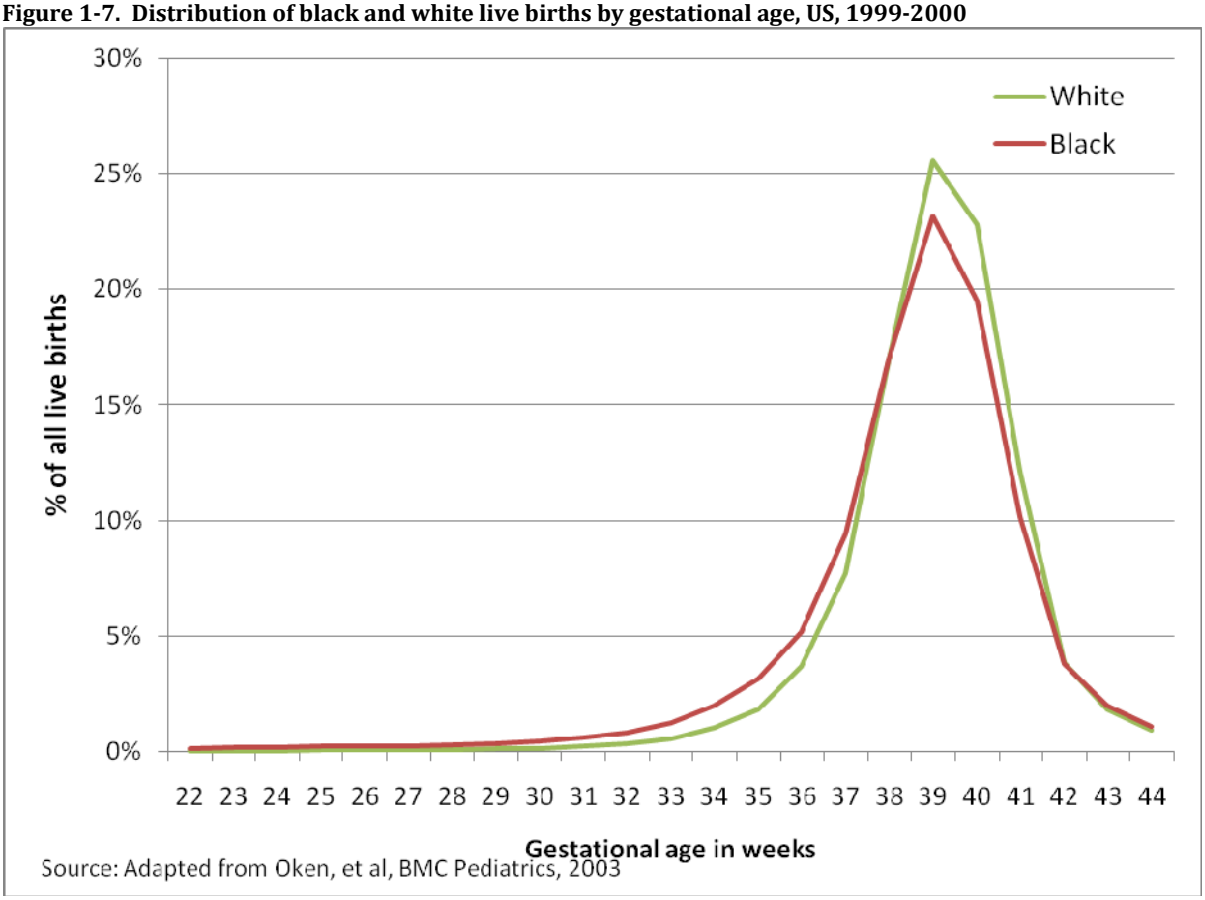


Categorization by gestational length

Gestational age at birth occurs in a left-skewed distribution. As Figure 1-7 demonstrates there can be differences in this distribution by race as well. For clinical and epidemiologic purposes, the continuous metric of gestational age is typically categorized. There are many cutpoints used. Preterm birth is defined by the World Health Organization as birth prior to 259 days gestation or <37 weeks.(148) Because mortality and morbidity increase with decreasing gestational age, a more stringent cutpoint may be used to identify infants at

particularly high risk. This dissertation will imply a birth at less than 32 weeks whenever the term *very preterm* (VPT) birth is used. Other cutpoints such as 30 or 28 weeks create groups of infants at higher and higher risk, but also groups which are smaller and smaller in size. The challenge is in balancing identification of a group relatively homogenous in terms of risk and etiology, yet also representative of the maximal proportion of population risk.

Figure 1-7. Distribution of black and white live births by gestational age, US, 1999-2000



While the commonly used LBW metric has the previously mentioned problems (possible non-causal association with mortality and mixing of preterm with term growth retarded babies) the more stringent weight cutpoint of 1500 grams (subsequently termed *very*

low birthweight or VLBW) may be a more accurate proxy for truly at-risk babies, and has strong correlation with very preterm birth. For this reason, VLBW may be considered a reasonable substitute for very preterm birth in population research.

Measurement of gestational age

The actual measurement of duration of gestation is far from straightforward, and the challenges inherent in directly estimating gestational age at birth have been used as arguments to maintain birthweight as the relevant metric for public health surveillance.(149) The traditional way to estimate gestational age is to count from the first day of the last menstrual period (LMP). The estimated due date is calculated by adding 270 days to the LMP. This assumes that conception occurred 14 days after the reported LMP. This could be incorrect for a wide variety of reasons including variation in menstrual cycle length around the average 28-day cycle (150, 151), or non-menstrual bleeding (such as implantation bleeding or other first trimester bleeding) in early pregnancy.(152, 153, 154) Specifically, a large proportion of apparent post-term births (births after 42 weeks gestation) are likely due to longer than average menstrual length, rather than truly extended gestation.(155)

In addition to variations in estimated gestational duration due to non-menstrual bleeding and long cycles, there is also potential for faulty recall of the date itself. There is evidence for digit preference in LMP reporting with the 15th of the month the most common, and multiples of 5 more common than expected by chance alone.(156, 157, 158) Also, the quality of recall of the date of LMP declines with time from conception, so that women entering prenatal care late may have less accurate estimates of due date, and gestational duration.(159) Several studies have identified higher prevalence of missing and incomplete gestational age

data for minority and poor women, as well as women with lower education, all of whom represent groups at increased risk for preterm birth.(160, 161)

Several approaches have been taken to improve quality of gestational age determination both for clinical care, and for population research. Fetal ultrasound (U/S) before 20 weeks gestation is generally thought to provide a consistent and reliable estimate of gestational duration, because fetal growth in this early period is less variable.(145, 162) While there is some evidence that growth retardation biases early U/S estimates of gestational age, the error is likely on the order of days, rather than weeks, as may be seen with LMP-derived errors.(163) In general, early U/S estimates shorter gestational duration than LMP, most likely due to the tendency for LMP errors to result from longer rather than shorter than expected menstrual cycles.(164) While U/S may be more accurate, it is only so if done early in pregnancy, and thus does not reduce the error in estimating gestational age for women entering prenatal care later in pregnancy.

Other forms of 'clinical estimates' of gestational age are used to enhance LMP-derived calculations. Obstetric findings such as uterine fundal height and timing of first detected fetal heart tones can be used, although they are subject to as much or more error as LMP.(165) Finally, physical examinations of the newborn for hallmarks of maturity have been used, but are prone to variation by examiner, and systematically differ by race and ethnicity in ways that are inconsistent with other estimates of gestational age.(166, 167) The 1989 revision of the US standard certificate of birth allowed for entry of a clinical estimate of gestational duration, but the wording was unclear whether 'clinical estimate' included U/S, obstetric markers, or newborn exam. The 2003 revision to the standard certificate modified the language to 'obstetric estimate' to more clearly exclude newborn exams, but NCHS chose not to include an

item specifically specifying whether a pre-20 week U/S was conducted.(168) A recent analysis of 2002 birth records suggested there is significant disagreement between the LMP-based gestational age and the clinical estimate-based age, particularly for preterm births.(169)

Numerous algorithms have been developed and tested to allow population researchers to clean large natality datasets for minimal bias with respect to gestational duration. Approaches vary from exclusion criteria for gestational ages which are incompatible with a given birthweight, to imputations or classifications based on degree of agreement between LMP date, clinical estimate date and/or birthweight.(163, 170, 171, 172, 173) A combination of cleaning implausible age-weight combinations along with assessing the concordance of LMP and clinically estimated dates appears to maximize data quality, but the fact remains that many high-risk records also have high missing data rates and greatest number of data inconsistencies, making final determinations challenging.(159, 174)

TEMPORAL TRENDS IN PRETERM BIRTH

Tracking trends in preterm birth over time is challenging in large part because of the measurement and misclassification issues previously discussed. Changes by registrars of vital records to improve data quality make population rates hard to compare over many years. Systems for estimating gestational age, or even of defining a live birth versus a fetal death, vary in different countries as well, making international comparisons difficult. That being said, comparisons of annual rates of prematurity can be made for recent years, and extended by use of proxies such as very low birthweight. Similarly, recent cross-sectional international comparisons can be telling.

In the US in 2006, 12.8% of all live births were preterm (<37 weeks), and 2.04% were very preterm (<32 weeks), representing a 20.6% increase for PT, and 6% increase for VPT since

1990.(175) It is notable that while there has been significant interest in the public health community regarding the rising rates of overall preterm births, the change is not consistent between whites and blacks, nor is it happening equally for all gestational ages (see Figure 1-8 and Figure 1-9). While the early years of the upward trend in preterm births seems to be driven primarily by white women's rising risk, black women have seen similar rates of increase in the past 5 years. Both categories of exceptionally high risk infants (VLBW and VPT) suggest more modest, although similar changes over time.

In addition to trends over time in the occurrence of preterm birth, there have also been changes in the magnitude of the racial disparity of preterm birth, and the consequent mortality (see Figure 1-10). While important and persistent disparities exist for preterm birth in general, the consistently higher magnitude disparity for very preterm birth carries with it significantly higher risk. The racial disparity in neonatal mortality (mortality in the first 28 days of life) and VLBW births increased from the 1970's to the 1990's. From the early 1990's until about 2003, the racial disparity in PT, VPT, and VLBW decreased slightly, although they appear to have increased in the last 2-3 years of available data, so that the RR for VPT in 2006 was 2.46 (95% CI 2.43-2.51) and for VLBW was 2.62 (95% CI 2.57-2.67).(175) Despite the general downward trend in the magnitude of the racial difference, the disparity in neonatal mortality has been nearly constant for the past 15 years.

Figure 1-8. Trends in preterm birth (<37 weeks) by race, US, 1990-2006

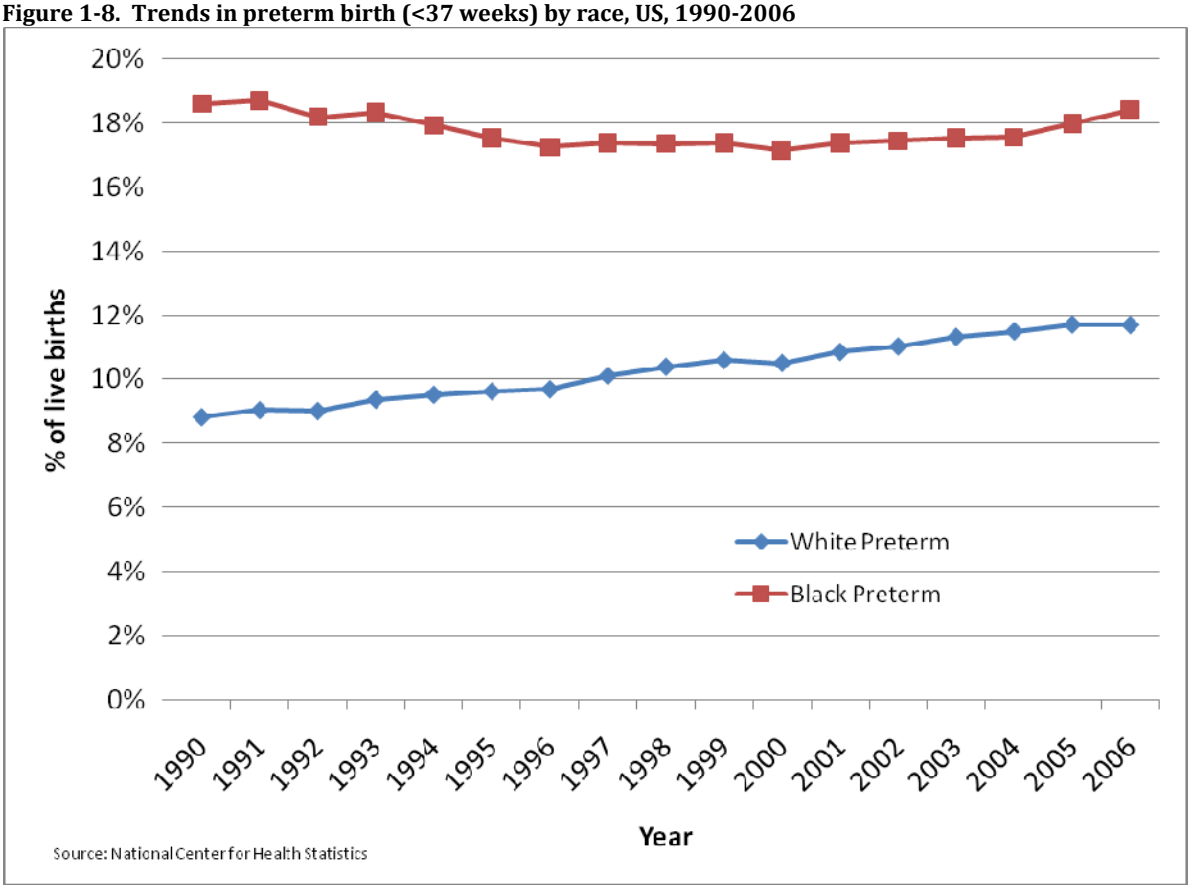


Figure 1-9. Trends in very preterm (<32 wks) and very low birthweight (<1500 gms) births by race, US, 1970-2006

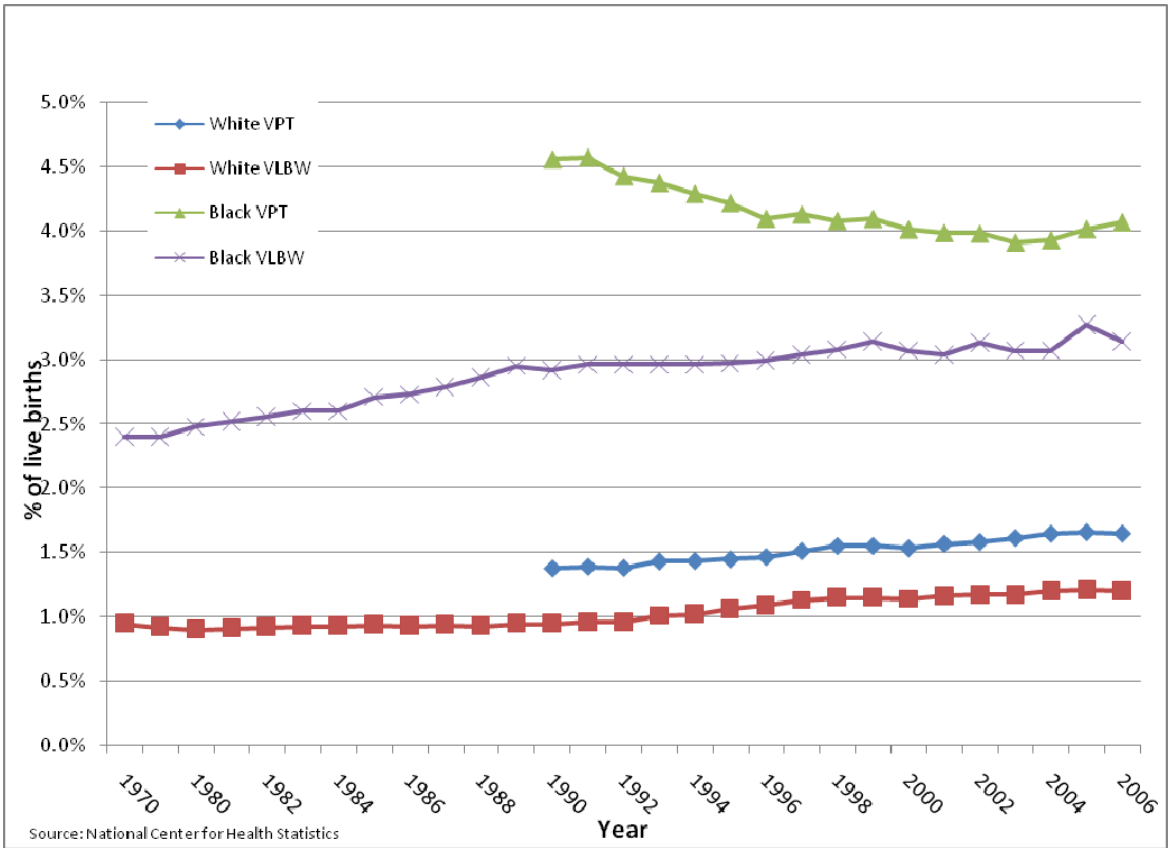
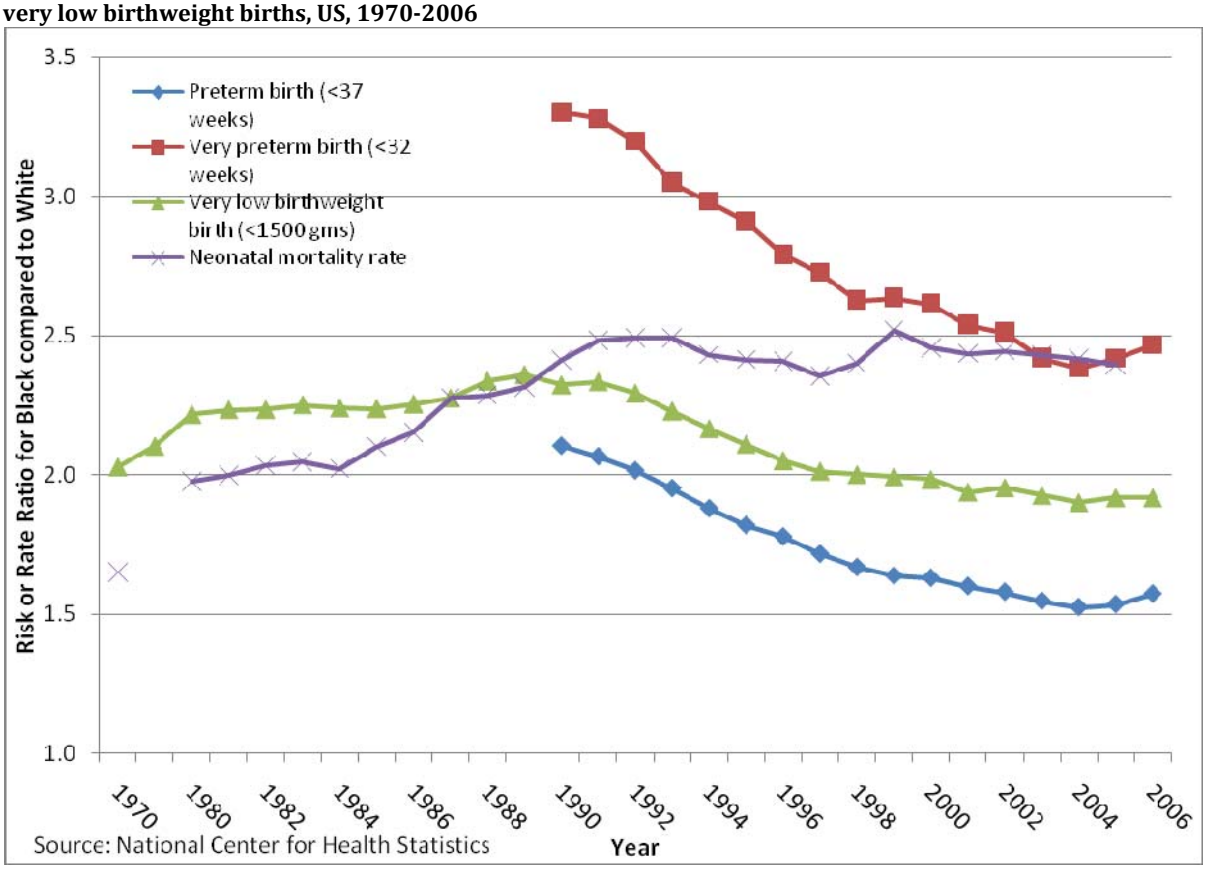


Figure 1-10. Trends in black-white racial disparities in neonatal mortality, and preterm, very preterm, and very low birthweight births, US, 1970-2006



Rates in the US may be significantly higher than many European countries to which we might otherwise be similar. Figure 1-11 demonstrates that the US rate for PT and VPT birth is significantly higher than every other country measured, and that even when rates are compared separately for US whites, the rate is among the highest. Figure 1-12 presents data from a WHO collaborative study comparing the US to several developed and developing nations. Several factors complicate comparisons of the rates of preterm birth between the US and countries with similar levels of economic development. Many countries, including France and the UK, do not routinely collect gestational age data on birth certificates, and must estimate rates from

population samples.(176) Local variations in approach to extremely premature births can make dramatic differences in calculated rates. For example, some countries (or regions) may take an aggressive approach to very premature infants, while in other countries heroic efforts for extremely premature infants are considered cruel to the parents, and therefore attending medical staff may call a live birth which quickly dies a stillborn, or vice versa a stillborn a live birth which could not be resuscitated. Because of variations in the gestational age threshold for registration of a stillbirth, ranging from 20 weeks (in the US) to 22 (most European countries) to 28 weeks (Denmark), this decision might simply misclassify a birth as stillborn versus live born, or if early enough may make the birth completely unregistered.(177) And finally, there is wide variation across Europe in the prevalence of pregnancy termination following prenatal identification of a fetal anomaly.(178) Termination of these high risk pregnancies could alter the subsequent stillbirth and preterm live birth rates. The World Health Organization and a European consortium of perinatal researchers have recently developed standards for definitions and data elements to collect at the national level for surveillance of perinatal health.(179) While this will help make comparable numbers, continuing regional differences in philosophy for categorizing extremely premature infants will make comparisons difficult.

Figure 1-11. International comparisons of preterm and very preterm rates (Adapted from Buitendijk, 2003)(176)

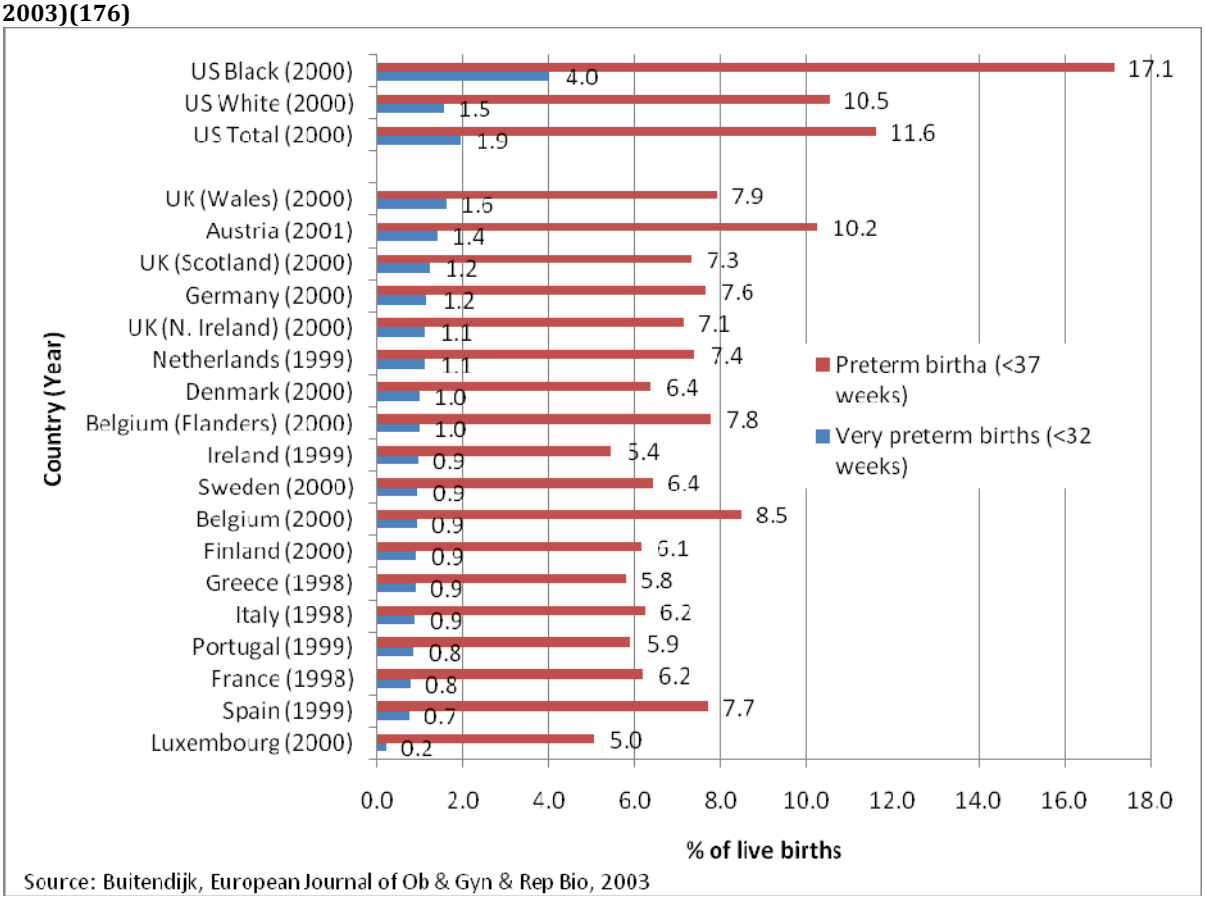
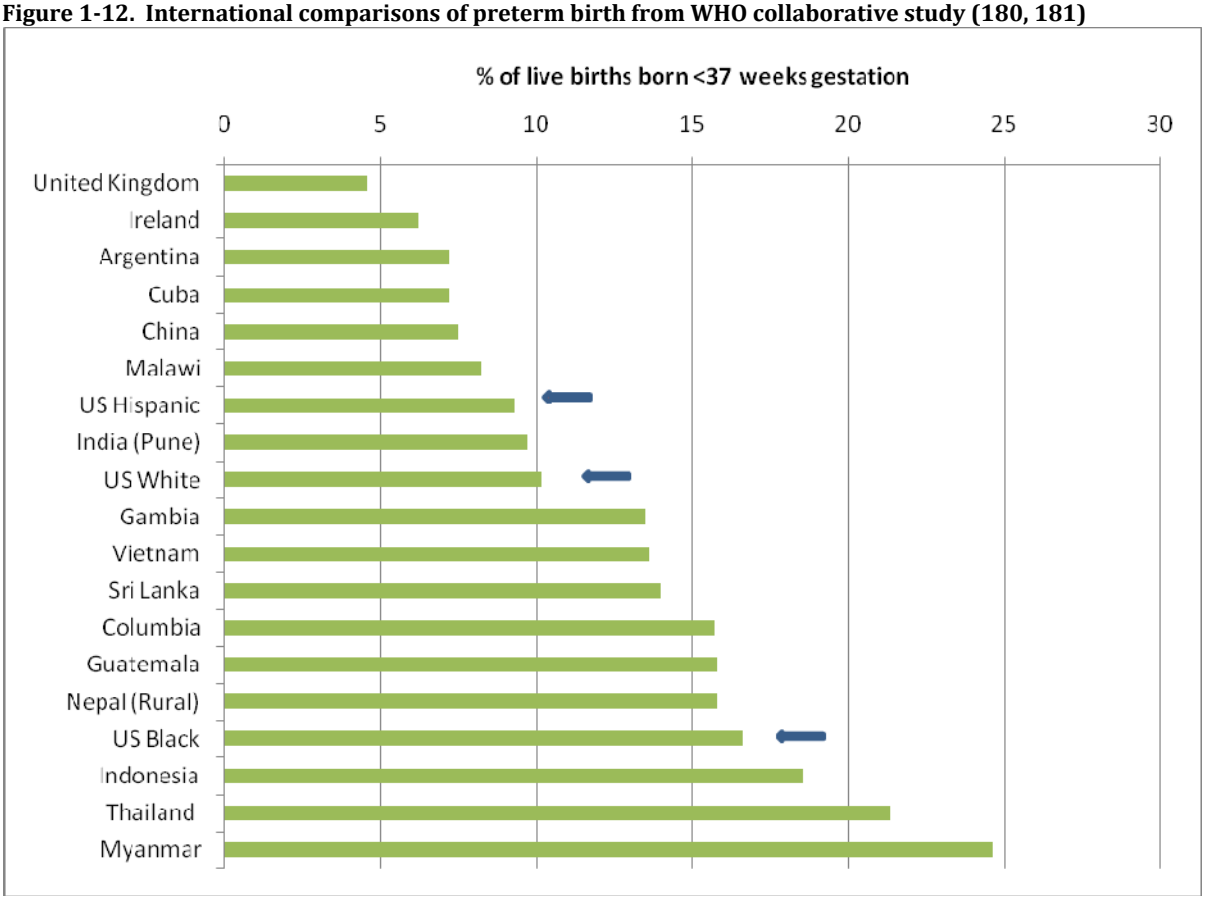


Figure 1-12. International comparisons of preterm birth from WHO collaborative study (180, 181)



SPATIAL DISTRIBUTION OF VERY PRETERM BIRTH

In addition to variations in preterm birth risk through time and across racial groups, there is notable variation geographically. Differences in infant mortality and low birthweight have been noted across neonatal intensive care regions(182), US Census regions(183), large metropolitan areas(184, 185), and across perinatal regions within the state of California.(186) In general, risk for mortality, low birthweight, and preterm are higher in the Southeastern region of the US, and lower in the West and Northeast. It is commonly reported that these variations are a function of population racial and socioeconomic composition across regions.(29) However in a descriptive project carried out in preparation for this dissertation, I

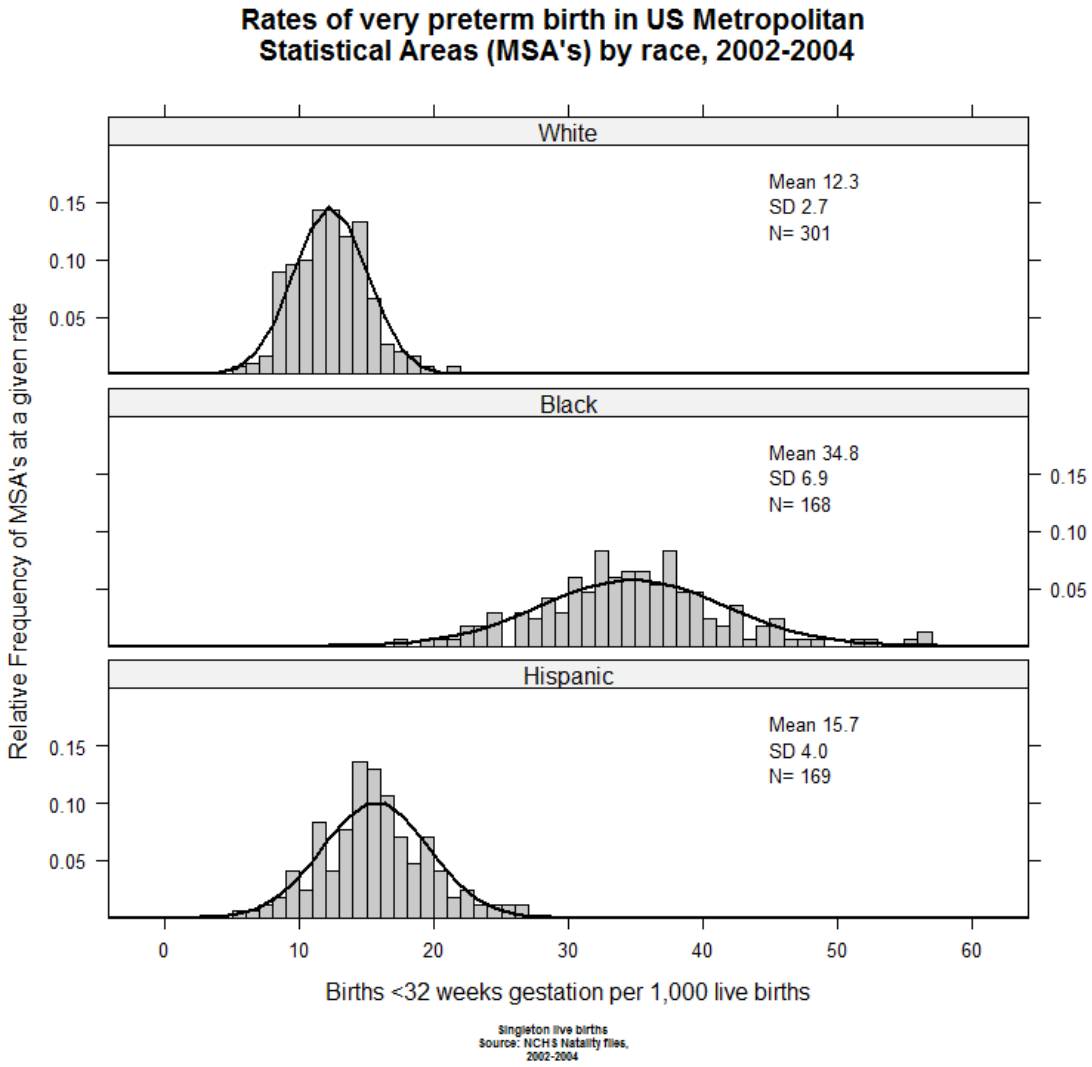
looked at the variations in rates of very preterm birth across cities, defined as Metropolitan Statistical Areas (MSA's). The manuscript describing this project is available as Appendix 1. The findings are summarized here.

Briefly, rates of very preterm birth were calculated using 2002-2004 birth files for each MSA-race group (analysis focused solely on non-Hispanic white, non-Hispanic black, and Hispanic). Then the distribution of MSA rates was evaluated for each race/ethnic group. The distribution of rates across MSAs for each race/ethnic group is depicted in the histogram in Figure 1-13. The x-axis is the rate of very preterm birth per 1,000 live births, and the y-axis is the relative frequency of MSAs; in other words it is the proportion of all MSAs at a given rate. For white women, the mean MSA rate of VPT birth was 12.3/1,000, with a standard deviation of 2.7; for black women the mean rate was 34.8/1,000 (SD=6.9), and for Hispanic women, the mean MSA rate was 15.7/1,000 (SD=4).

Three observations are apparent from Figure 1-13. First, the average MSA rate for black women is nearly three times that of white women. This is the ecologic corollary of the individual racial disparity in very preterm birth. Nonetheless it is quite striking, particularly in light of the second observation, which is that there is almost no overlap in the white and black distribution. The rate of VPT birth in the very best city for black women is virtually identical to the rate in the very worst city for white women. The final observation is that the variation or spread of the empiric distribution of rates by MSA is significantly greater for black women than for white women, with the SD for black women approximately 2.5 times greater than for white women ($p<.0001$). This increased spread remains after accounting for sample sizes, differences in distribution of key predictors of very preterm, and measurement error of the outcome. In

other words it appears that among black women the rate of VPT birth is more acutely sensitive to the city of residence than it is for white women.

Figure 1-13. Rates of very preterm birth in metropolitan statistical areas (MSA's) by race/ethnicity, 2002-4 (Kramer & Hogue, 2008)



The pattern seen here persisted despite control for education, parity, age, smoking, and characteristics of the MSA, such as city size, region of the country, proportion black, or proportion of black population living below the poverty line. Because of the possibility for

regional variation in the quality of gestational age reporting, the analysis was repeated using VLBW as the outcome, and again, the pattern remained (see Appendix I, Table 1).

CONSEQUENCES OF PREMATURITY: MORTALITY, MORBIDITY, AND ECONOMIC COST

Preterm birth is not a final health endpoint in and of itself. Rather it is a meaningful intermediate proxy for subsequent mortality and morbidity risk. The social, human, and economic impacts of this morbidity and mortality define preterm birth as a critical issue in public health.

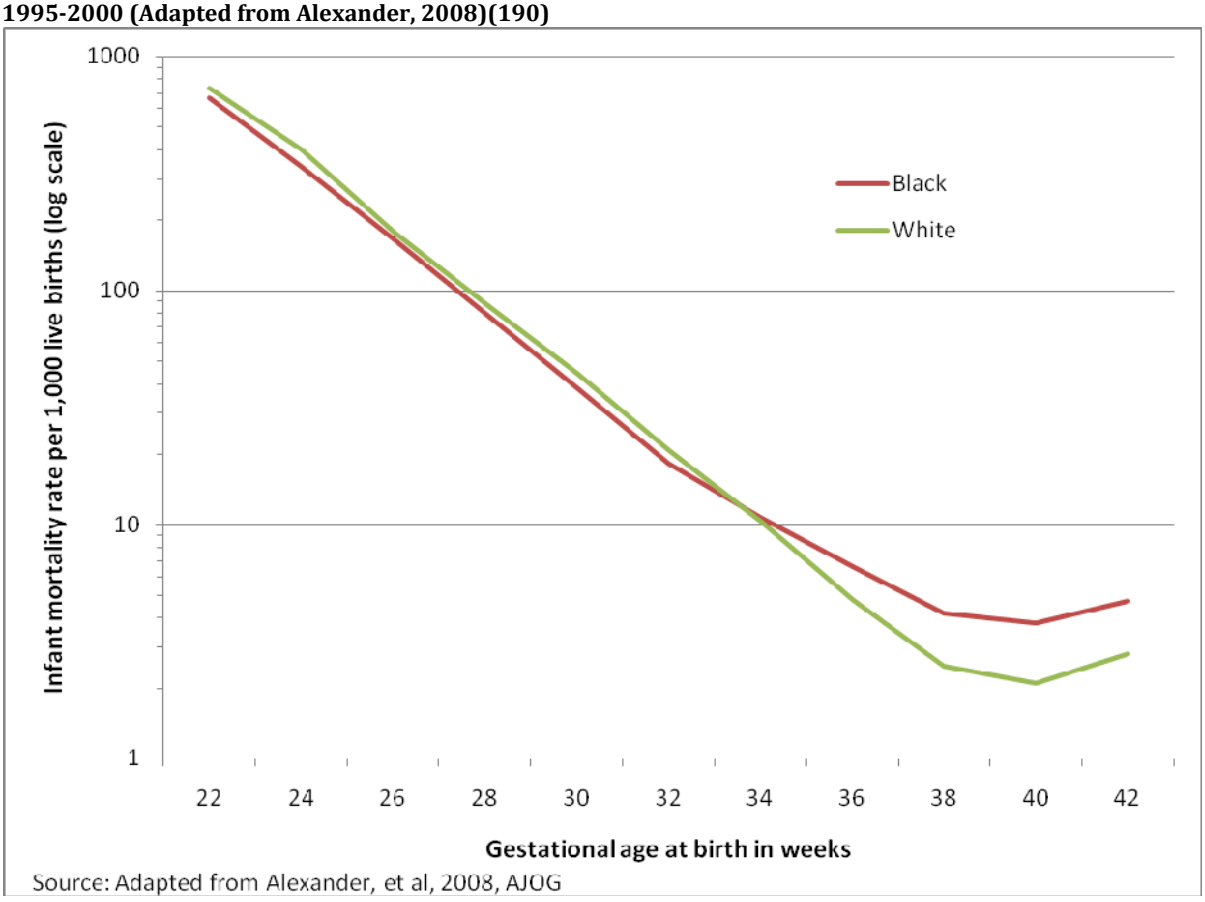
Mortality

Infant mortality is defined as death within the first year of life, and thus the infant mortality rate is the number of deaths over the number of live births. It is sub-categorized into neonatal mortality (alternately categorized as death in the first 7 days or 28 days of life), and post-neonatal mortality (28-365 days). Because it is unlikely relevant biologically or socially whether a death of an early gestation fetus occurs just prior or just after birth, some researchers use the perinatal mortality rate (number of late fetal deaths plus infant deaths within 7 days of birth divided by late fetal deaths plus all live births) as the most meaningful measure of prematurity associated mortality.

Greater than one third (34.3-36.5%) of all infant mortality in the US is attributable to complications of prematurity.(187, 188) As such, prematurity is the leading cause of infant mortality. The mortality rate is inversely associated with gestational age (Figure 1-14). The size of the sub-37 week population is much greater than the sub-32 week population (see Figure 1-7 above), and thus it is sometimes argued that the greatest public health impact is measured with the classification of prematurity before 37 weeks. However, of the infant deaths

attributable to prematurity, 95% occur among the small group of births who are both very preterm (<32 weeks) and very low birthweight (<1500 grams).(187) They also occur soon after birth, with 68% of the infant deaths attributable to prematurity occurring in the first 24 hours of life, and only 7% occurring after the first 28 days of life. The limit of viability is sometimes stated as the point at which mortality exceeds 50%. In the US, this currently occurs below 24 weeks or birthweights less than 500 grams.(189)

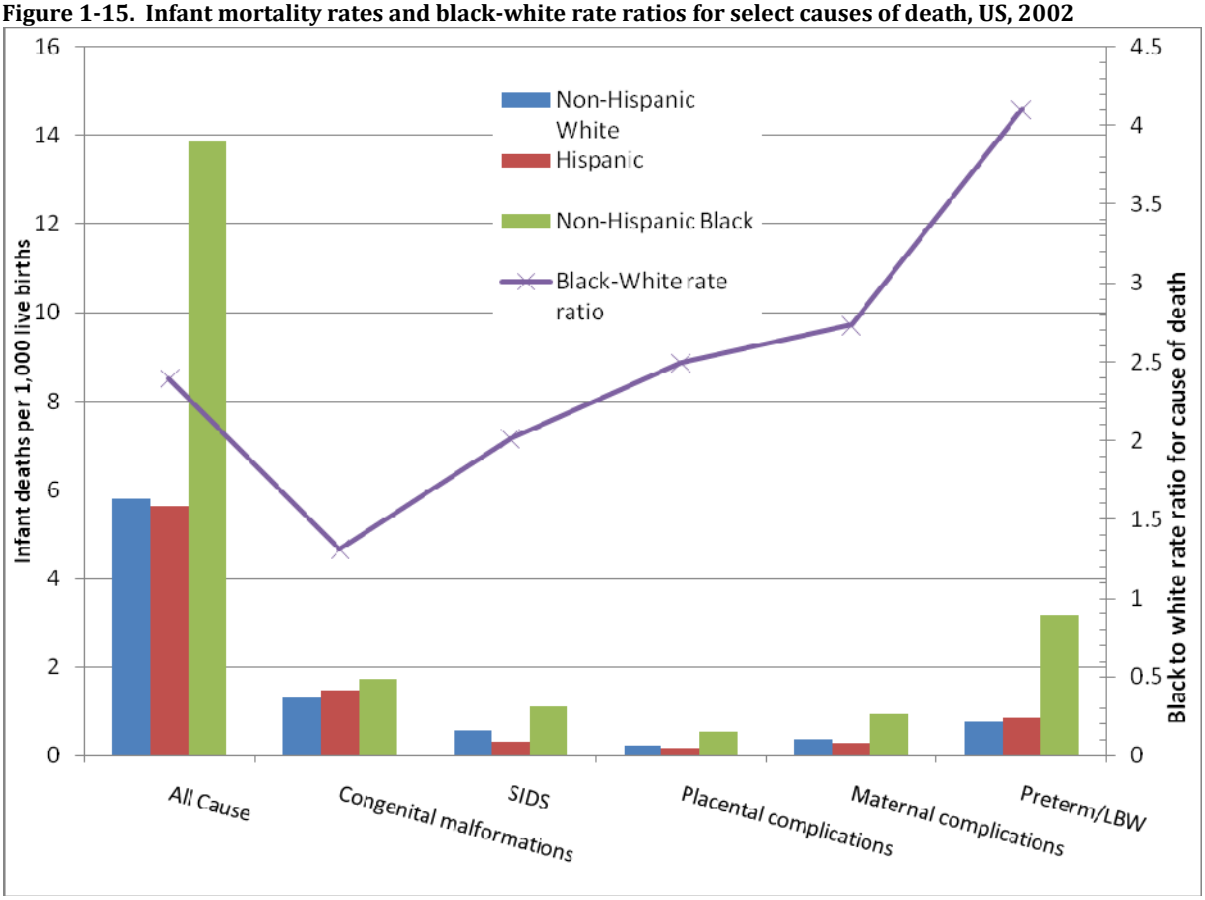
Figure 1-14. Infant mortality rates by gestational age at birth for black and white births to US born women, 1995-2000 (Adapted from Alexander, 2008)(190)



In 2005, black infants died at 2.4 times the rate of white infants.(191) This excess risk is due in large part to the excess risk of very preterm birth among black women. In 2004, nearly half (46.3%) of all black infant deaths was attributable to complications of prematurity, while

for whites, only 32.1% resulted from complications of shortened gestation.(188) The rate of preterm-related infant mortality is actually 3.5 to 4 times greater for black births as for white births, whereas the racial disparity for other common causes of infant mortality is closer to 2-fold (Figure 1-15). While infant mortality has been generally trending down throughout the 20th century, racial disparities in mortality may be increasing due to both the increasing disparity in very preterm birth in the past 3 years, and the relative lack of improvement in mortality for blacks as compared with whites over the past decade.(190)

Figure 1-15. Infant mortality rates and black-white rate ratios for select causes of death, US, 2002



Morbidity

Understanding preterm birth is important because it is the primary cause of infant mortality, the largest contributor to the racial disparity in infant mortality, as well as a significant contributor to the burden of morbidity resulting in social, health, and economic costs for years to decades after the birth itself. While most births after 32 weeks' gestation experience average risks for infectious and neurodevelopmental injuries, very preterm births are at significantly elevated risk for a range of complications including sepsis, brain hemorrhage, cerebral palsy, delays in cognitive, behavioral, and psychological development, and impairment in vision and hearing.(192) The prevalence among three-year old survivors of four common disabilities in the Metro Atlanta Developmental Disabilities Surveillance Program (MADDSP) for the 1981-1991 birth cohort are displayed in Table 1-3. Most research has focused on neurologic and cognitive developmental issues with preterm infants.

Cerebral palsy is the most common motor disability in children, affecting two infants per 1,000 live births.(193) In a population based cohort study in Sweden, the birth prevalence of cerebral palsy was 76.6/1,000 live births before 28 weeks gestation, 40.4/1,000 for 28-31 weeks, 6.7/1,000 for 32-36 weeks, and 1.1/1,000 for 37+ weeks.(194) The same study estimated that 25% of all cerebral palsy cases were a result of preterm birth. Similar findings were reported from studies in the UK and France.(195, 196)

Even for very preterm births that do not have cerebral palsy, long-lasting cognitive delays may occur. Marret, et al report that 35% of five year olds who were born at 30 weeks gestation had IQs in the range generally requiring special education.(195) Bhutta, et al conducted a meta-analysis of 16 studies of cognitive outcomes and preterm births. Preterm birth was associated with decreased cognitive scores in infancy and childhood, with a strong

positive association between gestational age at birth and scores.(197) Preterm birth was also associated with attention deficit hyperactivity disorder (ADHD) in 81% of the studies analyzed by Bhutta.

Table 1-3. Prevalence of select developmental disabilities by gestational age among 3 year olds for MADDSP birth cohort 1981-1991

	Cerebral Palsy		Mental Retardation		Hearing Loss		Vision Impairment	
Gestational age	Prev.*	95% CI	Prev.*	95% CI	Prev.*	95% CI	Prev.*	95% CI
20-23 wk	49.9	31.1-75.2	75.0	52.6-105.6	14.3	5.2-30.8	11.9	3.9-27.5
24-28 wk	49.9	41.5-59.5	60.9	51.6-71.3	6.3	3.6-10.4	16.1	11.4-22.0
29-32 wk	16.7	13.7-20.2	27.2	23.3-31.6	1.9	1.0-3.3	2.9	1.7-4.5
33-36 wk	3.2	2.6-3.9	12.9	11.7-14.2	1.0	0.6-1.4	1.0	0.7-1.4
37+ wk	1.3	1.2-1.4	6.8	6.5-7.1	0.7	0.6-0.8	0.5	0.4-0.6
TOTAL	2.2	2.0-2.3	8.2	7.9-8.5	0.8	0.7-0.9	0.7	0.6-0.8

***Cases per 1,000 live births**

Metropolitan Atlanta Developmental Disability Surveillance Program (MADDSP) as cited in IOM, 2007(2)

The decreasing gestational threshold for viability has not been matched evenly by drops in morbidity, resulting in increasing prevalence of the morbidities of prematurity. Several investigators have attempted to measure quality of life indicators for very premature infants either with or without neurologic impairments. Learning disabilities, behavior disorders, and below average progress through school have been identified as common among very preterm births, and associated with aspects of lower life satisfaction.(198) However other studies have found no difference in subjective and objective measures of quality of life for children who were born preterm.(199)

Economic impact

Calculating the economic impact of any disease with long-lasting consequences is difficult. The most comprehensive estimate to date was completed for the Institute of Medicine's report, Preterm Birth: Causes, consequences, and prevention. Preterm birth results in 26.2 billion dollars per year in combined costs for medical care, early intervention, special education, and lost productivity (see Table 1-4).(2) This estimate only considers long term costs for four major developmental disabilities (cerebral palsy, mental retardation, and visual and hearing deficits). Actual costs would be likely higher were it feasible to consider the impact of other sequelae of preterm birth.

Table 1-4. Economic costs of preterm birth in the US in 2005 dollars(2)

	Cost per case	Aggregate Cost (million)
Medical Care		
Birth to age 5	$31,290	$15,887
6+ years (for 4 DDs*)	1,920	976
TOTAL	33,210	16,863
Early intervention costs	1,203	611
Special education costs (4 DDs*)	2,150	1,094
Lost productivity costs (4 DDs*)	11,214	5,694
Maternal delivery costs	3,812	1,935
TOTAL COSTS	**$51,589**	**$26,197**
***Four developmental disabilities (DDs): cerebral palsy, mental retardation, visual and hearing impairment**		
Source: IOM, 2007		

While there are increased costs at all gestational ages, the distribution is strongly skewed towards very preterm births, with births before 28 weeks gestation accounting for a

third or more of the total medical expenses. While high cost neonatal intensive care accounts for a large portion of the early medical costs, subsequent medical and social needs are substantial.

INDIVIDUAL LEVEL RISK FACTORS FOR PRETERM BIRTH IN BLACK AND WHITE WOMEN

Beyond the description of temporal and spatial population trends in preterm birth, epidemiologists have put considerable resources into identifying etiologic risk factors for the occurrence of preterm birth. While numerous behaviors and exposures have been associated with pregnancy outcomes, the review here is limited to well-established risk factors (or factors which are notable for their lack of association) which are also likely associated with race. These can roughly be divided into demographic characteristics, medical risk factors, behavioral risk factors, and psychosocial exposures.

Demographic risk factors

Race

A primary goal of this dissertation is to better understand causes of racial differences in very preterm birth incidence. For this reason, race is addressed in nearly every section. This section will be limited to the variation in observed risk of preterm birth when parental race is discordant.

Two recent studies produced similar findings with slightly different datasets. Getahun, et al, used the 1995-2001 national vital statistics datasets to estimate the relative risk of very preterm birth among groups with different permutations of maternal and paternal race. They reported that birth before 32 weeks was least common in white mother-white father couples, followed by white mother-black father (RR 1.34, 95% CI 1.31-1.38), black mothers-white fathers (RR 2.02, 95% CI 1.94-2.10), and black mothers-black fathers (RR 2.70, 95% CI 2.68-

2.73), controlling for age, parity, maternal education, smoking , marital status, and prenatal care.(200) Palomar, et al, reported the same pattern using a population based Missouri database that also allowed control for socioeconomic status as indicated by Medicaid, WIC, and food stamp status.(201) Although the authors of this second paper attribute the finding to paternal genetic contribution to risk, there are notable differences in measured socioeconomic characteristics across these four groups, and possible differences in unmeasured characteristics as well.

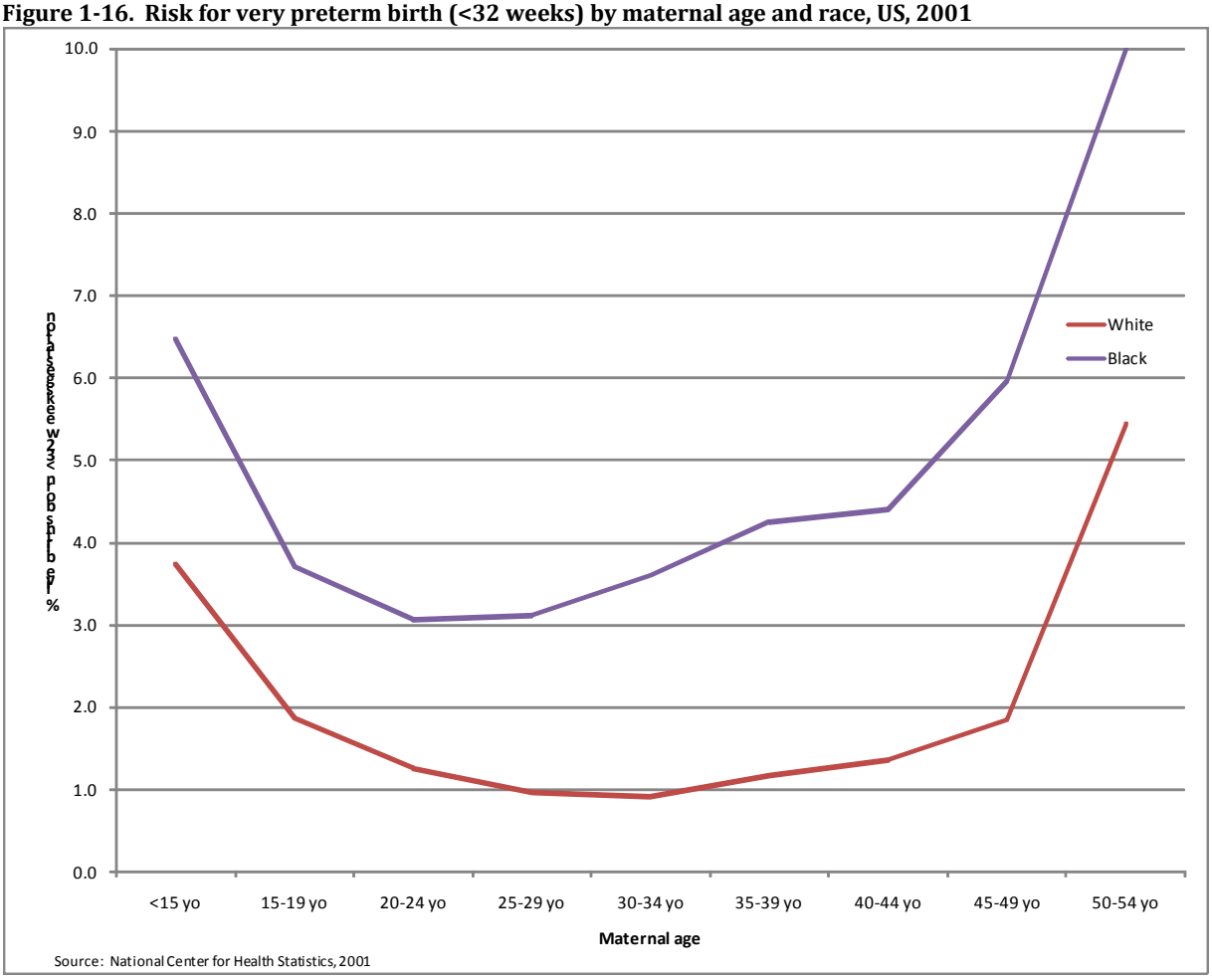
Age

Preterm birth rates—as well as most reproductive outcomes—vary by maternal age. The U-shaped age trend holds for preterm birth, with lowest risk experienced for mothers in their twenties to early thirties, and increasing risk for either younger or older mothers (Figure 1-16). The steepness of the U-shape has been noted to vary by race, with greater relative increased risk for black teens and older women. The age of lowest risk also varies by race, with a younger low-risk point for black women compared with white women. Geronimus has hypothesized that this left-shift in the age-preterm risk association could result from 'weathering' or accumulated deleterious exposures which prematurely age black women.(202, 203)

The increased risk for teens is likely primarily a result of lower socioeconomic status for teen mothers. Several studies have demonstrated that the excess teen risk for low birthweight and preterm birth is fully eliminated by control for poverty.(204, 205) The excess risk for older maternal age may be a combination of social factors and biologic changes of aging.(206) In an age-period-cohort analysis of preterm birth, Ananth, et al, identify consistent age effects, and suggest that the effect may be at least partly due to optimal reproductive capabilities at certain

ages.(207) There is also an interaction between parity and age, such that multiparous teen mothers have high risk, but primiparous older mothers have higher risk.(208)

Figure 1-16. Risk for very preterm birth (<32 weeks) by maternal age and race, US, 2001



Marital Status

Unmarried women in most industrialized nations have higher risk (25% to 75% increase) than married women for very preterm and preterm birth, as well as IUGR and infant mortality.(209, 210, 211, 212) In most studies this increased risk persists after control for socioeconomic status, age, and obstetric and medical risk factors. Cohabitation and common law marriage associate with risk that is intermediate between married and single mothers.(210,

211) Although marriage is protective at all ages and for both black and white women, the magnitude of the effect varies across these strata. Above age 20, white women experience a 37-63% risk reduction for married compared to unmarried, while black women experience a 22%-41% protection against risk if married.(2) Marital status likely proxies for a range of other risk factors including social support, health behaviors, and economic status.(213, 214) Differences in marital status could result in differential preterm birth risk directly by impacting exposure to sexually transmitted disease or maternal stress, anxiety or depression, and indirectly by its association with other risk factors or exposures such as smoking, drug use, deleterious work-place conditions, lower income, and education.

Socioeconomic status: Education & Income

Socioeconomic status (SES) is a multi-dimensional construct that is commonly proxied in epidemiologic and clinical research using single crude markers such as education or income. These categories do not necessarily capture the entirety of SES. For example, income varies by race within strata of education, and net worth (wealth) varies by race within strata of income, so that the health-relevant component of SES can be hard to summarize with a single variable.(215, 216, 217) However there is some evidence that maternal education is the most consistent proxy for reproductive outcomes.(218) With this in mind, investigators have explored a wide range of markers of SES in their association with preterm birth and have confirmed SES gradients in preterm risk across nations, races, and ages (see Table 1-5). The gradients between rich and poor nations are even larger than the variation within developed nations.(180, 219)

Table 1-5. Gradients in preterm birth risk by socioeconomic status (55, 210, 218, 220, 221, 222, 223, 224, 225, 226, 227, 228)

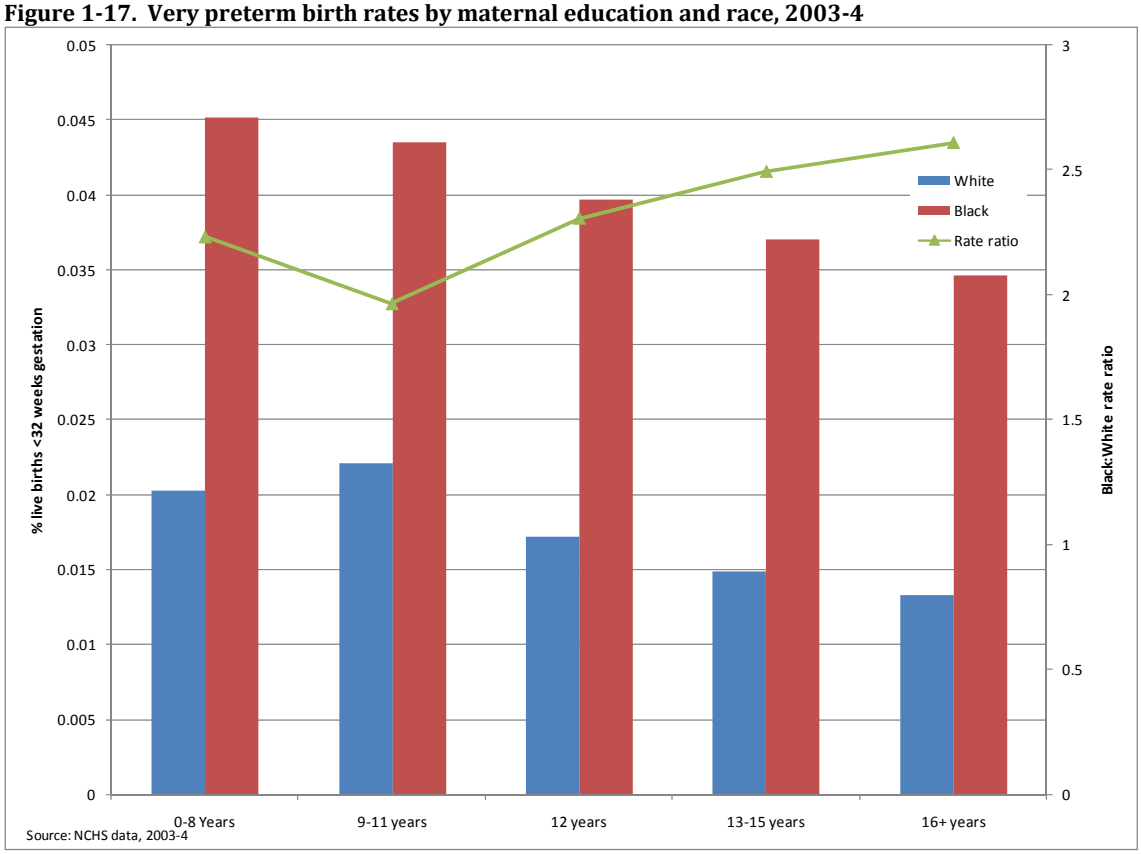
Population	Year	SES Measure	Category	PTB%
US Blacks	1988	Income (% poverty level)	<100%	12.2
			100-199%	9.4
			200%+	7.4
		Maternal education	<12 years	12.0
			12 years	12.0
			13-15 years	7.5
			16+ years	6.7
US Whites	1988	Income (% poverty level)	<100%	3.5
			100-199%	4.7
			200%+	3.4
		Maternal education	<12 years	4.5
			12 years	3.9
			13-15 years	3.8
			16+ years	2.8
Canada	1986	Income quintile	5	7.4
			4	6.6
			3	6.1
			2	5.6
			1	5.7
Czech Republic	1989-91	Maternal education	Primary	8.4
			Vocational	4.4
			Secondary	3.6
			University	3.5
Finland	1985-86	Maternal education	<= 8years	6.2
			>8 years	4.3
Quebec	1993	Maternal education	<11 years	7.9
			11-12 years	7.1
			13-15 years	5.9
			16+ years	5.4
Scotland	1981-84	Maternal occupation	Manual	5.6
			Non-manual	4.6

Population	Year	SES Measure	Category	PTB%
Spain	1988	Paternal occupation	Manual	3.4
			Non-manual	2.7
Sweden	1989-91	Maternal education	Primary	6.4
			Vocational	5.5
			Secondary	4.9
			University	4.5
Norway	1980-98	Maternal education	Low	5.8
			Middle	4.9
			High	4.1
Nova Scotia	1988-1995	Family income	<$7,500	5.9
			$7,500-13,399	5.2
			$13,400-20,299	4.6
			$20,300-29,299	4.9
			$29,300+	
Scotland	2000-03	Area based deprivation index	Quintile 1	4.6
			Quintile 2	5.1
			Quintile 3	5.5
			Quintile 4	5.8
			Quintile 5	6.6
UK (Trent region)	1994-2003	Area based deprivation index	Decile 1	0.1
(Very preterm birth rates)			2	1.0
			3	1.0
			4	1.3
			5	1.3
			6	1.4
			7	1.4
			8	1.6
			9	1.6
			Decile 10	1.6
Adapted from Kramer, MS, 2000				

In many of the studies in Table 1-5, the presence of nationalized healthcare suggests that medical access alone is not the explanation for this social gradient in preterm birth risk.

In the US, the magnitude of effect on preterm and low birthweight for high versus low income is 2-3 fold, and for education ranges from 40-80%, and in general is more pronounced for very preterm and very low birthweight.(228, 229, 230, 231) The protective effect of higher SES may also vary by race. As demonstrated in Figure 1-17, the racial disparity in very preterm birth increases with increasing maternal education, largely because of a greater protective effect of education for white mothers than for black mothers. Similarly the racial gap may widen at the upper ends of other SES characteristics such as family income or residence in wealthier neighborhoods.(232, 233, 234)

Figure 1-17. Very preterm birth rates by maternal education and race, 2003-4



The challenge of understanding the potential confounding by SES of the association of race and preterm birth is significant. Attempts to 'remove' the effects of SES have included studies restricted to college graduates(4, 235), women living in wealthy neighborhoods(233), or women in the military (where other social exposures are assumed to be equal)(236), and all have demonstrated lingering racial differences in risk. Socioeconomic status may even exert an effect over generations. A study of three generations of black women found that increased risk for low birth weight and preterm birth persisted after two generations of high SES mothers, but was lessened in the third generation.(237) Although maternal education has been demonstrated to be a useful proxy for SES in understanding the preterm risk gradient, there are still large racial differences in income and wealth distributions among college graduates, so that residual confounding by another characteristic of SES cannot be ruled out.(216, 238) Kaufman, et al explored the role of residual confounding by SES in observed racial differences in health. They consider four sources of residual confounding or misclassification: categorization of SES variables, measurement error in SES indicators, use of aggregated SES status measures, and incommensurate SES indicators (indicators which are surrogates for different aspects of social position in blacks and whites). Using simulations of varying scenarios, they report a bias towards estimated independent race effects (often interpreted as genetic or biologic in nature) after control for SES, even when SES is in fact the true independent risk factor.(239)

The mechanism by which SES impacts risk for preterm birth is not known. In general, risk factors such as smoking and cocaine use are more prevalent in poorer communities, but the relatively small impact these have on the overall prevalence of preterm birth limits their role in explaining the SES gradient.(220) Many investigators have hypothesized that maternal stress and genital tract infection could independently, or in interaction, explain SES (as well as racial)

disparities in preterm birth.(40, 45, 220) The literature on maternal stress and preterm birth will be reviewed in a subsequent section. Further literature on environmental characteristics of SES—such as neighborhood poverty, income inequality, and segregation—will be reviewed in Chapter 2.

Medical risk factors

Prenatal care

Prenatal care is notable for its lack of expected effect on preterm birth. Early observational research found a protective effect of adequate prenatal care on preterm and low birthweight risk.(240, 241) These results were likely a product of selection bias, as women at low risk for preterm birth are also high users of prenatal care. A randomized trial of aggressive prenatal education and care for high risk women found no difference in preterm birth risk between intervention and control group, nor any appreciable difference between study participants (who all received care) and population estimates for preterm birth.(242) Similarly a population based study limited to participants who all entered prenatal care in the first trimester reported rates and disparities of preterm birth and perinatal mortality similar to non-restricted populations.(243) The lack of effect of prenatal care is largely due to the absence of evidence-based perinatal interventions to modify risk of preterm birth.(220)

Prior obstetric history

The risk factor with the highest magnitude association with preterm birth is prior preterm birth in the same woman. As discussed in a previous section, a prior preterm birth confers a 2.5 fold increased risk for preterm in a subsequent pregnancy. (86) The risk of a subsequent preterm birth before 28 weeks was elevated 10-fold for women with *any* prior preterm birth and elevated 22-fold if the first preterm birth had occurred prior to 28 weeks.

Despite the large magnitude of the effect, the etiologic fraction is relatively small, and most women who deliver very preterm will have a subsequent term pregnancy, and most preterm births were not preceded by a previous preterm birth.(220, 244)

Shortened inter-pregnancy interval is also associated with increased preterm risk, and is more common in black women than white women. A pregnancy within 6 months of a previous pregnancy is associated with a 1.5-2 fold increased odds of preterm birth for both black and white women.(245, 246) However such short intervals are relatively rare for both black and white women, and thus do not account for a high proportion of the total preterm birth rate (247).

The effect of parity on preterm birth risk is difficult to disentangle from the already discussed role of maternal age. Parity and preterm birth appears to have a weak U-shaped association with relatively higher risk for primiparous and highly multiparous (4+ births), and lower risk for low multiparity.(248, 249) The magnitude of the effect is 20-30%, and unlikely a large contributor to overall very preterm birth risk, or the racial disparity.(213)

Hypertension and diabetes mellitus

Pre-existing maternal hypertension or diabetes mellitus (DM) can lead to placental insufficiency, and heightened risk for preeclampsia, and subsequent indicated preterm birth. The rising population prevalence at younger and younger ages of hypertension and type two diabetes may make these causes more important in pregnancy outcomes. Chronic and gestational diabetes increase risk for preterm birth 30-90%, and chronic hypertension can increase the risk approximately 2-fold.(250, 251, 252) While the magnitude of the effect is similar between races, the pre-conceptional prevalence of both diabetes and hypertension is higher among black women than white women.(252) However in one population based cohort

study, control for medical comorbidities did not appreciably diminish the racial disparity in very preterm birth.(253)

Pre-conceptional maternal body mass index

The association of pre-conceptional maternal weight and pregnancy outcome varies by clinical presentation. For spontaneous preterm birth (both spontaneous preterm labor and preterm premature rupture of membranes), the highest risk is among women who are underweight (commonly defined as a body mass index [BMI] below 20).(254, 255) The risk then drops with an apparent protective effect against preterm and very preterm birth for women with a BMI above 30.(143, 252, 254, 256) However, among medically indicated preterm birth obesity elevates risk, likely through its association with hypertension, diabetes, and preeclampsia.(143, 254) While it is not surprising that obesity increases risk for medically indicated preterm births, the explanation for the protective effect in spontaneous preterm birth is unknown, although it is possibly related to alterations in maternal inflammatory response associated with obesity.(2) Another possible explanation is that obese women have higher risk for stillbirth(257); perhaps high risk pregnancies in obese women are more likely to die in utero, leaving the relatively healthier pregnancies which would have delivered at term regardless.

Genital tract infections

The importance of ascending genital tract bacterial infection of the fetal membranes and preterm birth has been reviewed in the previous discussion of physiologic pathways to preterm birth. Important epidemiologic findings relating to infection, preterm birth, and racial disparities will be reiterated here.

Organisms such as *Ureaplasma urealytica, Mycoplasma hominis, Gardnerella vaginalis, Peptostreptococci,* and *Bacteroides spp* ascend from the vagina and cervix and have been associated with higher preterm birth incidence in both white and black women.(53) Bacterial vaginosis, a non-invasive overgrowth of these bacteria in the vagina, is also associated with preterm birth. While sexually transmitted infections with organisms such as Chlamydia and gonorrhea have been intermittently associated with preterm birth, these organisms are rarely isolated from fetal membranes or amniotic fluid.(61, 213, 258) The prevalence of ascending genital tract infection is inversely associated with gestational age at birth, so that over 90% of spontaneous preterm births before 24 weeks have an associated infectious cause, while infection may be responsible for as little as 15% of births between 34 and 36 weeks.(53)

Although infection appears to lead to preterm birth in all groups of women, the relatively higher prevalence of bacterial vaginosis in black and poor white women has been proposed as a partial explanation for the racial and SES disparities.(259) The magnitude of increased risk of preterm birth attributed to bacterial vaginosis is relatively modest (RR ~ 1.5-2.0), but the high prevalence in these populations could explain as much as 30% of the racial gap in preterm birth.(258) Unfortunately randomized trials of antimicrobial treatment for bacterial vaginosis have not demonstrated consistent protective effect. Risk factors for bacterial vaginosis include smoking, early age of first intercourse, receptive oral and anal sex, new or multiple sex partners, and douching more than once per week.(64)

Behavioral risk factors

Smoking

Although smoking is relatively strongly associated with infant mortality and intrauterine growth retardation (IUGR)(212), it is a relatively weak risk factor for preterm birth

with OR's from null to 1.5 for 10-20 cigarettes per day.(249, 253, 260, 261) The population attributable risk of smoking for preterm birth in a London population based study was 16% compared with approximately 30% attributable risk for low birth weight and IUGR.(262) This modest effect combined with generally lower prevalence of smoking in black compared to white women (263), make smoking an unlikely mediator of the racial disparity.

Drug & Alcohol Use

Cocaine is the only illicit drug that has been consistently found to have a positive association with preterm birth, conferring an approximately two-fold elevated risk.(213) However because of the relatively low prevalence of cocaine use in pregnancy, it is unlikely to have a large etiologic fraction, except perhaps in select inner city neighborhoods where use may be higher.(264, 265)

The evidence for impact of alcohol use during pregnancy on preterm birth risk is mixed. While some evidence suggests an elevated preterm birth risk associated with heavy use (7+drinks per week)(266) many studies find no such risk.(213) A vital records based study in Kansas City attempted to quantify the interactive effect of smoking, alcohol, and illicit drug use on preterm birth risk. While the authors report a significant interaction between tobacco and both alcohol and illicit drug use, the adjusted OR for users of all three substances was 1.6, which is not significantly different from most reported effects from smoking alone.(267) The adjustment for all three substances did not substantially reduce the racial difference in preterm birth.

Douching

Interest in vaginal douching as a risk factor for preterm birth stems from observed racial differences in prevalence of douching, and its association with bacterial vaginosis.

Approximately 27% of white women douche at least occasionally, while 59% of black women do so.(268) Douching has been associated with a 1.5-3 fold elevated prevalence of bacterial vaginosis in non-pregnant women.(269, 270) However a recent longitudinal study using a case-crossover design suggests that the use of douching may be in response to symptoms of bacterial vaginosis, with women three times more likely to douche in intervals where symptoms were present than symptom free intervals.(271) Perhaps because douching is relatively less common in pregnancy, or because it in fact is only a response to already existing bacterial vaginosis, no strong evidence has linked douching with increased preterm birth risk, except perhaps in a small group of very frequent users of douching.(272, 273)

Psychosocial risk factors

Numerous psychosocial characteristics have been associated with preterm birth over the years. In fact the notion that stressful experiences could precipitate labor dates at least to biblical times.

> ***1 Samuel 4:19*** *And his daughter-in-law, the wife of Phinehas, was with child and near the time when she would give birth; and when she had the news that the ark of God had been taken and that her father-in-law and her husband were dead, her pains came on her suddenly and she gave birth.(274)*

Interest in the role of psychosocial exposures and preterm birth has grown in recent years as evidence has begun to connect psychosocial experiences with measurable changes in endocrine and immune function, contributing to the biologic plausibility of a causal association with preterm birth. Many methodological challenges exist in this area. Competing definitions and measurement of stress, prospective study designs of adequately powered population based samples, and adequate attention to conceptualization of confounding, mediation, or interaction among psychosocial and other variables have been considered.(275) This review will briefly

summarize the literature for three broad categories of psychosocial exposure, and then consider three possible pathways by which psychosocial exposure could lead to preterm birth.

General anxiety and stress

Stress has been conceptualized in many ways, making interpretation of results and comparisons across studies difficult. Savitz' review of twenty studies of stress and preterm delivery suggested that anxiety states were not associated with preterm birth, while general stress was associated, with estimates of effect ranging from 1.2 to 1.8.(213) More recently, the 2007 Institute of Medicine Report review identified eleven new studies following the Savitz review, and suggested that anxiety might be more important in terms of preterm birth for white women, and depression and post-traumatic stress disorder might be more important for black women.(2)

Both general anxiety and pregnancy anxiety (anxiety about the pregnancy itself) have been evaluated for their association with preterm birth. Evidence for the role of general anxiety has been mixed. Goldenberg, et al reported that general anxiety was not associated with preterm birth in black or white low income women.(261) A French study found that anxiety was associated with preterm birth among women with a pre-pregnancy body mass index below 19, but not otherwise.(276) However evidence has been more consistently positive for pregnancy related anxiety. A population-based case-control study of births in Missouri found that women who 'almost always felt stress' during pregnancy had 60% higher odds for very low birth weight infant.(277) Two prospective studies measured pregnancy anxiety between 24 and 30 weeks and reported 50-100% increased risk for preterm birth among women with high anxiety scores.(278, 279) The background prevalence of anxiety in the larger of these two studies was 17%. Glynn, et al, reported that prospectively measured anxiety at 18-20 weeks,

and at 30-32 weeks were not independently associated with preterm birth, but the pattern of stress between measurements was. Women who delivered preterm tended to have an increase in perceived stress between the first and second measurement, while women who delivered at term had a decrease in stress.(280)

Findings also vary somewhat by race, with most of the positive anxiety studies having been in white populations.(279, 281) One study in black women, reported little impact of anxiety, but a significant association between intrusive thoughts and preterm birth.(282) This pattern is similar to that seen in post-traumatic stress disorder, suggesting an important role for pre-existing traumatic life experiences in the perception of stress during pregnancy.

Major life stresses and catastrophic events

Two kinds of major life stress exposures have been considered as risk factors for preterm birth: adverse life events (e.g. death of a parent or spouse, divorce, major illness) and perinatal exposure to a catastrophic event.

Approaches to measuring adverse life events range from counting the number of significant events in one's life time, to only considering events that occur during pregnancy. A small study of black women found that a higher number of adverse life events in the year prior to and during pregnancy was associated with shortened gestational age.(282) Similarly, Collins, et al found in a case control study that black women who delivered a VLBW infant were three times as likely to have experienced three or more negative life events during pregnancy as black women who delivered an infant over 2,500 grams.(283) Two studies in racially mixed populations found approximately 2-fold elevated risks for preterm birth associated with number of stressful major life events(278, 284), but two others found no such association.(261, 285)

The evidence for catastrophic events and preterm birth is mixed. A series of studies followed the September 11th bombing of the World Trade Center (WTC) in New York City. Lederman et al report that women who resided or worked within two miles of the WTC had significantly shorter gestations, lighter babies, and increased proportions of IUGR than NY women who lived and worked in other parts of the city.(286) A study focused on measuring the effects of environmental exposures resulting from the attack on health outcomes reported an increased risk of IUGR, but not preterm among pregnant women who were in the vicinity of the WTC during the attacks, as compared with NYC pregnant women who were not in the area on that day.(287) Rich-Edwards, et al, found a reduced risk for preterm birth among women who were in their first trimester during the attack, as compared with matched controls who delivered before.(288) Finally, a Dutch study evaluated the impact of maternal stress from media coverage of the attacks on September 11th in women who had no opportunity for other environmental exposures from the attack. They restricted to term births and found that women pregnant during the attacks had lower birthweight infants than women pregnant 1 year later, a difference not explainable by smoking, maternal age, parity, or other confounders.(289)

Glynn, et al reported a significantly shortened gestation in women who experienced an earthquake during their 1st or 2nd trimester, compared to women who did not.(290)

Life course accumulation of stress

Major stressors during pregnancy have been hypothesized to directly activate the placental-fetal HPA axis.(45, 275) The mechanism for an effect of stresses experienced prior to pregnancy may be via stress-sensitization or 'priming', such that women who have accumulated stressful experiences may have altered control of the neuroendocrine components of stress during pregnancy.(291)

While an increasing number of discrete adverse life events could lead to an altered stress response, it is also hypothesized that the accumulation of chronic, but perhaps less dramatic, stressful experiences negatively impacts women's perinatal health. Geronimus, McEwan, and Hogue have each proposed similar phenomena (termed respectively 'weathering', 'allostatic load', and 'stress age') as an explanation for poorer health outcomes among black and poor women.(203, 275, 292)

Testing these hypotheses can prove challenging as it suggests a departure from research where the relevant exposure occurs during pregnancy, to a paradigm where the relevant exposure could occur through the life-course.(293) Not only might exposure be spread over the preceding decades, but there may be particularly relevant developmental windows where exposure is more meaningful, and there may be significant interactions between the physiological results of accumulated stress and behavioral responses.

One type of exposure hypothesized to have this form is experiences of racism. Racism can be considered separately as institutional (differential opportunity patterns in access to educational, social and economic goods and services), interpersonal (discrimination carried out by an identifiable person or group), and internalized (acceptance or belief by the stigmatized group or person of the claims or limitations of their abilities and rights).(294) A brief review of evidence for racism as a prevalent and physiologically active exposure will precede the specific evidence for racism in preterm birth.

A late 2007 poll by the Pew Research center found that 81% of blacks report frequent experiences of discrimination in at least one of the following categories: applying for a job, eating in a restaurant, renting or buying a house, or applying to a university or college.(295) This would suggest that perceptions of discrimination and racism continue in 2007 to be a

prevalent exposure, although notably the same poll found that only 37% of whites believed that blacks experience such discrimination.

In addition to its high prevalence, perceived experiences of discrimination are associated with physiological stress responses. Krieger et al reported a positive association between number of episodes of experienced discrimination and systolic blood pressure in black participants in the CARDIA study.(296) Statistical control for experiences of discrimination reduced the racial disparity in systolic blood pressure. Guyll, et al similarly reported that experience of discrimination was associated with diastolic blood pressure reactivity in blacks but not whites, and that the association was strengthened when the discrimination was perceived as racial in nature.(297) Roberts, et al recently reported that black women in Pitt County, North Carolina had 2.3 (95% CI 1.09-5.02) times the odds of hypertension if they experienced nonracial discrimination (e.g. discrimination based on gender) frequently to always, something that 24% of the women reported.(298) Supporting the notion that racism is a unique category of stress, Klonoff, et al, found in a population based sample of blacks in California that racist events were independently associated with variation in symptoms of anxiety and depression, even when controlling for the role of generic stress, and adverse experiences.(299)

A handful of studies have evaluated experiences of discrimination and racism in relation to preterm birth. Collins et al had similar findings in two hospital based case-control studies serving a low income inner city population. In each study—restricted to black mothers and their infants—mothers of very low birth weight infants were approximately three times as likely to have experienced racial discrimination as mothers of normal birthweight infants.(300, 301) Mustillo, et al, used the previously mentioned CARDIA prospective cohort, and found that

experiences of discrimination increased risk of self reported preterm birth 2.4-fold.(302) In this study, control for experiences of discrimination reduced the black-white disparity by 50%. Finally, Rosenberg and Dole in two additional prospective studies found approximately 40% elevated risk of preterm birth associated with racism or discrimination.(278, 303) The only identified study of racism and pregnancy outcome which did not find an association was Murell, et al.(304) Conducted prospectively in an HMO, the instrument used to measure racism primarily captured perceptions and attitudes about race, and differed from instruments in previous studies in that it did not measure personal experiences of racism.(291)

Other relevant exposures

Two other stress-related exposures bear mention in relation to preterm birth, but do not fit discretely into single categories discussed here. Both pregnancy intention and experiences of interpersonal violence have been associated with preterm birth, and may be associated with socioeconomic and racial disparities.

A 1995 Institute of Medicine review reported that unintended pregnancy increased the risk of low birthweight 1.2 to 1.8.(305) A more recent population based case-control study of very low birthweight similarly found an OR of 1.4 for being 'unhappy about pregnancy'.(277) Orr, et al, found in a prospective study that unintended pregnancy increased the risk of preterm birth by 80% among a mostly poor and black urban population in Baltimore City.(306) A population based study using Pregnancy Risk Assessment and Monitoring (PRAMS) surveillance data from 1996 to 1999 in 18 states report an adjusted OR of 1.16 (95% CI 1.01-1.33) after controlling for age, smoking, alcohol, race, prenatal care, maternal education, and prior low birth weight infant.(307)

Interpersonal violence is prevalent among women of all races and economic levels. The CDC estimates the lifetime prevalence of interpersonal violence (defined as threatened and experienced physical violence and unwanted sex) is 23% (95% CI 22.9-24.3%), and as high as 30% among women of reproductive ages.(308) Women who have experienced IPV are three times as likely to have risk factors for STD's, and twice as likely to smoke or binge drink. Interpersonal violence is often associated with unintended pregnancy, as well as other risk factors for preterm birth. Results from PRAMS data found that women with unintended pregnancies are 2.5 times as likely to also experience violence during pregnancy.(309) Experience of violence or abuse during pregnancy is also associated with other risk factors for preterm birth such as maternal stress, illicit drug use, unmarried status, and poverty.(310) The degree to which domestic violence is an independent risk factor for preterm birth is unclear, but its contribution to maternal stress and association with other risk factors may be relevant.(311)

Mechanisms for stress-preterm birth association

Hypothesizing the role of psychosocial risk factors in causally mediating the excess risk for very preterm birth among black women requires understanding of possible mechanisms of action. Three physiologic and one behavioral mechanism have been proposed. It is possible that experiences and symptoms of stress, anxiety, or depression result in individual behaviors such as smoking, drug use, poor nutrition, or multiple sexual partners, which are risk factors for preterm birth. Physiologically, it is also possible that experiences of stress directly impact one of the four pathways to preterm birth discussed in the first part of this chapter.

Maternal stress and the placental-fetal HPA axis

First recall that corticotrophin releasing hormone (CRH) is normally produced by the hypothalamus, and during pregnancy is produced in large quantities by the placenta. The rise

in placental CRH late in gestation is involved in triggering the shift in the progesterone-estrogen ratio, as well as interacting with prostaglandins in preparation of the uterus. Wadhwa et al, have demonstrated that CRH levels measured at 28 weeks gestation are higher in women who subsequently deliver preterm than they are in term deliveries.(41) Elevated CRH levels at 33 weeks gestation increased risk of preterm birth by 3.3-fold.(35) Placental CRH levels are elevated in response to maternal stress hormones such as cortisol and adrenocorticotropin hormone (ACTH). Hobel, et al, reported that maternal stress measured at 18-20 weeks gestation was strongly associated with CRH both at 18-20 weeks and at 28-30 weeks.(38)

While the general patterns of maternal stress, elevated CRH, and spontaneous preterm birth are consistent across racial groups, differences do exist. In a small prospective study with serum measurement of CRH, ACTH, and cortisol at three points through pregnancy, black women had higher ACTH, but lower cortisol levels and a lower CRH trajectory than white women.(44) This pattern has been reported in chronic as opposed to acute stress states(312), and may represent something like the weathering phenomenon proposed by Geronimus.

Maternal stress and vascular reactivity

Associations between chronic stress and racism, and changes in vascular reactivity have been previously discussed. Stress could lead to preterm birth through a vascular pathway in several ways. To the degree that hypertension results from chronic stress experiences, the risk of indicated preterm birth as a result of preeclampsia or placental insufficiency increase. There is also evidence that hypertensive women have elevated CRH levels, possibly explaining the risk of spontaneous preterm birth with hypertension.

Maternal stress and infection

A large meta analysis of 300 studies of the relationship of psychological stress and immune response found that the impact varied depending on the chronicity of the stress.(313) Acute stressors tended to upregulate immune responses, while chronic stressors tended to suppress both cellular and humoral immune activity. Evidence from both pregnant and non pregnant populations supports the role of stress and immune status.

In a non-pregnant longitudinal follow up study of 3,614 women, stress was associated with overall prevalence of bacterial vaginosis, as well as incidence.(314) Using a case-crossover analysis, each point on a 5-point calculated stress scale conferred a 2-fold (95% CI 1.1-3.6) elevated risk of bacterial vaginosis. However in a smaller cross-sectional study of non-pregnant black women in New York City, the association with bacterial vaginosis was 1.4 (95% CI 0.95-2.1). A study of elderly Hispanics in California found a strong association between immune response to latent herpes virus infections and the individual's socioeconomic status, suggesting lower SES impaired normal immune response.(315)

In pregnancy, maternal stress and low social support was associated with depressed lymphocyte activity.(316) Culhane et al, found that moderate to high levels of perceived stress had an independent 2.2-fold (95% CI 1.1-4.2) increased risk for bacterial vaginosis in low income pregnant women. (40)

PRETERM BIRTH: SO, WHAT DO WE KNOW?

Preterm birth remains a profound public health burden and an important mark of inequality in health outcomes by race and class in the US. While very preterm birth impacts a relatively small proportion of all births, its occurrence is the leading cause of infant mortality, and the explanation for two thirds of the racial disparity in infant mortality. Very preterm

births are also leading risk factors for lifelong developmental disabilities such as cerebral palsy and mental retardation, as well as being economically burdensome to families and society at large.

In considering the most proximal events to the occurrence of preterm birth, it is hypothesized that most occur through one of four biological pathways. While pathologic uterine distention is unlikely to be a primary mediator of racial disparities in very preterm birth, the remaining three pathways reviewed may help shed light on mechanisms for disparity. Of particular interest for very preterm birth is the role of ascending genital tract infection. The racial disparity in the prevalence of infections such as bacterial vaginosis could independently—or in interaction with maternal stress and the placental-fetal HPA axis—mediate differential risk. It is also possible that life stress and maternal vascular reactivity interact to elevate preterm birth risk through placental insufficiency. The role for individual genetic variations interacting with environmental characteristics remains poorly defined. While there is certainly a genetic component to preterm birth in general, its role—if any—in explaining racial differences is partial, still leaving substantial risk differences unexplained.

Taking a step back in the causal chain from final biologic processes in pregnancy is the investigation into individual level risk factors for preterm birth. These risk factors, where consistently found, are pieces in a causal sequence to preterm birth, or are coincidentally associated with a factor which is. While numerous risk factors have been identified for the occurrence of preterm birth two important questions remain unanswered. What triggers preterm birth to occur in some but not all women with apparent etiologic risk factors? And why does a social gradient for very preterm birth exist along racial and economic lines? None of the literature to date has identified the components either necessary or sufficient for very preterm

birth to occur. Similarly, none—with the possible exception of a single study measuring the effect of experiences of racism on very low birth weight births(300)—have identified a set of risk factors which 'explain' the racial disparity, or even a substantial portion of it.

It is with this general background of preterm birth that two avenues stand out for ongoing investigation. The first is continued enhancement of our understanding of the biologic processes and underpinnings of preterm birth in hopes that this will lead to an intervention which reduces the risk of preterm birth or its sequelae for all groups of women through *secondary* and *tertiary* prevention. The second is an improved mapping of the 'social genome'—the processes and patterns by which subpopulations experience differential risk. This new knowledge of relevant social determinants and their mechanisms may suggest opportunities for *primary* or *secondary* prevention efforts at the population level.

Chapter 2 A SOCIAL EPIDEMIOLOGY OF PREGNANCY OUTCOMES[2]

As is the case with epidemiologic research on most complex chronic diseases in the 20th century, efforts to distinguish individual level behaviors and exposures which are modifiable risk factors for preterm birth have been powerful and yet incomplete. A few high-magnitude risk factors and a host of lower magnitude risk factors paint some of the picture of why and how some pregnancies end too early. Yet much of the variation in risk remains unexplained, for preterm birth generally, and particularly for excess preterm birth in black women. Geoffrey Rose suggested in his historic essay *Sick Individuals and Sick Populations* that efforts to identify the *cause of cases* of disease can explain some of the variation in occurrence, but this must be complemented by investigation of the *causes of incidence* of disease in populations.(317) Krieger writes that "…the causes of disease distribution [are] related to—but not simply reducible to—causes of disease mechanisms."(318) This is true in part because some exposures may be allocated at the group level, rather than purely at the individual level, thus making (nearly) all members of a given population homogeneous to the exposure. Study designs which look within the population will find no effect of the homogenously distributed factor; only by comparing populations heterogeneous to exposure can an association be tested. These distinctions suggest a public health-relevant role for understanding both social distribution and social determinants of disease at the population level.

Interest in social patterning (or social causation) of disease risk is not new. From Hippocratic times forward the individual's state of mind, position in the social hierarchy, and

[2] This chapter is partially summarized in two review articles. See Appendices 2 and 3.

relationship to the means of material production have been theorized to differentially distribute disease occurrence.(319) This tradition continued (and at times flourished) in the more recent development of public health and epidemiology. In the 17th century, John Graunt first tabulated mortality on a population level, noting significant variation by social class.(320) In the 19th century, Villerme and Virchow separately identified social class and working conditions as determinants of disease.(321) Even as public health in the US on the cusp of the 20th century eschewed social causes of disease in favor of the discrete causal pathways suggested by germ theory, it was clear that some diseases such as tuberculosis did not boil down to simply having the germ or not. With nearly 100% tuberculin infection rates in some cities, clinical disease still varied by characteristics which were socially patterned: nutritional status and poverty.(319) In the latter part of the 20th century, interest has returned again to more complex models of disease causation, due in part to the inadequacy of reductionist approaches in answering some questions. The complexity comes in integrating what is known about the biologic paths to diseases (which of course are inherently individual) and their interactions with the upstream social patterning of protective and deleterious exposures.

In this chapter, a framework will be developed for the use of social exposures in perinatal research. Overarching theories of causation, as well as updated methodological work on inference from ecologic research will be briefly reviewed. Segregation will be developed as a specific exposure, and its definitions and measurement will be reviewed. Finally, the literature on social exposures and preterm birth will be reviewed. The goal of this section is not to establish *a priori* a specific causal association, but rather to build a conceptual model from which testable hypotheses will be drawn.

SOCIAL EPIDEMIOLOGY THEORY

The role for social determinants of health states is premised on a multi-level or ecologic systems view of health determinants.(322, 323) This viewpoint simultaneously recognizes the role of the individual biological organism (which in itself is a dynamic multilevel system) existing within a social context; through biologically relevant exposures, behaviors, experiences, and processes, aspects of the social is 'embodied' or biologically incorporated.(324) In its simplest conceptualization, the multi-level view suggests that both nature and nurture matter, but the power of the approach comes from proposing a model for conceiving of and testing cross-level interactions and effects between nature and nurture. The utility for public health is identification of novel opportunities for disease prevention and health promotion.

Thus, causal chains (or causal networks) extend 'upstream' from the individual to the historical, social, and economic forces which impact the distribution of exposures, are then mediated through the individual's response (psychological, behavioral, or directly biological) to those exposures, and finally to the 'downstream' or proximal causes of disease at the cellular or sub-cellular level. Several categories of social exposures have been evaluated for pregnancy outcomes, including neighborhood or place effects, absolute poverty and relative income inequality, interpersonal or relational effects, and the effects of varying policy or economic environments. Two competing explanatory social theories which propose overarching causal pathways between these varied social exposures and health are psychosocial theory and neo-materialist theory. These hypothesized pathways were developed to explain socio-economic gradients in health, but may be equally insightful in considering racial disparities in health. Each theory will be discussed below. Additionally social capital—which is an explanatory model that can be seen as a subset of psychosocial theory—will be briefly reviewed.(325)

PSYCHOSOCIAL THEORY

Proponents of the psychosocial hypothesis for socioeconomic gradients in health suggest that *relative* social position within a society leads to poor health because of the individual's feeling of hopelessness, lack of control, stress, and other psychological as well as behavioral sequelae of their location in a social hierarchy.(326, 327) Evidence of the greater importance of relative rather than absolute poverty is used to suggest that it is perception and consequences of status rather than absolute material wealth (at least in developed nations) that is most health relevant. For example the correlation of gross national product (GNP) per capita (an absolute measure of average wealth) and life expectancy among Organization of Economic Cooperation and Development (OECD) members in Europe and North America is nearly non-existent (r=0.08).(327) However relative income inequality is highly correlated with life expectancy (r=-0.75) among these countries.(328) Similarly, infant mortality is positively associated with increasing income inequality (wider gap between rich and poor) in developing countries as well as in industrialized countries in Europe and the Americas.(329)

Robert Sapolsky reviewed the evidence for social hierarchy induced stress and its impact on adrenocortical, cardiovascular, reproductive, immunological and neurobiological systems in a wide range of social primates, including humans. He notes that while humans are not hierarchical in the same ways as other animals, the human socioeconomic health gradient is only partially explainable by behavior and access to health care, raising the question of whether biologic response to characteristics of social rank explains the remaining variance.(330)

Income inequality at the state level within the US has also been associated with infant mortality, after controlling for population racial composition, individual income, and smoking.(331) Huynh, et al, also found that county level income inequality in the US is

associated with preterm birth, controlling for maternal race, education, risk level (a composite variable made up of parity, marital status, and age), and county per capita income.(332, 333) This association was stronger for black than white women. Wilkinson et al report that when comparing states within the US as well as comparing Western industrialized nations, increasing income inequality is associated with not only higher mortality, but also lower population education performance, higher rates of imprisonment, higher rates of drug overdose mortality, and decreased upward social mobility.(334) In each case it is suggested that absolute income and system infrastructure are not as important as the experience and perception of low social standing. In short, the less egalitarian (in economic or other terms) a region is, the higher the prevalence of negative health risk factors, mortality, and morbidity.

Experiences of interpersonal and internalized racism could produce similar patterns.(335) The coping response to this discrimination could evoke the same behavioral, psychological, and neuroendocrine responses observed in economic inequality. One example of the way in which race, perceptions, and coping interact is Sherman James' 'John Henryism' hypothesis.(336, 337) James evoked the image of the black American folklore character who worked himself to death competing with a steam-powered hammer, suggesting that for poor blacks in particular, this coping response to adversity results in internalized stress, and subsequent poor health, such as elevated blood pressure.(338) A recent review of population based studies on the health effects of perceived racism found that 72% of the 206 studies looking at negative mental health outcomes found a significant association with perceived racism, 62% of the 34 studies evaluating health behaviors such as smoking and substance abuse found a significant association, and 36% of the 171 studies evaluating physical health found a significant association.(339)

Another mechanism attributed to the psychosocial theory is perception of control and autonomy at work or home. Meyer et al studied the effect of psychosocial characteristics of work environment and birth outcome using a Connecticut birth dataset with linkage to maternal employment. They reported that low birth weight and preterm delivery were weakly associated with jobs with low control and low substantive complexity, even after controlling for demographic and obstetric risk factors (LBW aOR 1.25, 95% CI 0.99-1.59; PTB aOR 1.06, 95% CI 0.95-1.19).(340) A recent Swedish study evaluated working conditions in relation to pregnancy outcomes. Low job control was associated with at 17-28% increased risk for very preterm birth, controlling for social class, job hazards, and individual pregnancy risk factors.(341) Collins, et al, considered perceptions of the safety and friendliness of residential neighborhoods in a group of mostly poor, urban, black women. They found that unfavorable perception of living environment increased odds of VLBW birth 2.9 fold (95% CI 1.0-8.4), after controlling for income and demographic and obstetric risk factors.(283) In a case-control study of 739 low-income black women, Misra et al simultaneously considered effects of biomedical risk for preterm (such as chronic disease and vaginal bleeding), social risks (such as lack of time, money, and support), and psychosocial risks (such as perceptions of stress and locus of control). While lack of time and money were associated with increased odds of preterm birth (aOR 1.61, 95% CI 0.97-2.68), stress remained the strongest independent predictor in the model (aOR 1.86, 95% CI 1.21-2.86).(342) Other evidence for the association of experiences of inequality and discrimination has been previously discussed in Chapter 1.

Social capital and health

Another general pathway which might mediate the racial and socioeconomic gradients in health is via social capital. Social capital can be conceived of as a macro version of the psychosocial pathway, in that community cohesion, trust, reciprocity, and organization lead to

better health by increasing political clout, sharing health relevant information, and providing social and economic support. As such, social capital is a community level resource, and while generally assumed to exert positive influence on health, it could conceivably be neutral or detrimental.(343) Because of its relational nature, it is harder to define and measure, and perhaps that explains the variety of findings for the role of social capital. One common measurement operationalized by Robert Putnam is a composite index of a community's volunteerism, social trust, involvement in public affairs, and availability of public use spaces for socializing.(344)

Holtgrave, et al used Putnam's state level index of social capital to investigate its impact on the incidence of sexually transmitted diseases. They report that social capital is highly correlated with chlamydia, gonorrhea, syphilis, and AIDS case rates.(345) In multiple regression, which included income inequality and proportion of the state living below the poverty line, social capital was the strongest predictor of each disease rate at the state level. Kawachi, et al considered state level social capital (operationalized as volunteerism and level of social trust) in relation to all cause mortality and infant mortality. They found the association of income inequality with infant mortality was mediated by area social capital.(346) Finally, Poortinga considered whether social capital effects on self-rated health were simply due to differences in health related behaviors. In a large, multi level population based survey in England, both area social capital and health behaviors such as smoking, alcohol use, and fruit and vegetable consumption were found to be associated with self-rated health. While higher social capital was associated with healthier behaviors, its association with self-rated health was not appreciably diminished by control for these behaviors, suggesting a persistent independent positive effect.(347)

NEO-MATERIALIST THEORY

Neo-materialism as an explanatory pathway to health disparities proposes that socioeconomic gradients in health are due to the ability of wealthier people to purchase different environments and exposures than poorer people. In effect, inequality by income (or by race if correlated with income) results in deleterious health outcomes as a result of increased negative exposures, decreased individual resources to ameliorate the effects of negative exposures, and systematic underinvestment in the health, human, and social infrastructure.(348) Proponents of this theory suggest that income inequality or decreased social capital are themselves effects of fundamental structural material problems, and thus their association with health results from confounding by the common structural cause, or is a function of their mediating role.(349) Clarkwest demonstrates that income inequality leads to under-investment in public and social infrastructure, which results in time-lagged lower life expectancies in subsequent years.(350) Neo-materialist hypotheses consider the roles of individual poverty and systematic underinvestment in infrastructure and health and social welfare systems as fundamental causes of disease.

Much evidence supporting neo-materialist hypotheses comes from ecologic cross-national comparisons where there is sufficient heterogeneity of material wealth and health outcomes to make comparisons. In one study of 16 OECD nations, Lynch, et al report that both infant mortality and low birthweight were positively associated with increasing income inequality.(328) However they note that indicators of social capital or psychosocial effects such as trust and volunteerism were non-significant, while proportion of women in government and participation in trade unions were both protective, presumably because they are indicative of higher investment in health and welfare infrastructure. Chung, et al, used another marker for

material distribution of wealth by comparing national expenditures on social and health services with low birth weight and infant mortality. They report that among 19 wealthy OECD nations, public medical expenditures were strongly associated with lower infant mortality, and proportion of votes for political parties supporting strong welfare programs were associated with decreased rates of low birth weight.(219) In a related study, Muntaner, et al reported that increased working class power, and presence of a pro-welfare government was associated with lower infant mortality and lower low birth weight rates, while social capital was not statistically important in explaining international variation in these outcomes.(351) Each of these studies build on Navarro's critique of the absence of class related political factors in understanding global health patterns.(352, 353)

Studies of the physical and economic characteristics of neighborhoods and working environment often assume this pathway mediates the effect of income or racial inequality on health outcomes. For example, associations of proximity to waste sites, exposure to lead, poor quality housing and overcrowding, poor nutrition, or lack of health insurance could each result in poor pregnancy outcomes as a result of material deprivation. Mayer, et al tested several neo-materialist hypotheses for state level infant mortality in the US. They found that increasing income inequality, increasing economic segregation, and decreasing state level health care expenditures were associated with increasing infant mortality rates.(354) Morello et al considered exposure to air pollution as a function of residential segregation and related it to health outcome. They found that for whites and blacks, income was not associated with increased exposure to pollution, but living in a highly segregated city disproportionately increased exposure among Hispanics and blacks, compared with whites.(355) Cox, et al, proposed that comparisons of adjacent neighborhoods could empirically test the psychosocial

versus neo-materialist hypotheses.(356) They looked at local neighborhood deprivation, and incidence of type 2 diabetes in Scotland, proposing that the psychosocial hypothesis would lead to increased disease risk in a deprived area surrounded by wealthier areas as a result of lower relative social standing. On the other hand the neo-materialist theory would suggest that the deprived area would benefit from the spatial proximity to enhanced material wealth in terms of recreational facilities, food retail choice, etc. Terming these the 'pull-up' versus 'pull-down' hypotheses, they found that living in a deprived neighborhood was associated with increased incidence of type 2 diabetes, but that the elevated risk was lessened if the surrounding area was wealthier, supporting the pull-up, neo-materialist theory.

APPLICATION OF SOCIAL THEORY

Vigorous debate exists about the relative utility of the neo-materialist versus the psychosocial (and social capital) explanations for socioeconomic and racial gradients in health. In pitting one theory against the other they are necessarily operationalized as mutually exclusive processes. However for health in general, and pregnancy outcomes in particular, they are more likely complementary and interconnected.(357) Two points are relevant here. First, health effects mediated by stress impacts on neuroendocrine processes are not solely part of the psychosocial pathway. While stress from interpersonal discrimination and perceptions of relative status fall under the psychosocial umbrella, daily hassles from poverty, living in a crime-ridden neighborhood, getting children to daycare and self to work without transportation could all result in activation of stress associated neuroendocrine processes, although the source of the stress is related to material wealth.

Secondly, Kroenke, et al points out that with a life-course perspective, psychosocial and material processes interact through time.(358) For example material deprivation in childhood

could negatively impact cognitive and behavioral development, so that as an adult, coping with stressful experiences may be more challenging or reliance on negative health behaviors such as substance use may be more likely. Alternatively, perceptions of inequality and low self esteem in youth could impact educational attainment, thus impacting material wealth in adulthood. Morello posits a different interaction, noting that cumulative psychosocial stresses (e.g. weathering, allostatic load) might increase susceptibility to disease from environmental exposures such as lead or air pollution, which may be more prevalent in neighborhoods of material deprivation.(359)

Psychosocial and neo-materialist social theories provide investigators with conceptual tools for understanding social determinants of health. While it may be artificial to make them mutually exclusive, it may be beneficial to clarify each distinct pathway for better causal understanding, and for intervention. If the fundamental social determinant of a given health state is material in nature, the intervention must address this, by providing housing vouchers, for example, or improving environmental regulation of toxins in population areas. However if the primary problem is relative inequality or decreased social capital, then efforts to build community strength or reduce income inequality may be necessary. No single intervention is mandated by either approach, but different questions, and different actions result from each approach.

SOCIAL EPIDEMIOLOGY METHODS

Testing hypotheses of social determinants of pregnancy outcomes requires both conceptualizations of causal pathways, and also attention to design and analysis issues. The hypothesized causal pathways reviewed above suggest a multi-level nature to disease causation: both individuals and their social, economic, or environmental context may be

relevant. As previously stated, the power of this conceptualization is in independent and interactive effects of factors at different levels. This section briefly reviews two concept developments from the past two decades which have facilitated this type of inquiry.

THE EFFECTS OF PLACE: CONTEXT AND COMPOSITION

Because the hypothesized role of social forces on health are often believed to be mediated through characteristics of the states, counties, cities, and neighborhoods in which we live or work, it is important to understand the interplay between person and place, composition and context. Cummins, et al, write that '…place is relevant for health variation because it *constitutes* as well as *contains* social relations and physical resources' (original italics).(360) At one time, aggregated group-level data were used in ecologic research as a surrogate for individual level data. As a result of concern about ecological bias, the practice of inferring individual level causal effects from ecological associations was replaced by the practice of inferring area-based contextual effects from these associations. This led to understanding of the joint effects of the ecologic environment (be it social, built, or environmental) and the attributes of individuals. This distinction, combined with new hierarchical statistical models, led to interest in decomposing the variation in health in places to compositional effects (individual behaviors and traits such as age, smoking or diet) and contextual effects (the independent role of forces not unique to the individual, such as political power, economic opportunity, or prevalence of infectious disease).

While it has often been assumed that contextual and compositional effects are mutually exclusive and thus competing explanations, many investigators suggest that context impacts composition and vice versa.(361, 362) For example poor individuals might move to a rundown neighborhood because of limited market choice, increasing the concentration of poor people in

this neighborhood. Thus context impacted subsequent composition. Similarly, poor people may have less political clout at city hall to bring improvements to their neighborhood in terms of infrastructure and service, so that composition impacts future neighborhood context. This reciprocal effect may mean that some individual exposures considered to be confounders are instead mediators of a contextual effect, and thus statistical control may bias the estimate.

Rather than thinking of contextual effects as the residual effect after controlling for (measured) individual level confounders, Macintyre, et al propose that neighborhoods impact health through one of five types of features (Table 2-1). These features and opportunity structures or resources vary not only by neighborhood, but within neighborhoods, interacting with individual characteristics.(363) For example close proximity to a hospital does not guarantee access to health care for uninsured individuals.

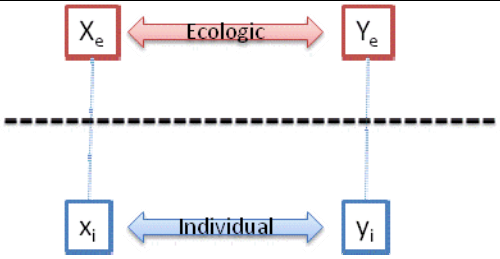
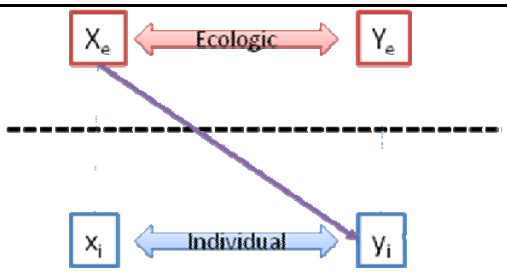
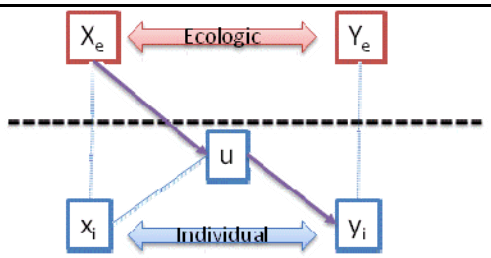
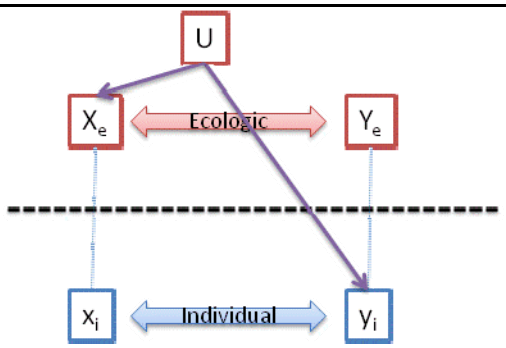
Table 2-1. Characteristics of neighborhood health

What constitutes a healthy neighborhood? (Adapted from Macintyre, et al, 2002)(362)	
Shared physical features of the broad area environment	Air and water quality, weather, and latitude impact everyone in an area.
Availability of healthy home, work, and play environments	Availability of decent housing, and safe work or play sites. These may impact people differently based on employment status, number of children, and special needs such as children's play area or accessible housing for elderly.
Publicly or privately provided services	Education, transport, lighting, policing, health and welfare services. These may be differentially relevant; public transit is unimportant if you own a car; public education is less important if you can afford private.
Socio-cultural features	Political, economic, ethnic and religious history of community. These could impact community integration, norms, values, levels of crime, and networks of community support.
Reputation of an area	Banks, investors, and service providers may make choices based on reputation which influences infrastructure. Residents' morale and perception impact self-esteem, mobility, neighborhood stability.

ECOLOGIC FALLACY TO MULTILEVEL INFERENCE

Legitimate concern about bias from the 'ecologic fallacy' significantly impeded efforts to investigate group level or ecologic exposures effects on health, until relatively recently. The inherent problems of ecologic correlation were described in the classic example by Robinson in 1950 concerning literacy rates and proportion of the population black, by state.(364) He demonstrated that regional or state level illiteracy and proportion of the population who are black were strongly correlated at the ecologic level (r=0.96), but much weaker at the individual level (r=0.23). He also demonstrated that not only can the strength of correlation be attenuated going from ecologic to underlying individual, but the sign can even change, largely as a result of confounding by the grouping variable. This appeared to suggest that ecologic estimates were so profoundly biased from the 'truth' of the individual correlation, as to be meaningless. Greenland and Morgenstern have illustrated numerous ways in which ecologic bias can occur, largely as a result of nuisance effects from confounding and aggregation bias.(365, 366) The conclusion from Robinson and others is that the individual level correlation is superior to the ecological correlation.

Table 2-2. Cross-level interactions

Examples of cross-level interaction: when both individual & ecologic estimates are biased	
A. 	Unbiased setup. In an unbiased situation, the aggregate exposure (X_e) associates with the aggregate outcome (Y_e) with the same magnitude as at the individual level (x_i and y_i).
B. 	An attribute of the aggregate measure is an independent risk factor for the individual level outcome. ***Example***: The association of neighborhood poverty (X_e) with preterm birth (Y_e) may differ from the individual poverty-PTB association due to independent effect of poverty concentration via crowding, crime, and social support.
C. 	Aggregate measure is associated with second individual level risk factor or effect modifier. ***Example***: Black men in urban ghettos have high risk for arrest. If X_e is % black, u is baby's father in prison, then the association between individual race (x_i) and PTB (y_i) is modified by u, whether father is home providing social support.
D. 	A separate ecologic process impacts grouping of individuals and the individual outcome. ***Example***: Segregation (U) groups people by income and race, thus changing the groupings and % black (X_e); segregation might also be an independent risk factor for PTB (y_i) by restricting economic opportunity, and increasing stress.

However there are instances in which neither accurately estimates the associations of interest. Specifically, the nuisance parameters which cause the ecologic fallacy may in fact be etiologically interesting in their own right. Three examples of such 'cross-level' interactions are described in Table 2-2. (361, 367) In each case a group level measure influences the individual risk of disease, thus biasing either the ecological or the individualistic correlation were they to be considered in isolation. The first example, in part B, assumes that an aggregate measure (mean neighborhood income or % in poverty) is solely an aggregation of individual level income. The cross-level contextual effect would occur if, for example, living in a neighborhood with >50% poverty were independently a risk for disease (via neighborhood degradation, low quality housing, limited food shopping choice, increased crime, etc), separate from the role of an individual person being poor. Parts C and D in the table suggest similar contextual effect, but mediated by a second individual level risk factor in B, and resulting from a broader contextual process (such as segregation) in C.

Thus several types of meaningful interaction (or confounding) could explain differences in individual and ecological level effect estimates. The question is how best to account for these interaction. While not a panacea, multi-level models, which simultaneously consider variation at the individual and group level, as well as their interaction, are one approach to look at these phenomena.(368) Robinson demonstrated the fallacy of the ecological approach, and promoted the superiority of the individual approach using race and illiteracy. However subsequent multi-level analyses which combined the individual level literacy and race variables with state funding of education, demonstrated a strong contextual effect (for both blacks and whites) of state educational policy on literacy.(369) Southern states, with relatively larger black populations, also tended to spend less on education. Thus the ecological estimate was

fallacious, but there is also risk of an individualistic fallacy by excluding relevant contextual variables.(324)

SEGREGATION

David Williams describes segregation as a "fundamental cause of racial disparities in health".(6) While causes, consequences, and patterns of segregation have been described for decades in the sociologic and geographic literature, it has only been in the past few years that much attention has been paid by public health researchers to its role in relation to health outcomes. Yet these forays into investigation of health-segregation associations are in their early stages, with incomplete conceptualization of causal pathways, minimal attention to the best means to measure the intended phenomena, and use of data sources not always appropriate for the intended hypothesis.(370) In short it is in the same state as many lines of inquiry in their early days. However in the case of segregation, epidemiologists can build on substantial theoretical and empirical work already completed in other disciplines.

This section reviews conceptual and methodological issues relevant to understanding and measuring residential segregation. The literature on the causes and consequences of segregation will be reviewed, including general associations with health. A more detailed review of studies focusing on pregnancy outcomes and residential segregation will follow in a subsequent section in this chapter.

SEGREGATION: CAUSES AND CONSEQUENCES

Segregation is both a process and a state. As a process, it sorts individuals into environments, and as a state, it prescribes the degree to which groups experience or occupy varying social and physical environments.(371) The process of segregation is discussed in this

section on causes and consequences, while the description of the state of segregation is attended to in the following section on measurement.

Segregation can occur by race, ethnicity, religion, class, or gender, and can occur in residential, educational, or employment spheres. These different forms could occur for different reasons, and could have a variety of consequences in terms of health. Segregation could occur as a result of state policy and laws, economic and social pressures, or as a result of cumulative individual choices. Additionally, segregation can be conceived of at different spatial scales from neighborhood to city to consolidated metropolitan area to state, region or even nation. Within each of these geographic units, the presence or absence of spatial separation between groups could be determined. For the purposes of this review, attention will be focused on residential segregation by race and class within metropolitan areas, cities, and neighborhoods.

Understanding segregation as a health-relevant exposure or process requires some knowledge of its history in American cities, as well its determinants, mechanisms, and consequences in terms of individual level opportunities.

A brief history of US urban residential segregation

Segregation of ethnic and racial minorities in US cities is neither new, nor unique to any one group. New European immigrants to American urban areas frequently resided in ethnic enclaves, a process which may be a critical component of assimilation.(372) This segregation of new immigrants typically subsides within a generation, as economic opportunity and upward mobility lead to fuller integration. Yet for black Americans, segregation has increased through much of the twentieth century.

Cutler, et al, portray black-white residential segregation in the twentieth century in three distinct periods.(373) The periods are distinct not only in terms of the patterns of migration from rural to urban areas, but also in the processes which resulted in (and subsequently maintained) racial residential segregation. The first period, termed by Cutler the *Birth of the Ghetto,* spanned from 1890-1940 (Cutler distinguishes 'ghetto' as a largely black area, as opposed to slum, which denotes quality of living conditions). Large scale migration of rural Southern blacks to urban areas in the Northeast was driven by changes in agricultural practices in the South and demand for manual labor in industry in the North. While the average urban black in 1890 lived in a neighborhood that was 27% black, by 1940 this had increased to 43%.(373) This period of increasing segregation parallels the segregation of any new immigrant group, and results largely from an affinity of newcomers to live near other newcomers (termed the *Port of Entry* theory by Cutler). This congregating in cities offered opportunity for job leads, connections to cultural and religious institutions, and social support. While evidence of housing markets during this period is limited, this early segregation may have been driven as much by black choice as by structured limitation to other options.

The period from 1940 to 1970 was one of consolidation and expansion of the urban black ghetto. While further migration of rural blacks into Southern and Northern urban areas continued to expand the size of the black population in many cities, racial tensions were increasing. In a process Cutler calls *collective action racism*, housing markets were manipulated by law, restrictive covenant, and overt acts of intimidation by whites to maintain and increase separation. In one estimate, 80% of housing deeds in some areas included restrictive covenants regarding race.(374) Massey and Denton argue that it was this period of sanctioned and institutionalized racism they likened to South African apartheid which formed segregation

persisting to today.(375) By most measures, black-white residential segregation reached its peak in 1970, when the average urban black lived in a neighborhood that was 68% black.(373)

Since 1970, national estimates of segregation have decreased modestly. This results mostly from the movement of some blacks to previously all-white areas, rather than the integration of largely black areas. While the overall measures of segregation may have decreased, the results of the previous decades persisted in terms of isolation and poverty concentration for many urban blacks. This period saw some areas (particularly in the South and West) where middle-class blacks integrated into white neighborhoods, but poor blacks became increasingly isolated physically and economically in areas which suffered from infrastructure disinvestment.(376) The Civil Rights Act (Fair Housing Act) of 1968 prohibited discrimination in housing sales and rental, and thus theoretically stopped the collective action racism which shaped segregation for the preceding decades. Although the Fair Housing Act considerably reduced the opportunities for collective or institutionalized housing discrimination, financial and interview audit studies demonstrate that redlining (the illegal process of systematically denying loans to certain portions of a city) and outright racial discrimination persist in urban housing markets.(377) While some aspects of collective discrimination play a role in ongoing segregation, Cutler, et al argues that decentralized racism became the operative process maintaining segregation since 1970. Using empiric data on housing prices (rental and purchase), they found that highly segregated cities were marked by whites willing to pay more for equivalent housing in predominantly white areas.(373) This is distinct from the previous decades, where the legal constraints to integrated living lead to higher housing costs for blacks, who had limited market choice. Concordant with housing

market studies, survey data supports the notion that blacks more than whites desire greater residential integration (64% of blacks versus 40% of whites in 2007).(295)

Consequences of residential segregation

"This is our basic conclusion: Our nation is moving toward two societies, one black, one white--separate and unequal."(378)

Kerner Commission Report, 1968

That segregation has consequences is relatively undisputed. This section briefly reviews the social and health consequences of segregation. Specific review of the association of pregnancy outcomes and segregation will follow in a subsequent section.

Social consequences

Segregation (spatial separation or isolation) is not inherently disadvantageous; in fact for whites it can be argued to be economically beneficial.(379) Even for blacks, it is not exposure to other blacks or lack of contact with whites that is the toxic exposure. Instead it is the association of racial segregation with economically related consequences that creates harm.(6) In fact strong evidence exists for an interaction of racial, economic, and perhaps even gender segregation in spatially concentrating poverty. Isolation of the poor increases with increasing racial segregation, as does income inequality, and this trend has increased between 1970 and 1990.(376) The majority of poor people in the US are white, yet most live in relatively economically integrated neighborhoods. In contrast most poor blacks live in poor neighborhoods.(380) The propensity for poor blacks to live in primarily poor neighborhoods has been termed 'double jeopardy'. In the US in 2000, 1.4% of white children lived in poor families inside poor neighborhoods, while 16.8% of black children experienced this double jeopardy.(381) In a study of the association of class mobility and racial segregation in three

metropolitan areas, Alba, et al find that middle class blacks are more likely to live in less segregated neighborhoods than poor blacks.(382) However middle class blacks never achieved income-matched parity with whites in terms of neighborhood quality, with blacks living in neighborhoods which are older, having lower tax bases, and amongst whites who have lower mean income than themselves. While racial segregation has generally declined since 1970, income segregation has increased slightly. But these general trends obscure subgroup differences. Fischer finds that poor black families are uniquely segregated, with relatively less improvement over time than either poor whites or middle class blacks.(383) Race, class, and gender can also interact. Massey and Lundy describe an audit study of interviews with potential landlords for a rental apartment in Philadelphia in 1999. While race and class were each independently important, poor black women were the most likely to be discriminated against in obtaining housing.(384)

Similar patterns are seen for education, housing quality, and proportion of single-parent households. In a comparative study of metropolitan areas, Sampson, et al concluded, "The worst urban context in which whites reside is considerably better than the average context of black communities."(385) As a result of the concentration of blacks in poorer neighborhoods, there are also large disparities in terms of the mechanisms typically considered to catalyze upward mobility: education, economic opportunity, role models, and social context. One of the most direct results of spatial sorting of individuals is that educational opportunities are impacted. If all schools were equal, this would be inconsequential, yet there is substantial evidence that poor urban schools perform worse than suburban schools on nearly all markers of quality including curricular variety, test scores, teacher and administrator experience, high school completion, and the social environment including violence, drugs, and teen

pregnancy.(386) In a study on the racial gap in SAT score, metropolitan level segregation explained one quarter of the gap (approximately 45 points) controlling for mothers and father's education, family income, school size, city size, city proportion black, and US region.(387) While both school and neighborhood segregation were significant in models, when considered together, neighborhood segregation was the strongest predictor.

Economic opportunity is also significantly dependent on the area of residence. In addition to the presence of positive role models, social networking for job opportunities and presence of childcare support (in the form of a two-parent household, extended family, or affordable child care) as determinants of economic opportunity, there also must be jobs. The concentration of poor blacks in central urban districts contrasts with the growth of job opportunities in suburban and rural areas, making a spatial mismatch.(6) Some businesses explicitly use the racial composition of an area in making relocation choices, and decisions regarding layoffs, and restructuring can disproportionately impact black workers.(388, 389) In a longitudinal study of the 95 largest metropolitan areas in the US from 1970 to 1990, Dickerson reported that increasing segregation was associated with increased unemployment for blacks, after accounting for other characteristics of local labor markets.(390) The effect was particularly strong for extreme clustering and unevenness in segregation.

Finally, the social context of highly segregated, poor neighborhoods can be detrimental. High levels of male incarceration, death from homicide, low quality housing, and unemployment all impede the efforts of individuals and communities to maintain optimal health. In many cases direct exposures from material deprivation could mediate the harm, while in others it is stress, behavioral response to the environment, and hopelessness which might mediate poor health outcomes. Additionally, segregation can undermine some characteristics of social capital by

restricting social ties outside the neighborhood.(391) However it should be noted that some aspects of racial clustering could be health protective by increasing black political power and representation in government. Laveist demonstrates that in 176 cities with populations over 50,000, black political empowerment moderates the negative health effects of increasing segregation.(392)

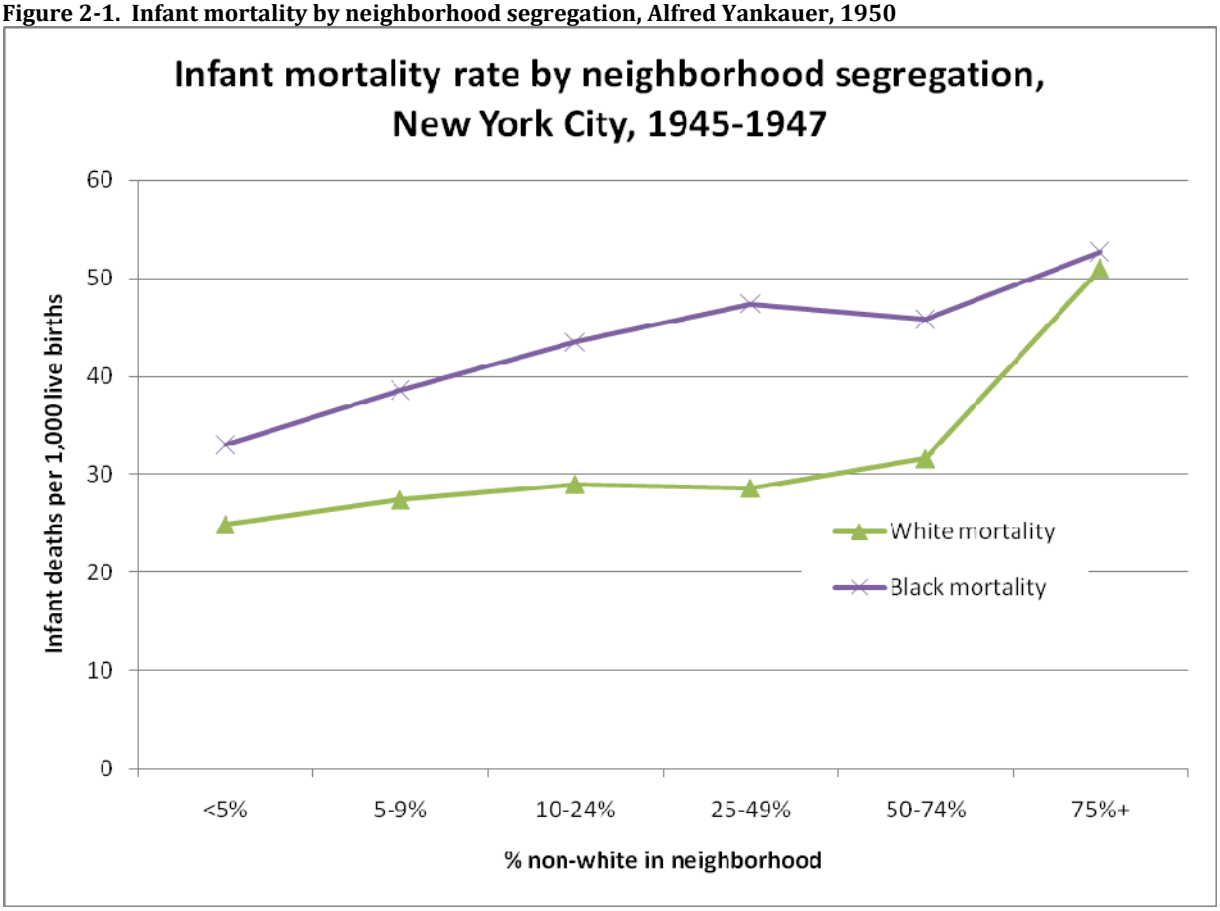
In summary, segregation is a process which sorts individuals into different environments on the basis of both race and class. These environments differ in many respects, and result in vastly different educational, economic, and social opportunities. While segregation is not unique to blacks in the US, its persistence through generations is troubling. The lack of integration over the course of this century is due in part to overt racial discrimination in housing laws prior to passage of the 1968 Civil Rights Act, as well as decentralized racialized residential choice by whites to live separately from blacks. While the current patterns of segregation reflect historical trends, they also perpetuate those trends to some degree, by the mismatch of services and opportunities with population need. Although most evidence supports a deleterious role for segregation, there is some evidence that when it leads to black political empowerment, adverse effects can be diminished.

Health consequences

In 1950, Dr. Alfred Yankauer proposed that residential segregation of blacks in New York City explained some of the excess black infant mortality. His paper, titled "The relationship of fetal and infant mortality to residential segregation: An inquiry into social epidemiology" was both the first to hypothesize a segregation-health association, and incidentally also the first coining of the term 'social epidemiology'.(393) He found that fetal,

neonatal, post-neonatal, and overall infant mortality all increased for both white and non-white women as neighborhood segregation increased (see Figure 2-1).

Figure 2-1. Infant mortality by neighborhood segregation, Alfred Yankauer, 1950



Following Dr. Yankauer's empirical argument for an association between residential segregation and health, little attention was paid to segregation in the public health literature. While sociologic studies often included mortality or life expectancy as one in a list of dependent variables in segregation models, the focus of these studies was on the process of segregation, rather than on describing health patterns. However within the last 5-15 years, interest has returned to understanding how segregation could pattern population health, and how such understanding might improve public health prevention efforts. The basic framework for

hypothesizing an association between segregation and health outcomes have been developed in the previous section: segregation patterns economic and educational opportunities, as well as exposure to concentrated poverty, crime, dilapidated housing, infectious disease, and stress. This section will briefly review evidence for an association of segregation with health. The association with pregnancy outcomes will be reviewed in a subsequent section, with the exception of infant mortality, which is frequently used by social science and public health researchers as a general population health indicator.

Acevedo-Garcia reviewed the health and social science literature prior to 2000 regarding associations between residential segregation (racial and economic) and mortality (both infant and adult) (394). Fourteen studies were identified, six of which evaluated infant mortality, and the remaining evaluated adult all-cause mortality, or mortality from homicide or cancer. Study designs, measures of segregation, levels of aggregation, and analytic approach varied widely across studies. While two studies (1 each for infant and adult mortality (395, 396)) had no significant association, the remaining had modest associations. In one case increasing clustering of elderly blacks in zip code area was protective for mortality (395), but otherwise increased segregation was detrimental.

Since Acevedo-Garcia's review, several more studies of health impacts of segregation have been published, expanding the health outcome from mortality (397, 398, 399, 400, 401, 402) to infectious disease (403), exposure to air pollution (355), intentional injury (404), and health risk factors such as injection drug use (405), obesity (406), physical activity (407) , and self rated health (408). These are summarized in Table 2-7, at the end of this chapter. One shortcoming of the studies prior to 2000 was over reliance on ecologic design, with minimal control for either compositional variation or evaluation of pathways of effect. While many of

these more recent studies continue to use very coarse geographic units, and some were purely ecologic, the more recent studies are notable for inclusion of multiple data sources, including longitudinal data, multi-level design, and greater consideration for different dimensions of segregation. In short, the evidence suggests that varying segregation explains some of the racial variance in health conditions, although the magnitude of this association and the manner in which it is mediated is not entirely clear.

MEASURING SEGREGATION

This section shifts from segregation as a process, to segregation as a state. Quantitatively describing the meaningful components of segregation is necessary to consider it as an explanatory variable in any association with health.

Dimensions of segregation

Residential segregation suggests a pattern which describes the degree to which people in different groups are in close living proximity to members of their own group as compared with members of another group. It is this spatial proximity which is thought to relate to the equitability of access to resources, exposures, and opportunities. Until the late 1980's, segregation was assumed to be a relatively simple uni-dimensional spectrum that could be approximated by the minority proportion in a subarea, or by a measure termed the index of dissimilarity. The index of dissimilarity is a mathematical summary which essentially measured how evenly a minority group was dispersed across an area; a perfectly even distribution would result in the same proportion of a minority group in every single neighborhood as is present in the city as a whole, while a perfectly uneven distribution would occur when minorities only resided in 100% minority neighborhoods, and majority members only resided in 100% majority neighborhoods. The index of dissimilarity ranged from 0 to 1, and could be interpreted

as the proportion of the minority population who would have to move to achieve an even distribution across the city.

Massey and Denton first proposed the notion that segregation was a more complex phenomenon in a 1988 paper where they outlined five distinct dimensions of segregation.(409) These dimensions included evenness (which was the single previous dimension), but added to it exposure, concentration, centralization, and clustering (see Table 2-3). In addition to describing the dimensions, Massey and Denton also provided data supporting the use of five mathematical indices to measure each of the five dimensions. They argued that these distinct dimensions could be, but were not necessarily, correlated for a given group or in a given area. So, for example, one group could be highly segregated in terms of clustering and centralization but not so on evenness. When a group is highly segregated on all five dimensions, it is termed hypersegregation, a condition which has been described in some cities for blacks, but not other racial or ethnic groups.(410)

Table 2-3. Massey and Denton's dimensions of segregation(409)

Dimension	Description	Index of measurement
Evenness	The degree to which two or more groups are distributed in even proportions across spatial sub-units (e.g. census tracts) of a larger area (e.g. metropolitan area)	***Dissimilarity index*** **Range**: 0 to 1 **Interp**: % of minority pop who must move to different area for all areas to be even
Exposure	The likelihood of two individuals of different groups sharing the same neighborhood. Also conceived of as the degree of isolation, or the probability that a member from one group would randomly meet someone from another group in their neighborhood.	$_{x}P^{*}_{y}$ **Range**: 0 to 1 **Interp**: prob that a randomly drawn X individual shares a unit with random Y individual

Dimension	Description	Index of measurement
Concentration	This refers to relative population density, so that a group which is concentrated has a high number of its members in relatively small spatial areas.	***RCO (relative concentration)*** **Range**: -1 to +1 **Interp**: 0 implies two groups equally concentrated, while 1 and -1 mean that one group or the other is maximally concentrated
Centralization	The degree to which a group lives primarily in the central portion of a metropolitan area as opposed to its suburbs.	***ACE (absolute centralization)*** **Range**: -1 to +1 **Interp**: 0 implies uniform distribution of groups in city center and suburbs, while 1 or -1 suggest maximal location of one group in city center
Clustering	The spatial proximity of neighborhoods to one another. A neighborhood of high minority proportion would be part of a cluster if other such neighborhoods are adjacent. Alternatively the neighborhood would be relatively isolated if it were surrounded by neighborhoods dominated by a different group.	***SP (spatial proximity)*** **Range**: 1 to ∞ **Interp**: degree of clustering for each group, so that 1 occurs if all members of area live equal distances apart, regardless of group membership. Numbers greater than 1 occur if individuals in one group live closer to same group members than non-group members.

Actually calculating the indices is not equally practical for each of the dimensions, and for this reason many investigators who pay lip service to the five dimension concept still utilize only the indices which are most convenient to calculate. In practice, census tracts are most often used as proxies for neighborhoods, and all calculations are made comparing the composition of an individual census tract to its broader metropolitan context. For clustering and centralization, formulas require calculating distance and proximity between neighborhoods and in relation to a central business district. These calculations are thus less automatable with

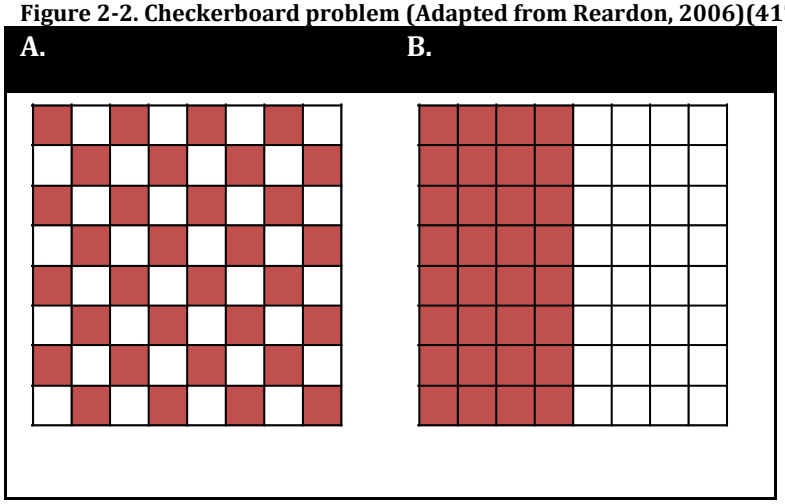
tabulated census tract data. Furthermore they must assume the proximities from some single point within a tract, thus risking some misclassification for those who live near borders of tracts.

While the five-dimensional conceptualization of segregation has been widely accepted by many investigators, it is largely these concerns about the use of aggregated census data, often without regard to the spatial relation of tracts to one another, which has drawn criticism to the Massey and Denton framework. For instance, two dimensions—evenness and exposure—were assumed by Massey and Denton to be aspatial in nature (the location of the neighborhood in relation to other neighborhoods is less relevant than the proportion of group members within the neighborhood). However Wong suggested much information on segregation patterns even within the dimension of evenness is lost due to the aspatial nature of the measurement.(411, 412) This argument has been extended by several other groups, noting that residential segregation is an inherently spatial phenomenon and that it is only the arbitrary choice of geographic units (typically census tracts) and the aspatial nature of some measures which make the five dimensions distinct.(371, 413, 414, 415) These two features result in three problems: the 'checkerboard' phenomenon, the modifiable areal unit problem, and issues of spatial scale. They will be described in turn.

Despite the acceptance of the five-dimensional conceptualization of segregation, many empiric studies use a single measure of segregation, namely the dissimilarity index. As previously discussed, this index compares the population composition within each sub area to the composition of the area as a whole. However, because of the failure to acknowledge the spatial proximity of neighborhoods to one another, the dissimilarity index can fail to indicate a change in composition that occurs across neighborhoods. This is termed the checkerboard

problem, and is visually depicted in Figure 2-2 (416) Each square represents an area, such as neighborhood, in which individuals are aggregated and the color represent the proportion of one group in each area. The aspatial dissimilarity index would register both panel's A and B to represent the same amount of segregation, as determined from the comparison of each neighborhood's composition to the composition overall. The Massey and Denton clustering dimension would register a change from panel A to B, but this example points to similarities in evenness and clustering, which are dependent on the size of the unit being measured.

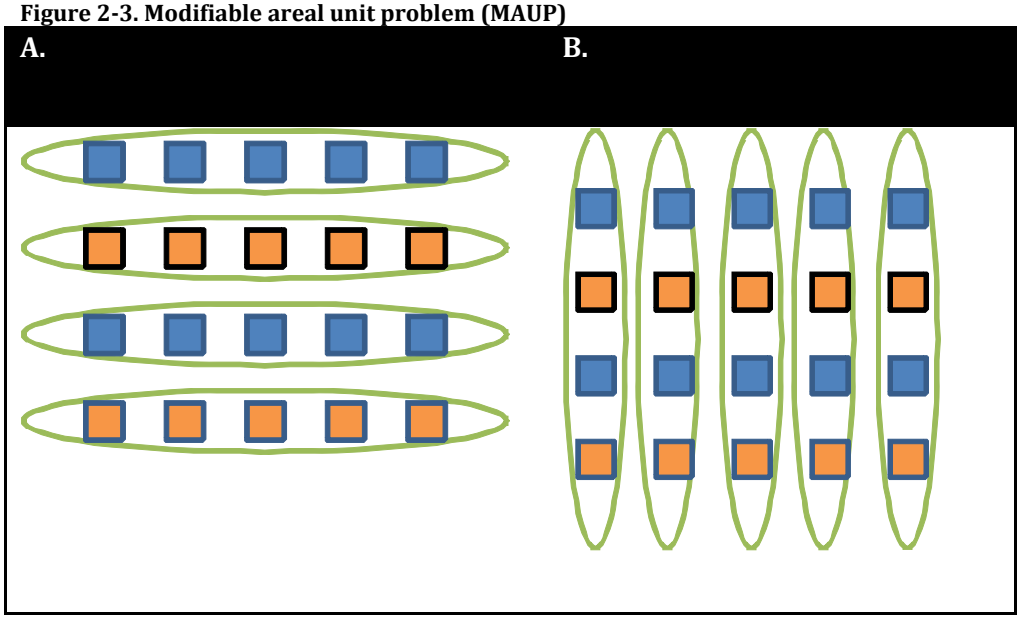
Figure 2-2. Checkerboard problem (Adapted from Reardon, 2006)(417)



The modifiable areal unit problem (MAUP) occurs because of the use of arbitrary geographic boundaries within which individuals are counted as an aggregate.(411) Some geographic boundaries are intimately connected to the exposure of interest. For example property taxes are paid based on whether a residence is within the tax district. Living within feet of the boundary or at the very center of the area does not matter in calculating taxes. However other geographic boundaries may be poorer proxies for the exposure of interest. Census tracts are frequently used as a base unit for estimating segregation but their boundaries may not coincide with the spatial units of research interest, such as neighborhoods. If they are

arbitrary in relation to the intended spatial unit, significant misclassification can occur. A simple and extreme example is displayed in Figure 2-3, where each square is an individual household, and each oval is a geographic area for the purposes of aggregate reporting. In panel A, there is complete segregation, and in panel B there is complete integration, while the actual location of residents did not change at all.

Figure 2-3. Modifiable areal unit problem (MAUP)



Related to the sometimes arbitrary use of geographic subareas, is the more general concept of spatial scale. Because spatial proximity is at the heart of segregation and proximity is not binary, but continuous, the size of the area around each person which is considered to represent their environment is extremely relevant in both the conceptualization of how segregation impacts health, as well as in the number generated from any formula.(418) Within a given metropolitan area, there could be finely-patterned, small scale segregation or there could be a broad, spatially coarse pattern. Fischer, et al, noted that this pattern could extend from below the tract level up to the level of the region of the US, with areas experiencing

different patterns of segregation at different scales.(419) In terms of a segregation-health relationship, the scale of measurement could tap into different processes, including local economic opportunity and service provision to regional patterns in industry and economic development. The point is that to fully account for the spatial nature of segregation, the scale of measurement is critical. While using census tracts as proxies for neighborhoods is not precisely aspatial in terms of scale, it is certainly arbitrarily spatial, in that the geographic boundaries of a given tract may or may not match up with the underlying social phenomena of interest. On the other hand the construction of census tracts was originally to create demographically homogenous spatial units. The degree to which they continue to be homogenous is debatable, but this goal is worthy of note as well.

In response to these and other concerns, several extensions of the five-dimensional Massey Denton approach have been proposed. Johnston, et al used a data driven process to argue that the five dimensions are not in fact distinct, but rather can collapse down to two dimensions which they termed separation and location.(420) Mele (413), Grannis (414), and Wong(412) have critiqued that aspatial approach to segregation, and each have recommended alternative spatial approaches. Reardon, et al, combine these concerns, and develop both a critique of the Massey-Denton dimensions as well as a spatial approach to measurement which addresses MAUP, the checkerboard problem, scale, and allows for additive decomposability of spatial subareas so as to estimate the proportion of total segregation occurring at specific levels.(371, 417)

Reardon et al surmised, as others have, that the distinction between evenness and clustering is a function of reliance on particular subareas. Thus they argue that unless the subarea boundaries are meaningful, any distinction is arbitrary. They collapse the five

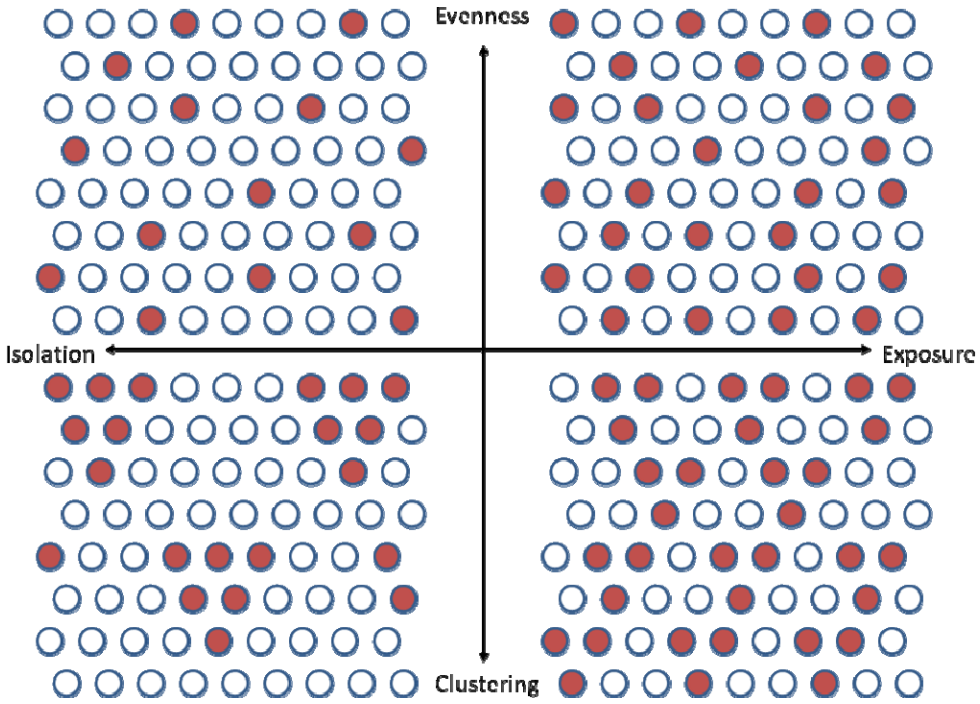
dimensions into two distinct dimensions, termed spatial exposure and spatial evenness. (371) Spatial exposure describes the average exposure of one group to another, and is thus a combination of composition and proximity. A highly segregated area in terms of exposure would be one in which blacks inhabit areas that are rarely inhabited by whites. Spatial evenness is independent of composition, and solely describes the degree to which population groups are evenly distributed across space. A highly segregated area in terms of evenness would be one in which blacks are distributed differently through space than are whites (see Table 2-4). Notably these theoretically derived dimensions are very similar to the two data-derived dimensions described by Johnston.(420)

Table 2-4. Reardon dimensions of segregation(371)

Segregation dimension	Definition	Corresponding Massey and Denton dimension
Spatial exposure	Extent to which members of one group encounter members of another group within a defined local spatial area. It describes the 'typical environment experienced by individuals'	Evenness, Clustering, and Exposure
Spatial evenness	Extent to which groups are similarly distributed in space. It is independent of the composition of the population (unlike exposure)	Centralization and Concentration as specific sub categories

Figure 2-4 graphically displays the various patterns these two dimensions could describe. While the top two panels have populations where black and white households are evenly distributed in space, they differ with respect to their relative isolation or exposure to one another. The bottom two panels, on the other hand have greater clustering of black neighborhoods together and white neighborhoods together, but again differ on whether these clusters tend to be isolated from one another or close to one another.

Figure 2-4. Spectrum of spatial evenness and exposure (Adapted from Reardon, 2004)



Updated measures of segregation

Measures of segregation have the goal of meaningful description in ways that allow comparison of one area to another, one group to another, or one dimension to another. Based on the arguments developed by Reardon and Johnston, spatial segregation measures for the collapsed two-dimensional segregation will be discussed, with the exception of the aspatial dissimilarity and exposure indices, which are introduced only for comparison to spatial measures. Only measures which meet accepted criteria for evaluation are included here.(421, 422) Reardon's notation is introduced in Table 2-5.

Table 2-5. Notation for segregation measures (Adapted from Reardon, 2006)

Notation	Description
R	A spatial region made up of r subareas
r	Subareas of region R
p	Points within area R
M	Mutually exclusive population sub-groups (such as racial groups)
m	Index for each subgroup within M
t	Population count for subarea r
$\mathbf{t_m}$	Population count of group m in subarea r, such that : $\sum_m t_{rm} = t_r$
τ	Population density
π	Population proportion
$\boldsymbol{\tau_p}$	Population density at point p
$\boldsymbol{\tau_{pm}}$	Population density of group m at point p
T	Total population in R such that $\sum_{r \in R} t_r = T$ and $\int_{p \in R} \tau_p dp = T$
$\boldsymbol{\pi_m}$	Proportion of group m in total population (e.g. proportion black)
$\boldsymbol{\pi_{rm}}$	Proportion of group m in subarea r
~	A super-positioned tilde (~) denotes the spatial environment of a point, rather than the point itself

The frequently used aspatial exposure measurement is denoted ${}_mP_n^*$, implying it measures the exposure of members of group *m* to group *n*. Commonly the subareas, *r*, are operationalized as census tracts so that the exposure could be calculated by:

Equation 2-1. Aspatial exposure index

$$ {}_m P_n^* = \sum_{r \in R} \frac{t_{rm}}{T_m} \pi_{rn} $$

The aspatial dissimilarity index, which measures evenness, is often interpreted as the proportion of members of one group who would need to move in order to equalize the distribution of that group across the entire area. The formula is:

Equation 2-2. Aspatial dissimilarity index

$$ D = \sum_{r \in R} \frac{t_r \left| \pi_{rm} - \pi_m \right|}{2T\pi_m (1 - \pi_m)} $$

The shortcoming of these aspatial measures is their reliance on arbitrary geographic units in their calculation, and the failure to account for proximity of units to one another. Although many spatial alternatives exist, the approach developed by Reardon, et al, is presented here. To begin with, $\sim\tau_p$ and $\sim\tau_{pm}$ are defined as the population-weighted total density or group density in the environment of point p, where the points are weighted according to their proximity to p. A spatial proximity function defines the proximity between every pair of points in area R. Reardon defines $\varphi(p,q)$ as a non-negative function describing proximity of points p and q so that $\varphi(p,q) = \varphi(q,p)$ and $\varphi(q,q) = \varphi(p,p)$ for all *p,q* contained in R. Therefore $\Phi_p = \int_{q \text{ in } R} \varphi(p,q)dq$. The function Φ(p,q) defines the extent of the local environment, and could be a straightforward bounded Gaussian distance-decay function which emphasizes closer points over further points, or could be a custom function which accounts for boundaries which block (interstate highways) or facilitate (mass transit) interaction.(371) The population density in

the area around point p is therefore the weighted average of the local environment of p, as defined by the proximity function Φ(q,p) as shown here:

Equation 2-3. Spatial area population density

$$\tilde{\tau}_p = \frac{1}{\Phi_p} \int_{q \in R} \tau_q \phi(p,q) dp$$

From this definition, a smoothed population density surface can be calculated for each group, and the population composition for a person of group m living at point p is:

Equation 2-4. Spatial area population composition

$$\tilde{\pi}_{pm} = \frac{\tilde{\tau}_{pm}}{\tilde{\tau}_p}$$

Spatial Exposure Index

Using this density surface and knowledge about the composition at each point p, a spatial exposure index is proposed by Reardon as:

Equation 2-5. Spatial exposure index

$$_n\tilde{P}^*_m = \int_{p \in R} \frac{\tau_{pm}}{T_m} \tilde{\pi}_{pn} \, dp$$

Like the aspatial exposure index, it ranges from 0 to 1, and can be interpreted as the average exposure of a member of group m living at point p to a member of group n. It depends on the proximity function, which allows specification of the scale and form of the local environment. For example an estimate of exposure where the local environment is defined as a 500 meter radius around point p would be different from one where the environment is defined with a radius of 4,000 meters.(418) The choice of proximity function thus defines the scale extent and type and should be hypothesis driven for a given study.

Spatial Evenness Indices

Several spatial measures for evenness have been proposed, and two will be discussed here. The spatial dissimilarity index is a generalization of the aspatial version:

Equation 2-6. Spatial dissimilarity index

$$\tilde{D} = \sum_{m=1}^{M} \int_{p \in R} \frac{\tau_p}{2TI} \left| \tilde{\pi}_{pm} - \pi_m \right| dp$$

Although no longer interpretable as the proportion of the population which would need to move to produce even distribution, it is still an index ranging from 0 to 1, and indicates similarity or differentness of local environments compared to the overall area. Reardon raises two concerns with the use of the dissimilarity index (either spatial or aspatial). First, the dissimilarity index will not always indicate a change, when a member of group m moves from an area with high proportion of m, to an area with a lower proportion. Secondly, the dissimilarity index is not readily decomposable into within and between area portions.(371, 421)

The relevance of the multi-dimensional and spatial nature of segregation has long been recognized (409, 412, 414), yet continued reliance by researchers on single, arbitrarily spatial indices result largely from lack of practical ways to use complex spatial measures. Wong and Reardon have each developed methods for calculating spatial indices of segregation using ArcGIS software.(423, 424, 425) These methods and their output will be further reviewed in Chapter 3.

SOCIAL DETERMINANTS OF PRETERM BIRTH

Thus far, this chapter has broadly reviewed methodological and substantive issues critical in understanding the role of social determinants—and segregation specifically—and

health. In this final section, focus is returned to determinants of preterm birth. Residential segregation is the primary exposure of interest in this dissertation, however segregation likely exerts influence on population health via numerous mediating characteristics, including neighborhood deprivation, relative economic opportunity, and exposure to stressful life events such as racism, crime, and high density living. Therefore this portion of the review is divided into two sections: neighborhood effects without consideration for segregation, and studies which specifically considered segregation. Although the volume of neighborhood effects studies conducted with low birth weight (<2500 grams) as the outcome is significantly larger than that for preterm birth, this review will focus primarily on studies explicitly considering preterm birth (<37 weeks gestation), very preterm birth (<32 weeks gestation), or very low birth weight (<1500 grams) as an outcome. The role of social exposures may generalize across many pregnancy outcomes including prematurity, growth retardation, birthweight, and infant mortality. Restriction to specific outcomes significantly reduces the number of studies available for review. However given the biologically distinct pathways through which preterm birth occurs, this focus on (somewhat) homogeneous outcomes improves comparability between studies. Notably, the focus of this dissertation is on the tail of this distribution, very preterm birth (<32 weeks), or the closely correlated category very low birthweight (<1500 grams). For this reason, even within the small literature on neighborhood effects on preterm birth defined as <37 weeks, important heterogeneity may remain. In the case of the segregation literature a handful of studies utilizing low birthweight as an outcome will be discussed because of their study designs.

NEIGHBORHOOD EFFECTS AND PRETERM BIRTH

Neighborhood deprivation and quality is operationalized in many ways using both aggregate (computed from individual, e.g. median household income) and integral (variables which do not have equivalent individual level measures, e.g. violent crime rate) variables.(426) Characterizations of neighborhoods can also be made with single constructs (e.g. proportion adult males unemployed) or with composite scores made up of several different variables. Composite scores may add depth to abstract concepts such as neighborhood quality, but can be difficult to translate into specific prevention efforts.

Four studies considered neighborhood or local area deprivation in relation to preterm birth among white women. In separate studies in British Columbia and Quebec, Luo et al categorized neighborhoods by income quintiles, and considered risk for birth prior to 37 weeks gestation. In British Columbia, women living in the poorest compared to wealthiest neighborhoods had increased risk of preterm birth (aOR 1.26, 95% CI 1.17-1.35), controlling for maternal age, ethnicity, comorbidities, and obstetric complications.(427) A similar study design in Quebec also included maternal education in the model. For urban women, women in the poorest compared with the richest neighborhoods experienced increased risk for preterm (aOR 1.16, 95% CI 1.12-1.20) controlling for obstetric risk factors as well as maternal education.(428) Dibben et al used a 10% sample of all live births from 1996 to 2000 in England and Wales.(429) Family income, social/occupational class, and maternal age were considered in addition to a composite measure of area deprivation (in quintiles). Area deprivation was non-significantly associated with odds for VLBW (aOR 1.14, 95% CI 0.92-1.41) after controlling for social class, age, and income. Finally, in a population based time-series study in Scotland, small area deprivation scores were calculated from a combination of male unemployment, car

ownership, social class, and domestic overcrowding. Odds for very preterm birth (<32 weeks) were increased for women in the worst compared with the best areas, controlling for smoking, obstetric risk factors and age (aOR range from 1.53 to 2.06 from 1980 through 2003, with all statistically significant).(226) There was a slight trend toward increasing disparity over the twenty year period.

Findings in the US have paralleled Canadian and European results to some degree, but the heterogeneity of risk by race is a unique part of neighborhood effects research in this country. A multi-level study of births in Louisiana in 1997-98 modeled gestational age as a continuous variable, and found that median household income and number of boarded up urban buildings in the neighborhood were associated with a shorter gestational length, controlling for race, maternal education, and obstetric risk factors.(430) In a multi-level modeling analysis controlling for individual income and age, Kaufman, et al, describe a protective effect for preterm birth for black women living in wealthier census tracts (median income >$30,000) compared to black women living in poorer tracts (aOR 0.59, 95% CI 0.36-0.96).(431) There was no such effect for white women. Pickett, et al, also reported racially different findings in a case-control study in San Francisco.(432) Not only were individual-level risks for preterm birth different by race (maternal education important for blacks but not whites, family 'working class' status important for whites but not blacks), but significant neighborhood contextual variables were different (for whites, only the change in male unemployment in the ten years between two censuses, while for blacks census tract % unemployed, median family income, and 10 year change in the tract proportion black were significant). Additionally, Pickett noted that the effects were often non-linear with, for example,

increased risk for preterm birth for black women who lived in tracts with both very high and very low magnitude changes in the proportion of the census tract which was black.

O'Campo, et al compared the effect of a neighborhood deprivation index on preterm birth risk in black and white women in eight different geographic areas in Michigan, Maryland, Pennsylvania, and North Carolina.(433) In contrast to the study by Kaufman, above, increasing neighborhood deprivation was a more potent predictor for white women than for black women (aOR white 1.57, 95% CI 1.41-1.74; aOR black 1.15, 95% CI 1.08-1.23). While the absolute effect varied across the eight distinct geographic areas, the pattern was similar in all. Finally, Reagan, et al attempted to describe the cumulative effect of living in poor neighborhoods since age 14 on preterm birth risk using a longitudinal follow up cohort.(434) Neighborhood poverty was associated with increased risk for very preterm birth (defined as <33 weeks in this study) only among blacks, but not whites. While blacks were more likely than whites to have cumulative exposure to states with greater income inequality (as measured with the Gini coefficient), this cumulative inequality exposure was not significantly associated with preterm birth risk.

Finally, in a study evaluating the role of a specific component of neighborhood quality, Messer, et al, assessed the impact of neighborhood crime on preterm birth risk.(230) All births in Raleigh, NC in 1999-2000 were geocoded and merged with geocoded crime data from the same period. Neighborhood deprivation was also calculated using the same index as in the O'Campo study above. While violent, theft, property, and vice crimes were all crudely associated with preterm birth risk, in adjusted multi-level analyses, only residence in very high violent crime neighborhoods was independently associated with preterm birth for both black and white women (aOR black 1.4, 95% CI 1.0-2.1; aOR white 1.5, 95% CI 0.9-2.6). Notably

neighborhood deprivation also maintained an independent association with preterm birth, controlling for crime, and maternal age, education, and marital status.

SEGREGATION AND PRETERM BIRTH

To consider segregation as a relevant determinant of excess preterm birth among black women, it must be plausible that it directly increases risk in individuals or that it causes black women to disproportionately live in environments which are themselves toxic. Evidence for both has been discussed. As a non-random sorting process, segregation assigns people to residential environments on the basis of race and income. Increasing isolation may increase exposure to racism and other forms of interpersonal stress, as well as to environments which are stressful for other reasons, such as high violent crime rates or overcrowding. Additionally racially and economically segregated neighborhoods may have inadequate health and social services, limiting access to material goods and services. Finally, either through peer influence on behavior or stress coping, negative health behaviors may be adopted as a result of the social environment in highly segregated neighborhoods.

The literature looking specifically at residential segregation and preterm birth is small (see Table 2-8 at the end of this chapter). Only four studies were identified which directly assess some dimension of segregation with preterm birth. Pickett, et al looked at census tract racial composition and income incongruity among all women who delivered live singleton births in Chicago in 1991.(435) They considered a tract to be predominantly black when 90%+ of its inhabitants were black, and mixed when the proportion was less than 90% (75% of blacks in Chicago live in such neighborhoods, with the remaining 25% spread equally across tracts that are <5% to 80% black). Positive income incongruity was defined as a woman living in a tract which had a median family income one standard deviation higher than the median income

for women of her age-race-education-marital status. Women living in such relatively wealthier census tracts had lower odds for preterm birth if the tract was also densely black (aOR 0.83, p<.01) controlling for individual characteristics, but there was no similar protection if the tract was mixed. The authors concluded that experiences of racism when living as a minority in a mixed neighborhood competed with the beneficial forces of living in a wealthier neighborhood. Following up on this study, Masi, et al considered the role of violent crime and neighborhood economic deprivation in these same Chicago neighborhoods, but reports no independent effect of either on preterm birth after controlling for individual characteristics.(436) Vinikoor, et al, used the estimates from the Pickett study as an informative prior in a Bayesian analysis of racial density and income incongruity in cities in North Carolina which are relatively less segregated than Chicago.(437) Because 75% of blacks in the NC cities lived in tracts which were 20% black, they used this as the cut point. Their results were similar, with a protective effect against preterm birth associated with living in a wealthier neighborhood if the tract also had a high proportion black, but no effect of income incongruity if the tract was mixed.

Bell et al measured two of the five Massey and Denton dimensions (isolation and clustering) in a comparative study of 225 metropolitan areas. In a multi-level model controlling for individual as well as metropolitan characteristics they report an increased adjusted odds for preterm birth (aOR 1.27, 95% CI 1.10-1.46) for black women living in cities with high isolation, but lower risk for black women living in cities with high clustering (aOR 0.86, 95% CI 0.75-0.99).(438) This is consistent with previous studies which suggest that dimensions of segregation which increase same-race social support are protective, while dimensions which increase isolation are deleterious.

In addition to studies directly assessing preterm birth risk, two studies have evaluated the association of segregation with pregnancy health relevant risk factors. Bell again compared metropolitan areas to determine whether smoking during pregnancy was associated with increasing segregation in black urban women.(439) For both isolation and clustering, they found a U-shaped association between segregation and smoking during pregnancy, with increased risk in both high and low segregation cities compared to moderate segregation cities. Finally, in a longitudinal nationally representative follow up study, Sucoff & Upchurch found that black women living in segregated census tracts had increased risk for non-marital adolescent pregnancy than women in less segregated neighborhoods (HR 1.54, 95% CI 1.06-2.23).

A series of studies of the associations of segregation with low birth weight conducted in New York City are informative because of their methods and study design. Grady found that increasing spatial isolation was associated with increased risk for low birth weight among black women controlling for individual income, behaviors, and risk factors(440), and that some of this risk was mediated through increased risk for chronic and pregnancy related hypertension.(441) While segregation initially appeared to impact all black women equally, evaluation of maternal nativity (country of birth) found that segregation had the strongest negative effect for US born black women, and no effect for foreign born black women, for whom all variation in risk was explained by control for individual level variables.(441)

While segregation has not been uniformly found to associate with preterm birth, important patterns are evident. One is that there does not appear to be any effect, protective or detrimental, for white women in segregated cities. This specificity for blacks may be supportive of segregation as a causal determinant rather than a correlate of some other city-level variable.

Another common theme among studies is that different dimensions of segregation may have different effects on preterm birth (e.g. isolation versus clustering), an observation which is strongly supported for non-health outcomes by the sociological literature. A final observation is that nearly all studies discussed operationalize neighborhoods as census tracts, and calculate all segregation measure from these geographic units. While the consistency of findings with this approach suggests there may be utility to this approach, there is no theoretical basis for this particular scale of measure.

PUBLIC HEALTH RELEVANCE: IS SEGREGATION A MODIFIABLE RISK FACTOR?

Given the stubborn persistence of segregation in the United States, it may not be unreasonable to ask whether research into the health consequences of segregation advances the public health agenda. In other words, what is the point of testing causal hypotheses of the deleterious effect of segregation if reducing its occurrence is beyond the purview of epidemiologists or public health more generally? Two responses could be made to this query: better understanding of causal associations may lead to unanticipated opportunity for health intervention; and the extension of the causal chain beyond the confines of the individual requires that we (re)turn to community focused public health interventions. Elaboration of each of these responses can be made in the traditional framework of public health prevention, where interventions are categorized as primary, secondary, or tertiary.

Primary prevention (clean water, vaccinations of children, improved nutrition) was largely responsible for the significant drop in infant mortality through the twentieth century, but most recent efforts have focused on secondary and particularly tertiary interventions. The dramatic reductions in mortality among very preterm and very low birthweight infants following use of surfactant and steroids over the past 25 years (a tertiary intervention in high

risk pregnancies and births to reduce mortality), as well as the regionalization of the neonatal medical care, represent important advances.(442) While the regionalization of care is an attempt to insure equal access to high-technology obstetric and perinatal services for all high risk pregnancies, disparities exist despite these interventions, and further mortality reductions in the absence of reduced incidence of very preterm or very low birthweight births seem unlikely. Other intermediate tertiary interventions such as tocolytics in the presence of preterm labor have as their most optimistic target, a 48 hour delay in delivery in order to transfer the mother to a tertiary care center.(443)

Efforts at secondary prevention have focused on identification of 'high risk' pregnancies, but efficacy has been hampered by low sensitivity and specificity of predictors of preterm birth, combined with inadequate interventions to ameliorate risk. The 2008 recommendation by the US Preventive Services Task Force against routine screening of pregnant women for bacterial vaginosis is indicative of both the poor specificity of BV for prediction of preterm, as well as the low efficacy of antibiotic treatment for BV.(444)

Pre-conceptional medical care represents one of the chief primary preventions for poor pregnancy outcomes. Adequate and appropriate nutrition, use of prenatal vitamins, and adequate access to and use of family planning services all constitute recommended preconception medical services.(445) Improved comprehensive health care for all women(442) and improved education about and access to full-spectrum family planning services(446) in particular may address a portion of the racial disparities in poor pregnancy outcomes, but may also miss important structural determinants of differential health states.

Even if accumulating evidence supports a causal role for segregation and excess black preterm birth, to suggest that altering segregation is a quick and easy solution is clearly naive.

On the other hand, segregation (and poverty and discrimination) are all socially created phenomena, and as such are theoretically modifiable. But what are the concrete implications for public health and policy more generally of negative segregation-health associations? In a recent commentary on policy addressing the ill effects of poverty and segregation on child health, Acevedo-Garcia, et al suggested that researchers "feel paralyzed by politically contentious redistributive policy implications of the literature on social determinants of health or suggest that absent systematic policies for reducing socioeconomic inequalities, only public health and health care interventions provide instruments for addressing health disparities."(381) They recommend two policy approaches for addressing the health effects of segregation: people-based interventions and place-based interventions.

Only a handful of intervention trials have been conducted to facilitate moving families out of hyper-segregated, poverty-concentrated neighborhoods.(447, 448) One example was the Moving To Opportunity (MTO) study, which randomly allocated housing vouchers and counseling to families living in public housing projects. Most interventions such as the MTO were designed with crime, educational, and income outcomes, and thus give limited insight into health effects of the intervention. These housing mobility interventions represent one kind of people-based approach to segregation. Other people-based action includes litigating civil rights actions against governmental housing authorities who formulate policies which increase rather than decrease segregation. A parallel between this as a public health approach and litigation of tobacco companies can be loosely made.

A place-based approach requires determination of what intermediate characteristics of the segregated neighborhood do the most harm. For example if lack of healthy food shopping choices within neighborhood is determined to contribute to higher BMI among the

neighborhoods' residents, policies which encourage locating supermarkets in those areas could be beneficial. The increased interest in the built environment and chronic disease has led to examples of large scale change in urban planning policy.(449) Other place-based policy approaches which might more directly impact segregation include support for mixed-income housing development, broadening the tax base for public schools, and continued regulation of practices such as mortgage redlining and overt housing discrimination.

Continued pursuit of secondary and tertiary preventions for preterm birth and its corresponding morbidity and mortality is clearly important. New medical therapies and interventions will likely reduce some of the burden. But it is unlikely that medical technology alone will erase decades of social disparity in health. That this implies interventions beyond medical service does not make it unfeasible for public health. Of the top ten public health achievements of the 20th century (Table 2-6), as determined by the Centers for Disease Control(450), most had a significant community intervention component, and four represent community policy choices completely outside of the medical services arena. The point is not that medical services are unimportant, but rather that public health has historically included community-level determinants of disease and injury within its realm. It remains unclear whether segregation causes (directly or indirectly) excess very preterm birth among black women. However, should a causal link be established, intervention is neither futile nor unrealistic. Understanding of the causal association increases the opportunity for interventions at intermediate steps, and may contribute to a larger call for addressing the underlying structural insults.

Table 2-6. Top 10 Public Health Achievements

Top 10 public health achievements of the 20th century(450)	
Achievement	**Medical or Community intervention**
1. Vaccination	Both
2. Motor-vehicle safety	Community
3. Safer workplaces	Community
4. Control of infectious diseases	Both
5. Decline in deaths from coronary heart disease and stroke	Medical
6. Safer and healthier foods	Community
7. Healthier mothers and babies	Both
8. Family planning	Medical
9. Fluoridation of drinking water	Community
10. Recognition of tobacco use as a health hazard	Both

SUMMARY

Just as individual level risk factors have not yet succeeded in explaining all variation in risk for preterm birth, neither have social determinants. However the past decade has seen significant growth in interest and development of methods allowing more complete accounting of the role for social environment. That some of the strongest risk gradients in very preterm birth are social in nature (income, education, and race) suggests that a substantial amount of the excess preterm birth burden experienced by black women is amenable to change by more complete understanding of the interplay of social environment, individual behavior, and host susceptibility. The research to date on segregation and preterm birth leaves a number of

questions unanswered, and a number of issues unresolved. These can be grouped by outcome, exposure, and study design.

Outcome

While there are many risk factors in common among low birthweight, growth retardation, preterm birth, fetal death, and infant mortality, these pregnancy outcomes represent overlapping but distinct biological phenomena. Even within the single category of preterm birth, it is clear that great heterogeneity of etiology can cloud determination of any particular association. The reasons for a late versus very early preterm birth could be drastically different, so that studies lumping all together may miss underlying patterns. In part because of this heterogeneity, and in part because of our general lack of understanding of the causes of preterm birth, most studies to date fail to propose a biologically plausible link between a social exposure and the occurrence of preterm birth, much less test the existence of that link. Focusing on births before 32 weeks gestation does not eliminate heterogeneity, but does bring much greater focus to a group of infants at exorbitantly high risk for morbidity and mortality, and a group who contribute disproportionately to the racial disparities in infant mortality.

Exposure

Segregation as an exposure is not entirely new, but has received very little substantive or methodological attention in the public health literature. While most early studies were purely ecological in nature, more recent studies have utilized individual and area based levels of data in multi-level designs. Yet several problems remain in associating segregation with preterm birth. Most studies use racial composition in a census tract as an indicator of level of segregation, but this is only one aspect of segregation, and not necessarily the most relevant.

Few studies specify a theoretically and biologically plausible link between segregation and health outcome. There are nearly no studies which measure segregation as a spatial feature, instead assuming that census tracts are spatially autonomous islands, with no relation to one another. Related is the lack of attention to a plausible scale for the effects of segregation. Studies are nearly universal in using the census tract as the proxy for neighborhood, but little attention has been paid to whether micro- or macro-segregation in neighborhoods is most relevant. It is also unclear what form the relationship between segregation and health might take, although most studies to date assume it is linear. The possibilities for non-linear or threshold effects have not been fully evaluated. Few studies to date have measured mechanisms by which segregation might impart its effect. Segregation could have both direct and indirect effects, which could be mediated through psychosocial, neo-materialistic, or social capital processes. While it is common to control for individual and metropolitan level confounders, it is less common to attempt to determine what area or individual level factors might *mediate* rather than *confound* the association between segregation and a biological pathway to preterm birth.

STUDY DESIGN

Improvements in study design, including simultaneous use of data from different levels (hierarchical or multilevel designs), have been one important advance. While this approach has been promising in explaining variation in risk attributable to different levels, making causal inference from such complex data arrays remains challenging.(451) In the case of racial disparities in preterm birth, decomposing variance along another dimension is also important. Racial disparities imply inter-racial variation, and it is an implicit goal of many studies to identify factors which 'explain' this inter-racial variation. However the geographical

distribution of MSA-level very preterm birth risk, as well as the race-specific slopes for education and income suggests that there is notably different intra-racial variation in risk. Many studies fit separate models for black and white women, implicitly acknowledging that risk factors may differ, but few explicitly discuss the degree to which the joint understanding of intra- and inter-racial variation in preterm birth risk might aid in identifying modifiable risk factors.

Finally, the choice of a statistical model for analyzing data generated from any study design deserves attention. While twentieth century epidemiology flourished with the application of the frequentist statistical techniques of Fisher, Neyman, and Pearson these approaches may not be best suited to the questions of the etiology and prevention of complex chronic disease facing epidemiologists today (452). Greenland argues that the consideration of a large number of potential exposures, with likely measurement error of, each with a possibly low prior probability of association is better suited to Bayesian analysis where prior belief is combined with the data to produce an updated posterior probability statement for a parameter, accounting for specified uncertainty (453). Rather than relying on the assumption that a given study could be repeated thousands of times (as is the case with frequentist inference), Bayesian statistics allows interpretation of model results as simply an update in belief resulting from a given set of conditions and data.

Many other aspects of study design are worthy of attention, but are not addressed in the design of this dissertation. For instance time-series or longitudinal approaches to the social environment-pregnancy health questions are needed to tease out temporality and time frame. A life course perspective on health may be illuminating etiologically but is challenging from an intervention point of view as the relevant window of an exposure may occur decades prior to

the observed health event. Integration of improved social measurement with biological processes is also largely missing from the current literature, and will likely bring greater insight to the questions at hand.

Table 2-7. Recent literature on association of segregation and health

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
ADULT MORTALITY						
Jackson, et al, 2000	Incidence of black and white adult mortality	Residential racial segregation	National Longitudinal Mortality Study, 1978-1989	% black in census tract in 1980	Survival analysis adjusting for age, family income	Black men aged 25-44 year old, adjusted hazard ratio of death 2.7 (95% CI 1.5-4.9) for those living in tracts 70%+ black compared to <10% black. Black women 25-44 year old, crude HR 2.1 (1.0-4.3), dropped to 1.7 (0.8-3.6) with control for family income
Cooper, 2001	Black and white adult mortality from coronary heart disease in 47 largest US cities	Residential racial segregation (evenness)	NCHS mortality files, 1996, and 1990 Census segregation estimates	Aspatial Gini coefficient calculated at census tract level	Ecologic correlation at MSA level. Considered interaction with MSA income inequality	Overall CVD mortality increases independently and interactively with increasing racial segregation and income inequality
Lobmayer & Wilkinson, 2002	Variation in black and white adult mortality and potential years	Residential economic segregation (evenness)	NCHS mortality files from 276 MSAs	Jargowsky Neighborhood Sorting index (ratio of neighborhood to	Multiple linear regression.	MSA level income inequality is correlated with economic segregation. 30% of

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
	of life lost (PYLL)			total income standard deviation) and ratio of within to between tract income inequality		variance in infant mortality is explained by economic segregation. Overall income inequality is more important than segregation in explaining adult mortality
Inagami, et al, 2006	Black adult mortality rates	Residential racial segregation	New York City mortality records 1999-2000 and Census 2000	Living in a zip code tabulation area that is predominantly (>70%) black or white	Linear multiple regression of effect of each 1% increase in same-race composition, controlling for area % in poverty, % high school graduated, % unemployed	Adult black mortality decreases (β= -1.47, se=0.1) for each 1% increase in zip code area blacks among 25-64 year old; Decrease is greater (β=-13.02, se=0.03) for 65+
INFANT MORTALITY						
Strait, 2006	Infant mortality rates (3-year averages) by race and black-white rate differences in large MSAs	Residential racial and economic segregation (evenness)	NCHS linked birth-death records from 92 MSAs in 1982-84, 1992-94, 1999-2001	Racial: Aspatial dissimilarity index at census tract level Economic: Neighborhood poverty rate (NPR: % of total population living	Multiple linear regression controlling for % teen births and %unmarried births. Models evaluate interaction between racial and economic segregation	1982-4: Among blacks, significant synergistic interaction between income segregation and racial segregation 1992-4 & 1999-2001: Racial and

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
				in tract 40%+ poverty) and Concentrated poverty rate (CPR: % of poor who live in tract 40%+ poverty)		economic segregation interaction for IMR among whites but not blacks.
Hearst, 2007	Black and white infant mortality rates in cities over 250,000 people	Residential racial segregation (isolation)	NCHS linked birth-death records for 1999-2002 in cities with pop 250,000+	Aspatial isolation index calculated for each census place (e.g. city not MSA) based on tract level data dichotomized into hyper segregated (>0.6) or not.	Used propensity score matching to compare excess black deaths in hypersegregated vs. not cities, stratifying on city tax and economic characteristics	No independent effect hyper-segregation vs. not
CHRONIC AND INFECTIOUS DISEASE						
Subramanian, et al, 2005	Black and white adult self-rated health in MSAs with pop 100,000+	Residential racial segregation (evenness and isolation)	2000 Current Population Survey (CPS) conducted for US Bureau of Labor Statistics	Aspatial dissimilarity and isolation indices (scaled from 0-100) at census tract level	Multi-level logistic regression model with individual and MSA level covariates	Increasing black isolation is associated with lower self-rated health among blacks (OR 1.05 for each 10 point change in isolation)
Chang, 2006	Black and white adult BMI	Residential racial segregation	BRFSS, 2000 and US Census 2000	Aspatial isolation index calculated at the census tract	Multi-level linear and logistic regression	Increasing black isolation independently

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
		(isolation)		level	controlling for individual and MSA level social and health characteristics	associated with increased BMI (p<.01) and increased odds of being overweight (OR for 1 SD increase in isolation index 1.14, 95% CI 1.05-1.24)
Morello, 2006	Tract level air toxin exposure and estimated cancer risk among black and white adults	Residential racial segregation (evenness)	1996 EPA tract level air toxics assessment, US Census 1990 for segregation and demographic measures in 309 MSAs	Aspatial dissimilarity index at the census tract level	Poisson regression controlling for area level covariates	Blacks living in extreme compared to low/mod segregated cities have RR of cancer from airborne toxin of 1.38 (95% CI 1.24-1.53) controlling for voter turnout, region of the country, poverty rate, and pop density
Acevedo-Garcia, 2001	Tuberculosis	Residential racial segregation, neighborhood poverty, housing density and quality (isolation and	NJ Dept of Public Health TB reports for 1985-1992, and 1990 Census	Aspatial isolation index at zip code area level	Boolean analytic methodology	Increasing black isolation associated with increasing black TB incidence, while increasing white isolation is protective for whites

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
		concentration)				
Fabio, et al, 2004	Intentional injury	Residential racial segregation (evenness)	County level Pennsylvania hospital discharge summary data, 1997-9	Aspatial Gini coefficient at county level	Ecologic analysis, using multiple linear regression, controlling for county poverty, education, employment, family structure	Racial segregation independently associated with increased intentional injury (β=1.10, p<.001)
Cooper, et al, 2006	Injection drug use prevalence in urban blacks	Residential racial segregation (isolation and concentration)	1998 estimates of injection drug use prevalence and 1990 Census within 93 MSAs	Aspatial isolation and relative concentration indices at tract level	Multiple linear regression, controlling for MSA size, region, and racial composition	Increasing black isolation, but not concentration, was significantly associated with increased prevalence of injection drug use (p<.05)
Lopez, 2006	Physical activity	Residential racial segregation (evenness)	BRFSS 2001 and Census 2000	Aspatial dissimilarity index (scaled from 0 to 100)	Multi-level linear regression, controlling for individual and city level covariates	Significant decrease in physical activity as dissimilarity increases (OR 1.007, 95% CI 1.003-1.011) for each 1-unit increase in dissimilarity index)

Table 2-8. Literature on segregation and pregnancy outcomes

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
SEGREAGATION AND PREGNANCY RISK FACTORS						
Sucoff & Upchurch, 1998	Premarital teen pregnancy among blacks in metropolitan areas	Residential racial segregation and neighborhood poverty	Longitudinal Panel Study of Income Dynamics, using black females born between 1953 and 1968	Census tract proportion black	Cox proportional hazards modeling evaluating racial and economic composition of neighborhood, controlling for family income, employment, education, residential mobility	Segregated blacks (both very poor and working class) had increased risk of teen pregnancy (HR 1.54, 95% CI 1.06-2.23) compared to racially mixed working class neighborhood
Bell, et al, 2007	Smoking during pregnancy among black and white women	Residential racial segregation (isolation and clustering)	NCHS birth files for 216 MSAs with 100,000+ pop, 2002	Aspatial dissimilarity index, and spatial proximity index at the census tract level	Multiple linear regression controlling for maternal education, parity, age, and MSA size, poverty level, region, and racial composition	U-shaped curve, where low (OR 1.30, 95% CI 1.06-1.58) and high (OR 1.42, 95% CI 1.09-1.85) isolation/ clustering increased odds of smoking compared to

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
						moderate segregation
SEGREGATION AND PRETERM BIRTH						
Pickett, et al 2004	Preterm birth (<37 weeks)	Racial density and income incongruity in census tract	Illinois Dept Vital Records: Black singleton live births in Chicago in 1991, and Census data from 1990	Racial density: live in tract with 90%+ black population vs. <90% Income incongruity: living in tract with 1 SD higher median income than predicted from race-age-marital status-education	Cross-sectional multi-level logistic regression controlling for maternal age, education, smoking and parity	Positive income incongruity (living in a wealthy tract) in a predominantly black tract was protective (aOR 0.83, p<0.01), but income incongruity not associated with preterm birth in racially mixed tracts (p=0.22)
Bell, et al 2006	Preterm birth (<37 weeks)	Residential segregation (isolation and clustering)	NCHS: Black singleton births in 225 MSAs with 100,000+ pop in 2002	Aspatial Isolation index and spatial proximity index, each in three categories: low	Cross-sectional logistic regression controlling for age, maternal education, MSA	High isolation increased odds for preterm birth (aOR 1.27, 95% CI 1.10-1.46) while high

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
				(≤0.3), moderate (>0.4 to ≤0.6) and high (>0.6)	proportion with HS degree, smoking, parity, prenatal care, obstetric complications	clustering decreased odds (aOR 0.86, 95% CI 0.75-0.99)
Vinikoor, et al 2008	Preterm birth (<37 weeks) (Study parallels Pickett above, using different geographic area)	Racial density and income incongruity in census tract	North Carolina Vital records: singleton live black births in Durham and Wake County, NC, 1999-2001	Racial density: live in tract with 20%+ black population vs. <20% Income incongruity (as in Pickett above	Bayesian logistic regression using Pickett, 2004 parameter estimates as prior probability	Posterior odds for preterm birth were 0.83 (95% CI 0.74-0.92) for black women living in wealthier tract with 20%+ black population. Black women living tract with <20% black population, had no protection from increasing tract wealth
Masi, et al, 2007	Preterm birth (<37 weeks)	Census tract racial density, economic	Illinois Dept Vital Records: Black singleton live	Racial density in tract in three categories: <10%	Multi-level logistic regression,	No significant effect of violent crime, economic

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
		disadvantage, and violent crime rates	births in Chicago in 1991, Census data from 1990, and Chicago PD crime records	black, 10-90% black, >90% black	controlling for maternal education, age, parity, smoking, marital status, economic disadvantage and violent crime	disadvantage or group density on black risk for preterm birth
SEGREGATION AND LOW BIRTH WEIGHT						
Ellen, 2000	LBW (<2500 grams)	Residential racial segregation (evenness and centralization)	NCHS linked birth-death records for 1990 in 220 MSAs with 100,000+ pop and 5,000+ black pop	Aspatial dissimilarity index and relative centralization index	Cross-sectional logistic regression models controlling in steps for behavioral, demographic, and metropolitan confounders	Centralization and to a lesser degree unevenness are associated with odds for LBW, with most effect mediated by differences in maternal education, marital status, and to a lesser extent smoking and drug use
Grady, 2006	LBW (<2500	Residential racial segregation	New York City Vital records,	Spatial segregation	Cross-sectional, multi-level	In random intercept models,

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
	grams)	(isolation)	white and black live births in 2000	index (Wong, 2002)	logistic model controlling for foreign born, marital status, maternal education, smoking, substance abuse, age, Medicaid status, and census tract poverty rate	1 SD increase in segregation increase odds of LBW 3-fold controlling for neighborhood poverty and individual.
Grady & Ramirez, 2007	LBW (<2500 grams)	Residential racial segregation (isolation) mediated via medical conditions	New York City Vital records, white and black live births in 2000	Spatial segregation index (Wong, 2002)	Cross-sectional, multi-level logistic model controlling for foreign born, marital status, maternal education, smoking, substance abuse, age, Medicaid status, census tract poverty rat, and maternal medical	Some but not all of the effect of racial isolation on LBW is mediated by prevalence of chronic hypertension and pregnancy related hypertension

Study	Outcome	Exposure	Data source	Measure of segregation	Analytic approach and mediating factors	Results
					conditions	
Grady & McLafferty, 2007	LBW (<2500 grams)	Residential racial segregation (isolation) and maternal nativity	New York City Vital records, black live births in 2000	Spatial segregation index (Wong, 2002)	Cross-sectional, multi-level logistic model controlling for foreign born, marital status, maternal education, smoking, substance abuse, age, Medicaid status, census tract poverty rat, and maternal country of birth	Isolation significantly predicts LBW in US born black women, but there is no contextual effect of segregation for foreign born black women, with all variation in risk accounted for by sending country and individual risk factors

Chapter 3 METHODS

Building on the literature review of the biology, epidemiology, and social determinants of very preterm birth, as well as the gaps in the literature highlighted at the end of Chapter 2, the overarching goal of this dissertation can be summarized in the following question: "Does residential segregation explain excess very preterm birth risk among African American women?" The specific dissertation aims outlined below address this goal by asking first, 'how is segregation best measured for epidemiologic research?', and then by posing a question repetitively at different population scales, 'does segregation explain inter- and intra-racial variation in very preterm birth risk?' The two population scales balance area-based heterogeneity (in the national study) with data richness (in the individual study). The specific questions this dissertation seeks to address are:

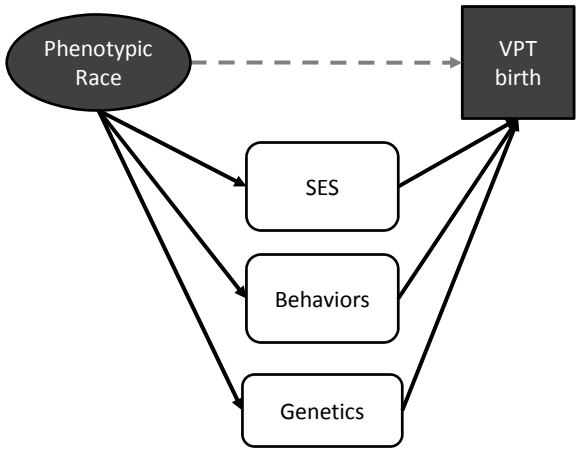
1. How should residential segregation be conceptualized and measured for effective epidemiologic research?
2. If residential segregation is associated with preterm birth, is the association similar for very and moderately preterm birth categories?
3. Through what pathways and at what scale (e.g. neighborhood, metropolitan area) is the segregation-preterm birth association mediated?
4. Does segregation explain any of the geographic variation in racial disparities of very preterm birth?

A GENERAL APPROACH TO THE PROBLEM

Because each of the following four chapters are stand alone manuscripts the relevant methods for each study are reviewed in each chapter. For clarity the data sources and measurement procedures are summarized below, in some cases in greater depth. Because the analysis plan differed for each study, the specifics of each analysis are reported in subsequent chapters.

The traditional approach to explaining racial disparities in preterm birth is summarized in Figure 3-1. In this view there are three possible reasons for observed racial disparities in health: racial differences in socioeconomic status, racial differences in behaviors, and racial differences in genetic predisposition. As discussed it is commonly assumed that adjustment for (known) socioeconomic and behavioral risk factors leaves only genetics as the explanation.

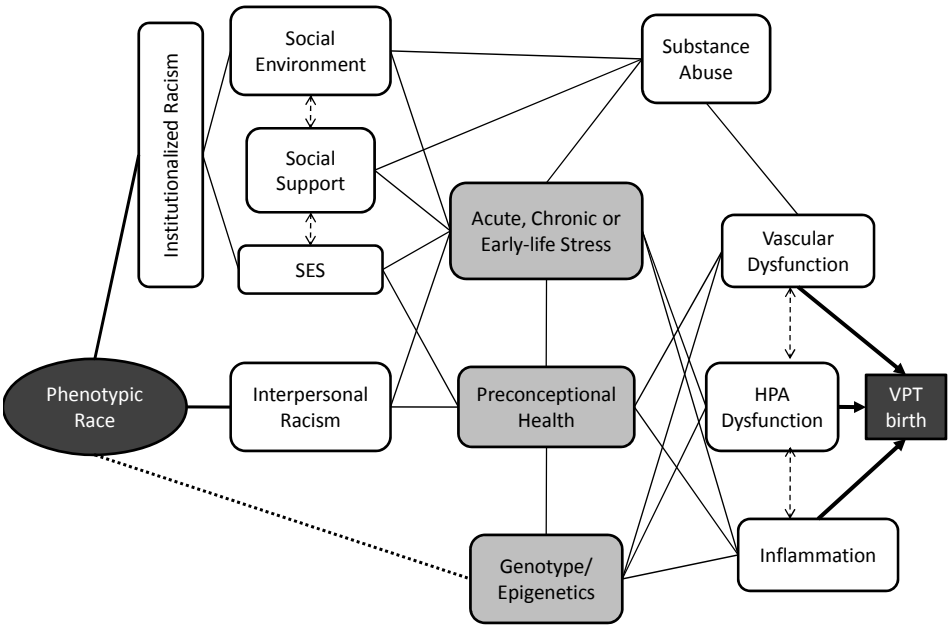
Figure 3-1. Traditional causal diagram for the association of race with very preterm birth (as previously published in Kramer & Hogue, 2009, (454))



A more complex (and possibly more realistic) version of the causal relationships is seen in Figure 3-2. While socioeconomic status, health behavior, and genetics remain as plausible explanations for (or mediators of) racial disparities, this diagram suggests the associations are not simple linear paths, but may include interaction with other aspects of political economy, social environment, personal experience, and physiologic functioning. It does not necessarily depict an *acyclic* causal pathway. As discussed in Chapter 2, individual and neighborhood characteristics

interact with one another, and behaviors do not fall deterministically from either. Nonetheless it suggests a series of plausible links which could explain an observed association between segregation and preterm birth.

Figure 3-2. Alternative causal web of pathways associating race with very preterm birth (as previously published in Kramer & Hogue, 2009 (454))

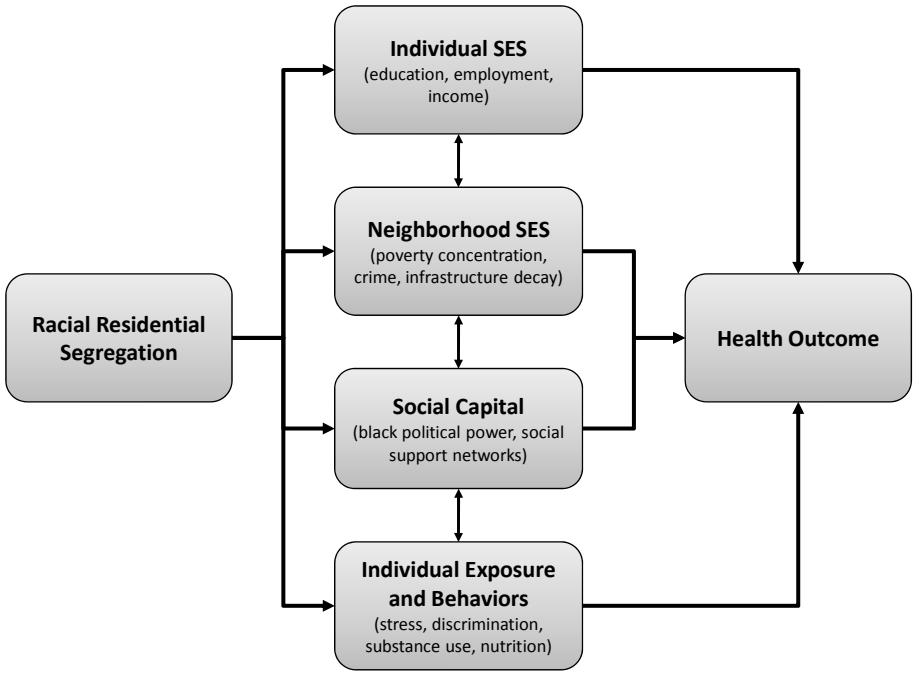


For example, psychosocial and neo-materialist social theories are utilized as a means of hypothesizing specific pathways through the conceptual model. Neither is presumed inerrant, but each facilitates articulation of specific hypotheses. Segregation is conceived of along two spatial dimensions: spatial exposure (isolation) and spatial evenness (clustering). Combining the social theory with the dimensions of segregation allows generation of testable hypotheses or pathways (see Table 3-1).

Table 3-1. Example relationships between segregation dimensions and social pathways to poor health

	Psychosocial	**Neo-materialist**
Spatial Exposure	↑Exposure = ↑exposure to discrimination=↑stress=↑PTB	↑Exposure = ↑ economic opportunity (networking) = ↑ SES =↓PTB
Spatial Evenness	↓ Evenness= ↑clustering=↑same-group social support=↓PTB	↑Evenness=↑equality of neighborhood services (e.g. schools) =↑economic opportunity (decrease spatial mismatch)= ↑Health=↓PTB

Figure 3-3. Mediating pathways between segregation and health (adapted from Kramer & Hogue, 2009, (455))



Finally, an observed association between segregation and preterm birth could be due to confounding (or other bias) or due to a direct or indirect causal effect. While segregation could conceivably have a nearly direct effect on preterm birth by increasing maternal stress, most hypothesized effects are likely indirectly mediated by economic, neighborhood, and social factors (see Figure 3-3). Given the important role of mediating factors in understanding the segregation-preterm birth association, the task of determining potential confounders is challenging. A confounder is by definition associated with the exposure, an independent risk factor for the outcome, and *not an intermediate on the causal pathway*. A mediator, on the other is a causal link between the general exposure and the specific individual outcome. Based on the literature reviewed, a table of potential mediators and confounders is proposed for use in the subsequent studies (Table 3-2). Just as statistical tests cannot prove causation from observational data,

similarly no fool proof manner for distinguishing mediators from confounders exists. None the less, strategies to grapple with this distinction will be discussed in the upcoming analysis section.

Table 3-2. Potential mediators and confounders of segregation-preterm birth association

Potential mediators		**Potential confounders**	
Ecologic	**Individual**	**Ecologic**	**Individual**
Metropolitan fragmentation (number of independent governments and joint policy making)	Drug use	Population size	Age
Variation of tax base among sub-areas	Smoking	Region	Parity
Crime rate (neighborhood level)	Marital status	Metropolitan tax base	Born in different state (stratifies on potential mobility)
Black centralization (proportion black population in city center as opposed to outlying areas)	Maternal education	% black in total MSA	Medical comorbidities
Poverty concentration (as opposed to poverty rate)	Maternal poverty	Overall MSA median household income	
Black political power and voter participation	Social support (fathers name on birth certificate)		
Housing quality in neighborhood/place	Medical comorbidities		
% female headed households			
% unemployed males			
%HS dropout vs. % college+			

DATA SOURCES

For each study, data on individuals and areas will be combined from various sources. In each case the goal is to keep individual measures of health status temporally linked to the measure of segregation which necessarily used 2000 Decennial Census data.

INDIVIDUAL LEVEL DATA

Birth data are for the years 2000-2002 in the national scale study, and from 2000-2003 in the Atlanta MSA study. The combination of years increases the number of events observed and improves power to detect smaller effects. For the national study all data were abstracted from National Center for Health Statistics natality files (NCHS) (456) which were themselves obtained from a National Bureau of Economic Research data repository. For the Atlanta study, individual level data for the twenty counties making up the Atlanta Metropolitan Statistical Area were obtained from the Georgia Department of Human Resources, Division of Public Health. In addition to birth certificate variables, these data included latitude and longitude of the residential address of the mother, as well as a field indicating whether the delivery was paid for by Georgia Medicaid. These additional variables allow the Atlanta study to situate each birth in a unique residential environment, and allow somewhat better adjustment for socioeconomic status by including Medicaid status.

In all cases the individual births of interest were from singleton pregnancies (because multiple gestation is itself a risk factor for preterm birth), born to mothers who self-report as non-Hispanic white or non-Hispanic black. For the national study, only births occurring in an MSA with a population of at least 100,000 and at least 5,000 black residents were included. The restriction to population sizes of 100,000 or greater was to correspond to NCHS health tabulation regulations

which only report when the population is sufficiently large to reduce risk of inadvertent disclosure of individuals' protected health information.

Gestational age data were drawn from natality file fields which have already been cleaned by state and national authorities. Specifically gestational age is typically calculated from maternally-reported last menstrual period (LMP). However in the cases where there is a discrepancy between birthweight and gestational age, birth certificate clinical estimate of age is used (167, 457). The clinical estimate may be ultrasound dating, record review by attending physician or physical assessment of the newborn. Births were then categorized as very preterm birth if at least 20 weeks gestation but less than 32; moderately preterm births were at least 32 weeks and less than 37 weeks gestation. In all analyses the comparison outcome was term births, defined as 37 to 44 weeks gestation. All births outside these parameters (e.g. less than 20 weeks or greater than 44) were omitted from analysis.

Area-Based Data

Data for approximating characteristics of each of the four hypothesized mediating pathways between residential segregation and health came from numerous sources. To approximate the domain of individual socioeconomic attainment two variables were chosen from the 2000 decennial Census, each stratified by race: percent of adults over 25 years of age without a high school degree or equivalent and percent of all households below the federal poverty level (458).

To approximate the socioeconomic environments in which metropolitan residents live we sought variables which reflect social aspects of the city context or environment. The ratio of black to white poverty rates represents one marker of relative racial inequality. As an indicator of relative poverty concentration, we also utilized Census derived measures of the exposure of poor children to high poverty neighborhoods as calculated by Acevedo-Garcia, et al (459). This variable

is the proportion of all black or white children under 18 years of age whose families are below the poverty line and who live in census tracts with median household incomes less than 80% of the median household income for the MSA as a whole. Finally, the murder rate per 100,000 residents for each MSA is obtained from FBI Uniform Crime Reports (460, 461).

For the final two domains of social capital and individual behaviors, there is no clear data source which represents all 231 eligible MSA's. For social capital, the best geographically comparative source of data is from the Saguaro Seminar's Social Capital Community Benchmark Survey (462). The phone survey was conducted in only 30 of our eligible MSA's. Each geographic area included a population based sample of at least 500 individuals, although the sampling frame was sometimes a single county rather than the entire MSA. We used a general social trust and an inter-racial trust variable from these surveys, taking the mean among respondents within each MSA. The social trust variable was coded as the mean response to a series of questions about trust of neighbors, police, store employees, and fellow church attendees and then was normalized to the national survey results. The inter-racial trust variable is the average response of trust of 'other' racial groups (including non-Hispanic white, non-Hispanic black, Hispanic and Asian) and is the mean response on a 1-4 scale with 4 being "I trust them a lot" and 1 being "I trust them not at all."

Data from the Behavioral Risk Factor Surveillance Survey (BRFSS) (463) was used to approximate the prevalence of two chronic disease risk factors: obesity (body mass index greater than 30) and current smoking status. BRFSS data were reportable at the MSA level for 72 of the 231 eligible MSA's. The population weighted prevalence of each risk factor was estimated among black and white adults.

PROTECTION OF HUMAN SUBJECTS IN RESEARCH ACTIVITIES

Each of the three studies composing this dissertation was reviewed by the Emory University Institutional Review Board (IRB). Because the first and second study use previously de-identified and publicly available data these were deemed exempt from further IRB review. The third study using individually geocoded birth records in the Atlanta metropolitan area received expedited approval by the IRB (IRB00010578, Emory University).

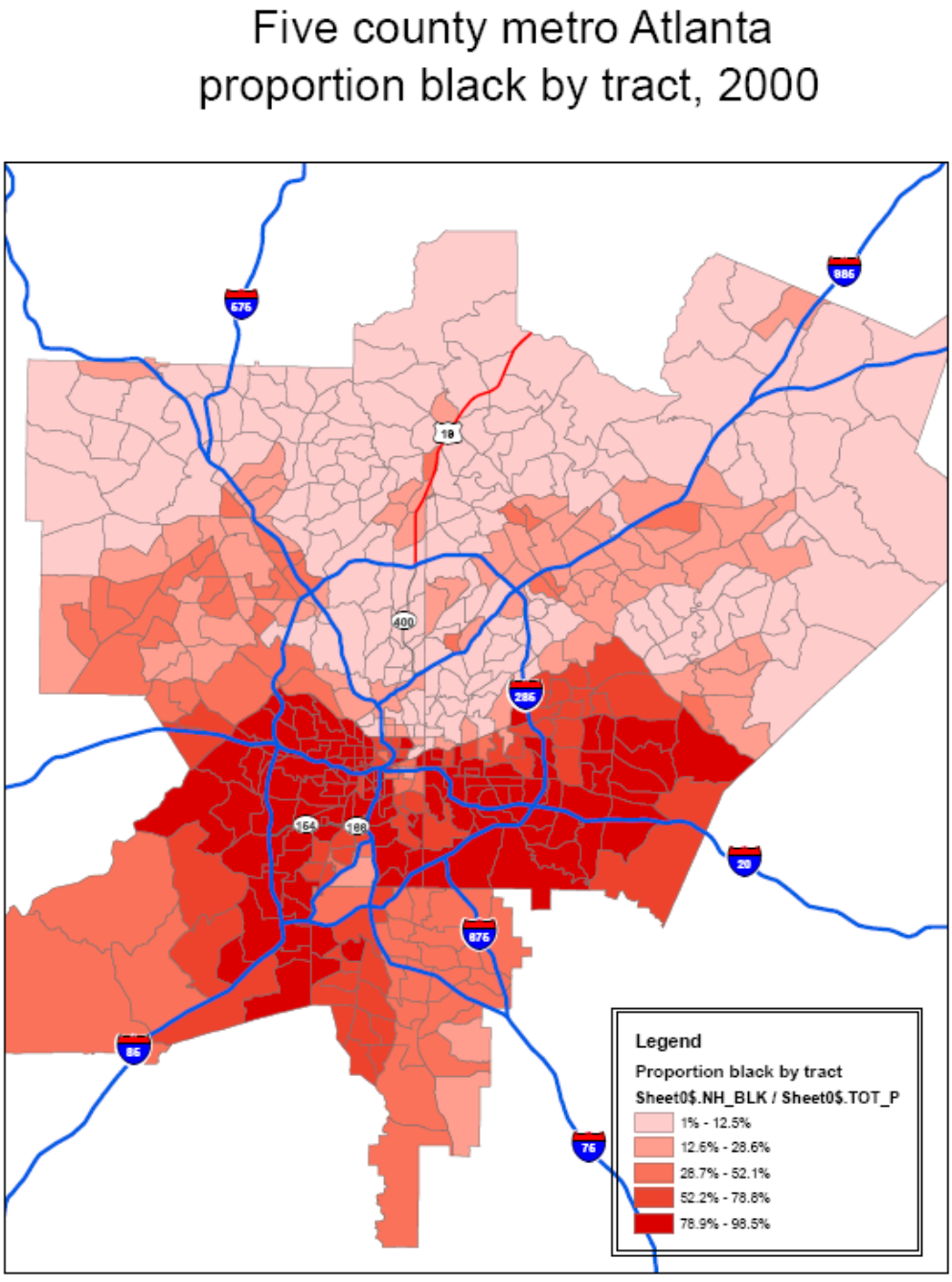
GENERAL METHODS FOR MEASURING SPATIAL SEGREGATION

The two segregation dimensions utilized in this dissertation (spatial evenness and spatial exposure) were measured using an ArcGIS software macro developed by Graham and O'Sullivan(464) to operationalize the previously described spatial measures described by Reardon and O'Sullivan.(371) Briefly, the macro begins with tabulated census data, uses a weight-preserving smoothing technique to smooth abrupt changes in composition at area boundaries, then estimates the composition of a 'local area' as defined by the user. The method for calculating indices and the subsequent output are reviewed in more detail here.

Segregation has traditionally been measured using census tracts as a proxy for neighborhoods. Census tracts are geographic units constructed by the Census Bureau to describe racially and economically homogenous population groups of optimally 4,000 people, although they range from 1,500-8,000 individuals.(465) A traditional aspatial (or arbitrarily spatial) segregation measure begins with the racial or economic composition of each census tract and compares it to tracts throughout a metropolitan area. For example, the five core counties of the 20-county Atlanta metropolitan area can be described in terms of the proportion black in each tract, as seen in Figure 3-4.

Census tracts have been demonstrated by Krieger, et al, to be superior to either the smaller census block or the larger zip code tabulation areas in terms of describing general and pregnancy related health relevant neighborhood context.(466, 467, 468) However for determining patterns of residential segregation, census tract may be too coarse or arbitrary a base unit. In the case of the five metro Atlanta counties, the census tracts have a median area of 1,372 acres, with a range from 22 to 45,757 acres (median 2.1 square miles, range from 0.03 to 71.5). The population in each tract ranges from 18 to 29,877, with a median of 5,627. Census blocks are sub-units of tracts and by no means describe a neighborhood, but they do offer a higher resolution view of the distribution of individuals in space. For example, the census blocks for the five counties in this example range in area from 0.03 to 1,885 acres, with a median of 9.6 (square miles: <0.0001 to 2.95, median 0.015). Their populations are also smaller, ranging from 1 to 3,912 in this example, with a median of 52. Census block groups are intermediate units with several block groups per tract, and each block group consisting of one or more blocks. Population counts by race are available from the Census Bureau at the block level, but indicators of income are available only at the block group level.

Figure 3-4. Atlanta area proportion black by census tract



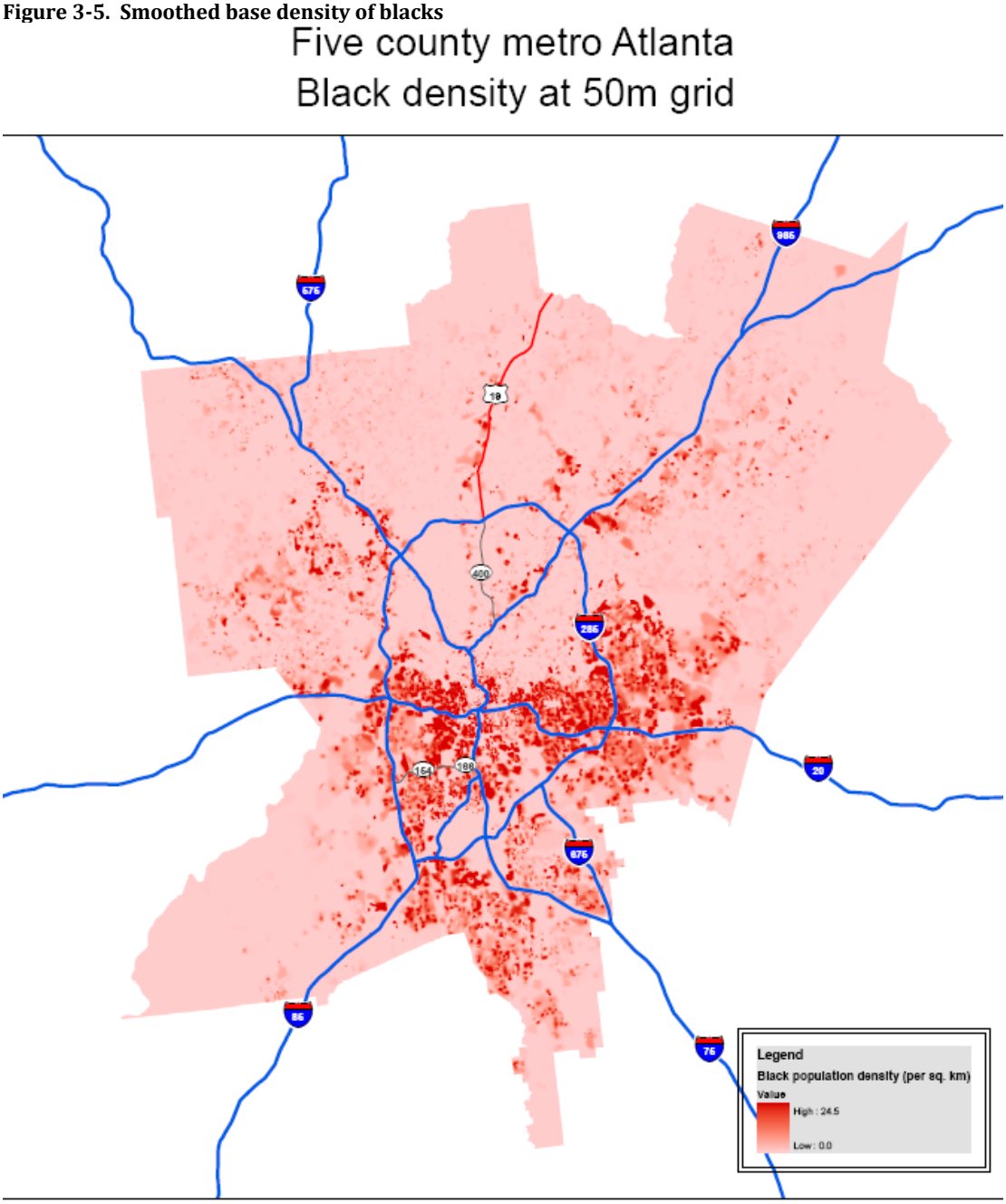
Source: US Census, 2000

The process of calculating a spatial index of segregation using the ArcGIS macro proceeded through a series of four steps.(418) First a grid of cells was laid down over the mapped area including the census block population estimates. The size of the grid is user defined, and for this analysis, 50 meter by 50 meter cells were deemed appropriate for block level data. Each cell was assigned a population density (persons per square kilometer) for each population group of interest (e.g. racial groups). The density assigned was that of the block it is contained by, or if on a boundary, the block with the greatest overlap.

The second step was to smooth these 50 square meter cell densities so there were not abrupt differences at the edges. The process used by the macro is termed pycnophylactic smoothing, and is one type of weight or mass preserving smoothing algorithm used in geospatial processes (469). Mass preserving refers to maintaining an absolute count (mass) within each areal unit while smoothing the location of individuals across the unit to minimize abrupt density changes at the boundaries. It has the advantage of creating what might be considered a more realistic depiction of population without excessively distorting the underlying data.

The smoothing process was iterative, stopping when a user-defined tolerance for change had been achieved. At this point a continuous surface density of each racial group or of the entire population exists. As seen in the five-county example in Figure 3-5 below, the resulting surface mirrors the general pattern seen in the census tract map, but has much finer resolution. Figure 3-5 is only the black density surface, but a similar map of white density, and total population density (and any other groupings designated by the user) were also produced. These density surfaces constitute the data inputs for Equation 2-5 and Equation 2-6 above, where population density or proportion (τ for density, π for proportion) for an overall area are required.

Figure 3-5. Smoothed base density of blacks



The third step of the process was to define the 'local' area. As discussed, traditional segregation measures assume that the census tract is equivalent to the 'local area' or neighborhood, for all of its residents regardless of whether they live in the center or at the boundary of the tract, and regardless of the actual size or shape of the tract. However with spatially continuous densities, it is possible to define any area as 'local'. While it is theoretically feasible to construct areas which observe neighborhood-defining features such as rivers, interstates, and railroad tracks, this is not practical to do for all MSAs in the US. Instead I used a bi-weight kernel spatial proximity function which defines the 'local area' of point p as the weighted average of all points within a given radius of point p. The weighting is determined by the distance from the primary point, with decreasing weights for increasing distances ('distance decay'). For example, the local area around my house could be defined using concentric circles with radius of a quarter mile, half mile, or more. Within each circle, the density of each racial group would define the population composition of the area.

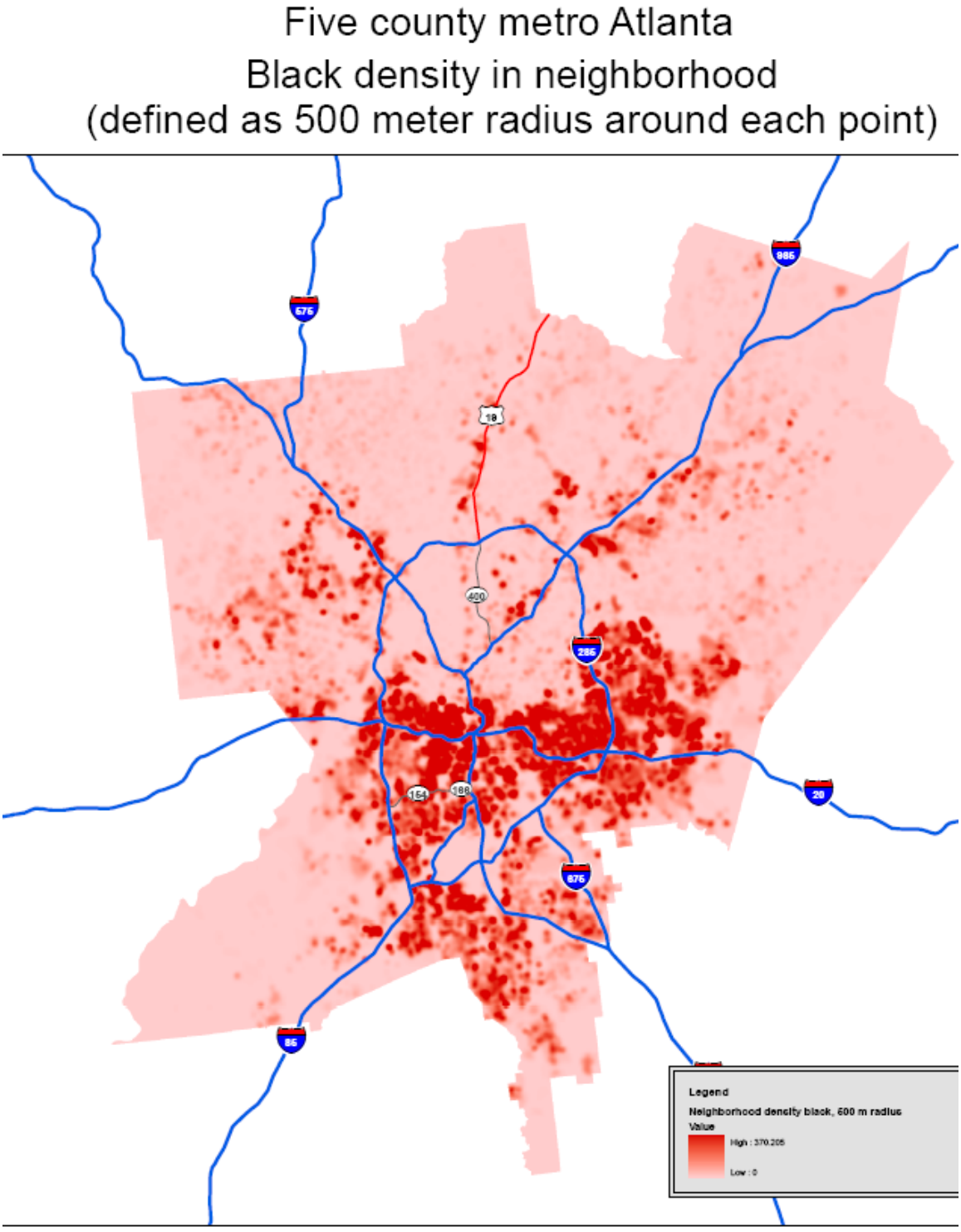
Using the macro, individual points were defined as the intersections of the 50 by 50 meter grid (e.g. if the average census tract is 1372 acres, this corresponds to ~10,000 points per tract). The racial composition and density of the area around each point was determined. Choice of definitions for 'local neighborhood' is not straightforward, and several were tested. Based on empiric research of resident perception, mobility, and commerce in various US cities (470, 471, 472), five alternative definitions of local area were considered in this dissertation: areas defined by a circle with 500 meter radius (a reasonable proxy for a walkable neighborhood, fear of crime, and social capital), or radii of 1 km, 2 km, or 4 km (this last definition is similar in size to a broad organizational area such as high school enrollment district, shopping area, travel to site of worship, etc), as well as the census tract.(418) Examples of the 'local area' density of blacks for all areas in the five-county example are displayed in Figure 3-6 and Figure 3-7 for 500 meter and 4 km radius

areas. As can be seen, the granularity of the 'local' experience of individuals changes based on changing definitions. This is extremely useful, as segregation might impact economic opportunities at a larger scale, but social exposures at a smaller scale. These 'local area' densities and proportions were the inputs for Equation 2-5 and Equation 2-6, where the density or proportion of a group surrounding point p is required (denoted in chapter 2 with a super-imposed tilde).

The final step of the process was to integrate across all points in the region using the equations described previously (in practice this was summing across a finite number of grid points), comparing either the evenness of the distribution, or the spatial proximity of individuals from different groups. A summary index which describes the entire metropolitan area was considered most relevant, although the description of the composition of each small area was also preserved.

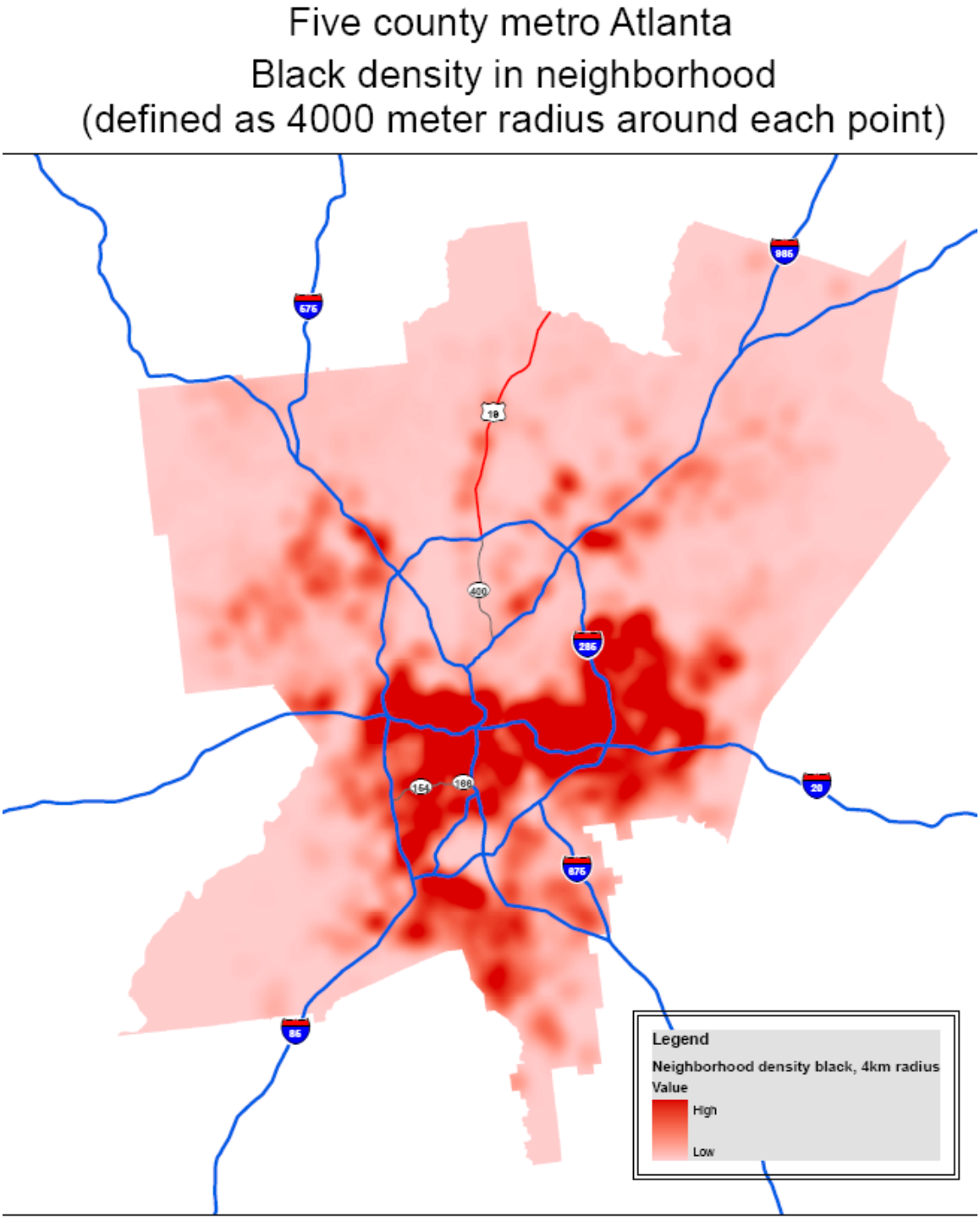
Because all previous segregation-health research have used aspatial indices and administrative boundaries such as the census tract, I also calculated these to facilitate comparison.

Figure 3-6. Black density with 500 meter radius neighborhood



Source: US Census, 2000
Method: Kernel density smoothing approximating the density of 500 meter radius circle around each point

Figure 3-7. Black density with 4 km radius neighborhood



Source: US Census, 2000
Method: Kernel density smoothing approximating the density of 4000 meter radius circle around each point

Chapter 4 MEASURES MATTER: VALIDATING NEW INDICES OF RESIDENTIAL RACIAL SEGREGATION FOR POPULATION HEALTH RESEARCH[3]

ABSTRACT

Interest in understanding the role of metropolitan residential segregation in spatially patterning racial disparities in health outcomes has increased, but little empirical work has compared measures of segregation for health research. We compare novel spatial measures of isolation and evenness segregation at four neighborhood scales in 231 metropolitan areas and compare these with census tract derived measures. We estimate how each measure predicts four hypothesized mediating pathways between segregation and population health. There is notable heterogeneity in the magnitude of correlations as a function of the dimensions of segregation, scale of the operationalized neighborhood, and hypothesized causal pathway. Investigators interested in the segregation-health association must consider measurement scale, dimension and causal mediators in choosing indices for research.

INTRODUCTION

[3] This chapter is a manuscript prepared for submission to a peer-reviewed journal. As such the structure, format and length are in keeping with journal requirements. Use of the plural pronoun 'we' refers to members of the dissertation committee who will be co-authors on this submission. Supplemental results tables are in Appendix 4.

The spatial segregation of urban individuals' residence by race and class has been described by sociologists throughout the twentieth century (373, 375, 473). W.E.B. DuBois (5) detailed differences in black mortality by residential neighborhood in Philadelphia, but it was not until the 1950's that Yankauer (393) explicitly restated residential segregation as a public health concern. More recently segregation has reemerged as a possibly "fundamental determinant" (6) of racial disparities in health outcomes such as all-cause mortality (474), preterm birth (438, 475), self-rated health (476), obesity (406), survival for individuals with end stage renal disease(477) or stage at cancer diagnosis (478).

The degree to which understanding segregation will prove useful in health promotion and disease prevention research efforts may well depend on the extent to which it can successfully be understood and incorporated into conceptual models of disease causation, thus providing illumination for intervention opportunities. Residential segregation can be conceived of as both a descriptive state or condition and an active process. As an adjective, 'segregated' describes the degree to which there is departure from a random spatial distribution of racial, ethnic, or economic groups within a city or metropolitan area. Alternatively 'segregate' as a verb evokes an active process of differential sorting of individuals into residential environments, thereby influencing these individuals' probability of experiencing a range of place-related exposures. It has been hypothesized that the condition and the process of segregation may represent geographically variable operationalizations of structural inequality or institutionalized racism, which may be toxic to health (394).

Acevedo-Garcia et al's (370) call for more rigorous conceptual and analytic approaches to understanding the association between segregation and health has been met with numerous advances in recent years. For instance multi-level hypotheses and statistical analysis are increasingly common (406, 408, 475, 478). Similarly important is the increased utilization of

different dimensions or patterns of segregation described by Massey and Denton (409), including evenness, clustering, isolation, concentration and centralization. Despite these and other improvements in the sophistication of segregation-health research, little attention has been paid to how different measures of residential segregation actually affect findings. Because segregation patterns can be so variably described, and because segregation is an upstream or distal determinant, either misspecification of the pattern or misclassification of the degree of segregation to which individuals are exposed potentially undermines the validity of study findings.

These concerns lead to three questions for any study of residential segregation and health:

1. Does either the pattern or dimension of segregation affect the associations with health-mediating pathways?

2. Do each of four commonly hypothesized health-mediating pathways correlate similarly with segregation?

3. Does the operationalization of neighborhood size or scale in measuring segregation affect the association with health-mediating pathways?

To answer these questions, we use two general approaches. First, we analyze both traditional Census tract-derived measures of segregation and novel measures which eliminate reliance on tract boundaries as definitions of neighborhoods. Second, rather than testing the associations between segregation and specific population health outcomes, we address the core questions with a broad-based conceptual model of commonly hypothesized pathways through which segregation's health-relevant effects may be mediated.

DIMENSIONS OF SEGREGATION

Segregation can occur along axes of race, ethnicity, class or a combination of social classifications. The focus here is on black-white residential segregation. The five dimensions of

segregation described by Massey and Denton (409) suggest unique patterns of urban residential settlement (see Table 2-3 in chapter 2). For instance evenness, the most commonly used dimension in public health research (370), measures the distribution of blacks in a city relative to the distribution of whites (or vice versa). In other words it is invariant to absolute population size or racial composition, simply reflecting departure from a random distribution of one group relative to another. In contrast, Massey and Denton describe isolation (or its inverse, exposure) as the absolute probability of exposure at the neighborhood level of an average individual of one race to someone of another race. In this way isolation is sensitive to overall metropolitan racial composition so that black isolation, for instance, can only occur when there are sufficient numbers of blacks to be isolated from others. Thus a city could be very uneven, but have low isolation, or vice versa.

Clustering, concentration, and centralization also describe patterns of how racial groups differentially occupy urban spaces, although whether they are conceptually distinct from evenness and isolation has been questioned (371, 420). For example Reardon and O'Sullivan argue that clustering of racially similar neighborhoods is an extension of unevenness beyond the bounds of a single neighborhood. Similarly concentration and centralization may be seen as specific cases of the general pattern of unevenness, where a racial group is primarily located in the central city (centralization) or is spatially concentrated in a given area (concentration).

For health researchers these segregation dimensions represent opportunities for honing research questions, as some patterns or dimensions may be more relevant for understanding a given health outcome than others (370). For instance it has been hypothesized that spatial clustering of a minority group could enhance social networks , support, and social capital (392). In contrast, isolation segregation may best describe patterns associated with spatial concentration of poverty and alienation from social and economic opportunity (375) while concentration may be

particularly relevant to understanding spread of infectious diseases such as tuberculosis (403). For example Bell, et al (438), reported that both clustering and isolation were independently associated with lower birthweight and higher risk for preterm birth in black women. However when considered jointly, living in areas with increased isolation was deleterious while areas characterized by higher clustering were relatively health protective, conditional on the degree of isolation.

CAUSAL PATHWAYS

As a distal contextual exposure, any causal segregation-health effect is most likely mediated by social, environmental, and behavioral risk factors. In other words the effect of segregation on health is due to its effect on slightly more proximate precursors such as environmental exposures, individual behaviors, and socioeconomic status. The most common mediating factors fall into one or more of four general domains: residential segregation constrains individual socioeconomic attainment; segregation reproduces unhealthy neighborhood environments; segregation affects empowerment and social capital; and exposure to segregation modifies individual health-relevant behaviors (Figure 4-1) (455). Segregation therefore may be a determinant of population health to the degree that these four domains are themselves predictors of health outcomes.

The association of individual socioeconomic status with a wide range of poor health outcomes is well documented (115). Segregation could influence individuals' adult socioeconomic attainment by influencing educational and employment opportunity. For instance metropolitan segregation is associated with a greater black-white gap in Scholastic Aptitude Test (SAT) scores controlling for other indicators of individual and family socioeconomic status (387). For blacks but

not whites, the degree of residential segregation influences high school graduation rates as well as adult employment, controlling for education and skills (390, 479).

Interest in the role of neighborhoods and other area-based contextual effects independent of individual factors has grown substantially (480). Segregation may create and perpetuate neighborhood environments which are characterized by overcrowding, resource deprivation, crime, and poverty concentration (375, 376). Overcrowding and poor housing stock have been associated with transmission of infectious diseases (481), and exposure to areas with high violent crime have been associated with intentional injury rates and poor pregnancy outcomes (404, 436).

Residential segregation could also enhance or reduce social capital for urban residents, possibly influencing health by modification of social support, group political power and opportunity structures (392, 482). Finally, living in a more compared with less segregated city could modify prevalence of individual health behaviors. For instance smoking among black women during pregnancy may be associated with segregation (439), and behaviors such as physical activity or healthy diet may similarly be associated with degree of segregation (407, 483).

OPERATIONALIZING NEIGHBORHOODS

In conceptualizing each dimension of segregation, the racial composition at two spatial scales is typically evoked: small neighborhood areas nested within a broader geographic context. The most commonly used segregation measures operationalize these two scales by using census tracts as neighborhoods, and variably by using cities, counties, metropolitan statistical areas, or states as the broader context. A critique of the common measures of segregation which is largely missing in the health literature (although present in the social science literature (484, 485)) is the reliance on census tracts as a proxy for neighborhood in estimation of segregation indices. This

reliance is problematic for two related reasons: the modifiable areal unit problem (MAUP), and the arbitrarily fixed scale of neighborhoods (411). The MAUP occurs when spatial areal units are determined without regard to the construct of interest (segregation or health). If arbitrary changes in census tract boundaries in the absence of any true movement of people would alter the racial proportion of a tract and thus register a change in the index of segregation, there will be misclassification.

Further compounding this problem may be the fixed (but arbitrary) scale of the 'neighborhood' represented by census tracts (471). Tracts are defined for the purposes of population enumeration but vary widely in area, population count, and shape (465). Segregation connotes racial separation by neighborhood, but it is not clear what size or scale of neighborhood is most relevant to health. Defining neighborhoods as small in size suggests that the health-relevant social interaction and economic opportunities occur in small spatial areas as might be seen with pedestrian access to public transit or healthy food options. In contrast, large definitions of neighborhoods allow broader types of social engagement and exposure as might be seen with sub-metropolitan access to employment opportunities, social or health services, or central city infrastructure decay (472, 486).

Recent attempts to address these theoretical critiques have come in the form of tools implemented in geographic information system (GIS) software (371). These approaches estimate residential segregation as a truly spatial phenomenon with measures amenable to scale changes in the definition of neighborhoods and lower sensitivity to the modifiable areal unit problem. Although not previously implemented for health research, these tools may further enhance conceptualizations and measurement of associations between residential segregation and health.

It is our goal to compare the relative performance of traditional tract-based segregation indices with these newer spatial indices in terms of their association with commonly hypothesized mediating pathways between segregation and health.

METHODS

The focus of this analysis is on black-white residential segregation because racial health disparities are significant and black Americans are among the most highly segregated groups in the United States (373). Choices of segregation measures and proxies for the four intermediate pathways (Figure 4-1) are therefore considered in light of this narrow focus.

The unit of analysis is the Metropolitan Statistical Area (MSA). The Office of Management and Budget defines MSA's as a central city of at least 50,000 persons and the surrounding counties which are determined to be economically integrated with the central city as defined in part by the proportion of outlying county residents who are employed in the central city (487). This definition therefore creates a geographic context defined by housing and labor markets, two critical components of the process and consequences of segregation.

To insure adequate linkage between included MSA's and commonly available population health data, we restricted analysis to MSA's for which the National Center for Health Statistics reports vital events, specifically birth records (456). MSA's eligible for analysis were defined as those with total populations of 100,000 or more, and black populations of at least 5,000. These inclusion criteria resulted in 231 eligible MSA's.

MEASURES OF SEGREGATION

The dissimilarity index and the isolation index are the two most commonly used measures of the evenness and isolation/exposure dimensions of segregation. Tract-based estimates of black-white dissimilarity and black isolation were obtained from the US Census Bureau (488).

Implementation of Reardon et al's spatial segregation indices is made possible by a freely available Visual Basic for Applications macro (464) for ArcGIS 9.2 (ESRI, Redlands, WA). The estimation process is more completely described elsewhere (485). Our implementation of the algorithm takes as input US Census 2000 block-level population counts which are the smallest spatial demographic data available for all MSA's. The data are transferred to a 50x50 meter grid across the entire MSA with each grid assigned the total and race-specific population density for the underlying block. A pycnophylactic (mass-preserving) smoothing algorithm smoothes density changes across blocks without unreasonably distorting the underlying data (469).

With the resulting continuous surface densities, local neighborhoods can be defined according to researcher parameters. Although it is theoretically possible to define neighborhood by highly customized local physical or social patterns, we instead use definitions which are readily applicable with the available macro across hundreds of MSA's but still allow exploration of different neighborhood scales in the estimation of segregation. Neighborhoods were alternately defined as a series of circles of increasing radius (500m, 1km, 2km, and 4km) around each point in space (each 50m square grid point). A biweight kernel density function produced a spatially-weighted estimate of the racial composition for each point in space. In other words, each point in space has its own unique neighborhood, and therefore a unique estimation of the racial composition of the neighborhood, whether it is defined as small (500 m kernel density bandwidth) or large (4 km bandwidth). These definitions are clearly abstractions of true neighborhoods, but are primarily informative in capturing the composition of micro versus macro residential areas. A neighborhood

defined by a 500m radius circle might be the typically pedestrian space around one's home while a 4000m radius describes a much large swathe where worship, shopping, or other economic activities might occur (486).

While the tract-based indices are population weighted averages calculated by summing across tracts, the spatial indices can be seen as population density weighted averages calculated by integrating across all points in space, although practically it is really summing across a finite (but large) number of grid points.

In summary, ten different segregation indices were calculated or obtained for each MSA. Measures of dissimilarity and isolation indices were calculated for census tracts and for four different neighborhood scales: circles with radii 500m, 1km, 2km, and 4km.

HEALTH MEDIATING VARIABLES

Data for approximating characteristics of each of the four hypothesized mediating pathways (Figure 4-1) between residential segregation and health came from numerous sources. To approximate the domain of individual socioeconomic attainment two variables were chosen from the 2000 decennial Census, each stratified by race: percent of adults over 25 years of age without a high school degree or equivalent and percent of all households below the federal poverty level (458).

To approximate the socioeconomic environments in which metropolitan residents live we sought variables which reflect social aspects of the city context or environment. The ratio of black to white poverty rates represents one marker of relative racial inequality. As an indicator of relative poverty concentration, we also utilized Census derived measures of the exposure of poor children to high poverty neighborhoods as calculated by Acevedo-Garcia, et al (459). This variable

is the proportion of all black or white children under 18 years of age whose families are below the poverty line and who live in census tracts with median household incomes less than 80% of the median household income for the MSA as a whole. Finally, the murder rate per 100,000 residents for each MSA is obtained from FBI Uniform Crime Reports (460, 461).

For the final two domains of social capital and individual behaviors, there is no clear data source which represents all 231 eligible MSA's. For social capital, the best geographically comparative source of data is from the Saguaro Seminar's Social Capital Community Benchmark Survey (462). The phone survey was conducted in only 30 of our eligible MSA's. Each geographic area included a population based sample of at least 500 individuals, although the sampling frame was sometimes a single county rather than the entire MSA. We used a general social trust and an inter-racial trust variable from these surveys, taking the mean among respondents within each MSA. The social trust variable was coded as the mean response to a series of questions about trust of neighbors, police, store employees, and fellow church attendees and then was normalized to the national survey results. The inter-racial trust variable is the average response of trust of 'other' racial groups (included non-Hispanic white, non-Hispanic black, Hispanic and Asian) and is the mean response on a 1-4 scale with 4 being "I trust them a lot" and 1 being "I trust them not at all."

We used data from the Behavioral Risk Factor Surveillance Survey (BRFSS) (463) to approximate the prevalence of two chronic disease risk factors: obesity (body mass index greater than 30) and current smoking status. BRFSS data were reportable at the MSA level for 72 of the 231 eligible MSA's. The population weighted prevalence of each risk factor was estimated among black and white adults.

ANALYSIS

Differences in segregation indices by geographic region or MSA population size were tested using F-tests. All MSA's were ranked from most to least segregated using each index to ascertain how much change in ranking occurs with different measures. Spearman rank correlation coefficients were estimated for each pair of segregation indices.

To assess the explanatory power of any single segregation index for any single pathway domain variable, linear regression models were fit with segregation indices as the independent variable and MSA-level pathway variables as the dependent. The adjusted R^2 was used as the primary measure of fit and can be roughly interpreted as the proportion of the variation in the dependent variable which is explained by the independent variables. While many other confounding or intermediary variables could be relevant we identified geographic region (defined as Northeast, Southeast, Midwest, and West using Census definitions) and metropolitan population size (defined as <500,000, 500k – 1 million, and > 1million persons) as two overarching potential confounders.

Modeling proceeded in three primary steps. The first group of models (denoted M1 models in the results) regress each health pathway variable on geographic region and MSA size, in order to determine a baseline R^2. The second group of models (M2 models) adds a single segregation index to the M1 model to estimate the additional variance explained above that from region and size. Finally the M3 models simultaneously consider isolation and dissimilarity at each spatial scale. The purpose of this third group of models is to explore the independent effects of either dimension conditioning on the other. High degree of correlation between the dissimilarity and isolation indices raises concern about multicollinearity, but plots of tertiles of isolation versus tertiles of dissimilarity (data not shown) suggest that there is general data support for these comparisons. To

further evaluate for deleterious multicollinearity, the variance inflation factor (VIF) was assessed for each M3 model. All analyses were conducted with SAS 9.2 (Carey, NC) and R 2.7 (489).

RESULTS

For all results, spatial segregation estimated with the 1km and 2km radius neighborhood definitions were between the values estimated for the smallest scale (500 meter radius) and the largest scale (4km radius). For this reason, only the 500m and 4km results are presented in primary results tables. Complete results for all neighborhood scales are available in the supplemental tables (Appendix 4).

Estimating segregation in the same city using different indices could result not only in different absolute values of segregation, but also in different ranking of MSA's relative to one another. Different indices for each city were highly correlated with one another (Figure 4-2), although this was more so for measures within each dimension of isolation and dissimilarity than between dimensions. As compared to MSA's ranked from most to least segregated with the tract-based dissimilarity index, the ranking changed on average by 21 (of 231 possible rank positions) when MSA's were measured with the 500 m dissimilarity index, and by 15 using the 4km dissimilarity index. The change in ranking going from the tract-derived isolation to the spatial measures of isolation was smaller, with an average rank change of 14 for isolation with the 500m definition and 12 for isolation using 4km radii neighborhoods.

The degree of residential segregation varied significantly among geographic regions and across categories of metropolitan population size (Tables 4-2 and 4-3, respectively). Both spatial and tract-derived dissimilarity indices suggest the highest segregation is in the Northeast and Midwest, while isolation appears to be highest in the Southeast. The Western US has the lowest segregation on each dimension. Segregation is highest in the largest cities as compared with the smallest, although the variation by population size is not as great as that seen by geographic region.

Measures of segregation varied consistently according to the scale of the operationalized neighborhood. In all cases segregation appears to be more profound (index value is greater) when using small neighborhoods and incrementally declines as the neighborhood size increases. The tract-derived indices appear to be most similar to the 2-km radius definition of a neighborhood for both isolation and dissimilarity indices (see Appendix 4, supplemental tables 1 and 2). For MSA's in this analysis, the interquartile range for the area of census tracts was 1.3 to 10.7 square kilometers with a median of 3.1. This corresponds to an area similar to a 3000m radius circle, or slightly less given the distance decay function of the kernel density, so it comes as no surprise that tract-derived indices would approximate one of the explicitly spatial scales.

Table 4-4 shows the adjusted R^2 for each mediating pathway variable when only geographic region and metropolitan population size are included in a linear regression model (M1 models), as well as the R^2 for the M2 models which additionally include segregation indices. The change in the R^2 can be interpreted as the additional variance in the mediating pathway variable explained by the segregation index. For the individual socioeconomic status domain, the strongest correlations with segregation are for the proportion of black adults without a high school degree and the black poverty rate. The 500m dissimilarity index explained an additional 19 percent of the variation in black high school attainment rates above that already explained by region and metropolitan size (0.47 – 0.28 = 0.19), and 12 percent for poverty rates.

Although the relevant indices are quite different, two variables in the environmental context pathway are also highly correlated with segregation indices: black poverty concentration (as measured by the proportion of poor black children who also live in high poverty neighborhoods) and the murder rate. The strongest predictor of poverty concentration among children is the census tract derived dissimilarity index, although 4 km dissimilarity is also strongly associated. The metropolitan area murder rate per 100,000 persons is closely associated with the

degree of isolation segregation particularly when larger neighborhoods are used. In addition, the black-white ratio of the poverty rate in each city is correlated primarily with dissimilarity, with little change across different neighborhood size definitions.

The social capital and behavioral risk factors domains differ in the number of eligible MSA's analyzed (30 for social capital and 72 for health behaviors) and have notably fewer associations with segregation. Isolation segregation, particularly using the 500m neighborhoods, explains a portion of the city-to-city variation in social trust and inter-racial trust, but dissimilarity has no apparent association.

The results are more varied in the M3 models (Table 4-5) which include both dissimilarity and isolation simultaneously in the same model. The variance inflation factor (VIF) for all models in the individual and area socioeconomic condition domains was below five, suggesting dissimilarity and isolation are sufficiently distinct to avoid multicollinearity. The VIF was between five and 10 for the variables in the social capital and health behavior domains.

Each dimension appears to be important in understanding at least some of the health mediating variables studied. Individual poverty rates, the proportion of adults without a high school degree, as well as the racial disparity in poverty rates and the spatial concentration of poverty among black children all seem to be primarily associated with the dissimilarity index. In contrast, metropolitan murder rate and the two measures of social and inter-racial trust are more strongly associated with isolation than dissimilarity. Interestingly the proportion of white adults who smoke appears to have a modest association with dissimilarity at the tract and 4000m radius neighborhood scale in these joint models, although there was no association for either dimension separately.

With some exceptions, segregation (measured by any index) has a stronger association with health mediating variables for blacks as compared with whites, with characteristics for whites often

not associated at all with variation in segregation. Notably, increasing isolation is associated with significant *decreases* in the proportion of white adults without a high school degree and *decreases* in the white poverty rate, each in stark contrast to the experience of blacks in the same cities (see Appendix 4, supplemental table 7). This reversal of direction of the association between segregation and race-stratified outcomes is not present for any measures of dissimilarity.

Because the sample of cities analyzed for the social capital and health behavior domains were much smaller than the original sample of MSA's, we conducted a sensitivity analysis with all individual and area based socioeconomic variables, limiting first to the 31 MSA's used in social capital analyses, and then to the 72 used for risk behavior analyses (see Appendix 4, supplemental tables 12-15). Most associations were no longer significant when restricting to the social capital sample with the exception of the murder rate which was still positively associated with segregation. In the larger sample defined by MSA's with BRFSS results, the overall patterns were much more consistent with the full sample of 231.

Our choice to focus on two of the commonly described five dimensions of segregation was due in part to the argument that spatial evenness and isolation are the primary general patterns of segregation, and that clustering, centralization, and concentration are specific cases of these general patterns. To test this assumption we modeled each domain variable with census tract indices for clustering (spatial proximity index), centralization (absolute centralization index), and concentration (relative concentration index) (see Appendix 4, supplemental table 11). In every case one of the primary indices had better model fit (based on R^2) than any of these three additional tract-derived indices.

DISCUSSION

Understanding whether and how segregation is a patterning force for racial health disparities in the US requires attention to the dimension, scale, and hypothesized causal pathway by which segregation is conceptualized and operationalized. These findings suggest substantial heterogeneity in absolute and relative estimates of segregation when segregation is measured with different tools. Similarly we find evidence for important differences in the strength of association between segregation measured with these various tools and a wide variety of commonly hypothesized intermediary pathways to poor health. Rather than being seen as a nuisance, these sources of heterogeneity represent an opportunity to further hone and enrich our understanding of residential racial segregation as a social determinant of health. They also suggest a series of ways to customize the operationalization of residential segregation for a given health research study.

DIMENSIONS OF SEGREGATION

It was commonplace in early research on the health effects of segregation to utilize the census tract-derived dissimilarity index as the sole measure of segregation (184, 392, 490, 491). Following Acevedo-Garcia and colleague's (370) suggestion that isolation and clustering may be better conceptual tools than evenness for understanding health patterns, researchers have increasingly used these indices singly or together (3, 402, 475). However we find that when multiple neighborhood scales are measured, dissimilarity and isolation are each useful in understanding health-relevant urban social processes.

One explanation for the unique importance of each dimension may be their differences with regard to sensitivity to overall MSA racial composition and total population size. The dissimilarity index is generally compositionally invariant; in other words it measures the evenness of the distribution of blacks and whites *regardless* of the absolute population percentage of either group.

In contrast, isolation of blacks from whites requires that a substantial proportion of the MSA be black. This distinction is supported by the observation that the difference in segregation estimates in the largest as compared with the smallest MSA's was bigger for isolation than dissimilarity. Dissimilarity may therefore capture segregation-relevant information in moderate sized MSA's without large black populations that is simply missed with the isolation index. Health researchers should therefore consider the target population of MSA's, as well as the segregation pattern of interest in choosing an index.

The performance of the isolation and dissimilarity indices compared with tract-derived indices for the other three dimensions (clustering, centralization, and concentration – see Appendix 4, supplemental table 11) supports the notion that spatial evenness and isolation are the two overarching dimensions of segregation. Particularly when considering multiple spatial scales of each dimension, it may be possible for health researchers to capture a great deal of information about residential segregation by using these two dimensions. That being said, there very well may be questions (for example study of communicable disease) where the special cases of spatial concentration or another dimension may best approximate the segregation-related effects of interest.

Segregation has not always been associated with negative health effects for blacks. In some studies, living in racially homogenous neighborhoods appears to have a health-protective effect often attributed to decreased exposure to discrimination and increased social support (395, 400). For instance unevenness, clustering, and isolation all appear to be associated with worse pregnancy outcomes separately, but when considered jointly, isolation is most toxic, while clustering or unevenness may be health protective (3, 438). While we were unable to consider proxies for experiences of discrimination or direct measures of social support, we do find support for differences in the independent effects of dissimilarity and isolation when considered jointly. The

high degree of correlation between dissimilarity and isolation requires caution in interpretation of results, but there is modest evidence that many individual socioeconomic indicators were primarily associated with dissimilarity, while exposure to violent crime, decreased social capital, and poorer individual health indicators among blacks are primarily associated with increased isolation segregation. It seems prudent for the investigator to continue the recent practice of evaluating multiple dimensions of segregation separately as well as jointly.

SEGREGATION AND PATHWAYS TO HEALTH

This project is largely based on the premise that if residential segregation patterns individual health, it occurs through some intermediary social process such as constraint of individuals' socioeconomic attainment, modifying or reproducing positive or negative neighborhood environments and networks, or influencing individual health behaviors. These "intermediaries" are themselves complex processes not easily boiled down to a single variable. For instance median household income could vary for reasons not directly linked to segregation such as regional economic health, dominant economic sectors (e.g. service industry as compared with creative or information-based industries), and state and local tax and social service policies.

It is notable, however, that there are significant differences in the associations between segregation and socioeconomic indicators for blacks and whites in the same city. These differences in magnitude and sometimes even direction of a correlation between segregation and socioeconomic markers for whites and blacks in the same MSA suggest that indices of black-white segregation truly tap into a construct which primarily adversely affects black urban residents.

We find strong evidence for the association of segregation with several of the chosen proxies for the individual socioeconomic status and area contextual socioeconomic environment

domains. Interpretations of the results from the social capital and individual risk factor domains are complicated by the smaller sample size. Results from the sensitivity analysis which repeated the models of individual and area-based socioeconomic status in these smaller samples suggests that the cities are not likely meaningfully different from the overall sample of 231, but simply fewer in number. Despite the smaller sample size there is some evidence that isolation segregation is associated with both markers of social capital.

These findings do not identify a 'best' domain or pathway explaining segregation's health-relevant effects. Rather they highlight the importance of prior specification of likely causal pathways and subsequent critical consideration of which index of segregation is most closely wed to the hypothesized pathway.

NEIGHBORHOOD SCALE

To our knowledge this is the first study to consider multiple neighborhood scales in estimating the degree of metropolitan segregation. Our approach most likely does not approximate the true neighborhoods which define residential urban experience. However this approach does demonstrate important variation in the social outcomes when we generally think of neighborhoods as a small or large area around one's home. Contrary to our expectations, small scale segregation—defined as such when the component neighborhoods are 500 meter radius circles around each home—was nearly uniformly a stronger predictor of negative social outcomes. The exceptions were for the murder rate and degree of social and inter-racial trust, where large scale isolation explained the greatest variance. While scale seemed important for many individual socioeconomic indicators, scale made little difference for many proxies of the socioeconomic contextual environment. It is worth pointing out that the commonly used census tracts were most

closely approximated by our 2000m definition of a neighborhood, a definition which was never the most robust scale for measurement in terms of the studied pathway proxy domains.

Exploring any spatial phenomenon at different spatial scales enhances understanding of the underlying process. As with the hypothesized causal pathways, we do not recommend any single scale as better; instead we find evidence that for some associations, the scale of neighborhood operationalization was important, and should therefore be considered in choosing a measure (or measures)of segregation.

LIMITATIONS

This study is cross-sectional and ecologic, and carries with it the shortcomings (and strengths) of this design. While our underlying premise is that segregation leads to many negative social and economic patterns, these data do not explicitly test that assumption. Much prior work by sociologists, demographers, and urban geographers has attempted to establish the temporal and causal links between the process of segregation and a multitude of social outcomes. Our goal here is simply to identify patterns of association between segregation measures and commonly hypothesized precursors to poor health and racial disparities in health outcomes.

Because we did not seek to test a specific hypothesis, little attention was paid to the possible false discovery that might result from the multitude of models run for these analyses. P-values are reported as a general indicator of strength of the evidence for a given model parameter, and for the most part they were either clearly non-significant, or extremely small with few between 0.05 and 0.001. The resulting inferences speak to general patterns in terms of the dimensions, scales, and social outcomes rather than any specific contrast.

Finally, the sample of MSA's used, particularly for the social capital and health behavior pathways, raise questions about the robustness of our findings to sample selection. Ideally we

would have all variables for all eligible MSA's. Given this was not feasible the sensitivity analysis which repeated analysis of the individual and contextual domain variables with only the MSA's used in the social capital or behavioral risk factor domains suggested that the primary problem is loss of precision and that the same general patterns appear in the smaller samples.

CONCLUSIONS

Understanding whether racial residential segregation is a fundamental determinant of racial disparities in population health outcomes contributes to our understanding of social patterns in health but more importantly illuminates a series of opportunities for intervention. To date this understanding has been limited by the conceptual models and tools we bring to a given research question. Although documentation of broadly patterned ecologic correlations have often and will continue to generate hypotheses in epidemiology, better understanding of the multi-level processes by which these associations are produced and reproduced is necessary, and this requires more sophisticated tools. We find strong evidence for segregation as a complex construct which can be variably measured with respect to dimension, neighborhood scale, and hypothesized intermediary factors. Rather than prescribing a specific measure researchers should use in future investigations, we recommend that future work should explicitly wed appropriate measures of segregation to the specific causal question at hand.

Table 4-1 Massey and Denton five dimensions of residential segregation

Dimension	Description	Common index of measurement
Evenness	The degree to which two or more groups are distributed in even proportions across spatial sub-units (e.g. census tracts) of a larger area (e.g. metropolitan area)	***Dissimilarity index*** **Range**: 0 to 1 **Interpretation**: % of minority group who must move to different area for all areas to be even
Isolation/ Exposure	The likelihood of two individuals of different groups sharing the same neighborhood. Attempts to measure the opportunity for interaction of members of a different group within a residential neighborhood.	***$_xP^*_x$ (isolation) $_xP^*_y$ (exposure)*** **Range**: 0 to 1 **Interpretation**: probability that two individuals sharing a neighborhood are of the same group (isolation) or of different groups (exposure)
Concentration	This refers to relative population density, so that a group which is concentrated has a higher proportion of its overall population in a smaller geographic area than other groups.	***RCO (relative concentration)*** **Range**: -1 to +1 **Interpretation**: 0 implies two groups equally concentrated, while 1 and -1 mean that one group or the other is maximally concentrated
Centralization	The degree to which a group lives primarily in the central portion of a metropolitan area as opposed to its suburbs.	***ACE (absolute centralization)*** **Range**: -1 to +1 **Interpretation**: 0 implies uniform distribution of groups in city center and suburbs, while 1 or -1 suggest maximal location of one group in city center
Clustering	The spatial proximity of neighborhoods to one another. A neighborhood of high minority proportion would be part of a cluster if other such neighborhoods are adjacent.	***SP (spatial proximity)*** **Range**: 1 to ∞ **Interpretation**: value of 1 occurs if all members of area live equal distances apart, regardless of group membership. Numbers greater than 1 occur if individuals in one group live closer to same group members than non-group members.
Massey and Denton, 1988(409)		

Figure 4-1 Hypothesized pathways between residential segregation and population health

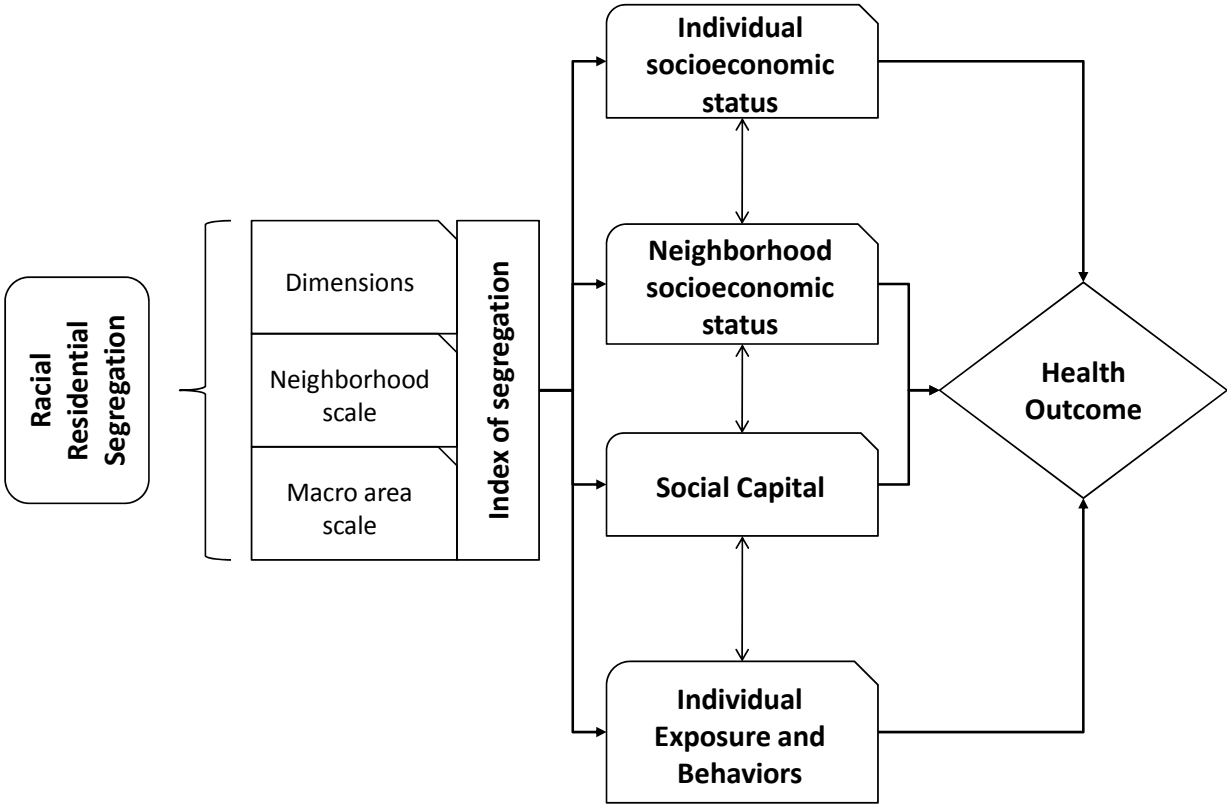


Figure 4-2. Histograms (on the diagonal) and correlations (plots below diagonal, Spearman rank correlation coefficients above the diagonal) of segregation indices for 231 US MSA's, 2000. P-values for all pair wise correlations are <0.0001. (Diss-tract: census-tract derived dissimilarity index; Diss-500m, Diss-4000m: spatial dissimilarity index for MSA's with neighborhoods defined with a 500m or 4000m kernel density function; Iso-tract: census tract derived isolation index; Iso-500m, Iso-4000m: spatial isolation index for MSA's with neighborhoods defined with a 500m or 4000m kernel density function)

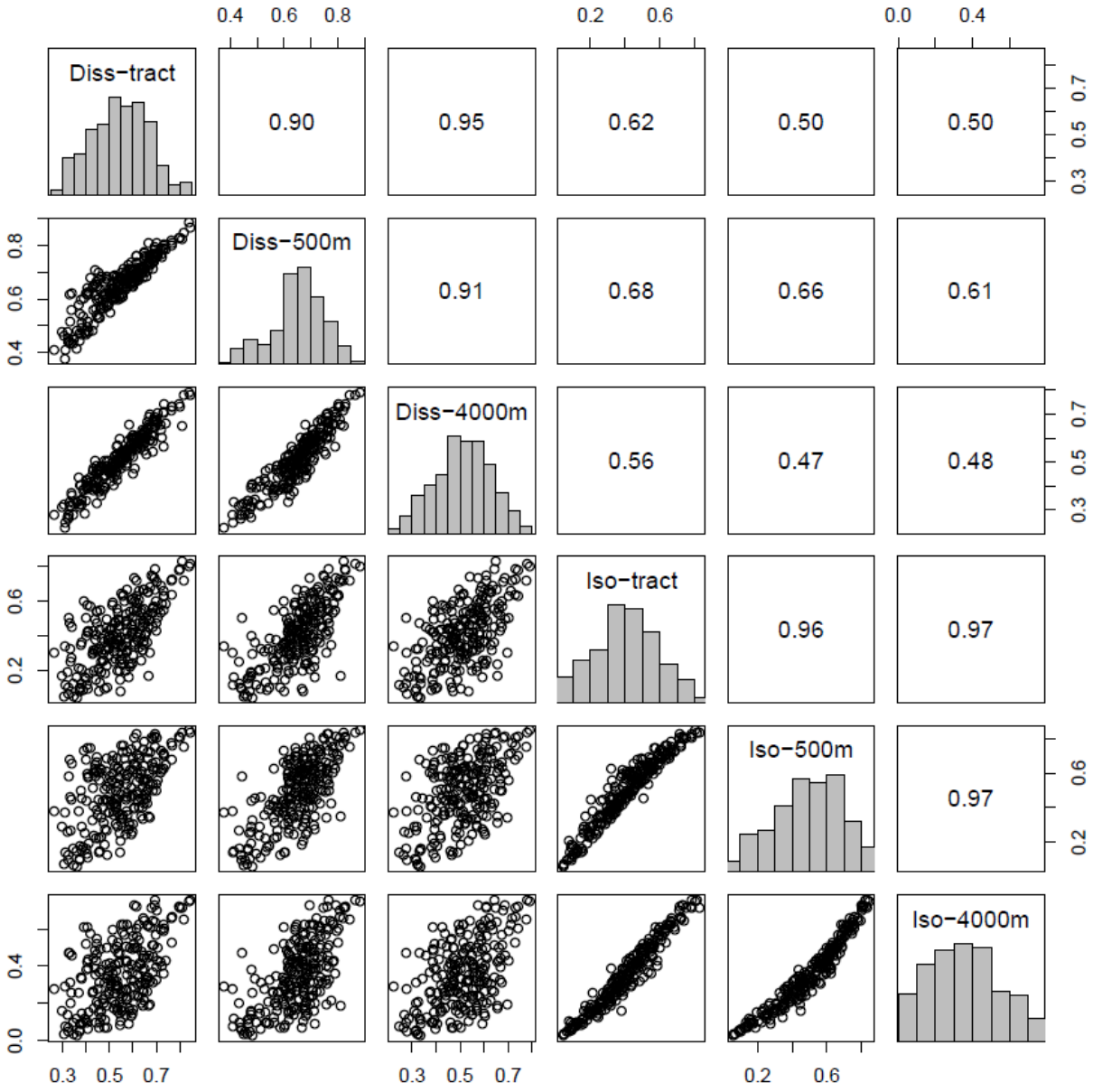


Table 4-2 Descriptive statistics of segregation indices and mediating pathway variables by geographic region

	TOTAL (N=231)		BY CENSUS REGION: Northeast (N=35)		Southeast (N=111)		Midwest (N=52)		West (N=33)		
	Mean	Std.Dev.	Mean	Std.Dev.	Mean	Std.Dev.	Mean	Std.Dev.	Mean	Std.Dev.	p-value[a]
Segregation Indices											
Diss-tract	0.55	0.12	0.63	0.09	0.52	0.10	0.61	0.12	0.45	0.10	<0.001
Diss-500	0.65	0.10	0.71	0.07	0.65	0.08	0.69	0.10	0.53	0.08	<0.001
Diss-4000	0.51	0.12	0.59	0.08	0.49	0.10	0.57	0.13	0.41	0.10	<0.001
Iso-tract	0.41	0.18	0.41	0.19	0.46	0.15	0.41	0.19	0.23	0.15	<0.001
Iso-500	0.49	0.19	0.47	0.18	0.58	0.15	0.48	0.18	0.26	0.16	<0.001
Iso-4000	0.36	0.18	0.32	0.17	0.43	0.16	0.34	0.19	0.19	0.14	<0.001
Individual socioeconomic status											
%Black adults <HS education	26.7%	7.4%	28.5%	5.9%	29.1%	7.3%	25.5%	5.2%	18.5%	6.3%	<0.001
%Black poverty rate	26.1%	6.5%	25.7%	7.8%	26.7%	5.9%	28.2%	4.7%	20.8%	6.8%	<0.001
%White adults <HS education	14.4%	4.5%	15.4%	3.3%	15.8%	4.6%	13.2%	3.2%	10.5%	4.2%	<0.001
%White poverty rate	8.1%	2.7%	7.1%	2.4%	9.0%	3.0%	7.4%	2.0%	7.6%	2.2%	<0.001
Area socioeconomic status/environment											
Black:White ratio of poverty rate	3.37	0.90	3.72	0.69	3.14	0.73	4.01	1.07	2.76	0.56	<0.001
%Poor children in low income tracts (Black)	72.4%	15.4%	81.1%	14.8%	66.8%	15.6%	83.4%	6.9%	67.3%	10.6%	<0.001
%Poor children in low income tracts (White)	31.0%	11.5%	33.0%	10.0%	26.0%	10.9%	37.4%	11.1%	35.7%	8.1%	<0.001
Murder rate (per 100,000 pop)	5.59	3.40	3.38	2.17	6.60	3.46	5.46	3.81	4.76	2.32	<0.001
Social capital	N=30		N=5		N=9		N=8		N=8		
Social trust (values standardized to national norm)	-0.04	0.10	0.02	0.14	-0.07	0.07	-0.01	0.07	-0.07	0.11	0.255
Inter-racial trust (1-4 scale with 4 being high trust)	2.04	0.07	2.11	0.07	2.01	0.07	2.07	0.05	2.00	0.07	0.016
Individual behaviors	N=72		N=13		N=30		N=17		N=12		
% Black adults obese	31.4%	7.1%	29.6%	8.8%	33.8%	5.6%	31.5%	7.5%	27.1%	5.8%	0.027
% White adults obese	19.9%	3.3%	18.3%	2.6%	19.8%	3.1%	22.5%	3.1%	18.1%	2.7%	<0.001
% Black adults current smoker	23.7%	6.3%	22.1%	6.0%	21.5%	3.9%	28.1%	5.9%	24.6%	8.9%	0.003
% White adults current smoker	22.1%	3.3%	20.1%	2.2%	23.3%	3.2%	23.1%	2.9%	19.7%	2.9%	<0.001

a. The p-value refers to the ANOVA F-test for the difference in mean index/mediating variable by region.

Table 4-3 Descriptive statistics of segregation indices and mediating pathway variables by metropolitan area population size

	BY POPULATION SIZE						
	<500,000 (N=131)		500k- 1 million (N=39)		>1 million (N=61)		
	Mean	Std.Dev.	Mean	Std.Dev.	Mean	Std.Dev.	p-value[a]
Segregation Indices							
Diss-tract	0.51	0.11	0.57	0.11	0.61	0.12	<0.001
Diss-500	0.64	0.09	0.66	0.11	0.68	0.10	0.008
Diss-4000	0.48	0.11	0.54	0.12	0.56	0.11	<0.001
Is0-tract	0.36	0.17	0.41	0.18	0.51	0.18	<0.001
Iso-500	0.46	0.19	0.48	0.20	0.56	0.18	0.005
Iso-4000	0.32	0.18	0.36	0.18	0.44	0.18	0.000
Individual socioeconomic status							
%Black adults <HS education	28.8%	7.6%	24.2%	6.8%	23.7%	5.7%	<0.001
%White adults <HS education	15.8%	4.7%	13.9%	3.9%	11.8%	3.0%	<0.001
%Black poverty rate	28.1%	6.2%	25.5%	6.5%	22.0%	5.2%	<0.001
%White poverty rate	9.1%	2.9%	7.7%	1.7%	6.2%	1.6%	<0.001
Area socioeconomic status/environment							
Black:White ratio of poverty rate	3.25	0.94	3.36	0.69	3.62	0.90	0.035
%Poor children in low income tracts (Black)	66.8%	17.5%	74.4%	12.8%	79.2%	10.0%	<0.001
%Poor children in low income tracts (White)	28.5%	12.9%	32.8%	9.4%	35.2%	7.8%	<0.001
Murder rate (per 100,000 pop)	5.07	3.14	6.02	3.19	6.31	3.86	0.050
Social capital	N=4		N=7		N=19		
General social trust	0.01	0.03	-0.05	0.14	-0.05	0.09	0.641
Inter-racial trust	2.06	0.03	2.03	0.10	2.03	0.07	0.790
Individual behaviors	N=13		N=18		N=41		
% Black adults obese	27.2%	10.3%	31.3%	5.5%	32.8%	6.0%	0.046
% White adults obses	21.5%	3.0%	21.0%	3.1%	18.8%	3.2%	0.008
% Black adult current smoker	28.4%	7.0%	22.7%	5.8%	22.6%	5.7%	0.010
% White adult current smoker	23.0%	3.5%	22.5%	2.6%	21.6%	3.5%	0.346

a. The p-value refers to the ANOVA F-test for the difference in mean index/mediating variable by population size.

Table 4-4 Variation in health mediator variables explained by segregation indices

	M1[a]	M2[b] Models: Dissimilarity Indices						M2[b] Models: Isolation Indices					
		Census tract		500 m		4000 m		Census tract		500 m		4000 m	
	R^2	R^2	p-value[c]	R^2	p-value[c]	R^2	p-value[c]	R^2	p-value[c]	R^2	p-value[c]	R^2	p-value[c]
Individual socioeconomic status (N=231 MSA's)													
%Black adults <HS education	0.28	0.37	<0.00001	0.47	<0.00001	0.37	<0.00001	0.37	<0.00001	0.42	<0.00001	0.36	<0.00001
%White adults <HS education	0.26	0.28	0.0208	0.34	<0.00001	0.30	0.0004	0.26	0.5303	0.27	0.0467	0.26	0.3655
%Black poverty rate	0.22	0.31	<0.00001	0.34	<0.00001	0.30	<0.00001	0.25	0.0034	0.26	0.0005	0.24	0.0066
%White poverty rate	0.25	0.25	0.6074	0.25	0.8084	0.40	0.4565	0.26	0.0920	0.25	0.3169	0.26	0.0518
Area socioeconomic status/environment													
Black:White ratio of poverty rate	0.26	0.37	<0.00001	0.37	<0.00001	0.37	<0.00001	0.33	<0.00001	0.32	<0.00001	0.33	<0.00001
%Poor children in low income tracts (Black)	0.34	0.60	<0.00001	0.46	<0.00001	0.51	<0.00001	0.41	<0.00001	0.37	0.0008	0.38	0.0007
%Poor children in low income tracts (White)	0.21	0.21	0.9622	0.24	0.0031	0.22	0.0745	0.22	0.1557	0.23	0.0121	0.23	0.0249
Murder rate (per 100,000 pop)	0.17	0.25	<0.00001	0.27	<0.00001	0.23	<0.00001	0.43	<0.00001	0.42	<0.00001	0.46	<0.00001
Social capital (N=30 MSA's)													
General social trust	0.04	0.10	0.1281	0.05	0.2912	0.02	0.6043	0.29	0.0061	0.23	0.0170	0.26	0.0099
Inter-racial trust	0.25	0.27	0.2161	0.25	0.3592	0.22	0.8153	0.41	0.0116	0.39	0.0177	0.41	0.0112
Individual behaviors (N=72 MSA's)													
% Black adults obese	0.16	0.15	0.7852	0.18	0.1096	0.16	0.3756	0.15	0.8457	0.16	0.3671	0.15	0.7739
% White adults obsese	0.28	0.28	0.4126	0.28	0.4403	0.29	0.2670	0.27	0.7560	0.27	0.7006	0.28	0.5580
% Black adults current smoker	0.26	0.26	0.3969	0.26	0.3252	0.25	0.5735	0.26	0.2933	0.27	0.2257	0.27	0.2523
% White adults current smoker	0.20	0.22	0.1193	0.21	0.1853	0.21	0.1649	0.19	0.8687	0.19	0.7580	0.19	0.7135

a. M1 models include the pathway variable plus three dummy variables for four regions and two dummy variables for three MSA sizes

b. M2 models include all variables in M1 models plus the indicated segregation index. The difference in R^2 between M1 and M2 models is a rough indicator of additional model fit attributable to inclusion of metropolitan level segregation

c. The listed p-value corresponds to the F-test for the significance of the segregation index

Table 4-5 Variation in health mediator variables explained by simultaneous inclusion of Isolation and Dissimilarity indices

	M3[a]								
	Tracts			500 m			4000 m		
	R^2	Diss p-value	Iso p-value	R^2	Diss p-value	Iso p-value	R^2	Diss p-value	Iso p-value
Individual socioeconomic status (N=231 MSA's)									
%Black adults <HS education	0.38	0.0061	0.0098	0.48	<0.00001	0.0390	0.39	0.0007	0.0039
%White adults <HS education	0.28	0.0130	0.2700	0.34	<0.00001	0.0630	0.30	0.0003	0.2200
%Black poverty rate	0.31	0.0000	0.6100	0.34	<0.00001	0.3500	0.30	<0.00001	0.9000
%White poverty rate	0.25	0.4700	0.0790	0.25	0.2100	0.1100	0.26	0.8700	0.0850
Area socioeconomic status/environment									
Black:White ratio of poverty rate	0.37	0.0002	0.0900	0.37	<0.00001	0.4200	0.37	<0.00001	0.0420
%Poor children in low income tracts (Black)	0.61	<0.00001	0.0089	0.48	<0.00001	0.0310	0.52	<0.00001	0.0820
%Poor children in low income tracts (White)	0.22	0.2600	0.0710	0.24	0.0860	0.4800	0.22	0.4900	0.1300
Murder rate (per 100,000 pop)	0.44	0.0770	0.0000	0.42	0.2300	0.0000	0.46	0.0960	0.0000
Social capital (N=30 MSA's)									
General social trust	0.28	0.3800	0.0170	0.24	0.2700	0.0180	0.26	0.3200	0.0078
Inter-racial trust	0.42	0.2700	0.0160	0.41	0.1900	0.0120	0.44	0.1800	0.0049
Individual behaviors (N=72 MSA's)									
% Black adults obese	0.14	0.8500	1.0000	0.17	0.1700	0.6800	0.15	0.3800	0.7700
% White adults obsese	0.29	0.1400	0.2000	0.29	0.1100	0.1500	0.30	0.0690	0.1200
% Black adults current smoker	0.25	0.8900	0.5300	0.26	0.9000	0.4800	0.25	0.8900	0.3200
% White adults current smoker	0.23	0.0390	0.1700	0.21	0.1000	0.3100	0.22	0.0450	0.1300

a. The M3 models include both isolation and dissimilarity indices simultaneously in order to estimate the independent effect of each. In each case the same eighborhood size (e.g. 500m or 4000m) were used. Interaction between isolation and dissimilarity w

Chapter 5 METROPOLITAN RESIDENTIAL SEGREGATION AND RACIAL DISPARITIES IN VERY PRETERM BIRTH[4]

ABSTRACT

Residential racial segregation has been associated with preterm birth and low birthweight among black women. Etiologic and epidemiologic differences between early and late preterm births raise questions about whether this association is similar across gestational ages, and through what pathways it might be mediated. Hierarchical Bayesian models are fit using all singleton births to black and white women in 231 metropolitan statistical areas (MSA) in 2000-2002, and novel spatial measures of the isolation and evenness dimensions of segregation. Isolation segregation measured with small spatial neighborhoods is associated with very preterm birth (OR 1.15 for each 1 standard deviation change in segregation, 95% CI 1.10, 1.19) and moderately preterm birth (OR 1.08, 95% CI 1.04, 1.11), while unevenness measured with large spatial neighborhoods (similar to tract-based clustering) is modestly protective to null. The association varies little with control for individual socioeconomic variables, or indicators of maternal health, and is only modestly attenuated with control for MSA murder rate. Although the association remains robust under various model specifications, segregation combined with all measured individual and area covariates explains only a third of the crude racial disparity. Isolation

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[4] This chapter is a manuscript prepared for submission to a peer-reviewed journal. As such the structure, format and length are in keeping with journal requirements. Use of the plural pronoun 'we' refers to members of the dissertation committee who will be co-authors on this submission.

segregation is a statistically significant determinant of excess risk for very and moderately preterm birth in black women, but leaves much risk to be explained.

INTRODUCTION

The disparity in occurrence of preterm birth between black and white women in the United States remains a serious public health and social equity problem. One challenge in understanding and addressing the causes of this disparity arises from the epidemiologic heterogeneity that exists in this pregnancy outcome and the complex nature of the etiologic pathways to prematurity (454). We briefly review two axes of heterogeneity—gestational age categories and geography—and then discuss the hypothesized role of residential racial segregation as a distal determinant of racial differences in preterm birth risk for black women.

EARLY AND LATE PRETERM BIRTHS

The category of preterm birth—commonly defined as birth prior to 37 weeks gestation—is associated with infant mortality, morbidity, and economic cost (2). However it is the lower tail of the gestational age distribution—operationalized here as very preterm birth, or birth before 32 weeks gestation—which accounts for the majority of this burden. One third of all infant mortality and two thirds of all neonatal mortality have been attributed to prematurity, and 95 percent of this arises from the roughly 2 percent of live births classified as very preterm (187, 188).

The size of the racial disparity also varies with respect to gestational age, with a black-white risk ratio of 1.6 for births <37 weeks, but 2.5 for births <32 weeks (1). The magnitude of this racial disparity combined with the mortality associated with extreme prematurity make very preterm birth the primary driver of the racial disparity in infant

mortality (442, 492). Similar trends exist for preterm-associated morbidities such as cerebral palsy and mental retardation (493, 494).

There may also be important heterogeneity in the etiology of very preterm birth as compared with moderately preterm birth. Infection and inflammation are leading causes of very preterm birth, but less important in near-term birth, a trend which is more prominent in black as compared with white women (13, 65). On the other hand, assisted reproductive technology, increases in the prevalence of labor induction and caesarean section, and societal changes in maternal age at conception have been linked to the recent increase in moderately preterm births, particularly for white women (495, 496, 497, 498).

PLACE-BASED RISK FACTORS

While numerous individual risk factors for preterm birth have been reported, their failure to explain a significant portion of the racial disparity has lead numerous investigators to look further upstream in the causal chain to neighborhood, metropolitan, and societal determinants of prematurity. Controlling for individual level risk factors, neighborhood violent crime and poverty rates have been associated with preterm birth (230, 431, 433, 436). Income incongruity is a measure of relative inequality between the individual's socioeconomic status and the median income of the neighborhood in which she lives. Two studies report a protective effect for preterm birth when black women live in neighborhood characterized by positive income incongruity (435, 499), while a third study did not find an association (500).

These associations could be mediated by a combination of material and psychosocial pathways related to access to safe living conditions, maternal perceptions of neighborhood quality, and exposure to discrimination or stressful life events (283, 300).

Such acute or chronic stressors may interact with maternal neuroendocrine function resulting in preterm birth, or could be mediated by the prevalence of poorly controlled chronic hypertension, or individual behavioral responses (e.g. smoking) to stressful environment, each of which could differentially pattern risk (454).

While residential neighborhoods have been a powerful construct for conceptualizing contextual rather than individual determinants of health disparities, some exposures may operate at different geographic scales. For instance racial disparities in infant mortality vary not just across neighborhoods but also at the city, county, and state level (185, 491, 501). Kramer and Hogue (3) report that for black women more than white women, the risk of very preterm birth and magnitude of racial disparity vary across metropolitan areas. This unique sensitivity to place for black women suggests at least a portion of the disparity may be mediated by forces which vary at the metropolitan scale.

RESIDENTIAL SEGREGATION AND PRETERM BIRTH

The spatial separation of blacks and whites in residential neighborhoods has been used as a marker of structural inequality and institutionalized racism in explaining metropolitan level disparities in infant mortality and low birthweight (393, 490, 502, 503). Recent study designs and conceptual models have become more sophisticated and broadened to include associations between segregation and preterm birth (438, 475), teen pregnancy (504), and smoking during pregnancy (439).

Residential segregation is often conceptualized as multi-dimensional spatial patterns of residential settlement in urban and suburban areas (409). Three dimensional constructs are commonly employed in research on segregation and health outcomes: evenness, clustering, and isolation. Evenness, measured with the dissimilarity index,

describes the difference between the racial composition of each neighborhood as compared with the metropolitan area overall. Clustering is the aggregation of racially homogenous neighborhoods in regions of a metropolitan area, and thus similar to evenness although at a larger scale. Isolation measures the probability of neighborhood contact or exposure between blacks and whites, and is often considered one of the most compelling segregation dimensions in terms of understanding health effects.

Although correlated, these patterns could represent unique types of health-relevant exposures. For example Bell, et al (438) report a protective effect against preterm birth when clustering of black neighborhoods is present, but a deleterious effect of isolation segregation. The authors suggest that conditional on the degree of isolation, clustering enhances social support and networks for black women and families, which may reduce risk by buffering against psychosocial stressors, and facilitating health protective behaviors. Isolation on the other hand may capture economic disenfranchisement and poverty concentration, and is associated with elevated violent crime rates, diminished access to healthy food options, and reduced access to preventive healthcare (505, 506, 507).

While most recent studies of the association between segregation and pregnancy outcomes have found modest but significant associations, Hearst, et al (402) found no association between isolation segregation and infant mortality. Their study differs from others in measuring only central cities (rather than the broader context of metropolitan areas) and in their novel use of propensity score matching as an approach to reducing bias from confounding. Acevedo-Garcia and Osypuk (508) in a commentary on the Hearst paper note the challenges of conceptualizing and modeling the causal pathways of segregation given the possibility that covariates could be confounders and/or mediators of the effect.

Continuing exploration of the multilevel relationships, causal framework, and spatial scale of the segregation-health association is needed (455).

Study Questions

This study is motivated by the three observations discussed above. First, racial disparity in prematurity may best be understood—both epidemiologically and etiologically—as a heterogeneous outcome with at least one axis of difference being very preterm versus moderately preterm births. Second, the magnitude of the racial disparity is not constant but varies geographically and at different spatial scales. This variation in relative risk may offer clues as to the causes of the disparity. Finally, residential segregation has been hypothesized to be a distal determinant of racial disparities in prematurity, but this relationship has never been looked at for very preterm birth, and is incompletely understood in terms of mediating pathways.

From these three observations we pose three questions.

1. Does residential segregation associate similarly with very preterm as compared with moderately preterm birth?

2. Through what contextual and individual pathways might segregation act?

3. How much of the geographic variation in the racial disparity of very preterm birth does segregation explain?

METHODS

The questions naturally fall into a multilevel framework, where births to individual women are situated within metropolitan areas characterized by degree of segregation and other socioeconomic characteristics.

DATA SOURCES

Individual level variables

At the individual level, all singleton live births born in 2000-2002 to non-Hispanic white or non-Hispanic black mothers who lived in eligible US metropolitan statistical areas (MSA's) were abstracted from National Center for Health Statistics natality files (456).

Gestational age was calculated from date of last menstrual period except where clear inconsistency between birthweight and gestational age exist in which case clinical estimates of gestational age including ultrasound dating are used (167, 457). Births were categorized as very preterm (from 20 to less than 32 weeks), moderately preterm (from 32 to less than 37 weeks), or term (37 to 44 weeks).

Maternal education and chronic disease status are considered as potential mediators of a segregation effect. Residential segregation may influence family social structure, area school quality and adult educational attainment (387, 479); maternal education and marital status are each associated with preterm birth. Pre-conceptional chronic diseases such as hypertension and diabetes are also associated with preterm birth (253), and there is some evidence from a study in New York City that prevalent chronic disease mediates some of the segregation effect on low birthweight for black women (509).

Measures of segregation

Metropolitan statistical areas were chosen as the contextual unit of analysis. We analyzed 231 MSA's which had a population of at least 100,000 (and thus have geographically reportable tabulations in natality files) and had a black population of at least 5,000 in the 2000 decennial census. MSA's represent contiguous counties surrounding a core city which are deemed by the Office of Management and Budget to be economically and socially integrated (487). While being a convenient geographic unit at which births are reported, the MSA also fits the conceptualization of residential segregation as a process of sorting individuals into living environments on the basis of race and class. This sorting process happens across a regional residential housing market, not just in some neighborhoods; therefore simultaneously recognizing the housing choices of economically and socially linked urban and suburban communities is beneficial.

Racial residential segregation in each MSA was measured using both a spatial isolation and a spatial dissimilarity index. These indices differ from traditional census tract-derived indices in that the operationalization of neighborhoods is uniquely defined for each point in space, rather than assumed to be demarcated by the boundaries of a census tract. Proposed by Reardon and O'Sullivan (371), these spatial indices reduce misclassification of neighborhood environment as a result of the arbitrary shape or size of tracts, and allow comparative exploration of segregation at multiple neighborhood scales. Massey and Denton (409) described five dimensions of segregation (evenness, isolation, clustering, concentration, and centralization). One consequence of varying the neighborhood scale is that these five may collapse into two overarching dimensions of spatial evenness and spatial isolation (485). In unpublished work we have demonstrated that, compared with tract-derived indices, these spatial measures have stronger correlations with commonly

hypothesized health-mediating variables such as poverty, adult educational attainment, and crime (510).

The actual measurement of spatial isolation and spatial dissimilarity are implemented via a freely available Visual Basic for Applications macro (464) for ArcGIS 9.2 (ESRI, Redlands, WA). The procedure is more completely described elsewhere (485). Briefly, for each MSA, a 50 by 50 meter grid is overlaid on US 2000 Decennial Census block data. The density (person per square kilometer) of whites or blacks in each block is transferred to the overlying grid points and then a pycnophylactic (mass-preserving) smoothing algorithm is applied to smooth population counts across block areas without altering the absolute count within a given block (469). Biweight kernel density functions are then applied to each area with bandwidths corresponding to a 500 meter or 4000 meter radius circle around each grid point. The resulting kernel densities capture the racial composition in the area (either a 500m or 4000m radius circle) surrounding each point in the grid. In other words each point in space has a unique value for its racial composition using two different size definitions of neighborhood. Spatial versions of the black isolation index ($_xP^*_x$) and the black-white dissimilarity index are then calculated with the following formulas adapted from Reardon and O'Sullivan (371):

Equation 5-1

$$ {}_xP^*_x = \sum_{r=1}^{R} \frac{\tau_r}{T} \tilde{\pi}_r $$

Equation 5-2

$$ D = \sum_{m=1}^{2} \sum_{r=1}^{R} \frac{\tau_r}{2TI} \left| \tilde{\pi}_{rm} - \pi_m \right| $$

Where r indexes all grid points in area R (the MSA); m indexes two racial groups, black and white; τ_r is the density per unit area of a given racial group at point r; T is the total MSA population count of the racial group; tilde-π_{rm} and tilde-π_r are the proportion of the racial group in the spatial neighborhood (within the 500 or 4000 m radius circle) of point r; I is two times the product of the overall proportion black and white; and π_m is the global MSA fraction of the population of the given racial group. This represents an extension of the traditional census tract formulas which are a population weighted average across all neighborhoods of the local isolation (for ${}_xP^*_x$) or the local difference in racial composition as compared to the MSA overall (for dissimilarity). In each case the resulting values range from 0 (least segregated) to 1 (most segregated). We then standardized each index to a N(0,1) distribution to facilitate interpretation in models.

Additional metropolitan level variables

Metropolitan population size (categorized as <500,000, 500,000-1 million, or greater than 1 million), and Census region (Northeast, Southeast, Midwest, West) were obtained from the Decennial Census 2000 (511) and included as potential confounders.

Potential mediators between segregation and prematurity at the metropolitan level were chosen based on evidence from neighborhood-level contextual determinants reviewed above, and findings from currently unpublished work on segregation and domains of health-mediating variables (510). Crime and poverty rates in each MSA are characteristics of the social and economic environment. The mechanisms for an effect could be chronic exposure to psychosocial stressors and subsequent 'weathering' or premature aging of maternal neuroendocrine and vascular function (202). Alternatively effects could be

material in nature, related to access to health promoting resources including health and dental care.

The murder rate per 100,000 persons in each metropolitan area was obtained from Federal Bureau of Investigation statistics for 2000 (460, 461). The black poverty rate as well as the ratio of black to white poverty rates in each MSA were calculated from Census 2000 SF3 tables to represent indicators of area-based racial inequity (458). As an indicator of spatial poverty concentration, we also utilized census-derived measures of the exposure of poor children to high poverty neighborhoods as calculated by Acevedo-Garcia, et al (459). This variable is the proportion of all black children under 18 years of age whose families are below the poverty line and who live in census tracts with median household incomes less than 80% of the median household income for the MSA as a whole.

ANALYSIS

The multi-level nature of our questions combined with our interest in both measured and unmeasured variation lead us to choose hierarchical Bayesian logistic modeling as an analytic tool (512). The setup for each model follows this template:

Equation 5-3

$$P(y_i = 1) = logit^{-1}(\alpha_j + \beta X_i)$$

$$\alpha_j \sim N(\gamma_0 + U_j\gamma_1, \sigma_\alpha^2)$$

$$\beta \sim N(0,10000)$$
$$\gamma \sim N(0,10000)$$
$$\sigma_\alpha \sim Unif(0,100)$$

In the likelihood or first level, y_i is the binary pregnancy outcome for the ith woman, α_j is a random intercept for the jth MSA, β is a vector of parameters for individual variables, and **X** is a matrix of individual level covariates. In a Bayesian setup every parameter is stochastic, and so each is assigned a prior distribution. Relatively uninformative flat priors are assigned to the β-parameters, while the α-intercept has an informative prior, which is the second level of the model. The alphas are assumed to come from a normal distribution with a variance of σ^2. The mean of the distribution is the sum of a global intercept, γ_0, plus the vector of γ- parameters corresponding to the MSA-level covariates in matrix **U**.

For question one, concerning the association of segregation with very preterm and moderately preterm births, only births to black mothers were analyzed, acknowledging that prior research has demonstrated little to no association between segregation and preterm birth in white women. Additionally the spatial isolation index using the smaller 500m radius circle neighborhood definition is our segregation measure of choice, based on the empirical and conceptual strength of this dimension (370).

Bayesian models were fit with WinBUGS 1.4 (513) using R 2.7 (489) and the R2WinBUGS package (514). All models were run with three chains, each for 10-20,000 iterations with the first half discarded; approximate convergence was determined by visual inspection of the trace plots of the posterior parameter estimates from each chain, as well as an R-hat statistic of 1.1 or lower for each parameter (512). Separate logistic models were fit with very preterm and moderately preterm birth as the dependent variable; in each case term births are the comparison group. Relative improvements in model fit were assessed using the deviance information criterion (DIC). All models include a random intercept, and adjust for census region and metropolitan size as MSA-level confounders.

For question two, concerning possible mediating mechanisms, we consider hypothesized pathways between segregation and prematurity (454, 455) using the same models as in question 1. For this question we treat maternal age, parity, and history of prior preterm or small for gestational age infant as potential confounders, and models controlling for these variables are denoted M1. Two mediating pathways are then considered: socioeconomic condition of the mother (model M2) and prevalence of chronic disease and health behaviors (model M3). Model M4 includes all of the above covariates. While the spatial isolation index is the primary measure of segregation, models including the spatial dissimilarity index measured with a large neighborhood definition (operationalized as a 4 km radius circle around each 50 meter square grid point in the MSA) is used to approximate the same kind of neighborhood unevenness typically captured by the tract-based clustering measures, and these dual-dimension models are denoted M5.

At the metropolitan level, murder rate, poverty concentration, and the racial disparity in poverty rates are candidate mediators between segregation and subsequent preterm birth. In all cases, mediation was evaluated by comparing the magnitude of the segregation-preterm birth association with and without the candidate mediator, with meaningful attenuation suggestive of mediation or confounding.

Question three, concerning the geographic variation in the racial disparity of preterm birth explained by segregation also uses the spatial isolation index, but includes births to white and black mothers. The model structure is similar to that in Question 1 with the addition of a binary variable for race, and an associated random slope for this variable:

Equation 5-4

$$P(y_i = 1) = logit^{-1}(\alpha_j + \delta_j * Black_i + \beta X_i)$$

$$\delta_j \sim N(\gamma_{race0} + U_j \gamma_{race1}, \sigma^2_{race})$$

The random intercept, α, and the priors remain the same as the previously described model. δ_j is the MSA-specific relative black-white disparity accounting for individual and area covariates. γ_{race0} is then the global excess risk across all MSA's for black as compared with white women, and γ_{race1} is the vector of second-level parameters corresponding to the matrix, **U**, of MSA-level covariates including isolation segregation. σ_{race} is the variation in the disparity across MSA's.

RESULTS

Of 6,180,544 eligible births during the study period, 23.5% were born to black mothers (Table 5-1). Overall black women experienced 3.17 times the risk (95% CI 3.13, 3.20) for very preterm birth as white women, and moderately preterm birth occurred 1.6 times as often (95% CI, 1.61, 1.63) for black as compared with white women. Racial differences in the importance of individual risk factors result in variation in the racial disparity across covariates. For instance, higher maternal education and being married are more strongly protective for white women than for black women, so that the relative racial disparity is smaller among women without a high school degree, or unmarried women.

For both black and white women, risk for preterm birth varied regionally, with the Western metropolitan areas having substantially lower risk than other areas for black women; for white women risk is higher in the Northeast and Midwest but lower in the West and Southeast.

Across the 231 metropolitan areas analyzed, isolation segregation ranged from 0.06 (Salt Lake City, UT) to 0.86 (Gary, IN), with a median value of 0.51 and an interquartile range of 0.29. The dissimilarity index ranged from 0.22 (Lawton, OK) to 0.79 (also in Gary, IN) with a median value of 0.51 and an interquartile range of 0.16. The Spearman rank correlation of MSA isolation and dissimilarity was 0.49.

Table 5-2 reports odds ratios for very preterm birth among black women calculated from the mean of the posterior distribution for each parameter, as well as 95% credible intervals for models with segregation, individual covariates, and control for region and population size. In crude models each standard deviation change in isolation increased risk of very preterm birth for black women by 11% (OR 1.11, 95% CI 1.08, 1.14). Models M1-M4 consider this association under different specifications of covariates. While characteristics such as history of prior preterm birth, chronic hypertension, or tobacco use are each important predictors of very preterm birth risk, the independent effect of isolation segregation on risk remains relatively unchanged, with the single largest difference seen between model M2 which includes individual socioeconomic variables where the odds ratio was 1.10 (95% CI 1.07, 1.14) and model M3 with variables from the hypothesized maternal health pathway where the effect of isolation increased over crude estimates to 1.13 (95% CI 1.10, 1.17).

In model M5, with both isolation and neighborhood clustering (as measured with dissimilarity using a 4000m kernel bandwidth neighborhood definition), the odds for very preterm birth increased 15% (95% CI 1.10, 1.19) for each standard deviation change in isolation, while the independent effect of clustering appears to be protective to null (OR 0.95, 95% CI 0.92, 0.99).

Table 5-3 reports the same modeling procedure as Table 5-2 except with moderately preterm birth as the outcome. While the overall relative pattern is very similar in these models as compared to Table 5-2, the most notable difference is the absolute magnitude of the odds ratios associated with isolation. Isolation appears to have just over half the effect on moderately preterm birth risk as it did on very preterm risk. While a one standard deviation change in isolation conditional on dissimilarity and all individual covariates increased very preterm birth odds 15%, it increased moderately preterm birth odds only 8%.

Table 5-4 builds on these models with all individual covariates by considering metropolitan characteristics which could mediate the effects of segregation. For murder rate alone is there any appreciable change in the association between segregation and either very or moderately preterm birth, and this is small with attenuation of the odds ratio for very preterm birth to 1.12 (95% CI 1.07, 1.17). For very preterm more than moderately preterm there is also reduction in the inter-MSA variation (σ^2_α) in risk with inclusion of the murder rate and individual covariates. For moderately preterm births this variance parameter is nearly unchanged in models in Table 5-3 or Table 5-4 (0.131-0.134), whereas for very preterm births the value changes from 0.135 in model M2, Table 5-2 to 0.12 with control for murder rate.

In Table 5-5, models with both black and white women including all previous covariates are assessed to determine the change in the racial disparity for very preterm birth under various model specifications. Inclusion of all individual covariates reduced the crude black-white odds ratio by approximately 25%. The addition of isolation segregation reduced the disparity an additional 8%, and there was a concomitant decrease in the inter-

MSA variation in the disparity (σ^2_{race}) from a variance of 0.107 to 0.077 with control for isolation. Addition of clustering added little to the model in terms of model fit or explanation of the disparity.

DISCUSSION

The racial disparity in preterm birth is a stubborn problem which defies simple explanations. Preterm birth is being increasingly viewed as a complex disease process not unlike chronic metabolic and vascular disease, where single individual-level risk factors are incomplete in predicting or preventing poor health (515). Residential segregation has been proposed as a fundamental cause of racial disparities in health because of the manner in which segregation may constrain individuals' economic attainment, health, and welfare (6). This study finds evidence that for black women, independent of individual and some area level risk factors, living in a highly segregated metropolitan area significantly increases risk for preterm birth generally and particularly for the extreme outcome of very preterm birth.

The different magnitude of effect of isolation segregation by extremity of prematurity is important because of the higher public health burden and wider racial gap for very preterm birth as compared with moderately preterm birth. But it may also hint towards etiologic pathways by which social structure and environment become embodied as individual biological events. For example the greater importance of infections such as bacterial vaginosis in very preterm births (516) raise questions of whether social environment interacts with immune status producing either differences in susceptibility or exposure to genital tract infections. Moderately preterm births are increasingly driven by medical interventions such as labor induction and caesarean section (498). Differences in

clinical practices or access to health care could plausibly vary by degree of segregation, modifying black women's risk for such near-term births.

Other clues as to pathways linking segregation and preterm birth were hard to find empirically. Attenuation of an association of interest with inclusion of additional covariates could indicate confounding or mediation depending on whether the exposure (segregation) is causally associated with the covariate. Although we hypothesized mediating pathways, in this observational design we are unable to distinguish between mediation and confounding. However the robustness of the association between isolation segregation and preterm birth to inclusion of groups of variables indicating maternal socioeconomic status and maternal health status suggest that neither pathway (nor the two jointly) mediates (or confounds) this association to any large degree.

Isolation is the dimension of segregation most strongly linked to violent crime rates, and the slight attenuation of the segregation-preterm birth association with adjustment for murder rate supports the conceptual choice of isolation in understanding this health outcome. While murder per se may not directly influence women's risk for preterm birth, living in areas with higher social isolation and dysfunction could increase exposure to stress, decrease access to areas of economic and health promotion opportunities, and affect patterns of social support. Notably we found, as have other investigators (438), that isolation and racial spatial unevenness have different independent effects on prematurity. Conditional on the degree of spatial isolation, spatial clustering of blacks in urban areas was modestly protective (in the case of very preterm birth) or at least null in effect (in the case of moderately preterm birth). This has been suggested to result from the buffering effects of social networks and support as well as black political empowerment (392).

Although residential segregation appears to have a statistically significant association with excess risk of preterm birth in black women, it accounts for only a small portion of this excess risk, leaving a large racial disparity unexplained. Kramer and Hogue (3) reported large racial differences in both overall risk and in the city-to-city variation in risk for very preterm birth. Black women appear to have increased sensitivity to place (as evidenced by greater inter-city variation) while white women experienced relatively constant risk regardless of locale. However the pattern observed suggested that the racial disparity may be decomposed into two components: determinants which are geographically varying (and thus explain the city-to-city variation for black women) and determinants which are geographically constant and explain the persistence of the disparity regardless of locale. In the case of understanding the racial disparity in preterm birth, relative variation in segregation can only account for the portion which is geographically variable. In fact modeled inter-MSA variance does decrease by about 28% when segregation is added to the models. What is not accounted for is any unmeasured, geographically constant risk including many lifecourse health behaviors, residual confounding by socioeconomic status, pervasive exposures to chronic stress, or genetic and epigenetic interactions with any of the above.

LIMITATIONS

Use of vital records for outcome or covariate data raises concern for misclassification of both exposure and outcome. Accurate gestational age is notoriously hard to capture even in prospective clinical studies and differential misclassification by race and class remain concerns. Very low birthweight (VLBW) is highly correlated with very preterm birth and more reliably measured. To assess misclassification of gestational age, models were fit with VLBW as an alternate outcome. Parameter strength and conclusions

were similar in these models, suggesting misclassification of gestational age is not a significant source of bias.

Any inference from observational data is limited by the possible importance of unmeasured variables, and this is particularly true with such a complex etiologic hypothesis. Possibly important missing variables include measures of the neighborhood environment where women lived (in addition to the metropolitan level contextual variables), and greater detail with respect to biologic or clinical variables for each woman including genital tract infection, substance use, obstetric complications and chronic disease. Although these shortcomings limit the richness of detail in piecing together links in the causal chain, the persistence of an effect of segregation in light of measured covariates suggests that the broad pattern is meaningful.

CONCLUSIONS

Residential segregation, previously associated with risk for low birthweight and preterm birth, is most strongly associated with very preterm birth where the racial gap is also largest and the burden of mortality and morbidity is most severe. The association between racial isolation and preterm birth persists under numerous model specifications, and is only attenuated modestly with control for individual socioeconomic variables and metropolitan murder rate. While meaningful, this association remains small in magnitude and explains only a small portion of the racial disparity. Future work should continue to explore the manner in which structural processes in urban areas influence health. These efforts will likely be strongest if combined with improved measurement at all scales of study from individual clinical and biological information, to neighborhood environment, and metropolitan characteristics.

Table 5-1 Distribution of singleton live births by maternal race, selected demographics, and outcome, 231 Metropolitan statistical areas, 2000-2002

	Non-Hispanic black mothers			Non-Hispanic white mothers			B/W Risk Ratio	
	N births	%VPT	%MPT	N births	%VPT	%MPT	VPT	MPT
TOTAL	1,452,943	3.45	12.38	4,727,601	1.09	7.62	3.17	1.62
Maternal age								
<15	8,036	6.25	17.26	2,875	3.90	14.50	1.60	1.19
15-19	259,919	3.71	13.30	331,585	1.88	9.36	1.97	1.42
20-24	462,992	3.05	11.89	931,881	1.26	8.06	2.42	1.48
25-29	335,450	3.16	11.41	1,260,933	0.94	7.28	3.36	1.57
30-34	235,487	3.69	12.18	1,377,871	0.89	7.01	4.15	1.74
35-39	121,912	4.17	14.15	681,430	1.08	7.66	3.86	1.85
40+	29,147	4.85	16.04	141,026	1.36	9.34	3.57	1.72
Maternal education[a]								
<12 years	346,198	3.92	14.30	485,564	1.83	9.99	2.14	1.43
12 years	555,945	3.44	12.53	1,322,573	1.31	8.30	2.63	1.51
>12 years	525,107	3.01	10.93	2,879,627	0.84	6.91	3.58	1.58
Marital status								
Married	467,200	2.83	10.94	3,736,839	0.89	7.16	3.18	1.53
Unmarried	985,743	3.74	13.06	990,762	1.85	9.37	2.02	1.39
Parity								
Primiparous	432,811	3.42	11.49	1,609,656	1.24	7.80	2.76	1.47
Multiparous	1,020,132	3.46	12.76	3,117,945	1.01	7.53	3.43	1.69
Prior preterm or SGA birth[a]								
Yes	20,637	11.18	26.25	54,813	3.84	22.22	2.91	1.18
No	1,420,965	3.32	12.18	4,618,748	1.05	7.44	3.16	1.64
Chronic hypertension[a]								
Yes	20,519	8.54	21.34	35,256	3.46	16.31	2.47	1.31
No	1,421,083	3.36	12.25	4,628,305	1.07	7.55	3.14	1.62
Diabetes[a]								
Yes	41,956	3.42	16.92	135,907	1.17	11.94	2.92	1.42
No	1,399,646	3.44	12.25	4,537,654	1.08	7.49	3.19	1.64
Tobacco use[a]								
Yes	122,275	4.94	15.85	576,214	1.84	10.02	2.68	1.58
No	1,237,533	3.33	12.15	3,707,273	0.99	7.38	3.36	1.65

	Non-Hispanic black mothers			Non-Hispanic white mothers			B/W Risk Ratio	
	N births	%VPT	%MPT	N births	%VPT	%MPT	VPT	MPT
Region								
Northeast	275,059	3.36	11.42	1,017,475	1.01	6.68	3.33	1.71
Southeast	741,877	3.52	12.84	1,639,918	1.19	8.48	2.96	1.51
Midwest	316,917	3.60	12.68	1,213,167	1.13	7.65	3.19	1.66
West	119,090	2.77	10.94	857,041	0.94	7.07	2.95	1.55

Source: National Center for Health Statistics Natality Files, 2000-20002

Abbreviations: VPT: Very preterm birth (greater than 20 but less than 32 weeks gestation); MPT: Moderately preterm birth (greater than or equal to 32 weeks but less than 37 weeks gestation)

a. Demographic factor does not sum to total due to missing values in natality files

Table 5-2 Posterior parameter estimates for models of very preterm birth born to black women

	Crude[a]			M1 -- Age, parity and prior preterm birth			M2 -- Socioeconomic condition pathway			M3 -- Maternal health pathway			M4 -- All covariate model			M5 -- Dual segregation model		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Individual level																		
Maternal age																		
<15	2.12	1.93	2.34	2.23	2.03	2.45	1.66	1.51	1.83	2.29	2.08	2.50	1.80	1.62	1.97	1.80	1.64	1.99
15-19	1.18	1.15	1.21	1.22	1.18	1.25	0.97	0.94	1.00	1.23	1.19	1.27	1.02	0.98	1.05	1.02	0.98	1.05
20-24	0.96	0.93	0.98	0.96	0.94	0.99	0.86	0.84	0.89	0.97	0.94	0.99	0.88	0.85	0.90	0.88	0.86	0.90
25-29	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
30-34	1.21	1.17	1.24	1.21	1.17	1.24	1.30	1.26	1.34	1.19	1.16	1.23	1.26	1.23	1.30	1.27	1.23	1.31
35-39	1.42	1.37	1.47	1.41	1.37	1.46	1.54	1.49	1.60	1.35	1.31	1.40	1.46	1.41	1.51	1.46	1.41	1.51
40+	1.71	1.62	1.82	1.71	1.61	1.81	1.85	1.74	1.96	1.58	1.49	1.68	1.70	1.60	1.80	1.70	1.61	1.80
Parity																		
Primiparous	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Multiparous	1.07	1.05	1.09	1.00	0.97	1.02	0.97	0.95	0.99	0.97	0.95	1.00	0.96	0.94	0.98	0.96	0.94	0.98
Prior preterm or SGA birth																		
Yes	4.75	4.54	4.98	4.77	4.57	5.00	4.69	4.47	4.91	4.56	4.34	4.79	4.53	4.31	4.74	4.54	4.34	4.75
No	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Maternal education																		
<12 years	1.27	1.25	1.30				1.21	1.18	1.24				1.15	1.11	1.18	1.15	1.12	1.18
12 years	1.10	1.08	1.12				1.08	1.06	1.11				1.06	1.04	1.09	1.06	1.04	1.09
>12 years	1.00	--	--				1.00	--	--				1.00	--	--	1.00	--	--
Marital status																		
Married	1.00	--	--				1.00	--	--				1.00	--	--	1.00	--	--
Unmarried	1.36	1.33	1.39				1.47	1.44	1.51				1.43	1.40	1.47	1.43	1.40	1.47
Chronic hypertension																		
Yes	3.03	2.87	3.18							2.77	2.64	2.93	2.75	2.61	2.90	2.75	2.61	2.90
No	1.00	--	--							1.00	--	--	1.00	--	--	1.00	--	--

	Crude[a]			M1 -- Age, parity and prior preterm birth			M2 -- Socioeconomic condition pathway			M3 -- Maternal health pathway			M4 -- All covariate model			M5 -- Dual segregation model		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Diabetes																		
Yes	0.95	0.90	1.00							0.90	0.85	0.95	0.91	0.87	0.97	0.91	0.87	0.96
No	1.00	--	--							1.00	--	--	1.00	--	--	1.00	--	--
Tobacco use																		
Yes	1.58	1.54	1.63							1.53	1.48	1.57	1.38	1.34	1.42	1.38	1.34	1.42
No	1.00	--	--							1.00	--	--	1.00	--	--	1.00	--	--
MSA-level																		
Isolation[b]	1.11	1.08	1.14	1.12	1.08	1.15	1.10	1.07	1.14	1.13	1.10	1.17	1.11	1.08	1.15	1.15	1.10	1.19
Dissimilarity/ clustering[b]	1.05	1.02	1.08													0.95	0.92	0.99
Population size																		
<500,000	1.09	1.04	1.16	1.10	1.04	1.16	1.08	1.02	1.14	1.08	1.03	1.14	1.07	1.01	1.13	1.05	0.99	1.11
500k - 1 million	1.08	1.01	1.15	1.09	1.02	1.16	1.09	1.01	1.16	1.08	1.01	1.15	1.07	1.00	1.14	1.07	1.00	1.14
1 million +	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Region																		
Northeast	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Southeast	0.98	0.92	1.05	1.04	0.96	1.12	1.07	0.99	1.15	1.07	1.00	1.15	1.09	1.02	1.17	1.04	0.97	1.13
Midwest	0.98	0.91	1.06	1.01	0.93	1.09	1.00	0.92	1.08	1.01	0.93	1.09	1.00	0.93	1.09	1.01	0.94	1.09
West	0.84	0.76	0.92	0.86	0.78	0.95	0.88	0.80	0.98	0.93	0.84	1.03	0.94	0.85	1.03	0.91	0.83	1.01
σ^2_α				0.134			0.135			0.126			0.129			0.125		
DIC				416696			415134			414758			413557			413559		

Abbreviations: VPT: very preterm birth (birth <32 weeks gestation); MSA: metropolitan statistical area

a. Crude models for individual covariates all include random intercepts for MSA, and adjustment for region and population size

b. The odds ratios for segregation indices refer to the change in risk of very preterm birth for a 1-standard deviation change in segregation index

Table 5-3 Posterior parameter estimates for models of moderately preterm birth born to black women

	Crude[a]			M1 -- Age, parity and prior preterm birth			M2 -- Socioeconomic condition pathway			M3 -- Maternal health pathway			M4 -- All covariate model			M5 -- Dual seg model		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Individual level																		
Maternal age																		
<15	1.63	1.53	1.73	1.89	1.78	2.01	1.45	1.37	1.54	1.95	1.83	2.06	1.54	1.44	1.64	1.54	1.44	1.63
15-19	1.17	1.15	1.19	1.28	1.26	1.31	1.06	1.04	1.08	1.31	1.29	1.33	1.10	1.08	1.12	1.10	1.08	1.12
20-24	1.03	1.01	1.04	1.05	1.04	1.07	0.97	0.95	0.98	1.06	1.05	1.07	0.98	0.97	0.99	0.98	0.97	0.99
25-29	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
30-34	1.10	1.09	1.12	1.10	1.08	1.11	1.15	1.13	1.17	1.08	1.07	1.10	1.13	1.11	1.15	1.13	1.11	1.15
35-39	1.33	1.31	1.36	1.32	1.29	1.34	1.40	1.37	1.42	1.27	1.25	1.29	1.34	1.31	1.36	1.34	1.31	1.37
40+	1.57	1.51	1.62	1.54	1.49	1.59	1.63	1.57	1.68	1.45	1.40	1.50	1.52	1.47	1.57	1.52	1.47	1.57
Parity																		
Primiparous	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Multiparous	1.17	1.15	1.18	1.16	1.15	1.18	1.13	1.12	1.14	1.15	1.13	1.16	1.12	1.11	1.13	1.12	1.11	1.14
Prior preterm or SGA birth																		
Yes	3.05	2.95	3.15	2.98	2.88	3.08	2.94	2.85	3.05	2.89	2.81	2.99	2.87	2.78	2.97	2.87	2.78	2.97
No	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Maternal education																		
<12 years	1.33	1.32	1.35				1.29	1.27	1.31				1.25	1.23	1.26	1.25	1.23	1.26
12 years	1.15	1.13	1.16				1.13	1.12	1.15				1.12	1.10	1.13	1.12	1.11	1.13
>12 years	1.00	--	--				1.00	--	--				1.00	--	--	1.00	--	--
Marital status																		
Married	1.00	--	--				1.00	--	--				1.00	--	--	1.00	--	--
Unmarried	1.24	1.23	1.26				1.24	1.22	1.26				1.22	1.21	1.24	1.22	1.21	1.24
Chronic hypertension																		
Yes	1.99	1.92	2.05							1.89	1.83	1.96	1.88	1.82	1.95	1.88	1.82	1.95

	Crude[a]			M1 -- Age, parity and prior preterm birth			M2 -- Socioeconomic condition pathway			M3 -- Maternal health pathway			M4 -- All covariate model			M5 -- Dual seg model		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
No	1.00	--	--							1.00	--	--	1.00	--	--	1.00	--	--
Diabetes																		
Yes	1.41	1.37	1.44							1.39	1.35	1.42	1.40	1.36	1.44	1.40	1.36	1.44
No	1.00	--	--							1.00	--	--	1.00	--	--	1.00	--	--
Tobacco use																		
Yes	1.40	1.38	1.42							1.36	1.33	1.38	1.24	1.22	1.26	1.24	1.22	1.26
No	1.00	--	--							1.00	--	--	1.00	--	--	1.00	--	--
MSA-level																		
Isolation[b]	1.06	1.04	1.09	1.07	1.04	1.10	1.06	1.03	1.09	1.08	1.05	1.11	1.07	1.04	1.09	1.08	1.04	1.11
Dissimilarity/clustering[b]	1.04	1.02	1.07													0.99	0.96	1.02
Population size																		
<500,000	1.10	1.04	1.15	1.08	1.03	1.14	1.07	1.01	1.13	1.07	1.02	1.13	1.06	1.01	1.11	1.06	1.01	1.11
500k - 1 million	1.09	1.03	1.14	1.09	1.03	1.16	1.09	1.02	1.15	1.08	1.02	1.14	1.08	1.02	1.14	1.08	1.02	1.14
1 million +	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Region																		
Northeast	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Southeast	1.14	1.08	1.22	1.19	1.12	1.27	1.21	1.13	1.28	1.23	1.15	1.30	1.23	1.16	1.31	1.22	1.14	1.30
Midwest	1.10	1.03	1.17	1.11	1.04	1.20	1.11	1.03	1.18	1.12	1.05	1.20	1.11	1.04	1.19	1.11	1.04	1.19
West	1.02	0.94	1.10	1.05	0.97	1.15	1.07	0.99	1.18	1.12	1.03	1.22	1.12	1.04	1.22	1.11	1.02	1.22
σ^2_α				0.134			0.134			0.131			0.132			0.132		
DIC				1065390			1062570			1062380			1060170			1060180		

Abbreviations: MPT: moderately preterm birth (birth 32-36 weeks gestation); MSA: metropolitan statistical area

a. Crude models for individual covariates all include random intercepts for MSA, and adjustment for region and population size

b. The odds ratios for segregation indices refer to the change in risk of very preterm birth for a 1-standard deviation change in segregation index

Table 5-4 Metropolitan level mediating variables for association between segregation and very or moderately preterm birth in black women

Very preterm birth

	Murder			Poverty			Poverty rate ratio			Poverty concentration		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Isolation[a]	1.12	1.07	1.17	1.15	1.10	1.20	1.15	1.10	1.20	1.16	1.11	1.21
Dissimilarity[a]	0.95	0.91	0.98	0.95	0.91	0.99	0.96	0.92	0.99	0.95	0.91	1.00
Murder rate[b]	1.12	1.03	1.21									
Black poverty rate[c]				1.03	0.98	1.07						
Black-white poverty rate ratio							1.00	0.97	1.03			
Black poverty concentration[d]										0.98	0.96	1.01
σ_α		0.120			0.125			0.127			0.122	
DIC		410126			413558			413558			406547	

Moderately preterm birth

	Murder			Poverty			Poverty rate ratio			Poverty concentration		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Isolation[a]	1.05	1.01	1.10	1.07	1.04	1.11	1.08	1.04	1.11	1.06	1.01	1.10
Dissimilarity[a]	0.99	0.96	1.02	0.98	0.95	1.01	0.99	0.96	1.02	1.03	0.98	1.07
Murder rate[b]	1.09	1.01	1.18									
Black poverty rate[c]				1.04	1.00	1.08						
Black-white poverty rate ratio							0.99	0.96	1.02			
Black poverty concentration[d]										0.98	0.96	1.00
σ_α		0.131			0.132			0.132			0.131	
DIC		1051260			1060170			1060180			1041650	

a. Odds ratios for the isolation and dissimilarity indices correspond to the change in the outcome for a 1 standard deviation change in segregation

b. Murder rate is scaled so that a 1-unit change in murder rate is equivalent to 10 murders/100,000 persons

c. Black poverty rate is scaled so that a 1-unit change is equivalent to 10% change in poverty rate

d. Black poverty concentration is the proportion of children in poor families who also live in high poverty neighborhoods. It is scaled so that a 1-unit change is equivalent to 10% change in this proportion.

Table 5-5 Black-white disparities in very preterm birth under different model specifications

	OR	95%CI		% disparity explained	σ^2_{race}	DIC
Crude	3.24	3.20	3.28	0.00		
All individual variables	2.68	2.37	3.02	0.25	0.107	960703
Individual + isolation	2.49	2.25	2.77	0.33	0.077	960681
Individual + isolation + clustering	2.51	2.25	2.80	0.33	0.075	960677

Chapter 6 DOES METROPOLITAN RESIDENTIAL SEGREGATION INTERACT WITH AGE-SPECIFIC RISK FOR PRETERM BIRTH IN BLACK AND WHITE WOMEN? A TEST OF THE WEATHERING HYPOTHESIS[5]

ABSTRACT

The two- to three-fold relative racial disparity in very preterm birth is an important driver of disparities in infant mortality and morbidity. The frequently observed U-shaped age-specific risk for poor pregnancy outcomes is shifted to the left in black women compared to white women. This shift has been attributed to the premature aging or weathering of maternal immune, endocrine, and vascular function as a result of chronic exposure to psychosocial and material stress. Metropolitan residential segregation is hypothesized to be an upstream determinant of poor health outcomes among black infants, children, and adults. As a test of the weathering hypothesis, hierarchical Bayesian models of the age-specific risk for very and moderately preterm birth in black and white women in relation to metropolitan segregation (spatial isolation index) are fit. In non-interaction models, each standard deviation increase in metropolitan segregation increases risk of very preterm birth (OR 1.11, 95% CI 1.08, 1.15). In models including age-segregation interaction there is modest evidence for increased risk of very preterm birth in older (but not younger) black women living in highly segregated metropolitan areas. No such interaction is seen for white women with

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[5] This chapter is a manuscript prepared for submission to a peer-reviewed journal. As such the structure, format and length are in keeping with journal requirements. Use of the plural pronoun 'we' refers to members of the dissertation committee who will be co-authors on this submission.

very or moderately preterm birth or for black women with moderately preterm birth. These findings provide support for the weathering hypothesis as a mediator of segregation-associated racial disparities in very preterm birth.

INTRODUCTION

In the United States black women experience 60% greater risk for moderately preterm births (32-36 weeks gestation) and 2.5 times the risk of very preterm births (<32 weeks) as compared with white women (1). Long observed, and poorly understood, this racial disparity drives the disparity in infant mortality, and contributes to racial disparities in cerebral palsy, mental retardation, and other less-severe but long lasting neurodevelopmental sequelae (187, 493, 517).

Individual risk factors such as prior preterm birth, lower maternal education, smoking, genital tract infection, and prevalent chronic disease such as hypertension are independently associated with preterm birth risk, but explain only a small portion of the racial disparity (2). The persistence of the disparity after statistical control for such risk factors leads some investigators to attribute the residual racial difference to genetic predisposition, although the complex etiology of preterm birth leaves alternative hypotheses open (454). One such alternative proposed by Geronimus (203) is the "weathering" hypothesis. This hypothesis posits that chronic exposure to psychosocial stressors resulting from discrimination, poverty, or abuse prematurely age or weather black women's immune and neuroendocrine systems with resulting ill health effects. For instance the risk of preterm birth and low birthweight is known to vary by age, with higher risk in the extremes of reproductive life stage (births to adolescents or to mothers older than 35), and the lowest risk in early adulthood. However this U- or J-shaped curve differs by race with the rising risk for older women shifted to younger ages in black as compared with white women (202). When

further stratified on residential area socioeconomic status, the effect of this left shift was found to be strongest among women living in poorer areas.

The effects of chronic stressors may be particularly relevant for preterm birth because of the mechanisms by which stress could plausibly lead to prematurity. Prevalence of bacterial vaginosis, a strong risk factor for preterm birth, is associated with chronic stress, and this effect tends to be stronger for black women (314, 518). Stress is also associated with alterations in neuroendocrine systems which are largely responsible for the initiation of parturition (41). The patterns of such hormones differ by race, with black women having patterns consistent with chronic stress syndromes such as post-traumatic stress disorder (519).

Racial residential segregation refers to the spatially differential distribution of individuals in metropolitan areas as a function of race or class. While black-white segregation is a complex, historically rooted phenomenon, the degree of urban segregation today may serve as a proxy for regionally varying structural inequality or institutionalized racism. Such structural inequality could modify individuals' lifecourse socioeconomic attainment, lead to unhealthy neighborhoods characterized by crime or infrastructure disinvestment, or modify health-relevant risk behaviors or exposures (455).

The earliest comparisons of health effects by racial segregation were for infant mortality (5, 393), but more recently studies have broadened in scope and improved in study design. Residential segregation has been associated with racial differences in self rated health (408), intravenous drug injection (405), tuberculosis (403), and infant mortality in some (490, 491, 502), but not all (402) studies.

Racial disparities in low birthweight and preterm birth have also been linked to segregation (438, 503). Two recent studies considered the possible interaction between maternal age, birth outcomes, and segregation and related neighborhood poverty. Osypuk and Acevedo-Garcia (475)

report elevated risk for preterm birth in older black mothers in metropolitan areas characterized by hypersegregation (highly segregated on four out of five dimensions), as compared with non-hypersegregated areas. In a study of neighborhood variation in birthweight, Cerda et al (520) find differences in the regression slope for maternal age according to the degree of neighborhood poverty concentration, suggesting that increasing age was riskier for women residing in poor neighborhoods than wealthier areas.

We extend this line of thought for preterm birth, using hierarchical Bayesian models to test for the cross-level interaction between individual mother's age at delivery and metropolitan isolation segregation measured with a novel spatial index that does not rely on census tracts as proxies for neighborhood. Acknowledging that the mortality and morbidity burden of prematurity results primarily from very preterm births (<32 weeks gestation) and that the racial disparity increases with decreasing gestational age, we evaluate very preterm birth and moderately preterm birth separately.

METHODS

INDIVIDUAL LEVEL VARIABLES

All singleton live births born in 2000-2002 to non-Hispanic white or non-Hispanic black mothers who lived in eligible US metropolitan statistical areas (MSA's) were abstracted from National Center for Health Statistics natality files (456). Gestational age was calculated from date of last menstrual period except where clear inconsistency between birthweight and gestational age exist. In these cases clinical estimates of gestational age including ultrasound dating are used (167, 457). Births were categorized as very preterm (from 20 to less than 32 weeks), moderately preterm (from 32 to less than 37 weeks), or term (37 to 44 weeks). Maternal education, age, and

marital status as well as pregnancy risk factors such as chronic hypertension, diabetes, history of a previous preterm birth, and smoking were also obtained.

METROPOLITAN LEVEL VARIABLES

Metropolitan statistical areas were chosen as the contextual unit of analysis. We analyzed 231 MSA's which had a population of at least 100,000 (and thus have geographically reportable tabulations in natality files) and had a black population of at least 5,000 in the 2000 decennial census. MSA's represent contiguous counties surrounding a core city which are deemed by the Office of Management and Budget to be economically and socially integrated (487). While being a convenient geographic unit at which births are reported, the MSA also fits the conceptualization of residential segregation as a process of sorting individuals into living environments on the basis of race and class. This sorting process happens across regional residential housing market, not just in some neighborhoods; therefore simultaneously recognizing the housing choices of economically and socially linked urban and suburban communities is beneficial.

Metropolitan population size (categorized as <500,000, 500,000-1 million, or greater than 1 million), and census region (Northeast, Southeast, Midwest, West) were obtained from the Decennial Census 2000 (511). They were considered potential confounders of the target association.

Racial residential segregation in each MSA was measured using a spatial isolation index. The isolation dimension of segregation refers to the neighborhood-level exposure of blacks and whites and is thought to have strong conceptual linkage to negative health effects because it is strongly associated with socioeconomic disenfranchisement of black communities (6). The spatial isolation index differs from traditional census tract-derived isolation measures (409) in that the operationalization of neighborhoods is uniquely defined for each point in space, rather than

assumed to be equal to a census tract. Proposed by Reardon and O'Sullivan (371), such spatial indices reduce misclassification of neighborhood environment as a result of the arbitrary shape or size of tracts, and allow comparative exploration of segregation at multiple neighborhood scales.

The actual measurement of spatial isolation is implemented via a freely available Visual Basic for Applications macro (464) for ArcGIS 9.2 (ESRI, Redlands, WA). The procedure is more completely described elsewhere (485). Briefly, for each MSA, a 50 by 50 meter grid is overlaid on US 2000 Decennial Census block data. Following a smoothing procedure of the population density across grid points, biweight kernel density functions are applied to each area with bandwidths corresponding to a 500 meter radius circle around each point. The resulting kernel densities capture the racial composition in the area (e.g. a 500m radius circle) surrounding each point in the grid. In other words each point in space has a unique value for its neighborhood racial. A spatial version of the black isolation index ($_xP^*_x$) was then calculated with the following formula adapted from Reardon and O'Sullivan (371):

Equation 6-1

$$_xP^*_x = \sum_{r=1}^{R} \frac{\tau_r}{T} \tilde{\pi}_r$$

Where r indexes all grid points in area R (the MSA); τ_r is the density per unit area of a given racial group at point r; T is the total MSA population count of the racial group; and tilde-π_r is the proportion black in the spatial neighborhood (within the 500 m radius circle) of point r. This represents an extension of the traditional census tract formula which is a population weighted average across all neighborhoods of the local isolation (for $_xP^*_x$). The resulting values range from 0 (least segregated) to 1 (most segregated), but were subsequently standardized to a N(0,1) distribution to facilitate interpretation in models. Exploratory comparison of the association of

very preterm birth and isolation segregation measured using varying neighborhood scales (500m-, 1000m-, 2000m-, 4000m-kernel bandwidths, and census tracts) suggested that model fit (deviance explained) was maximized with the 500m definition (unpublished data). We therefore use this definition for this study.

ANALYSIS

Hierarchical Bayesian modeling was chosen as the best approach given the naturally hierarchical nature of the question, and our interest in measured and unmeasured variation at each level (512). The setup for each model follows this template:

$$P(y_i = 1) = logit^{-1}(\alpha_j + \delta_j * Age_i + \beta X_i)$$

$$\alpha_j \sim N(\gamma_0 + U_j\gamma_1, \sigma_\alpha^2)$$

$$\delta_j \sim N(\gamma_{age0} + Segregation_j * \gamma_{age}, \sigma_{age}^2)$$

$$\beta \sim N(0,10000)$$
$$\gamma \sim N(0,10000)$$
$$\sigma^2 \sim Unif(0,100)$$

In the likelihood or first level, y_i is the binary pregnancy outcome for the ith woman, α_j is a random intercept for the jth MSA, δ_j is a random slope for age; β is a vector of parameters for individual variables, and **X** is a matrix of individual level covariates. Individual covariates include maternal education, marital status, and prior history of preterm birth, chronic hypertension, diabetes, or smoking. In a Bayesian setup every parameter is stochastic, and so each is assigned a prior distribution. Relatively uninformative flat priors are assigned to the beta parameters, while the α-intercept and δ-slopes have informative priors, which make up the second level of the model. Each random effect is assumed to come from a normal distribution with a variance of σ^2_α or σ^2_{age} .

The mean of the distribution is the sum of a global intercept (γ_0 in the case of the intercepts, γ_{age0} in the case of slopes) plus the vector of γ_1 parameters corresponding to the MSA-level covariates in matrix **U**. The MSA-level covariates are isolation, and dummy variables for region and population size.

Although the age-preterm birth risk is approximately quadratic in form, we use six dummy variables for seven age categories (25-29 years old as referent) to allow greater flexibility in describing the shape of the curve. To answer the question of cross level interaction between segregation and maternal age, inspection of the posterior distributions for γ_{age0} and $\gamma_{age1\text{-}6}$ (one set for each of six dummy variables) corresponding to segregation was conducted. γ_{age0} can be interpreted as the overall relative estimate of very preterm birth in that age group compared to the referent, while $\gamma_{age1\text{-}6}$ are the interacted effects of the six age dummy variables with residential segregation.

Bayesian models were fit with WinBUGS 1.4 (513) using R 2.7 (489) and the R2WinBUGS package (514). All models were run with three chains, for 10-20,000 iterations with the first half discarded; convergence was determined by visual inspection of the traceplots of the posterior parameter estimates from each chain, as well as an R-hat statistic of 1.1 or lower for each parameter node (512). Separate models were fit for black and white women with very preterm and (for comparison) moderately preterm as the dependent variable; in each case term births are the comparison group. Relative improvements in model fit were assessed using the deviance information criterion (DIC).

RESULTS

During the study period there were 6.2 million singleton live births in eligible MSA's, 23.6% of whom were born to black women. Distributions of births by race and demographic or medical

risk factors for preterm birth are displayed in Table 6-1. In this birth cohort, births to black women occurred at younger ages on average than for white women. There were also large racial differences in the proportion of births to married women (78.9% for white, 32.1% for black), prevalence of chronic hypertension (0.7% for white, 1.4% for black), and tobacco use (12.2% for white women, 8.4% for black women). Half of all births to black women occurred in the Southern region of the United States while only a third of white births occurred there.

Isolation segregation ranged from 0.06 (Salt Lake City, UT) to 0.86 (Gary, IN), with a median value of 0.51 and an interquartile range of 0.29. To permit crude comparisons of very preterm birth risks by segregation, MSA's were divided into tertiles according to their isolation index. In Table 6-2, the distribution of risk by maternal age, race, and tertile of MSA segregation is reported. Only 8.6% of all births to black women occurred in MSA's in the lowest tertile of segregation with 17.8% and 73.6% respectively occurring in second and third tertile MSA's. In contrast for white women the distribution by degree of MSA segregation was 25.5%, 27.8% and 46.7% for least to most segregated areas.

Looking at the risk ratios comparing 2nd and 3rd tertiles to the first as a referent group, segregation appears to be associated with increasing risk for black women, but less so for white women regardless of age (RR 3rd:1st tertile for black women 1.24, 95% CI 1.20, 1.28; RR for white women 1.05, 95% CI 1.03, 1.07). For black women there is also some variation in the magnitude of the risk ratio across age strata, with smaller effects of segregation at younger ages than at older ages. For white women no such pattern is apparent.

In random intercept models without an interaction between age and segregation (Table 6-3) segregation is independently associated with very preterm birth among black women in both crude and individual risk factor adjusted models (adjusted OR 1.11 for each 1 standard deviation

change in segregation, 95% CI 1.08, 1.15). The anticipated U-shaped age-risk association is also evident in these models with the lowest risk among black women who are 20-24 years old and increasing risk for both teen births and older maternal ages.

Crude models with random slopes had modestly improved model fit as measured with the deviance information criteria (DIC) (adjusted model without random slopes 419894, adjusted model with random slopes 419862 – smaller is better) (Table 6-3 and Table 6-4). However there was no change in DIC between covariate-adjusted models with and without age by segregation interactions. Information on statistical precision in a Bayesian model is obtained from examination of credible intervals (similar to confidence intervals in frequentist inference) of the posterior distribution for each parameter. Only in the parameter representing the interaction between segregation and the 15-19 year old age group (as compared with the referent 25-29 year olds) does the interaction term 95% credible interval exclude zero (parameter estimate on the logit scale: -0.039, 95% CI -0.075, -0.003). However using 90% credible intervals, three age groups (<15, 15-19, 30-34) deviate significantly from the referent age group in their interaction with segregation.

Figure 6-1 plots model-predicted risk (adjusted for education, marital status, prior preterm birth, parity, hypertension, smoking, diabetes, region and population size) of very preterm birth for white and black women under three contrasting degrees of segregation. 'Low' segregation refers to MSA's 1.5 standard deviations below the mean index level (e.g. Colorado Springs, CO; Madison, WI; Scranton, PA). 'Average' segregation refers to MSA's with mean values of isolation (e.g. Syracuse, NY; Wichita, KS; Fort Worth, TX). Finally, the 'high' value of segregation represents MSA's 1.5 standard deviations above the mean index value (e.g. Flint, MI; New Orleans, LA; Memphis, TN). For white women, varying metropolitan segregation has no effect on the age-very preterm birth risk

curve. In contrast for black women, varying segregation has the least effect for younger ages, but as maternal age increases the gap between low and high segregated areas increases.

Figure 6-2 displays the same plots for moderately preterm birth. Here the influence of segregation on black women appears to be consistent across maternal age, supporting the deleterious effect of segregation, but without any evidence for interaction with age.

DISCUSSION

The weathering hypothesis of accumulated wear and tear on individuals' immune and endocrine functions as a result of lifecourse exposure to socially and materially stressful environments is one appealing answer to the question of why some black women experience excess risk for poor pregnancy outcomes. Residential segregation has been called a fundamental cause of racial disparities in health because of the multifaceted manner in which it patterns health-relevant exposures, opportunities, and resources (6). It therefore seems that weathering could be a mediating link between the distal construct of segregation and the individual occurrence of preterm birth.

The plotted model-predicted risk for very preterm birth in black women suggests a meaningful interaction between metropolitan residential segregation and maternal age. Specifically it appears that among black teens, the degree of metropolitan segregation has little effect on very preterm birth risk, but that after adolescence, age-risk trajectories diverge with residence in highly segregated areas conferring greater risk than for similar women in less segregated areas. However the strength of this finding is limited by uncertainty in Bayesian models. The credible intervals for the age-isolation parameters primarily (with the exception of one age group) include the null value of zero. In what is both a curse and blessing of using a Bayesian analytic framework there is no single p-value to tell us whether this interaction term is

significant on the whole. Rather, viewed through the lens of Bayes Theorem, uninformatively broad prior beliefs in the association combined with the data give us modest but not conclusive posterior evidence in support of an interaction.

Perhaps of greater interest, though, is the difference in pattern by race and outcome. There is simply no hint of variation in risk by segregation for white women. And for moderately preterm birth the ill-effects of segregation are apparent, but the interaction with age is not. This heterogeneity by outcome is important and often obscured by use of a single preterm birth definition. Very preterm births are more likely to result from maternal infection and vascular dysfunction while moderately preterm births may be associated with obstetric and medical interventions (75, 498, 521). Material status including access to high quality prenatal and obstetric services may therefore vary by segregation and associate with moderately preterm births, while the effects of weathering on immune, endocrine, and vascular function may be exhibited in differences in very preterm birth.

An alternate explanation for this observation is a version of the 'healthy migrant' selection bias. It is possible that upwardly mobile black women leave low-opportunity cities, with relatively higher risk women remaining. Wingate et al (522) report fewer pregnancy risk factors, and better birth outcomes among black women who were themselves born in a different state than where they delivered the index pregnancy. Other studies on the lifecourse socioeconomic status of black women suggest that cumulative exposure is important (233, 523, 524), but it is unclear whether metropolitan context modifies this association.

LIMITATIONS

Reliance on birth certificate data hinders understanding of pathways to prematurity because of possible misclassification of the outcome, covariates, and because of the absence of

clinical and biological variables. While more detailed, prospectively collected data would allow further elaboration of these findings, the benefits of comparing millions of births across a diverse range of urban environments is also a strength.

Any statistical model is a specified simplification of relationships. The true posterior confidence in the findings is dependent on the correctness of model specification, both conceptually and statistically. Bayesian models permit explicit consideration of uncertainty in final inference and are therefore useful in social epidemiologic questions where much uncertainty exists.

Finally, the weathering hypothesis is a lifecourse model of socio-biological interaction. Given the importance of lifecourse exposure to any ill effects of segregation, measurement of maternal residence only at delivery of a child limits inference. Study designs which allow cumulative measure of residential environment are clearly needed.

CONCLUSIONS

Residential isolation segregation increases risk of very preterm birth in black but not white women. Furthermore, for very preterm but not moderately preterm birth there is modest evidence that the effects of metropolitan segregation may interact with maternal age in black women in a manner consistent with the weathering hypothesis. Further investigation into the social and biological pathways by which segregation influences black women's health is necessary in order to develop interventions to reduce this disparity.

Table 6-1Distribution of risk factors for very preterm birth by maternal race, 231 Metropolitan Statistical Areas, 2000-2002

		White	Black
		(n=4,727,601)	(n=1,452,943)
Maternal age		%	%
	<15	0.1	0.6
	15-19	7.1	17.9
	20-24	19.8	31.9
	25-29	26.7	23.1
	30-34	29.1	16.2
	35-39	14.4	8.4
	40+	3.0	2.0
Maternal Education			
	<HS	10.3	23.9
	HS	28.0	38.3
	>HS	60.7	36.0
	Missing	0.9	1.8
Married		78.9	32.1
Previous preterm or SGA birth		1.2	1.4
Primiparous		34.1	29.8
Chronic hypertension		0.7	1.4
Diabetes		2.9	2.9
Tobacco use		12.2	8.4
Region	Northeast	21.4	18.8
	Southeast	34.5	50.8
	Midwest	25.5	21.7
	West	18.5	8.7
Population size			
	<500,000	19.0	15.8
	500k - 1 million	13.4	10.7
	1 million +	67.6	73.6

Table 6-2 Distribution of birth outcomes by maternal age and metropolitan area segregation in tertiles for black and white women

BLACK WOMEN

	Lowest tertile segregation[a]		Middle tertile segregation[a]		Highest tertile segregation[a]		2nd:1st tertiles			3rd:1st tertiles		
	Total births	% VPT	Total births	% VPT	Total births	% VPT	RR	95% CI		RR	95% CI	
Maternal age												
<15	530	6.2	1536	6.2	5969	6.3	1.00	0.68	1.47	1.02	0.72	1.44
15-19	21229	3.3	49836	3.7	188730	3.8	1.12	1.03	1.22	1.15	1.07	1.24
20-24	40591	2.5	87395	3.0	334714	3.2	1.20	1.12	1.29	1.28	1.20	1.36
25-29	29096	2.5	58780	3.1	247363	3.3	1.24	1.14	1.35	1.32	1.22	1.42
30-34	20259	3.1	37655	3.7	177447	3.8	1.19	1.09	1.31	1.23	1.13	1.33
35-39	10061	3.5	18598	4.1	93203	4.3	1.17	1.03	1.33	1.23	1.10	1.37
40+	2412	3.8	4514	4.6	22208	5.0	1.21	0.95	1.54	1.32	1.07	1.62
TOTAL	124178	2.9	258314	3.4	1069634	3.5	1.17	1.13	1.22	1.24	1.20	1.28

WHITE WOMEN

	Lowest tertile segregation[a]		Middle tertile segregation[a]		Highest tertile segregation[a]		2nd:1st tertiles			3rd:1st tertiles		
	Total births	% VPT	Total births	% VPT	Total births	% VPT	RR	95% CI		RR	95% CI	
Maternal age												
<15	703	3.7	883	4.0	1261	4.0	1.08	0.66	1.78	1.08	0.68	1.72
15-19	86814	1.8	101404	1.9	139039	2.0	1.06	0.99	1.13	1.11	1.04	1.18
20-24	253972	1.2	268477	1.3	390852	1.3	1.08	1.03	1.14	1.08	1.04	1.13
25-29	323607	0.9	343490	1.0	573553	1.0	1.11	1.06	1.17	1.11	1.06	1.16
30-34	329698	0.9	366334	0.9	669732	0.9	1.00	0.95	1.05	1.00	0.96	1.04
35-39	160372	1.0	179745	1.1	336644	1.1	1.10	1.03	1.17	1.10	1.04	1.17
40+	34207	1.3	36865	1.4	69045	1.4	1.08	0.95	1.22	1.08	0.96	1.20
TOTAL	1189373	1.0	1297198	1.2	2180126	1.1	1.11	1.08	1.13	1.05	1.03	1.07

a. Spatial isolation segregation was categorized into tertiles of metropolitan statistical areas. The intervals for the tertiles are: 0-0.412, 0.413-0.608, 0.609-1

Table 6-3 Crude and adjusted random intercepts model (non-interaction models) for very preterm birth in black women

	Crude no-interaction model[a]				Adjusted no-interaction model[b]			
	Fixed effect	95% CI[c]		DIC	Fixed effect	95% CI[c]		DIC
Maternal age								
<15	2.12	1.93	2.34	419894	1.80	1.62	1.97	413557
15-19	1.18	1.15	1.21		1.02	0.98	1.05	
20-24	0.96	0.93	0.98		0.88	0.85	0.90	
25-29	1.00	--	--		1.00	--	--	
30-34	1.21	1.17	1.24		1.26	1.23	1.30	
35-39	1.42	1.37	1.47		1.46	1.41	1.51	
40+	1.71	1.62	1.82		1.70	1.60	1.80	
Isolation segregation[d]	1.11	1.08	1.14		1.11	1.08	1.15	

Abbreviations: DIC: deviance information criterion

a. The crude model includes age as the only individual covariate, and a random intercept for MSA with isolation, region, and size contributing to the prior for the intercept

b. Adjusted models have the same basic structure but add control for education, marital status, parity, history of prior preterm birth, chronic hypertension, smoking, and diabetes

c. 95% credible intervals are the 2.5th and 97.5th percentile of the sampled posterior distribution for the parameter

d. The odds ratios for segregation refers to the change in risk of very preterm birth for a 1-standard deviation change in metropolitan segregation index

Table 6-4 Crude and adjusted random slopes model for very preterm birth interaction between maternal age and metropolitan segregation among black women

	Crude Interaction Model[a]							
	Fixed effect	95% CI[d]		Interaction effect	95% CI[d]		σ^2_{age}	DIC[c]
<15	0.800	0.631	0.937	-0.077	-0.217	0.078	0.196	419862
15-19	0.192	0.159	0.224	-0.027	-0.056	0.000	0.022	
20-24	-0.049	-0.080	-0.013	0.004	-0.031	0.034	0.024	
25-29	*referent*							
30-34	0.201	0.157	0.241	-0.022	-0.067	0.017	0.072	
35-39	0.342	0.288	0.395	0.004	-0.042	0.059	0.110	
40+	0.486	0.386	0.588	0.053	-0.047	0.135	0.096	
Isolation								
	Adjusted Interaction Model[b]							
	Fixed effect	95% CI[d]		Interaction effect	95% CI[d]		σ^2_{age}	DIC[c]
<15	0.640	0.476	0.812	-0.097	-0.257	0.056	0.235	413557
15-19	0.055	0.014	0.109	-0.041	-0.081	-0.002	0.033	
20-24	-0.128	-0.171	-0.089	-0.001	-0.035	0.036	0.026	
25-29	*referent*							
30-34	0.257	0.204	0.302	-0.029	-0.070	0.017	0.061	
35-39	0.384	0.319	0.445	-0.011	-0.065	0.053	0.089	
40+	0.492	0.404	0.583	0.033	-0.046	0.105	0.088	
Isolation	0.123	0.083	0.165					

All effects and credible intervals are on the logit scale as the OR scale is not meaningful without specification of the value for segregation

a. Crude model includes a random slope for age with cross-level interaction with isolation segregation, controlling for region and population size

b. Adjusted models add control for education, marital status, parity, history of prior preterm birth, chronic hypertension, smoking, and diabetes

c. Deviance information criterion for model fit.

d. 95% credible intervals are the 2.5th and 97.5th percentile of the sampled posterior distribution for the parameter

Figure 6-1 Model predicted risk of very preterm birth in white and black women according to metropolitan area residential segregation

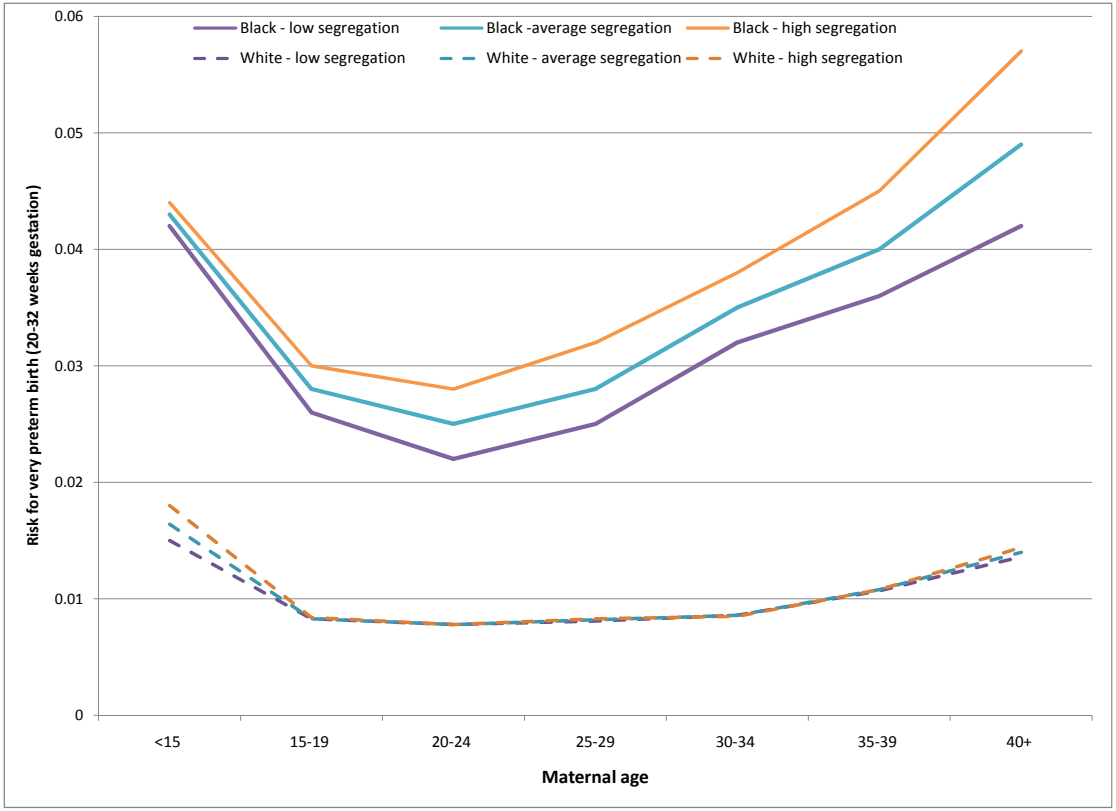
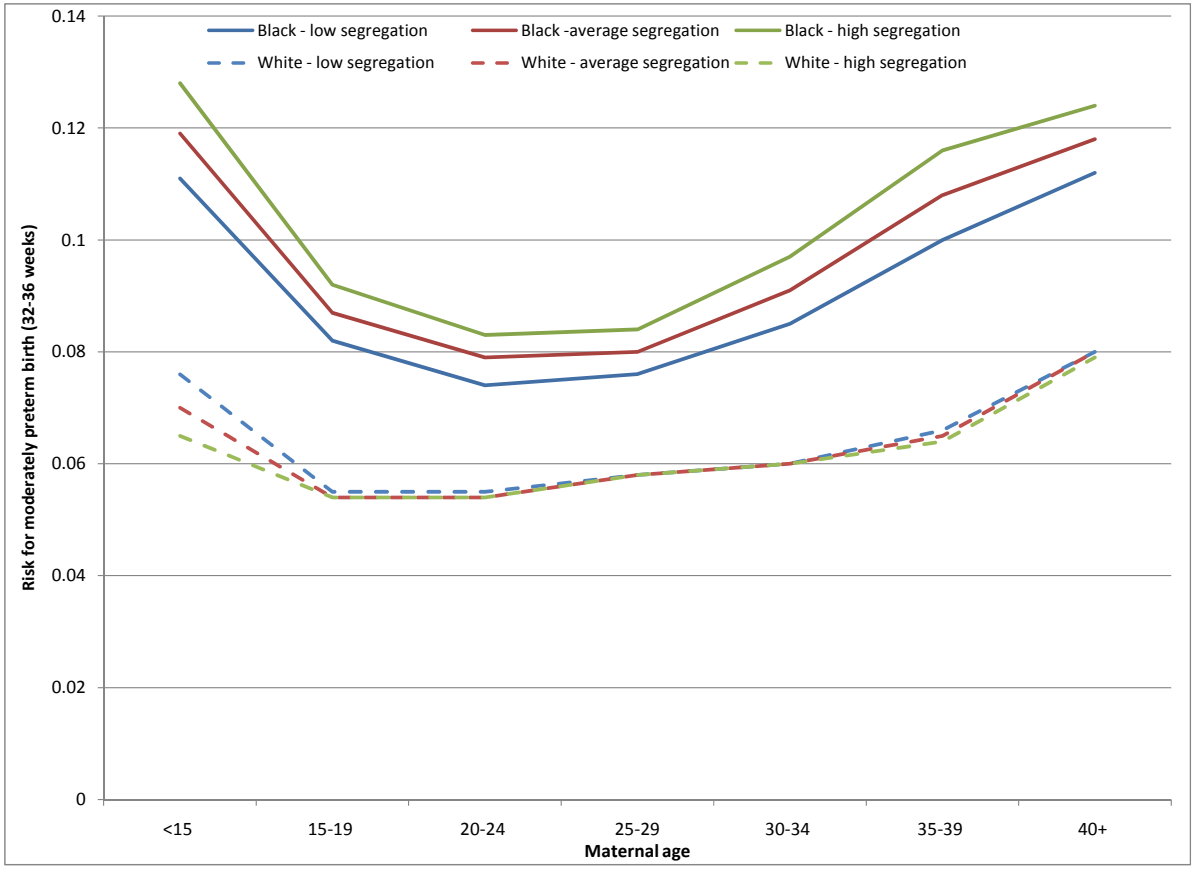


Figure 6-2. Model predicted risk of moderately preterm birth in black and white woman according to degree of metropolitan segregation



Chapter 7 RACE AND PLACE IN ATLANTA: NEIGHBORHOOD SEGREGATION AND RACIAL DISPARITIES IN VERY PRETERM BIRTH[6]

ABSTRACT

Background. Black women experience very preterm birth (gestation <32 weeks) at 2-3 times rate of white women, leading to racial disparities in infant mortality and morbidity. Residential isolation segregation defined at the metropolitan level has been associated with excess risk of preterm birth (gestation <37 weeks) but has not been assessed for the more serious outcome of very preterm birth. It is unclear whether the ill-effects of metropolitan segregation correlate to similar effects of neighborhood-level racial isolation.

Methods. We utilize a unique spatial (non-census tract derived) measure of neighborhood isolation to examine the spatial variation in risk for very preterm birth among black women in Atlanta. Generalized additive models with spatial smoothing terms and generalized linear mixed models are used to account for spatial autocorrelation.

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[6] This chapter is a manuscript prepared for submission to a peer-reviewed journal. As such the structure, format and length are in keeping with journal requirements. Use of the plural pronoun 'we' refers to members of the dissertation committee who will be co-authors on this submission. Supplemental results for this chapter are presented in Appendix 6.

Results. Births to black women occurred in neighborhoods ranging from minimal (index value of 0) to maximal (index value of 1) racial isolation. Each 0.1 ($1/10^{th}$ of the index range) increase of neighborhood racial isolation increased the odds of very preterm birth among black women 2% (OR 1.02, 95% CI 1.00, 1.04) controlling for individual and area covariates. A significant interaction between isolation and smoking suggests that the odds ratio for non-smokers in neighborhoods with the highest isolation compared to the lowest was 1.18 (95% CI 1.09, 1.28), but among smokers it was 2.56 (95% CI 2.35, 2.75). In models including both black and white births, the neighborhood isolation term explained an additional 7-12% of the excess risk for black women beyond that explained by individual risk factors.

Conclusions. Patterns of neighborhood racial isolation consistent with residential segregation modestly increase the risk of very preterm birth among black women and explain a small portion of the racial disparity. Further investigation of the interplay of neighborhood context, maternal smoking, and maternal health status may illuminate one possible pathway to excess preterm birth.

INTRODUCTION

Preterm birth is an increasingly common outcome of pregnancy with serious consequences including infant mortality, pediatric morbidity, economic cost and family stress (2). Many questions remain unanswered about preterm birth, not least of which is the explanation for the large racial disparity in its occurrence. In the United States black women experience 60% greater risk for moderately preterm birth (32-36 weeks) and 2.5 times the risk of very preterm birth (<32 weeks) as white women (1). The magnified racial

disparity among these more extreme preterm births combines with the drastically elevated risk to these infants, making racial disparities in very preterm birth a leading cause of the racial disparity in infant mortality and morbidity (187, 442).

Persistence of such disparities has lead investigators to consider many potential individual-level determinants including socioeconomic status, prevalence of genital tract infections such as bacterial vaginosis, risk behaviors such as smoking and cocaine use, access to prenatal and health care services, and exposure to interpersonal discrimination and other psychosocial stressors (142). While each of these is associated with elevated risk for preterm birth, the population pattern of a social disparity suggests preceding upstream steps which differentially allot or influence these exposures (or susceptibility to these exposures) by race (454).

Social inequity as seen with income inequality, poverty concentration, and residential segregation are examples of upstream institutionalized (e.g. structural) forces which have been hypothesized to pattern individual risk experience and thus be lifecourse determinants of preterm birth risk (293, 332, 525). Residential racial segregation in metropolitan areas may influence individuals' health risks as a result of the manner in which it sorts or constrains—by race and/or class—the neighborhood environments available (6). Racial segregation, operationalized at the scale of metropolitan areas, has been associated with low birth weight and preterm birth for black but not white women net of individual risk factors (438, 475, 503).

While segregation as a sorting process is best conceptualized at the scale of metropolitan areas (or a similarly large proxy for labor and housing markets), many of the hypothesized ill-effects are transmitted at the scale of neighborhoods. The neighborhood

effects literature has documented the ways in which residential area violent crime (230), socioeconomic deprivation (433), decreased access to retail food outlets (526), lower household affluence (527), and perception of safety (283) could be associated with poor pregnancy outcomes, particularly for black women. Neighborhood racial composition has also been evaluated as a possible corollary to metropolitan segregation and a determinant of poor pregnancy outcomes, but with mixed results (440, 528, 529).

While acknowledging the primacy of the metropolitan scale for best understanding the health effects of residential segregation, we explore the association of spatial isolation of blacks and whites at the neighborhood level with risk for very preterm birth in a highly segregated city. Specifically we adapt a unique spatial (non-census tract derived) index of metropolitan isolation segregation for point-specific linkage to geocoded birth records in Atlanta. Two questions drive this analysis:

1. Is neighborhood isolation associated with risk for very preterm birth in black women net of individual and area risk factors?

2. Does neighborhood racial isolation explain any of the black-white racial disparity in very preterm birth in Atlanta?

METHODS

CONCEPTUAL MODEL

Metropolitan residential segregation is hypothesized to affect health outcomes through several pathways including constraint of individual lifecourse socioeconomic attainment and perpetuation of unhealthy living environments (455). Racial disparities in very preterm birth may also be explained by several pathways including racial differences

in socioeconomic status, exposure to discrimination and chronic stress, and differences in maternal health including prevalent hypertension, diabetes, or smoking (454). Each of these pathways in turn may affect maternal vascular, immune and neuroendocrine function.

These intermediate variables between the contextual construct of racial isolation and the individual occurrence of very preterm birth make causal inference difficult. For instance, maternal education or prevalent chronic hypertension could be mediators in the causal pathway, but they could also plausibly confound the association. Acknowledging that it is not possible to distinguish between mediation and confounding in this observational study design, we group covariates in meaningful ways in an effort to tease apart independent effects of maternal socioeconomic status and maternal health status.

INDIVIDUAL-LEVEL VARIABLES

Birth certificate data for all live singleton births to non-Hispanic white or non-Hispanic black mothers residing in the twenty-county Atlanta Metropolitan Statistical Area (MSA) from 2000-2003 were obtained from the Georgia Department of Human Resources. Georgia DHR routinely geocodes birth records to the maternal residential street address latitude and longitude, and these data were also obtained. In a recent validation study, median spatial error of Atlanta MSA birth record geocodes compared to tax parcel records of a sample of maternal residences was found to be less than 100 meters (530). Geocode match quality is classified as street-level, census block level, tract level, or county level. Results are restricted to birth records with street-level or block-level matches, although there was no significant difference when all records were included in models.

Gestational age was measured from maternally-reported last menstrual period (LMP) or from clinical estimate (e.g. ultrasound dating) when the birthweight was

inconsistent with LMP (457). The outcome of interest was very preterm birth (any live birth between 20 and 32 weeks gestation) with term births (37-44 weeks) as the comparison group.

Additional variables obtained from birth records were maternal age (categorized into 7 age groups), education (<12 years, 12 years, 13-15 years, or 16+ years), marital status (married or unmarried), parity (primiparous or multiparous), presence of chronic hypertension or diabetes, prior history of pregnancy complicated by preterm birth or intrauterine growth retardation, and smoking status during pregnancy. Whether Georgia Medicaid paid for the delivery of the index pregnancy was also made available. Because Medicaid has means-tested eligibility, only low-income women are eligible; therefore this variable complements maternal education in describing socioeconomic status.

MEASURES OF NEIGHBORHOOD SEGREGATION

Massey and Denton (409) described five dimensions of segregation (evenness, isolation, clustering, concentration, and centralization). The isolation dimension refers to the degree to which two groups live physically separate from one another, and is one of the conceptually strongest dimensions in terms of understanding health outcomes (370). Black isolation is associated with poverty concentration (376), violent crime (385, 505), and access to social capital and networks necessary for economic security (391).

The traditional metropolitan-level measure of isolation is a population-weighted average of the racial composition in each neighborhood (as approximated by census tracts) across the entire metropolitan area (409). The index ranges from 0 to 1, and is interpreted as the probability that any two randomly chosen individuals are from the same racial group. A value of zero corresponds to maximum exposure of a minority group member to the

majority group, while a value of one is maximum isolation (no interracial exposure at the neighborhood level).

As a neighborhood corollary to the metropolitan black isolation index we use the proportion black in the neighborhood in which each woman resides. Rather than relying on census tracts as proxies for neighborhood we adapt an explicitly spatial measure of residential segregation proposed by Reardon and O'Sullivan (371) to reduce measurement error resulting from the arbitrary boundaries and spatial scale of census tracts. The spatial measure permits comparison of multiple scale definitions of neighborhood for each residence.

The actual measurement of spatial isolation is implemented via a freely available Visual Basic for Applications macro (464) for ArcGIS 9.2 (ESRI, Redlands, WA). The procedure is more completely described elsewhere (485). Briefly, for each MSA, a 50 by 50 meter grid is overlaid on US 2000 Decennial Census block data. The density (person per square kilometer) of whites or blacks in each block is transferred to the overlying grid point and a smoothing algorithm is applied to reduce unrealistically abrupt density changes at boundaries. Neighborhoods are then approximated by using a series of biweight kernel density functions with varying bandwidths. A small bandwidth (say 500 meters) would describe a neighborhood as a 500m-radius circle around each point in space, with the resulting value representing the racial composition for that circle around that point. Repeated processes with different bandwidths allow consideration of the same point in space (e.g. same residence) using different definitions of neighborhoods ranging from quite small to quite large, thus distinguishing micro versus macro segregation patterns (486). Using the kernel density information for each 50m square grid point, a continuous surface

of neighborhood isolation was created. The local spatial isolation index is essentially the proportion black in the neighborhood in which the mother resided.

We estimated neighborhoods using 500m, 1000m, 2000m, and 4000m bandwidths. This exploratory analysis demonstrated that residential segregation in Atlanta is somewhat unique among US metropolitan areas in that nearly all of the segregation is at macro scales, with little difference in measures using the 4000m and the 500m neighborhood definition. In fact of 231 MSA's analyzed in a separate study, Atlanta ranked 8th for the ratio of 4000m/500m isolation segregation (unpublished data). This coarse granularity to the segregation pattern of Atlanta leads us to use only the 4000m index for this study.

OTHER NEIGHBORHOOD VARIABLES

In addition to racial isolation, values for poverty rate, proportion of adults over 25 years of age without a high school degree, and median household income were obtained for each Census tract for blacks and whites and linked to birth records.

ANALYSIS

The spatial isolation index ranges from 0 to 1, but was scaled to be from 0 to 10 for modeling so that odds ratios in models reflecting the effect of a 1-unit change in isolation could be interpreted for more reasonable differences, e.g. 1/10th of the range of the index. Each woman was assigned a unique value of spatial residential segregation, but there is still possible spatial autocorrelation due to other unmeasured characteristics. A modeling approach which allows control for individual covariates while simultaneously adjusting for continuous spatial correlation is generalized additive models (GAM's) (531). Following Bivand, et al (532) we used the **mgcv** package (533) in R to fit GAM models with penalized spline smoothing of the latitude and longitude coordinates of each residence. Because GAM

models may over fit data (534), we fit comparison generalized linear mixed models (multilevel models) with random intercepts for each census tract using the **lmer** package in R (512).

Crude and adjusted models of the association between isolation and very preterm birth were fit for black women only. Then models with black and white women were fit to estimate change in the magnitude of the racial disparity with addition of individual and area covariates and isolation. All two-way interactions between isolation and individual and area covariates were assessed.

Spatial linkage and analysis were conducted in ArcGIS 9.2 (Redlands, WA), and R (489). This study was reviewed and approved by the Institutional Review Board of Emory University.

RESULTS

There were 215,334 births to black (39.6%) and white (60.4%) women during the study period (Table 7-1). The overall black-white risk ratio for very preterm birth was 2.77 (95% CI 2.61, 2.94), although this varied greatly across covariates. For instance being married and having higher education status were more strongly protective against very preterm birth for white women than for black women, resulting in smaller racial disparities among unmarried women, and those without a high school degree. There is also a racial difference in the significance of having Medicaid pay for delivery. For black women, Medicaid status was associated with lower risk (3.2% versus 3.6% for women without Medicaid) but for white women Medicaid is associated with higher risk (1.7% versus 1.1% for women without Medicaid).

The overall isolation segregation index for the Atlanta MSA in 2000 using the 4000m definition of neighborhood was 0.66, ranking 10th most isolated of the 100 largest US metropolitan areas (data not shown). Among births to black women, the neighborhood isolation index (the proportion black in each neighborhood) ranged from 0.001 to 0.998 with a median of 0.702 and an interquartile range of 0.575. The distribution of neighborhood isolation among black women delivering term births stratified on maternal education is shown in Figure 7-1. Regardless of education, the modal neighborhood environment had a high proportion black, but there is representation in each educational group of neighborhoods ranging from nearly zero isolation to the maximum value of one.

Table 7-2 displays results from generalized additive models of the association between isolation and individual covariates and very preterm birth in black women. The crude effect of isolation is small but significant, with 2% elevated odds of very preterm birth for each 0.1 unit increase in isolation (OR 1.02, 95% CI 1.00, 1.04). Prior preterm birth (OR 6.40, 95% CI 5.00, 8.20) and presence of chronic hypertension (OR 5.86, 95% CI 4.78, 7.20) are each strong risk factors for very preterm birth.

The M1 model includes isolation, age, parity and prior history of preterm birth. The OR for isolation increases slightly in this model to 1.03 (95% CI 1.01, 1.05). M2 and M3 models add, in turn, socioeconomic and maternal health variables, with similarly small changes in the effect of isolation. In the M4 model, all individual covariates as well as neighborhood isolation are jointly adjusted, and the effect of isolation remains at 1.025 (95% CI 1.006, 1.045). The estimated p-value for the GAM smoothing parameters is an indicator of spatial variation in risk beyond that accounted for in the individual covariates. The term becomes non-significant when socioeconomic variables are controlled, suggesting

no further spatial variation conditional on these variables. All model results were similar from generalized linear mixed models with random intercepts for census tract (data not shown).

Table 7-3 extends the M4 model with all individual covariates by adding small area characteristics of neighborhood poverty rate, median household income and proportion of adults without a high school degree. Because these variables are aggregated at the level of census tract, comparison is made between GAM models (spatially continuous) and multilevel generalized mixed models with random intercept for tract. For each model type the effect of isolation is most attenuated with control for the black poverty rate, although this attenuation is only from an odds ratio of 1.025 to 1.021 (GAM), and remains significant. The neighborhood-to-neighborhood variation expressed in the standard deviation of the random intercepts in the mixed model suggests lower inter-neighborhood variation with control for black poverty rate (standard deviation=0.08 as compared to 0.11).

All possible two-way interactions between isolation and other covariates were assessed. There was a significant interaction (p=0.003) between neighborhood isolation and maternally reported smoking during pregnancy (Table 7-4). For non-smokers the risk of very preterm birth increased modestly with increasing isolation so that women in the most as compared with least racially isolated neighborhoods had 1.18 times the odds (95% CI 1.09, 1.28) of very preterm birth. In contrast among smokers the risk of very preterm birth in the most segregated neighborhoods was 2.55 times (95% CI 2.35, 2.75) that of the least segregated neighborhoods, controlling for all individual level covariates. The prevalence of smoking among black women also increased with neighborhood isolation from 2.4% of pregnancies in the least isolated neighborhoods to 3.9% in the most. It should

be noted that these prevalence rates are lower than national averages although it is unknown whether this is a function of data quality or true differences.

Table 7-5 displays results of models with both black and white women to assess the importance of isolation in explaining the racial disparity in very preterm birth. In GAM models, individual level covariates combined explain only about 8% of the observed racial disparity, and the addition of isolation explains an additional 7%. The difference in racial disparity between the generalized linear mixed models and GAM models is likely due to the presence of the spatial smoothing term in the GAM model which adjusts for place-based or spatial determinants of the disparity which are unmeasured in this study.

DISCUSSION

Residential segregation defined at different scales does not necessarily measure the same thing. The black isolation segregation index calculated for each of numerous metropolitan areas may approximate the relative degree of structural economic disenfranchisement of blacks in each environment. In contrast, racial composition among neighborhoods within a single metropolitan area must be viewed in the context of that city as a whole. While neighborhoods of concentrated poverty and crumbling infrastructure may indicate structural inequity, predominantly black neighborhoods could also occur by individual choice as might be seen with a middle class black family's preference for predominantly black suburbs.

Atlanta is a large Southern city with a strong black middle class, black political empowerment, and very preterm birth risks for black women slightly below the national average of 4.03 per 100 live births. Atlanta is also a highly racially and economically segregated metropolitan area, particularly on the isolation dimension, and as noted has a

unique pattern of macro segregation characterized by coarsely granular racial isolation rather than isolation of smaller pockets.

We find that racial isolation measured with this spatially large definition of neighborhood is modestly and significantly associated with the risk of very preterm birth among black women. The persistence of this finding with control for individual and area-based covariates is meaningful given the range of isolation exposure represented in this dataset. In other words, contrary to cities such as Chicago where 75% of black mothers live in tracts with 90% or higher black population (435), in this sample 38% of births to black women (48,495) occurred to those living in neighborhoods with 50% or lower black population. This broader range of isolation exposure strengthens the inference of negative health effects of increasing isolation by allowing comparison of isolation among groups exchangeable on measured covariates.

Although we anticipated greater reduction in the magnitude of the effect of isolation with statistical control for socioeconomic or maternal health variables, little attenuation was observed. Control for the socioeconomic variables of maternal education, marital status, and Medicaid reduced the odds ratio very slightly compared to models adjusted only for age, parity, and prior preterm birth. Because segregation could influence health by constraint on socioeconomic attainment, this could represent partial mediation of the effect of isolation. Alternatively it is possible that unmeasured variables confound the association by limiting neighborhood choice for reasons other than segregation (451).

The interaction between smoking and isolation provides stronger evidence for a mediating pathway between segregation and very preterm birth. Black women historically smoke during pregnancy at lower rates than white women (263). Bell, et al (439) reported

increased smoking prevalence in black pregnant women living in both the most and least segregated metropolitan areas. They suggest that elevated smoking rates in highly segregated areas may be a behavioral response to chronic stress. While prevalence of smoking increased slightly in our cohort with increasing isolation, the steeper slope for the effect of isolation on very preterm birth among smokers suggests something else. Smoking may be more common among individuals experiencing greater stress and thus be a marker for stressful stimuli in general. There is growing evidence that experience of chronic stress is associated with infectious causes of preterm birth such as bacterial vaginosis (535) and with disruption of normal neuroendocrine control of the timing of birth (44, 536).

Alternatively smoking may be interacting with environmental stressors and access to preventive health services in exacerbating the effects of chronic hypertension on preterm birth risk. Grady and Ramirez (509) find that some of the effect of black isolation on low birthweight in neighborhoods in New York City is mediated by increased prevalence of chronic hypertension. Black women's experience of social isolation or interpersonal discrimination has been associated with increased blood pressure, cardiac reactivity, and poor birth outcomes (296, 297, 537). Whether smoking is a result of stress or a cause of vascular dysfunction (or both) cannot be discerned from these data, but is suggestive of one (potentially modifiable) pathway linking isolation to prematurity.

LIMITATIONS

Reliance on vital statistics for outcome and covariate data may result in misclassification of both exposure and outcome, and that risk applies to this study. Of equal or greater importance is concern for unmeasured variables which may be associated with preterm birth risk and neighborhood isolation. In particular there may be residual

confounding due to incompletely measured socioeconomic status, maternal health characteristics, and clinical risk factors for preterm birth which are not captured in birth records.

Causal inference about the association of neighborhood context on individual preterm birth risk is also limited by the cross-sectional nature of the study. Although the hypothesized mechanisms by which residential segregation might affect black women are cumulative in nature (lifecourse socioeconomic position, chronic stress), our measures of residential location are limited to residence at time of delivery of the woman's child.

CONCLUSIONS

Explanations for the racial disparity in very preterm birth remain incomplete. We find modest evidence for an independent effect of neighborhood racial isolation as a determinant of excess risk for very preterm birth in black women, and an important interaction with smoking as a possible mediator. However these variables explain only a small portion of the racial disparity, leaving many questions unanswered.

Research at any single scale is incomplete. This study focused on the scale of individual's risk factors and neighborhood environments as determinants of preterm birth. However it could not include two other scales likely important to understanding the complexity of prematurity: proximate biologic pathways, and variations in social equity and structure across regions. Future work which integrates information from the scales of biology up to political economy may allow improved description of pathways and development of adequate interventions to reduce the burden of excess very preterm birth in black women.

Figure 7-1 Distribution of neighborhood isolation among black women delivering term births, by maternal education, Atlanta MSA, 2000-2003

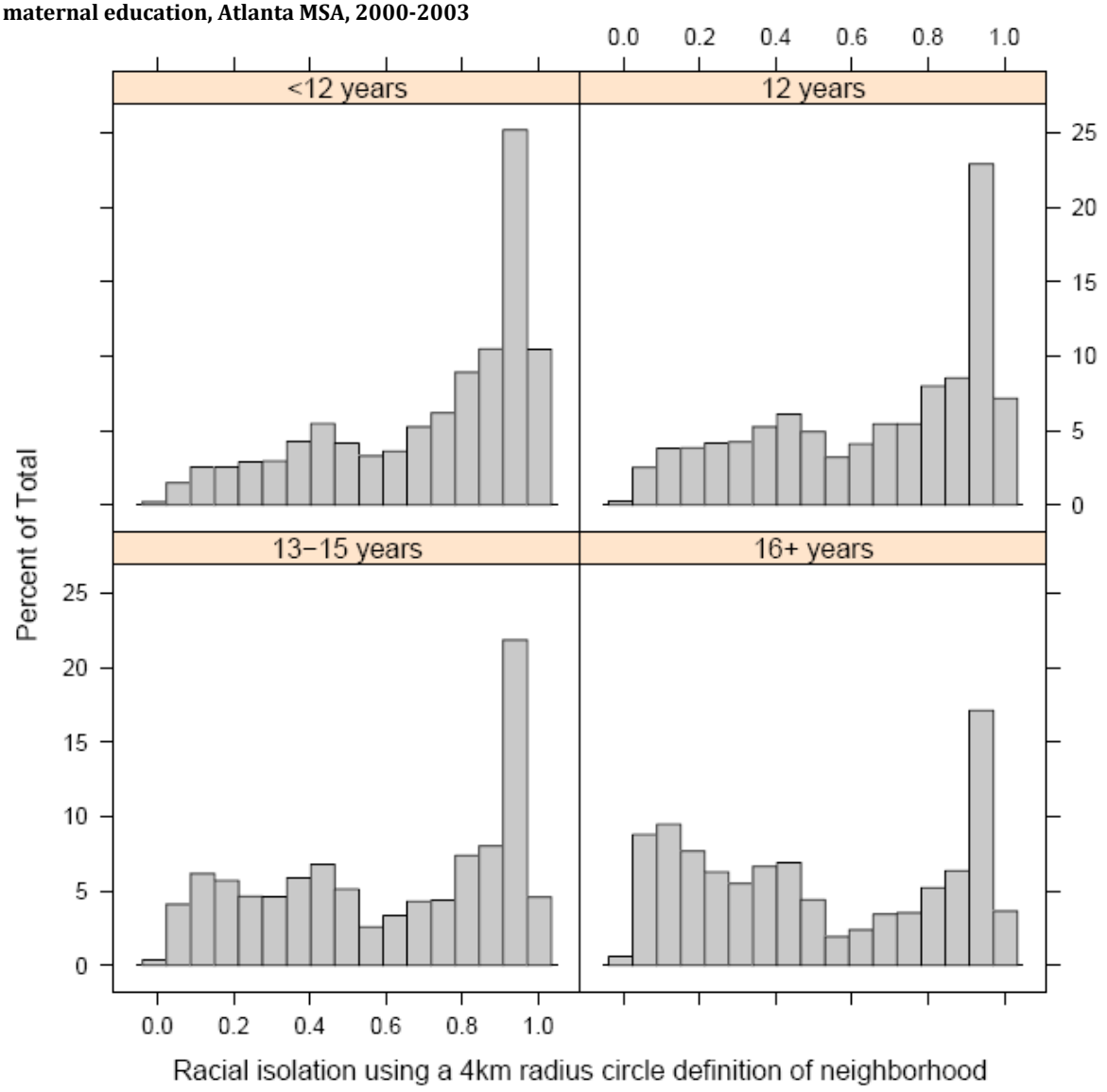

Table 7-1Distribution of singleton live births by maternal race, selected demographics, and outcome, Atlanta Metropolitan Statistical Area, 2000-2003

	Non-Hispanic black mothers		Non-Hispanic white mothers		B/W Risk Ratio		
	N births	%VPT	N births	%VPT	RR	95% CI	
TOTAL	85,327	3.38	130,007	1.22	2.77	2.61	2.94
Maternal age							
<15	318	5.97	87	5.75	1.04	0.40	2.70
15-19	11,712	3.58	8,671	2.08	1.72	1.45	2.04
20-24	24,061	3.01	22,419	1.41	2.13	1.87	2.43
25-29	21,371	3.12	34,386	1.05	2.97	2.62	3.37
30-34	17,292	3.55	41,143	0.96	3.70	3.26	4.19
35-39	8,696	3.94	19,701	1.32	2.98	2.55	3.50
40+	1,877	5.11	3,600	1.83	2.79	2.05	3.80
Maternal education							
<12 years	15,766	3.58	14,516	2.02	1.77	1.54	2.04
12 years	27,740	3.50	29,949	1.42	2.46	2.20	2.76
13-15	22,445	3.38	26,487	1.19	2.84	2.49	3.24
16+	18,086	2.76	57,217	0.87	3.17	2.81	3.59
Marital status							
Married	50,798	3.72	108,650	1.06	3.51	3.26	3.77
Unmarried	34,529	2.87	21,357	2.04	1.41	1.26	1.57
Parity							
Primiparous	33,780	3.79	56,775	1.48	2.56	2.35	2.79
Multiparous	51,547	3.11	73,232	1.02	3.05	2.80	3.32
Prior preterm or SGA birth							
Yes	552	14.49	1,236	4.61	3.14	2.27	4.35
No	84,775	3.30	128,771	1.19	2.77	2.61	2.95
Chronic hypertension							
Yes	805	14.41	871	3.79	3.80	2.61	5.53
No	84,522	3.27	129,136	1.20	2.73	2.56	2.90
Diabetes							
Yes	1,440	3.89	2,736	1.57	2.48	1.67	3.67
No	83,887	3.37	127,271	1.21	2.79	2.62	2.96
Tobacco use							
Yes	2,879	6.18	11,265	2.14	2.89	2.39	3.49
No	82,448	3.28	118,742	1.13	2.90	2.72	3.10
Medicaid paid for delivery							
Yes	46,565	3.18	29,233	1.73	1.84	1.66	2.03
No	38,762	3.61	100,774	1.07	3.37	3.12	3.65

Source: Georgia Department of Human Resources

Abbreviations: VPT: Very preterm birth (greater than 20 but less than 32 weeks gestation)

Table 7-2 Generalized additive modeling[a] of the risk for very preterm birth among black women, Atlanta Metropolitan Area, 2000-2003

	Crude			M1 -- Age, parity and prior preterm birth			M2 -- Socioeconomic condition pathway			M3 -- Maternal health pathway			M4 -- All covariate model		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Isolation[b]	1.023	1.004	1.043	1.031	1.010	1.054	1.024	1.005	1.043	1.031	1.010	1.053	1.025	1.006	1.045
Maternal age															
<15	1.93	1.20	3.10	1.61	1.00	2.60	1.16	0.70	1.91	1.70	1.06	2.74	1.28	0.78	2.12
15-19	1.12	0.99	1.27	0.99	0.87	1.13	0.76	0.65	0.88	1.02	0.89	1.16	0.80	0.69	0.94
20-24	0.94	0.84	1.04	0.91	0.81	1.01	0.80	0.71	0.89	0.92	0.82	1.02	0.82	0.73	0.92
25-29	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
30-34	1.18	1.05	1.32	1.19	1.07	1.33	1.27	1.13	1.43	1.17	1.05	1.31	1.24	1.11	1.40
35-39	1.35	1.18	1.54	1.38	1.21	1.58	1.49	1.30	1.72	1.28	1.12	1.47	1.38	1.20	1.58
40+	1.76	1.41	2.20	1.82	1.46	2.27	1.95	1.55	2.45	1.65	1.32	2.07	1.76	1.40	2.21
Parity															
Primiparous	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Multiparous	1.22	1.13	1.31	1.34	1.24	1.46	1.42	1.30	1.55	1.36	1.26	1.48	1.43	1.31	1.56
Prior preterm or SGA birth															
Yes	6.40	5.00	8.20	7.02	5.47	9.02	7.09	5.49	9.15	6.78	5.25	8.74	6.81	5.25	8.82
No	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--	1.00	--	--
Maternal education															
<12 years	1.29	1.14	1.47				1.66	1.42	1.95				1.57	1.34	1.84
12 years	1.27	1.13	1.42				1.54	1.35	1.74				1.52	1.34	1.72
13-15 years	1.22	1.09	1.37				1.36	1.21	1.54				1.36	1.20	1.53
16+ years	1.00	--	--				1.00	--	--				1.00	--	--
Marital status															
Married	0.77	0.71	0.83				0.67	0.61	0.74				0.69	0.63	0.76
Unmarried	1.00	--	--				1.00	--	--				1.00	--	--

	Crude			M1 -- Age, parity and prior preterm birth			M2 -- Socioeconomic condition pathway			M3 -- Maternal health pathway			M4 -- All covariate model		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Medicaid															
Yes	0.83	0.77	0.90				0.76	0.70	0.84				0.77	0.70	0.84
No	1.00	--	--				1.00	--	--				1.00	--	--
Chronic hypertension															
Yes	5.86	4.78	7.20							5.29	4.28	6.55	5.36	4.32	6.66
No	1.00	--	--							1.00	--	--	1.00	--	--
Diabetes															
Yes	1.33	1.02	1.75							0.93	0.70	1.23	0.90	0.67	1.21
No	1.00	--	--							1.00	--	--	1.00	--	--
Tobacco use															
Yes	2.05	1.75	2.40							2.10	1.79	2.46	1.91	1.62	2.26
No	1.00	--	--							1.00	--	--	1.00	--	--
p-value for smooth terms[c]				0.003			0.216			0.010			0.218		

a. Generalized additive model: logistic regression controlling for specified covariates with inclusion of a penalized spline smoothing term for latitude/longitude coordinates of each mother's residence

b. For modeling, isolation is scaled from 0-10 so the OR refers to a 1-unit change in scaled isolation, or 1/10th of the range of the index

c. Approximate Bayesian p-values for the penalized spline smoothers are reported

Table 7-3 Association between isolation and very preterm birth among black women with control for tract level variables using generalized linear mixed and generalized additive models

	GLMM[a]					GAM[b]				
Adjustments:	OR [c]	95% CI		σ_α [d]	Deviance	OR [c]	95% CI		p-value smooth[e]	Deviance
Individual covariates only (M4)	1.028	1.014	1.042	0.107	23259	1.025	1.006	1.045	0.218	23243
M4+ Black poverty rate	1.022	1.009	1.037	0.084	23247	1.021	1.003	1.039	0.610	23236
M4 + Black median household income	1.022	1.008	1.037	0.152	23253	1.021	1.003	1.040	0.770	23240
M4+ % adults without high school degree	1.026	1.013	1.040	0.087	23250	1.024	1.006	1.042	0.800	23240
M4 + all tract variables	1.020	1.000	1.040	0.15	23248	1.022	1.003	1.040	0.620	23235

a. Generalized linear mixed model: logistic regression controlling for specified covariates with random intercept for census tract

b. Generalized additive model: logistic regression controlling for specified covariates with inclusion of a penalized spline smoothing term for latitude/longitude coordinates of each mother's residence

c. Odds ratios are for the effect of isolation. For modeling isolation is scaled from 0-10 so the OR refers to a 1-unit change in scaled isolation, or 1/10th of the range of the index

d. σ_α is the standard deviation of the random intercept for census tract

e. Approximate Bayesian p-values for the penalized spline smoothers are reported

Table 7-4 Interaction of maternal smoking and isolation segregation in risk for very preterm birth in black women

	Non-smokers			Smokers			Prevalence of smoking
Quintiles of Isolation[a]	OR	95% CI		OR	95% CI		%
1st quintile	1.00	--	--	1.00	--	--	2.4
2nd:1st	1.06	0.98	1.14	1.35	1.25	1.46	3.1
3rd:1st	1.12	1.04	1.21	1.88	1.74	2.04	3.5
4th:1st	1.17	1.08	1.26	2.36	2.18	2.55	3.9
5th:1st	1.18	1.09	1.28	2.55	2.35	2.75	3.9

a. Quintiles of isolation are calculated from the distribution of term births to black mothers. The contrasts are calculated with the median value within each quintile.

Table 7-5 Black-white racial disparity for very preterm birth under different model specifications

	GLMM[a]				GAM[b]			
	OR	95% CI		% disparity explained	OR	95% CI		% disparity explained
Modeled crude disparity	2.89	2.71	3.08	0.00	2.73	2.53	2.94	0.00
Adjusted for individual covariates[c]	2.68	2.49	2.88	0.11	2.58	2.38	2.81	0.08
Individual covariates + isolation	2.45	2.24	2.68	0.23	2.47	2.26	2.70	0.15

a. Generalized linear mixed model: logistic regression controlling for specified covariates with random intercept for census tract

b. Generalized additive model: logistic regression controlling for specified covariates with inclusion of a penalized spline smoothing term for latitude/longitude coordinates of each mother's residence

c. Individual covariates include age, education, marital status, parity, history of previous preterm or SGA birth, chronic hypertension, diabetes, smoking and Medicaid

Chapter 8 DISSERTATION IN CONTEXT: STRENGTHS, WEAKNESSES AND PUBLIC HEALTH CONTRIBUTIONS

The persistent racial disparity in preterm birth in the United States represents public health, policy, and social justice challenges that have proved difficult to meet. A key premise from the outset in this project is that simplistic models are incomplete, and there is potential gain from appreciating the complex interplay of society, culture, behavior, and biology. That being said, no single study (including this one) has thus far incorporated a sufficient level of complexity under a single analytic umbrella. Rather than recommending that any study meet this criterion, the recommendation derived from this project is for future investigators to develop smaller, more manageable hypotheses articulated within the context of a broader conceptual model. In this way, each study will fill a gap in the puzzle.

In many ways this dissertation project was framed and driven by the observation that racial disparities in very preterm birth may result from determinants which can be decomposed into two potential categories (paper, Appendix 1). The first category is the substantial across-the-board excess risk for very preterm birth in black as compared with white women. This excess occurs regardless of education, income, age, or health behavior. It also occurs without regard to geography, and spans excess risk for black women in all states, metropolitan areas, or neighborhoods. Such patterns likely arise from determinants which are geographically invariant. Persistent residual confounding by socioeconomic status, a baseline level of discrimination in interpersonal relations or in access to health

promoting resources and genetic predisposition are all candidate exposures in this first category.

The second category includes place-varying exposures, which result in observed racial differences in inter-metropolitan area risk variation for very preterm birth. If some characteristics of the places people live and work can be identified as upstream determinants of risk, there is potential to eliminate the portion of the disparity attributable to these causes. The problem of course is that only geographically heterogeneous exposures can be identified using a place-based approach. Any exposure which is spatially homogenous (perhaps racism or perhaps genetic and epigenetic interactions) could be a powerful determinant of absolute risk, but is obscured by the absence of any (or many) unexposed individuals. Thus, taking a place-based approach provides opportunities to discover some patterns previously ignored, but also necessarily results in incomplete explanation of the sources of racial disparities.

CONTRIBUTIONS

This project had many notable findings. First, in taking a fresh look at the measurement and conceptual issues around using a construct like racial residential segregation in health research, new tools were introduced to the public health literature. Early interest in segregation and health used the most readily-available measures around, and provided important findings from them. However the application of explicitly spatial measures using various neighborhood scales permits new questions about the scale and pattern of urban life that influence health.

It is interesting that in the validation study of spatial measures of the isolation and evenness dimensions of segregation, the spatial dissimilarity index was typically more

strongly correlated with the chosen health mediating variables than was isolation. In contrast, in both studies of the association of segregation with very preterm birth, isolation measured with 500m-radius circle neighborhoods had the best model fit. This difference could result from several factors. The dissimilarity index may be more strongly correlated with individual and area socioeconomic characteristics (except murder) because of its invariance to population composition, allowing it to register segregation in MSA's with moderately sized black populations where the degree of measured isolation is limited by total proportion black. However when regressed on a specific health outcome (rather than census-derived proxies for health related exposures), the role of isolation becomes more clear. Alternatively dissimilarity may truly outperform isolation in capturing some effects of segregation, but they are simply not the relevant pathways to prematurity.

The consistent relationship between isolation, violent crime rates, and preterm birth suggests that an important part of any association between segregation and very preterm birth in black women is mediated through the destruction of the social fabric and stability in spatially isolated communities with concentrated poverty. Perhaps this more than individual socioeconomic attainment or social capital is the most toxic exposure. What is also interesting is that the association is strongest across MSA's when isolation is measured with small rather than large neighborhoods. In the Atlanta study macro- rather than micro-segregation predominates, so it was not possible to discern a scale difference. The importance of micro-isolation suggests that it is not only the crumbling of central cities and white flight to the suburbs (emblematic of a macro-segregation pattern) which results in ill-health. Rather patterns of sub-regional neglect within central cities and perhaps within suburbs and exurbs play a role as well. Gentrification of urban neighborhoods with

concomitant changes in property tax and rental patterns could be one example of such sub-regional variation.

However beyond this association between isolation, violent crime and preterm birth, mediating pathways were difficult to describe. It was somewhat surprising how little impact control for socioeconomic and medical risk factors made in the estimate of the segregation effect on preterm birth. The modest evidence for an age-segregation interaction in the national study and the evidence for smoking-segregation interaction in the Atlanta study each beg further questions about mediating pathways.

Finally, it is worth commenting on the meaning of results comparing MSA's across the nation to those comparing neighborhoods across the Atlanta MSA. Throughout this dissertation, residential segregation as marker or indicator of regionally varying racial or economic inequity has been emphasized. Operationalizing this idea requires comparison of different areas some of which are highly segregated and some of which have less segregation, in order to estimate an effect. The tradeoff in typically available datasets is the loss of spatial resolution with regards to a specific woman's residential environment. In essence what is measured in the national study is the contextual effect of more or less segregation on all black women in a given MSA, rather than any particular aspect about a particular woman's experience. In contrast the Atlanta study allows much finer resolution of each woman's neighborhood, but suffers from only a single global context (a single MSA), thus lacking heterogeneity with regards to overall sorting. Put another way, the national study may suffer from ecologic fallacy whereas the Atlanta study could be subject to individualistic fallacy. To test for the presence of either requires data rich at all scales including individual, neighborhood, and metropolitan.

The consistency between studies bolsters the notion that ill effects of metropolitan segregation are primarily transmitted to residents of segregated neighborhoods, and less so to women living in racially mixed neighborhoods situated within a highly segregated MSA. However this support is only circumstantial.

LIMITATIONS

The notion of scale has been touched on at several points; the spatial scale of neighborhoods in measuring segregation or the geographic scale of study design in choosing neighborhoods or MSA's as the unit of analysis were each important in these studies. Yet one of the greatest limitations of inference from this project relates to omitted scales of importance. The missing neighborhood information in the national study and the missing MSA comparisons in the neighborhood study limit each. But missing from each is richer interpersonal exposure, clinical, and biologic data which could greatly improve our understanding of relationships and pathways.

Related to this point is the reliance on vital records for all birth outcome data. These data have many known problems with misclassification of outcome and covariate data, and are lacking in other variables of interest. The focus on preterm live births also meant ignoring fetal deaths. This is important because it is plausible that a common etiology results in preterm fetal death, and preterm live birth closely followed by neonatal death. Nonetheless it is unlikely that many of the questions addressed herein could have been accomplished with any other form of prospective data collection. The numbers of births needed to have adequate power across a range of demographic and metropolitan areas would be practically impossible without reliance on vital records.

Finally any causal inference is limited by the cross-sectional nature of the study designs. Although segregation was measured using 2000 census data and births were followed from this point forward, this is not a sufficient temporal gap. Future work which includes changing segregation over time with related temporal changes in birth outcomes may further strengthen (or discredit) these findings.

CONCLUSIONS

This project has established a seemingly independent association between metropolitan and neighborhood segregation and excess very preterm birth among black women. While far from sufficient to establish a causal relationship, these findings deserve further attention by epidemiologists and at least passing consideration by policy makers. The possibility that modification of public housing and urban planning policy might change future generations' pregnancy outcomes may seem extraordinary, but it is in concordance with the history of public health.

Despite the findings reported here, segregation (and all measured risk factors combined!) still accounts for a fraction of the racial disparity. Future work which broadly considers the role of environment (e.g. political economy, regional, neighborhood, social, and ambient), the choices and behaviors of individuals, and the functions of biologic processes may well illuminate what has thus far remained elusive.

APPENDIX 1

The analysis which generated the primary questions driving this dissertation is described in the following manuscript, included as an appendix with the permission of the journal Public Health Reports.

Kramer MR, Hogue CR. Place matters: Variation in the black/white very preterm birth rate across U.S. metropolitan areas, 2000-2004. *Public Health Reports*. 2008. 123;576-85.

Place Matters: Variation in the Black/White Very Preterm Birth Rate Across U.S. Metropolitan Areas, 2002–2004

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SYNOPSIS

Objective. We reported on the distribution of very preterm (VPT) birth rates by race across metropolitan statistical areas (MSAs).

Methods. Rates of singleton VPT birth for non-Hispanic white, non-Hispanic black, and Hispanic women were calculated with National Center for Health Statistics 2002–2004 natality files for infants in 168 MSAs. Subanalysis included stratification by parity, age, smoking, maternal education, metropolitan size, region, proportion of MSA that was black, proportion of black population living below the poverty line, and indices of residential segregation.

Results. The mean metropolitan-level VPT birth rate was 12.3, 34.8, and 15.7 per 1,000 live births for white, black, and Hispanic women, respectively. There was virtually no overlap in the white and black distributions. The variation in mean risk across cities was three times greater for black women compared with white women. The threefold disparity in mean rate, and two- to threefold increased variation as indicated by standard deviation, was maintained in all subanalyses.

Conclusion. Compared with white women, black women have three times the mean VPT birth risk, as well as three times the variance in city-level rates. The racial disparity in VPT birth rates was composed of characteristics that were constant across MSAs, as well as factors that varied by MSA. The increased sensitivity to place for black women was unexplained by measured maternal and metropolitan factors. Understanding determinants of differences in both the mean risk and the variation of risk among black and white women may contribute to reducing the disparity in risk between races.

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Birth prior to 32 weeks gestation, called very preterm (VPT) birth, occurs in 2% of all pregnancies ending in live birth.[1] One-third of all infant deaths are attributable to complications of prematurity, and 95% of those are from the small population of sub-32-week births.[2] In addition to increased mortality, VPT birth results in increased morbidity, such as respiratory disease, developmental delays, and cerebral palsy.[3–5] Variation in risk for VPT birth by maternal race is well described, although the sources of this disparity remain unresolved. African American women experience VPT birth at 2.5 times the rate of non-Hispanic white women,[1] and this disparity attenuates little with statistical control for education, income, medical comorbidities, or behaviors associated with risk.[6,7] The persistence of this disparity in the face of control for (measured) confounders has led some to suggest the difference is largely genetic,[8] yet nativity studies comparing the experience of immigrant women of African ancestry to U.S.-born African American women suggest the toxic exposure may be more environmental than ancestral.[9,10]

Interest in the role of maternal residential environment—variably conceptualized from the local census tract up to the national level—has increased in recent years.[11] Place-based exposures that have been associated with pregnancy outcomes include neighborhood crime,[12] access to retail food outlets,[13] city-level segregation,[14] city-level air pollution,[15] state-level income inequality,[16] and national politics and welfare state status.[17] Most studies of social or environmental determinants of racial disparities compare mean risk among racial groups, providing interracial contrasts. Less is known about the role, if any, of intraracial variation in understanding determinants of VPT birth disparities.

This article describes the distribution of metropolitan-level rates of VPT birth by race and ethnicity to characterize the inter- and intraracial variation across cities.

METHODS

Data

Birth files from the National Center for Health Statistics (NCHS) for 2002–2004 were combined. These files include an observation for every birth in the U.S. during the given time period. Births were restricted to singletons born to mothers who self-report race and ethnicity as non-Hispanic white, non-Hispanic black, or Hispanic. A further restriction was to mothers residing in one of the 311 metropolitan statistical areas (MSAs) with populations of 100,000 or more in the 2000 census. An MSA is a geographical unit defined by the U.S. Office of Management and Budget as a county or group of counties around a core city that are socially and economically integrated.[18] New England City and Town Area Divisions (NECTAs) are parallel units used in New England, and for this analysis were analyzed as MSAs.

Gestational age was calculated from maternally reported last menstrual period (LMP) for the vast majority of births. In 2002–2003, 4.6% of births used clinical estimates of gestational age because of missing LMP or birth weight incompatible with LMP.[19,20] In 2004, 5.9% of births used clinical estimates of gestational age.[21]

There were 11.8 million singleton live births from 2002 to 2004, with 56.2% born to non-Hispanic white mothers, 14.1% to non-Hispanic black mothers, and 22.7% to Hispanic mothers. Because VPT birth is a rare event, to insure stability of rates we restricted analyses to MSAs with at least 1,000 live births in 2002–2004 for each racial group. Exclusion of MSAs with fewer than 1,000 race-specific births resulted in 301, 168, and 169 MSAs for white, black, and Hispanic mothers, respectively. The vast majority of all births in the U.S. (76% of all white, 84% of black, and 87% of Hispanic births) occurred in these eligible MSAs. Rates of VPT birth were calculated separately for each racial/ethnic group within each MSA.

Analysis

The unit of analysis was the MSA. Rates were first described graphically with race-stratified histograms of all eligible MSAs. Subsequent analyses were limited to the 168 MSAs with adequate numbers of both white and black births. Of these MSAs, 115 also had adequate numbers of Hispanic births. It is plausible that national distribution of births by race (there were 4.2 million births to white women in the 168 MSAs, but only 1.5 million births to black women) could result in differing observed variances that reflect sample size rather than true variation. Because we were interested in both the mean rate in each MSA and the variance in rates across MSAs, we assessed the effect of sample size on variance by taking a random sample of all white births in the 168 MSAs with sufficient black births, so as to simulate exactly equal numbers of black and white births. Because sample size did affect variance to a small degree, all stratified analyses were conducted on the equalized sample.

Descriptive statistics for each racial/ethnic group include the mean and standard deviation (SD) of the empiric distribution of city-level rates. Variances of black and Hispanic distributions were compared with the white distribution with F-statistics, with the respective number of MSAs as the numerator and denominator degrees of freedom.

Different distributions of women in cities by proportion native-born, and by maternal age, education, marital status, smoking status, or parity, could drive an observed difference among cities. To assess these possibilities, the analysis was repeated after further restriction to U.S.-born women, to primiparous women, and to nonsmokers. Additionally, we reported on distributions adjusted for age and stratified on maternal education and marital status.

Because broad-ranging regional variation and population composition of metropolitan areas could influence distributions of rates, analyses were repeated within each of four Census regions, and for three different sizes of MSAs. All MSAs with sufficient number of black births were categorized according to quintiles of the proportion of total MSA population that was black, as well as quintiles of the black population living below the poverty line, as reported in the 2000 U.S. Census. The MSA distribution within racial/ethnic groups was reported for the MSAs in the first and fifth quintile of each spectrum. Regional variation in other pregnancy outcomes has been partially explained by racial segregation[22] and income inequality.[23] Multiple dimensions of segregation have been described, including evenness/unevenness (the degree to which a minority group is evenly distributed across sub-areas of the MSA) and exposure/isolation (the probability that a randomly drawn minority member shares a neighborhood with someone in his/her own group [isolation] or in a different group [exposure]).[24]

For this analysis, we used two indices calculated by the Census Bureau, each assessing black-white segregation. Theil's Entropy Index (sometimes termed H) is a measure of unevenness, and xPx measures isolation. Each ranges from 0 to 1, with 0 being complete integration, and 1 being complete segregation. Income inequality was measured by the Census Bureau with the Gini coefficient, which ranges from 0 (where income is equally distributed across the population) to 1 (where all income is held by one person).

True length of gestation was likely causally associated with infant mortality and morbidity. However, measurement error in common proxies for true gestational length can influence rate estimates. For investigators interested in racial disparities, this may be more concerning, as there is evidence that the measurement error is differential with respect to race or ethnicity.[25–27] Birth weight, on the other hand, is much more reliably measured, although perhaps less causally plausible.[28] Controversy exists about the causal association of low birth weight (<2,500 grams) to infant mortality and morbidity, but the more extreme very low birth weight (VLBW) (<1,500 grams) infants overlap significantly with VPT infants (83% of singleton VLBW infants in this dataset were also VPT). Because quality of gestational age reporting might vary regionally, the analysis was repeated using birth weight <1,500 grams as the outcome.

To explore metropolitan-level sources of variation for black women, multivariate linear regression models were fit, with the rate of VPT birth per 1,000 births as the outcome. Variables initially considered for the model were region, MSA size (in three categories), proportion of MSA population that was black, proportion of black population below poverty line, median household income (both overall and for black households), proportion of black adults >25 years of age with a college degree, and proportion without a high school degree, both segregation indices, and the Gini coefficient. Backward stepwise regression proceeded, and subsequent analysis for colinearity was conducted.

For every analysis, the calculation of whether an MSA-race-stratification group had at least 1,000 total births was repeated, thus insuring stable rates in each subanalysis. However, this did result in varying numbers of MSAs being eligible for each analysis.

All data analysis was conducted using SAS 9.2.[29]

RESULTS

The population distribution of 168 MSAs with sufficient numbers of black and white births is detailed by race, region, and metropolitan size in Table 1. The Southeast region had the largest number of MSAs, with the remainder roughly evenly divided among the other three regions. Segregation by either index tended to be lower in the West, as did black poverty rates. Smaller MSAs also had slightly lower levels of segregation, while the largest MSAs had lower black poverty rates.

The Figure displays the distribution of VPT birth rates by race across all eligible MSAs for each racial/ethnic group. The x-axis is the rate of VPT birth per 1,000 live births, and the y-axis is the relative frequency of MSAs; in other words, it is the proportion of all MSAs at a given rate. For white women, the mean MSA rate of VPT birth was 12.3/1,000 (SD=2.7); for black women, the mean rate was 34.8/1,000 (SD=6.9); and for Hispanic women, the mean MSA rate was 15.7/1,000 (SD=4.0). Restricting the analysis to the 168 MSAs, which had sufficient white and black births, changed these estimates very little, as seen in Table 2. F-tests comparing the variance in white and black distributions of MSA rates were statistically significant ($p<0.0001$) for every stratum investigated. Similarly, the random selection of white births to equalize sample sizes only reduced the white SD by 7%, from 2.7 to 2.5, leaving

Table 1. Population distribution by metropolitan characteristics[a]

	Non-Hispanic white population		*Non-Hispanic black population*		*Hispanic population*			*Percent blacks in MSA below poverty line*			*Black segregation/ isolation[b]*			*Black segregation/ evenness[c]*		
	Mean	*SD*	*Mean*	*SD*	*Number of MSAs*	*Mean*	*SD*	*Mean*	*Low*	*High*	*Mean*	*Low*	*High*	*Mean*	*Low*	*High*
Metropolitan size 100,000–500,000 (*n*=73)[d]																
Northeast (*n*=4)	221	95	45	20	4	37	6	22	19	26	0.48	0.29	0.61	0.31	0.18	0.42
Southeast (*n*=54)	182	98	59	39	17	33	17	29	17	44	0.48	0.26	0.70	0.27	0.09	0.50
Midwest (*n*=15)	288	98	33	18	7	19	5	31	25	39	0.39	0.14	0.72	0.35	0.18	0.59
Metropolitan size 500,000–l million (*n*=35)																
Northeast (*n*=6)	581	213	54	13	5	97	97	29	23	36	0.43	0.25	0.62	0.38	0.27	0.44
Southeast (*n*=12)	510	139	152	83	9	25	11	26	17	34	0.52	0.37	0.69	0.35	0.21	0.50
Midwest (*n*=9)	536	114	76	36	6	38	20	27	19	32	0.52	0.35	0.80	0.45	0.25	0.71
West (*n*=8)	385	109	43	13	8	183	131	21	8	36	0.27	0.12	0.39	0.19	0.11	0.26
Metropolitan size 1 million (*n*=60)																
Northeast (*n*=13)	1,904	1,405	402	604	12	375	686	22	10	34	0.57	0.31	0.81	0.48	0.24	0.64
Southeast (*n*=23)	1,188	636	408	324	23	322	395	22	13	33	0.55	0.36	0.78	0.37	0.21	0.50
Midwest (*n*=11)	1,982	1,173	449	454	11	204	429	26	20	33	0.61	0.31	0.88	0.51	0.31	0.71
West (*n*=13)	1,547	621	201	238	13	844	1,150	19	10	24	0.32	0.09	0.65	0.26	0.11	0.48

[a]All population estimates are derived from U.S. Census 2000 data and reported in thousands.

[b]Isolation segregation (xPx) is interpreted as the probability of two randomly chosen people from a given area (e.g., Census tract) being from the same group. It ranges from 0 (full integration) to 1 (complete segregation).

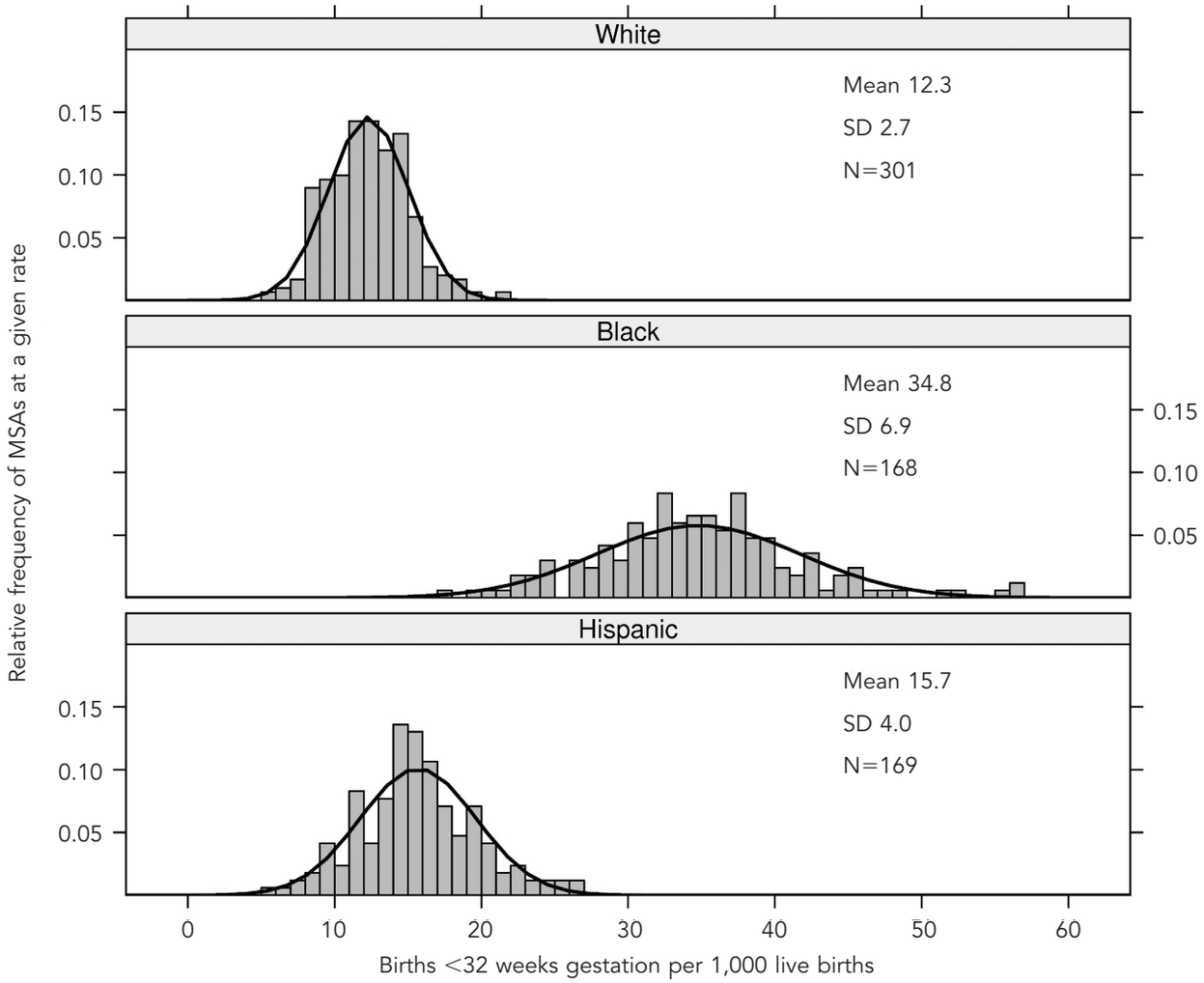
[c]Evenness segregation (Theil's H index) is interpreted as the degree to which a minority group is evenly distributed across sub-areas (e.g., Census tracts) in a metropolitan area. It ranges from 0 (full integration) to 1 (complete segregation).

[d]West was *n*=0, so it is not included.

MSA = metropolitan statistical area

SD = standard deviation

Figure. Rates of very preterm birth in U.S. metropolitan statistical areas (MSAs) by race, 2002–2004



SOURCE: National Center for Health Statistics Natality Files, 2002–2004; Singleton live births.

SD = standard deviation

the ratio of the variance in the black distribution to the white distribution relatively unchanged.

Within each racial group, the lowest mean rate was in Western cities (9.9, 26.2, and 13.6 per 1,000 live births for white, black, and Hispanic women, respectively), among married mothers (10.3, 29.4, and 12.7), and college-graduated mothers (7.9, 29.4, and 10.9). The respective high rates for each group varied, with white mothers seeing the highest mean rate among unmarried women (18.7) and women without a high school degree (19.0). Black women also had a high risk of VPT birth among unmarried mothers (37.7), as well as mothers residing in cities with the highest quintile of proportion black (39.2) and highest quintile of black women below the poverty line (37.5). For Hispanic women, high rates occurred among unmarried women (18.7), cities in the Northeast region (18.7), for nulliparous women (17.1) and women residing in cities with the highest quintile black population below poverty line (18.0). Cities with the highest unevenness segregation had lower VPT birth rates for white women (11.6 vs. 13.1 in the lowest quintile), while the opposite was true for black women (first quintile = 33.9, fifth quintile = 35.5). The effect of higher isolation segregation in black women was even stronger, with a range of 30.8 to 37.1 from the first to fifth quintiles.

Given equalization of the sample size, the SD of the distribution of city rates in each stratum could be

Table 2. Distribution of rates of very preterm births aggregated at the MSA level by race, 2002–2004

	Non-Hispanic white			*Non-Hispanic black*			*Hispanic*		
	Number of MSAs[a]	*Mean MSA rate*[b]	*SD of MSA rates*	*Number of MSAs*[a]	*Mean MSA rate*[b]	*SD of MSA rates*[c]	*Number of MSAs*[a]	*Mean MSA rate*[b]	*SD of MSA rates*
All eligible MSAs	301	12.3	2.7	168	34.8	6.9	169	15.7	4.0
Restricted to 168 MSAs with adequate black and white births	168	12.2	2.5	168	34.8	6.9	115	16.1	3.8
Equalized sample sizes[d]	168	12.1	2.7	168	34.8	6.9	115	16.1	3.8
Restriction to subset of mothers									
U.S.-born	168	12.2	2.5	164	35.3	6.7	71	17.2	4.1
Nonsmoking	156	11.1	2.3	143	34.6	6.4	92	15.8	3.5
Nulliparous	160	13.7	3.1	86	35.3	6.4	76	17.1	4.5
Stratification on maternal characteristics									
Age adjusted	168	12.2	2.5	168	34.9	6.9	131	16.3	4.0
Marital status									
Married	167	10.3	2.7	71	29.4	6.4	80	12.7	3.6
Unmarried	134	18.7	3.4	120	37.7	7.8	76	18.7	4.5
Maternal education									
<High school	108	19.0	4.1	70	37.2	7.5	115	16.2	4.3
High school	154	13.9	3.0	96	34.6	5.8	65	15.3	4.1
1–3 years of college	146	11.2	2.3	71	32.4	5.7	46	14.1	3.8
≥4 years of college	150	7.9	1.8	42	29.4	5.6	35	10.9	2.7
Stratification on metropolitan characteristics									
Metropolitan size									
100,000–500,000	73	13.5	2.6	73	37.0	7.4	28	18.4	4.1
500,000–1 million	35	12.1	1.9	35	33.9	6.5	28	16.0	3.6
>1 million	60	10.7	1.8	60	32.5	5.7	59	15.0	3.3
Census region									
Northeast	23	11.0	1.7	23	34.9	4.6	21	18.7	3.1
Southeast	89	13.0	2.6	89	36.8	6.9	49	15.9	3.7
Midwest	35	12.4	1.7	35	34.8	5.1	24	16.0	3.8
West	21	9.9	2.1	21	26.2	5.4	21	13.6	3.2
Percent of MSA population black									
Highest quintile	38	12.9	3.2	38	39.2	7.2	13	15.2	4.0
Lowest quintile	31	10.9	2.3	31	29.3	6.5	28	15.6	3.8
Percent of black women in MSA below poverty line									
Highest quintile	38	12.7	1.8	38	37.5	7.0	15	18.0	4.1
Lowest quintile	31	10.8	2.8	31	31.4	5.7	30	15.6	3.5
Segregation/isolation (xPx)[e]									
Highest quintile	34	11.8	2.0	34	37.1	5.7	21	15.7	3.6
Lowest quintile	33	12.1	2.5	33	30.8	6.6	24	15.2	3.6
Segregation/evenness (H)[f]									
Highest quintile	32	11.6	1.9	32	35.5	5.2	25	15.9	3.0
Lowest quintile	35	13.1	3.5	35	33.9	9.4	20	16.0	4.9
Income inequality (Gini)[g]									
Highest quintile	34	11.8	3.1	34	36.5	8.9	18	14.8	3.8
Lowest quintile	31	13.1	2.7	31	33.5	6.5	22	17.9	4.8
Alternate outcome									
Very low birth weight	168	8.5	1.6	168	26.0	4.4	115	10.4	2.5

SOURCE: National Center for Health Statistics Natality File, 2002–2004

[a]Only MSAs having at least 1,000 live births in 2002–2004 within a given racial/ethnic group and within given strata were included for analysis.

[b]Singleton births <32 weeks gestation per 1,000 live births

[c]For every analysis in this table, F-tests comparing the variance in the non-Hispanic black distribution with the variance in the non-Hispanic white distribution were statistically significant at $p<0.0001$.

[d]A simple random sample of all white births in the 168 MSAs with sufficient black births was drawn to simulate the effect of an equalized sample size of white and black births. The full number of black and Hispanic births was used.

[e]Evenness segregation (Theil's H index) is interpreted as the degree to which a minority group is evenly distributed across sub-areas (e.g., Census tracts) in a metropolitan area. It ranges from 0 (full integration) to 1 (complete segregation).

[f]Isolation segregation (xPx) is interpreted as the probability of two randomly chosen people from a given area (e.g., Census tract) being from the same group. It ranges from 0 (full integration) to 1 (complete segregation).

[g]The Gini Index is a measure of distribution of income across a population. It ranges from 0 (each person has an equal share income) to 1 (all income is received by one person, while others receive none).

MSA = metropolitan statistical area

SD = standard deviation

a rough indicator of the similarity or variation among cities. For all three groups, the greatest city-to-city variation was seen when restricting to unmarried mothers (SD=3.4, 7.8, and 4.5 for white, black, and Hispanic women, respectively). Black women also had greater city-to-city variation in the group of cities with the lowest unevenness segregation (SD=9.4) and the highest income inequality (SD=8.9), while for white women, high variation was seen when restricting to mothers without a high school diploma (SD=4.1). For all three groups, city-to-city variation was lowest when restricting to mothers with a college education, and in the cities with the largest populations.

In addition to describing the within-race patterns of VPT birth rates, the means and SDs suggest varying interracial patterns. Black women consistently had two to three times the city-to-city variation for any given analysis as compared with white and Hispanic women. Although increasing education and marital status were protective for all groups, the magnitude of protection varied so that the black-white rate ratio among college-graduated mothers was 3.7 as compared with a ratio of 1.9 among women without a high school degree. The mean rate for U.S.-born Hispanic mothers was greater than the overall rate, suggesting increased risk with subsequent generations (mean of 15.7 overall, 17.2 for U.S.-born mothers). Hispanic women without a high school degree had lower rates than similarly schooled white or black women (16.2 vs. 19.0), although this advantage waned with increasing education.

The overall pattern of a threefold black-white racial disparity in mean rates, as well as a threefold increased variance, persisted with the use of VLBW as an alternate outcome. There was moderate correlation within cities of white and black VPT birth rates ($r^2 = 0.21$, $p<0.01$) and of white and Hispanic rates ($r^2 = 0.20$, $p<0.01$). Related is the observation that MSA-specific black/white rate ratios varied across MSAs with a median ratio of 2.8, and a range from 1.5 to 5.8.

Metropolitan area size and region of the country explained 26% of the black inter-city variance in VPT birth rates (Table 3). The black poverty rate and black median household income did not provide any better model fit than overall median household income alone,

Table 3. Linear regression of metropolitan characteristics and black very preterm birth rates per 1,000 live births

	Crude		*Model 1*		*Model 2*		*Model 3*	
	ß	*SE*	*ß*	*SE*	*ß*	*SE*	*ß*	*SE*
Intercept	34.80[a]	0.5	34.10[a]	1.3	43.00[a]	5.0	42.40[a]	4.9
Metropolitan size								
100,000–500,000	4.50[a]	1.2	2.30[b]	1.2	0.04	1.3	0.30	1.5
500,000–1 million	1.40	1.4	1.60	1.3	0	1.3	0.40	1.3
>1 million	Ref.							
Census region								
Northeast	Ref.							
Southeast	1.80	1.4	1.00	1.5	−0.30	1.6	−1.70	1.7
Midwest	−0.10	1.6	−0.70	1.7	−1.30	1.6	−0.90	1.6
West	−8.70[a]	1.8	−8.50[a]	1.8	−8.10[a]	1.8	−7.30[a]	2.0
Median household income[c]	−3.60[a]	0.6	−1.60	1.0	−1.40	1.0		
Percent blacks >25 years of age with college degree[d]	−0.60[a]	0.1			−0.24	0.2	−0.20	0.1
Isolation segregation[e]	2.30[a]	0.5					2.70[a]	0.9
Evenness segregation[f]	0.80	0.5					−2.00[b]	1.0
R^2			0.26		0.31		0.35	

[a] $p<0.01$

[b] $p<0.05$

[c] The median household income was scaled so that the beta is the change in very preterm birth rate for a $10,000 change in median household income.

[d] The proportion of black women with a college degree was centered around its mean (13.6%) and scaled to integers. The beta was interpreted as a change in very preterm birth rate for a 1% change from mean black college percent.

[e] The isolation index (xPx) was standardized so that the beta could be interpreted as the change in the very preterm birth rate for one standard deviation change in isolation.

[f] The evenness index (Theil's H) was standardized so that the beta could be interpreted as the change in the very preterm birth rate for one standard deviation change in isolation.

SE = standard error

Ref. = reference group

and so were dropped. The Gini coefficient was not significant in base models including region and metropolitan size, although both segregation indices were independently predictive in all models tested. A one SD increase in isolation segregation was associated with an increase in the black VPT birth rate of 2.7/1,000, while a one SD increase in unevenness reduced VPT rates to 2/1,000.

DISCUSSION

Three observations are apparent from the Figure. First, the mean MSA rate for black women is nearly three times that of white women. This is the ecologic corollary of the individual racial disparity in VPT birth. Nonetheless, it is quite striking, particularly in light of the second observation, which is that there is almost no overlap in the white and black distribution. The rate of VPT birth in the very best city for black women was virtually identical to the rate in the very worst city for white women. The final observation is that the variation or spread of the empiric distribution of rates among MSAs was significantly greater for black women than for white women, with the SD for black women approximately 2.5 times greater than for white women ($p<0.0001$). This increased spread remains after accounting for sample sizes, differences in distribution of key predictors of VPT birth, and measurement error of the outcome.

The first two observations suggest that regardless of where black women live, they experience excess risk of VPT birth, implying an exposure that is ubiquitous or constant across space. The third observation suggests that in addition to this excess risk experienced in all cities, there is increased sensitivity to city of residence for black women as compared with white women. While regional differences in mean risk for various pregnancy outcomes have been reported,[30–32] to our knowledge no study to date has described the extent of regional variation in VPT birth, nor reported racial differences in both means and variance.

Explanations for the persistent excess rates of poor pregnancy outcomes among black women have been stubbornly hard to find. The increasing magnitude of the racial disparity among seemingly lower-risk, college-graduated, married black and white women has been previously reported[7,33] and suggests either residual confounding by socioeconomic status or a negative exposure that counterbalances the protective effects of increasing socioeconomic status among black women. Candidate exposures for persistent elevated risk despite statistical control for (measured) socioeconomic status include exposure to interpersonal racism,[34,35] "weathering" of biologic systems as a result of lifelong exposure to stress,[36] or genetic predisposition to preterm birth.[37] Any of these factors, or an epigenetic combination of them,[38] could potentially represent the ubiquitous exposure accounting for elevated VPT birth rates for black women across cities.

The increased city-to-city variance for black women as compared with either white or Hispanic women suggests metropolitan-level exposures that are uniquely relevant for black women. While differences in population composition could still explain some of this variation, the persistent pattern after stratifying on the strongest risk factors for VPT birth, including marital status, maternal education, parity, and age, suggest that structural or contextual factors rather than purely compositional factors are the source of observed variance. State-level income inequality has been found to associate with infant mortality—an outcome strongly correlated with VPT birth—in several recent studies.[23,39] Increasing income inequality could associate with infant mortality through poverty concentration, lower social capital, and level of investment in social and welfare systems. We found increased VPT birth rates for black women in cities with the highest compared with the lowest inequality, but the reverse was true for white and Hispanic women, although the remaining inter-city variance in all cases was larger than the change in the mean. Income inequality was not independently predictive in multivariate models. It is not clear whether income inequality at the state level has the same meaning as inequality at the MSA level.

Residential segregation has also been associated with increased black but not white infant mortality and VPT birth.[40,41] Segregation is a process of sorting individuals into residential environments on the basis of race or income, and has been termed a fundamental cause of racial health disparities.[42,43] These neighborhoods influence school quality, educational attainment, economic opportunity, and exposure to crime, high crowding, and quality of housing.[42] The evenness dimension of segregation (measured here with Theil's H index) describes how evenly a minority group is distributed across sub-areas of a city. The exposure (or isolation) dimension describes the potential for interaction between individuals of the same or different groups. Although evenness is frequently used in research (the dissimilarity index is another measure of the same dimension), it may be less theoretically compelling for health outcomes than the exposure dimension.[44] We found that cities with higher isolation had higher black VPT birth rates, but cities with higher unevenness had lower black and white VPT birth rates. For both white and black people, there was less city-to-city variation in

rates among MSAs with highest segregation in either evenness or isolation.

Findings of paradoxically low rates of pregnancy outcomes among Hispanic women have been consistently noted.[45,46] We found that U.S.-born Hispanic mothers had higher rates of VPT birth than immigrant Hispanic women, although Hispanic people overall have an inter-city distribution that is closer to white women than black women. If immigrants are more likely to be without a high school degree, this healthy immigrant effect may explain the Hispanic advantage over white women without a high school degree. However, as seen with black women, the protective effect of education is weaker for Hispanic women than it is for white women.

Neither the persistence of disparity in mean risk nor the heterogeneity of variation after the adjustments reported in this article should be seen as immutable. Rather, they are as yet unexplained clues that open opportunities for improved understanding of and intervention on excess VPT birth. Notably, this analysis suggests an interaction between race and factors associated with MSAs. The moderate amount of correlation of MSA rates among races suggests that what is a "bad" city for one group is not necessarily bad for all, and some factor or group of factors cause great variation in risk for black women while having almost no effect (in the aggregate at least) on white women.

Limitations

The cross-sectional use of vital statistics data to understand the social or environmental experience of mothers is limited in many regards. Residence is recorded only for the point at time of delivery, but does not necessarily represent the residential environment either preconceptionally or perinatally. Additionally, place of residence is only reported by NCHS when the place has a population in excess of 100,000, thus limiting inference regarding smaller metropolitan, micropolitan, or rural areas. However our requirement that there be at least 1,000 births to a given group in an area would likely have excluded all such smaller areas had they been available. Vital statistics data are also limited by measurement error not only of gestational age, but also of maternal residence and maternal characteristics.

CONCLUSIONS

This analysis demonstrates that rates of VPT birth vary not only among races, but also by city of residence for black women as compared with white women. Explanations for racial disparities in VPT birth may include determinants that are ubiquitous across cities and that vary by city. The apparent enhanced sensitivity to location of maternal residence among black women suggests a possible interaction between race and characteristics of MSAs, such as degree of segregation.

This observation raises opportunities and challenges for further research focused on understanding and eventually eliminating racial disparities in preterm birth. One implication is that future analyses comparing rates across MSAs must be wary of statistical assumptions in their model for homogeneity of variance. Identification of factors that explain the wide variation in black MSA rates could illuminate determinants for excess VPT birth, as well as opportunities for intervention. Disparities should not be conceived of as simply a shift in the mean of a distribution, but possibly also involving interaction with environmental characteristics, resulting in a change in variation around the mean.

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APPENDIX 2

The following manuscript was modified from Chapters 1, 2 and 3, and reviews the literature for biological and social explanations for racial disparities in very preterm birth. Although the full manuscript is not included here, the URL below allows free access to a PDF of the final published version from Oxford University Press.

Kramer MR, Hogue CR. *What Causes Racial Disparities in Very Preterm Birth? A Biosocial Perspective.* Epidemiologic Reviews 2009; doi: 10.1093/ajerev/mxp003

URL TO PDF:

http://epirev.oxfordjournals.org/cgi/reprint/mxp003?ijkey=KwLtQkwCeIsBKJN&keytype=ref

APPENDIX 3

The following manuscript was modified from Chapter 2, and reviews the literature for the health effects of residential segregation. Although the full manuscript is not included here, the URL below allows free access to a PDF of the final published version from Oxford University Press.

Kramer MR, Hogue CR. *Is Segregation Bad for Your Health?* Epidemiologic Reviews 2009; doi: 10.1093/epirev/mxp001

URL TO PDF:

http://epirev.oxfordjournals.org/cgi/reprint/mxp001?ijkey=zC76kevasV12iVz&keytype=ref

APPENDIX 4. SUPPLEMENTAL TABLES FOR CHAPTER 4

Below are supplemental results tables from the manuscript titled, "Measures matter: validating new indices of residential racial segregation for population health research," which is in Chapter 4. These tables present the full range of neighborhood scales (500m, 1000m, 2000m, 4000m, and tract-derived indices), as well as results from sensitivity analyses with subsets of MSA's (to match the social capital and BRFSS samples) and for comparisons to other tract-derived measures of centralization, concentration, and spatial proximity.

Appendix 4 - 1 Descriptive statistics of segregation indices and mediating pathway variables by metropolitan area population size

		TOTAL (N=231)		BY POPULATION SIZE <500,000 (N=131)		500k- 1 million (N=39)		>1 million (N=61)		
		Mean	Std.Dev.	Mean	Std.Dev.	Mean	Std.Dev.	Mean	Std.Dev.	p-value
Segregation Indices (N=231 MSA's)										
Dissimilarity	Tract	0.55	0.12	0.51	0.11	0.57	0.11	0.61	0.12	<0.001
	500 m	0.65	0.10	0.64	0.09	0.66	0.11	0.68	0.10	0.008
	1000 m	0.61	0.11	0.59	0.10	0.62	0.11	0.65	0.11	0.001
	2000 m	0.57	0.11	0.54	0.11	0.58	0.12	0.61	0.11	<0.001
	4000 m	0.51	0.12	0.48	0.11	0.54	0.12	0.56	0.11	<0.001
Isolation	Tract	0.41	0.18	0.36	0.17	0.41	0.18	0.51	0.18	<0.001
	500 m	0.49	0.19	0.46	0.19	0.48	0.20	0.56	0.18	0.005
	1000 m	0.46	0.19	0.42	0.19	0.45	0.19	0.53	0.19	<0.001
	2000 m	0.41	0.19	0.37	0.18	0.41	0.19	0.49	0.18	0.002
	4000 m	0.36	0.18	0.32	0.18	0.36	0.18	0.44	0.18	0.000

Appendix 4 - 2 Descriptive statistics of segregation indices and mediating pathway variables by geographic region

		BY REGION								
		Northeast (N=35)		Southeast (N=111)		Midwest (N=52)		West (N=33)		
		Mean	Std.Dev.	Mean	Std.Dev.	Mean	Std.Dev.	Mean	Std.Dev.	p-value
Dissimilarity	Tract	0.63	0.09	0.52	0.10	0.61	0.12	0.45	0.10	<0.001
	500 m	0.71	0.07	0.65	0.08	0.69	0.10	0.53	0.08	<0.001
	1000 m	0.68	0.07	0.61	0.09	0.65	0.11	0.49	0.09	<0.001
	2000 m	0.64	0.08	0.55	0.09	0.61	0.12	0.45	0.10	<0.001
	4000 m	0.59	0.08	0.49	0.10	0.57	0.13	0.41	0.10	<0.001
Isolation	Tract	0.41	0.19	0.46	0.15	0.41	0.19	0.23	0.15	<0.001
	500 m	0.47	0.18	0.58	0.15	0.48	0.18	0.26	0.16	<0.001
	1000 m	0.43	0.18	0.54	0.15	0.44	0.19	0.24	0.15	<0.001
	2000 m	0.39	0.18	0.48	0.15	0.40	0.19	0.21	0.15	<0.001
	4000 m	0.32	0.17	0.43	0.16	0.34	0.19	0.19	0.14	<0.001

Appendix 4 - 3 Variation in health mediator variables explained by segregation indices: Individual socioeconomic status

			% Black adults no high school			Black poverty rate			% White adults no high school			White poverty rate		
			R^2	β^c	p-value	R^2	β^c	p-value	R^2	β^c	p-value	R^2	β^c	p-value
M1[a]		Base Model R^2	0.28			0.22			0.26			0.25		
M2[b]	Dissimilarity	Tract	0.37	2.96	0.000	0.31	2.60	0.000	0.28	0.78	0.021	0.25	-0.11	0.607
		500 m	0.47	4.06	0.000	0.34	2.89	0.000	0.34	1.56	0.000	0.25	0.05	0.808
		1000 m	0.45	3.82	0.000	0.33	2.77	0.000	0.32	1.41	0.000	0.25	-0.02	0.923
		2000 m	0.41	3.33	0.000	0.32	2.56	0.000	0.31	1.24	0.000	0.25	-0.09	0.654
		4000 m	0.37	2.81	0.000	0.30	2.26	0.000	0.30	1.11	0.000	0.25	-0.17	0.363
	Isolation	Tract	0.37	2.77	0.000	0.25	1.40	0.003	0.26	0.20	0.530	0.26	-0.33	0.092
		500 m	0.42	3.59	0.000	0.26	1.73	0.000	0.27	0.67	0.047	0.25	-0.21	0.317
		1000 m	0.40	3.39	0.000	0.26	1.63	0.001	0.27	0.55	0.096	0.25	-0.26	0.196
		2000 m	0.39	3.10	0.000	0.25	1.51	0.002	0.26	0.41	0.214	0.26	-0.33	0.096
		4000 m	0.36	2.72	0.000	0.24	1.29	0.007	0.26	0.29	0.365	0.26	-0.38	0.052

a. M1 models include the pathway variable as dependent variable and three dummy variables for four regions and two dummy variables for three MSA sizes as independent variables

b. M2 models include all variables in M1 models plus the indicated segregation index as independent variables. The difference in R^2 between M1 and M2 models is a rough indicator of additional model fit attributable to inclusion of metropolitan level segregation

c. Beta coefficients represent the change in the health mediating variable for each 1 standard deviation change in segregation index, conditional on geographic region and population size

Appendix 4 - 4 Variation in health mediator variables explained by segregation indices: Area socioeconomic status/environment

			Black:White ratio of poverty rate			%Poor children in low income tracts (Black)			%Poor children in low income tracts (White)			Murder rate (per 100,000 pop)		
			R^2	β^c	p-value	R^2	β^c	p-value	R^2	β^c	p-value	R^2	β^c	p-value
M1 [a]		Base Model R^2	0.26			0.34			0.21			0.17		
M2 [b]														
	Dissimilarity	Tract	0.37	0.40	0.000	0.60	10.37	0.000	0.21	-0.04	0.962	0.25	1.31	0.000
		500 m	0.37	0.38	0.000	0.46	6.91	0.000	0.24	-2.50	0.003	0.27	1.43	0.000
		1000 m	0.37	0.39	0.000	0.48	7.39	0.000	0.23	-2.24	0.008	0.27	1.39	0.000
		2000 m	0.37	0.38	0.000	0.50	7.85	0.000	0.22	-1.84	0.029	0.25	1.26	0.000
		4000 m	0.37	0.37	0.000	0.51	8.11	0.000	0.22	-1.49	0.075	0.23	1.11	0.000
	Isolation	Tract	0.33	0.32	0.000	0.41	5.65	0.000	0.22	-1.22	0.156	0.43	2.28	0.000
		500 m	0.32	0.31	0.000	0.37	4.38	0.001	0.23	-2.23	0.012	0.42	2.33	0.000
		1000 m	0.33	0.31	0.000	0.38	4.46	0.000	0.23	-2.08	0.018	0.43	2.34	0.000
		2000 m	0.33	0.32	0.000	0.38	4.41	0.000	0.23	-1.96	0.023	0.44	2.34	0.000
		4000 m	0.33	0.30	0.000	0.38	3.92	0.001	0.23	-1.90	0.025	0.46	2.35	0.000

a. M1 models include the pathway variable as dependent variable and three dummy variables for four regions and two dummy variables for three MSA sizes as independent variables

b. M2 models include all variables in M1 models plus the indicated segregation index as independent variables. The difference in R^2 between M1 and M2 models is a rough indicator of additional model fit attributable to inclusion of metropolitan level segregation

c. Beta coefficients represent the change in the health mediating variable for each 1 standard deviation change in segregation index, conditional on geographic region and population size

Appendix 4 - 5 Variation in health mediator variables explained by segregation indices: Social capital

			Social Trust			Inter-racial trust		
			R^2	β^c	p-value	R^2	β^c	p-value
M1[a]		Base Model R^2	0.04			0.25		
M2[b]	Dissimilarity	Tract	0.10	-0.05	0.128	0.27	-0.03	0.216
		500 m	0.05	-0.03	0.291	0.25	-0.02	0.359
		1000 m	0.04	-0.03	0.341	0.24	-0.02	0.421
		2000 m	0.03	-0.02	0.471	0.23	-0.01	0.535
		4000 m	0.02	-0.02	0.604	0.22	-0.01	0.815
	Isolation	Tract	0.29	-0.07	0.006	0.41	-0.04	0.012
		500 m	0.23	-0.07	0.017	0.39	-0.05	0.018
		1000 m	0.23	-0.07	0.015	0.40	-0.04	0.015
		2000 m	0.25	-0.06	0.012	0.41	-0.04	0.012
		4000 m	0.26	-0.06	0.010	0.41	-0.04	0.011

Note: N=30 MSA's

a. M1 models include the pathway variable as dependent variable and three dummy variables for four regions and two dummy variables for three MSA sizes as independent variables

b. M2 models include all variables in M1 models plus the indicated segregation index as independent variables. The difference in R2 between M1 and M2 models is a rough indicator of additional model fit attributable to inclusion of metropolitan level segregation

c. Beta coefficients represent the change in the health mediating variable for each 1 standard deviation change in segregation index, conditional on geographic region and population size

Appendix 4 - 6 Variation in health mediator variables explained by segregation indices: Individual behaviors

			% Black adults obese			% White adults obese			% Black adults current smoker			% White adults current smoker		
			R^2	β^c	p-value	R^2	β^c	p-value	R^2	β^c	p-value	R^2	β^c	p-value
M1[a]		Base Model R^2	0.16			0.28			0.26			0.20		
M2[b]	Dissimilarity	Tract	0.15	0.00	0.785	0.28	0.00	0.413	0.26	-0.01	0.397	0.22	0.01	0.119
		500 m	0.18	0.02	0.110	0.28	0.00	0.440	0.26	-0.01	0.325	0.21	0.01	0.185
		1000 m	0.17	0.01	0.206	0.28	0.00	0.418	0.26	-0.01	0.321	0.21	0.01	0.135
		2000 m	0.16	0.01	0.297	0.28	0.00	0.383	0.26	-0.01	0.362	0.21	0.01	0.124
		4000 m	0.16	0.01	0.376	0.29	0.01	0.267	0.25	-0.01	0.573	0.21	0.01	0.165
	Isolation	Tract	0.15	0.00	0.846	0.27	0.00	0.756	0.26	-0.01	0.293	0.19	0.00	0.869
		500 m	0.16	0.01	0.367	0.27	0.00	0.701	0.27	-0.01	0.226	0.19	0.00	0.758
		1000 m	0.16	0.01	0.499	0.27	0.00	0.657	0.27	-0.01	0.227	0.19	0.00	0.863
		2000 m	0.15	0.00	0.654	0.27	0.00	0.607	0.27	-0.01	0.238	0.19	0.00	0.970
		4000 m	0.15	0.00	0.774	0.28	0.00	0.558	0.27	-0.01	0.252	0.19	0.00	0.714

Note: N=72 MSA's

a. M1 models include the pathway variable as dependent variable and three dummy variables for four regions and two dummy variables for three MSA sizes as independent variables

b. M2 models include all variables in M1 models plus the indicated segregation index as independent variables. The difference in R^2 between M1 and M2 models is a rough indicator of additional model fit attributable to inclusion of metropolitan level segregation

c. Beta coefficients represent the change in the health mediating variable for each 1 standard deviation change in segregation index, conditional on geographic region and population size

Appendix 4 - 7 Variation in health mediating variables explained by joint adjustment for isolation and dissimilarity indices: Individual socioeconomic status

	M2 R^2	Iso-500m: .42, Diss-500m: .47			Iso-500m: .26, Diss-500m: .34			Iso-500m: .27, Diss-500m: .34			Iso-500m: ns, Diss-500m: ns		
		% Black adults no high school			Black poverty rate			% White adults no high school			White poverty rate		
		R^2	β	p-value	R^2	β	p-value	R^2	β	p-value	R^2	β	p-value
Dissimilarity	Tract	0.42	1.28	0.04	0.31	2.40	0.00	0.27	0.59	0.15	0.25	0.02	0.93
	500 m	0.48	3.21	0.00	0.34	3.26	0.00	0.34	2.08	0.00	0.25	0.33	0.21
	1000 m	0.46	2.75	0.00	0.33	3.02	0.00	0.32	1.79	0.00	0.25	0.20	0.44
	2000 m	0.44	1.99	0.00	0.32	2.51	0.00	0.31	1.37	0.00	0.25	0.05	0.83
	4000 m	0.43	1.42	0.01	0.30	1.95	0.00	0.30	1.09	0.00	0.25	-0.10	0.66
Isolation	Tract	0.47	0.28	0.64	0.35	-0.76	0.19	0.37	-1.34	0.00	0.26	-0.61	0.02
	500 m	0.48	1.31	0.04	0.34	-0.58	0.35	0.34	-0.80	0.06	0.25	-0.44	0.11
	1000 m	0.48	1.07	0.09	0.35	-0.63	0.30	0.35	-0.94	0.03	0.26	-0.53	0.05
	2000 m	0.47	0.73	0.23	0.35	-0.68	0.25	0.35	-1.08	0.01	0.26	-0.63	0.02
	4000 m	0.47	0.41	0.47	0.35	-0.73	0.19	0.35	-1.04	0.01	0.27	-0.65	0.01

Note: In each model the health mediating variable is the dependent variable. All results for Dissimilarity indices represent the R2 for that index controlling for Isolation 500m; All results for Isolation indices represent the R2 for that index controlling for Dissimilarity 500m. All models are also adjusted for geographic region and population size.

Appendix 4 - 8 Variation in health mediating variables explained by joint adjustment for isolation and dissimilarity indices: Area socioeconomic environment

	M2 R^2	Iso-500m: .32, Diss-500m: .37			Iso-500m: .37, Diss-500m: .46			Iso-500m: .23, Diss-500m: .24			Iso-500m: .42, Diss-500m: .27		
		Black:White ratio of poverty rate			%Poor children in low income tracts (Black)			%Poor children in low income tracts (White)			Murder rate (per 100,000 pop)		
		R^2	β	p-value	R^2	β	p-value	R^2	β	p-value	R^2	β	p-value
Dissimilarity	Tract	0.37	0.32	0.00	0.63	13.89	0.00	0.24	1.91	0.08	0.42	-0.21	0.50
	500 m	0.37	0.34	0.00	0.48	9.74	0.00	0.24	-1.95	0.09	0.42	-0.40	0.23
	1000 m	0.37	0.35	0.00	0.49	10.60	0.00	0.23	-1.47	0.20	0.42	-0.46	0.17
	2000 m	0.37	0.32	0.00	0.51	10.48	0.00	0.23	-0.86	0.42	0.42	-0.42	0.18
	4000 m	0.37	0.30	0.00	0.52	9.75	0.00	0.23	-0.52	0.60	0.42	-0.30	0.29
Isolation	Tract	0.38	0.12	0.12	0.46	1.16	0.46	0.24	0.65	0.55	0.43	2.45	0.00
	500 m	0.37	0.07	0.42	0.48	-4.07	0.03	0.24	-0.85	0.48	0.42	2.64	0.00
	1000 m	0.37	0.09	0.29	0.47	-3.11	0.08	0.24	-0.64	0.58	0.43	2.67	0.00
	2000 m	0.37	0.11	0.17	0.47	-2.05	0.21	0.24	-0.53	0.63	0.44	2.62	0.00
	4000 m	0.38	0.11	0.13	0.46	-1.44	0.32	0.24	-0.61	0.56	0.46	2.49	0.00

Note: In each model the health mediating variable is the dependent variable. All results for Dissimilarity indices represent the R2 for that index controlling for Isolation 500m; All results for Isolation indices represent the R2 for that index controlling for Dissimilarity 500m. All models are also adjusted for geographic region and population size.

Appendix 4 - 9 Variation in health mediating variables explained by joint adjustment for isolation and dissimilarity indices: Social capital

		M2 R^2	Iso-500m: .23, Diss-500m: ns			Iso-500m: 0.39, Diss-500m: ns		
			Social Trust			Inter-racial trust		
		R^2	β	p-value	R^2	β	p-value
Dissimilarity	Tract	0.20	0.02	0.72	0.38	0.02	0.48
	500 m	0.25	0.05	0.24	0.41	0.04	0.19
	1000 m	0.25	0.05	0.21	0.42	0.04	0.16
	2000 m	0.24	0.04	0.25	0.41	0.03	0.23
	4000 m	0.22	0.03	0.44	0.40	0.02	0.29
Isolation	Tract	0.35	-0.12	0.00	0.46	-0.07	0.00
	500 m	0.25	-0.10	0.01	0.41	-0.07	0.01
	1000 m	0.26	-0.10	0.01	0.43	-0.07	0.01
	2000 m	0.27	-0.10	0.01	0.44	-0.07	0.01
	4000 m	0.27	-0.09	0.01	0.43	-0.06	0.01

Note: In each model the health mediating variable is the dependent variable. All results for Dissimilarity indices represent the R2 for that index controlling for Isolation 500m; All results for Isolation indices represent the R2 for that index controlling for Dissimilarity 500m. All models are also adjusted for geographic region and population size.

Appendix 4 - 10 Variation in health mediating variables explained by joint adjustment for isolation and dissimilarity indices: Individual behaviors

	M2 R^2	Iso-500m: ns, Diss-500m: ns			Iso-500m: ns, D500: ns			Iso-500m: ns, Diss-500m: ns			Iso-500m: ns, Diss-500m: ns		
		% Black adults obese			% White adults obese			% Black adults current smoker			% White adults current smoker		
		R^2	β	p-value	R^2	β	p-value	R^2	β	p-value	R^2	β	p-value
Dissimilarity	Tract	0.15	-0.01	0.63	0.29	0.01	0.14	0.26	0.00	0.98	0.22	0.01	0.06
	500 m	0.17	0.02	0.17	0.29	0.01	0.11	0.26	0.00	0.90	0.21	0.01	0.10
	1000 m	0.16	0.01	0.38	0.29	0.01	0.10	0.26	0.00	0.88	0.22	0.01	0.06
	2000 m	0.15	0.01	0.56	0.29	0.01	0.12	0.26	0.00	0.91	0.22	0.01	0.07
	4000 m	0.15	0.01	0.67	0.29	0.01	0.09	0.26	0.00	0.82	0.20	0.01	0.13
Isolation	Tract	0.19	-0.02	0.17	0.28	-0.01	0.21	0.25	-0.01	0.62	0.21	-0.01	0.26
	500 m	0.17	-0.01	0.68	0.29	-0.01	0.15	0.26	-0.01	0.48	0.21	-0.01	0.31
	1000 m	0.18	-0.01	0.48	0.29	-0.01	0.14	0.26	-0.01	0.48	0.21	-0.01	0.25
	2000 m	0.18	-0.01	0.34	0.29	-0.01	0.13	0.26	-0.01	0.50	0.22	-0.01	0.17
	4000 m	0.18	-0.01	0.29	0.29	-0.01	0.14	0.26	-0.01	0.52	0.23	-0.01	0.09

Note: In each model the health mediating variable is the dependent variable. All results for Dissimilarity indices represent the R2 for that index controlling for Isolation 500m; All results for Isolation indices represent the R2 for that index controlling for Dissimilarity 500m. All models are also adjusted for geographic region and population size.

Appendix 4 - 11 Variation in health mediating variables explained by other tract-based measures of concentration, centralization and clustering segregation dimensions

	Absolute centralization index[a]			Relative concentration index[b]			Spatial proximity index[c]		
	R^2	β	p-value	R^2	β	p-value	R^2	β	p-value
Individual socioeconomic status (N=231 MSA's)									
%Black adults <HS education	0.28	-0.65	0.14	0.28	-0.46	0.35	0.32	13.08	0.00
%White adults <HS education	0.26	0.01	0.96	0.27	0.61	0.04	0.26	1.36	0.53
%Black poverty rate	0.27	1.50	0.00	0.27	1.71	0.00	0.24	7.53	0.02
%White poverty rate	0.28	0.52	0.00	0.26	0.31	0.09	0.25	-1.98	0.13
Area socioeconomic status/environment									
Black:White ratio of poverty rate	0.25	-0.01	0.86	0.26	0.10	0.09	0.32	1.99	0.00
%Poor children in low income tracts (Black)	0.39	3.99	0.00	0.45	6.03	0.00	0.41	33.50	0.00
%Poor children in low income tracts (White)	0.23	1.93	0.01	0.22	1.28	0.11	0.21	-5.03	0.38
Murder rate (per 100,000 pop)	0.17	0.28	0.20	0.16	0.08	0.75	0.37	12.85	0.00
Social capital (N=30 MSA's)									
General social trust	0.00	0.01	0.75	0.06	0.05	0.24	0.25	-0.29	0.01
Inter-racial trust									
Individual behaviors (N=72 MSA's)									
% Black adults obese	0.15	-0.01	0.61	0.15	0.00	0.82	0.15	0.00	0.97
% White adults obese	0.33	0.01	0.02	0.28	0.01	0.37	0.28	-0.02	0.33
% Black adults current smoker	0.26	0.01	0.31	0.26	0.01	0.31	0.27	-0.05	0.26
% White adults current smoker	0.20	0.01	0.21	0.19	0.00	0.67	0.19	-0.01	0.68

a. Absolute centralization index measures the centralization dimension of segregation. It ranges from -1 to 1

b. Relative concentration index measures the concentration dimension of segregation. It ranges from -1 to 1

c. Spatial proximity index measures the clustering dimension of segregation. It equals 1 when there is no differential clustering between two groups; when differential clustering it is greater than 1

Note: See Massey & Denton, 1988(409) for further description of these indices. Indices calculated by US Census Bureau(488)

Appendix 4 - 12 Sensitivity analysis restricted to 30 MSA's with social capital measures: Individual socioeconomic status

		% Black adults no high school			Black poverty rate			% White adults no high school			White poverty rate		
		R^2	β	p-value	R^2	β	p-value	R^2	β	p-value	R^2	β	p-value
Dissimilarity	Tract	0.29	0.10	0.94	0.34	1.01	0.49	0.44	-0.11	0.91	0.46	0.54	0.31
	500 m	0.30	0.56	0.69	0.34	1.01	0.50	0.44	-0.09	0.93	0.45	0.44	0.41
	1000 m	0.30	0.40	0.77	0.34	0.97	0.52	0.44	-0.21	0.84	0.44	0.37	0.49
	2000 m	0.29	-0.08	0.96	0.34	1.13	0.45	0.44	-0.34	0.75	0.44	0.31	0.57
	4000 m	0.30	-0.54	0.70	0.35	1.45	0.33	0.44	-0.29	0.78	0.44	0.24	0.67
Isolation	Tract	0.36	1.75	0.12	0.33	-0.24	0.85	0.44	0.32	0.71	0.44	0.24	0.60
	500 m	0.39	2.26	0.07	0.33	-0.47	0.73	0.44	0.41	0.67	0.44	0.20	0.70
	1000 m	0.38	2.09	0.08	0.33	-0.48	0.72	0.44	0.39	0.68	0.44	0.18	0.72
	2000 m	0.37	1.88	0.10	0.33	-0.46	0.72	0.44	0.37	0.67	0.43	0.15	0.75
	4000 m	0.36	1.57	0.13	0.33	-0.52	0.65	0.44	0.35	0.66	0.43	0.09	0.84

Appendix 4 - 13 Sensitivity analysis restricted to 30 MSA's with social capital measures: Area socioeconomic environment

		Black:White ratio of poverty rate			%Poor children in low income tracts (Black)			%Poor children in low income tracts (White)			Murder rate (per 100,000 pop)		
		R^2	β	p-value	R^2	β	p-value	R^2	β	p-value	R^2	β	p-value
Dissimilarity	Tract	0.40	-0.12	0.60	0.67	0.44	0.93	0.16	2.89	0.38	0.28	3.25	0.02
	500 m	0.40	-0.08	0.73	0.67	-0.94	0.84	0.14	1.35	0.68	0.28	3.30	0.02
	1000 m	0.40	-0.06	0.79	0.67	-0.57	0.90	0.14	1.35	0.68	0.27	3.18	0.02
	2000 m	0.39	-0.01	0.98	0.67	-0.78	0.87	0.14	1.66	0.62	0.25	3.21	0.03
	4000 m	0.40	0.08	0.73	0.68	-3.19	0.50	0.14	1.66	0.62	0.20	2.84	0.07
Isolation	Tract	0.42	-0.19	0.33	0.68	2.10	0.59	0.13	0.15	0.96	0.41	3.12	0.00
	500 m	0.43	-0.23	0.28	0.68	2.76	0.53	0.13	-0.07	0.98	0.40	3.43	0.00
	1000 m	0.42	-0.22	0.29	0.68	2.79	0.51	0.13	0.06	0.98	0.42	3.39	0.00
	2000 m	0.42	-0.18	0.35	0.68	2.14	0.59	0.13	-0.06	0.98	0.44	3.35	0.00
	4000 m	0.41	-0.15	0.41	0.67	1.02	0.78	0.13	-0.25	0.92	0.47	3.18	0.00

Appendix 4 - 14 Sensitivity analysis restricted to 72 MSA's with individual behavioral variables: Individual socioeconomic status

		% Black adults no high school			Black poverty rate			% White adults no high school			White poverty rate		
		R^2	β	p-value	R^2	β	p-value	R^2	β	p-value	R^2	β	p-value
Dissimilarity	Tract	0.37	1.63	0.03	0.24	2.02	0.02	0.32	1.27	0.02	0.15	0.50	0.17
	500 m	0.42	2.13	0.00	0.27	2.26	0.00	0.35	1.49	0.00	0.16	0.54	0.11
	1000 m	0.41	2.01	0.00	0.26	2.06	0.01	0.35	1.44	0.01	0.16	0.48	0.15
	2000 m	0.39	1.71	0.01	0.25	1.98	0.01	0.34	1.40	0.01	0.15	0.47	0.16
	4000 m	0.36	1.31	0.06	0.24	1.86	0.02	0.34	1.36	0.01	0.14	0.36	0.29
Isolation	Tract	0.45	2.38	0.00	0.17	0.25	0.75	0.26	0.06	0.91	0.15	-0.41	0.21
	500 m	0.47	2.71	0.00	0.17	0.33	0.68	0.26	0.24	0.65	0.14	-0.35	0.31
	1000 m	0.47	2.61	0.00	0.17	0.25	0.76	0.26	0.14	0.79	0.15	-0.41	0.21
	2000 m	0.46	2.43	0.00	0.17	0.14	0.85	0.26	0.02	0.97	0.16	-0.47	0.14
	4000 m	0.44	2.15	0.00	0.17	-0.01	0.99	0.26	-0.08	0.87	0.16	-0.51	0.10

Appendix 4 - 15 Sensitivity analysis restricted to 72 MSA's with individual behavioral variables: Area socioeconomic environment

		Black:White ratio of poverty rate			%Poor children in low income tracts (Black)			%Poor children in low income tracts (White)			Murder rate (per 100,000 pop)		
		R^2	β	p-value	R^2	β	p-value	R^2	β	p-value	R^2	β	p-value
Dissimilarity	Tract	0.38	0.17	0.19	0.71	9.33	0.00	0.23	-2.55	0.15	0.35	2.56	0.00
	500 m	0.39	0.18	0.12	0.71	8.76	0.00	0.29	-4.32	0.01	0.33	2.23	0.00
	1000 m	0.39	0.19	0.11	0.72	9.58	0.00	0.28	-4.01	0.01	0.32	2.14	0.00
	2000 m	0.39	0.20	0.09	0.72	9.62	0.00	0.26	-3.61	0.02	0.31	2.09	0.00
	4000 m	0.41	0.24	0.04	0.72	9.41	0.00	0.25	-3.28	0.04	0.29	1.94	0.00
Isolation	Tract	0.39	0.19	0.10	0.75	11.51	0.00	0.26	-3.53	0.02	0.48	2.92	0.00
	500 m	0.39	0.17	0.17	0.75	12.36	0.00	0.29	-4.41	0.01	0.44	2.88	0.00
	1000 m	0.39	0.18	0.12	0.75	12.07	0.00	0.28	-4.17	0.01	0.45	2.88	0.00
	2000 m	0.40	0.20	0.08	0.75	11.51	0.00	0.27	-3.80	0.01	0.47	2.87	0.00
	4000 m	0.40	0.20	0.06	0.74	10.42	0.00	0.26	-3.40	0.02	0.48	2.83	0.00

APPENDIX 5. SUPPLEMENTAL TABLES TO CHAPTER 5

Supplemental table A5-1 reports results of multilevel (non-Bayesian) models fit with isolation and dissimilarity indices using different specification of neighborhood size. Isolation at the 500m-bandwidth size was chosen for the national study because of its slightly better model fit (as demonstrated with difference in deviance between model with and without segregation index) than any other specification. It should be noted that for moderately preterm birth, dissimilarity using a 500m-bandwidth neighborhood definition had the best fit, although in models which jointly consider isolation and dissimilarity, it was isolation which had the independent effect (not shown here).

Appendix 5- 1 Comparison of segregation indices for very preterm birth risk in black women, 2000-2002

		VPT					MPT				
		OR	95% CI		Difference in deviance[a]			**OR**	95% CI		Difference in deviance
	D500	**1.10**	1.06	1.15	173		D500	**1.07**	1.04	1.1	379
	D2000	**1.09**	1.05	1.13	145		D2000	**1.07**	1.04	1.1	337
	D4000	**1.08**	1.03	1.12	118		D4000	**1.06**	1.03	1.09	277
	I500	**1.11**	1.06	1.16	192		I500	**1.06**	1.03	1.09	303
	I2000	**1.10**	1.05	1.14	186		I2000	**1.05**	1.02	1.09	299
	I4000	**1.09**	1.04	1.13	175		I4000	**1.05**	1.02	1.08	270
	Note: all models are multilevel (random intercept for MSA) with control for region and population size. They were fit in lmer() function in R.										
	a. Deviance is a measure of fit (smaller is better). Difference in deviance compares the deviance in models without segregation to that in models with segregation measures. Therefore *larger* differences are better fit.										

APPENDIX 6. SUPPLEMENTAL FIGURES FOR CHAPTER 7

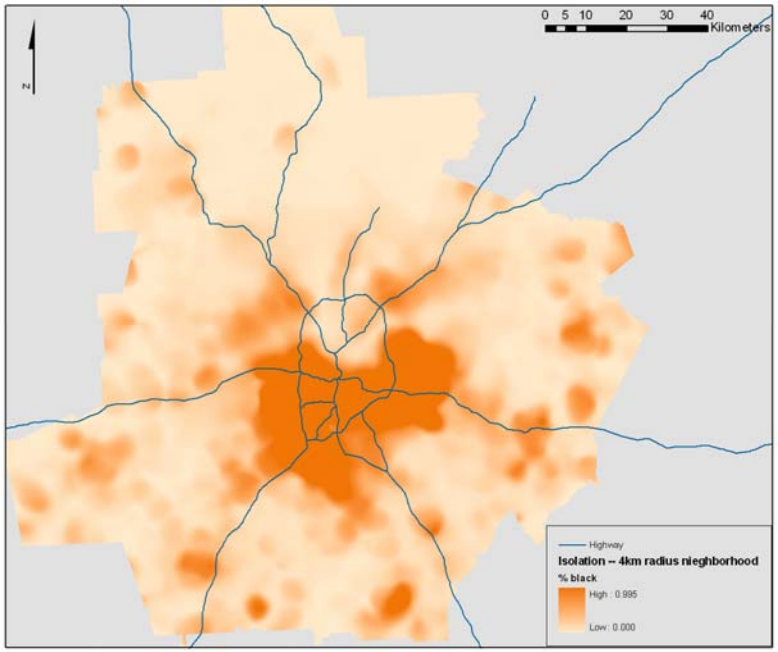
An additional research question was considered but omitted from the primary manuscript in Chapter 7. The question is whether there is measurable spatial variation in the risk for very preterm birth in black women in the Atlanta MSA.

In order to answer this question we mapped all very preterm and term births using their geocoded residence. Kernel intensity smoothing of the preterm and term births allows comparison of their spatial variation. Under the null hypothesis of spatially homogenous risk, the spatial distribution of term and preterm births arise from a common heterogeneous Poisson point process (534). Therefore conditional on the location of the observed births, the ratio between preterm and term birth intensities should be constant (532). To test this we employ Monte Carlo simulation and randomly re-label births as term or preterm, keeping the overall proportion of preterm births constant (538). Results from 999 Monte Carlo simulations therefore express the expected spatial variation in the risk due to chance alone. Areas observed to have variation in excess of this expectation are highlighted.

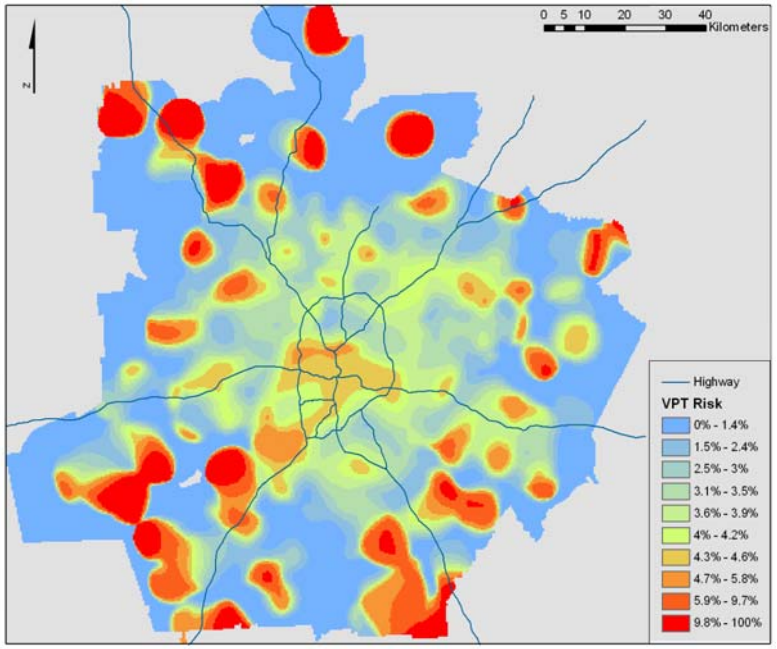
Figure Appendix 6- 1 displays the neighborhood isolation in Atlanta using the 4000m kernel bandwidth neighborhood definition. Neighborhoods with the highest proportion black are in the central-south portion of the MSA including the city of Atlanta and inner suburbs. There are a few predominantly black and many mixed race neighborhoods in the outer suburbs and northern part of the city. Figure Appendix 6- 2 is the spatially smoothed risk surface for very preterm birth among black women, and includes the highways to facilitate comparison with the first figure. Figure Appendix 6- 3 is

the identical risk surface as figure Appendix 6- 2, but with 90% confidence limit contours from the Monte Carlo simulations. The blue lines enclose areas with significantly higher risk than expected, while the yellow lines enclose areas with significantly lower risk. The diverging color scheme is centered at 3.39% which is the overall risk of very preterm birth for black women in Atlanta during the study period. In other words green areas represent average risk, blue areas are risk for black women below the Atlanta average, and red areas are higher than average risk. In some areas in the central and southern part of the metropolitan area the elevated risk appears to coincide with higher neighborhood isolation, although other high risk areas do not correlate with high racial isolation.

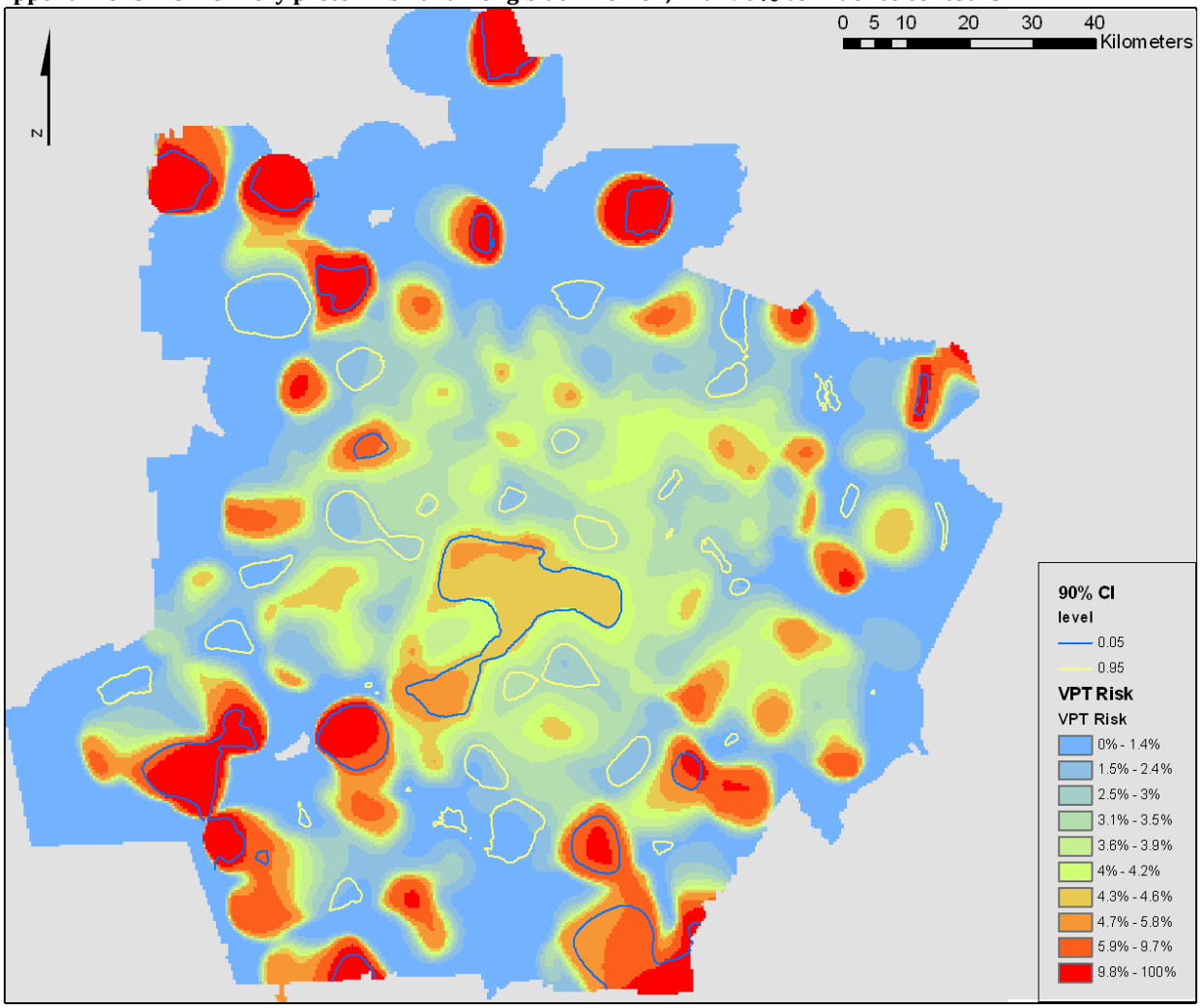
Appendix 6- 1 Neighborhood proportion black, 4000m kernel bandwidth, Atlanta, MSA, 2000



Appendix 6- 2 Risk for very preterm birth among black women, Atlanta MSA, 2000-2003



Appendix 6- 3 Risk for very preterm birth among black women, with 90% confidence contours



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