NEIGHBORHOOD-LEVEL SOCIOECONOMIC POSITION DURING EARLY PREGNANCY AND THE RISK OF GASTROSCHISIS

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ABSTRACT

Dayna Tulsi Neo: Neighborhood-level socioeconomic position during early pregnancy and the risk of gastroschisis
(Under the direction of Andrew F. Olshan)

Background: Studies have shown that pregnant women in low socioeconomic neighborhoods are at a higher risk of adverse pregnancy outcomes, including birth defects. However, few studies have explored this association with gastroschisis. Using data from the National Birth Defects Prevention Study (NBDPS), we investigated the association between neighborhood-level socioeconomic position (nSEP) during early pregnancy and the risk of gastroschisis, and evaluated whether nSEP modifies the associations between maternal age at conception and pre-pregnancy body mass index (BMI) and gastroschisis.

Methods: We analyzed data from singleton case infants diagnosed with gastroschisis and singleton non-malformed control infants delivered between 1997 and 2011. To characterize nSEP, two principal component analysis (PCA)-derived indices were constructed including the Neighborhood Deprivation Index (NDI) and a Neighborhood-level Socioeconomic Position Index (nSEPI). Maternal neighborhood was defined as the self-reported address mothers lived at the longest between one month prior to conception to the third month of pregnancy. Generalized estimating equations were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs), and relative excess risks due to interaction (RERI) were calculated to assess modification by nSEP on the additive scale.

Results: Mothers in moderate (NDI aOR: 1.25; 95% CI: 1.05, 1.49 and nSEPI aOR: 1.25; 95% CI: 1.04, 1.49) or low SEP neighborhoods (NDI aOR; 1.27; 95% CI: 1.05 1.54 and nSEPI aOR: 1.32, 95% CI: 1.09, 1.61) were more likely to deliver an infant with gastroschisis compared with mothers in high SEP neighborhoods. Residing in low SEP neighborhoods sub-additively modified the association between maternal age at conception and gastroschisis. Young mothers (< 20 years) in high SEP neighborhoods had double the risk of having an infant with gastroschisis (aOR: 6.55; 95% CI: 4.59, 9.35) compared with young mothers in low SEP neighborhoods (aOR: 3.13, 95% CI: 2.59, 3.78). However, nSEP did not modify the association between pre-pregnancy BMI and gastroschisis. Regardless of nSEP, young maternal age at conception and normal or underweight BMI were consistently associated with elevated odds of gastroschisis.

Conclusions: Future studies of nSEP should consider examining potential mechanisms through which contextual factors may influence individual-level characteristics and/or its association with gastroschisis.

This dissertation is dedicated to my parents, Chris and Eva Neo, for their unconditional love and support; and to my sister, Shina Neo, for always making me laugh in the most stressful of times and continuing to hold my hand through life.
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LIST OF ABBREVIATIONS

aPR	Adjusted prevalence ratios
aRR	Adjusted risk ratios
aOR	Adjusted odds ratios
ACS	American Community Survey
BDS	Slone Epidemiology Unit Birth Defects Study
BMI	Body mass index
CATI	Computer-assisted telephone interview
CBDMP	California Birth Defects Monitoring Program
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
DAG	Directed acyclic graph
EQI	Environmental quality index
FIPS	Federal Information Processing Standards
GEE	Generalized estimating equations
IPI	Interpregnancy interval
IRB	Institutional Review Board
NBDPS	National Birth Defects Prevention Study
NDI	Neighborhood Deprivation Index
nSEP	Neighborhood-level socioeconomic position
nSEPI	Neighborhood-level Socioeconomic Position Index
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbons

PCA	Principal component analysis
RERI	Relative Excess Risk due to Interaction
SEP	Socioeconomic Position
SGA	Small for gestational age
STI	Sexually transmitted infection
US	United States
UTI	Urinary tract infection

CHAPTER 1: INTRODUCTION AND SPECIFIC AIMS

Pregnant women residing in low socioeconomic neighborhoods are at a higher risk of experiencing adverse pregnancy outcomes.[1–6] Accumulating evidence suggests that neighborhoods contain physical, service, and social characteristics, above and beyond individual-level factors, that influence an individual's health through proposed mechanisms that involve psychosocial, behavioral, and biological factors.[7] Individuals residing in socioeconomically disadvantaged or deprived neighborhoods are more likely exposed to chronic stressors and daily difficulties through lack of access to quality resources,[8] inadequate housing quality, and lack of educational and/or employment opportunities. Neighborhood effects may also influence individual health behaviors through social norms shared amongst residents.[9] In addition, previous studies have reported that individuals living in areas of lower income and education had higher levels of inflammatory markers, independent of individual-level risk factors.[10–12] These inflammatory markers have been linked to adverse pregnancy outcomes, such as fetal growth restriction and neonatal complications.[13]

Studies examining neighborhood socioeconomic characteristics and adverse pregnancy outcomes have shown modest associations with preterm birth,[1,2] low birth weight,[14] and more recently neural tube defects[6] and orofacial clefts[3,15], independent of individual-level factors. Considering the etiology of many birth defects are unknown, examining the contextual effect of neighborhoods may provide important etiologic clues given the social and biological consequences neighborhoods exert on individuals. This dissertation seeks to examine the association between the contextual effects of neighborhood-level SEP (nSEP) and the risk of gastroschisis and its influence on the associations between well-established individual-level risk factors and gastroschisis.

Gastroschisis is an abdominal wall birth defect characterized by the herniation of intestines and other abdominal organs outside the fetal body. It occurs between the fifth and eighth gestational week[16] and is associated with increased infant morbidity[17]. Gastroschisis has significant public health relevance due to its increasing prevalence from 3.6 (1995-2005) to 4.3 (2012-2016) per 10,000 live births.[18,19] The epidemiologic pattern is unique in which it disproportionately affects mothers who are young,[20–23] have normal or low body mass index (BMI),[24–27] and are of non-Hispanic white race.[18,19,28–30] Despite these findings, the etiology remains largely unknown, indicating the need to explore other factors that may be at higher-order levels. To date, only one study has examined the association between specific nSEP domains and gastroschisis.[31] Although this study reported a modest association, after adjusting for individual factors, it was limited by exposure measurementerror and residual confounding. Solely looking at the individual level may be insufficient in understanding the complex etiology of gastroschisis. Examining higher order, or contextual, effects may provide clues into other factors that either influence individual-level characteristics or directly affect risk. Given the increasing prevalence, there is a need to expand our understanding of non-individual level risk factors and the contextual role neighborhoods may have on gastroschisis. Thus, the purpose of this dissertation project is to further understand the etiology of gastroschisis by examining the contextual influence of nSEP. The specific aims of this dissertation project are as follows:

Specific Aim #1. Estimate the association between nSEP during early pregnancy and the risk of gastroschisis, independent of individual-level characteristics. To characterize neighborhood-level socioeconomic position, principal component analysis (PCA) will be conducted to construct two neighborhood indices, Neighborhood Deprivation Index (NDI) and Neighborhood-level Socioeconomic Position Index (nSEPI), based on census socioeconomic indicators corresponding to the census tract associated with the address mothers lived at the longest during the periconceptional period. Generalized estimating equations will be used to account for potential correlation and non-independence of outcomes among mothers living in the same neighborhood. The hypothesis for this aim is that residing in low-SEP neighborhoods will be associated with increased odds of gastroschisis relative to residing in high-SEP neighborhoods.

Specific Aim #2. Examine whether nSEP modifies the association between two well-established associations including (1) maternal age at conception and gastroschisis and (2) maternal BMI and gastroschisis. The extent to which contextual factors modify the effect of individual-level characteristics on the risk of gastroschisis is unknown. This aim focuses on the interrelationships between individual-level attributes and nSEP as both likely influence maternal health, and subsequently pregnancy outcomes. Given neighborhood effects may influence maternal health behaviors, the hypothesis for this aim is that nSEP will modify the association between (1) maternal age and gastroschisis and (2) maternal BMI and gastroschisis.

Results from this dissertation project will extend current gastroschisis literature, contribute to the studies examining neighborhood-level effects on individual health, and prompt future research to explore the effect of contextual factors on other birth defects.

CHAPTER 2: BACKGROUND

2.1 Epidemiology of gastroschisis

Gastroschisis is an abdominal wall birth defect characterized by the protrusion of intestines and other abdominal organs outside the fetal body without an amniotic membrane coverage. This abdominal birth defect occurs early in gestation, between the 5th and 8th gestational week, and the etiology remains unknown.[16,32] Between 2012 and 2016, the prevalence of gastroschisis, in the United States (US), was 4.3 cases per 10,000 live births, based on data from 42 population-based state birth defects surveillance programs.[19]A previous study, using data from 14 state surveillance programs reported that the prevalence of gastroschisis increased from 3.6, in 1995 – 2005, to 4.9, in 2005 – 2012, per 10,000 live births, representing a 30% increase in prevalence.[18] Despite the relative rarity of this birth defect, the epidemiologic pattern of gastroschisis is distinct due to its inexplicably increasing prevalence worldwide and consistent association with young maternal age (< 20 years).[18,20,21,23,29,33,34] Other striking risk factors unique to gastroschisis include mothers who are normal or underweight (compared with overweight/obese)[24,26] and non-Hispanic White (compared non-Hispanic Black mothers).[18,19,28–30] In addition, gastroschisis has been observed to occur within geographic clusters, possibly indicating that environmental and sociodemographic factors may play a role in the etiology of gastroschisis.[35–37]

Gastroschisis is primarily an isolated defect and is rarely associated with genetic conditions, such as chromosomal anomalies.[21,38,39] Advances in prenatal monitoring, neonatal intensive care, parenteral nutrition, and surgical techniques have improved the survival rate to over 90%. [40–42] However, depending on the severity of the case, gastroschisis is associated with short- and long-term morbidity and medical costs. Difficulties transitioning from parenteral to enteral nutritional feedings and changes in the absorption of nutrients prompt digestive complications and feeding intolerance, resulting in consequential effects on the infant.[17] Fortunately, the prognosis of infants with gastroschisis is largely optimistic and the overall quality of life is expectedly normal.[43]

2.2 Embryology of gastroschisis

The embryologic pathogenesis of gastroschisis is unknown; however, several hypotheses have been proposed.[32,44–48] To understand these hypotheses, a summary of normal embryonic development is first described.

During the 3rd and 4th week of normal embryonic development following fertilization (~5th or 6th gestational week), the embryo is at a high risk of developmental defects as several significant events occur to prepare for organogenesis. These events include gastrulation (a process that converts the bilaminar embryo to a trilaminar embryo with three germ layers – ectoderm, mesoderm, and endoderm), neurulation (formation of neural tube and neural crest), mesoderm formation (subdivision of the mesoderm into three masses: paraxial mesoderm, intermediate mesoderm, and lateral plate mesoderm), and folding of the ventral body wall.[49] The folding process entails a downward extension of the body wall at the cranial and caudal ends to form the “fetal” position. In addition, lateral body folds draw the amniotic membrane ventrally over the embryo, with an opening that forms the umbilical ring which contains two stalks: yolk and connecting stalk. The yolk stalk contains vitelline vessels and the yolk sac,while the connecting stalk contains the allantois and umbilical vessels.[49,50] During this process, the gut tube lengthens to form the primary intestinal loop, which is attached to the yolk sac via the vitelline duct in the yolk stalk and contributes to the formation of the gastrointestinal tract. As the lateral folds continue to move ventrally toward the midline, the vitelline duct in the yolk stalk contracts and the two stalks (yolk and connecting stalks) are brought closer together, eventually merging to form the umbilical cord.[32] By the 7th week of embryonic development (~9th gestational week), the umbilical cord is fully formed and the intestines begin to normally herniate out of the embryo through the umbilical ring. This herniation allows for the proper rotation of the intestines while the abdominal cavity grows.[51] By the end of the 10th gestational week, the intestines return to the larger abdominal cavity and ultimately, the lateral body folds fuse at the midline.[32,49,50] However, closure of the ventral body wall is not well understood, impeding the progress to fully understand the embryonic pathogenesis of gastroschisis.

To date, seven hypotheses have been proposed to explain the formation of gastroschisis; though, all have some limitations.[32,44–48] The first hypothesis suggests that differentiation of the embryonic mesenchyme, the layer that gives rise to the body's connective tissue, fails to occur due to a teratogen (agent or factor that causes a birth defect).[44] However, this hypothesis fails to explain the type of teratogen involved and why the defect consistently occurs to the right of the umbilicus.[32] The second hypothesis states that a rupture of the amniotic membrane at the base of the umbilical cord during normal physiologic herniation or a delay in the umbilical ring closure causes the ventral body wall to weaken and thus, allow herniation of the bowel.[47] However, if a rupture were to occur at the base of the umbilicus, the umbilical cord would not be normal upon delivery. Yet, in most cases, gastroschisis occurs with an intact umbilical cord.[32] The third hypothesis suggests that an abnormal involution of the right umbilical vein affects the viability of the surrounding mesenchyme.[46] This hypothesis was based on earlier work on pigs, by Smith et al., claiming that the ventral body wall is supported by the umbilical veins.[52] However, current evidence shows that the umbilical veins do not support the mesenchyme of the ventral body wall.[32,53] Thus, regardless of any insults to the umbilical veins, support to the surrounding mesenchyme of the paraumbilical region would remain uninterrupted. The fourth hypothesis states that vascular disruption of the vitelline artery may lead to necrosis of the ventral body wall and subsequent herniation of the bowel.[45] Up until recently, this was the most widely accepted hypothesis given the epidemiologic evidence showing a positive association between vasoactive substances and gastroschisis.[54–56] However, this hypothesis was disputed by Feldkamp et al. because (1) it is unknown why only vessels to the right of the umbilicus are prone to infarction and (2) the vitelline vessels do not support the skin of the paraumbilical region, but rather the guttube and yolk sac. Thus, vascular disruption of the vitelline arteries would not damage the abdominal wall. Given these limitations, Feldkamp et al. proposed the fifth hypothesis, which suggests that gastroschisis is a result of defects in the folding and/or fusion of the ventral body wall.[32] Although the authors note that the intrinsic forces required for ventral wall closure, such as cell proliferation and cell migration, may be targets for teratogens, no known teratogens have been identified to specifically disrupt these processes. In addition, Stevenson et al. notes that in some cases, failure of the ventral body wall closure would entail the inability for the amnion to close over the gut and adhere to the umbilical ring. This would result in exposing the gut to the extraembryonic celomic cavity rather than just the amniotic cavity.[48] As a result, Stevenson et al. proposed the sixth hypothesis which states that failure to combine the yolk stalk (and accompanying vitelline structures) with the connecting stalk results in a second perforation of the abdominal wall separate from the umbilicus. Given the gut is normally tethered to the vitelline structures of the yolk stalk, this would result in herniation of the gut at a second location, resulting in gastroschisis. In addition, the occurrence of the gut extrusion to the right of the umbilicus is explained to be a result of a rapid ingrowth of the left lateral wall,[57] pushing the yolk stalk and attached vitelline structures to the right. However, no explanation has been proposed for why the vitelline structures fail to combine with the connecting stalk and no teratogens have been identified in relation to this hypothesis. Thus, the seventh, and most recent hypothesis, proposed by Bargy and Beaudoin et al.[58,59], suggests that gastroschisis is likely due to an amniotic rupture along the umbilical cord during normal physiologic hernia, between the 8th and 11th gestational week. However, the cause of the rupture is unclear. Overall, despite the numerous hypotheses, the embryologic pathogenesis of gastroschisis and linkage with specific risk factors remains unknown.

2.3 Risk factors of gastroschisis

2.3.1 Genetic risk factors of gastroschisis

The majority of gastroschisis cases are sporadic events; however, a few studies have observed a familial recurrence of cases,[60–62] indicating a genetic contribution to gastroschisis. An early study by Torfs et al. found that among the 127 families studied, 4.7% had a family history of gastroschisis with a sibling recurrence risk of 3.5%.[60] A recent study examining all population-based studies of familial cases observed a recurrence risk of 2.4%; though, the authors note that this is likely an underestimate due to higher-degree relatives missing in some studies.[62]

Although the possibility of shared social, lifestyle, and environmental factors among family members cannot be excluded, the genetic role in the etiology of gastroschisis is further supported by studies observing an association with chromosome abnormalities and gene polymorphisms. One study using data from 24 birth defects surveillance systems reported that 1.2% of infants with gastroschisis had chromosome abnormalities,[38] while another study reported 2% of gastroschisis infants had associated chromosomal syndromes.[39] In addition, few studies also observed an association between certain common gene variants (i.e., ICAM-1 gl214arg, NOS3 glu298asp, NPPA T2238c) and an increased risk of gastroschisis.[63,64] Furthermore, when the joint effect of maternal smoking and certain gene variants were examined, a strong interaction was observed, indicating a possible gene-environment interaction.[64] Given the rapidly increasing prevalence of gastroschisis, it is unlikely that genetics is the sole cause of this birth defect, but rather part of a multifactorial etiology involving both genetic and non-genetic factors.

2.3.2 Non-genetic risk factors of gastroschisis

The etiology of gastroschisis is unknown; however, several epidemiologic studies have examined non-genetic and genetic risk factors.

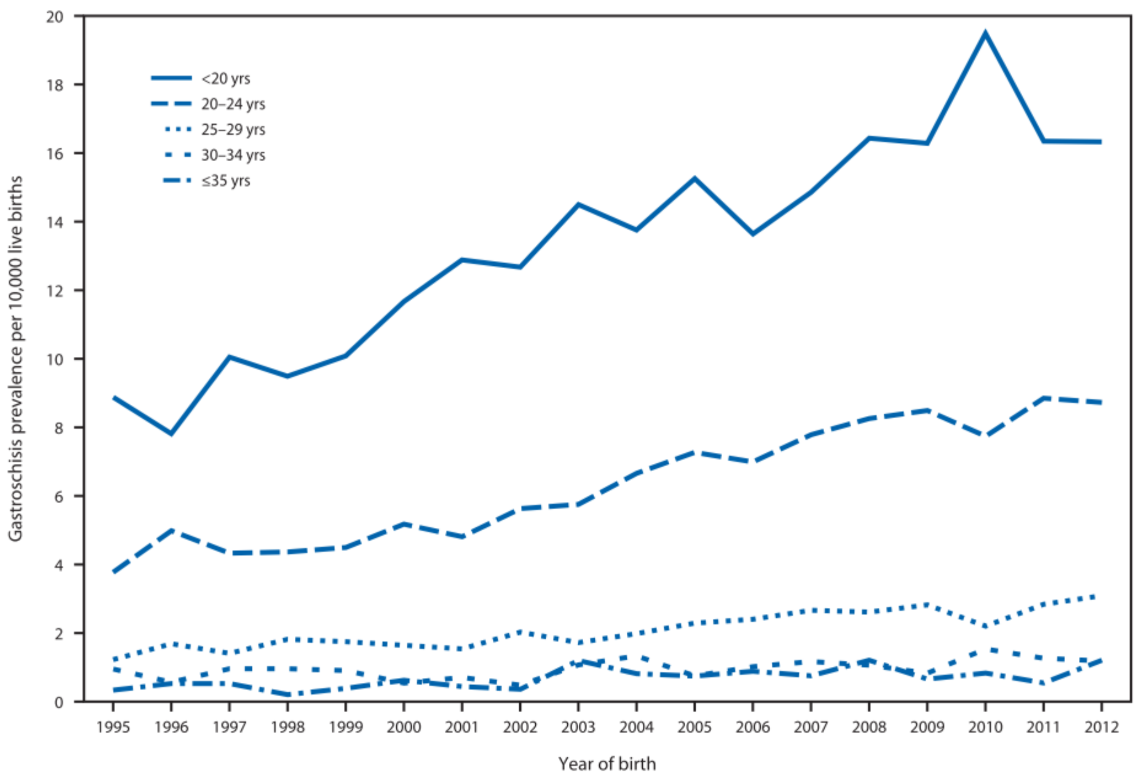
2.3.2.1 Maternal age at conception

Young maternal age at conception (< 20 years) has consistently been identified as a strong and significant risk factor for gastroschisis.[18,21,22,33,65,66] One study, utilizing data from the California state surveillance program, observed mothers ages 12-15 and 16-19 years were four (adjusted prevalence ratio [aPR]: 4.2; 95% Confidence Interval (CI): (2.5-7.0)) and three (aPR: 2.9; 95% CI: 2.1, 4.0) times the prevalence, respectively, of having an infant with gastroschisis compared with 25 – 29-year-old mothers.[67] Another study in Metropolitan Atlanta observed infants born to teenage mothers were seven times as likely to have an infant with gastroschisis compared with infants born to mothers aged 25 – 29 years (odds ratio [OR]: 7.2; 95% CI: 4.4 –

11.8).[65] Most recently, in 2012, a case-control study using data from the National Birth Defects Prevention Study (NBPDS) reported that infants born to mothers less than 20 years were six times the risk of delivering an infant with gastroschisis compared with infants born to mothers aged 25 – 29 years (aOR: 6.1; 95% CI: 4.8 – 8.0).[66]

The prevalence of gastroschisis has increased over the past couple decades. However, there is significant heterogeneity in the rates of increase, with the largest increase seen among teenage mothers (Figure 1).[18,34]

Figure 1. Gastroschisis prevalence by maternal age, 1995 – 2012, Jones et al.[18]



Between 1995 – 2005, the percentage increase in the prevalence of gastroschisis was 0.2% among mothers 35 years and older compared to an increase of 6.5% among teenage mothers.[34] One hypothesis for this association is that young mothers may be biologically immature to support a pregnancy. Given that young mothers are growing themselves and often have an inadequate diet with low micronutrient intake,[68] adolescent mothers may be competing with the developing fetus for essential vitamins and micronutrients.[69,70] With effect estimates ranging from three to seven, young maternal age may be a marker for nutritional and other biologic factors for gastroschisis.

2.3.2.2 Diet/nutritional status

The strong association between young maternal age and gastroschisis has suggested that diet and nutritional status may be a risk factor for this birth defect. However, few studies have investigated these associations. Torfs et al. conducted an age-matched case-control study of 55 gastroschisis cases using a 100-item food-frequency questionnaire administered during the three months prior to conception. An increased risk of gastroschisis was observed among mothers with low α-carotene (OR: 4.3; 95% CI: 1.9-9.8), low total glutathione (OR: 3.3; 95% CI: 1.4 – 7.6), and high nitrosamines (OR: 2.6; 95% CI: 1.3-5.4). α-carotene and glutathione are antioxidants that protect the developing fetus from reactive oxygen species; whereas, nitrosamines are carcinogenic compounds. These associations indicate that poor nutritional status is associated with an increased risk of gastroschisis.[70] Another age-matched case-control study of 91 cases examined the association between diet in the first trimester and gastroschisis. However, detailed questionnaires such as the food-frequency questionnaire were not used to assess diet. Rather, diet during the first 12 weeks of pregnancy was assessed using the question ‘How often do you typically eat a portion of (each type of food group, e.g., white meat, red meat, fruit, vegetables, and fish)?’. This analysis found that high intakes of fruits and vegetables (aOR: 0.2; 95% CI: 0.04 – 0.6) and taking at least 6 weeks of folic acid during the first trimester (aOR: 0.3; 95% CI: 0.12 – 0.8) were associated with a reduced risk of gastroschisis.[71]

Although both studies found an association between poor nutritional status and gastroschisis, an NBDPS analysis of 694 cases of gastroschisis observed null results. Feldkamp et al. used a modified Willett 58-item food frequency questionnaire and reported no associations between gastroschisis and micronutrients, macronutrients, amino acids, or fatty acids. Upon examining the nutrients in Torfs et al.'s study, this study found a weak and nonsignificant decrease in the risk of gastroschisis among mothers in the intermediate and highest tertile of α-carotene (intermediate aOR: 0.82; 95% CI: 0.66 – 1.02; highest aOR: 0.79; 95% CI: 0.63 – 1.01. The authors note, however, that the difference in food frequency questionnaires may explain the difference in study results.[72] Furthermore, as a marker for deficiency in nutritional reserves short interpregnancy intervals (IPIs) have been examined as a risk factor for gastroschisis. Using data from the NBDPS, Getz et al. found that short IPIs, defined as an interpregnancy interval of less than 12 months, were associated with an increased risk of gastroschisis (aOR: 1.7; 95% CI: 1.1 – 2.5).[73]

2.3.2.3 Maternal body mass index (BMI)

Studies have reported an inverse association between maternal body mass index (BMI) and gastroschisis, after adjusting for maternal age.[24,26,56] A previous case-control study that examined BMI using maternal self-reported pre-pregnancy height and weight, observed an ~11% decreased risk of gastroschisis for every unit increase in BMI. When BMI was assessed as a categorical variable, underweight mothers (BMI < 18.1 kg/m^2) were more likely to have an infant with gastroschisis (aOR: 3.20; 95% CI: 1.37 – 7.42), whereas, overweight mothers were less likely (aOR: 0.19; 95% CI: 0.04 – 0.83).[26] In addition, an NBDPS analysis reported that mothers of obese BMI (≥ 30 kg/m^2) had a reduced risk (aOR: 0.2; 95% CI: 0.1 – 0.3) of having an infant with gastroschisis compared with mothers of normal weight BMI.[24] Studies in the UK also observed similar associations. Based on 144 gastroschisis cases, a UK case-control study using age-matched controls also observed an inverse association with maternal weight [overweight aOR: 0.3; 95%CI: 0.2, 0.7 and underweight aOR: 2.0; 95% CI: 1.1, 3.7].[56]

This inverse association suggests a competition for nutrients or a nutrient deficit for the developing embryo among mothers of low BMI. An NBDPS study that examined the joint effects of maternal BMI and age found that young mothers with low BMI have the highest risk of gastroschisis. For example, a 15-year-old mother with a BMI of 17kg/m^2 was seven times as likely (aOR: 7.0; 95% CI: 4.2, 11.5) to have an infant with gastroschisis, compared with a 24-year-old mother with a BMI of 23 kg/m^2. This indicates that the nutrient deficit hypothesis may play a role in the etiology of gastroschisis.[27]

2.3.2.4 Maternal race/ethnicity

Several studies have examined the association between maternal race/ethnicity and gastroschisis. Compared with white, non-Hispanic mothers, studies have consistently reported that infants born to black, non-Hispanic mothers have a lower risk of gastroschisis, after adjusting for maternal age.[23,74,75] One study using data from the National Vital Statistics System found that black, non-Hispanic mothers were 0.44 (95% CI: 0.41 – 0.48) times as likely to have an infant with gastroschisis compared with white, non-Hispanic mothers.[75]

Although other studies found similar black-white disparities, differing results for Hispanicity were reported.[75,76] An NBPDS analysis observed a lower risk of gastroschisis among black, non-Hispanic mothers (aOR: 0.54; 95% CI: 0.34 – 0.85), compared with white, non-Hispanic mothers; while, infants born to mothers of Hispanic ethnicity had a slightly higher risk of gastroschisis (aOR: 1.15; 95% CI: 0.81 – 1.61) compared with the same reference group.[23] Similar results were found in a New York study using white, non-Hispanic mothers as the reference group (black, non-Hispanic aOR: 0.8; 95% CI: 0.6 – 1.2; Hispanic aOR: 1.5; 95% CI: 1.1 – 2.0).[77] However, one study using data from the Florida Birth Defects Registry (1998 – 2003), reported that after adjusting for maternal age, both black, non- Hispanic (aPR: 0.19; 95% CI: 0.13, 0.26) and Hispanic mothers (aPR: 0.60; 95% CI: 0.43, 0.83) had a lower risk of having a gastroschisis infant, compared with white, non-Hispanic mothers.[76] Similar results were reported in a population-based study of US live births from 2005 – 2013 (black, non-Hispanic aRR: 0.44, 95%CI: 0.41 – 0.48; Hispanic aRR: 0.69, 95% CI: 0.64, 0.73).[75] Given differences in study results, the risk of gastroschisis among Hispanic women is uncertain; though, it can be concluded that black, non-Hispanic mothers have a lower risk of having a gastroschisis infant compared with white, non-Hispanic mothers.

2.3.2.5 Smoking/alcohol/ illicit and recreational drug use

A common hypothesis for the pathogenesis of gastroschisis is vascular disruption during early embryogenesis.[45] Studies examining this hypothesis have investigated the association between vasoactive exposures, such as smoking, alcohol, and illicit and therapeutic drug use, and the risk of gastroschisis.

Several studies have reported a modest increase in the risk of gastroschisis with maternal cigarette smoking. An early, hospital-based, case-control study of 76 gastroschisis cases, using data from the Slone Epidemiology Unit Birth Defects Study (BDS), reported that mothers who self-reported smoking 1-14 cigarettes per day anytime during their pregnancy were 1.5 times as likely (aOR: 1.5; 95% CI: 0.9 – 2.7) to deliver an infant with gastroschisis, compared with mothers who did not smoke, after adjusting for maternal age.[33] In addition, an updated analysis using data from the same study showed a possible dose-response association with first-trimester exposure (1-9 cigarettes/day: aOR: 1.3, 95%CI: 1.1 – 2.2; 10-19 cigarettes/day: aOR: 1.4, 95% CI: 0.9 – 2.4; ≥ 20 cigarettes/day: aOR: 1.8, 95% CI: 1.1- 2.8).[55]

Maternal alcohol consumption has also been reported to increase the risk of gastroschisis, after adjustment for maternal age.[23,33,78] The first of two NBDPS studies observed a 1.4 – fold increased risk among mothers who self-reported any alcohol consumption during the periconceptional period (defined as one month before pregnancy through the third month of pregnancy) compared to no alcohol consumption (aOR: 1.38; 95% CI: 1.06, 1.79).[23] The second NBDPS study reported a dose-response pattern for binge drinking (1-3 drinks/occasion: aOR: 1.27, 95% CI: 1.01 – 1.59; ≥ 4 drinks/occasion: aOR: 1.53, 95% CI: 1.21 – 1.92), compared with no drinking during the periconceptional period.[78] These results support an older study using BDS data (1976 – 1990) that observed a higher age-adjusted estimate among mothers who reported ≥ 5 drinks at any one time (aRR: 3.8; 95%CI: 1.5 – 6.7) compared to mothers who reported 0 drinks. However, the sample size was small (n = 76) as reflected by the wide confidence interval.[33]

Many studies have also observed an association between maternal self-reported illicit drug use and gastroschisis.[22,55,56,79] Given the method of self-report data collection, these studies are vulnerable to social desirability bias. However, despite this challenge, two studies have attempted to objectively measure recreational drug use through the use of biological samples.[56,80] One UK case-control study examined drug use through both maternal self-report and maternal hair samples. Using the self-reported measurement, results showed that any recreational drug use during the first trimester was associated with a two-fold increased risk of gastroschisis (aOR:

2.2; 95% CI: 1.2 – 4.3); however, recreational drug use was not specifically defined. When the analysis was restricted to only vasoactive illicit drugs, defined as cocaine, amphetamines, and ecstasy, the risk increased (aOR: 3.3; 95% CI: 1.0 – 10.5) using self-reported data but attenuated when using hair samples (OR: 2.0; 95% CI 0.8 - 5.0). The authors note that the reduced risk was likely due to reduced power; though, 98.6% (n = 142) and 97.9% (n = 423) of cases and controls, respectively, provided a hair sample.[56] In another observational study, slightly higher odds were reported using hair samples to assess exposure to vasoactive illicit drugs, defined as amphetamines, methamphetamines, barbiturates, cocaine, methadone, benzodiazepines, and opiates; however, estimates were not adjusted for maternal age.[80] Nevertheless, age-adjusted results of studies that examined this association, using self-reported data, suggest that mothers who use recreational drugs have an increased risk of gastroschisis.[22,55,56,79,80] Various vasoactive therapeutic drugs have been shown to be associated with increased risks of gastroschisis, adjusting for maternal age.[21,54,55,81] For example, one study observed a 2.7-increased risk among mothers who disclosed any use of aspirin during the first trimester of pregnancy (aOR: 2.7; 95% CI: 1.2 – 5.9),[82] with other reports of similar estimates ranging from 1.5 to 3.5.[38,79] Other vasoactive medications, including ibuprofen, acetaminophen, and variousdecongestants have been assessed, though results are inconsistent.[54,55]

2.3.2.6 Maternal stress

Many of the observed risk factors known to be associated with gastroschisis, such as young maternal age at conception, cigarette smoking, alcohol use, and others, may indicate a common underlying factor that explains the unique pattern of risk factors for gastroschisis. Given many of the risk factors induce a biologic stress response, including DNA damage, oxidative stress, etc., a few studies have examined the association between maternal stress and gastroschisis.[83–85]

In a recent NBDPS analysis, Werler et al. observed a strong, monotonic dose-response association between cumulative stressors, defined to have some biologic evidence of oxidative or inflammatory response, and gastroschisis for all age groups. Specifically, mothers who self-reported 1, 2,3, and ≥ 4 stressor exposures were 1.3 (95% CI: 1.1, 1.6), 1.7 (95% CI: 1.4, 2.1), 2.5 (95% CI: 2.0, 31), and 3.6 (95% CI: 2.9, 4.4) times the odds, respectively, of having a gastroschisis infant compared with mothers who self-reported zero stressors, after adjusting for maternal age.[85] In addition, a previous NBDPS analysis conducted by Carmichael et al. examined the effect of cumulative social stressful-life events and noted a three-fold increased risk of gastroschisis among non-teenage mothers who self-reported three or more stressful life events. However, no association was found among teenaged mothers.[84] One study in the UK also examined social life stressors and reported that mothers with ≥ 2 stressful-life events in the first trimester had a five-fold increased risk of gastroschisis, after adjusting for maternal age (aOR: 4.9; 95% CI: 1.2, 19.4). Age-specific estimates were not assessed.[83]

One interesting paradox, however, of the hypothesized association between the biological consequence of maternal stress and gastroschisis is the reduced risk associated with a high BMI. Given that psychosocial stress is positively associated with BMI,[85–87]and combined with the chronic inflammatory state of being obese,[88]mothers of high BMI would be expected to experience enhanced activation of stress-inducing inflammatory responses. Yet, despite observed increases of inflammatory cytokines associated with high BMI,[89,90] epidemiologic studies have shown that overweight and obese mothers have a reduced risk of delivering an infant with gastroschisis.[24,26] However, given the generally consistent evidence of a strong association between maternal stress and gastroschisis, stress-induced inflammation may play a role in the etiology of gastroschisis.

2.3.2.7 Maternal infections

Multiple studies have documented an association between gastroschisis and maternal genitourinary infections early in pregnancy, including urinary tract infections and sexually transmitted infections (STIs).[56,91–95] However, infection assessment, including the collection method and type of assay used to analyze biological samples, vary by study resulting in inconsistent results. A few studies assessed STI infection using serological assays to detect antibodies.[93,94] One study observed a four-fold increased risk of gastroschisis among women seropositive for anti-Chlamydia trachomatis (CT) immunoglobulin G3 (IgG3) antibodies (aOR: 3.9; 95% CI: 1.1 – 13.2), after adjustment for maternal age.[93] However, another study, using data from a Finnish cohort, found no association between two types of CT antibodies (immunoglobulin G antibodies and Chlamydial heat shock protein) and gastroschisis (aOR: 1.05; 95% CI: 0.73 – 1.52); though, estimates were only adjusted for seropositivity to herpes simplex virus 2 (HSV-2). The authors note that the difference in study results was likely due to the type of assay used. Their assay was unable to distinguish between different types of IgGs and likely captured subtypes known to have a low response for CT infection which may explain the null effects.[94] One study that examined the association between maternal antibodies to herpes virus antigens (HSV-1 or HSV- 2) and gastroschisis found that mothers with a recent infection had a two-fold increase in the risk of gastroschisis, after adjustment for maternal age (aOR: 1.94; 95% CI: 0.74, 5.12).[95]

Among studies that assessed UTI and STIs through maternal self-report[56,91,92,96], mothers with a UTI between three months prior to conception to the end of first trimester had similar increases in risk (aOR: 1.5; 95% CI: 1.3 – 1.8) as mothers with a self-reported STI (aOR: 1.6, 95% CI: 1.2 – 2.3),[90] compared with mothers with no self-reported infection.[91] Similar results for STIs were found in a BDS analysis (aOR: 1.2; 95% CI: 1.0 – 1.5) that examined infection during the first trimester; however, higher odds were found for UTIs (aOR: 2.3; 95% CI: 1.3 – 2.4).[92] Furthermore, a synergistic effect was observed when examining the joint effect of UTIs and maternal age, but not for STIs and maternal age.[91,92] Specifically, compared to mothers with no infection, mothers less than 25 years with a UTI during the first trimester had a higher risk of having an infant with gastroschisis (OR: 2.6; 95% C: 1.7 – 4.0) while older mothers with a UTI had a slightly lower risk (aOR: 1.8; 95% CI: 0.6 – 5.9).[92]

2.3.2.8 Occupational exposures

To date, three studies have examined the role of occupational exposures in the risk of having an infant with gastroschisis.[79,97,98] One study examined exposure to polycyclic aromatic hydrocarbons (PAH)[98] and two studies assessed exposure to organic solvents[79,97].

A NBDPS analysis reported an increased risk of gastroschisis (aOR: 1.75; 95% CI: 1.05 – 2.92) associated with occupational exposure to PAH and gastroschisis. However, when stratified by maternal age, an increased risk was found among mothers 20 years and older (aOR: 2.53; 95% CI: 1.27 –5.04), but no association was found among teenage mothers (aOR: 1.14; 95% CI: 0.55 – 2.33).[98] The authors hypothesized that this is likely due to prolonged exposure to PAHs; however, data on maternal occupation prior to conception was not available.[98] The two studies that examined exposure to organic solvents reported conflicting results. One study, using data from the California Birth Defects Monitoring Program (CBDMP), reported that mothers exposed to aromatic, gaseous aliphatic, or liquid aliphatic hydrocarbons were almost three times as likely to have an infant with gastroschisis (aOR: 2.55; 95% CI: 1.10 – 5.89).[79] However, in a more recent NBDPS analysis of 879 gastroschisis cases, no association was observed with occupational exposure to any solvent (aOR: 1.0; 95% CI: 0.75 – 1.32). The authors noted that differences in study results may be due to differences in power, inclusion/exclusion criteria, and possible exposure misclassification. The CBDMP study used one industrial hygienist to assign the type of exposure based on mothers' occupation; whereas the NBDPS study used a multiple expert rater system to assign solvent exposure.[97]

2.3.2.9 Environmental exposures

Few studies have examined the relationship between environmental exposures and gastroschisis. Amongst these studies, inconsistent results have been reported. A case-control study in Europe, based on 13 gastroschisis cases, observed an elevated odds of gastroschisis among women living within 3 km of a landfill (OR: 3.19; 95% CI: 0.95, 10.77).[99] However, in another study based in Scotland, a much weaker association was found among mothers living within 2 km of a landfill (aOR: 1.22; 95% CI: 0.28, 5.38).[100] In addition, one case-control study examining the effect of periconceptional exposure to atrazine, anagrichemical, found an increased risk of gastroschisis among women who resided < 25 km from a high-concentration site compared with women living >50 km from the site (aOR: 1.60; 95% CI:1.10, 2.34).[101] Lastly, a recent case-control study utilized the Environmental Quality Index (EQI) to examine the effects of overall county-level environmental quality on ten birth defects, one of which was gastroschisis. Results showed a positive association between worst overall EQI and gastroschisis (aPR: 1.55; 95% CI: 1.30, 1.86), after adjusting for individual-level characteristics. Moreover, when each domain of the EQI (air, water, land, built, and sociodemographic) was examined separately, a reduced association was found with worst environmental quality in the built domain (aPR: 0.67; 95% CI: 0.48, 0.92); and, an increased risk of gastroschisis was observed with worsening sociodemographic quality (aPR: 1.53; 95% CI: 1.02, 2.31). The land, water, and air domains had no associations with gastroschisis.[102]

To date, individual-level assessment of environmental exposures has not been examined in relation to gastroschisis. Given these inconsistent associations, further research is needed to conclude whether environmental exposures increase the risk of gastroschisis.

2.3.2.10 Individual-level socioeconomic position and gastroschisis

Overall, the epidemiologic evidence suggests that individual-level socioeconomic position (SEP) may be associated with gastroschisis, after adjustment for maternal age. Various indicators have been used as a proxy to measure SEP.

One study found that mothers with an annual family income of < $10,000 were more likely to have an infant with gastroschisis compared with mothers with an annual family income of ≥ $50,000 (aOR: 4.5; 95% CI: 1.4 – 14.4), after adjustment for maternal age. In addition, mothers whose father was absent during childhood were four times as likely to have an infant with gastroschisis (aOR: 4.0; 95% CI: 1.4 – 11.5).[22] Two studies examined the effect of maternal education; however, conflicting results werereported. One case-control study, using data from BDS, measured education in years and reported no association between maternal education and gastroschisis, after adjustment for maternal age. Compared with mothers that had < 12 years of education, mothers with 13-15 years of education had an age-adjusted estimate of 1.1 (95% CI: 0.5, 2.2).[33] However, another US population-based study observed an increased risk of gastroschisis among mothers who graduated high school compared with mothers who had less than a 9th-grade education (aRR: 1.40; 95% CI: 1.23, 1.59). In the same analysis, mothers with a master's or doctorate/professional degree had a decreased risk of having a gastroschisis infant (aRR: 0.51; 95% CI: 0.32, 0.82), using the same reference group.[75]

The strong effect of maternal age makes it difficult to examine the effects of individual-level SEP on gastroschisis because the opportunity for young mothers to acquire a high SEP, which is often measured by education and/or income, is limited by their age. It is also important to note that indicators of SEP represent different aspects of overall socioeconomic factors and association with health indicators. Using single indicators as a proxy for SEP obscures the multidimensional nature of SEP and how each aspect of SEP may affect maternal health. Despite these limitations, however, individual-level SEP has been suggested to play a role in the risk of gastroschisis.[21,22]

2.4 Neighborhood-level socioeconomic position

2.4.1 Overview

Neighborhoods or residential environments have recently been shown to be an important contextual factor that may affect maternal health, and subsequently pregnancy outcomes.[103] The study of neighborhood effects on an individual's health has important implications not only on traditional health policies but policies that may affect health through other means, such as urban planning policies.[8] Furthermore, while the examination of neighborhood-level effects may contribute to better understanding the hypothesized mechanisms linking contextual factors to individual health outcomes, it is also helpful to examine these factors for exploratory etiologic research.[15,31] The influence of contextual factors, such as nSEP, may provide important etiologic clues or help improve our understanding of contextual factors as a potential confounder or effect measure modifier for the associations with individual-level risk factors.

2.4.2 Neighborhoods and health

Neighborhoods contain physical, service, and social characteristics, above and beyond individual-level factors, that affect an individual's health through proposed mechanisms involving psychosocial, behavioral, and biological factors.[103] The physical features of neighborhoods include exposure to air pollution, water quality, various toxicants, housing quality, noise pollution, and the built environment such as greenspaces. The social environment refers to the level of social cohesion and/or connectedness amongst neighbors. Related attributes include residential stability, reciprocity amongst residents, levels of social disorder, and crime/violence. The service environment reflects the availability of resources, goods, and services – such as access to recreational facilities, healthcare, healthy foods, and municipal services.[8,103,104] Figure 2, created by Culhane et al.[103], depicts a conceptual framework that outlines the pathways by which the neighborhood context may affect maternal health and subsequently, birth outcomes.

Figure 2. Conceptual framework linking neighborhood factors to maternal health, by Culhane et al.[103]

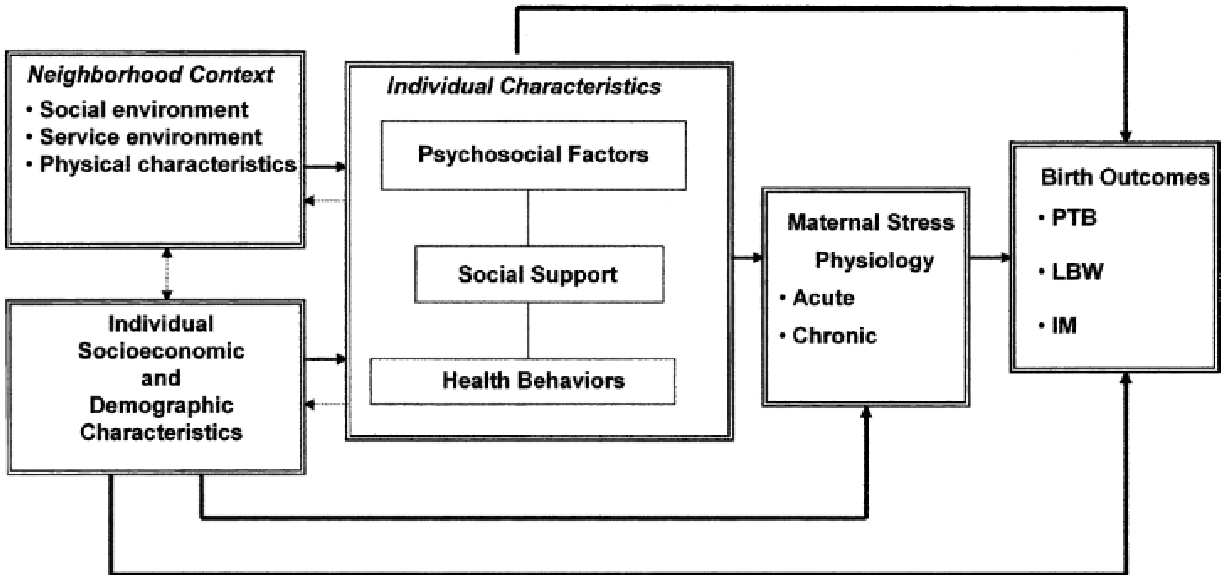


Figure Conceptual framework.

Numerous studies have linked socioeconomically deprived neighborhoods to adverse health outcomes, including cardiovascular disease,[105,106] depression,[107,108] and mortality,[109,110] independent of individual-level risk factors.[109] Although the idea that neighborhoods "independently" affect health outcomes is perhaps misleading, given that health outcomes are expressed at the individual level,[111] these "independent" effects refer to the contextual factors that affect an individual's vulnerability to adverse health outcomes through individual-level mechanisms, such as biological processes or changes in maternal health behavior. Furthermore, studies examining neighborhood-level attributes are often difficult to compare given the various indicators and indices used to characterize neighborhood socioeconomic position. However, there is generally consistent evidence to show that the socioeconomic context of a neighborhood affects individual health and continues to persist even after controlling for individual-level characteristics.[7,8]

2.4.3 Domains and indicators of nSEP

Various domains and indicators are used to characterize nSEP. Since each domain measures unique, yet related aspects of nSEP, there is no single best domain/indicator to capture the multidimensional nature of this contextual factor. Sociologists and social epidemiologists have long recognized the importance of choosing domains/indicators based on the research question and hypothesized mechanisms by which nSEP influences the health outcome of interest.[112] However, given the mechanisms linking nSEP to health outcomes is unknown, particularly with adverse pregnancy outcomes, much of the neighborhood-level literature is often an exploration to further identify and elucidate these mechanisms. A brief summary of SEP domains/indicators and their interpretations are reported in Table 1.

Table 1. Common domains and indicators of socioeconomic position[112–115]

SEP Domain	Interpretation/Operational Definition	Examples of census indicators[115]
Education	• Reflects knowledge, cognitive skills, learned effectiveness, builds resilienceand coping mechanisms • Influences access to material and intellectual resources and educationalopportunities • Enhances responsiveness to health education messages and communicationwith appropriate services • Establishes a sense of personal controlover one's life	• % adults with < high schooleducation • % adults with Bachelor's degree • % adults with > Bachelor's degree
Housing	• Markers of material and economicresources • Key component of wealth • Housing quality reflects direct effects onhealth through the spread of infectious diseases; influences exposure to allergens, pollutants, and other environmental contaminants	• Crowding: % homes with > 1person/room • % owner-occupied housing • Wealth: % owner-occupied homes > $300,000 • Median house/unit value • % renter-occupied units whosegross rent as a percentage of household income is ≥ 30%
Income andPoverty	• Reflects access to quality material resources; health-enhancing commoditiesand services; autonomy • Determines material living standards • Influences self-esteem, social standing through an outward reflection of materialgoods, psychosocial stressors, and socialconnections that may lead to increased	• % individuals at/below the poverty line • Median household income • % individuals with income topoverty ratio < 1 • % households earning <$30,000 • % female-headed households with dependents

SEP: Socioeconomic position

2.4.4 Neighborhood-level socioeconomic position composite indices

Deprivation indices, which are composite measures of various nSEP indicators, have been created as a means to easily identify deprived neighborhoods to guide policy resource allocation decisions. While these indices are appealing as they summarize a complex, multidimensional concept into a single index, they fail to consider the theoretical framework by which it may influence different health outcomes. Nevertheless, the use of composite indices has become extremely popular and is often used in many neighborhood-level studies.

Common composite indices include the Townsend Deprivation Index[116], the Carstairs-Morris Index[117], Area Deprivation Index by Singh et al.[118], and the Neighborhood Deprivation Index by Messer et al.[115]. In brief, the Townsend Deprivation index is a census-based index that combines four variables from the 1991 British census including unemployment, households without a car, overcrowded households, and non-owner occupied households, as a proportion of all households in a given census area.[116] The Carstairs-Morris Index reflects area deprivation in relation to Scotland and combines four census variables, including households without a car, overcrowded households, social class distribution, and male unemployment.[117] The Area Deprivation Index, developed by Singh et al., combines 17 census variables using the 1990 US Census[118]; and, most recently, the NDI created by Messer et al., incorporates eight 2000 US census variables including overcrowded households, female-headed households with dependents, households with public assistance, households in poverty, households earning <$30,000 per year, unemployment, and percent of residents with less than a high school education that represents five sociodemographic domains, including income/poverty, education, employment, housing, and occupation.[115] However, other self-composed indices are often used to measure nSEP.

Although various indicators and indices have been used to measure nSEP, there is no gold standard to capture the multidimensional nature of this contextual factor. While it may be an easy and efficient solution to measure neighborhood deprivation, most indices involve assumptions that may not be applicable over time, across different populations, or pertain to the mechanistic pathway hypothesized to influence the outcome of interest.[112] For example, indicators used to create a composite index may vary across countries. In some countries, education is measured as literacy rate while in other countries it is measured as entry into higher education.[119] Deprivation indices created in other countries, such as the Townsend Deprivation Index, may not coincide with the deprivation in the country of interest. There is also evidence showing that different socioeconomic indicators do not have the same effect on influencing health outcomes. For example, income and education can both affect health through material resources; however, education can further influence how one understands and implements knowledge and/or critically thinks about situations.[112] Furthermore, standardized indices do not account for the quality gradient of each individual indicator. For example, simply accounting for years of education does not capture the educational quality an individual receives, which may be relevant to certain health outcomes.[112]

The construction of these composite indices is often seen as pragmatic since the choice of indicators used to construct the composite index is often based on the availability of data (census, administrative, and/or geospatial data) and geographic areas.[119] What is lacking in the use of these composite indices, however, is the need to critically think about the mechanism by which neighborhood socioeconomic indicators influence specific health outcomes. Ideally, neighborhood-level SEP is characterized based on the research question and the plausible

Explanatory pathways specific to the outcome of interest; however, much research remains to identify these mechanisms, specifically in the context of reproductive health outcomes.[112]

2.4.5 Neighborhood-level socioeconomic position and adverse pregnancy outcomes

Pregnant women living in socioeconomically disadvantaged neighborhoods have a higher risk of experiencing adverse pregnancy outcomes. Many studies have shown modest associations between neighborhood deprivation and preterm birth,[1,5,120] low birthweight,[111,120,121] and small-for-gestational-age (SGA),[122,123] independent of various individual-level characteristics. For example, one study utilizing data from Johns Hopkins Hospital reported that infants delivered in the most disadvantaged neighborhoods were approximately 300 g lighter, on average than infants born to women who lived in the least disadvantaged neighborhood, after adjusting for individual-level risk factors.[111] Another study conducted in Canada found that women in the lowest neighborhood income quintile consistently had higher odds of preterm birth (aOR: 1.14; 95% CI: 1.10, 1.17), SGA (aOR: 1.18; 95% CI: 1.15, 1.21), and stillbirths (aOR: 1.30; 95%CI: 1.13, 1.48), after adjustment for individual-level factors.[124]

Evidence of significant interactions between neighborhood- and individual-level characteristics suggest that the contextual setting where a mother resides may differentiallyaffect certain mothers and modify their risk of having an adverse pregnancy outcome.[125] One study using data from eight geographic areas in the US reported that non-Hispanic, White mothers living in a socioeconomically deprived neighborhood, based on the NDI created by Messer et al., had a 1.6-fold increased odds (95% CI: 1.41, 1.74) of having a preterm birth; whereas, non-Hispanic, Black mothers had a 1.2-fold increased odds (95% CI: 1.08, 1.23).[1] Another study conducted in New York observed modification in the effect of neighborhood deprivation on term, low birthweight infants by different racial/ethnic groups. Mexican women living inthe most deprived neighborhood had a 1.5-fold increased odds of delivering a term, low birthweight infant (aOR: 1.5; 95% CI: 1.02, 2.10), whereas no association was found among Asian women.[120] Given other studies have observed modification of different individual-level risk factors by nSEP,[126,127] there is broad agreement that neighborhood-level factors may not affect mothers equally.[8,128]

Studies have examined the association between neighborhood-level deprivation and birth defects including orofacial clefts, neural tube defects, and conotruncal heart defects, though results are conflicting (Table 2).[3,6,15,129–131] Among the studies that examined orofacial clefts (OFCs), two UK studies employed the same deprivation index but observed differing results.[130,131] The authors note that this difference was likely due to differences in sample size given the first study was based on 73 OFC cases[131] and the second study was based on 834 OFC cases.[130] In addition, one case-control study using data from the Texas Birth Defects Registry observed a modest increase in the risk of OFCs among mothers living in socioeconomically deprived neighborhoods (Q4 vs. Q1 aOR: 1.20; 95% CI: 1.05, 1.37).[3] However, results from a California case-control study observed null effects, for both OFCs and conotruncal heart defects.[15] Although both US studies used the same census indicators, differences in study results for OFCs may be due to differences in geographical scales used to define ‘neighborhood’, such as census tracts versus census blocks. In addition, given the spatial size of census tracts and census blocks may vary in different parts of the US based on the density of the population, this could also lead to differences in study results. Of the three studies that examined neural tube defects (NTD), one study found a positive association with neighborhood deprivation while two studies observed a weak to no association. In the UK, Vrijheid et al. conducted a case-control study of 107 NTD cases and observed a weak association with increasing neighborhood deprivation, using the Carstairs Deprivation Index (OR: 1.23; 95% CI: 0.63, 2.37).[131] Among the two US studies, Wasserman et al. observed an increased gradient risk of NTDs with increased census-block indicators of nSEP;[6] whereas, Grewal et al. found no association, using the same indicators as Wasserman et al.[129] Although both studies used similar methodologies, Grewal et al. hypothesized that the difference in study results was probably due to the timing of data collection in relation to the 1998 mandatory fortification of enriched cereal-grain products with folic acid. Due to this mandate, differences in the occurrence of NTDs likely contributed to the difference in study results.[7] Lastly, in the UK case-control study Vrijheid et al. conducted, an increased risk of digestive system anomalies was observed among mothers who resided in the most deprived neighborhoods compared with the most affluent. However, in this analysis, digestive system anomalies were not clearly defined, and given this outcome likely consisted of a group of etiologically heterogenous defects, effect estimates may be biased. Furthermore, this analysis was based on a small sample size (n = 44).[131]

Overall, although results from these neighborhood-level studies are inconsistent due to differences in study design, indicators/indices used to measure nSEP, and modeling techniques (i.e. single-level vs. multi-level logistic regression models), these studies suggest that nSEP may influence the risk of other birth defects, such as gastroschisis.[3,6,15,129,132]

Table 2. Summary of neighborhood-level studies and birth defects

Study	Sample size	Measurement of nSEP	Effect estimate
Orofacial clefts (CL± P)			
Vrijheid et al.,2000[131]	n = 73	Carstairs DeprivationIndex	Deprived vs. affluent aOR: 0.95 (95% CI: 0.44, 2.05)
Clark et al., 2003[130]	n = 834	Carstairs DeprivationIndex	Deprived vs. affluent RR: 2.33 (95% CI: 1.23, 4.43)

Carmichael et al., 2009[15]*	n = 434	Six census block indicators: (1) education, (2) poverty, (3) unemployment, (4) occupation, (5) rental occupancy, (6) crowding	1-3 vs. 0 indicators OR: 1.0 (95% CI: 0.8, 1.4) 4-6 vs. 0 indicators OR: 0.9 (95% CI: 0.6, 1.3)
Lupo et al., 2015[3]	n = 2,555	Six census block indicators: (1) education, (2) poverty, (3) unemployment, (4) occupation, (5) rental occupancy, (6) crowding	Q2 vs. Q1 aOR: 1.12 (95% CI: 0.99, 1.26)
			Q3 vs. Q1 aOR: 1.16 (95% CI: 1.02, 1.33)
			Q4 vs. Q1 aOR: 1.20 (95% CI: 1.05, 1.37)
Neural Tube Defects			
Vrijheid et al., 2000[131]	n = 107	Carstairs Deprivation Index	Deprived vs. affluent aOR: 1.23 (95% CI: 0.63, 2.3)
Wasserman et al., 1998[6]	n = 538	Six census block indicators: (1) education, (2) poverty, (3) unemployment, (4) occupation, (5) rental occupancy, (6) crowding	1 vs. 0 OR: 1.6 (95% CI: 1.0, 2.4)
			2 vs. 0 OR: 1.6 (95% CI: 1.0, 2.6)
			3 vs. 0 OR: 1.9 (95% CI: 1.0, 3.3)
			4 vs. 0 OR: 2.8 (95% CI: 1.6, 4.8)
			5 vs. 0 OR: 4.9 (95% CI: 2.1, 11.4)
			6 vs. 0 OR: 18.8 (95% CI: 2.5, 390.6)
Grewal et al., 2009[129]*	N = 283	Six census block indicators: (1) education, (2) poverty, (3) unemployment, (4) occupation, (5) rental occupancy, (6) crowding	1 vs. 0 OR: 1.2 (95% CI: 0.8, 1.8)
			2 vs. 0 OR: 1.2 (95% CI: 0.7, 2.0)
			3 vs. 0 OR: 1.4 (95% CI: 0.8, 2.3)
			4 vs. 0 OR: 0.9 (95% CI: 0.5, 1.6)
			5 vs. 0 OR: 0.9 (95% CI: 0.5, 1.6)
			6 vs. 0 OR: 1.3 (95% CI: 0.5, 3.0)
Heart defects			
Carmichael et al., 2009[15]*	Tetralogy of Fallot n = 152	Six census block indicators: (1) education, (2) poverty, (3) unemployment, (4) occupation, (5) rental occupancy, (6) crowding	1-3 vs. 0 indicators OR: 1.2 (95% CI: 0.8, 1.8)
			4-6 vs. 0 indicators OR: 0.9 (95% CI (0.6, 1.5)
	d-Transposition		1-3 vs. 0 indicators OR: 0.9 (95% CI: 0.6, 1.3)

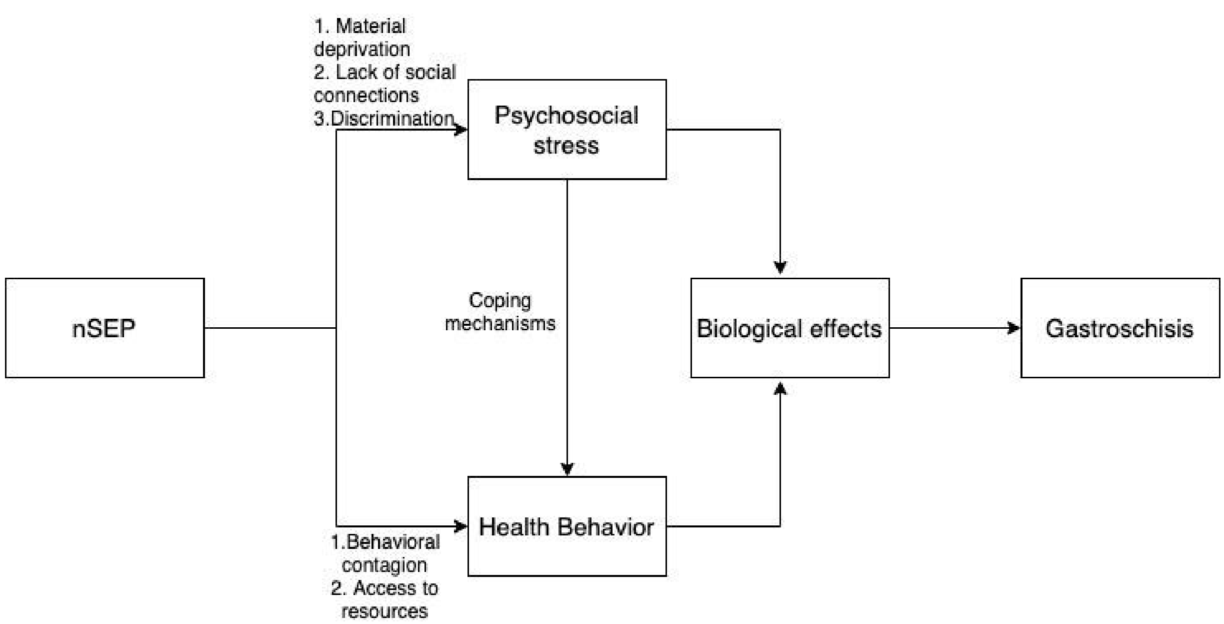
	of the great arteries n = 125		4-6 vs. 0 indicators OR: 0.6 (95% CI (0.4, 1.1)
	Digestive System Anomalies		
Vrijheid et al., 2000[131]	n = 44	Carstairs Deprivation Index	Deprived vs. affluent aOR: 3.53 (95% CI: 1.11, 11.18)

*Only unadjusted results were presented; authors stated adjusted results were not substantially different from unadjusted results

2.4.6 Hypothesized explanatory mechanisms linking nSEP and gastroschisis

It is well known that neighborhoods influence health.[137] However, the mechanisms linking neighborhood-level characteristics to maternal and fetal health, and more specifically gastroschisis, are unknown. Thus, to aid in hypothesizing mechanisms linking nSEP to gastroschisis, we will consider the theorized pathways linking nSEP to other pregnancy-related outcomes.[138] These mechanisms have been posited to mediate through psychosocial, biological, and behavioral factors (Figure 3).

Figure 3. Simplified conceptual framework hypothesized explanatory mechanisms linking nSEP and gastroschisis



First, pregnant women who live in socioeconomically deprived neighborhoods are more likely to experience greater psychosocial stress.[10,133–135] Exposure to acute and chronic stressors can result in the dysregulation of biological systems (i.e. high allostatic load);[12] increased concentrations of inflammatory markers (i.e. C-reactive proteins and interleukin-6);[13,136,137] and overall influence major biochemical and immunological pathways[10–12] that may not only impair the physical and mental well-being of the mother but may also affect embryogenesis and fetal development.[138] For example, one study observed high levels of interleukin-6 among mothers whose infants had a congenital heart defect compared with their controls;[139] while other studies observed an increased risk of preterm birth, fetal growth restriction neonatal morbidity, and low birthweight among mothers with high levels of C-reactive protein and interleukin-6.[13,136–138]

In addition to the independent, stress-inducing biological effects, increased exposure to stressors may influence the adoption of stress-related risky health behaviors as a coping mechanism, such as smoking, alcohol, and illicit drug use. Also, the social influence of fellow neighbors may encourage the adoption of similar behaviors (i.e. behavioral contagion theory).[140] If residents of socioeconomically deprived neighborhoods are less likely to practice a healthy lifestyle, this will likely impact a mother's view on health-promoting behaviors and encourage the adoption of high-risk behaviors seen among fellow neighbors. Furthermore, the availability of goods and services in a neighborhood may function as an "exposure opportunity" for the adoption of risky health behaviors. For example, neighborhoods with greater availability of illicit substances may influence mothers to adopt these behaviors.[141]

The second way in which mothers adapt to stressful environments may, in part, rely on access to informal resources that are often created through social connections, networking, and relationships amongst fellow residents. In advantaged neighborhoods, mothers may benefit from other residents who engage in social activities throughout their community. Whether it be through minor tasks to networking with others to gain health-related advice and information, social connections can enhance the overall well-being of a mother and foster resilience to overcome potential stressors. This will mitigate stress-induced biological effects, in addition to, potentially reducing risky health behaviors likely influencing the risk of having a gastroschisis-affected pregnancy.

Third, disadvantaged neighborhoods tend to be resource limited and often have poor quality resources, including health care services, recreational facilities, options for healthy foods, dilapidated housing, and other amenities that inhibit healthy living. For example, maternal health, and subsequently pregnancy outcomes, in lower socioeconomic neighborhoods may be related to the irregularity of prenatal visits needed during pregnancy through the lack of quality healthcare services. In addition, limited access to healthy food resources may inhibit mothers from getting adequate nutrition and prenatal vitamins needed to support a healthy pregnancy.

The last hypothesized mechanism linking nSEP and gastroschisis is through the environmental justice framework. This framework suggests that socioeconomically disadvantaged neighborhoods are often disproportionately located near landfills, superfund sites, hazardous waste facilities, and industries that have polluting facilities that emit harmful substances that may adversely affect individual health and pregnancy outcomes.[142] Studies examining the association between maternal residence near landfills/hazardous waste sites and birth defects, including gastroschisis report conflicting results.[99,100,143–146] However, it is unclear whether the lack of association found in some studies is due to a true absence of a causal relationship or if it is due to a lack of detailed exposure assessment. Nevertheless, the shared physical environment may potentially increase the risk of gastroschisis through exposure to harmful substances.

For this dissertation, we hypothesize that nSEP influences the risk of gastroschisis through psychosocial stress-mediated pathways for four reasons: (1) low-nSEP has been shown to influence the amount of stress individuals are exposed to,[10–12] (2) studies have observed that maternal stress, defined as stressful life events or stressors that have biologic evidence of inducing an inflammatory stress response, is associated with gastroschisis,[84,85] (3) although stress biomarkers have not been studied in relation to gastroschisis, other studies have found increased concentrations of stress biomarkers to be associated with other adverse pregnancy outcomes,[13,139] and (4) psychosocial stressors influence the adoption of risky health behaviors,[8] such as smoking, that have also been found to be associated with gastroschisis.

2.5 Review of the epidemiologic literature and proposed study innovations

To date, only one known study has examined the association between measures of nSEP and gastroschisis. Root et al.[31] conducted a case-control study in North Carolina (1998 – 2004) of 264 cases of gastroschisis, obtained from the North Carolina Birth Defects Monitoring Program (NCBDMP), and 12,488 controls, randomly selected from the North Carolina Composite Linked Birth File. Five SEP indicators were used to estimate nSEP including the: percent of residents living below 100% and 200% of the federal poverty level, percent of residents with less than a high school education, percent of residents unemployed, and percent of residents reporting African American race. Residential address at delivery was used to define maternal neighborhood using six geographical sizes: 2000, 2500, 3000, 3500 m radius, census tracts, and census blocks. However, results were only reported for neighborhood sizes of 2500 and 3000 m radius. Multilevel models were conducted to estimate odds ratios and 95% confidence intervals. Additionally, a cross-level interaction between Medicaid status and neighborhood poverty was assessed to examine if the association between nSEP and gastroschisis is modified by iSEP.

The study found that neighborhoods high in poverty and unemployment were associated with an increased odds of gastroschisis, after adjustment for maternal age, race/ethnicity, parity, smoking, and Medicaid status. Specifically, for neighborhoods with a 2500m and 3000m circular radius, mothers residing in the 3^{rd} quartile of poverty (30-40% of residents living below the 200% federal poverty level) were nearly two times as likely to have an infant with gastroschisis compared with mothers residing in the 1^{st}quartile [(2500m aOR: 1.85; 95% CI: 1.19, 2.83); (3000m aOR: 1.79; 95% CI: 1.18, 2.80)]. Similarly, a two-fold increase in the risk of gastroschisis was observed among mothers residing in the 3^{rd} quartile of unemployment (~7% of residents are unemployed) compared with mothers in the 1^{st} quartile [(2500m aOR: 1.61; 95% CI: 1.08, 2.44); (3000m aOR: 1.89; 95% CI: 1.25,2.94)]. Although increased odds of gastroschisis were also seen among women living in neighborhoods in the 4^{th} quartile of poverty [(2500m aOR: 1.15; 95% CI: 0.73, 1.88); (3000maOR: 1.20; 95% CI: 0.76, 1.95)] and unemployment [(2500m aOR: 1.27; 95% CI: 0.82, 1.98); (3000m aOR: 1.50; 95% CI: 0.96, 2.39)], the strength of association decreased.[31]

Results of the cross-level interaction between Medicaid status and neighborhood poverty showed that Medicaid mothers in high-poverty neighborhoods had the highest risk of having an infant with gastroschisis, compared with non-Medicaid mothers in low-poverty neighborhoods (aOR; 2.45; 95% CI: 1.57, 3.91). However, the risk of gastroschisis did not differ between low poverty/Medicaid, high poverty/non-Medicaid, and high poverty/Medicaid mothers relative to low poverty/non-Medicaid mothers.[31] Although a synergistic effect was not observed between iSEP and nSEP, the use of a single indicator to measure iSEP likely resulted in residual confounding.

Overall, the study observed an association between nSEP and gastroschisis. However, limitations of the study prompt the need for additional studies to address and expand upon these issues.

The first limitation of Root et al.'s study is the small sample size of 264 cases of gastroschisis and the limited generalizability of study results. Although this birth defect is relatively rare, a small sample size will reduce the study's statistical power to adequately detect a true association. In addition, given this study only utilized data from one state (NC), between 1998 and 2004, this will also limit the generalizability of study results. By leveraging NBDPS data, our study will include a larger sample size of gastroschisis cases which will allow our analysis to be better powered and provide more precise estimates. In addition, given our study will utilize 14 years of data, our study will be more temporally inclusive which will provide more generalizability to other time periods. Moreover, by incorporating data from nine US states, our study will include a larger variety of neighborhoods that are not only geospatially diverse but likely demographically diverse, further enhancing the generalizability of study results.

The potential for exposure misclassification is the second limitation. Maternal neighborhood was defined based on geocoded maternal addresses at delivery. Considering the critical window of gastroschisis development is approximately between the 8^{th} – 11^{th} gestational week[58,59], use of residential addresses during delivery may lead to exposure misclassification. Although residential mobility has not been shown to be extensive during pregnancy, with approximately 25-30% of pregnant mothers moving within short distances[147,148]; there are iSEP-driven disparities that are obscured by the overall trends. Studies have reported higher mobility rates for mothers who are young and White[149]; less educated[150]; have lower household incomes[147]; and have a higher pre-pregnancy BMI[151]. Given these disparities, using maternal addresses at delivery as a proxy for nSEP during the critical period of gastroschisis development may be subject to exposure misclassification. Our analysis will define maternal neighborhoods as the census tract corresponding to self-reported addresses during the periconceptional period, defined as one month prior to conception to the third month of pregnancy. If multiple addresses were reported, we will use the address lived at the longest because neighborhood impact will be the most significant for a longer duration. This will ensure the exposure occurs during the appropriate etiologic window for gastroschisis and reduce the potential for exposure misclassification.

Lastly, the third limitation of the study is residual confounding by iSEP. While this bias is likely present in most epidemiologic studies, Root et al. only used one indicator, Medicaid status, to measure iSEP. Without including additional measures of iSEP, the contextual effect of nSEP may be inappropriately confounded by iSEP characteristics that were not accounted for. Our analysis will include different and additional measures of iSEP, including maternal education and household income. Although we do not claim to have "controlled" for iSEP, it is plausible that the use of additional iSEP measures will reduce the effects of residual confounding.

Overall, this dissertation will improve upon the limitations of the previous study in the following ways: (1) use of a larger sample of gastroschisis cases spanning a national geographical range, (2) maternal neighborhoods defined based on geocoded addresses around conception to reduce exposure misclassification, and (3) the inclusion of additional measures of iSEP to reduce residual confounding. Moreover, we will meaningfully expand upon the previous study by not only investigating the associations between single SEP indicators and gastroschisis, but also examine the relationship between overall nSEP, using two composite neighborhood-level indices, and gastroschisis.

CHAPTER 3: STUDY DESIGN AND METHODS

3.1 Study overview

The objective of this dissertation is to explore the potential influence of contextual risk factors for gastroschisis using data from the National Birth Defects Prevention Study (NBDPS). In Specific Aim 1, we will examine the overall association between nSEP during early pregnancy and the risk of gastroschisis, using two composite neighborhood-level indices to characterize nSEP. In Specific Aim 2, we will examine whether the associations between young maternal age at conception, pre-pregnany BMI, and gastroschisis differ by nSEP. For both aims, the study design, study population, and characterization for nSEP will be the same.

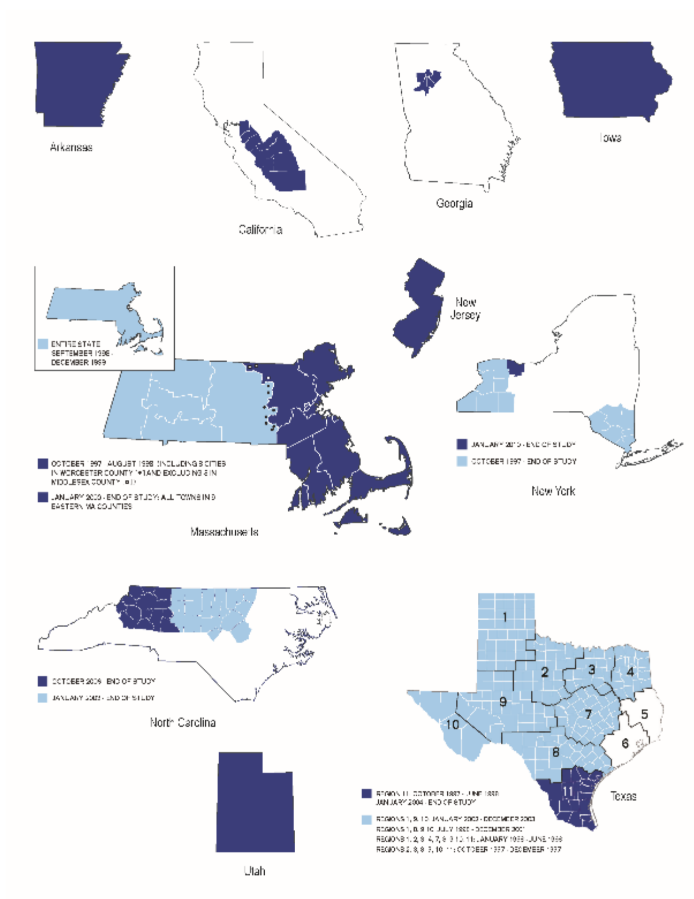
3.2 Study design and study population

The National Birth Defects Prevention Study is a population-based, multi-center case-control study designed to examine potential risk factors for over 30 individual types of major structural birth defects. Pregnancies ending between October 1, 1997, to December 31, 2011, were eligible to participate from ten participating centers in the following states: Arkansas (AR), California (CA), Georgia (GA), Iowa (IA), Massachusetts (MA), North Carolina (NC), New York (NY), New Jersey (NJ), Texas (TX), and Utah (UT).

3.2.1 Case and control ascertainment

Eligible cases included livebirths, stillbirths (≥ 20 weeks' gestation), and terminations with at least one eligible birth defect. Cases were ascertained through each participating center's birth defects surveillance registry from selected counties (CA, GA, MA, NC, NY, TX) or the entire state (AR, IA, NJ, UT) (Figure 4). Controls were live born infants without a major birth defect and were randomly selected in proportion to the number of births in the same month of the prior year using birth certificates or hospital records from the same study geographic catchment area as the cases.[152] The selection of controls in the NBDPS has been shown to be generally representative of the source population that gave rise to the cases.[153]

Figure 4. NBDPS catchment areas[152]



All eligible mothers were sent an introductory packet and invited to participate in the study. Mothers that provided an informed consent were asked to complete a computer-assisted telephone interview (CATI) within 6 weeks to 24 months after the estimated date of delivery.

Over the 14-year study period, 67% and 65% of eligible cases and controls, respectively, consented and participated in the interview. The interview collected information on a variety of factors including demographics; medical and pregnancy history; residentially history; diet; physical activity; nutrition; and lifestyle factors.

3.2.2 Case classification

All NBDPS cases were verified by clinical geneticists using information abstracted from medical records and a standardized, study-wide classification protocol. Cases were classified as 'isolated' (vs. non-isolated) if there was a single major birth defect or co-occurring defects that are anatomically related or pathogenetically similar.[160] In addition, cases with known etiologies, such as single-gene conditions or chromosomal abnormalities, were excluded. Case classification was standardized across all participating centers.

3.2.3. NBDPS and US Census/American Community Survey linkage

As part of the NBDPS interview, mothers were asked to self-report all residential addresses they lived at for at least 30 days between three months prior to pregnancy to the end of pregnancy. Residential addresses from each participating center, except New Jersey, were geocoded by the Geospatial Research, Analysis, and Services Program (GRASP) of the Agency for Toxic Substances and Disease Registry (ATSDR) at the Centers for Disease Control and Prevention (CDC), using Centrus version 6.00.00N and linked to the 2000 and 2010 US Census Tracts using ArcGIS. Dates of occupancy at each address were recorded. Residential addresses were successfully geocoded for 97% of all NBDPS participants. NBDPS data were linked to the US Decennial Census and the 5-year American Community Survey (ACS), by Federal

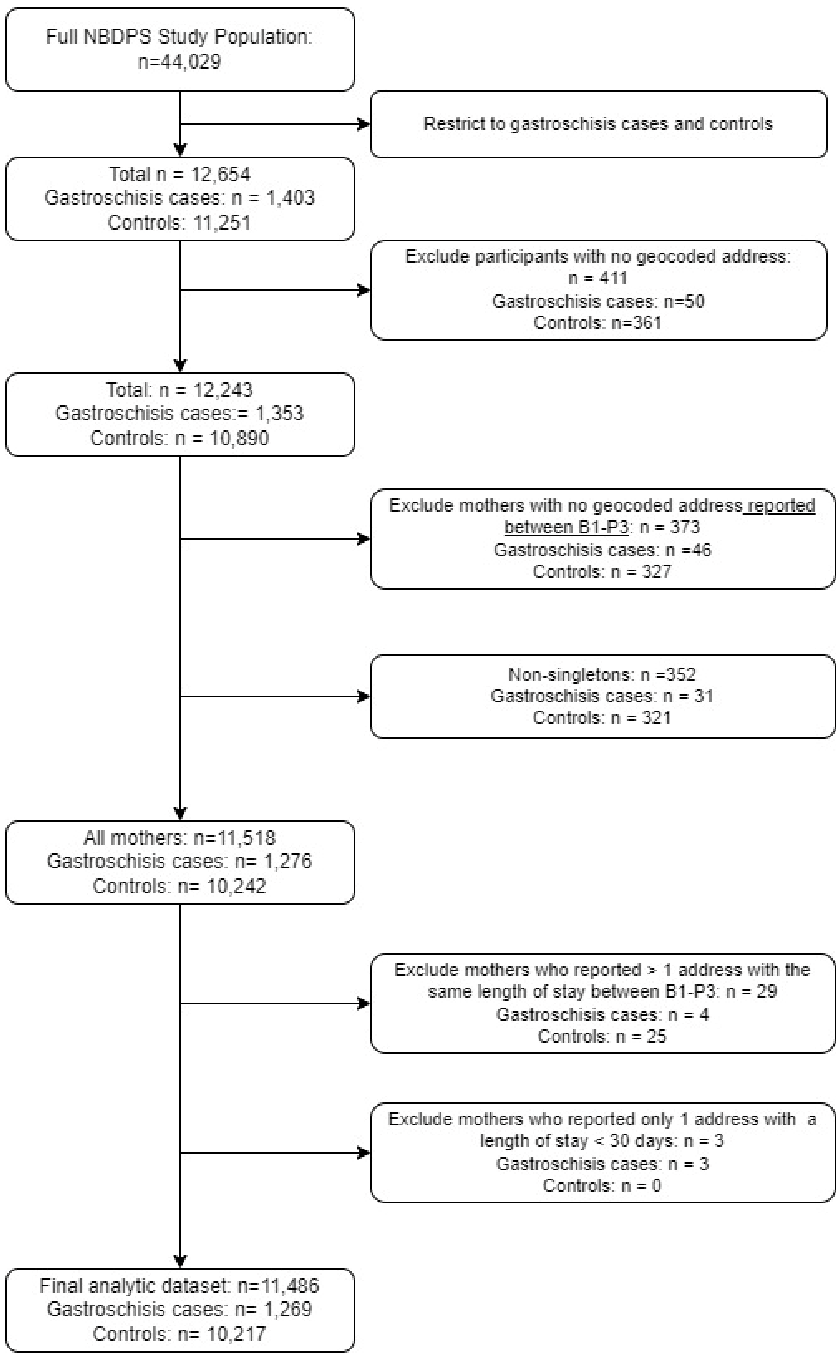
Information Processing Standards (FIPS) codes and infant birth year, to obtain census-tract level SEP information. Specifically, infants born between 1997-2004, 2005-2009, and 2010-2011 were linked to the 2000 U.S. Decennial Census, 2005-2009 ACS, and 2010-2014 ACS, respectively. The US Decennial Census occurs every 10 years and accounts for every resident in the US;[154]whereas, the ACS, which began in 2005, is conducted yearly and is based on a sample of the overall US population.[155]

3.2.4 Study population

The study population for both aims of this dissertation will include all eligible singleton cases of gastroschisis (British Pediatric Association (BPA) modification of the International Classification of Diseases, 9th revision (ICD-9): 756.710) and controls enrolled in the NBDPS between 1997 and 2011. Isolated and non-isolated cases of gastroschisis are included in this study since isolated cases make up the majority of cases and because previous studies observed that the distribution of risk factors are similar between both isolated and non-isolated cases. The participation rates for eligible case and control mothers, for this dissertation, is 65% and 64%, respectively.

Per NBDPS protocol, mothers of case and control infants were excluded if they previously participated in the study with a prior pregnancy, were unable to complete the interview in English or Spanish, were incarcerated, or did not have legal custody of their child at the time of the interview.[35] In addition to the NBDPS exclusion criteria, for this analysis, participants were excluded if they (1) were missing geocoded addresses during the periconceptional period, defined as one month prior to conception to the third month of pregnancy, (2) reported more than one address during the periconceptional period with the same length of stay since it was unclear which address would have a greater impact on the risk of gastroschisis, and (3) reported only one address during the periconceptional period with a length of stay of fewer than 30 days (Figure 5).

Figure 5. Inclusion and exclusion criteria for study population



3.3 Characterization of neighborhood-level socioeconomic position

3.3.1 Maternal neighborhood

For this analysis, maternal neighborhood will be geographically defined as the census tract corresponding to the longest address lived at during the periconceptional period, defined as one month prior to conception to the third month of pregnancy. According to the US Census Bureau, census tracts are statistical subdivisions of counties with approximately 4,000 individuals. The spatial size of a census tract varies based on the population density of the area.[156] Census tracts were designed to be fairly homogenous in regards to the living condition, population characteristics, and social and economic factors.[164] In addition, differences between census tract and block group area-level socioeconomic measures have been shown to be relatively small;[157,158] and, compared with other geographical units (i.e. ZIP-code level areas), census tracts have detected stronger socioeconomic gradients while maintaining the fairly homogenous contextual factors within each census tract.[158] Prior studies that have assessed neighborhood effects on pregnancy outcomes have employed census tracts as their geographical unit to define 'neighborhood'.[3,15,159] Moreover, use of neighborhood-level socioeconomic measures at the census-tract level have been shown to be meaningfully useful in relation to birth outcomes.[158] Thus, for these reasons, we will use census tracts to proxy maternal neighborhoods.

3.3.2 Neighborhood-level indices

For this dissertation, nSEP is defined as the social and economic contextual factors that reflect the distribution of a neighborhood's physical, social, and service characteristics that influence the health and well-being of an individual's lived experience above and beyond individual-level characteristics.[1,2] We will characterize nSEP using two methods: (1) the

Neighborhood Deprivation Index (NDI) developed by Messer et al. and (2) the Neighborhood Socioeconomic Position Index we create based on seventeen socioeconomic indicators.

3.3.2.1 Neighborhood Deprivation Index

The NDI, developed by Messer et al.[115], is a measure of nSEP that has been widely used in previous epidemiologic studies to examine the associations between neighborhood-level factors and birth outcomes, including low birth weight, preterm birth, and small-for-gestational age.[1,120,160] The NDI represents five socioeconomic domains (income/poverty, occupation, housing, employment, and education) and is comprised of eight census-tract level indicators including: percent of males in management and professional occupations, percent of crowded housing, percent of households in poverty, percent of female-headed households with dependents, percent of households on public assistance, percent of households earning less than $30,000 per year, percent earning less than a high school education, and percent unemployed (Table 3). The index was created based on data between 1995 and 2001 from eight study areas that represented three urban centers (Philadelphia, PA; Baltimore City, Maryland; and 16 pooled cities in Michigan) and five racially heterogenous counties (three Maryland counties near Washington D.C. and Baltimore, MD; and two in North Carolina). Census-tract level data from the 2000 U.S. Census was used to develop this deprivation index.

To construct the NDI for our study population, we will follow the methods outlined by Messer et al.[115] Census-tract level data from all nine NBDPS participating centers will be pooled and the data reduction technique, principal component analysis (PCA), will be performed. The first principal component will be retained because it accounts for the largest proportion of the total variation among the component measures. The component loadings represent the correlation between each SEP indicator and the principal component. Using the loadings, we will weight each SEP indicator to create a continuous index score for each census tract. The index will be standardized to have a mean of 0 and a standard deviation of 1, with low scores indicating less deprivation (or high SEP) and high scores indicating greater deprivation (or low SEP). The NDI will then be linked to NBDPS participants and categorized into tertiles based on the distribution among controls, to examine a potential gradient in the risk of gastroschisis. Tertiles will represent low (reference), moderate, and high neighborhood deprivation.

This index will be used for four reasons: (1) it was specifically developed to assess the relationship between neighborhood deprivation and birth outcomes, (2) it employs the same geographical unit as our proposed study (i.e., census tract), (3) it has previously been used in a number of studies examining adverse pregnancy outcomes, and (4) it will allow our study results to be comparable to other neighborhood-pregnancy related studies that have used the same nSEP characterization.

However, there are limitations to using a standardized index, such as the NDI. Although convenient, using a standardized index may not be applicable over time, across different study populations, or span various geographical regions. Specifically, the NDI was developed based on data from birth years between 1998 and 2001 using a non-nationally representative sample based on four states in the eastern region of the US. Given our study will use data from birth years between 1997 and 2011 from nine states spanning the US, use of this NDI may not apply to our specific study time period and population. Due to these limitations, we will characterize nSEP using a second method, the Neighborhood Socioeconomic Position Index.

3.3.2.2 Neighborhood Socioeconomic Position Index

Studies have suggested that socioeconomic position, both at the individual and neighborhood level, should be measured with as much relevant information as possible. In addition, although socioeconomic indicators are often correlated, studies have shown that they are generally not strong enough to be proxies for one another. Thus, to characterize this multidimensional construct, we will create a second index, the Neighborhood Socioeconomic Position Index (nSEPI), using the same methods as the NDI. The nSEPI will represent the same five socioeconomic domains (income/poverty, occupation, housing, employment, and education) but will include additional socioeconomic indicators, in particular measures of socioeconomic advantage, to provide a richer representation of each domain.

The nSEPI will be comprised of the same eight indicators in the NDI plus nine additional indicators including the: percent of residents with a bachelor's degree or higher; percent of employed residents who are nature, construction, or transportation workers; percent of employed residents who reported being an unpaid family worker or self-employed; median household income; percent of owner-occupied homes with values greater than \$300,000; percent of owner-occupied homes with a mortgage and monthly owner costs of 30% or more of household income; percent of owner-occupied homes without a mortgage and monthly owner costs of 30% or more of household income; percent of renter-occupied units among total occupied housing units; and percent of renter-occupied units with a monthly rent that costs 30% or more of household income (Table 3). The same data reduction technique that was used to construct the NDI (i.e. PCA) will be conducted to create the nSEPI. The nSEPI will be similarly be categorized into tertiles to represent high (reference), moderate, and low nSEP.

Table 3. Description of census indicators used to create the Neighborhood Deprivation Index and Neighborhood Socioeconomic Position Index

Socioeconomic domain	**Census indicator**	**Description**
Education	% Low education[a.b]	% Residents whose highest education level at the age of 25 is less than high school
	% High education[b]	% Residents whose highest education level at the age of 25 is a bachelor's degree or higher
Housing	% Crowding[a.b]	% Housing units with > 1 occupant per room
Employment	% Unemployed[a.b]	% Residents unemployed
Occupation	% Males in Management[a.b]	% Males in professional and management occupations
	% Manual occupation[b]	% Employed civilian population ≥ 16 years who are nature, construction, or transportation workers
	% Workers class[b]	% Employed civilian population ≥ 16 years who repor being an unpaid family worker or self-employed
Poverty/Income	% Female house[a.b]	% Female headed households with dependents
	% Public assistance[a.b]	% Households on public assistance
	% Income below 30[a.b]	% Households earning less than $30,000 per year
	% Poverty[a.b]	% Residents with an income to poverty ratio <1
	Median income[b]	Median household income
	% Wealth[b]	% Owner-occupied homes with values of ≥ $300,000
	% Affordable housing with mortgage[b]	% Owner-occupied homes with a monthly mortgage that costs ≥ 30% of household income
	% Affordable housing with no mortgage[b]	% Owner-occupied homes without a monthly mortgage that costs ≥ 30% of household income
	% Renters occupancy[b]	% Renter-occupied units among total occupied housing units
	% Renters affordable housing[b]	% Renter-occupied units with a monthly rent that costs ≥ 30% of household income

[a]Census indicators used to construct the Neighborhood Deprivation Index
[b]Census indicators used to construct the Neighborhood Socioeconomic Position Index

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3.4 Methodology for Specific Aim 1

For this aim, the study design, study population, and characterization of nSEP described in Section 3.2 and 3.3, respectively, will be used to examine the overall association between nSEP during early pregnancy and the risk of gastroschisis. The exposure of interest is nSEP, characterized by the NDI and nSEPI, and the outcome of interest is gastroschisis.

3.4.1 Covariate selection

All covariate information will be abstracted from the NBDPS maternal interview. For this analysis, potential confounders were identified *a priori* using existing literature and a directed acyclic graph (DAG; Figure 6).[161] Table 4 presents all covariates identified in the minimally sufficient adjustment set and the specification of each covariate. In addition, for this dissertation, race/ethnicity is conceptualized as a socially-constructed classification system created to order individuals within society based on phenotypic characteristics (i.e., skin complexion, hair texture, eye shape, and etc.). Given this country's long history of perceiving minorities as inferior, this classification system governs the opportunities and risks individuals are exposed to in our race-conscious society and is deeply entwined with residential and socioeconomic segregation.

Figure 6. Directed Acyclic Graph (DAG) for the association between nSEP and gastroschisis

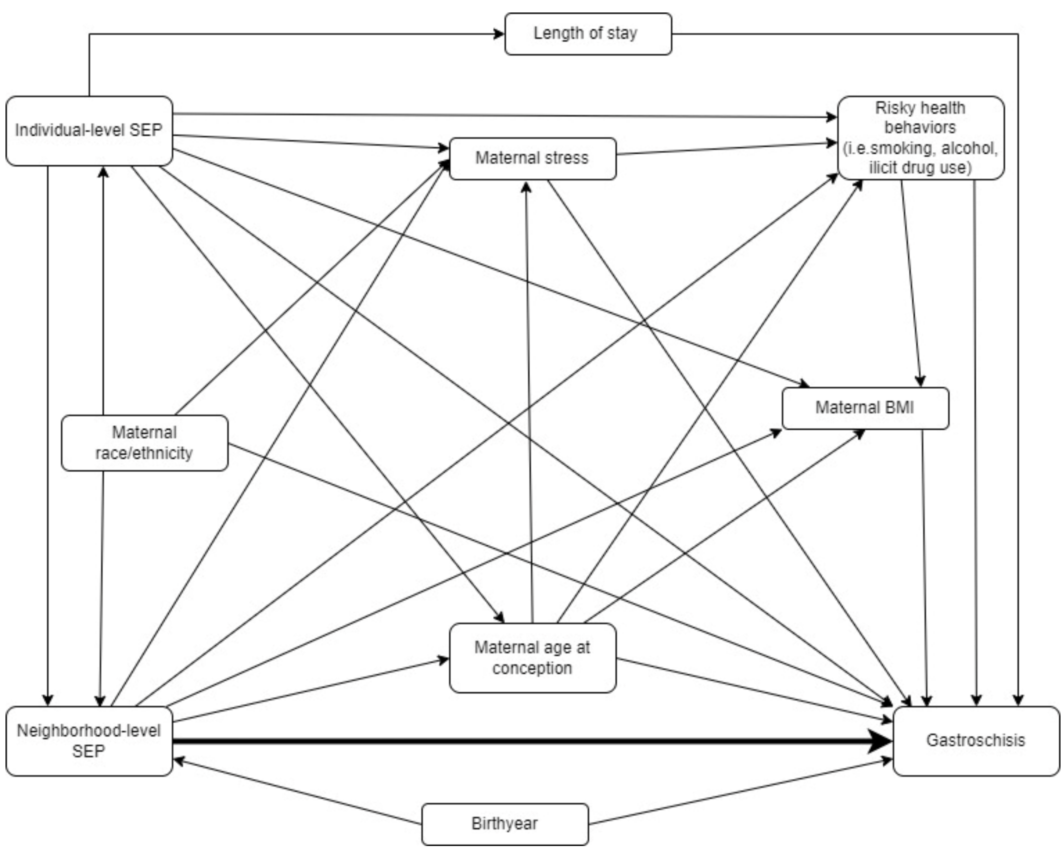


Table 4. Covariates and specification of each covariate for Specific Aim 1

Covariate	**Specification**
Maternal race/ethnicity	Non-Hispanic Black Non-Hispanic White Hispanic Other
Infant birth year	1997 – 2004 2005 – 2009 2010 – 2011
Maternal education (years)	0 – 11 12 > 12
Household income ($USD)	<$10,000 $10,000 - $50,000 > $50,000
Duration of residency	Continuous

3.4.2 Data analysis

3.4.2.1. Missing data

Multiple imputation with fully conditional specification will be used to account for missing data, assuming data are missing at random. This process will be carried out in three steps: (1) imputation for ten cycles, (2) analysis within each dataset, and (3) combination of results using *proc mianalayze* in SAS[162].

For this aim, maternal education and household income are missing for 9% and 2%, respectively, among eligible study participants. In addition, the range of missingness for census-tract SEP indicators is 0.01% - 0.29%. The imputation model will include the outcome (gastroschisis), auxiliary variables associated with missing data (maternal age at conception and employment status), and variables in the analytic model (all census SEP indicators, maternal race/ethnicity, birth year, education, household income, and duration of residence). In addition, we will compare the results from the multiple imputation analysis to the complete case analysis (Supplementary Table 1a and 1b).

3.4.2.2 Statistical analysis

Descriptive statistics for all covariates will be examined using median (interquartile range) or frequencies (relative frequencies) based on the type and distribution of the variable. Generalized estimating equations (GEEs) with logistic links and robust errors will be used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). GEEs account for potential correlation and non-independence among mothers clustered within the same neighborhood. We will examine the association between individual SEP indicators and gastroschisis. In addition, using the NDI and nSEPI, we will investigate the overall association between nSEP during early pregnancy and the risk of gastroschisis. Two separate models will be conducted for each association examined: (1) unadjusted and (2) adjusted for the covariates identified in the minimally sufficient adjustment set. Furthermore, we will conduct a Spearman Correlation test to examine the correlation between the two neighborhood-level indices. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA)

3.4.2.3 Power calculations

Minimum detectable odds ratios were calculated assuming a fixed sample size of 1,200 cases of gastroschisis, with a 1:8 case:control ratio, using PS Power and Sample Size software.[163] All effect estimate calculations assume a two-sided hypothesis test with a type 1 error rate of 5% and power of 80%. Table 5 presents the minimum detectable odds ratios for varying prevalence of exposure to low nSEP among controls. At minimum, we will have sufficient power to detect small to moderate effect estimates (OR range: 1.19 – 1.43). Furthermore, given we plan to categorize the SEP indicators and nSEP indices into tertiles, we should have adequate power (β = 80%) to detect ORs of approximately 0.83 to 1.196 at exposure frequencies of 33%, based on the distribution of controls.

Table 5. Minimum detectable odds ratios for Specific Aim 1

Exposure prevalence	**Minimum detectable ORs**
5%	1.426
10%	1.306
25%	1.212
35%	1.194
50%	1.188

OR: Odds Ratio

3.5 Methodology for Specific Aim 2

In Specific Aim 2, we will examine whether the associations between maternal age at conception, pre-pregnancy BMI, and gastroschisis, differ by nSEP. Similar to Specific Aim 1, this aim will use the same study design, study population, and characterization of nSEP described in Section 3.2 and 3.3, respectively.

3.5.1 Exposure assessment

The exposures of interest for Specific Aim 2 are maternal age at conception and pre-pregnancy BMI. Data were obtained from the NBDPS interview. Maternal age at conception will be dichotomized at 20 years (<20 vs. ≥ 20 years (reference)) since epidemiologic studies have identified that the risk of gastroschisis changes at this age.[65,84,164] In addition, maternal pre-pregnancy BMI was calculated using self-reported weight and height and categorized into three groups, representing underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), and overweight/obese (≥ 25.0 kg/m^2; reference). Overweight and obese categories were combined and used as the reference because studies have shown that overweight and obese mothers have similar reduced risks of gastroschisis.[56]

3.5.2 Covariate selection

Similar to Aim 1, all covariate information will be abstracted from the NBDPS maternal interview. Two directed acyclic graphs (DAGs) were created to identify minimally sufficient adjustment sets for the associations between (1) maternal age at conception and gastroschisis (Figure 7) and (2) maternal pre-pregnancy BMI and gastroschisis (Figure 8). Table 6 presents all covariates identified in the minimally sufficient adjustment sets for each association and the specification of each covariate.

Figure 7. Directed Acyclic Graph (DAG) for the association between maternal age at conception and gastroschisis

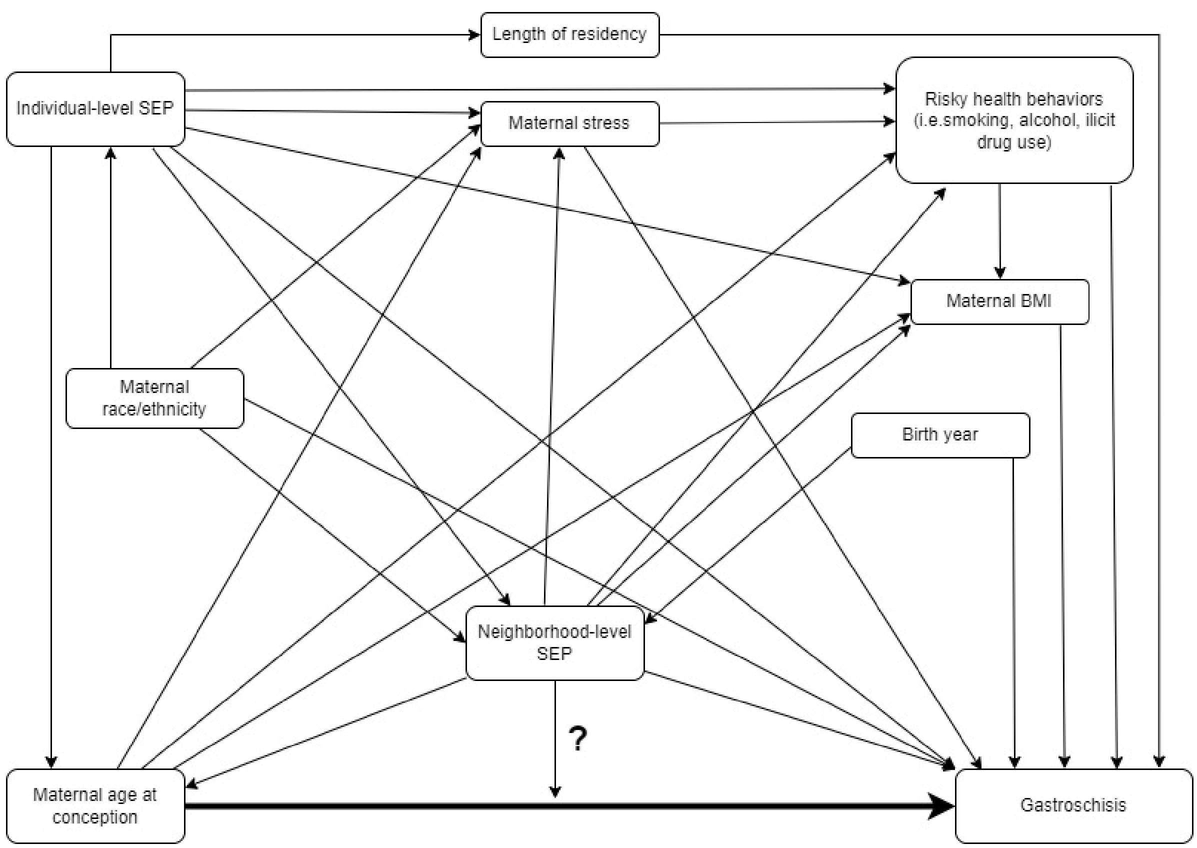


Figure 8. Directed Acyclic Graph (DAG) for the association between maternal pre-pregnancy BMI and gastroschisis

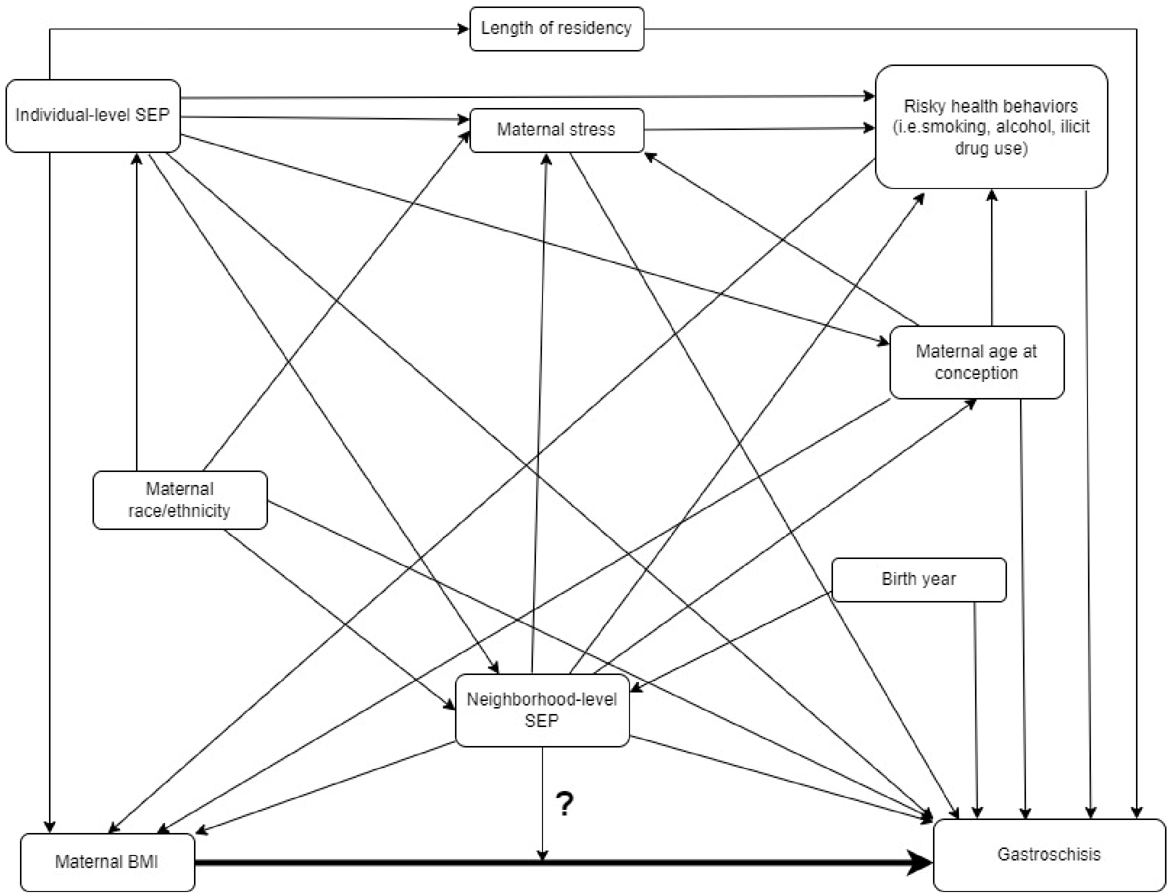


Table 6. Covariates and specification of each covariate for Specific Aim 2

Maternal age at conception and gastroschisis	
Maternal education (years)	0 – 11 12 > 12
Household income ($USD)	<$10,000 $10,000 - $50,000 > $50,000
Maternal pre-pregnancy BMI and gastroschisis	
Maternal education (years)	0 – 11 12 > 12
Household income ($USD)	<$10,000 $10,000 - $50,000 > $50,000
Smoking[a]	Yes (any) No
Recreational drug use[a]	Yes (any) No
Alcohol[a]	Yes (any) No
Maternal age at conception	Quadratic term

BMI: Body Mass Index; USD: US Dollars
[a]Self-reported use between one month prior to conception to the third month of pregnancy

3.5.3 Data analysis

3.5.3.1. Missing data

To account for missing data, multiple imputation with fully conditional specification will be used to impute missing values for the following variables, assuming data are missing at random: household income (9%), pre-pregnancy BMI (3.8%), education (2%) alcohol use (2%), substance use (1.8%), smoking (1.7%), and census-tract SEP indicators (0.01% missing). Data will be imputed for 10 imputation cycles and the process will include: imputation, analysis, and combination of results, similar to Specific Aim 1 (see Section 3.4.2.1). The imputation model will include the outcome (gastroschisis), auxiliary variables associated with missing data (employment status), and variables in the analytic model (all census SEP indicators, maternal education, household income, BMI, smoking, alcohols use, and substance use).

3.5.3.2 Statistical analysis

Descriptive analysis will be conducted to examine the distribution of data using median (interquartile range) or frequencies (relative frequencies), depending on the type of variable. We will use GEEs with logistic links and robust errors to estimate ORs and 95% CIs. The use of GEEs will account for potential correlation and non-independence among mothers residing in the same neighborhood. To assess potential effect measure modification by nSEP, we will compare OR estimates within strata of nSEP to see if there are any observable differences in the magnitude of associations by levels of nSEP. Effect measure modification will be evaluated on the additive scale due to its relevance for public health purposes. The additive scale is recommended to indicate whether the effect of a risk factor is greater in a specific sub-population to help target potential interventions and resource allocations. Thus, we will calculate the relative excess risk due to interaction (RERI) with 95% CIs based on standard errors obtained using the delta method.[165] All models will be adjusted for the covariates identified in the minimally sufficient adjustments, corresponding to the association of interest. All analyses will be conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA)

3.5.3.3 Power calculations

To detect statistically significant odds ratios for the associations between maternal age at conception, pre-pregnancy BMI, and gastroschisis, we will calculate statistical power using a fixed sample size of 1,200 cases of gastroschisis, with a 1:8 case:control ratio, using the QUANTO software (https://quanto.software.informer.com/1.2/). The power calculations for both associations will assume 33% of mothers reside in low nSEP, an estimate OR of 1.2 for the association between nSEP and gastroschisis, a two-sided hypothesis test with a type 1 error rate of 5%, and a baseline gastroschisis prevalence of 5 per 10,000[18].

For the association between maternal age at conception and gastroschisis, we will assume an exposure prevalence of 15% and an estimated OR of 7.0 for the association between young maternal age (< 20 years) and gastroschisis[65]. For the association between maternal pre-pregnancy BMI and gastroschisis, we will assume an exposure prevalence of 5% and an estimated OR of 3.0 for the association between low pre-pregnancy BMI and gastroschisis. Power calculation results are presented in Table 7.

Table 7. Statistical power for Specific Aim 2

Detectable OR	Maternal age at conception	Pre-pregnancy BMI
1.3	0.4323	0.4123
1.5	0.7649	0.7708
1.7	0.9262	0.9437
1.9	0.9797	0.9902

OR: Odds Ratio; BMI: Body Mass Index

CHAPTER 4: NEIGHBORHOOD-LEVEL SOCIOECONOMIC POSITION DURING EARLY PREGNANCY AND THE RISK OF GASTROSCHISIS

4.1 Introduction

Pregnant women residing in low socioeconomic neighborhoods are at higher risk of experiencing adverse pregnancy outcomes.[1,166,167] Neighborhood contextual factors encompass various physical, social, and service characteristics, such as ambient pollutants, levels of social cohesion, and access to goods and services, respectively. The combination of adverse conditions in these contextual factors is often correlated with the neighborhood's socioeconomic position (nSEP) and is hypothesized to influence maternal health through psychosocial, behavioral, and biologic mechanisms.[103,104] Exploratory etiologic studies have reported modest associations between measures of nSEP and birth outcomes, including preterm birth,[1,167] low birth weight,[14] neural tube defects,[6] and more recently, orofacial clefts,[168] and conotruncal heart defects,[15,159] after accounting for individual-level SEP (iSEP). However, few studies have examined this association with gastroschisis.[31]

Gastroschisis is an abdominal birth defect characterized by the herniation of intestines and sometimes other abdominal organs outside the fetal body.[18,19] In the United States, the gastroschisis prevalence increased from 3.6 (1995 – 2005)[18] to 4.3 (2012-2016)[19] cases per 10,000 livebirths, suggesting that environmental factors may have an etiologic role in the development of this birth defect. Gastroschisis disproportionately affects infants of mothers who are young (<20 years),[20,22,164] have low body mass index (BMI),[24–27] smoke,[164] and are of non-Hispanic White and Hispanic race/ethnicity.[21,74,164] Despite these findings, the etiology remains unknown. Proposed underlying mechanisms include rupture of the amnion due to unidentified teratogens during normal physiologic hernia[58,59] and the disruption of inflammatory pathways.[83,85] Identifying neighborhood-level factors that may influence teratogenic exposures or induce an inflammatory response, such as psychosocial stress related to neighborhood deprivation, may provide further insight into the etiology of gastroschisis.

To our knowledge, only one study, using data from North Carolina (1998 – 2004), investigated the relationship between contextual factors and gastroschisis. The study reported a slight increase in the risk of gastroschisis associated with residing in areas characterized by high poverty and unemployment, after adjustment for maternal age, race/ethnicity, smoking, and Medicaid status; however, estimates were imprecise.[31] Our analysis expands this study by including a larger sample of gastroschisis cases spanning a wider geographical area, use of composite neighborhood indices, maternal neighborhoods based on addresses around conception, and the inclusion of additional measures of iSEP.

Neighborhoods may influence known risk factors of gastroschisis through shaping health behaviors, access to resources, and individual opportunities. The association between these risk factors and gastroschisis may, in part, be explained by neighborhood-level factors. Thus, the purpose of this study is to examine the overall association between neighborhood-level socioeconomic position during early pregnancy and the risk of gastroschisis.

4.2 Materials and methods

Study population

We analyzed data from the National Birth Defects Prevention Study (NBDPS). Details about the NBDPS have been described previously.[152] Briefly, the NBDPS is a large, multi-center case-control study sponsored by the Centers for Disease Control and Prevention (CDC) to examine potential risk factors of major structural birth defects, including gastroschisis. Eligible pregnancies between 1997 and 2011 were included from ten participating centers in the following states: Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New York, New Jersey, Texas, and Utah. However, in this analysis, New Jersey participants were excluded since geocoded addresses were not available from this center. The NBDPS was approved by the Institutional Review Board (IRB) at the CDC and at each participating center.

Liveborn, stillborn, or terminated pregnancies with a diagnosis of gastroschisis (cases) (British Pediatric Association (BPA) modification of the International Classification of Diseases, 9th revision (ICD-9): 756.710) were ascertained through surveillance registries from selected counties (CA, GA, MA, NC, NY, TX) or the entire state (AR, IA, UT). Cases were verified by clinical geneticists and classified as isolated (vs. non-isolated) if gastroschisis was the only major defect or if it occurred with another developmentally related defect.[152,169] In this analysis, isolated (90.7%) and non-isolated (9.3%) singleton cases were included. Singleton liveborn infants without a birth defect (controls) were randomly sampled using birth certificates or hospital records from the same geographic catchment area and time period as the cases. Mothers were invited to participate in a computer-assisted telephone interview (CATI) between 6 weeks and 24 months after their estimated date of delivery. Approximately 65% of case mothers and 65% of control mothers participated in the interview. Mothers were asked to report information on a variety of exposures and lifestyle factors, including their residential history.

Geocoding addresses and linkage to U.S. census-tract socioeconomic indicators

During the interview, mothers self-reported all residential addresses where they lived for at least 30 days between the three months before pregnancy to the end of pregnancy. Address(es) were successfully geocoded by the Agency for Toxic Substances and Disease Registry's Geospatial Research, Analysis, and Services Program using the Centrus software version 6.00.00N for 97% of NBDPS participants and subsequently linked by the CDC to the 2000 and 2010 U.S. Census Tracts using ArcGIS. Census-tract level data from the 2000 US Census and 5-year American Community Survey (ACS) were linked to maternal addresses by Federal Information Processing Standards (FIPS) codes and infant birth year.

Maternal periconceptional neighborhood

We defined "maternal neighborhood" as the census tract corresponding to each participant's self-reported address during the periconceptional period of her pregnancy (i.e., one month before conception to the third month of pregnancy) to ensure nSEP is captured during the critical period of gastroschisis development (i.e., 8^{th} – 11^{th} gestational week[58]). If multiple addresses were reported for that period, we selected the address with the longest duration. Participants were excluded if they (1) reported multiple addresses during the periconceptional period with the same duration since it was unclear which address would have a larger influence on the risk of gastroschisis or (2) reported only one address with a duration of < 30 days (Figure 5).

Among all 12,243 NBDPS gastroschisis cases and controls with at least one geocoded address, we assigned a periconceptional address as described above to 97% (n=11,838). Overall, ~6% of cases and controls were excluded due to missing geocoded addresses during the periconceptional period. Geocoding at the census tract level for maternal neighborhoods was successful for 93% of cases and 94% of controls. 6,315 census tracts were represented in our study sample.

Neighborhood Deprivation Index

To characterize nSEP, two indices were used: the neighborhood deprivation index (NDI) developed by Messer et al.[115] and the neighborhood socioeconomic position index (nSEPI) we created using additional census indicators.

Detailed methods used to create the NDI are described elsewhere.[115] In brief, eight census-tract level indicators representing five socioeconomic domains (income/poverty, occupation, housing, employment, and education) were selected to construct this index: percent of crowded housing, percent of males in management and professional occupations, percent of households in poverty, percent of households on public assistance, percent of female-headed households with dependents, percent of unemployed residents, percent of households earning < $30,000 per year, and percent of residents with less than a high school education (Table 3).

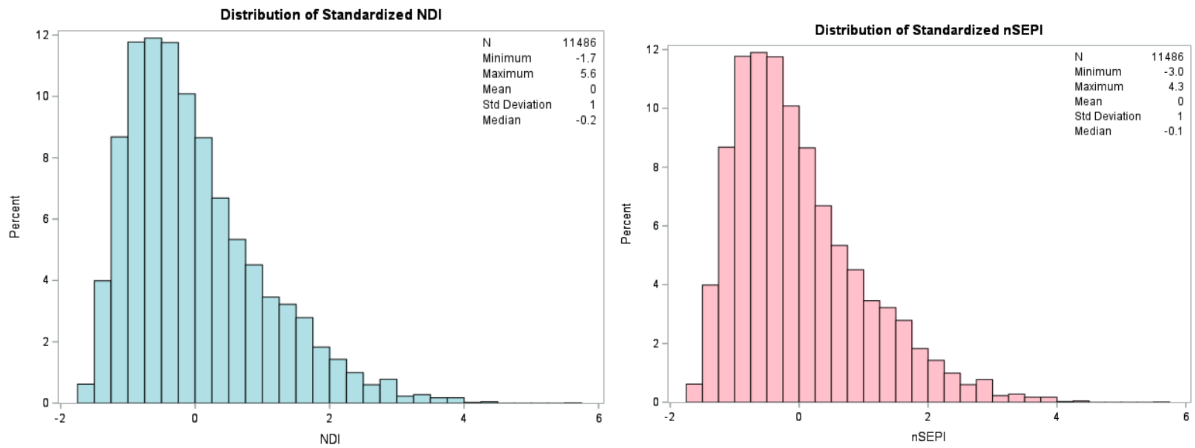
All census-tract level indicators were pooled across our study sample and principal component analysis (PCA) was performed. The first principal component was retained because it accounted for the largest proportion of the total variation among the component measures,[115] and the component loadings were used to weight each census variable's contribution to the index score. The index was standardized to have a mean of 0 and a standard deviation of 1 (Figure 9, Range: -1.7, 5.6), with low scores indicating less deprivation and high scores indicating greater deprivation. The NDI was linked to NBDPS participants and categorized into tertiles (low [reference], moderate, and high neighborhood deprivation) based on the distribution among controls, to examine a potential gradient in the risk of gastroschisis.

Neighborhood Socioeconomic Position Index

Socioeconomic position, both at the individual and neighborhood level, is a multidimensional construct that should be measured with as many indicators as possible to reflect each socioeconomic domain.[112] Although socioeconomic indicators are correlated, they are generally not strong enough to be proxies for one another.[112] Thus, the nSEPI includes additional indicators, in particular, measures of socioeconomic advantage, to provide a richer representation of each socioeconomic domain.

The nSEPI is composed of the eight single-census indicators in the NDI and nine additional indicators: percent of residents with a bachelor's degree or higher; percent of employed residents who are nature, construction, or transportation workers; percent of employed residents who reported being an unpaid family worker or self-employed; median household income; percent of owner-occupied homes with values greater than $300,000; percent of owner-occupied homes with a mortgage and monthly owner costs of 30% or more of household income; percent of owner-occupied homes without a mortgage and monthly owner costs of 30% or more of household income; percent of renter-occupied units among total occupied housing units and percent of renter-occupied units with a monthly rent that costs 30% or more of household income (Table 3). The nSEPI was constructed following the same methods as the NDI (Figure 9, Range: -3.0, 4.3), with low scores indicating high nSEP and high scores indicating low nSEP. Tertiles represent high (reference), moderate and low nSEP.

Figure 9. Distribution of Neighborhood Deprivation Index (NDI) and Neighborhood Socioeconomic Position Index (nSEPI), National Birth Defects Prevention Study, 1997 - 2011



Individual-level covariates

Individual-level variables were obtained from the NBDPS interview. Potential confounders were selected *a priori* using a directed acyclic graph (DAG)[161] (Figure 6) and included infant birth year (1997-2004, 2005-2009, 2010-2011); iSEP measured by maternal years of education (0-11, 12, > 12 years) and household income (<$10,000, $10,000 - $50,000, >$50,000); self-identified maternal race/ethnicity (Non-Hispanic Black, Non-Hispanic White, Hispanic, and Other); and duration of residency (continuous). Race/ethnicity is conceptualized as a socially-constructed classification system, based on phenotypic characteristics. This system often governs the opportunities and risks individuals are exposed to and is deeply entwined with residential and socioeconomic segregation. Additional descriptive variables that are included but not in the covariate adjustment set are in Table 8.

Statistical analysis

Multiple imputation with fully conditional specification was used to account for missing data, including household income (9% missing), maternal education (2% missing), and census-tract SEP indicators (0.01% – 0.29% missing), assuming data were missing at random. Ten imputation cycles were conducted. PCA and generalized estimating equations (GEEs) were conducted on each imputation dataset and results were pooled using the *proc mianalyze* procedure in SAS.[162]

Generalized estimating equations (GEEs) with logistic links and robust errors were used to estimate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). The use of GEEs accounted for potential correlation and non-independence of outcomes among mothers clustered within the same neighborhood. We first modeled single-tract-level nSEP indicators on gastroschisis to explore the association between specific aspects of nSEP and gastroschisis, adjusting for the individual-level covariates identified above. Additionally, we examined the association between two neighborhood-level indices (NDI and nSEPI) and gastroschisis. Estimates were adjusted for covariates identified in the DAG. The correlation between the two neighborhood-level indices was examined using Spearman correlations. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

4.3 Results

Study population description

We analyzed data from 11,486 NBDPS participants, including 1,269 gastroschisis infants and 10,217 controls. Compared with control mothers, case mothers were more likely to be young (< 25 years), nulliparous, Hispanic, have a BMI < 25 kg/m^2, smoke, use recreational drugs, have a household income of < \$10,000, and have ≤ 12 years of education. The average total duration of residency was approximately three years, with case mothers having a shorter mean length of stay (~2.6 years) relative to control mothers (~3.5 years) (Table 8). Case mothers (45-46%) were also more likely to reside in higher deprivation areas compared to control mothers (33%) (Table 9).

The neighborhood-level indices were highly correlated (r = 0.99). The first principal component of the NDI and nSEPI explained about 57% and 41% of the total variability among the component measures, respectively. The top three indicators that were strongly correlated with the first principal component of both indices were low education, households earning < $30,000 per year, and poverty (Table 10).

Single census-tract socioeconomic indicators

Mothers residing in areas characterized by adverse census indicators, such as high unemployment, had a higher unadjusted risk of having an infant with gastroschisis, whereas, mothers residing in areas characterized by favorable indicators, such as males in management and/or professional occupations, had a reduced unadjusted risk. Adjustment for maternal-level characteristics attenuated the crude effect estimates such that the majority of single census-tract nSEP indicators had odds ratios around the null; however, few associations remained (Table 11).

Neighborhood-level indices

Results were similar for both neighborhood-level indices (Table 12). We observed a monotonic increase in the unadjusted odds of gastroschisis. Upon covariate adjustment, the patterns of association remained similar to the crude estimates, though the estimates were attenuated towards the null. Mothers residing in moderate (NDI Tertile 2: aOR: 1.25; 95% CI: 1.05, 1.49) or high deprivation (NDI Tertile 3 aOR: 1.27; 95% CI: 1.05, 1.54) neighborhoods, characterized by adverse census indicators, were more likely to deliver an infant with gastroschisis compared with mothers residing in low deprivation areas. Similarly, mothers residing in areas of moderate (nSEPI Tertile 2 aOR: 1.25; 95% CI: 1.04, 1.49) or low nSEP (nSEPI Tertile 3 aOR: 1.32, 95% CI: 1.09, 1.61) had elevated risks of having an infant with gastroschisis (Figure 10) compared with mothers residing in high nSEP areas.

Table 8. Maternal and infant characteristics for mothers of participants with gastroschisis (cases) and infants without a birth defect (controls), National Birth Defects Prevention Study, 1997 - 2011

	Gastroschisis Cases n = 1,269	**Controls n = 10,217**	**Total n = 11,486**
Maternal age at conception (years)			
<20	540 (42.6)	1294 (12.7)	1834 (16.0)
20-25	541 (42.6)	2969 (29.1)	3510 (30.6)
26-35	178 (14.0)	5106 (50.0)	5284 (46.0)
≥36	10 (0.8)	848 (8.3)	858 (7.5)
Parity			
0	830 (65.4)	3986 (39.0)	4816 (41.9)
1	272 (21.4)	3334 (32.6)	3606 (31.4)
≥2	166 (13.1)	2891 (28.3)	3057 (26.6)
Missing	1 (0.1)	6 (0.1)	7 (0.1)
Maternal race/ethnicity			
Non-Hispanic White	644 (50.8)	5978 (58.5)	6622 (57.7)
Non-Hispanic Black	107 (8.4)	1089 (10.7)	1196 (10.4)
Hispanic	410 (32.3)	2484 (24.3)	2894 (25.2)
Other	108 (8.5)	666 (6.5)	774 (6.7)
Maternal pre-pregnancy BMI (kg/m^2)			
Underweight (<18.5)	109 (8.6)	508 (5.0)	617 (5.4)
Normal weight (18.5≤BMI<25)	830 (65.4)	5198 (50.9)	6028 (52.5)
Overweight (25≤BMI<30)	223 (17.6)	2251 (22.0)	2474 (21.5)
Obese (≥30)	71 (5.6)	1858 (18.2)	1929 (16.8)
Missing	36 (2.8)	402 (3.9)	438 (3.8)
Maternal education (years)			
<12	346 (27.2)	1687 (16.5)	2032 (17.7)
12	489 (38.5)	2439 (23.9)	2927 (25.5)
>12	435 (34.3)	6092 (59.6)	6526 (56.8)
Annual household income ($USD)			
<$10,000	441 (34.7)	2012 (19.7)	2453 (21.4)
$10,000 - $50,000	679 (53.5)	4668 (45.7)	5347 (46.6)

>$50,000	149 (11.7)	3537 (34.6)	3685 (32.1)
Maternal employment			
Employed	852 (67.1)	7213 (70.6)	8065 (70.2)
Unemployed	376 (29.6)	2839 (27.8)	3215 (28.0)
Unknown	0 (0.0)	5 (0.1)	5 (0.04)
Missing	41 (3.2)	160 (1.6)	201 (1.8)
Maternal recreational drug use[a,b]			
Yes	170 (13.4)	456 (4.5)	626 (5.5)
No	1057 (83.3)	9600 (94.0)	10657 (92.8)
Missing	42 (3.3)	161 (1.6)	203 (1.8)
Maternal smoking[a]			
Yes	438 (34.5)	1812 (17.7)	2250 (20.0)
No	793 (62.5)	8250 (80.8)	9043 (78.7)
Missing	38 (3.0)	155 (1.5)	193 (1.7)
Maternal alcohol[a]			
Yes	518 (40.8)	3752 (36.7)	4270 (37.2)
No	708 (55.8)	6284 (61.5)	6992 (60.9)
Missing	43 (3.4)	181 (1.8)	224 (1.9)
Gestational age at delivery (weeks)			
Very preterm (<32 wks)	80 (6.3)	107 (1.0)	187 (1.6)
Preterm (32-36 wks)	710 (55.9)	725 (7.1)	1435 (12.5)
Term (37-45 wks)	478 (37.7)	9384 (91.8)	9862 (85.9)
Missing	1 (0.1)	1 (0.01)	2 (0.02)
Duration of residence (days)	952 (30 – 14,152)	1,274 (30 – 14,456)	1,239 (30 – 14,456)

Data presented as n (%) or mean (range)
BMI: Body mass index
[a]Self-reported use between one month prior to conception to third month of pregnancy
[b]Recreational drug use includes: marijuana, hash, cocaine, crack, hallucinogens, heroin, hallucinogenic mushrooms

Table 9. Distribution of gastroschisis cases and controls by neighborhood indices, NDI and nEPI

	Gastroschisis Cases n = 1,269	**Controls n = 10,217**
Neighborhood Deprivation Index (NDI)		
T1 (Low deprivation)	246 (19.4)	3407 (33.3)
T2	454 (35.8)	3406 (33.3)
T3 (High deprivation)	569 (44.8)	3405 (33.3)
Neighborhood Socioeconomic Position (nSEPI)		
T1 (High nSEP)	240 (18.9)	3406 (33.3)
T2	449 (35.4)	3406 (33.3)
T3 (Low nSEP)	580 (45.7)	3405 (33.3)

Data presented as n (%)
Neighborhood indices were created within each imputed dataset via principal component analysis. Counts and frequencies were averaged over the 10 imputed datasets.
NDI: Neighborhood Deprivation Index; nSEPI: Neighborhood Socioeconomic Position Index: nSEP: Neighborhood Socioeconomic Position
High tertile scores reflect high deprivation (NDI) or lower nSEP (nSEPI). Low tertile scores reflect low deprivation (NDI) or high nSEP (nSEPI).

Table 10. Neighborhood-level index component loadings

	NDI component loadings	nSEPI component loadings
Crowding	0.73269	0.67584
Low education	0.89459	0.87929
Unemployment	0.63385	0.58647
Males in management and professional occupations	-0.66328	-0.73436
Female headed households with dependents	0.47965	0.45906
Poverty	0.88975	0.84535
Households earning < $30,000 per year	0.86481	0.87896
Public Assistance	0.76763	0.71253
Affordable housing with mortgage	---	0.40177
Renters affordable housing	---	0.32866
High education	---	-0.81017
Median income	---	-0.80242
Rental occupancy	---	0.52012
Workers class	---	-0.0441
Manual occupation	---	0.73154
Affordable housing without mortgage	---	0.17981
Wealth	---	-0.48562

NDI: Neighborhood Deprivation Index; nSEPI: Neighborhood Socioeconomic Position Index

Table 11. Association between single census-tract level socioeconomic indicators and gastroschisis among women with at least one geocoded address during the periconceptional period, National Birth Defects Prevention Study, 1997 - 2011

	Gastroschisis Cases n = 1,269	Crude ORs (95% CIs)	Adjusted ORs (95% CIs)[a]
Crowding[b,c]			
T1	341	Ref	Ref
T2	417	1.22 (1.05 – 1.42)	1.07 (0.92 – 1.26)
T3	511	1.50 (1.29 – 1.74)	1.06 (0.89– 1.26)
Low education[b,c]			
T1	288	Ref	Ref
T2	422	1.47 (1.25 – 1.72)	1.06 (0.90 – 1.26)
T3	559	1.94 (1.67 – 2.26)	1.11 (0.92 – 1.34)
Unemployment[b,c]			
T1	299	Ref	Ref
T2	407	1.44 (1.23 – 1.68)	1.20 (1.01 – 1.41)
T3	563	1.92 (1.65 – 2.23)	1.35 (1.13 – 1.62)

Males in management and professional occupation[b,c]			
T1	526	Ref	Ref
T2	452	0.86 (0.75 – 0.98)	1.09 (0.94 – 1.26)
T3	291	0.55 (0.47 – 0.64)	0.87 (0.72 – 1.04)
Female-headed households w/ dependents[b,c]			
T1	286	Ref	Ref
T2	460	1.60 (1.38 – 1.87)	1.27 (1.08 – 1.49)
T3	523	1.83 (1.57 – 2.13)	1.27 (1.06 – 1.52)
Poverty[b,c]			
T1	264	Ref	Ref
T2	455	1.72 (1.47 – 2.02)	1.21 (1.02 – 1.43)
T3	550	2.08 (1.78 – 2.43)	1.18 (0.98 – 1.42)
Households earning < $30,000[b,c]			
T1	281	Ref	Ref
T2	449	1.59 (1.36 – 1.87)	1.13 (0.95 – 1.34)
T3	539	1.92 (1.64 – 2.23)	1.09 (0.91 – 1.30)
Public Assistance Income[b,c]			
T1	339	Ref	Ref
T2	376	1.11 (0.95 – 1.29)	0.92 (0.78 – 1.08)
T3	554	1.63 (1.42 – 1.89)	1.13 (0.96 – 1.33)
High education[c]			
T1	575	Ref	Ref
T2	442	0.77 (0.67 – 0.88)	0.95 (0.83 – 1.10)
T3	252	0.44 (0.37 – 0.51)	0.76 (0.64 – 0.92)
Affordable housing w/ mortgage[c]			
T1	415	Ref	Ref
T2	445	1.15 (0.99 – 1.34)	1.09 (0.94 – 1.27)
T3	409	1.39 (1.21 – 1.61)	1.14 (0.97 – 1.34)
Affordable housing w/out mortgage[c]			
T1	358	Ref	Ref
T2	412	1.07 (0.93 – 1.24)	1.02 (0.88 – 1.18)
T3	499	0.98 (0.85 – 1.14)	0.91 (0.78 – 1.06)
Manual occupation[c]			
T1	275	Ref	Ref
T2	444	1.61 (1.37 – 1.89)	1.16 (0.98 – 1.37)
T3	550	2.00 (1.72 – 2.32)	1.19 (1.00 – 1.41)
Workers class			
T1	446	Ref	Ref
T2	404	0.91 (0.78 – 1.05)	0.98 (0.85 – 1.14)
T3	419	0.94 (0.81 – 1.08)	0.91 (0.79 – 1.06)

Renters affordable housing[c]			
T1	363	Ref	Ref
T2	427	1.18 (1.02 – 1.37)	1.10 (0.94 – 1.28)
T3	479	1.32 (1.14 – 1.53)	1.06 (0.91 – 1.25)
Renter occupancy[c]			
T1	341	Ref	Ref
T2	414	1.23 (1.06 – 1.43)	1.01 (0.86 – 1.18)
T3	514	1.52 (1.31 – 1.76)	1.14 (0.97 – 1.33)
Wealth[c]			
T1	438	Ref	Ref
T2	477	1.09 (0.95 – 1.25)	1.19 (1.03 – 1.38)
T3	354	0.81 (0.70 – 0.94)	1.13 (0.95 – 1.34)
Household median income[c]			
T1	503	Ref	Ref
T2	492	0.98 (0.86 – 1.12)	1.13 (0.97 – 1.31)
T3	274	0.54 (0.47 – 0.64)	0.87 (0.73 – 1.06)

NDI: Neighborhood Deprivation Index; nSEPI: Neighborhood Socioeconomic Position Index; T1: Tertile 1; T2: Tertile 2; T3: Tertile 3; OR: Odds Ratio; CI: Confidence Interval

High tertile scores reflect a high proportion of residents that meet census indicator definition. Low tertile scores reflect a low proportion of residents that meet census indicator definition.

Separate models were run for each census indicator.

[a] Adjusted for maternal race/ethnicity (Non-Hispanic Black, Non-Hispanic White, Hispanic, Other), infant birth year (1997 – 2004, 2005 – 2009, 2010 – 2011), household income (<$10,000 $10,000 - $50,000, >$50,000), maternal education (0-11, 12 and > 12 years), and duration of residence

[b] Census indicator used to create the NDI

[c] Census indicator used to create the nSEPI

Table 12. Association between neighborhood indices and gastroschisis among women with at least one geocoded address during the periconceptional period, National Birth Defects Prevention Study, 1997 - 2011

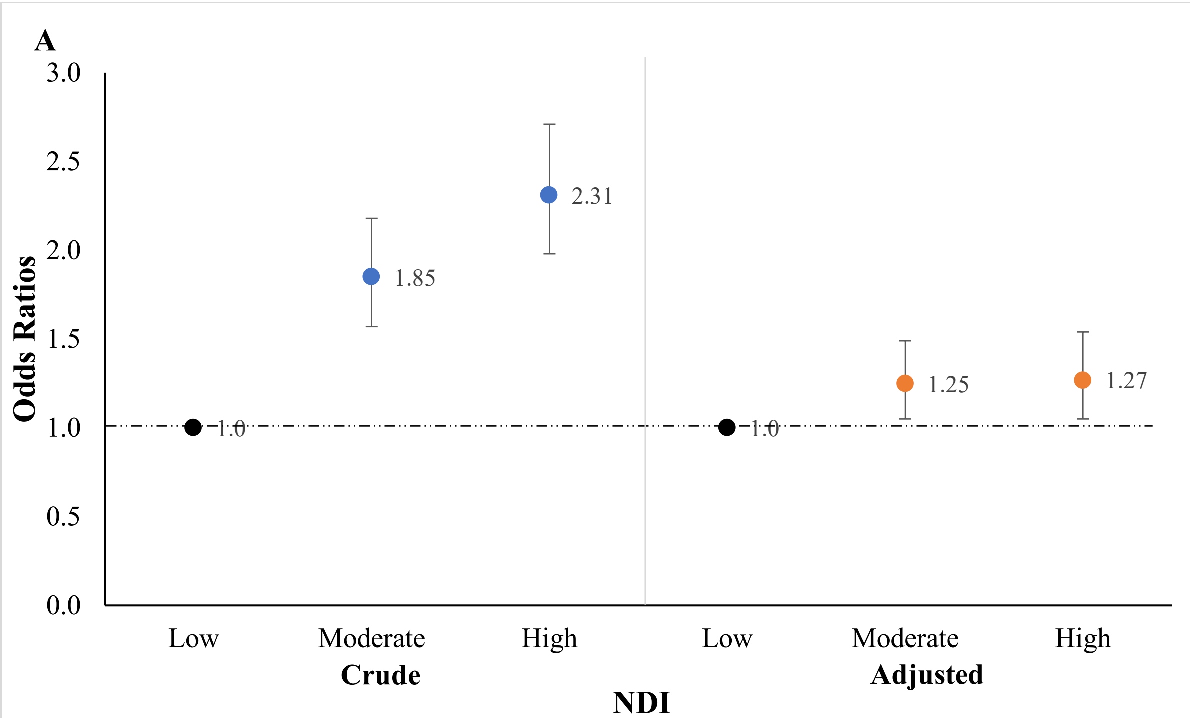
	Case n = 1,269	Crude ORs (95% CIs)	Adjusted ORs (95% CIs)[a]
NDI			
T1 (Low deprivation)	246	Ref	Ref
T2	454	1.85 (1.57 – 2.18)	1.25 (1.05 – 1.49)
T3 (High deprivation)	569	2.31 (1.98 – 2.71)	1.27 (1.05 – 1.54)
nSEPI			
T1 (High nSEP)	240	Ref	Ref
T2	449	1.87 (1.59 – 2.20)	1.25 (1.04 – 1.49)
T3 (Low nSEP)	580	2.42 (2.06 – 2.83)	1.32 (1.09 – 1.61)

T1: Tertile 1; T2: Tertile 2; T3: Tertile 3; NDI: Neighborhood Deprivation Index; nSEPI: Neighborhood Socioeconomic Position Index

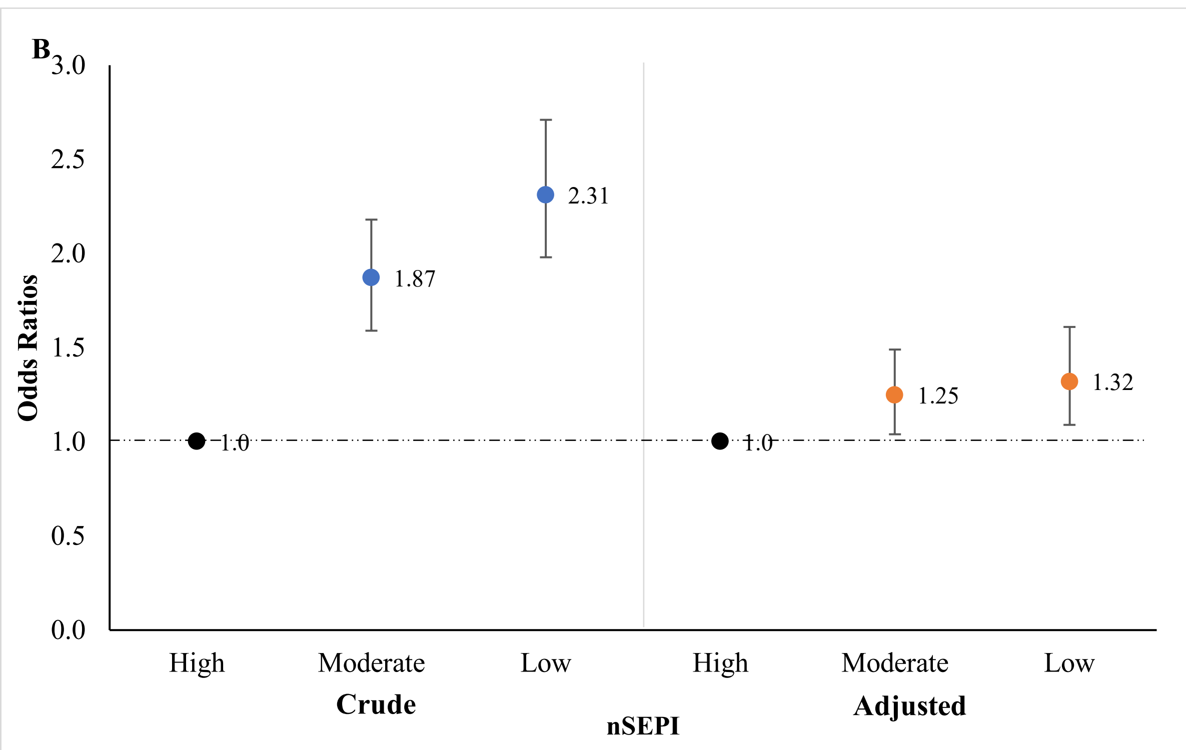
High tertile scores reflect high deprivation (NDI) or lower nSEP (nSEPI). Low tertile scores reflect low deprivation (NDI) or high nSEP (nSEPI).

[a] Adjusted for maternal race/ethnicity (Non-Hispanic Black, Non-Hispanic White, Hispanic, Other), infant birth year (1997 – 2004, 2005 – 2009, 2010 – 2011), household income (<$10,000 $10,000 - $50,000, >$50,000), maternal education (0-11, 12 and > 12 years), and duration of residence

Figure 10. Crude and adjusted ORs (95% CIs) for the association between (a) Neighborhood Deprivation Index (NDI) (b) Neighborhood Socioeconomic Position Index (nSEPI) and gastroschisis



Adjusted for maternal race/ethnicity, education, household income, birth year, and duration of residence



Adjusted for maternal race/ethnicity, education, household income, birth year, and duration of residence

4.4 Discussion

Principal findings

This study examined the overall association between measures of nSEP during early pregnancy and risk of gastroschisis. We constructed two weighted neighborhood-level indices (NDI and nSEPI) and results were similar. Given the NDI is a standardized index that has been widely used to describe associations between neighborhood-level factors and other birth outcomes, we believe the NDI may be a better measure of nSEP. Our findings suggest an overall elevation in risk of gastroschisis among mothers residing in neighborhoods characterized by moderate and high levels of socioeconomic deprivation during early pregnancy.

Literature review

To date, only one known study has explored the relationship between measures of nSEP and gastroschisis. Root et al.[31] conducted a case-control study in North Carolina (1998 – 2004) of 242 gastroschisis cases. Five socioeconomic position indicators were used to estimate nSEP including percent of residents living below 100% and 200% of the federal poverty level, percent of residents with less than a high school education, percent of residents unemployed, and percent of African American residents. Although estimates were imprecise, residing in census tracts characterized by high levels of residents living below 200% of the federal poverty level (aOR: 1.25; 95% CI: 0.81, 1.97) and unemployment (aOR: 1.21; 95% CI: 0.81,1.84) was modestly associated with gastroschisis, after adjustment for maternal age, race/ethnicity, parity, smoking, and Medicaid status.[31]

Similarly, we observed a modest increase in the risk of gastroschisis associated with neighborhoods characterized by moderate to high unemployment and poverty. However, direct comparison of results is difficult due to differences in nSEP measures, study size, covariate adjustment sets, and geographical areas of the study population. Our analysis expands meaningfully on Root et al.'s study[31] in four ways. First, we evaluated this association in a much larger sample of 1,269 gastroschisis cases spanning a national geographical range. Second, we not only examined single socioeconomic position indicators but also composite neighborhood-level indices. Third, we used the address during the periconceptional period to define maternal neighborhood to reduce exposure misclassification. Lastly, we included additional measures of iSEP, specifically, maternal education and household income, to account for factors associated with residential selection.

Our findings add to a small body of literature examining the overall associations between nSEP and birth defects. In general, results of these studies are inconsistent. Two studies[3,15] using similar nSEP factors as in our analysis reported a modest association with cleft lip with or without palate, whereas, one study[131] using the Carstairs index reported no associations. Inconsistent findings with neural tube defects[6,129] and conotruncal heart defects have also been reported.[15,159]

Studies of neighborhood-level effects on pregnancy outcomes have typically adjusted for iSEP, as in our analysis. While adjustment theoretically mitigates bias due to confounding, there may be compelling reasons to consider the interpretation of unadjusted estimates when investigating nSEP. Epidemiologic evidence suggests that iSEP, measured by low household income, insurance status, and mothers whose fathers were absent, may be associated with gastroschisis, after adjustment for maternal age.[21,22,75] In our study, adjustment for household income had the most impact on the change between crude and adjusted estimates (Supplementary Table 2). However, if nSEP during the periconceptional period influences, at least in part, iSEP, the unadjusted estimates may be more appropriate because adjusting for it may remove part of the neighborhood-level effect. For example, if residing in deprived neighborhoods with few career opportunities affects an individual's income, adjusting for iSEP measures would lead to overadjustment bias,[170] producing estimates that may be attenuated. If so, the crude models may be more appropriate. However, if iSEP is more likely influenced by socioeconomic factors of the mother's neighborhood at birth or at another point along the life course, including it in the model will account for residential selection during the periconceptional period and produce neighborhood-level effect estimates above and beyond individual-level factors. Furthermore, studies have shown that residents tend to remain in neighborhoods within a given socioeconomic stratum[171,172] and that there is a low degree of social mobility in the United States.[173] Thus, it is plausible that an individual's current neighborhood has less of an impact on iSEP than originally thought and is the basis for including it as a confounder in this analysis.

In addition, we did not identify maternal age at conception, one of the strongest risk factors for gastroschisis, as a confounder, but rather a mediator based on our DAG. Studies have shown that there are many social, cultural, and economic factors that influence childbearing age.[174,175] For instance, women with access to career opportunities are likely to pursue professional occupations, which may increase labor force participation, further postponing childbearing age.[174,176] Additionally, given it is often not simply childbearing but childrearing instead, raising a child is often intertwined with the social support and material resources available to mothers within their community, such as support among residents and quality childcare services.[175–177] Thus, despite the strong association between maternal age and gastroschisis, we believe that nSEP in part influences when a woman conceives. This reasoning can similarly be applied to other risk factors of gastroschisis, such as BMI and risky health behaviors, given that nSEP likely influences other individual-level characteristics.[8,103,111,166,178,179]

Since our analysis is focused on examining the total effect of nSEP and gastroschisis, adjusting for maternal age at conception would introduce bias. However, it is important to acknowledge that the strong correlation between maternal age and iSEP is difficult to deconstruct. Adjustment for iSEP may inadvertently also adjust for maternal age. Thus, it may be more appropriate to consider the unadjusted and adjusted estimates as a range that contains a more accurate estimate of this overall association.[180] Nevertheless, our results suggest that lower nSEP during early pregnancy may increase the risk of gastroschisis.

Potential mechanisms linking neighborhoods to gastroschisis

There are multiple mechanisms by which neighborhoods influence individual health.[8,103,179] It is hypothesized that the physical, social, and service environment of a neighborhood impacts individual health by mediating through biological and/or social factors, such as psychosocial stress and health behaviors, that may directly or indirectly affect biological processes.[103,111,166,178,179] However, these mechanisms are unknown, partially because the etiology and pathogenesis of this defect are unknown. To aid in hypothesizing these mechanisms, we considered the theorized pathways proposed in other neighborhood-birth outcome studies.

The first hypothesized mechanism is through the physical characteristics, or built environment, of the neighborhood. This includes exposure to air/noise pollution, environmental toxins, water quality, dilapidated housing, and the overall physical space. Given some studies have shown increased odds of gastroschisis with pesticide exposure[181] and overall environmental exposures, as assessed by the Environmental Quality Index,[102] neighborhood physical characteristics may have direct biological consequences on gastroschisis development.

Additionally, these characteristics may have indirect biological effects through its influence on the social environment of the neighborhood.[8] The social environment refers to the relationships among residents, level of cohesion or disorganization, and overall degree of community integration.[182] This mechanism may influence maternal health, and subsequently gastroschisis, through exposure to acute and chronic psychosocial stress. Although no studies to date have examined the association between stress-related biomarkers and gastroschisis, cumulative stress exposures defined to have biologic evidence of inducing an inflammatory stress response[85] and stressful life events[183] have been shown to increase the odds of gastroschisis, indicating that social factors may directly affect biological processes and play a role in gastroschisis development. Furthermore, social factors may indirectly affect biological processes through downstream factors by influencing the adoption of stress-related health behaviors as coping mechanisms, such as smoking and alcohol, which have been shown to be associated with gastroschisis.[21]

Depending on the extent to which residents cohesively work together to demand services for their community, the social environment may indirectly influence the service environment of the neighborhood. The service environment reflects the availability of goods and services such as health care, transportation systems, police and fire safety, and healthy foods.[128,179] Depending on the level of neighborhood socioeconomic deprivation, necessary and high-quality services, such as prenatal care and municipal services, may not exist or be relatively inaccessible in certain communities. Areas with poor access to services may not only have a direct impact on the safety and health of residents but may also indirectly contribute to additional levels of psychosocial stress influencing the risk of gastroschisis, especially among women exposed to other negative aspects of their neighborhood.

Although our study was not aimed to assess a specific causal mechanism linking nSEP factors and gastroschisis, our findings confirm there is a contextual element that may directly or indirectly influence maternal factors associated with gastroschisis.

Strengths and limitations

The use of NBDPS data provided many strengths including geographic diversity, population-based ascertainment of cases and controls, a large sample of gastroschisis cases, clinically verified outcomes, and extensive covariate information. We extended the current literature on the relationship between nSEP and gastroschisis by including multiple socioeconomic position indicators and two neighborhood-level indices.[115] Furthermore, this analysis was also strengthened by defining maternal neighborhood based on the address during the periconceptional period to ensure the nSEP was present during the critical period of gastroschisis development.

This analysis, however, is not without limitations. First, although we adjusted for covariates identified in our DAG, residual confounding may occur due to unmeasured factors.[112] Additionally, given iSEP is strongly correlated with maternal age at conception, a mediator in this study, adjustment for iSEP may inadvertently adjust for maternal age. Second, neighborhoods were geographically defined using census tracts rather than the mother's perception of her neighborhood. Nevertheless, census tracts are often used in neighborhood-level studies and have been shown to be meaningfully useful in relation to birth outcomes.[158] Third, if factors associated with participation or having a geocoded address were systematically different from nonparticipants and women without a geocoded address, the exclusion of both would lead to bias. However, a previous study reported that NBDPS control mothers were generally representative of their base populations.[153] Also, given only 3% of NBDPS participants were excluded due to missing geocoded addresses, selection bias is likely minimal. Finally, assessment of neighborhood-level factors at one point in time may not only conceal how disparate neighborhoods truly are since neighborhoods may change over time, but may also inaccurately reflect a mother's cumulative lifetime exposure to these contextual factors. The lack of data on the historical context of periconceptional neighborhoods and the neighborhoods mothers were born into and/or raised likely understates the true impact of neighborhoods on birth outcomes.[171]

Conclusions and future directions

Our study suggests that lower nSEP during early pregnancy is modestly associated with an elevated odds of gastroschisis. These findings require replication in additional epidemiologic studies. Future studies should assess neighborhoods mothers resided in over the life course. Additionally, given nSEP may differentially affect certain mothers, studies should examine nSEP as a potential effect measure modifier and the interactions between neighborhood- and individual-level characteristics, such as iSEP and nSEP, on the risk of gastroschisis.[128] Lastly, future studies should further explore the degree to which individual-level factors, such as maternal age at conception and risky health behaviors, account for the influence of nSEP on the risk of gastroschisis. Greater insight into mechanisms linking nSEP and gastroschisis will potentially help identify modifiable neighborhood characteristics that may be critical in shaping future public health interventions.

CHAPTER 5: DOES NEIGHBORHOOD-LEVEL SOCIOECONOMIC POSITION MODIFY THE ASSOCIATION BETWEEN MATERNAL AGE, PRE-PREGNANCY BODY MASS INDEX, AND GASTROSCHISIS?

5.1 Introduction

Gastroschisis is an abdominal birth defect characterized by the protrusion of intestines and sometimes other abdominal organs outside the body.[18,19] The prevalence has been increasing worldwide, possibly driven by an increase among young mothers. Between 1995 and 2005, the percentage increase in the prevalence of gastroschisis among mothers younger than 20 years was 6.5% compared with an increase of 0.2% among mothers 35 years or older.[34] To date, much of the gastroschisis literature has focused on individual-level risk factors.

Epidemiologic studies have consistently observed strong associations with young maternal age and low body mass index (BMI).[24–27,65,66] However, the mechanisms underlying these associations remain unknown. A study by Reefhuis and Honein reported that women ages 14 -19 years were seven times as likely to have an infant with gastroschisis compared with women ages 25 - 29 years (OR: 7.2; 95% CI: 4.4 – 11.8).[65] Similar results were observed in a more recent study using data from the National Birth Defects Prevention Study (NBDPS). Women younger than 20 years were six times as likely to have an infant with gastroschisis compared with women ages 25-29 years (OR: 6.1; 95% CI: 4.8 – 8.0).[66] For the association between BMI and gastroschisis, a previous study reported a three-fold increased risk (OR: 3.2; 95% CI: 1.4 – 7.4) associated with underweight BMI (<18.1 kg/m^2) and a reduced risk (OR: 0.2; 95% CI: 0.04 – 0.8) associated with overweight BMI (> 28.3 kg/m^2), after adjusting for maternal age and race/ethnicity. Additionally, when BMI was specified as a continuous variable, the risk decreased by ~11% for every unit increase in BMI.[26] Although these unique associations are thought to reflect lifestyle behaviors and/or biological factors, such as smoking or decreasing nutrient availability for the developing embryo with decreasing BMI, the mechanisms underlying these associations remain unknown.[18,34]

In recent decades, it has been suggested that neighborhood contextual factors influence the risk of adverse pregnancy outcomes.[103] Previous studies have observed modest associations between measures of neighborhood socioeconomic characteristics and suboptimal maternal health,[166,184] in addition to, birth outcomes, including low birth weight,[14] preterm birth,[1] orofacial clefts,[168] neural tube defects,[6] and congenital heart defects,[15,159] after accounting for individual-level socioeconomic position (iSEP). For gastroschisis, one study using data from North Carolina (1998 – 2004) observed an increased risk among mothers residing in areas characterized by high poverty and unemployment.[31] Additionally, in a previous analysis using data from the National Birth Defects Prevention Study (NBDPS) between 1997 and 2011, we observed a monotonic increase in the risk of gastroschisis associated with decreasing nSEP during early pregnancy (Neo et al., submitted).

Neighborhood conditions closely related to the neighborhood's socioeconomic position may not only influence the risk of gastroschisis by patterning individual-level risk factors, such as age at conception or pre-pregnancy BMI; but the effect of these factors may behave differently depending on the shared characteristics of the neighborhood through social and environmental stressors. Insight into these relationships may provide important etiologic clues. For instance, if these associations persist irrespective of contextual factors associated with nSEP, this may suggest that other unidentified factors potentially play a larger role in influencing the risk of gastroschisis. Alternatively, if these associations disappear in certain strata of nSEP, such that young mothers or mothers of low or normal BMI in high SEP areas are no longer at a higher risk of having an infant with gastroschisis, this may indicate that factors associated with low SEP areas largely influence these strong associations. Thus, in this analysis, we examine whether the associations between young maternal age at conception and low or normal pre-pregnancy BMI and the risk of gastroschisis, differ by nSEP.

5.2 Materials and methods

Study population

This study used data from the National Birth Defects Prevention Study (NBDPS). Detailed study methods have been published elsewhere.[152] In brief, the NBDPS is a population-based, multi-site, case-control study sponsored by the Centers for Disease Control and Prevention (CDC) that investigates risk factors associated with more than 30 major birth defects, including gastroschisis. The NBDPS included pregnancies between October 1997 and December 2011 in ten participating states: Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New York, New Jersey, Texas, and Utah. The NBDPS was approved by the Institutional Review Board (IRB) at the CDC and at each participating center.

For this analysis, we included cases that were singleton livebirths, stillbirths (fetal deaths ≥ 20 weeks' gestation), or terminations with a diagnosis of gastroschisis (British Pediatric Association (BPA) modification of the International Classification of Diseases, 9th revision (ICD-9)). Cases were ascertained through the participating centers' birth defects surveillance program from the entire state (AR, IA, NJ, UT) or from selected counties (CA, GA, MA, NC, NY, TX). Using standardized case classification guidelines, case medical records were systematically reviewed by clinical geneticists to confirm diagnoses, exclude cases with genetic etiologies, and classify cases as isolated (vs. non-isolated), if there was no concurrent major anomaly, or sequence, if there were additional major defects that were developmentally related to one another.[152,169] Liveborn singleton infants without a birth defect were randomly selected as controls from hospital records and/or birth certificates from the same geographic area and time period as the cases.

Eligible mothers of case and control infants who provided informed consent participated in a computer-assisted telephone interview (CATI) approximately 6 weeks to 24 months after their estimated date of delivery. The interview included questions regarding sociodemographic information, residential history, lifestyle and behavioral factors, medical history, and other exposures that occurred between three months prior to conception through the end of the pregnancy. Overall, participation rates were approximately 65% for case and 64% for control mothers.

Defining maternal neighborhood

During the interview, mothers self-reported all residential addresses they lived at for at least 30 days between three months prior to pregnancy to the end of pregnancy. For this study, we geographically defined "maternal neighborhood" as the census tract corresponding to the address mothers lived at during the periconceptional period, defined as one month prior to conception to the third month of pregnancy. If a participant reported multiple addresses for this period (13%), we selected the address with the longest duration. Mothers were excluded if they reported more than one address with the same length of stay during the periconceptional period on the basis that it was unclear which address would have a larger influence on the risk of gastroschisis (<1%) or if they only reported one address with a length of stay fewer than 30 days (<1%).

Geocoding addresses and linkage to U.S. census-tract socioeconomic indicators

Maternal addresses from all NBDPS participating centers except NJ were centrally geocoded by the Agency for Toxic Substances and Disease Registry's Geospatial Research, Analysis, and Services Program using the Centrus software version 6.00.00N. All successfully geocoded addresses (~97% of eligible NBDPS participants) were linked by the CDC to the 2000 and 2010 U.S. Census Tracts using ArcGIS. Census information from the 2000 U.S. Census and 5-year American Community Survey (ACS) was linked with the NBDPS analytic data set based on Federal Information Processing Standards (FIPS) codes and infant birth year. Specifically, census-tract level data from the 2000 U.S. Decennial Census, 2005-2009 ACS, and 2010-2014 ACS were linked to infants born between 1997-2004, 2005-2009, and 2010-1011, respectively.

Among the 12,243 NBDPS participants in our study population with at least one geocoded address, 97% were assigned a maternal neighborhood during the periconceptional period, as described above. Geocoding at the census tract level was successful for 93% of the interviewed cases and 94% of the controls. Overall, 6,315 census tracts were represented in our study sample.

Effect measure modifier: neighborhood-level socioeconomic position

Neighborhood-level SEP was characterized using the Neighborhood Deprivation Index (NDI) developed by Messer et al.[115] The NDI is a standardized index that represents five socioeconomic domains including income/poverty, education, employment, housing, and occupation, and has been commonly used to examine the relationships between neighborhood socioeconomic deprivation and pregnancy outcomes.[1,120,160] The NDI is comprised of eight census-tract level indicators including the percent of crowded housing, percent of males in management and professional occupations, percent of households in poverty, percent of households on public assistance, percent of female-headed households with dependents, percent of unemployed residents, percent of households earning < $30,000 per year, and percent of residents with less than a high school education (Table 3). To create this index, census-tract level data from all NBDPS geocoding participating centers were pooled and the data reduction technique principal component analysis (PCA) was performed. The component loadings of the first principal component were used to weight each census variable's contribution to the index score. The index score was standardized to have a mean of 0 and a standard deviation of 1 (Range: -1.7, 5.6), with high values indicating higher levels of neighborhood deprivation and low values indicating lower levels of neighborhood deprivation. The continuous index score was categorized into tertiles to represent low (reference), moderate, or high neighborhood deprivation and subsequently linked to NBDPS participants based on the periconceptional residence, as described above.

Individual-level variables

Data on maternal characteristics were obtained from the NBDPS interview. Self-reported maternal age at conception was dichotomized at 20 years (< 20 vs. ≥ 20 years), since epidemiologic studies have identified a definitive change in risk at this age threshold.[65,84,164] Maternal pre-pregnancy BMI was calculated using self-reported weight and height (kg/m^2) and subsequently categorized into three groups, representing underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), and overweight/obese (≥ 25.0 kg/m^2).[56]

We developed directed acyclic graphs (DAG) to identify minimally sufficient adjustment sets to mitigate confounding in our analysis of the associations between (1) maternal age at conception and gastroschisis (Figure 7) and (2) maternal BMI and gastroschisis (Figure 8) with potential effect measure modification by nSEP. Based on our DAGs, the adjustment set for our analyses of maternal age included years of education (0-11, 12, > 12 years) and household income (<$10,000, $10,000 - $50,000, >$50,000); and the adjustment set for analyses of BMI included years of education (0-11, 12, > 12 years), household income (<$10,000, $10,000 - $50,000, >$50,000), smoking (yes, no), alcohol (yes, no), substance abuse (yes, no), and maternal age at conception modeled as a quadratic term to allow for flexible adjustment.

Statistical analysis

Missing values for the following covariates were imputed using 10 cycles of multiple imputation: household income (9%), pre-pregnancy BMI (3.8%), education (2%) alcohol use (2%), substance use (1.8%), smoking (1.7%), and census-tract SEP indicators (0.01%). For each of the 10 imputation datasets, a PCA was performed to construct the NDI. In addition, to account for potential correlation and non-independence among mothers clustered within the same neighborhood, generalized estimating equations (GEEs) with logistic links and robust errors were conducted on each imputation dataset to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs). All imputation datasets were analyzed separately and the results were combined for inference using the proc mianalyze procedure in SAS.[162]

To assess potential effect measure modification by nSEP, we compared results within strata of NDI, adjusting for the appropriate minimally sufficient adjustment set. Effect measure modification was evaluated on the additive scale due to its relevance for public health purposes. The additive scale is recommended to indicate whether the effect of a risk factor is greater in a specific sub-population to help target potential interventions and resource allocations. Thus, we calculated the relative excess risk due to interaction (RERI) with 95% CIs based on standard errors obtained using the delta method.[165] All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and independently replicated (Co-author: SE).

5.3 Results

Description of study population

We analyzed data from 1,269 infants with gastroschisis and 10,217 control infants. Compared to mothers of controls, mothers of gastroschisis case infants were more likely to be young (< 20 years); nulliparous; Hispanic; be of normal or underweight; have completed fewer than 12 years of education; have a household income of less than $50,000; and self-report smoking, alcohol and recreational drug use during the periconceptional period (Table 8). In our study population, mothers of case infants were more likely to reside in highly deprived ("low" SEP) neighborhoods (NDI: 45%) and have a shorter mean duration of residence at their periconceptional neighborhood (~2.6 years) compared with mothers of control infants (NDI: 33%, ~3.5 years) (Table 9).

The first principal component of the NDI explained 57% of the total variability among the component measures. The top three indicators that were strongly associated with the first principal component were low education, households earning < $30,000 per year, and poverty (Table 10).

Does nSEP modify the association between maternal age at conception and gastroschisis?

Within each stratum of neighborhood socioeconomic deprivation, young maternal age at conception (< 20 years) was associated with a higher risk of gastroschisis. However, the magnitude of the association with young maternal age was higher among mothers residing in low deprivation ("high" SEP) neighborhoods (aOR: 6.55; 95% CI: 4.59, 9.35) than the association among mothers residing in high deprivation ("low" SEP) neighborhoods (aOR: 3.13, 95% CI: 2.59, 3.78). Furthermore, we observed evidence of antagonistic effect measure modification, on the additive scale, by high deprivation neighborhoods (RERI: -2.81; 95% CI: -4.93, -0.68) for the association between young maternal age at conception and gastroschisis. In other words, residing in high deprivation neighborhoods diminishes the effect of young maternal age at conception on the risk of gastroschisis, contrary to expectation. However, no modification was observed for moderate deprivation neighborhoods (RERI: -1.96; 95% CI: -4.12, 0.20).

Overall, as neighborhood deprivation increased, the magnitude of the association between young maternal age at conception and gastroschisis decreased, though age was still associated with an elevated odds of gastroschisis (Table 13).

Table 13. Association between maternal age at conception and gastroschisis, stratified by NDI, National Birth Defects Prevention Study, 1997 - 2011

Maternal age at conception (years)	Neighborhood Deprivation Index (NDI)	Cases, n	Controls, n	Stratified OR (95% CI)[a]	Single reference OR (95% CI)	RERI (95% CI)[b]
≥ 20	Low deprivation	168	3268	1.00 (Ref)	1.00 (Ref)	---
< 20		78	138	6.55 (4.59 – 9.35)	6.55 (4.59 – 9.35)	---
≥ 20	Moderate deprivation	273	2999	1.0 (Ref)	1.32 (1.06 - 1.63)	---
< 20		181	406	3.73 (2.96 – 4.69)	4.91 (3.72 – 6.47)	-1.96 (-4.12, 0.20)
≥ 20	High deprivation	288	2656	1.0 (Ref)	1.29 (1.02 – 1.63)	
< 20		281	750	3.13 (2.59 – 3.78)	4.04 (3.12 – 5.22)	-2.81 (-4.93, -0.68)

NDI: Neighborhood Deprivation Index
[a] Odds ratio (95% Confidence Interval), within strata of neighborhood index
[b]Relative excess risk due to interaction (95% Confidence Interval)
Adjusted for household income and maternal education

Does nSEP modify the association between maternal pre-pregnancy BMI and gastroschisis?

Normal (18.5 kg/m^2 ≤ BMI < 25 kg/m^2) or underweight BMI (<18.5 kg/m^2) were consistently associated with an increased risk of gastroschisis compared to overweight/obese BMI (≥25 kg/m^2), irrespective of the neighborhood socioeconomic deprivation level. Specifically, within each stratum of NDI, underweight (aOR range: 1.49 – 2.09) and normal (aOR range: 1.96 – 2.24) weight mothers had approximately two times the odds of having an infant with gastroschisis compared to mothers of overweight/obese BMI, after covariate adjustment. Furthermore, upon examination of the RERI estimates, residing in moderate or high deprivation neighborhoods did not modify the odds of gastroschisis for normal (moderate deprivation RERI: 0.04, 95% CI: -0.57, 0.64; high deprivation RERI: -0.19, -0.80, 0.41) or underweight (moderate deprivation RERI: 0.63, 95% CI: -0.48, 1.73; high deprivation RERI: 0.39, 95% CI: -0.71, 1.49) mothers (Table 14).

Table 14. Association between maternal pre-pregnancy BMI and gastroschisis, stratified by NDI, National Birth Defects Prevention Study, 1997 - 2011

Maternal BMI (kg/m^2)	NDI	Cases, n	Controls, n	Stratified OR (95% CI)[a]	Single reference OR (95% CI)	RERI (95% CI)[b]
Overweight/ obese	Low deprivation	16	161	1.00 (Ref)	1.00 (Ref)	---
Normal		181	2070	2.24 (1.59 – 3.16)	2.24 (1.59 – 3.16)	---
Underweight		49	1176	1.49 (0.81 – 2.75)	1.49 (0.81 – 2.75)	---
Overweight/ obese	Moderate deprivation	48	189	1.0 (Ref)	1.04 (0.71 – 1.49)	---
Normal		307	1740	2.24 (1.75 – 2.87)	2.31 (1.66 – 3.20)	0.04 (-0.57, 0.64)
Underweight		99	1477	2.09 (1.40 – 3.11)	2.15 (1.37 – 3.38)	0.63 (-0.48, 1.73)
Overweight/ obese	High deprivation	48	182	1.0 (Ref)	1.09 (0.77 – 1.56)	---
Normal		365	1571	1.96 (1.58 – 2.43)	2.14 (1.54 – 2.97)	-0.19 (-0.80, 0.41)
Underweight		155	1652	1.81 (1.22 – 2.68)	1.98 (1.23 – 3.17)	0.39 (-0.71, 1.49)

NDI: Neighborhood Deprivation Index
BMI: Body Mass Index: Underweight: <18.5 kg/m^2; Normal weight: 18.5 ≤ BMI < 25 kg/m^2; Overweight/obese: ≥ 25 kg/m^2
[a] Odds ratio (95% Confidence Interval), within strata of neighborhood index
[b]Relative excess risk due to interaction (95% Confidence Interval)
Adjusted for household income, maternal education, maternal age at conception, smoking, alcohol, and substance use

5.4 Discussion

In our study, young mothers (< 20 years) and mothers of low or normal BMI were consistently associated with elevated odds of gastroschisis regardless of the level of nSEP. Contrary to expectation, we observed that nSEP sub-additively modified the association between maternal age at conception and gastroschisis, such that young mothers in low deprivation ("high" SEP) neighborhoods had nearly double the risk of having an infant with gastroschisis than young mothers in high deprivation ("low" SEP) neighborhoods. However, nSEP was not found to modify the association between maternal pre-pregnancy BMI and gastroschisis.

Prior studies have consistently reported associations of gastroschisis with maternal age and BMI, yet we are unaware of any other studies that have evaluated the potential influence of contextual socioeconomic factors on these unique associations. In a previous analysis using data from the same study population used in this study (Neo et al., submitted), we observed a monotonic increase in the odds of gastroschisis among mothers residing in moderate and low nSEP, after adjusting for maternal race/ethnicity, education, household income, length of residency and birth year. Moreover, since nSEP may differentially affect certain mothers, this indicates the importance of examining how contextual factors may impact the relationships between individual-level risk factors and gastroschisis. Thus, our analysis expands upon the previous study by exploring how nSEP may influence these unique associations.

Our results are consistent with the strong evidence in the existing literature that mothers younger than 20 years are at a higher risk of having an infant with gastroschisis relative to mothers older than 20 years.[20,22,23] The reason(s) that young mothers are at higher risk remains unknown. It is suspected that lifestyle behaviors, environmental exposures, and other risk factors known to be more prevalent among younger mothers likely play a role in the risk of gastroschisis. In addition, to some degree, it is plausible that these risk factors are in some ways influenced by the social, service, and physical characteristics of a mother's residing neighborhood, which is closely related to the nSEP. Although we observed that nSEP modifies the association between maternal age at conception and gastroschisis, young mothers consistently had a higher risk regardless of the nSEP, suggesting that the underlying etiology of gastroschisis among adolescent mothers is likely driven by other, unidentified non-biologic or biologic factor(s) that may be unrelated to nSEP. For instance, the etiologic mechanism may involve aspect(s) of maternal biology that inversely change with increasing age, in the same manner as the prevalence of gastroschisis does with increasing age. However, the exact biological mechanism underlying this association is unknown, in part, because the etiology and pathogenesis of gastroschisis are unknown. Thus, our findings suggest that there are potentially other factor(s) unrelated to nSEP but specific to young mothers that may be better targets of intervention. However, it is unknown what those factor(s) are.

It is unclear why young mothers residing in high SEP neighborhoods have a substantially higher risk of gastroschisis relative to young mothers in low SEP neighborhoods. However, a possible explanation is the relative social deprivation hypothesis, which suggests that the inequality between a mother's social experience relative to their resident counterparts may cause psychological strain leading to higher levels of psychosocial stress.[185,186] Although adolescent mothers tend to be more socially disadvantaged irrespective of the level of nSEP,[187] residing in high SEP areas may cause increased levels of psychosocial stress associated with relative social standing comparisons and a sense of relative deprivation. This may explain, at least in part, why the risk of gastroschisis among young mothers in high SEP areas was nearly double that of young mothers in low SEP areas.

Our results for the association between maternal BMI and gastroschisis are consistent with prior literature demonstrating that mothers of low and normal BMI have an increased risk of having an infant with gastroschisis. Although neighborhood socioeconomic factors have been shown to be associated with BMI through access to physical activity opportunities[188] or healthy foods,[189] our results indicate that nSEP did not modify the association between maternal BMI and gastroschisis, suggesting that individual-level factors associated with BMI, such as maternal diet or undernutrition, may play a more important role in the development of gastroschisis.

This study has some limitations. First, non-differential exposure misclassification may have resulted from two sources. The first is the use of census tracts to define maternal neighborhoods. This geographical unit may not accurately represent the neighborhood to which a mother perceives she belongs. However, census tracts have been used in prior neighborhood-level studies and have been shown to be meaningfully useful in the context of adverse birth outcomes.[158] The second potential source of non-differential exposure misclassification is due to the lack of data regarding the amount of interaction mothers may have with their residential environment. Mothers who do not often interact with their neighborhoods may be misclassified in regards to the level of neighborhood socioeconomic deprivation they are exposed to. However, the impact of this potential misclassification cannot be determined with the data available. Another limitation of this study is selection bias that may have been introduced at two levels. The first is factors associated with non-participation in the NBDPS, since participation was 65% and 64% for case and control mothers, respectively. However, a previous study reported that participants and non-participants had similar demographic characteristics.[153] The second is if maternal characteristics differed between mothers with and without a geocoded address. We observed that excluded mothers without a geocoded address were more likely to be less than 20 years and of non-Hispanic Black or Hispanic race and ethnicity compared with included mothers with a geocoded address. However, given only 3% of NBDPS participants were excluded due to missing geocoded addresses, the potential impact of this selection bias is minimal. Lastly, the potential for residual confounding should be noted. Although we adjusted for several covariates identified by our DAG, it is possible that residual confounding from unknown confounders or misspecified variables contributed to our results.

Despite these limitations, this study also has several strengths. This is the first known study to examine if nSEP modifies the associations between maternal age, pre-pregnancy BMI, and the risk of gastroschisis. Although few studies have observed a modest association between nSEP and gastroschisis, no studies, to date, have examined how contextual factors may modify the effect of two, well-established risk factors. Another strength of this study is the use of NBDPS data. The NBDPS provided population-based ascertainment of cases and controls, extensive covariate information, standardized case classification verified by clinical geneticists, and a large sample size of cases with gastroschisis. In addition, maternal residential addresses were centrally geocoded at the CDC increasing data consistency and improving quality control of geocoded addresses used to characterize nSEP. Lastly, our study was strengthened by defining maternal neighborhood based on addresses during the periconceptional period. This ensures that any potential influence by nSEP occurs during the critical period of gastroschisis development.

The results of this study suggest that neighborhood socioeconomic factors may play a modifying role of the relationships between maternal age at conception, BMI, and gastroschisis. In particular, we observed that the association between young maternal age at conception and gastroschisis is stronger for women residing in high SEP neighborhoods compared to women residing in low SEP neighborhoods. In addition, our findings provide evidence that the strong association with young maternal age at conception may be due, in part, to non-biologic or biologic factors that is unlikely to be strongly related to nSEP, given that elevated odds were observed irrespective of the level of neighborhood socioeconomic deprivation. This study highlights the importance of evaluating the contributions neighborhood socioeconomic conditions may have on individual-level attributes and/or its influence on the risk of gastroschisis. Future epidemiologic studies are needed to corroborate these findings and to investigate why young mothers in high SEP neighborhoods have a higher risk of having an infant with gastroschisis compared with young mothers in low SEP neighborhoods.

CHAPTER 6: DISCUSSION AND CONCLUSIONS

6.1 Summary of specific aims

In recent decades, “neighborhoods” have emerged in the epidemiologic literature as an important upstream factor that may impact maternal and reproductive health. Several studies have reported an association between measures of neighborhood socioeconomic deprivation and adverse birth outcomes, including birth defects. However, very few studies have examined this association with gastroschisis and its potential influence on the relationships between well-established individual-level risk factors and gastroschisis. Thus, the goal of this dissertation research is to address this gap in knowledge through two aims. In Aim 1, we examined the overall association between neighborhood-level socioeconomic position (nSEP) during early pregnancy and the risk of gastroschisis. We first examined the associations between single SEP indicators and gastroschisis. In addition, we evaluated the overall association between nSEP and gastroschisis, using two PCA-derived neighborhood-level indices to characterize nSEP. In Aim 2, we examined whether the associations between (1) young maternal age at conception and (2) low or normal BMI and the risk of gastroschisis, differ by nSEP, using the same study population and nSEP characterization as in Aim 1.

6.1.1 Aim 1: Summary of findings

Upon examining single SEP indicators, we observed that mothers residing in neighborhoods characterized by adverse SEP indicators were more likely to have an infant with gastroschisis compared with mothers residing in areas characterized by favorable SEP indicators.

Adjustment for maternal race/ethnicity, household income, maternal education, birth year, and duration of residence attenuated the crude effect estimates. Only a few associations remained such as the percent of unemployed residents, female-headed households with dependents, and residents with at least a bachelor's degree or higher. All other associations were either suggestive of an association or generally around the null and imprecise.

The results for the associations between nSEP and gastroschisis were similar for both neighborhood-level indices. We observed a monotonic increase in the unadjusted odds of gastroschisis with increasing neighborhood socioeconomic deprivation. This pattern of association remained after adjustment for maternal race/ethnicity, household income, maternal education, birth year, and duration of residence. Furthermore, the two neighborhood-level indices were highly correlated ($r = 0.99$). Given that the NDI is a standardized, validated index that has been previously used to describe the relationships between neighborhood-level effects and birth outcomes, our study suggests that the NDI may be a better measure of nSEP, despite the additional census indicators used to characterize the nSEPI.

Overall, our findings suggest that nSEP during early pregnancy is modestly associated with an increased odds of gastroschisis.

6.1.2. Aim 2: Summary of findings

Neighborhood-level socioeconomic position was found to modify the association between maternal age at conception and gastroschisis, but not the association between maternal pre-pregnancy BMI and gastroschisis. Contrary to expectation, the magnitude of the association between young maternal age at conception (<20 vs. ≥ 20 years) and gastroschisis decreased as nSEP decreased. Young mothers in low SEP neighborhoods had nearly half the risk of having an infant with gastroschisis compared with young mothers in high SEP neighborhoods. However, it is unknown why young mothers residing in high SEP areas have the highest risk of gastroschisis. The magnitude of the associations between low (<18.5 kg/m^2 vs. ≥ 25 kg/m^2) or normal BMI (18.5 kg/m$^2 \leq$ BMI $<$ 25 kg/m^2 vs. ≥ 25 kg/m^2) and gastroschisis were similar across all strata of nSEP. Both underweight and normal-weight mothers had nearly two times the odds of having an infant with gastroschisis suggesting that other unidentified, potentially biological factors, specific to being of low or normal BMI, may have a larger influence on the development of gastroschisis. On the contrary, it may be plausible that there is a protective, unidentified factor specific to overweight/obese mothers that may reduce the risk of having an infant with gastroschisis. If so, insight into these potentially protective factors may help elucidate the etiology of gastroschisis.

Overall, regardless of the level of neighborhood socioeconomic deprivation, young maternal age at conception and low and normal BMI were consistently associated with elevated odds of gastroschisis. This suggests that other unidentified biological or non-biological factors unrelated to nSEP may be more important contributors to the risk of gastroschisis.

6.2 Strengths and limitations

6.2.1 Strengths

To date, only one known epidemiologic study has examined the association between measures of nSEP and gastroschisis. This dissertation not only adds to the limited body of literature but meaningfully expands upon the previous study in several ways. First, we examined this association in a larger sample of gastroschisis cases spanning a wider geographical range, resulting in more precise effect estimates and increasing the generalizability of study results. Second, we attempted to reduce exposure misclassification by using self-reported addresses during the periconceptional period to ensure the exposure occurs during the critical window of gastroschisis development. Third, we used additional measures of iSEP to account for factors related to residential selection, reducing the potential for residual confounding. Fourth, we characterized nSEP using two PCA-derived indices, the NDI and nSEPI. Although the NDI is a standardized index that has been previously used in neighborhood-birth outcome studies, the use of the nSEPI verified the assumptions involved in using a standardized index, including its applicability over time and across different study populations spanning various geographical areas. Both indices had similar results. Fifth, we examined both single SEP indicators and composite neighborhood-level indices to explore specific aspects of nSEP, in addition, to the overall nSEP effect on the risk of gastroschisis. Sixth, a major strength of this dissertation is that Aim 2 is the first study to investigate whether the associations between two well-established, individual-level risk factors, including maternal age and pre-pregnancy BMI, and gastroschisis differ by levels of nSEP. Neighborhoods may differentially affect mothers of certain individual-level characteristics. Thus, it is important to explore how nSEP may affect the risk of gastroschisis for young mothers and mothers of low or normal BMI, as these individual-level risk factors are uniquely specific to this birth defect. Finally, the use of NBDPS data strengthened both aims of this dissertation by providing a geographically diverse study population, population-based ascertainment of cases and controls, a larger sample size of gastroschisis cases, clinically verified outcomes, and extensive covariate information.

6.2.2 Limitations

Despite the many strengths of this dissertation, interpretation of our results should be considered in the context of our study's limitations. The first major limitation of both aims of this dissertation is the lack of data on neighborhoods mothers resided in over their life course. Although nSEP was examined during the etiologically-relevant period for gastroschisis, it is plausible that the neighborhoods mothers were born into and/or raised may have a greater influence on their reproductive health, and subsequently pregnancy outcomes. Solely assessing nSEP around conception may understate the true impact of neighborhood effects on gastroschisis. Another major limitation is the lack of data on the historical context of the periconceptional neighborhood. Neighborhood features may change over time in response to federal and/or local government initiatives. For instance, currently deprived neighborhoods may have experienced years of deprivation whereas other deprived neighborhoods may have only become deprived rather recently. Assessment of neighborhood-level factors at one point in time may conceal how different neighborhoods truly are and its potential influence on reproductive health. In addition, although we adjusted for covariates identified in the minimally sufficient adjustment sets based on our DAGs, residual confounding from unmeasured, unknown, or misspecified variables cannot be ruled out as a possible explanation of our study results. Furthermore, in Aim 1 maternal age at conception was identified as a mediator and was thus, not included in the models. However, given maternal age is correlated with education, a confounder in our study, adjustment for education may inadvertently also adjust for maternal age at conception, possibly resulting in overadjustment bias. This would likely bias the observed estimates towards the null. Lastly, selection bias may have resulted if there were factors associated with non-participation or missing geocoded addresses. Unfortunately, we do not have data on non-participants; however, a previous study reported that NBDPS control mothers were generally representative of their base populations. In addition, given only 3% of NBDPS participants were excluded due to missing geocoded addresses, selection bias from these two sources is likely minimal.

6.3 Public health impact and future research directions

6.3.1 Public health impact

Gastroschisis has a significant public health impact due to its increasing prevalence worldwide and unique epidemiologic pattern. While the majority of epidemiologic studies on gastroschisis have focused on individual-level factors, there is a need to explore the broader social context to aid in identifying the etiology of this birth defect. Very little research has examined the association between neighborhood contextual factors and the risk of gastroschisis. This dissertation research adds to the accumulating body of literature examining neighborhood-level effects on reproductive health and adverse pregnancy outcomes. In particular, our findings suggest that there is a contextual element influencing the risk of gastroschisis; however, among young mothers and mothers of low or normal pre-pregnancy BMI, there may be unidentified biological or social factors unrelated to nSEP that may either increase their vulnerability to known, identified exposures or directly influence the pathogenesis of gastroschisis. Overall, these results provide new insight into contextual risk factors for gastroschisis above and beyond the individual level and potentially provide etiologic clues that may be missed by solely examining individual-level characteristics.

6.4.2 Future research directions

There are multiple ways to meaningfully advance our understanding of the relationship between neighborhood contextual factors and gastroschisis. First, the results of this study require replication in other epidemiologic studies to confirm our findings. Second, much of the criticism of neighborhood-level studies focuses on the notion that individuals do not randomly select into neighborhoods. Thus, there is a need to conduct longitudinal studies to explore the life course perspective and gain a better understanding of how neighborhood socioeconomic deprivation at birth influences iSEP, which in turn likely influences residential selection. Furthermore, to the extent that there is a window of vulnerability along the life course that may have the greatest impact on factors related to residential selection, identification of this critical window and insight into the neighborhood's socioeconomic deprivation is needed. Third, additional work is needed to elucidate the mechanisms through which neighborhoods influence pregnancy outcomes. Although studies have theorized multiple pathways, the causal relationship between neighborhood characteristics and gastroschisis remains unknown. Exploring specific mechanisms may identify modifiable neighborhood characteristics that may not only reduce the risk of gastroschisis but also improve overall maternal and reproductive health. Furthermore, future studies should investigate the degree to which individual-level characteristics and their possible interaction with neighborhood-level factors, account for the effect of nSEP on the risk of gastroschisis. In this dissertation study, we identified maternal age at conception and risky health behaviors, such as smoking, as mediators rather than confounders. Additionally, given studies have observed plausible epigenetic mechanisms, such as DNA methylation, as a result of psychosocial stress exposures from neighborhood characteristics[190], future studies should explore the mediation of neighborhood-level effects through individual-level characteristics and epigenetic mechanisms. Lastly, it remains unclear why gastroschisis disproportionately affects mothers younger than 20 years and mothers of low or normal BMI. While a myriad of risk factors has been identified to be associated with gastroschisis, perhaps it is time to collect biological samples, such as measures of inflammatory cytokines or biomarkers of diet quality. Biological evidence may help explain the unique epidemiology of this birth defect and elucidate the etiology of gastroschisis.

6.4 Conclusions

The results of this dissertation suggest that neighborhood-level socioeconomic position during early pregnancy is associated with an increased odds of gastroschisis. These findings indicate that there is a contextual element that may influence maternal health and subsequently pregnancy outcomes; however, further research is needed to replicate these findings. Furthermore, individuals residing in the same neighborhood may differentially be affected by their socioeconomic environment based on their individual-level characteristics. In our analysis, we found that young mothers residing in high SEP neighborhoods had nearly double the risk of having an infant with gastroschisis compared with young mothers residing in low SEP neighborhoods. However, we did not observe the same modification by nSEP for the association between low or normal pre-pregnancy BMI and gastroschisis. Furthermore, we consistently observed elevated odds of gastroschisis associated with young maternal age and low or normal pre-pregnancy BMI, irrespective of nSEP. This indicates that there are potentially unidentified biological or non-biological factors, unrelated to nSEP, that may play a greater role in influencing the risk of gastroschisis.

While the relationship between neighborhood-level effects and individual health has long been recognized, this dissertation is one of the few studies to explore neighborhood-level effects on gastroschisis. It is clear that additional work is needed to further investigate the mechanisms by which nSEP may influence the risk of gastroschisis. However, while contextual studies may provide hypotheses and etiologic clues about potential causes of gastroschisis, perhaps what is urgently required is a more direct biological assessment of biomarkers that may be related to known risk factors of gastroschisis

APPENDIX: SUPPLEMENTARY TABLES

Supplementary Table 1a. Association between single census-tract level socioeconomic indicators and gastroschisis among women with at least one geocoded address during the periconceptional period *using complete case analysis*, National Birth Defects Prevention Study, 1997 - 2011

	Gastroschisis Cases n = 1,269	**Crude ORs (95% CIs)**	**Adjusted ORs (95% CIs)[a]**
Crowding[b,c]			
T1	341	Ref	Ref
T2	417	1.22 (1.05 – 1.42)	1.13 (0.96 – 1.34)
T3	511	1.50 (1.30 – 1.74)	1.08 (0.90– 1.30)
Low education[b,c]			
T1	288	Ref	Ref
T2	422	1.47 (1.25 – 1.72)	1.13 (0.94 – 1.34)
T3	559	1.95 (1.67 – 2.26)	1.11 (0.91 – 1.36)
Unemployment[b,c]			
T1	299	Ref	Ref
T2	407	1.44 (1.23 – 1.69)	1.18 (1.00 – 1.41)
T3	563	1.93 (1.66 – 2.24)	1.33 (1.09 – 1.61)
Males in management and professional occupation[b,c]			
T1	526	Ref	Ref
T2	452	0.86 (0.75 – 0.98)	1.09 (0.94 – 1.28)
T3	291	0.55 (0.48 – 0.65)	0.82 (0.68 – 1.00)
Female-headed households w/ dependents[b,c]			
T1	286	Ref	Ref
T2	460	1.61 (1.38 – 1.87)	1.24 (1.04 – 1.47)
T3	523	1.83 (1.57 – 2.13)	1.20 (0.99 – 1.45)
Poverty[b,c]			
T1	264	Ref	Ref
T2	455	1.72 (1.47 – 2.01)	1.26 (1.05 – 1.50)
T3	550	2.08 (1.78 – 2.43)	1.20 (0.99 – 1.46)
Households earning < $30,000[b,c]			
T1	281	Ref	Ref
T2	449	1.60 (1.36 – 1.87)	1.16 (0.97 – 1.38)
T3	539	1.82 (1.64 – 2.23)	1.13 (0.93 – 1.36)
Public Assistance Income[b,c]			
T1	339	Ref	Ref
T2	376	1.11 (0.95 – 1.29)	0.92 (0.78 – 1.10)
T3	554	1.64 (1.42 – 1.89)	1.15 (0.97 – 1.37)

High education[c]			
T1	575	Ref	Ref
T2	442	0.77 (0.67 – 0.88)	0.95 (0.81 – 1.11)
T3	252	0.44 (0.37 – 0.51)	0.77 (0.64 – 0.93)
Affordable housing w/ mortgage[c]			
T1	415	Ref	Ref
T2	445	1.15 (0.99 – 1.34)	1.11 (0.94 – 1.31)
T3	409	1.40 (1.21 – 1.61)	1.14 (0.96 – 1.36)
Affordable housing w/out mortgage[c]			
T1	358	Ref	Ref
T2	412	1.07 (0.93 – 1.24)	1.03 (0.88 – 1.20)
T3	499	0.98 (0.85 – 1.14)	0.92 (0.78 – 1.09)
Manual occupation[c]			
T1	275	Ref	Ref
T2	444	1.61 (1.37 -1.89)	1.14 (0.95 – 1.36)
T3	550	2.00 (1.72 – 2.32)	1.17 (0.98 – 1.41)
Workers class			
T1	446	Ref	Ref
T2	404	0.91 (0.78 – 1.05)	1.02 (0.87 – 1.20)
T3	419	0.94 (0.81 – 1.08)	0.90 (0.77 – 1.05)
Renters affordable housing[c]			
T1	363	Ref	Ref
T2	427	1.17 (1.02 – 1.37)	1.09 (0.93 – 1.28)
T3	479	1.32 (1.14 – 1.52)	1.05 (0.89 – 1.25)
Renter occupancy[c]			
T1	341	Ref	Ref
T2	414	1.22 (1.05 – 1.42)	1.02 (0.86 – 1.20)
T3	514	1.51 (1.30 – 1.75)	1.16 (0.99 – 1.37)
Wealth[c]			
T1	438	Ref	Ref
T2	477	1.09 (0.95 – 1.25)	1.16 (0.99 – 1.36)
T3	354	0.81 (0.70 – 0.94)	1.07 (0.89 – 1.29)
Household median income[c]			
T1	503	Ref	Ref
T2	492	0.98 (0.86 – 1.12)	1.07 (0.92 – 1.26)
T3	274	0.54 (0.47 – 0.64)	0.83 (0.68 – 1.02)

T1: Tertile 1; T2: Tertile 2; T3: Tertile 3
High tertile scores reflect a high proportion of residents that meet census indicator definition. Low tertile scores reflect a low proportion of residents that meet census indicator definition.
Separate models were run for each census indicator.
[a] Adjusted for maternal race/ethnicity (Non-Hispanic Black, Non-Hispanic White, Hispanic, Other), infant birth year (1997 – 2004, 2005 – 2009, 2010 – 2011), household income (<$10,000 $10,000 - $50,000, >$50,000), maternal education (0-11, 12 and > 12 years), and duration of residence
[b] Census indicator used to create the NDI
[c] Census indicator used to create the nSEPI

Supplementary Table 1b. Association between neighborhood indices and gastroschisis among women with at least one geocoded address during the periconceptional period, *using complete case analysis,* National Birth Defects Prevention Study, 1997 – 2011

	Case n = 1,269	**Crude ORs (95% CIs)**	**Adjusted ORs (95% CIs)[a]**
NDI			
T1 (Low deprivation)	246	Ref	Ref
T2	454	1.85 (1.57 – 2.18)	1.27 (1.06 – 1.53)
T3 (High deprivation)	569	2.31 (1.98 – 2.71)	1.28 (1.04 – 1.57)
nSEPI			
T1 (High nSEP)	240	Ref	Ref
T2	449	1.87 (1.59 – 2.20)	1.27 (1.05 – 1.54)
T3 (Low nSEP)	580	2.42 (2.06 – 2.83)	1.36 (1.11 – 1.67)

T1: Tertile 1; T2: Tertile 2; T3: Tertile 3; NDI: Neighborhood Deprivation Index; nSEPI: Neighborhood Socioeconomic Position Index

High tertile scores reflect high deprivation (NDI) or lower nSEP (nSEPI). Low tertile scores reflect low deprivation (NDI) or high nSEP (nSEPI).

[a] Adjusted for maternal race/ethnicity (Non-Hispanic Black, Non-Hispanic White, Hispanic, Other), infant birth year (1997 – 2004, 2005 – 2009, 2010 – 2011), household income (<$10,000 $10,000 - $50,000, >$50,000), maternal education (0-11, 12 and > 12 years), and duration of residence

Supplementary Table 2. Crude and adjusted odds ratios (ORs) and 95% Confidence Intervals (CI) of gastroschisis per tertiles of NDI and nSEPI

	NDI	nSEPI
Model 1: Crude		
T1 (Low deprivation)	Ref	Ref
T2	1.85 (1.57 – 2.18)	1.87 (1.59 – 2.20)
T3 (High deprivation)	2.31 (1.98 – 2.71)	2.42 (2.06 – 2.83)
Model 2: Model 1 + birth year		
T1 (Low deprivation)	Ref	Ref
T2	1.85 (1.57 – 2.18)	1.89 (1.61 – 2.23)
T3 (High deprivation)	2.33 (1.99 – 2.73)	2.46 (2.10 – 2.88)
Model 3: Model 1 + birth year + race		
T1 (Low deprivation)	Ref	Ref
T2	1.88 (1.59 – 2.21)	1.92 (1.63 – 2.27)
T3 (High deprivation)	2.31 (1.93 – 2.77)	2.46 (2.05 – 2.94)
Model 4: Model 1 + birth year + race + duration of residence stay		
T1 (Low deprivation)	Ref	Ref
T2	1.85 (1.55 – 2.15)	1.87 (1.58 – 2.21)
T3 (High deprivation)	2.24 (1.89 – 2.68)	2.37 (1.98 – 2.84)
Model 5: Model 1 + birth year + race + duration of residence stay + education		
T1 (Low deprivation)	Ref	Ref
T2	1.52 (1.28 – 1.80)	1.53 (1.29 – 1.82)
T3 (High deprivation)	1.66 (1.37 – 2.00)	1.74 (1.44 – 2.11)
Model 6: Model 1 + birth year + race + duration of residence stay + income		
T1 (Low deprivation)	Ref	Ref
T2	1.33 (1.12 – 1.58)	1.33 (1.12 – 1.59)
T3 (High deprivation)	1.39 (1.15 - 1.69)	1.46 (1.20 – 1.78)
Model 7: Model 1 + birth year + race + duration of residence stay + income + education		
T1 (Low deprivation)	Ref	Ref
T2	1.25 (1.05 – 1.49)	1.25 (1.04 – 1.49)
T3 (High deprivation)	1.27 (1.05 – 1.54)	1.32 (1.09 – 1.61)

T1: Tertile 1; T2: Tertile 2; T3: Tertile 3; NDI: Neighborhood Deprivation Index; nSEPI: Neighborhood Socioeconomic Position Index

High tertile scores reflect high deprivation (NDI) or lower nSEP (nSEPI). Low tertile scores reflect low deprivation (NDI) or high nSEP (nSEPI).

Maternal race/ethnicity (Non-Hispanic Black, Non-Hispanic White, Hispanic, Other), infant birth year (1997 – 2004, 2005 – 2009, 2010 – 2011), household income (<$10,000 $10,000 - $50,000, >$50,000), maternal education (0-11, 12 and > 12 years), and duration of residence

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