ABSTRACT

Dissertation Title:	AREA-LEVEL POVERTY AND CARDIOMETABOLIC RISK AMONG UNITED STATES ADOLESCENTS: A HIERARCHICAL ANALYSIS OF PATHWAYS TO DISEASE
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Background: In the United States, 26% of deaths are attributable to cardiometabolic diseases. Cardiometabolic risk in adolescence tracks over time and can presage cardiometabolic health during adulthood. Area-level determinants of cardiometabolic risk among adolescents are underexamined. This study contributes evidence regarding the association between area-level poverty and cardiometabolic risk among U.S. adolescents.

Methods: 1999-2012 National Health and Nutrition Examination Survey data was linked via census tract with 2000 Census data and 2005-2009 and 2009-2013 American Community Survey data. The sample included 10,415 adolescents, aged 12-19 years. Area-level poverty was parameterized by percent population living in poverty, grouped into quartiles for analysis. Cardiometabolic risk was parameterized by summing z-scores of systolic and diastolic blood pressure, glycosylated hemoglobin, waist circumference, HDL cholesterol, and total cholesterol. Hierarchical linear models were used to examine

the relationship between area-level poverty and cardiometabolic risk. Cotinine levels and physical activity were assessed as mediators. Post-hoc analysis explored associations between area-level poverty and family poverty-to-income ratio. Analyses were conducted for the overall sample and by race/ethnicity.

Results: For the overall sample, compared to the first quartile of area-level poverty, residence in second (.218, 95% CI: .012, .424), third (.438, 95% CI: .213, .665), and fourth (.451, 95% CI: .204, .698) quartiles of area-level poverty was associated with increased cardiometabolic risk. Area-level poverty was associated with cardiometabolic risk among non-Hispanic Whites and Mexican Americans, but not among non-Hispanic Blacks. No evidence of mediation was observed. In post-hoc analysis, overall mean family Poverty-income-ratio declined from 3.34 in quartile 1 to 1.42 in quartile 4 ($p<$ .001), however, this differed by race/ethnicity.

Discussion: Residence in the highest area-level poverty quartiles was associated with increased cardiometabolic risk. Race/ethnicity specific analyses are consistent with literature on the Hispanic Paradox, and exposure to adversity among non-Hispanic blacks. Evidence suggests specific biomarker choice results in different cardiometabolic profiles within the same racial/ethnic group. Post-hoc analyses suggest the effect of area-level poverty on family PIR is greatest among non-Hispanic whites. Efforts to improve cardiometabolic health and reduce racial/ethnic disparities in cardiometabolic diseases should include targeted community-level investments aimed to improve the social conditions for all residents.

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STATES ADOLESCENTS: A HIERARCHICAL ANALYSIS OF PATHWAYS TO
DISEASE

by

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Chapter I. Overview

The primary aim of this study was to examine the association between exposure to area-level stress during adolescence and cardiometabolic risk during adolescence, independently of individual-level determinants of these biomarkers. The secondary aim of this study was to examine whether lifestyle behaviors mediate the relationship between area-level stress and cardiometabolic risk, and whether these lifestyle behaviors partially explain racial/ethnic disparities in cardiometabolic risk of adolescents.

In the United States, 26% of all deaths are attributable to cardiometabolic diseases such as cardiovascular disease and diabetes.[1] Consequently, the Office of Disease Prevention and Health Promotion has identified prevention of mortality from cardiometabolic diseases as a national public health priority.[2] Prevention of cardiometabolic disorders is predicated on identifying its earliest precursors. While evidence is accumulating that precursors to cardiometabolic disorders manifest as early as adolescence,[3–9] the majority of research on cardiometabolic disorders has been conducted among adult populations.[10–14] Additionally, the American Academy of Pediatrics[15] and the American Heart Association[16] have identified adolescence as a key period for cardiovascular disease prevention efforts.

Cardiometabolic functions, such as blood pressure[17–19] and glucose metabolism,[20,21] track over time. Accordingly, cardiometabolic functions during adolescence can presage cardiometabolic health during adulthood. Thus, although approximately 99% of adolescents do not meet diagnostic criteria for any cardiometabolic diseases,[22] adolescents with cardiometabolic function deviating

significantly from population-level norms are considered to be at elevated risk of developing cardiometabolic disease as adults.[6,8,9] For example, among a population-based sample (n=814) of Ohio youth, high cardiometabolic risk at mean age 13 was associated with elevated risk (OR: 11.5, 95% CI: 2.1, 63.7) of developing type-2 diabetes during adulthood (mean age 38 years).[8] Similarly, among a population-based sample (n=1,453) of Finnish youth, high cardiometabolic risk at mean age 13 year was associated with elevated risk of type-2 diabetes (RR: 2.54 95% CI 1.25-5.17) during adulthood (mean age 23).[23] Among this cohort, high cardiometabolic risk during adolescence also predicted elevated risk for cardiovascular disease during adulthood (RR: 1.76 95% CI 1.26-2.43).[23] Similarly, among a sample from Louisiana (N=486), high cardiometabolic risk during ages 4-17 predicted elevated risk of cardiovascular disease at ages 25-37 years (OR: 1.42, 95% CI:1.14-1.78).[9] Given this evidence, an improved understanding of determinants of cardiometabolic risk during adolescence may provide opportunities to reduce risk of disease over the life-course.

Additionally, racial disparities in deaths attributable to cardiometabolic diseases have long been recognized.[24] Among adolescents in the U.S., non-Hispanic Black adolescents have the lowest prevalence of high cardiometabolic risk compared to non-Hispanic Whites and Hispanics. This observed disparity is temporally consistent. Non-Hispanic Black adolescents have the lowest prevalence of high cardiometabolic risk (range: 1.6% – 6.4%), followed by non-Hispanic Whites (range: 2.2% – 14.7%), and closely followed, typically within 1%, by Hispanic adolescents (range: 2.6% – 17.5%).[3,4,25–30] Furthermore, other evidence points to racial/ethnic differences in health behaviors, such as smoking[31] and physical activity,[32] which have been identified as

predictors of cardiometabolic risk.[28,29] No study to date has explored whether racial differences in lifestyle behaviors explain racial disparities in cardiometabolic risk among U.S. adolescents.

Individuals' residential area is another under-examined determinant of disparities in cardiometabolic risk among US adolescents. Health is shaped, in part, by social and economic conditions within individuals' residential area.[33,34] Although an inverse association between area-level socioeconomic status (SES) and cardiometabolic health among adults is well established,[14] research on this association among adolescents is limited to studies of adiposity and blood pressure.[14,35–38] With 2 exceptions,[39,40] studies conducted in the previous decade consistently observe an association between exposure to low-SES areas and elevated risk of adiposity during adolescence.[41–56] These studies have been conducted among large population-based samples (range: 775-73,079) from various countries. [41–56] Of the 16 studies observing an association, 10 conducted hierarchical analysis.[41–43,46,48,52–56] Six longitudinal studies suggest individuals residing in low-SES areas are heavier at baseline, and gain more weight during adolescence than individuals in high-SES areas.[43,50–53,55]

In contrast, only four studies (sample range: 24 – 325) have examined the link between area-level SES and blood pressure among adolescents,[35–38] and one found an association.[35] None of these four studies conducted appropriate hierarchical analyses,[35–38] and two included only individuals with a family history of cardiometabolic disease.[36,38]

To date, the potential association between area-level SES and other cardiometabolic factors, including glucose metabolism and lipid levels[13,57–60] among

adolescents remain unexamined. Furthermore, cardiometabolic functions cluster[6,13,58,61] and are often considered together in an index representing an individual's cardiometabolic risk.[6,13,58,61] To date, no studies have examined the association between area-level poverty and a continuous index of cardiometabolic risk among adolescents.

Additionally, evidence among adults suggests area-level SES contributes to racial disparities in cardiometabolic health,[62,63] yet similar studies among adolescents are sparse and have focused solely on adiposity. Four studies of population based samples (range: 17,100 – 20,745) of U.S. children and adolescents using hierarchical methods suggest area-level SES contributes to racial disparities in adiposity.[48,54,64,65] For example, among US adolescents, accounting for area-level SES resulted in 18% reduction in odds of adiposity for non-Hispanic black girls compared to non-Hispanic white girls.[65] Among another sample of US children and adolescents, the racial-ethnic disparity in the odds of adiposity was explained away by addition of area-level SES.[54] To date, no study has examined the link between area-level SES and racial disparities in cardiometabolic risk using a cardiometabolic risk index among adolescents.

This study describes associations between area-level poverty (as an indicator of area-level SES) and cardiometabolic risk among adolescents. We also examine racial/ethnic disparities in this association. Furthermore, mediation by lifestyle behaviors is also assessed. We fit hierarchical models, for the full sample and by race, to determine the association between area-level poverty and cardiometabolic risk among a nationally representative sample of adolescents free of diagnosed cardiometabolic disease. We hypothesized that residing in areas with high poverty would result in an increased

cardiometabolic risk score, and exposure to tobacco smoke and physical activity would partially explain observed differences by race.

To better understand the potential link between area-level poverty and cardiometabolic risk, and to examine the role of lifestyle behaviors, the following specific aims were proposed:

1. Determine the relationship between area-level poverty and cardiometabolic risk, independent of individual- and area-level covariates.

2. Determine if the relationship between area-level poverty and cardiometabolic risk differs by race/ethnicity.

3. Determine if exposure to tobacco smoke, as a mediator between area-level poverty and cardiometabolic risk, partially explains racial/ethnic disparities in cardiometabolic risk.

4. Determine if physical activity, as a mediator between area-level poverty and cardiometabolic risk, partially explains racial/ethnic disparities in cardiometabolic risk.

Chapter II. Area-level Determinants of Health

Both individual- and area-level determinants of health are important in understanding the panoply of influences that determine health. Area-level determinants of health include physical, social, and environmental exposures. A key area-level determinant of health is area-level socioeconomic status (SES). Area-level SES is related to both indirect and direct determinants of health, such as access to resources (e.g. food stores, health care)[54] and exposure to environmental toxins.[66] How area-level SES is assessed is important and is a key aspect in understanding how area-level SES impacts health.

Racial/ethnic composition at the area-level has been utilized as a measure of SES,[35] yet may be an inappropriate measure of SES, as areas with high racial/ethnic minority populations can have high SES, just as areas with high racial/ethnic majority populations can have low SES.[67,68] Moreover, racial/ethnic composition is associated with health, even after controlling for area-level SES, suggesting that while these two constructs are related, they are separate area-level exposures.[69–71] It stands to reason that a more direct method of assessing area-level socioeconomic status can be more useful.

Economic indices are useful indicators of both area-level SES and are considered area-level stressors. They are easily interpretable, consistently measured over time, and relate well to multiple other measures of area-level SES such as housing quality, crowded living spaces, and the built environment.[72–75] Concentration of poverty, the percent of individuals living below the federal poverty line, is a common measure of area-level SES.[54,64,72–74] Other measures including educational attainment, median household

income, percent unemployment, and median home value are indicative of access to resources (e.g. healthy food, insurance coverage, safe housing) and other area-level stressors (e.g. crime and violence).

Singular indices of area-level SES allow for greater ease in interpretation, yet may not fully depict area-level stressors. Multivariate indices are conceptualized to allow for a more robust complete assessment of the area-level stress, yet due to their complexity, it may be difficult to determine which economic factors are driving an association. Multivariate indices that have transformed and averaged multiple indicators of area-level SES (e.g. educational attainment, employment, concentration of poverty, percentage of female-headed households) have been linked with health outcomes.[54,64] Yet, using concentration of poverty at the census-tract level as a singular indicator is easily interpretable, and has been shown to produce similar results as multivariate indices.[54,72–74]

Among adolescents, the potential association between area-level exposures and biomarkers that predict future development of disease have rarely been examined. As exposure to area-level SES during adolescence has been linked with adult health outcomes,[76,77] examining the potential links between area-level SES and biomarkers of cardiometabolic risk which track over time (such as blood pressure and glycosylated hemoglobin) among adolescents may allow for a better understanding of area-level factors' contribution to future disease risk.

Chapter III. Blood Pressure among Juveniles

As this study attempts to better understand the pathways to disease, blood Pressure (BP) is an appropriate biomarker to examine as it is a good indicator of health, and can be tracked across the lifespan. Literature reviewed in this chapter incorporates both children (less than 12 years of age) and adolescents, (between 12 and 19 years of age) as the extant literature as largely considered these distinct age group together. BP during adulthood is associated with risk of cardiovascular disease, stroke, premature death, and other health problems in adulthood.[78–82] Longitudinal studies provide evidence that BP tracks over time among juveniles. BP in early childhood is independently predictive of BP in adolescence.[83] BP has also been tracked during adolescence, as BP at age 13 correlates with BP at age 17.[84] Most relevant to the proposed study, is the consistent observation that adolescents with high BP levels are likely to have high BP levels in adulthood.[17–19]

Measurement of blood pressure

There are two components to blood pressure (BP): systolic blood pressure (SBP) is the blood pressure *during* a heartbeat, and diastolic blood pressure (DBP) is the blood pressure *between* heart beats.[85,86] Hypertension is diagnosed when SBP or DBP are at or above the 95th percentile based on age, gender, and height.[87] Another measure is blood pressure reactivity (i.e., rise and fall of BP) in response to a stressor.[88–91] This review focused on BP levels and hypertension, as these two indicators are considered to be risk factors for development of future disease.[17–19]

Additionally, SBP and DBP are highly correlated and have many of the same determinants, these shared determinants were identified as a determinant of overall BP.[85,86] Determinants of only SBP or only DBP were identified as such. However, SBP is considered a stronger predictor of disease,[85,86] and determinants unique to SBP (i.e. sodium intake[18,92]) have been identified.

Distribution of BP among juveniles

Age-gender-height specific BP charts based on 1999-2000 National Health and Nutrition Examination Survey (NHANES) data can be used to provide normative references for juvenile BP.[87] For example, according to this chart the 50th percentile for systolic blood pressure (SBP) for a 5 year old female at the 50th percentile for height is 93, while the 50th percentile for SBP for a similar male is 95.[87] The gender difference becomes more apparent in adolescence, as the 50th percentile for SBP for a 17 year old female at the 50th percentile for height is 111, while the 50th percentile for SBP for a similar male is 118.[87]

From NHANES 1999-2012, for youth aged 8-12 years, boys had mean SBP of 102.96 mean DBP of 52.97, and girls had mean SBP of 102.09, and mean DBP of 54.39.[93] For youth aged 13-17 years, boys had mean SBP of 111.99, and mean DBP of 58.74, and girls had mean SBP of 106.48, and mean DBP of 61.57. [93] Also from NHANES 1999-2012, the prevalence of prehypertension and hypertension among youth aged 8-17 years has remained near 10 percent for much of the previous decade.[7]

Demographic correlates of BP in juveniles

Blood pressure co-varies with age, gender, and height. Among juveniles age has an independent and positive association with blood pressure (BP).[18,94–96] This age-related increase in BP is normative, and is not considered a risk factor among this population.

Furthermore, male juveniles have elevated BP levels compared to females, with large increases in SBP observed in males during adolescence, yet not in females.[18,84,94] Physiologic changes in adolescence likely drive gender-based differences in BP. For example, males have larger skeletal and muscle growth, and larger gains in red blood cell mass than females, and this contributes to higher increases in BP levels seen in males during adolescence.[18,94,97] While hormonal pathways are not yet well specified, differences in estrogen receptors between genders may be partially responsible for elevated levels of BP in males.[84]

Finally, BP also co-varies with height.[18,83,87,94,95,98] Therefore, age, gender, and height must be taken into account when determining normal levels of BP in juveniles.

Determinants of BP among juveniles

Although there is a wealth of knowledge of determinants of blood pressure (BP) among adults, research on juveniles is not as prevalent. Twenty-six studies have examined individual- and area-level determinants of adolescent SBP and DBP, and hypertension.[17,18,35–38,75,83,84,92,94–96,98–110] Studies measuring BP at 5 years of age and above are of particular interest to this review in order to examine BP levels tracking over time in childhood and adolescence. In the review below children below age 12 and adolescents aged 12-19 are referred to as juveniles.[111,112]

Prenatal and neonatal factors play an important role in juvenile BP. Maternal age and height, pre-pregnancy BMI, number of previous pregnancies, and smoking throughout pregnancy, are all independently and positively associated with juvenile SBP.[109] Birthweight is also inversely related with BP among adolescents.[83,96] Additionally, juveniles who were breastfed at least 6 months have lower SBP in childhood.[109,110]

Family characteristics are also linked with juvenile BP.[37,94,96,103,106,107] Juveniles from families with a history of hypertension or cardiac arrest are more likely to have high BP levels.[96,107] This relationship may signal hereditary factors in BP, or it could be indicative of the health behaviors of the family or other shared influences such as SES. Family SES correlates well with exposure to stress, and various indicators of low family SES (i.e. low income and assets, poor parental education, female-headed household, low paternal education) are associated with elevated juvenile BP.[37,103,106] However, one study found that juveniles with low family SES had lower BP levels than others.[94] Additionally, family SES is also related to access to resources, yet it may be more appropriate to measure health behaviors related to certain resources in order to better understand how family SES is linked to juvenile BP.[37]

Access to healthy food and quality housing are intrinsically tied to family SES, and influence health behaviors such as diet and sleep.[113–115] Sodium intake is positively associated with SBP, and sugar intake is positively associated with overall BP levels.[18,92,100,109] High sodium intake may further elevate SBP in obese juveniles, as sodium may interact with obesity-related health conditions (e.g. metabolic syndrome, hyperinsulinemia) leading to elevated SBP.[18,92] High sugar intake effects BP levels by

increasing production of nitric oxide in the kidneys, leading to elevated BP.[100] Inefficient

sleep is thought to lead to metabolic and endocrine disorder, in turn leading to elevated

SBP in juveniles.[99]

Adolescent Growth and BP

Measures of body size, other than height, are also independently associated with

BP levels. While increases in weight, head circumference, waist circumference, and

waist-to-height ratio are associated with elevated BP, Body Mass Index (BMI) is the most

widely used measure.[18,83,94–96,98,101,102,104,108] The association between BMI and BP

becomes stronger as BMI increases.[94–96] Normative increases in BMI are associated with

normative increases in BP, yet excessive increases in BMI greatly increase risk for

prehypertension and hypertension.[101] [94–96] The relationship between BMI and BP is

complicated by rate of growth during childhood. Children with high BMI may grow

faster than others, leading to higher than average height for their age. [94] This interaction

between height, BMI, and growth is physiologically complicated, not allowing the true

relationship between BMI and BP to be clearly distinguished.[94]

Rate of growth may play an important role in adolescent BP levels, as

adolescence is the only developmental period after infancy in which the rate of growth

accelerates, and great physiological changes occur to prepare the body for adulthood.[97,116]

A study of rate of growth from infancy to age 5 observed an inverse relationship

between rate of growth during early childhood and adolescent BP; whereas, rate of

growth from age 5 to 15 was independent of adolescent BP.[83] However, rate of growth in

adolescence is age and gender dependent. For instance, until approximately age 10, males

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and females have similar height, yet during early adolescence (approximately 10-12 years of age), females make larger gains in height than males.[116] Later in adolescence (approximately 12-13 years of age), males catch up to and overtake females in terms of height and rate of growth. [116] Measuring rate of growth over a 10 year period encompassing both childhood and early adolescence may have obscured the true relationship between rate of growth and BP in juveniles. Due to accelerated rate of growth and physiologic changes associated with adolescence, children and adolescents should not be considered a single group when assessing BP levels and other health outcomes.[87,97]

Many of the reviewed studies are either cross-sectional studies unable to measure rate of growth,[17,18,35–38,75,92,94–96,98–109] or longitudinal studies that did not measure growth over time.[84,110] As age is related to growth in children and adolescents, these studies account for age in analysis. Accounting for age may partially account for growth, yet the true relationship between rate of growth and BP cannot be observed in cross-sectional studies.

Area-level studies

To date five studies have considered the association between area-level determinants (i.e., concentration of poverty, proportion of residents with less than high school level of education, multivariate index of SES, built environment) of juvenile BP.[35–38,75] The only study to observe a relationship between area-level SES and BP examined concentration of poverty at the census tract level.[35] In contrast, the studies with null findings used indicators of area-level SES at the block group level.[36–38] These

findings, in the context of the discussion of area-level units of analysis in chapter 6, suggest that constructs may operate differently depending on unit of analysis, and this can result in different effects.

Additionally, the study to observe a relationship fit hierarchical models to nest individuals within schools.[35] In contrast, studies with null findings estimated bivariate correlations [37,38] and another conducted a multivariate analysis of covariance but without considering the two levels of analysis. Given that in all these studies individuals are nested within various contexts, such as neighborhoods and schools, hierarchical models are most appropriate.[36–38] (See chapter 6 for a discussion of hierarchical models).

Furthermore, of the studies with null findings, one study sampled participants from a single school district, [37] while others sampled from a small number of schools.[36,38] Additionally, two studies included only individuals with a family history of cardiovascular disease in the sample.[36,38] The studies with null findings were likely limited in the variability of the outcome variable, as well as the predictor variables at both the individual and area levels.

The study to observe an association between area-level SES and BP sampled 212 students from two schools.[35] The sample was diverse in regards to racial/ethnic background and socioeconomic status, yet the small sample resulted in all tract-level factors to be treated as individual-level factors, thus not allowing for true hierarchical analysis of the relationship between area-level SES and BP.[35] A large, nationally representative sample allows for better generalizability, as well as the potential for a sufficient number of juveniles within area-level units to allow for hierarchical analysis.

Exposure to Stress and Blood Pressure

BP is responsive to stress. In the face of acute stressors, BP rises and returns to basal levels once the stressor is mitigated.[82,117–119] As discussed in chapter 5, the HPA axis releases hormones such as epinephrine when faced with a stressor.[119] These hormones increase heart rate and narrow blood vessels, thus increasing blood pressure.

Evidence has also linked area-level stressors with elevated basal levels of BP, yet research examining this relationship among juveniles is scarce.[35] Exposure to place-based stress may lead to continual HPA activity and resultant physiologic consequences, as discussed in chapter 5.

Chapter IV. Glycosylated Hemoglobin among Juveniles

This study focuses on the relationship between exposure to placed-based stressors and stress-related biomarkers to better understand how physiologic reaction to stressors may provide a pathway to disease. Glycosylated hemoglobin (HbA1c) is an important biomarker of exposure to chronic stress,[120–122] and it is also a marker of prediabetes[123–127] and cardiovascular disease.[128–131] Much of the research on the relationship between chronic stress and HbA1c has occurred among adults, yet examining this potential relationship among juveniles may provide a better understanding of the link between chronic stress and future disease. Literature reviewed in this chapter incorporates both children (less than 12 years of age) and adolescents, (between 12 and 19 years of age) as much of the relevant research has focused on diabetic individuals under the age of 19.

Glycosylated hemoglobin

HbA1c represents the average blood glucose level over approximately three months, with high HbA1c levels suggesting poor blood glucose regulation.[123,124] While traditionally used to determine average glucose levels among diabetics, HbA1c levels have recently been recommended for use in screening for prediabetes among adults.[123–127] Prediabetes is a condition in which blood glucose levels are higher than normal, yet below diagnostic criteria for diabetes; prediabetes is often a precursor to Type 2 diabetes.[132] Cross-sectional studies have identified a link between HbA1c and cardiovascular disease among adults, with evidence suggesting the severity of cardiovascular disease increases with elevated HbA1c.[128,131] In a longitudinal study among adults examining how well various biomarkers of glucose regulation (HbA1c, fasting glucose, 2 hour post prandial glucose) predict onset of cardiovascular disease,

HbA1c was the most accurate predictor of cardiovascular disease and mortality over a 10 year period.[129] Another longitudinal study found that adults without diabetes with elevated HbA1c (≥6.2%) over a 5 year period were more likely to have cardiovascular disease compared to individuals with lower levels of HbA1c (<6.2%).[130]

Among diabetic juveniles, HbA1c is a key biomarker of glucose regulation, and much of the existing research on HbA1c among juveniles has focused on this population.[20,123,133–147] Research examining HbA1c among juveniles without diabetes has largely focused on high-risk (e.g. overweight or obese) populations, as weight and Body Mass Index are key risk factors for diabetes and heart disease.[148,149] Among obese juveniles, initial studies suggested HbA1c may not be an appropriate screen for prediabetes or diabetes,[123,148,149] yet more recent studies suggest measuring HbA1c levels is a valid screen for prediabetes and diabetes.[150,151] While all studies found the same association, initially observers[123,148,149] were hesitant to recommend HbA1c as a screen for prediabetes and diabetes due to lack of research, while the more recent studies[150,151] reflect a better understanding of HbA1c as a screening measure. However, no clinically relevant cut point for HbA1c levels for use in screens has been established. [123,148–151] As utility of HbA1c as a biomarker of disease among high-risk and non-high-risk populations increases,[152] this study focuses on the general population in order to better understand the effect area-level exposures have on HbA1c. Additionally, HbA1c tracks over time among diabetic[20] and non-diabetic children,[21] underlining the importance of examining early influences on HbA1c in the general population.

Glucose Regulation and Chronic Stress

Among adults, exposure to chronic stress has been linked with elevated levels of HbA1c among both diabetics[121] and non-diabetics.[120,122] Insulin is a key factor in the pathway linking exposure to chronic stress with elevated levels of HbA1c.[120,121]

Insulin is a hormone produced by the pancreas that plays a major rule in blood glucose regulation.[153] When blood glucose levels are high, insulin is released and triggers cells to store glucose for future use and inhibits additional glucose secretion, thus lowering blood glucose levels.[153] If insulin production is inhibited, this can lead to chronically high blood glucose levels and severe health consequences, such as diabetes and cardiovascular disease.[125–129] Exposure to chronic stress has been linked with inhibited insulin production and poor glucose regulation.[120,121]

As discussed in chapter 5, chronic exposure to stress can lead to a continual activation of the HPA axis and continual release of adaptation hormones such as cortisol. Continual release of cortisol, can lead to both an increased production of glucose and inhibited production of insulin.[154–157] Exposure to chronic stress is also linked with elevated levels of c-reactive protein, a marker of inflammation,[158] in turn, inflammation has been linked with insulin resistance.[120,159] In sum, chronic stress leads to elevated levels of HbA1c as glucose production is increased, insulin levels are reduced, and inflamed cells are less likely to respond to insulin.[120,154–159]

Distribution of HbA1c among Juveniles

Among a nationally representative sample of juveniles without diagnosed diabetes, the mean HbA1c among individuals aged 5 to 9 years is 4.98% (10th- 95th percentile: 4.46-5.47); among individuals aged 10 to 14 years, the mean is 5.03% (10th -

95th percentile: 4.53 - 5.57); those aged 15-19 years had a mean of 4.97% (10th - 95th percentile: 4.45 - 5.51).[152] The heightened HbA1c levels among those aged 10-14 years is likely due to normative insulin resistance that occurs in early adolescence.[160,161] Among juveniles from NHANES 1988-1994 data, the prevalence of elevated HbA1c ($\geq$6 percent) was 0.39%.[162]

Gender differences in HbA1c levels among juveniles have also been observed across age groups in large, nationally representative studies.[152,163–165] In studies utilizing NHANES 1988-1994 data, males had higher average HbA1c in the overall sample, and when stratified by age and race/ethnicity.[152,163] In the study of adolescent blood donors, boys had higher prevalence of elevated HbA1c overall, and when stratified by race/ethnicity. [164]

Determinants of HbA1c among juveniles without diabetes

Studies examining the distribution of HbA1c and prevalence of elevated HbA1c among juveniles observed differences by racial/ethnic group. [152,163–165] Studies utilizing NHANES 1988-1994 data found that across each age group, non-Hispanic Blacks had the highest mean HbA1c, followed by Mexican-Americans, and non-Hispanic Whites, respectively. [152,163] In the study of adolescent blood donors, prevalence of elevated HbA1c ($\geq$5.7 percent) was highest among non-Hispanic Blacks (32.7 percent), followed by Asians (19.7 percent), Hispanics (13.1 percent), and non-Hispanic Whites (8 percent).[164] Studies suggest that race/ethnicity is a key predictor of HbA1c among juveniles, with racial/ethnic differences remaining after controlling for other determinants such as SES, and body mass index.[163]

Among NHANES (1988-1994), determinants of HbA1c among juveniles without diabetes include juvenile BMI, maternal BMI, and family income to poverty ratio, yet these relationships became non-significant in multivariate models once race/ethnicity was included.[163] Among Dutch children without diabetes, HbA1c was found to be independent of ethnicity, BMI, waist circumference, parental diabetes status, and maternal BMI.[166] A study of Native American juveniles observed a relationship between intrauterine exposure to diabetes and HbA1c, yet body fat percentage was not a determinant.[167] In sum, demographic factors (i.e., age, gender, race) are the only factors that have been consistently linked with HbA1c.

Stress and HbA1c among Juveniles

Eleven studies have examined the relationship between stress and HbA1c among juveniles with diabetes.[20,133–142] These studies suggest that individual- and family-level stressors, such as negative life events and family socioeconomic status, are linked with HbA1c among this population.[20,133–142] None of these studies considered area-level stressors.

Two studies have examined the relationship between stress and HbA1c among juveniles without diabetes.[143,144] A cross-sectional study of 6 year olds examined the relationship between family-level stressors and HbA1c, yet neither parent-reported negative life events nor family socioeconomic status were associated with HbA1c levels; area-level stressors were not considered in this study.[143] The sole study examining area-level stressors and HbA1c was a longitudinal study among 11,100 adolescents.[144] Results suggest that living in a context with low collective efficacy during adolescence was

associated with increased odds of having elevated HbA1c (>5.7 percent) in early adulthood.[144]

While the literature on stress and HbA1c among juveniles without diabetes is sparse, current findings suggest a potential relationship. Findings are consistent with the notion that exposure to stress must accumulate in order to negatively impact health. The link between stress and HbA1c was not observed among 6 year olds as they have not accumulated enough exposure to stress to influence a physiologic outcome.[143] As exposure to stress accumulates, physiologic consequences are observed, as evidenced in the longitudinal study of adolescents.[144]

Exposure to chronic stress has been linked with biomarkers of future disease among adults, yet this remains understudied among adolescents. As discussed in chapter 5, the physiologic response to chronic stress may shift the body's physiologic balance to a new equilibrium.

Chapter V. Stress and hypothalamic-pituitary-adrenal activity during adolescence

Homeostasis refers to the body's physiologic balance, the optimal ranges that physiologic systems operate within under normal conditions.[168,169] This homeostatic state is maintained by the hypothalamic-pituitary-adrenal (HPA) system through its interconnections with multiple biologic systems (i.e., central nervous, immune, cardiovascular, inflammatory, and endocrine systems).[154,156,170–173] Exposure to stressors results in the release of two sets of hormones by the HPA axis: adaptation hormones and growth hormones.[174] *Adaptation* hormones provide energy for the fight or flight response through increased heart rate, blood flow, respiration, as well as immune and inflammatory responses.[154,156,170–174] For example, cortisol, a key adaptation hormone, breaks down proteins and regulates glucose levels, providing energy for the fight or flight response.[154–156] After an acute stressor is resolved, *growth* hormones, such as insulin, growth hormone[174] and dehydroepiandrosterone (DHEA), allow a return to homeostasis by counteracting the arousal effects of adaptation hormones.[155,174–176] More specifically, as an acute stressor is mitigated, release of growth hormones allow cells to store glucose for future use and the body to relax, this is referred to as a "restorative break."[174,177]

A critical distinction between acute and chronic stressors in terms of HPA activity is that exposure to chronic stress prevents the onset of restorative breaks. Chronic exposure to stressors results in continued and excessive release of adaptation hormones, causing a shift in the adaptation-growth hormone balance in favor of adaptation hormones. This shift reduces the effect of growth hormones, preventing onset of restorative breaks.[174] Lacking restorative breaks, the HPA continues release of adaption

hormones with physiologic consequences.[174] As discussed below, continual HPA activity may have severe consequences, especially among adolescents.

Another possible consequence of repeated exposure to stressors that cease (due in part to some action of the individual) is development of a sense of mastery over that stressor. This sense of mastery is physiologically expressed as a less pronounced spike in cortisol when faced with the acute stressor, allowing for a quicker onset of restorative breaks and return to homeostasis. [174] For example, novice pilots experience elevated levels of *both* cortisol and growth hormone following exposure to experimentally induced stressors while expert pilots have increased levels of growth hormone only.[174,178] The elevated levels of growth hormone in conjunction with low levels of cortisol suggest that the expert pilots had learned to manage the stressor; therefore, a quicker onset of a restorative break occurs, allowing energy to be available for functions other than stress management. Likewise, in animal studies, repeated exposure to acute stressors early in life leads to lower basal cortisol levels and smaller spikes in cortisol in response to similar stressors later in life. [174,179–182] In summary, exposure to chronic stressors inhibits onset of restorative breaks. Inhibition of restorative breaks may uniquely effect adolescents due to a normative period of heightened HPA activity during this developmental period.

HPA activity during Adolescence

Adolescence is a unique period of HPA activity. For reasons that are not fully understood,[183–185] adolescents enter a normative period in which basal levels of both adaptation and growth hormones are elevated.[183–193] To the extent that exposure to acute

stressors of adolescence, such as changing social roles and integration into the larger society, is prevalent, adolescence is a time of particularly high HPA activity.[183,186,194–197] Furthermore, during adolescence the HPA axis responds to stressors in an exaggerated manner.[183,184,186,195–200] For example, compared to adult rats, adolescent rats experience larger spikes in HPA hormones in reaction to stressors, and require a longer period to return to basal HPA levels following the spike.[198–200] In humans, when children and adolescents are exposed to a similar stressor, adolescents have a larger spike in cortisol than children.[183,184,186,201] With age, individuals' stress response becomes less pronounced, with lower spikes in hormonal levels and a quicker return to basal levels throughout adulthood.[198–200,202]

Consequence of Exposure to Chronic Stress

Chronic physiologic reaction to stressors and anticipation of exposure to stress may lead physiologic systems (such as the cardiovascular system and the immune system) to operate at levels that are below diagnostic thresholds.[112,156,170–173,201–208]

Chapter VI. Methods

The purpose of this study was to determine the relationship between area-level poverty (a measure of area-level stress) and cardiometabolic risk in adolescents. This chapter describes the data sources, variables analyzed in this study, and analysis.

Individual-level Data

All individual-level data was drawn from the 1999-2012 waves of the National Health and Nutrition Examination Survey (NHANES). NHANES is a continuous, cross-sectional survey that provides vital and health statistics for the United States population. [209,210] NHANES began as a series of surveys in the 1960s, and since 1999 has been a continuous survey, releasing data every 2 years. [209,210] The survey utilizes a population-based, nationally-representative sample of the non-institutionalized United States population. [209,210] NHANES uses a 4 stage sampling procedure. [211] Stage 1 identifies and selects Primary Sampling Units (PSUs) that typically consist of one county, or groups of contiguous counties. Stage 2 divides PSUs into segments equivalent to the size of a city block. Stage 3 identifies and selects households within each selected segment, and a sample is randomly drawn from the existing households. Stage 4 identifies and selects individuals within each household, and randomly selects a participant by age, sex and race/ethnicity. [211] Certain groups are of particular interest to public health officials and researchers, and NHANES is designed to oversample these groups in order to provide reliable statistics. [209–213] In the 2007-2012 waves of NHANES, Hispanics, Non-Hispanic Blacks, Non-Hispanic Asians, Non-Hispanic Whites at or below 130 percent of the poverty level, and Non-Hispanic whites aged 80 years and older were oversampled. [212,213]

This procedure results in a sample of approximately 5,000 people across 15 PSUs per year.[209,210] NHANES data are collected via a Household Interview, a Mobile Examination Center (MEC) visit, and Post-Mobile Examination Center procedures using standardized questionnaire interviews, clinical examinations and laboratory procedures.[209,210,214]

During the Household Interview, a trained interviewer first screens the household and residents for participation. The screening process gathers information on age, gender, race/ethnicity, and income; this information is used in an algorithm to randomly select participating households and participants. For selected households, the relationship questionnaire divides all household residents into family units in order to identify the number of families residing in a household. Informed consent is obtained for all selected participants, who are then interviewed for information related to demographics, socioeconomics, dietary and health history. For each family unit within a sampled household, a family questionnaire obtains information on education, race/ethnicity, family income, occupation and other household characteristics.

After the Household Interview, selected participants are scheduled for an appointment at the Mobile Examination Center (MEC) for laboratory and clinical assessment. The MEC set up in a location easily accessible to participants in a selected PSU. The MEC is a combination of 4 trailers containing exam rooms and equipment needed for data collection. During the MEC visit, trained staff collect data related to components such as audiometry, anthropometry, blood pressure, body composition, bone density, cardiovascular fitness, oral health, and a physician examination, among others. Participants also complete a dietary interview, and a private health interview (covering

topics such as current health status, substance use and physical activity) during the MEC visit. Biospecimen samples of blood, hair, nasal swab, urine, vaginal swab, and glucose tolerance are collected and sent to external laboratories for analysis.[214]

A sub-sample of participants are also recruited to participate in Post-MEC Data Collection. This data collection includes allergen data, dietary interview, physical activity monitoring, health questionnaire, and urine sample. Post-MEC Data Collection is completed via phone interview, in-home questionnaire, and mailed return of completed tasks (i.e. urine collection and physical activity monitoring) to appropriate laboratories for analysis.[214]

Sample

Individuals were drawn from the 1999-2012 waves of NHANES. Combining 14 years of NHANES data provides greater statistical reliability, is more representative of the United States population, and provides greater geographic variability in the sample. This study focuses on a subset of male and female adolescents aged 12 to 19 from NHANES. The sample included individuals from all racial/ethnic groups. Individuals with a self-reported diagnosis of diabetes that are currently using medication/insulin to control their blood glucose levels were not included in the subset as medication/insulin use may result in altered HbA1c levels. Individuals with a self-reported diagnosis of hypertension that are taking medication to treat hypertension were not included in the subset as medication use may result in altered BP levels. Individuals reporting current pregnancy were not included in the subset as pregnancy influences cardiometabolic biomarker levels.[215][216]

The analytic sample was drawn from 13,343 adolescents, ages 12–19 years who completed examination in the mobile examination center (MEC). We excluded respondents who reported to be pregnant (n=181), had been told by health professional to have hypertension or diabetes and using medication for hypertension or diabetes (n=83). Of the remaining 13,079 adolescents, 2,934 were excluded due to missing data on cardiometabolic outcome variables, leaving a final analytic sample of 10,415 adolescents (79% of sample who completed the mobile examination center component).

Area-level Data

Area-level data were drawn from the 2009-2013 American Community Survey, the 2005-2009 American Community Survey, and the 2000 Decennial Census. 3,140 census tracts were included in analysis.

Fully implemented in 2005, the American Community Survey (ACS) is a continuous survey of demographic, social, and economic indicators (e.g., poverty, education, family makeup, and housing). Since 2010, the ACS has replaced the long form Decennial Census in order to provide contemporary statistics for the United States population. The United States Census Bureau collects and releases data annually. The ACS samples approximately 3,500,000 addresses in the United States each year. Data are released in 1-year, 3-year, and 5-year estimates, with multiyear estimates combining data from the previous 3- or 5-year periods.[217] This study used 5-year estimates as they include the largest sample size, are considered the most accurate, and provide estimates for small geographic units.

The 2000 decennial census was a cross-sectional survey that collected

demographic, social, and economic indicators (e.g., poverty, education, family makeup,

and housing). As the decennial census collects data from all households in the United

States, decennial census data accurately describes the United States population in the year

2000. Decennial census data provides statistics for multiple levels of geography in the

United States.[218] With multiple levels of geography available in Census and ACS data, it

is important to identify an appropriate geographic unit of analysis with which to depict

area-level poverty.

Area-level Units of Analysis

When examining area-level determinants of health it is important to determine the

appropriate geographic unit of analysis that allows for observation of the construct of

interest as well as adequate statistical power to observe an association reliably.

Area-level units of analysis range from census blocks to nations. Larger

geographic units include many smaller geographic units that have been shown to be

relevant to the health of individuals within those units.[72] While factors such as income

inequality measured at national or state levels[219–221] have been linked to health outcomes,

much of the research on area-level determinants of health utilizes smaller geographic

units, such as census block group, census tract, or ZIP codes. Additionally, some

constructs are more relevant at smaller geographies (e.g. social cohesion) while others are

only relevant in larger geographies (e.g. income inequality).[222]

Krieger et al examined how heterogeneity of various units relates to consistency

of observations. Relatively smaller geographic units have more homogenous populations

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and allow for the most consistent observations.[72–74] Census block groups (on average, 1,000 residents) and census tracts (on average, 4,000 residents) are considered to have relatively homogeneous populations, and both block groups and census tracts yielded consistent observations between area-level exposures and health outcomes.[72–74] In contrast, ZIP codes (on average, 30,000 residents) have relatively more heterogeneous populations, and inconsistent observations.[72–74] Furthermore, similar relationships at the block group and tract levels exist.[223,224] For many social constructs related to area of residence, census tracts are also considered to be the more socially relevant geographic unit.[225,226] Tract boundaries are derived with input from local communities in attempt to capture natural neighborhood boundaries.[227] Furthermore, aggregating resident-reported data to the tract level can result in socially relevant variables (e.g. collective efficacy) that have links to health outcomes.[228,229] Additionally, tracts are utilized by federal, state, and local entities for resource allocation and to determine eligibility for social programs. [225–227] Due to these factors, census tracts are considered to best approximate social context compared to other small geographic units of analysis.

Other considerations are statistical power, precision of estimates, and reliability that a particular unit of analysis allows. High margins of error occur when population among a particular unit is small.[223,224] Census tracts, on average, have a larger population than block groups.[72–74] Therefore, while similar relationships at the block group and tract levels exist, results at the tract level are more reliable, due to relatively higher statistical power in census tracts.[223,224] Finally, census tracts have also been shown to be ideal for geocoding individuals within their contexts, with approximately 95% accuracy in placing

individual within appropriate tracts.[226,230] Consequently, for the reasons outlined above,

NHANES data was linked with ACS and census data at the census tract level.

Data Linkage

Individuals from NHANES were linked with contemporary area-level data using

census tract identifiers For example, 1999-2000 NHANES data were linked with 2000

Decennial Census data via 2000 census tract identifiers, and 2011-2012 NHANES data

were linked with 2009-2013 ACS data via 2010 census tract identifiers (Figure 1).

Linking NHANES data with contemporary area-level data was beneficial in that

individuals were placed in their relevant social context.

Cardiometabolic Biomarkers

All biospecimen were obtained by trained technicians during the MEC.

Glucose Metabolism*:* A single measurement of glycosylated hemoglobin, representing

the average blood glucose level over approximately three months, was assessed with a

high performance liquid chromatography analyzer.[231]

Blood Pressure: systolic and diastolic blood pressure (mmHg) were assessed up to three

times with a mercury sphygmomanometer according to standards of the American Heart

Association.[231] When multiple measurements were available (n= 10266; 98%), they were

averaged to obtain mean systolic and diastolic blood pressure. Z-scores based on age,

gender, and height were calculated using the following formula:[87]

$$Zsbp = (X - \mu)/\sigma$$

X: Observed value

μ: Expected value based on age, gender, height

σ: Gender $-$ specific standard deviation (Male: 10.7128, Female: 10.4855)[87]

Lipid Metabolism: Two measures of lipid metabolism were used: 1) HDL Cholesterol (mg/dL) levels are analyzed using an endpoint reaction technique specific for HDL cholesterol.[231] 2) Total cholesterol (mg/dL) levels are analyzed using a single-reagent endpoint technique specific for cholesterol.[231] Previous analyses of cardiometabolic risk have utilized triglycerides instead of total cholesterol, in an attempt to diagnose Metabolic Syndrome.[25,30] As the aim of this study is to examine pre-clinical indicators of disease, the use of total cholesterol is appropriate as total cholesterol tracks better over time compared to other biomarkers of lipid metabolism.[232] Additionally, using triglycerides would have reduced the sample size by 51.8 percent (n= 5019), limiting hierarchical analyses due to a potentially small number of individuals residing in each census tract.[233]

Adiposity: Waist circumference (cm) is measured by a trained health technician.[231]

Index of Cardiometabolic Risk

We created a continuous index of cardiometabolic risk by summing z-scores for glycosylated hemoglobin levels, [234–236] waist circumference,[14] and HDL cholesterol and total cholesterol,[57,58,234] and for systolic and diastolic blood pressure.[17–19] All z-scores were age and gender specific, except the z-score for blood pressure which was based on age, gender, and height.[87] Higher scores indicate higher risk (HDL was multiplied by -1). Parametrization of this cardiometabolic index was informed by evidence indicating a

multivariate measure better predicts future development of disease than any individual biomarker alone.[61] Additionally, a continuous measure reflects population-level variation in cardiometabolic risk[237,238] and, thus, better predicts adult health compared with a categorical measure.[239] A related point is that false positive and false negative errors may arise when categorical measures are used. Finally, a continuous measure allows more statistical power, an important consideration given that prevalence of high cardiometabolic risk during adolescence may be only 4% (depending on the definition used).[3,237]

Individual-level Variables - Figure 2 identifies variables that have been linked with cardiometabolic risk in previous studies, and which variables have been included for this study.

Survey Wave – Indicator variables for waves of NHANES data were included to account for potential period effects. Survey wave was coded as 1/0, with 1 indicating wave of data. This is included in the Demographic Variables and Sample Weights file from NHANES.

Age – Age in years is reported as a continuous variable (parental/guardian report for individuals <16 years of age). This was collected during the Household Interview portion of data collection.

Gender – Gender is reported as a categorical variable: Male, Female. Gender was dummy coded as 1/0 with 1 indicating female (parental/guardian report for individuals <16 years of age). This was collected during the Household Interview portion of data collection.

Race/ethnicity – Race/ethnicity is reported as a categorical variable: non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian, Mexican American, Other Hispanic, and Other Race/Ethnicity Non-Hispanic (parental/guardian report for individuals <16 years of age). Non-Hispanic Asian, Other Hispanic and Other race/ethnicity were grouped together as "Other." Because the group of participants identified as belonging to "other" races/ethnicities is small and heterogeneous, race-specific regression results are not presented for this group, although they were included in the analytic sample and overall results. Race/ethnicity was coded as 1/0, with 1 indicating belonging to that racial/ethnic group. This was collected during the Household Interview portion of data collection.

Cotinine Levels – Cotinine (ng/mL) is a metabolite of nicotine exposure. Cotinine is collected via blood sample from the participant as part of the Mobile Examination Center. This is collected for participants aged 3 years and above, and was measured using an isotope dilution-high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry.[231] Cotinine was kept as continuous.

Physical Activity – Self-reported "Over the past 30 days, did you do moderate activities for at least 10 minutes that cause only light sweating or a slight to moderate increase in breathing or heart rate? Some examples are brisk walking, bicycling for pleasure, gold, and dancing." This is reported as a categorical variable: Yes, No, Unable to do activity, Refused, Don't know. This was coded as 1/0 with 1 indicating any physical activity. For individuals aged 12 to 15 years, this was asked during an interview at the Mobile Examination Center. Individuals aged 16 to 19 years were asked this question during Home Interview portion of data collection.

Hypertension Status – For individuals over >= 16 years of age, a self-reported diagnosis of hypertension, "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?" is reported as a categorical variable: Yes, No, Refused, Don't Know. Hypertension status was coded as 1/0 with 1 indicating a previous hypertension diagnosis. Refused and Don't Know was treated as missing. This was collected during the Household Interview portion of data collection.

Hypertensive using medication – For individuals over >= 16 years of age, a self-reported use of medication to treat hypertension, "Are you now taking prescribed medicine?" is reported as a categorical variable: Yes, No, Refused, Don't Know. This was coded as 1/0 with 1 indicating taking medication to treat hypertension. Refused and Don't Know was treated as missing. This was collected during the Household Interview portion of data collection.

Diabetes Status – A self-reported previous diagnosis of diabetes (parental/guardian report for individuals <16 years of age), "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" is reported as a categorical variable: Yes, No, Borderline, Refused, Don't Know. Diabetes status was coded as 1/0 with 1 indicating a previous diabetes diagnosis. Borderline individuals were included in the No category for the previous diabetes diagnosis variable. Refused and Don't Know was treated as missing. This was collected during the Household Interview portion of data collection.

Diabetic using insulin – A self-reported use of insulin (parental/guardian report for individuals <16 years of age), "Are you now taking insulin?" asked of individuals self-

reporting as diabetics. Reported as a categorical variable: Yes, No, Refused, Don't Know. This was coded as 1/0 with 1 indicating diabetic taking insulin. This was collected during the Household Interview portion of data collection.

Diabetic using pills – A self-reported use of pills (parental/guardian report for individuals <16 years of age), "Are you now taking diabetic pills to lower your blood sugar?" asked of individuals self-reporting as diabetics. Reported as a categorical variable: Yes, No, Refused, Don't Know. This variable was coded as 1/0 with 1 indicating diabetic using pills to control blood sugars. This was collected during the Household Interview portion of data collection.

Family Poverty Income Ratio (PIR) – PIR represents the ratio of family income to their appropriate federal poverty threshold.[240] Ratio < 1 indicates a family below the federal poverty threshold, while ratios >=1 indicate a family above the federal poverty threshold. PIR is reported as a top-coded continuous variable, with all values ≥5 coded 5. This was reported by the Household Reference Person during the Household Interview portion of data collection.

Area-level Variables

Area-level Poverty – The percentage of individuals below the poverty line was used as the measure of area-level SES. From Census 2000, the variable is "All individuals for whom poverty status is determined – Percent Below Poverty Level." From 2005-2009 ACS, the variable is "Population for whom poverty status is determined – Percent Below Poverty Level." From 2009-2013 ACS, the variable is "Population for whom poverty status is determined – Percent Below Poverty Level." This measure is available at the

census tract level and is available from decennial Census data and American Community

Survey data. This is reported in Census and ACS data as a continuous variable. To avoid

assuming a linear relationship with CM risk, area-level poverty was grouped into

quartiles for analysis. Indicator variables for each poverty quartile were created, with

Quartile 1 ($\leq 25^{th}$ percentile) used as the reference category.

Percent Non-Hispanic Black Population – Racial/ethnic concentration at the census tract

level is available from Census 2000, ACS 2005-2009 and ACS 2009-2013 data. The

percent non-Hispanic Black population at the census tract level was used as a measure of

racial/ethnic concentration. This is reported as a continuous variable.

Missing Data

Responses of "Don't Know," "Refused," and "Missing" were treated as missing

values. Missing values for body mass index, cotinine, and Family PIR were imputed

using SAS MI PROC MI procedure in SAS 9.3.[241] Indicator variables were not imputed,

as imputed values may fall between 0 and 1, and rounding these values may introduce

bias. Multiple imputation was carried out using the entire sample in SAS 9.3.[241] Multiple

imputation models used truncated regression with the PROC MI procedure. PROC MI

produced 10 imputed datasets. Hierarchical linear models for each of the 10 imputed

datasets were fit using PROC MIXED. PROC MIANALYZE is then used to combine the

estimates produced from the imputed datasets, and produces 1 set of estimates based on

results from the 10 imputed datasets.[242]

Analytic Plan

1) Descriptive statistics were reported for index of cardiometabolic risk and individual cardiometabolic biomarkers by individual-level and area-level covariates. The mean and 95% confidence interval were reported.

2) A model estimating the crude association between area-level poverty and cardiometabolic risk was fit to establish a baseline effect of area-level poverty. Indicator variables for survey cycle were included at the individual level. Indicator variables for area-level poverty quartiles were included on the intercept, with area-level poverty quartile 1 (i.e. lowest quartile of area-level poverty) serving as the reference category. Regression coefficients, standard errors and 95% confidence intervals were reported.

3) Next, a model to determine the effect of area-level poverty, independent of individual-level covariates was fit. Race/ethnicity, and family PIR were included in the model. Regression coefficients, standard errors and 95% confidence intervals were reported.

4) Next, a model to determine the effect of area-level poverty, independent of individual-level and area-level covariates was fit. Tract-level percentage non-Hispanic black and group mean values for family PIR were added to the intercept. Regression coefficients, standard errors and 95% confidence intervals were reported (Specific Aim 1).

5)   To determine if the association between area-level poverty and cardiometabolic

risk differs by race/ethnicity, models in steps 2-4 were fit by racial/ethnic groups: non-

Hispanic White, non-Hispanic Black, Mexican Americans and Other. Regression

coefficients and 95% confidence intervals were reported (Specific Aim 2).

6)   I evaluated exposure to tobacco smoke and physical activity as potential

mediators of the association between area-level poverty and cardiometabolic

risk.[28,29,243,244] To test mediation, I first fit regression models for each potential

mediator:[245]

> a) The net association between area-level poverty and cardiometabolic risk
> without adjusting for mediators.

> b) The association between area-level poverty and the mediator.

> c) The association between the mediator and cardiometabolic risk.

If significant associations were observed in each of the first three steps, a model was fit

for the association between area-level poverty and cardiometabolic risk, adjusting for

the mediator. Partial mediation is considered to exist if both area-level poverty and the

lifestyle behaviors have a significant association with cardiometabolic risk in the full

model. Full mediation occurs if the effect of area-level poverty becomes non-

significant when adjusting for lifestyle behaviors.

I examined potential mediators for the overall sample and by race to determine if the

pathway of area-level poverty to lifestyle behavior to cardiometabolic risk partially

explains disparities in cardiometabolic risk (Specific Aims 3 & 4).

In post-hoc analysis, I explored associations between area-level poverty and family PIR,

and whether these associations differ by race/ethnicity. I compared mean Family PIR by

area-level poverty for the overall sample, and by race/ethnicity.

All analysis was conducted in SAS 9.3.[241]

Hierarchical Linear Models

Hierarchical linear models (HLM) were used to examine the relationship between

area-level poverty and biomarkers that predict development of future disease among

adolescents. As this study linked individual-level data (NHANES) and area-level data

(ACS and Census) with area-level data, HLM allowed for more appropriate statistical

conclusions than other statistical techniques such as ordinary least squares or logistic

regression.

The multistage sampling of NHANES results in selection of individuals based on

geographic location.[211] Therefore, in this analysis, individual-level data are clustered, or

dependent on the census tract in which residents reside.[233,246] A key assumption of

ordinary least squares and logistic regression is independence of the residuals. However,

statistical dependency, that occurs when individuals are nested within a census tract,

violates this assumption and leads to negatively biased standard errors and thus a greater

likelihood of Type I error.[233,246]

Statistical dependency of multilevel data also suggests that covariance of the outcome variable exists within each geographic unit. For example, within a census tract, BP of individuals are likely to co-vary. Additionally, variance in the outcome may exist between census tracts as the relationship between a predictor variable and the outcome variable may differ between census tracts.[233,246] Data with statistical dependency (e.g. survey data, multilevel data) is often analyzed with general estimating equations in order to properly estimate variance. However, in general estimating equations, variance is controlled for, and not explicitly examined. Without partitioning variance into within- and between-tract components, it is difficult to understand total variability in the outcome.

HLM provides an error term for both the individual- and area-level models, allowing variance to be partitioned into within- and between-unit components. HLM accounts for statistical dependency by assigning one statistical model to the individual-level and one statistical model to the area-level. Standard errors are estimated for parameter estimates at both the individual- and area-level; this produces unbiased standard error estimates, allowing for more appropriate statistical conclusions.[233,246]

As this study aims to understand the relationship between area-level poverty and cardiometabolic risk among adolescents (independent of individual- and area-level covariates), a random intercept model with fixed slopes is appropriate. This type of model allows for area-level predictors (e.g. area-level poverty) and confounders (e.g. racial/ethnic concentration) to be included, as well as individual-level covariates. The intercept (average outcome within each census tract) varies as a condition of the area-

level poverty within each census tract, while the slope (effect of individual-level covariates) is constant across census tracts.

Linear Regression Model Components

The following describes the hierarchical linear regression model, with random intercepts, using the cardiometabolic index as the outcome.

CMI_{ij}: Cardiometabolic Index of Individual i in census tract j

Area-level Poverty: Poverty rate quartiles of census tract j

Racial Concentration$_{Centered}$ = (Racial Concentration$_j$ – X $_{Racial\ Concentration..}$) : Percent non-Hispanic Black of census tract j grand mean centered

Level 1 Components

β_{0j}: Intercept (Average outcome when all covariates at the mean, and all dummy variables are at 0)

$\begin{bmatrix} \beta_{1j} \\ ... \\ \beta_{xj} \end{bmatrix}$: Vector of individual-level coefficients

$\begin{bmatrix} X_{2ij} & ... & X_{nij} \end{bmatrix}$: Matrix of individual – level covariates (n= number of covariates)

r_{ij}: Individual – level residual

Level 2 components

γ_{00} : Intercept (Average outcome when all covariates at mean, and all dummy variables are at 0)

$\gamma_{01} \dots \gamma_{03}(Area - level\ poverty\ Quartiles)$: Effect of Area-level Poverty

quartile of unit j on the intercept (average effect of area-level poverty)

$\gamma_{04}(Racial\ Concentration_{Centered}) = :$ Effect of Racial Concentration of unit j

on the intercept (average effect of racial concentration)

$\begin{bmatrix} \gamma_{1j} \\ \dots \\ \gamma_{xj} \end{bmatrix}$: Coefficient for Level-1 covariates (effect of individual-level covariates on

CMI_{ij})

u_{0j}: Area $-$ level residual

Hierarchical Model

$$CMI_{ij} = \beta_{0j} + \begin{bmatrix} \beta_{1j} \\ \dots \\ \beta_{xj} \end{bmatrix} [X_{1ij} \dots X_{nij}] + r_{ij}$$

$$\beta_{0j} = \gamma_{00} + [\gamma_{01} \dots \gamma_{03}(Area - level\ SES_j)] + \gamma_{04}(Racial\ Concentration_j) + u_{0j}$$

$$\begin{bmatrix} \beta_{1j} \\ \dots \\ \beta_{xj} \end{bmatrix} = \begin{bmatrix} \gamma_{1j} \\ \dots \\ \gamma_{xj} \end{bmatrix}$$

Mixed Model

$$CMI_{ij} = \gamma_{oo} + [\gamma_{01}(Q2\ Area - level\ Poverty_j) + \gamma_{02}(Q3\ Area - level\ Poverty_j)$$

$$+ \gamma_{03}(Q4\ Area - level\ Poverty_j)] + \gamma_{04}(Racial\ Concentration_j)$$

$$+ \begin{bmatrix} \gamma_{1j} \\ \dots \\ \gamma_{xj} \end{bmatrix} [X_{1ij} \dots X_{nij}] + r_{ij} + u_{0j}$$

Centering

All individual-level variables were group mean centered (centered on the mean value for the census tract), excluding the dichotomous variables. The group mean of all individual-level group mean centered variables was included at the area-level. Area-level variables were grand mean centered.

This method of centering is preferred when testing "2-1-1" mediation, in that an individual-level variable is the potential mediator between an area-level exposure and an individual-level outcome.[245] By centering individual-level variables at the group mean and including the group mean at the area-level, the relationship between the potential mediator (i.e. cotinine, physical activity) and the outcome (i.e. cardiometabolic index) is decomposed into within-tract and between-tract components. Decomposing the relationship is important for two reasons: First, mediation can occur both within and between tracts. Secondly, the effect of the area-level group mean variable on the outcome may be different than the effect of the group-mean centered individual-level variable.[245] This may help identify three distinct types of mediation. First, mediation could mainly occur between tracts, and the relationship between the mediator and outcome within tracts may be weak. Second, mediation could mainly occur within tracts, and the relationship between the mediator and outcome between tracts may be weak. Third, there may be a moderately strong relationship between the mediator and the outcome both within and between tracts. These distinct types of mediation would be confounded under grand-mean centering or no centering of the individual-level variables, as the individual - level coefficient is then a composite of the within- and between-tract variation.[245]

Weighting

        Weights were utilized in NHANES data to account for the complex sample design

of NHANES data, and survey non-response. Using these weights are important, as

analyses without weights will likely result in biased estimates and inaccurate significance

levels. Additionally, use of weights allows for generalizations about the United States

non-institutionalized population between 1999 and 2012.

        NHANES data also includes various weights for analysis. For example, weights

are provided for the in-home interview data from NHANES, and separate weights are

available for the clinical and biomarker data. It is recommended that the weight for the

smallest subpopulation that includes all variables in analysis be used. The analysis

includes data collected during the in-home interview (e.g. age, race/ethnicity) and data

collected at the Mobile Exam Centers. Due to this, the Mobile Exam Center weight was

used, because the Mobile Exam Center population represents the smallest subpopulation

represented in the data. When combining 14 years of data, a 14-year weight was

constructed. This 14-year weight consists of a 4-year weight from the 1999-2002 waves

of NHANES, and 2-year weights from each of the waves from 2003-2012. SAS code

used to construct this 14 Year Weight is in Appendix C.1.[247]

        As this study uses hierarchical models, sampling weights were scaled to the

census tract level. Scaling weights is suggested as it better allows for investigations of

variance between and within clusters.[248] It is recommended to use two methods of

scaling, and compare results. With Method A, weights are scaled so that the new weights

sum to the cluster sample size.[248] This method may provide smaller standard error

estimates if interested in reporting point estimates, and may be more appropriate with a

large number of Level 2 units. With Method B, weights are scaled so that the new weights sum to the effective cluster size.[248] This method may be more appropriate if discussion of variance-covariance is of greater importance. Models were initially fit with Method A scaled weight, as point estimates are of interest, and there are a large number of Level 2 units (n= 3140). Models were fit with 14 Year MEC Weight and Method B scaled weight. Estimates and standard errors across weighting methods were compared to determine which method provides the most precise estimates.[248] The recommended SAS code is in Appendix C.2.[248]

Linearity

In this study, the relationship between the continuous predictor variables and the outcome variables is assumed to be a linear relationship. This was assessed by plotting the residuals against predictor variables. If the likelihood of linearity is low, this may be addressed by transforming the predictor variables. The type of transformation performed depends on the relationship observed between the predictor and the outcome.

Assumptions of Hierarchical Linear Regression

The following assumptions of hierarchical linear models were tested[233]:

1. Individual-level r_{ij} are independent and normally distributed with a mean of 0 and variance for every individual within each census tract.

    a. This was tested by obtaining a Q-Q Plot of the Level-1 residuals. Homogeneity of variance was tested by plotting frequencies of individual-level variances.

2. The individual-level predictors $[X_{1ij} \ldots X_{nij}]$ are independent of r_{ij}.

   a. This was tested by plotting the individual-level residuals against the individual-level predicted values.

3. Area-level $u's$ are multivariate normal, each with a mean of 0, some variance and covariance. $u's$ are independent among the area-level units.

   a. This was tested by obtaining a Q-Q Plot of the area-level residuals. Homogeneity of variance was tested by plotting frequencies of area-level variances.

4. The set of area-level predictors are independent of every u.

   a. This was tested by plotting the area-level residuals against the area-level predicted values.

5. The individual-level errors and area-level errors are independent of one another.

   a. This was tested by plotting the individual-level residuals against area-level residuals.

6. The predictors at each level are independent of the residuals at the other level.

   a. This was tested by plotting predictors against the residuals from the other level.

Chapter VII. Results

Descriptive Statistics

The analytic sample includes 10,415 adolescents and 3140 census tracts, resulting in 3.34 adolescents per tract, on average. Descriptive statistics appear in Table 1. Mean area-level poverty across census tracts is 14.46 percent (interquartile range 6.1, 19.8), and mean percent non-Hispanic Black population is 12.90 percent (interquartile range: .58, 12.84).

Mean score on the index of cardiometabolic risk for the total sample is -.810 (95% CI: -.884, -.737). Residents in the fourth quartile of area-level poverty (highest area-level poverty) had the highest average cardiometabolic risk score (-.535, 95% CI: -.669, -.371), followed by third (-.531, 95% CI: -.694, -.367), second (-.855, 95% CI: -.984, -.726), and first quartiles (-1.048, 95% CI: -1.182, -.915). Differences in mean cardiometabolic risk were observed by race. Non-Hispanic blacks have highest average cardiometabolic risk score (-.643, 95% CI: -.759, -.526), followed by Mexican Americans (mean: -.692, 95% CI: -.817, -.567), and non-Hispanic Whites (-.855, 95% CI:-.963, -.747).

Hierarchical Linear Model Results

Table 2 includes results of hierarchical models estimating the association between area-level poverty and the index of cardiometabolic risk. In the crude model (model 1), increasing area-level poverty is associated with increasing cardiometabolic risk scores, and this pattern is independent of individual-level covariates (model 2) as well as racial concentration (model 3). In the fully adjusted model, relative to the first quartile of area-

level poverty, residents of the second, third, and fourth quartiles of area-level poverty experienced .218 (95% CI: .012, .424), .438 (95% CI: .213, .665), and .451 (95% CI: .204, .698) elevated cardiometabolic risk scores, respectively (Figure 3).

Of note is inclusion of individual-level covariates (model 2) reduced the coefficients of the second, third, and fourth quartiles of area-level poverty by 19.6%, 18.2%, and 22.2%, respectively, yet all remain statistically significant. This suggests individual-level covariates partially explain the association between area-level poverty and cardiometabolic risk. In contrast, when including area-level racial concentration in the model (Model 3), the coefficients for the quartiles of area-level poverty increased by 1.8%, 2.5%, and 4.8%, respectively, when compared to Model 2. This suggests that the association between area-level poverty and cardiometabolic risk is not explained by concentration of racial minorities.

Model Fit

Log likelihood ratio tests for the overall sample suggest including additional individual-level variables in Model 2 did not improve model fit compared to Model 1 (x^2: 2.49 df=5 p=.778). Compared to Model 2, addition of area-level covariates in Model 3 improved model fit (x^2: 10.48 df=1 p=.001). Compared to Model 1, the full model improved model fit (x^2: 12.97 df=6 p=.043).

Race/Ethnicity Specific Analysis

In race/ethnicity specific analyses (Table 2), area-level poverty is associated with cardiometabolic risk among non-Hispanic Whites and Mexican Americans, but not among non-Hispanic Blacks.

Mediation Analyses

We did not find any evidence of mediation by exposure to tobacco smoke (Table 3) and physical activity (Table 4) for the full sample or by race/ethnicity.

Post-hoc analysis

In post-hoc analysis, we explored associations between area-level poverty and family poverty-to-income ratio (PIR), and whether these associations differ by race/ethnicity (Table 5). Overall, mean family PIR declined from 3.34 in quartile 1 to 1.42 in quartile 4 (p< .001). Within each racial/ethnic group, mean family PIR declined across area-level poverty quartiles. However, the magnitude of this difference varied by race/ethnicity. Between the first and fourth quartiles, non-Hispanic Whites had a 1.93 unit decline (p<.001), non-Hispanic Blacks had a 1.27 unit decline (p<.001), and Mexican Americans experienced a 1.22 unit decline (p<.001).

Within each quartile of area-level poverty, racial/ethnic differences in mean family PIR are attenuated as area-level poverty increases. For example, in quartile 1, mean family PIR for non-Hispanic whites is .92 units higher than mean family PIR for non-Hispanic blacks, and this difference is only .26 in quartile 4 (Table 5).

Variance Components

Variance components for overall models and models by race/ethnicity are included in Table 2. Total variance explained ($\tau_{00} + \sigma^2 = 5.93$) does not differ across models for the overall sample. The intraclass correlation does not change across models for the overall sample, as approximately 25 percent of the variance in cardiometabolic

risk is found between tracts and approximately 75 percent of the variance is found within tracts.

Comparison of model weights

Table 6 includes area-level results of full models weighted with scaling method A, scaling method B, and MEC 14 year weights. Models were initially fit with method A scaled weights. In models using method A scaled weights, coefficient estimates and standard errors of the second, third, and fourth quartiles of area-level poverty were .218 (se: .105), .438 (se:.115), and .451 (se:.126), respectively. Method B scaled weights coefficient estimates and standard errors of the second, third, and fourth quartiles of area-level poverty were .229 (se:.107), .454 (se:.117), and .466 (se:.128), respectively. Compared to method A scaled weight results, method B scaled weight results in a 3 to 5 percent increase in coefficient estimates, and a 2 percent increase in standard errors. Using MEC 14 year weights, results of the second, third, and fourth quartiles of area-level poverty were .218 (se: .105), .443 (se:.120), and .459 (se:.136), respectively. Compared to method A scaled weight results, MEC 14 year weight results in no change for the second quartile, and an approximately 1 percent increase in coefficient estimates and 4 to 7 percent increase in standard errors.

Assumptions of Hierarchical Linear Regression

The six assumptions for hierarchical linear regression were tested for the overall model as outlined in the methods section. Plots for each assumption are in Figure 4.

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For assumption 1, a Q-Q plot and a histogram of individual-level residuals were obtained to observe distribution of individual-level residuals. Initial results suggest the individual-level residuals are not normally distributed (Figure 4a). Outliers (observations with individual-level residuals ≥ 14) were deleted, and this improved the distribution of individual-level residuals (Figure 4b). To test independence of individual-level residuals, residuals were plotted against predicted values for both the initial model, and model with deleted observations (Figure 4c). The independence assumption was violated in both the initial model and the model with deleted observations. Inclusion of physical activity and cotinine at the individual level, and percent of female-headed households and percent of individuals receiving public assistance at the area-level did not result in independence of individual-level residuals (Figure 4d). Homogeneity of variance was tested with Levene's test of homogeneity. Homogeneity of variance was violated for the initial model (F=1.45, p<.001) and for the model with deleted observations (F=1.45, p<.001).

For assumption 2, the individual-level residuals were plotted against all individual-level predictor variables, and results suggest assumption 2 has been met (Figures 3e - 3f).

For assumption 3 a Q-Q plot and a histogram of area-level residuals were obtained to observe distribution of area-level residuals. Initial results suggest the area-level residuals are not normally distributed (Figure 4g). Outliers were deleted, and this improved the distribution of area-level residuals (Figure 4h). To test the independence of area-level residuals, residuals were plotted against the predicted value of the intercept. The independence of area-level residuals was met in the initial model, and in the model with deleted observations (Figure 4i).

For assumption 4, the area-level residuals were plotted against all area-level predicted values, and the results suggest assumption 4 has been met (Figure 4j).

For assumption 5, the individual-level residuals were plotted against the area-level residuals, and results suggest an association (Figure 4k). In an attempt to address this violation of assumption 5, additional area-level predictors of percent of female-headed households and percent of individuals receiving public assistance were added to the model, yet the association between individual- and area level residuals remained (Figure 4k). Additionally, the association between individual- and are-level residuals remained after the addition of interactions between area-level poverty and racial concentration were added to the model to the model (Figure 4k).

For assumption 6, individual-level residuals were plotted against area-level predictors, and area-level residuals were plotted against individual-level predictors, with results suggesting this assumption has been met (Figures 4l-4n).

Chapter VIII. Discussion

In this examination of the association between area-level poverty and cardiometabolic risk among a nationally representative sample of U.S. adolescents, we found that among US adolescents there is a dose-response association between area-level poverty and cardiometabolic risk. Moreover, this was the first study to identify important distinctions by race/ethnicity.

Area-level poverty is associated with cardiometabolic risk among non-Hispanic whites and Mexican Americans but not among non-Hispanic blacks. Notably, among non-Hispanic whites and Mexican Americans, a non-linear association was observed as the effect of residence in quartile 4 of area-level poverty was not larger than the effect of residence in quartile 3 of area-level poverty. This suggests that while exposure to high levels of area-level poverty has negative consequences on cardiometabolic risk, the dose-response effect plateaus within quartiles 3 and 4 of area-level poverty. Additionally, there may be few non-Hispanic whites and Mexican Americans residing in quartile 4 of area-level poverty, resulting in more unstable estimates. This possibility is supported by the wider confidence intervals for the estimates of quartile 4 of area-level poverty for both non-Hispanic whites and Mexican Americans.

Among our sample, the association between area-level poverty and cardiometabolic risk was similar for both non-Hispanic whites and Mexican Americans. Additionally, post-hoc analysis suggests non-Hispanic whites have a higher average family PIR than Mexican Americans (Table 5). Taken together, these observations are accordant with literature on the Hispanic paradox. The Hispanic paradox suggests that in

the United States, despite generally lower socioeconomic status among Hispanic populations, they have similar or better outcomes to non-Hispanic whites.[249,250]

In contrast, among non-Hispanic blacks, area-level poverty was independent of cardiometabolic risk. These findings are in line with previous work which observed a greater gradient in the association between individual-level SES and health among non-Hispanic whites than other racial/ethnic groups.[251–254] The improvement in health-related outcomes associated with higher SES appears to be greater for non-Hispanic whites than for other racial/ethnic groups. Additionally, evidence suggests non-Hispanic blacks experience greater levels of social adversity across all levels of socioeconomic status,[254] and the experience of social adversity is an under-addressed determinant of health.[254,255] This suggests when examining the role of area-level poverty in racial/ethnic disparities in health, the individual-level experience of individuals within a particular socioeconomic group (i.e. residence in a specific quartile of area-level poverty), and not solely their membership within that particular socioeconomic group, is an important determinant of health.

Racial/ethnic differences in cardiometabolic risk scores were observed, as non-Hispanic blacks have the highest cardiometabolic risk score (Table 1). The observed racial/ethnic disparities in cardiometabolic risk differed from the racial/ethnic disparities reported in previous literature.[3,4,25–30] The differences in reported racial/ethnic disparities in cardiometabolic risk are likely due to biomarker-specific racial/ethnic differences for lipid metabolism and glucose metabolism (Table 1). Among biomarkers for lipid metabolism, non-Hispanic whites have lowest average levels of HDL cholesterol, and there are no racial/ethnic differences in total cholesterol levels. For glucose metabolism,

non-Hispanic blacks have highest average levels of HbA1c. These racial/ethnic differences among specific biomarkers are in line with extant literature.[4,25,27] Additionally, the observed racial/ethnic disparities in cardiometabolic risk in the current study is consistent with studies among adults suggesting non-Hispanic blacks have higher prevalence of cardiometabolic diseases in adulthood.[24]

The estimated degree of racial/ethnic disparities in cardiometabolic risk can depend, in part, on the choice of biomarkers used to measure lipid metabolism and glucose metabolism. This is because the biomarkers that can be used to assess lipid metabolism and glucose metabolism yield distinct cardiometabolic risk profiles.[4,25,27] For example, among biomarkers of lipid metabolism, non-Hispanic whites consistently have lower HDL cholesterol and triglycerides than both non-Hispanics and Mexican Americans, while there are no differences by race/ethnicity in total cholesterol levels.[4,25,27] Among biomarkers of glucose metabolism, non-Hispanic whites have fasting glucose levels that are similar to that of Mexican-Americans and higher than fasting glucose levels observed among non-Hispanic blacks.[4,25,27] However, when examining Hba1c levels, non-Hispanic blacks have a three-fold higher prevalence of elevated Hba1c than both non-Hispanic whites and Mexican Americans.[27]

In turn, these differences are reflected in the performance of indices of cardiometabolic risk. For example, when fasting glucose and triglycerides were included in an index of cardiometabolic risk among a nationally representative sample of US adolescents,[30] Hispanics had the highest cardiometabolic risk, followed by non-Hispanic whites and non-Hispanic blacks, respectively.[30] In contrast, for the current study, we used

glycosylated hemoglobin and total cholesterol in our index of cardiometabolic risk, and found non-Hispanic blacks to have the highest cardiometabolic risk.

Our choice of biomarkers was informed by evidence that total cholesterol tracks better over time compared to other biomarkers of lipid metabolism,[232] and availability of total cholesterol measures in NHANES allows for sufficient sample size for analyses. Similarly, HbA1c represents a three-month average of glucose metabolism tracks over time, thus is a more stable indicator of glucose metabolism than fasting glucose tests as it is less influenced by recent diet or illness.[236,256,257] Thus, for the purposes of our study, total cholesterol and HbA1c are appropriate biomarkers for use in our index of cardiometabolic risk. Furthermore, the racial/ethnic disparities observed in the current study are similar to racial/ethnic disparities in cardiometabolic health among adults,[24] suggesting our parameterization of cardiometabolic risk is consistent with findings from previous studies.

Post hoc analysis was conducted to determine if the economic experience of residing in areas with high poverty differed by race/ethnicity. We explored associations between area-level poverty and family PIR, and whether these associations differ by race/ethnicity. Across the range of area-level poverty quartiles, non-Hispanic whites have greater variability in their family-level economic conditions than non-Hispanic blacks and Mexican Americans. More specifically, with lower area-level poverty, there is a more pronounced increase in family PIR among non-Hispanic whites than among non-Hispanic blacks and Mexican Americans. Additionally, within quartiles of area-level poverty, the differences in mean family PIR between racial/ethnic groups are attenuated as area-level poverty increases. This suggests that at higher levels of area-level poverty,

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the economic experience of non-Hispanic whites is more similar to that of non-Hispanic

blacks and Mexican Americans. Racial/ethnic differences in the associations between

area-level poverty and cardiometabolic risk may be related to the different relationships

between area-level poverty and family-level SES by race/ethnicity.

Discrimination and health

Discrimination, manifest as both an individual- and area-level stressor, is a key

determinant of racial/ethnic disparities in health,[258–261] thus, discrimination may partially

explain racial/ethnic disparities in cardiometabolic risk observed in this study.

Race is a social construct, which individuals are grouped into social strata based

on phenotype.[260] In race-conscious societies, like the United States, social advantages

(e.g. educational and employment opportunities, access to resources, political

participation, etc.) are distributed based on these strata.[260–262] Discrimination, which is

premised on this distribution of advantages, is a system in which the advantages are

differentially allocated towards a racial group in power, and away from other racial

groups.[261] Historically, in the United States, social advantages are allocated towards the

white population, and allocated away from other racial groups as a means of maintaining

power.[260–262]

At the individual level, discrimination includes intentional and unintentional

actions that manifest itself as, yet are not limited to, lack of respect, devaluation,

dehumanization, and oppression.[260,263–266] One hypothesis on the link between

discrimination at the individual level and disparities in cardiometabolic health is John

Henryism.[267] This hypothesis states that individuals exposed to discrimination (a stressor)

exert more energy to respond to consequences associated with exposure to stress (as detailed in Chapter V). However, not all individuals respond the same way, as some individuals may have a greater physiologic reaction to discrimination than others.[267] Furthermore, under this hypothesis, individuals that jointly are of low SES and react more actively to discrimination will experience worse cardiometabolic health as a result.[267]

More related to the current study, discrimination at the area-level, referred to as structural discrimination, operates independently of individual-level discrimination.[268] Structural discrimination (including but not limited to racial segregation, low level of political participation among racial minorities, poor judicial treatment of racial minorities) is the result of laws, policies, and political infrastructures at the federal, state, and local levels, aimed to protect advantages of Whites while denying advantages to other racial groups in the United States.[260,269–271] Resource Deprivation Theory[267] hypothesizes that structural discrimination is associated with racial/ethnic disparities in cardiometabolic health, as racial/ethnic minorities in the United States are less likely to reside in areas with the necessary infrastructure to promote good cardiometabolic health.[267] The lack of access to resources is a source of stress, and is associated with a lack of healthy food options and lack of access to medical care.[267]

Individual-level discrimination and cardiometabolic health

Recent evidence among non-Hispanic black adolescents (n = 47) suggests perceived discrimination (i.e. treated with less respect, poor service at restaurants), an individual-level stressor, is associated with increased cardiometabolic risk.[263] This aligns

with a more substantial body of evidence among adults suggesting perceived

discrimination is associated with cardiometabolic health.[264,272–276] Among a small sample

of U.S. adults (n=176), evidence suggests perceived discrimination lies on the pathway

between race/ethnicity and disparities in cardiometabolic risk.[264]

Structural discrimination and cardiometabolic health

The Resource Deprivation Theory aligns with evidence of racial segregation, the

forced residence of certain racial groups into specific areas, as a fundamental social

determinant of racial/ethnic disparities in health.[258,259] Racial segregation is associated

with racial differences in educational and employment opportunities, thus, is a key factor

in racial differences in SES in the United States. [258,259] These racial differences in SES

lead to areas with high levels of poverty, a reduction in the tax base in segregated areas,

and a lack of services which promote good health.[258,259] Racial segregation is associated

with racial disparities in cardiometabolic health among adults,[277–279] and recent evidence

suggests a link between racial segregation and cardiometabolic risk among children and

adolescents.[280,281]

While state-level measures of structural discrimination (i.e. ratio of blacks versus

whites in terms of political participation, employment and job status, educational

attainment, and judicial treatment) are understudied, a nationally-representative study

among adults (n = 32752) observed that blacks residing in states with a high degree of

structural discrimination against blacks had higher risk of cardiometabolic disease

compared to blacks residing in states with a low degree of structural discrimination

against blacks.[269] Among whites, those residing in states with a high degree of structural

discrimination against blacks had lower risk for cardiometabolic disease than whites residing in states with a low degree of structural discrimination against blacks.[269]

As the focus on this study is on the association between area-level poverty at the census tract level and cardiometabolic risk among adolescents, exposure to discrimination was not accounted for in this study. Variables representing perceived discrimination are not available in NHANES data, thus, exposure to discrimination at the individual level cannot be accounted for in this study. At the area level, racial concentration (a crude measure of racial segregation) was accounted for in analysis. However, evidence suggests racial segregation is best measured at larger geographies, (i.e. Metropolitan Statistical Areas, cities, or counties)[258,277–279] as measures of racial segregation will then depict a more racially and geographically diverse population, allowing for a better understanding of how different racial groups are distributed.

Mediation Analysis

The lack of association observed between cotinine levels and cardiometabolic risk may be due to the use of linear models, and mixing of effects. As the aim of this study is to examine pre-clinical indicators of disease, the linear association between cotinine levels and cardiometabolic risk was tested, yet a lack of association was observed. This differs from prior studies, which observed an association between cotinine levels and cardiometabolic risk among adolescents when using a diagnostic approach when measuring cardiometabolic risk.[29] Furthermore, the association between cotinine levels and cardiometabolic risk may be biomarker specific.[282–285] Evidence suggests cotinine levels are associated with glucose metabolism,[282] adiposity,[285] and blood pressure.[283]

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However, among nationally representative sample, cotinine levels were not associated with cholesterol levels.[284] The lack of association observed between cotinine levels and cardiometabolic risk in this study may be due to a mixing of effects, as the index of cardiometabolic risk incorporates multiple biomarkers of cardiometabolic risk.

The physical activity variable used in mediation analysis is self-reported, thus, measurement error and self-report bias are inherent. Social desirability may have contributed to individuals reporting more frequent or intense physical activity than was actual. This introduces measurement error, thus lowering the reliability of the data. Less reliable data increases the chance of observing a nonsignificant association when a significant association is true, and lowers the strength of association. Also, the question asked of physical activity was, "Over the past 30 days, did you do moderate activities for at least 10 minutes that cause only light sweating or a slight to moderate increase in breathing or heart rate? Some examples are brisk walking, bicycling for pleasure, gold, and dancing." This suggests individuals with only one 10-minute period of physical activity in the past 30 days are included in the same category as individuals with much more frequent and intense physical activity. Thus, this categorical variable doesn't represent this potentially wide variability of physical activity in the sample, which may contribute to the lack of association between physical activity and cardiometabolic risk observed in this study.

Comparison of weighting method

Results suggest that the coefficient estimates for the association between area-level poverty and cardiometabolic risk does not significantly differ based on weighting

method. Additionally, the standard errors for Method A scaled weights are the smallest,

yet do not significantly differ from standard errors for Method B scaled weights for MEC

14 year weights. As coefficient estimates and standard errors do not significant differ

across weighting methods, this increases confidence in the observed association between

area-level poverty and cardiometabolic risk.[247] Based on our interest in reporting point

estimates, the large number of census tracts in analysis, convergent results across

weighting methods, and the smallest standard errors for Method A scaled weights, results

from Method A scaled weights are most appropriate to report. All models in Table 2 were

weighted using Method A scaled weights.

Assumptions of Hierarchical Linear Regression

As assumptions 2, 4, and 6 were initially met, this suggests there are no errors in

the estimates for the fixed effects. As the primary purpose of this study is to examine the

association between area-level poverty and cardiometabolic risk, a lack of errors in the

fixed effects increases confidence in the results reported in Table 2. As assumptions 1, 3,

and 5 were violated in the initial model, and attempts to address these violations were

largely unsuccessful, this suggests model misspecification. Models presented here could

be under specified due to the absence of important predictors – at both the individual- and

area-levels - of cardiometabolic risk not included in the model, known or unknown. Thus,

the observed regression coefficients may be biased, and may not represent the true

strength of association.

Strengths and Weaknesses

These findings should be considered in the context of this study's strengths and weaknesses. This current study adds to the body of evidence on racial disparities in cardiometabolic risk among adolescents, and the race-specific associations between area-level poverty and cardiometabolic risk among adolescents, and improves upon limitations in previous work. To date, Theall et al is the only other study to observe an association between area-level socioeconomic status and cardiometabolic risk among a national representative sample of U.S. adolescents.[286] However, the previous study utilized a dichotomous outcome to identify individuals with high cardiometabolic risk, did not utilize contemporary area-level data, and did not account for area-level covariates, such as racial concentration.[286]

The use of a continuous measure of cardiometabolic risk better reflects population-level variation in cardiometabolic risk[237,238] and may be a better predictor of adult health.[239] It also reduces potential misclassification of an individual's cardiometabolic risk. Our use of contemporary area-level data also minimizes potential misclassification of an individual's area-level poverty due to temporality. For example, for an individual in NHANES 2011-2012, the poverty rate of their census tract of residence will be more accurately reflected in ACS 2009-2013 data than in Census 2000 data. Results from the current study are in line with previous work that area-level racial concentration is a unique area-level exposure, and should be considered as an important covariate.[69–71] Furthermore, by using hierarchical models, parameter estimates and standard errors are estimated at both the individual- and area-level, allowing for proper

variance estimates that account for the clustered nature of the data, which allows for more appropriate statistical conclusions.

This study is limited by its cross-sectional approach, prohibiting causal conclusions. However, findings are in line with prospective studies suggesting exposure to high area-level poverty is associated with future disease.[43,50–53,55] The modifiable areal unit problem is a potential source of bias when data are aggregated at the area level,[287,288] however, Census 2000 and ACS 5-year estimates are considered the most accurate and reliable estimates for smaller geographic areas such as census tracts.[289] It should also be noted that ACS data has sampling error, while Census 2000 data does not. These sampling errors were not included in regression models, which may result in artificially smaller standard errors.

Another limitation relates to the arbitrary geographic boundaries used to define contexts. Individuals residing within the arbitrarily defined contexts may not identify with those boundaries. Results were interpreted in terms of census tracts, and implications and recommendations of the findings should recognize this limitation. Results may be subject to residual confounding if important area-level predictors of cardiometabolic risk were not included in the model, such as environmental exposures.[290,291]

Chapter IX. Implications

The implications of this study are discussed in this chapter. Interventions should target disadvantaged communities, with the aim of improving the area-level economic and social conditions residents are exposed to, in order to improve population-level health. Individuals with high cardiometabolic risk may be more susceptible to additional exposures, and reducing cardiometabolic risk during adolescence may reduce risk for poor health outcomes across the life course.

Implications for Public Health Policy and Practice

United States health promotion objectives include identifying social determinants of racial/ethnic disparities in cardiometabolic disease,[2] especially among adolescents[15,16] Results of this study highlight the importance of addressing upstream factors such as social determinants of health, (e.g., area-level poverty) in order to reduce cardiometabolic risk among adolescents.

In order to reduce disparities, policy interventions should target disadvantaged communities, identified by indicators of area-level economic and social conditions such as area-level poverty.[292] Poverty is an economic indicator of area-level disadvantage, and relates well to other measures of area-level determinants of health, such as housing quality, crime and violence, and the built environment,[72–75] and these factors are associated with poor health outcomes.[293–295] However, area-level economic and social conditions of a community are not solely comprised of indicators of disadvantage. Indicators of area-level advantage (e.g. civic engagement, social cohesion, existing infrastructure) should also be considered, as these exposures (i.e. greater political participation by women, high social cohesion) are associated with better health

outcomes,[296,297] and should be incorporated into interventions aiming to improve the health of the population. Community-based participatory research may facilitate a better understanding of a given community's economic and social conditions, allowing communities to build upon their unique advantages (e.g. social cohesion, high civic engagement) while addressing economic and social disadvantages in order to improve population-level health and reduce racial/ethnic disparities. This approach also allows residents to take ownership of various policies and programs aiming to improve the area-level economic and social conditions in which they reside, facilitating the development and implementation of geographically, socially, and culturally acceptable solutions to the economic, social and population health problems that disadvantaged communities often face.

As discussed in Chapters II and VIII, social determinants of health, such as area-level poverty, are related to intertwined historic, social, economic, and political factors that, over time, result in differential distribution of resources based on social strata such as race/ethnicity or socioeconomic status.[298] Thus, no single policy or program intervention can sufficiently address the unique area-level economic and social conditions disadvantaged communities face. Policymakers, funders, and community members should identify a spectrum of policy and program interventions that, in conjunction, aim to improve population health.

Policies targeting disadvantaged communities aiming to improve area-level economic and social conditions are in line with recent federal- and state-level efforts. The Community Preventive Services Task Force, through systematic review of program evaluations, has recommended initiatives aiming to improve health outcomes by

addressing area-level economic and social conditions.[292] One approach recommended by the Community Preventive Services Task Force are, tenant-based rental assistance programs, which typically target low SES or racial/ethnic minority populations to address discrimination in housing.[299][300] These programs are designed to offer financial assistance to low-income families residing in low-SES or segregated areas in order for these families to move to areas that are of higher SES or less segregated.[299] These interventions (e.g., Moving to Opportunity[300]) have been shown to reduce exposure to crime and social disorder, while limited evidence suggests emotional and behavioral health benefits. [300] Evidence also suggests these programs have similar benefits across racial/ethnic populations in the United States. [300] Taking the results of the current study into consideration, moving to a lower poverty area may reduce cardiometabolic risk in adolescence. Expansion of tenant-based rental assistance programs would give families greater control over the economic and social climate they are exposed to, and could be a contributing factor in reducing population-level cardiometabolic risk, and reducing racial/ethnic disparities in cardiometabolic health.

Other initiatives aim to improve the area-level economic and social conditions of disadvantaged neighborhoods, with the goal of improving living conditions for all residents in these communities. These neighborhood revitalization initiatives are often the result of citizen groups, local healthcare organizations, or business associations working together to address the challenges their communities face. For example, the Dudley Street Neighborhood Initiative (DSNI), is a Boston-area resident-led effort formed to address intergenerational poverty, a lack of investment, and environmental hazards in a historically racially and economically segregated community.[301–303] To address a history

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of discriminatory practices in housing and property ownership in the neighborhood,[301–303] DSNI established a land trust to use vacant lots for affordable housing, while taking an anti-displacement approach to housing aiming to limit the potential of residents being pushed out due to gentrification.[301,302] Current programs include a Promise Neighborhood designation (from the U.S. Department of Education and the Boston Promise Initiative), in which DSNI is taking a multi-faceted "cradle-to-career" approach, focusing on early childhood education, healthy families and career development in order to break the cycle of intergenerational poverty in their community.[301,302]

Funding organizations, whether governmental or non-governmental, that are interested in improving their communities, should provide funding to neighborhood revitalization initiatives. Taking an equitable approach to neighborhood revitalization initiatives allows disadvantaged communities greater support and funding in order to meet their neighborhood revitalization goals and fully achieve their potential. Policy makers and community groups should collaborate on multi-faceted neighborhood revitalization initiatives promoting equitable opportunities for all citizens in an effort to improve population health and reduce racial/ethnic disparities.[301]

Tenant-based rental assistance and neighborhood revitalization initiatives aiming to improve the area-level economic and social conditions populations are exposed to are intermediate- to long-term solutions to improving population health. Targeted community-level initiatives can also aim to have a more immediate impact on the health of residents. For example, the Community Preventive Services Task Force recommends community-wide campaigns to increase physical activity levels.[304] Community-wide campaigns focused on physical activity typically combine medical-model interventions,

such as health screenings, physical activity counseling, and support groups, with ecologically focused efforts such as creating and maintaining walking paths and parks.[304]

One example of a community-wide campaign is Shape Up Somerville, which originated as an attempt to reduce childhood obesity in Somerville, MA.[305,306] This campaign brought together 25 stakeholder groups to engage the community as a whole, including businesses, government, schools, and citizen groups.[305,306] Shape Up Somerville included providing healthier food options at local restaurants and at school, retraining clinicians and school nurses to identify and address childhood obesity, and expanding and renovating parks in Somerville.[305,306]Within the first school year after Shape Up Somerville was implemented (2003-2004), 1st to 3rd grade students in Somerville reduced their body mass index, and gained less weight than children in comparable communities.[305,306] Similar benefits have been observed in the following decade for students at other grade levels in Somerville.[305,306]

The policy and programmatic interventions similar to those presented here should be taken in concert in order to address a community's unique area-level economic and social climate. Building upon the area-level advantages of a community may allow communities to better address the disadvantages they are faced with. By involving an array of stakeholders, such as businesses, governments, schools, and citizen groups, the community will be better reflected as these interventions are designed and implemented. Policymakers and funders should recognize the importance of these multi-faceted approaches in an attempt to improve the population of all residents in their communities.

Future Research on Double Jeopardy

The concept of double jeopardy suggests that the same exposure can have more adverse consequences among individuals with high allostatic load than among others. For example, among a nationally representative sample of US adults, the association between blood lead levels and BP was stronger among individuals with high allostatic load than among individuals with low allostatic load.[170] Similarly, among a group of industrial workers, smoking interacted with allostatic load, resulting in greater risk for cardiovascular disease.[307]

While the physiology of double jeopardy is not well understood, dysfunction across multiple physiologic systems may indicate compromised immune function. For example, this compromised immune function may be expressed in an inability to contain inflammation, a key factor in development of disease.[308–310] If a compromised immune system is faced with an external insult, there may be an excessive release of pro-inflammatory cytokines, leading to excessive inflammation and damage to healthy cells, which in turn can lead to insulin resistance and endothelial dysfunction, both of which are signs if high cardiometabolic risk.[308,310]

The concept of cardiometabolic risk, as assessed here, is similar to the concept of allostatic load. In the current study, exposure to chronic stress (i.e. area-level poverty) is associated with increased cardiometabolic risk, and allostatic load is also considered a consequence of exposure to chronic stress.[203–206] Additionally, both concepts are considered to reflect functioning across similar physiologic systems (i.e. metabolic,

cardiovascular, adipose tissue), and both are concerned with preclinical levels of physiologic functioning.[203–206]

Based on these similarities, the concept of double jeopardy in the allostatic load literature may be applicable to individuals with high cardiometabolic risk. As individuals with high cardiometabolic risk are considered to have poor functioning across multiple physiologic systems, their immune systems may not be capable of properly responding to additional external insults. Thus, compared to individuals with low cardiometabolic risk, individuals with high cardiometabolic risk may also have worse outcomes when exposed to hazards. This is in line with evidence suggesting adults with diagnosed diabetes, when compared to healthy individuals, have a higher risk of poor cardiovascular outcomes when exposed to ambient air pollution.[311]

Further research is warranted to better understand cardiometabolic risk during adolescence, the potentially increased susceptibility to additional exposures, and how these factors influence health and racial/ethnic health disparities across the life course. Specifically, prospective longitudinal research is needed to better understand the relationship between cardiometabolic risk in adolescence and various chronic diseases in adulthood. These studies may provide evidence to support efforts to reduce cardiometabolic risk in adolescence, as this may be protective against increased susceptibility to external insults (such as air pollution and tobacco smoke) and the resulting increased risk for disease.

Research should take advantage of natural experiments (e.g. tenant-based rental assistance programs, neighborhood revitalization initiatives) to better understand how

addressing various social determinants of health can reduce the risk for multiple poor health outcomes, especially among adolescents. Reducing cardiometabolic risk in adolescence may result in lower prevalence of cardiometabolic diseases such as diabetes and cardiovascular disease later in life. In turn, the concept of double jeopardy suggests that reducing cardiometabolic risk in adolescence could facilitate better physiological resilience to external insults such as the exposure to ambient air pollution or second-hand smoke, potentially mitigating the negative consequences of these exposures. More research is needed to better understand how programs aiming to improve area-level economic and social conditions can maximize their return on investment, reducing the prevalence of various chronic diseases and negative health outcomes throughout the life course.

In conclusion, we observed that residence in the highest area-level poverty quartiles was associated with increased cardiometabolic risk among U.S. adolescents, independent of individual-level and area-level covariates. Additionally, we found evidence that these associations differ by race/ethnicity. Specifically, findings suggest a stronger association between area-level poverty and cardiometabolic risk among non-Hispanic whites and Mexican Americans then among non-Hispanic blacks. Efforts taken to improve cardiometabolic health at the population-level and reduce racial/ethnic disparities in cardiometabolic diseases should include targeted area-level interventions that consider the strengths and weaknesses of the targeted areas, in order to improve the social conditions for all residents.

Appendix A. Tables

Table 1. Weighted mean cardiometabolic index scores and biomarkers by independent variables (NHANES 1999-2012)

Variable *(Unweighted N; %)*	CMI Mean 95% CI	SBP Mean 95%CI	DBP Mean 95%CI
Total *(10415; 100)*	-.810 (-.884, -.737)	109.62 (109.34, 109.90)	60.72 (60.41, 61.04)
Area-level Poverty			
Quartile 1(2599; 24.95)	-1.048 (-1.182, -.915)	109.06 (108.55, 109.58)	60.68 (60.10, 61.26)
Quartile 2(2615; 25.10)	-.855 (-.984, -.726)	109.57 (109.04, 110.10)	60.70 (60.11, 61.29)
Quartile 3(2584; 24.81)	-.531 (-.694, -.367)	109.98 (109.39, 110.58)	60.86 (60.16, 61.55)
Quartile 4(2595; 24.91)	-.535 (-.669, -.371)	110.56 (110.00, 111.12)	60.69 (60.04, 61.33)
Racial Concentration			
Quartile 1(2599; 24.95)	-.792 (-.921, -.662)	109.14 (108.59, 109.68)	61.30 (60.71, 61.88)
Quartile 2(2604; 25.00)	-.837 (-.992, -.682)	109.59 (109.04, 110.15)	60.88 (60.23, 61.53)
Quartile 3(2605; 25.01)	-.869 (-1.011, -.726)	109.65 (109.13, 110.16)	60.06 (59.50, 60.62)
Quartile 4(2599; 24.95)	-.700 (-.845, -.556)	110.73 (110.22, 111.24)	60.22 (59.93, 60.91)
Family PIR			
< 1 (3074 ; 29.52)	-.590 (-.734, -.445)	109.99 (109.49, 110.49)	60.72 (60.12, 61.32)
1-2.9 (4005; 38.45)	-.685 (-.809, -.561)	109.71 (109.27, 110.15)	60.53 (60.02, 61.05)
3-4.9 (1606; 15.42)	-.929 (-1.091, -.767)	109.61 (108.95, 110.26)	60.85 (60.15, 61.56)
≥ 5 (967; 9.28)	-1.225 (-1.422, -1.028)	108.92 (108.07, 109.78)	61.12 (60.21, 62.03)
Missing (763; 7.33)	-.834 (-1.127, -.541)	109.65 (108.52, 110.77)	60.39 (58.90, 61.88)
Age			
12-14 (3981; 38.22)	-.810 (-.930, -.690)	106.86 (106.45, 107.28)	51.98 (57.44, 58.52)
15-17 (3964; 38.06)	-.759 (-.874, -.645)	110.49 (110.06, 110.93)	61.65 (61.17, 62.12)
18-19 (2470; 23.72)	-.896 (-1.054, -.738)	112.60 (111.99, 113.21)	63.60 (62.97, 64.22)
Gender			
Female (5015; 48.15)	-.659 (-.763, -.034)	106.83 (106.48, 107.18)	61.74 (61.32, 62.16)
Male (5400; 51.85)	-.952 (-1.055, -.849)	112.23 (111.82, 112.64)	59.78 (59.31, 60.24)
Race/Ethnicity			
White (2756; 26.46)	-.855 (-.963, -.747)	109.42 (109.01, 109.83)	61.27 (60.80, 61.74)
Black (3052; 29.30)	-.643 (-.759, -.526)	111.83 (111.40, 112.25)	60.71 (60.21, 61.21)
Mex.Am. (3342; 32.09)	-.692 (-.817, -.567)	109.34 (108.90, 109.79)	58.33 (57.79, 58.87)

CMI: Cardiometabolic risk index is a sum of z-scores for glycosylated hemoglobin levels, waist circumference, HDL cholesterol and total cholesterol, and for systolic and diastolic blood pressure. All z-scores were age and gender specific. Blood pressure z-score based on age, gender, and height. SBP: Systolic Blood Pressure (mmHg); DBP: Diastolic Blood Pressure (mmHg); HbA1c: Glycosylated Hemoglobin (% blood glucose); WC: waist circumference (cm); TC: total cholesterol (mg/dL); HDL-C: High Density Lipoprotein Cholesterol (mg/dL). Due to small cell size, missing values not reported for Area-level Poverty (n=22) and Racial Concentration (n= 8). Other race/ethnicity not reported here.

Table 1 (cont.). Table 1. Weighted mean cardiometabolic index scores and biomarkers by independent variables (NHANES 1999-2012)

Variable *(Unweighted N; %)*	HbA1c Mean 95%CI	WC Mean 95% CI	TC Mean 95% CI	HDL-C Mean 95% CI
Total *(10415; 100)*	5.15 (5.15, 5.16)	81.42 (81.04, 81.81)	159.83 (159.00, 160.65)	50.69 (50.37, 51.01)
Area-level Poverty				
Quartile 1(2599; 24.95)	5.13 (5.11, 5.14)	79.97 (79.31, 80.62)	160.14 (158.61, 161.66)	50.81 (50.21, 51.41)
Quartile 2(2615; 25.10)	5.14 (5.13, 5.16)	81.57 (80.85, 82.29)	159.76 (158.19, 161.33)	50.38 (49.78, 50.98)
Quartile 3(2584; 24.81)	5.18 (5.16, 5.19)	82.72 (81.82, 83.61)	159.63 (157.85, 161.40)	50.62 (49.94, 51.29)
Quartile 4(2595; 24.91)	5.20 (5.19, 5.22)	82.83 (82.00, 83.66)	159.40 (157.87, 160.94)	51.05 (50.38, 51.72)
Racial Concentration				
Quartile 1(2599; 24.95)	5.14 (5.12, 5.15)	81.54 (80.86, 82.23)	159.91 (158.38, 161.44)	50.08 (49.49, 50.66)
Quartile 2(2604; 25.00)	5.14 (5.12, 5.15)	81.54 (80.74, 82.34)	159.34 (157.65, 161.03)	50.48 (49.84, 51.12)
Quartile 3(2605; 25.01)	5.16 (5.14, 5.17)	81.44 (80.71, 82.17)	159.92 (158.36, 161.48)	50.93 (50.28, 51.59)
Quartile 4(2599; 24.95)	5.21 (5.20, 5.23)	80.89 (80.11, 81.67)	160.36 (158.80, 161.93)	52.02 (51.38, 52.66)
Family PIR				
< 1 (3074 ; 29.52)	5.18 (5.16, 5.19)	82.84 (82.08, 83.16)	159.58 (158.03, 161.12)	50.37 (49.75, 50.99)
1-2.9 (4005; 38.45)	5.15 (5.14, 5.17)	81.86 (81.22, 82.05)	160.26 (158.92, 161.60)	50.19 (49.68, 50.70)
3-4.9 (1606; 15.42)	5.15 (5.13, 5.17)	80.54 (79.66, 81.41)	158.71 (156.77, 160.65)	50.54 (49.77, 51.30)
≥ 5 (967; 9.28)	5.12 (5.10, 5.14)	79.62 (78.62, 80.63)	160.49 (158.08, 162.90)	52.12 (51.20, 53.04)
Missing (763; 7.33)	5.18 (5.15, 5.21)	81.65 (80.18, 83.12)	160.41 (157.59, 163.24)	51.62 (50.42, 52.82)
Age				
12-14 (3981; 38.22)	5.18 (5.17, 5.19)	77.65 (77.07, 78.24)	158.59 (157.33, 159.85)	51.70 (51.18, 52.22)
15-17 (3964; 38.06)	5.15 (5.13, 5.16)	82.35 (81.75, 82.95)	158.03 (156.68, 159.38)	49.99 (49.48, 50.51)
18-19 (2470; 23.72)	5.13 (5.11, 5.14)	85.94 (85.13, 86.75)	164.82 (163.03, 166.61)	50.21 (49.54, 50.89)
Gender				
Female (5015; 48.15)	5.14 (5.13, 5.15)	80.81 (80.28, 81.35)	162.54 (161.36, 163.72)	53.14 (52.67, 53.62)
Male (5400; 51.85)	5.17 (5.16, 5.18)	81.99 (81.45, 82.54)	157.29 (156.15, 158.43)	48.39 (47.97, 48.82)
Race/Ethnicity				
White (2756; 26.46)	5.12 (5.10, 5.13)	81.54 (80.97, 82.12)	160.17 (158.93, 161.42)	49.82 (49.34, 50.30)
Black (3052; 29.30)	5.26 (5.25, 5.28)	80.66 (80.03, 81.29)	160.26 (159.09, 161.42)	54.25 (53.75, 54.75)
Mex.Am. (3342; 32.09)	5.17 (5.16, 5.19)	83.44 (82.83, 84.06)	158.78 (157.60, 159.96)	50.36 (49.83, 50.89)

CMI: Cardiometabolic risk index is a sum of z-scores for glycosylated hemoglobin levels, waist circumference, HDL cholesterol and total cholesterol, and for systolic and diastolic blood pressure. All z-scores were age and gender specific. Blood pressure z-score based on age, gender, and height. SBP: Systolic Blood Pressure (mmHg); DBP: Diastolic Blood Pressure (mmHg); HbA1c: Glycosylated Hemoglobin (% blood glucose); WC: waist circumference (cm); TC: total cholesterol (mg/dL); HDL-C: High Density Lipoprotein Cholesterol (mg/dL). Due to small cell size, missing values not reported for Area-level Poverty (n=22) and Racial Concentration (n= 8). Other race/ethnicity not reported here.

Table 2. HLM models estimating the association between area-level poverty and cardiometabolic risk index

	Overall Sample (n= 10415) Estimate (95% CI)	White NH (n= 2756) Estimate (95% CI)	Black NH (n= 3052) Estimate (95% CI)	Mexican American (n = 3342) Estimate (95% CI)
Model 1: Crude Model†				
Area-level Poverty				
Quartile 1	Ref.	Ref.	Ref.	Ref.
Quartile 2	.266 (.069, .463)	.260 (-.032, .552)	-.121 (-.057, .335)	.445 (.004, .885)
Quartile 3	.522 (.322, .722)	.807 (.452, 1.162)	-.086 (-.513, .339)	.679 (.257, 1.100)
Quartile 4	.552 (.354, .751)	.735 (.265, 1.204)	.238 (-.163, .639)	.508 (.086, .930)
Variance in intercept (τ_{00})	1.52*	1.84*	1.64*	1.50*
Variance within tracts (σ^2)	4.41*	5.44*	3.88*	3.39*
Model Fit: -2LL	52496.20	13277.5	15534.6	16989.6
Model 2: Individual Covariates††				
Area-Level Poverty				
Quartile 1	Ref.	Ref.	Ref.	Ref.
Quartile 2	.214 (.008, .420)	.142 (-.161, .446)	-.083 (-.548, .422)	.445 (-.004, .894)
Quartile 3	.427 (.203, .651)	.591 (.203, .978)	-.025 (-.473, .422)	.678 (.234, 1.122)
Quartile 4	.430 (.191, .670)	.462 (-.046, .972)	.325 (-.119, .771)	.508 (.048, .969)
Variance in intercept (τ_{00})	1.53*	1.82*	1.64*	1.51*
Variance within tracts (σ^2)	4.40*	5.43*	3.88*	3.38*
Model Fit: -2LL	52498.69	13279.2	15541.1	16993.1
Full Model†††				
Area-Level Poverty				
Quartile 1	Ref.	Ref.	Ref.	Ref.
Quartile 2	.218 (.012, .424)	.155 (-.149, .460)	-.071 (-.538, .394)	.440 (-.009, .890)
Quartile 3	.438 (.213, .665)	.634 (.240, 1.028)	-.001 (-.456, .453)	.663 (.217, 1.109)
Quartile 4	.451 (.204, .698)	.541 (.014, 1.067)	.369 (-.098, .836)	.487 (.023, .952)
Racial Concentration	-.001 (-.004, .002)	-.005 (-.016, .004)	-.001 (-.005, .003)	.003 (-.005, .012)
Variance in intercept (τ_{00})	1.53*	1.81*	1.64*	1.51*
Variance within tracts (σ^2)	4.40*	5.43*	3.88*	3.38*
Model Fit: -2LL	52509.17	13282.5	15551.1	17001.4

CMI: Cardiometabolic Risk Index. Models predicting Cardiometabolic Index did not include Age, Gender, or BMI. †Model includes NHANES Survey Cycle. ††Model includes Race/Ethnicity (except race-specific models), Family Income to Poverty ratio, and NHANES survey cycle. †††Model includes all variables in model 2 plus area-level racial concentration. *p<.001

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Table 3. HLM Models estimating cotinine as a mediator

Variable	Overall Sample (n= 10415) Estimate 95% CI	White NH (n= 2756) Estimate 95% CI	Black NH (n= 3052) Estimate 95% CI	Mexican American (n = 3342) Estimate 95% CI
CardioMet Index as outcome†				
Area-Level Poverty				
Quartile 1	Ref.	Ref.	Ref.	Ref.
Quartile 2	.222 (.020, .424)	.260 (-.032, .552)	-.121 (-.057, .335)	.445 (.004, .885)
Quartile 3	.444 (.228, .660)	.807 (.452, 1.162)	-.086 (-.513, .339)	.679 (.257, 1.100)
Quartile 4	.458 (.228, .689)	.735 (.265, 1.204)	.238 (-.163, .639)	.508 (.086, .930)
Cotinine as outcome model †				
Area-Level Poverty				
Quartile 1	Ref.	Ref.	Ref.	Ref.
Quartile 2	6.47 (2.33, 10.60)	8.25 (.57, 15.93)	1.98 (-6.496, 10.460)	-1.47 (-6.06, 3.11)
Quartile 3	6.41 (1.95, 10.86)	6.76 (-3.20, 16.73)	8.97 (.786, 17.169)	-2.43 (-6.90, 2.03)
Quartile 4	6.24 (1.49, 10.99)	20.75 (7.52, 33.98)	11.22 (2.847, 19.607)	-2.15 (-6.69, 2.37)
Cotinine predicting CardioMet Index††				
Cotinine	-.002 (-.003, .001)	-.002 (-.003, .0008)	-.003 (-.005, .001)	-.002 (-.006, .0009)
Full mediation model†††				
Cotinine	-.002 (-.003, .001)	-.002 (-.003, .0008)	-.003 (-.005, .001)	-.002 (-.006, .0009)
Area-Level Poverty				
Quartile 1	Ref.	Ref.	Ref.	Ref.
Quartile 2	.222 (.016, .429)	.159 (-.154, .457)	-.067 (-.533, .399)	.440 (-.009, .890)
Quartile 3	.446 (.219, .673)	.632 (.237, 1.027)	.010 (-.445, .465)	.662 (.215, 1.108)
Quartile 4	.458 (.211, .706)	.552 (.023, 1.080)	.388 (-.080, .857)	.487 (.023, .952)

CarMet Index: Cardiometabolic Risk Index. Models predicting Cardiometabolic Index did not include Age, Gender, or BMI.

† Model includes area-level racial concentration, Race/Ethnicity, Family Income to Poverty ratio, and NHANES survey cycle.

†† Model includes Race/Ethnicity, Family Income to Poverty ratio, and NHANES survey cycle at Level 1. No area-level poverty or racial concentration at level 2.

†††Model includes all variables in model 2 plus area-level racial concentration and group-mean cotinine.

Table 4. HLM Models estimating physical activity as a mediator

Variable	Overall Sample (n= 10415) Estimate 95% CI	White NH (n= 2756) Estimate 95% CI	Black NH (n= 3052) Estimate 95% CI	Mexican American (n = 3342) Estimate 95% CI
CardioMet Index as outcome†				
Area-Level Poverty				
Quartile 1	Ref.	Ref.	Ref.	Ref.
Quartile 2	.222 (.020, .424)	.260 (-.032, .552)	-.121 (-.057, .335)	.445 (.004, .885)
Quartile 3	.444 (.228, .660)	.807 (.452, 1.162)	-.086 (-.513, .339)	.679 (.257, 1.100)
Quartile 4	.458 (.228, .689)	.735 (.265, 1.204)	.238 (-.163, .639)	.508 (.086, .930)
PhysAct as outcome model ††				
Area-Level Poverty				
Quartile 1	Ref.	Ref.	Ref.	Ref.
Quartile 2	-.138 (-.289, .011)	.094 (-.164, .354)	.283 (-.080, .647)	-.005 (-.398, .387)
Quartile 3	-.178 (-.344, -.013)	.205 (-.128, .538)	.103 (-.245, .451)	.115 (-.266, .497)
Quartile 4	-.269 (-.447, -.090)	.274 (-.165, .715)	.433 (.079, .788)	.101 (-.287, .491)
PhysAct predicting CardioMet Index†††				
PhysAct	.089 (-.021, .200)	.231 (.023, .439)	.079 (-.132, .291)	-.111 (-.311, .088)
Full mediation model†				
PhysAct	.082 (-.028, .193)	.204 (-.003, .411)	.063 (-.149, .275)	-.118 (-.318, .081)
Area-Level Poverty				
Quartile 1	Ref.	Ref.	Ref.	Ref.
Quartile 2	.227 (.020, .433)	.147 (-.157, .452)	-.052 (-.524, .419)	.518 (.065, .972)
Quartile 3	.442 (.215, .670)	.637 (.242, 1.032)	-.014 (-.472, .444)	.733 (.283, 1.18)
Quartile 4	.478 (.231, .752)	.578 (.052, 1.103)	.391 (-.005, .003)	.606 (.142, 1.070)

CarMet Index: Cardiometabolic Risk Index. Models predicting Cardiometabolic Index did not include Age, Gender, or BMI.

† Model includes area-level racial concentration, Race/Ethnicity, Family Income to Poverty ratio, and NHANES survey cycle.
†† Logistic regression Model includes area-level racial concentration, Race/Ethnicity, Family Income to Poverty ratio, and NHANES survey cycle.
††† Model includes Race/Ethnicity, Family Income to Poverty ratio, and NHANES survey cycle at Level 1. No area-level poverty or racial concentration at level 2.

Table 5. Mean Family Income-Poverty Ratio by area-level poverty quartile and race/ethnicity

	Area-level Poverty				
	Quartile 1 Mean (se)	**Quartile 2 Mean (se)**	**Quartile 3 Mean (se)**	**Quartile 4 Mean (se)**	**Trend p-value**
Overall (*n= 10415*)	3.34 (.03)	2.59 (.02)	1.95 (.02)	1.42 (.02)	<.001
White (n= 2756)	3.53 (.04)[b,c]	2.79 (.04) [b,c]	2.20 (.07) [b,c]	1.60 (.10) [b,c]	<.001
Black (n= 3052)	2.61 (.07)[a]	2.29 (.06)[a,c]	1.84 (.04) [a,c]	1.34 (.03)[a]	<.001
Mex.Am. (n= 3342)	2.55 (.07)[a]	1.91 (.04)[a,b]	1.54 (.03) [a,b]	1.33 (.03)[a]	<.001

Trend assessed with multiple means comparisons.

a. Significant difference from White (p<.05)

b. Significant difference from Black (p <.05)

c. Significant difference from Mexican American (p<.05)

Table 6. Comparison of scaled and mobile exam center weights: Full model

	Method A Scaled Weights		Method B Scaled Weights		Mobile Exam Center Weights	
	Estimate (se)	95% CI	Estimate (se)	95% CI	Estimate (se)	95% CI
Intercept	-0.831 (0.161)	-1.14, -.515	-0.857 (.165)	-1.181, -.533	-.873 (.165)	-1.198, -.548
Area-level Poverty						
Quartile 1	Ref.	-	Ref.	-	Ref.	-
Quartile 2	.218 (0.105)	.012, .424	.229 (.107)	.019, .438	.218 (.105)	.012, .425
Quartile 3	.438 (0.115)	.213, .665	.454 (.117)	.223, .684	.443 (.120)	.206, .680
Quartile 4	.451 (0.126)	.204, .698	.466 (.128)	.215, .718	.459 (.136)	.191, .727
Percent Black NH	-.001(0.001)	-.004, .002	-.0007 (.001)	-.004, .002	-.002 (.001)	-.006, .001

Models include NHANES Survey Cycle, Race/Ethnicity, Family Income to Poverty ratio, and area-level racial concentration.

Appendix B. Figures

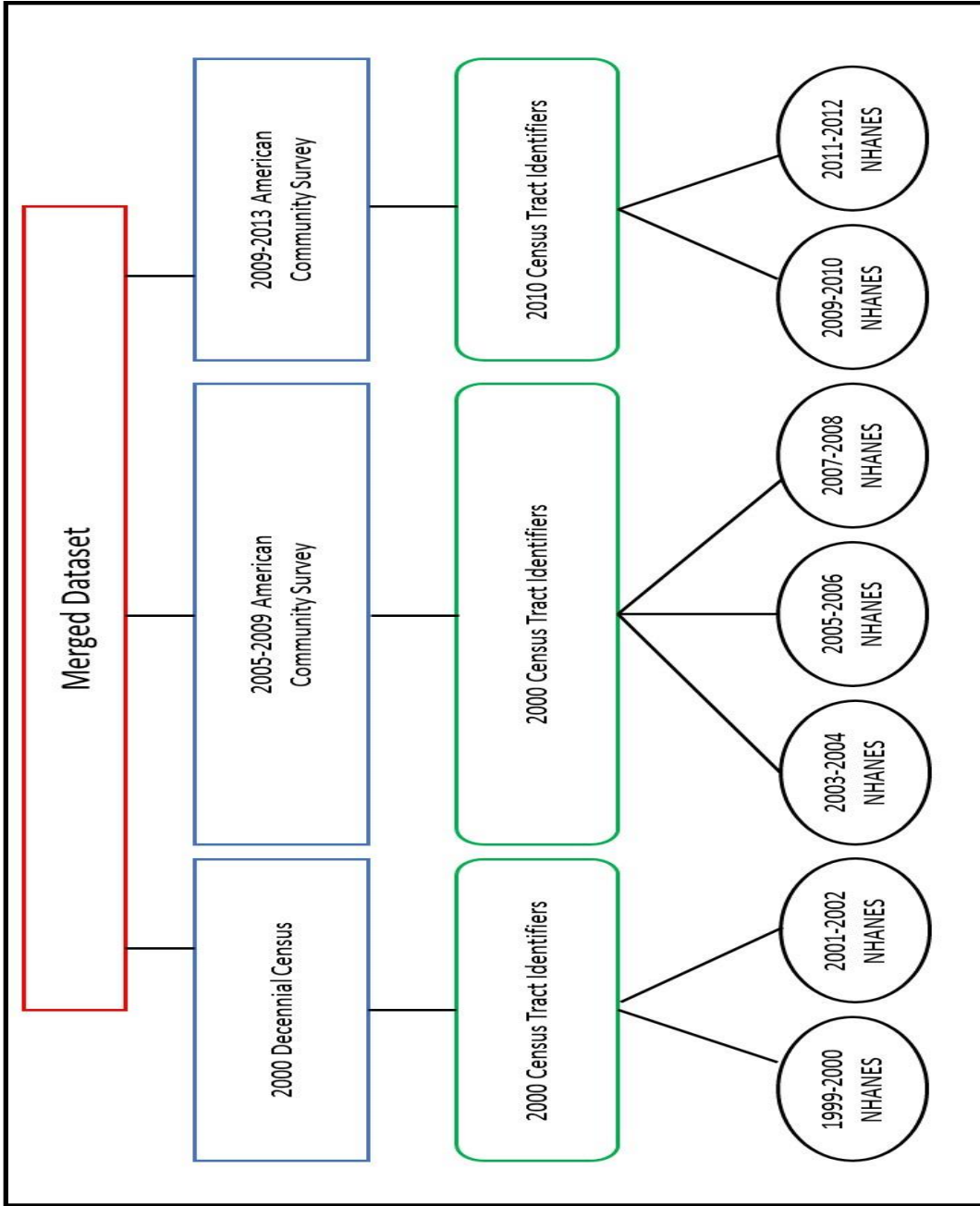**Figure 1. Linking NHANES data with contemporary Census/American Community Survey data**

Figure 2. Determinants of Cardiometabolic Risk

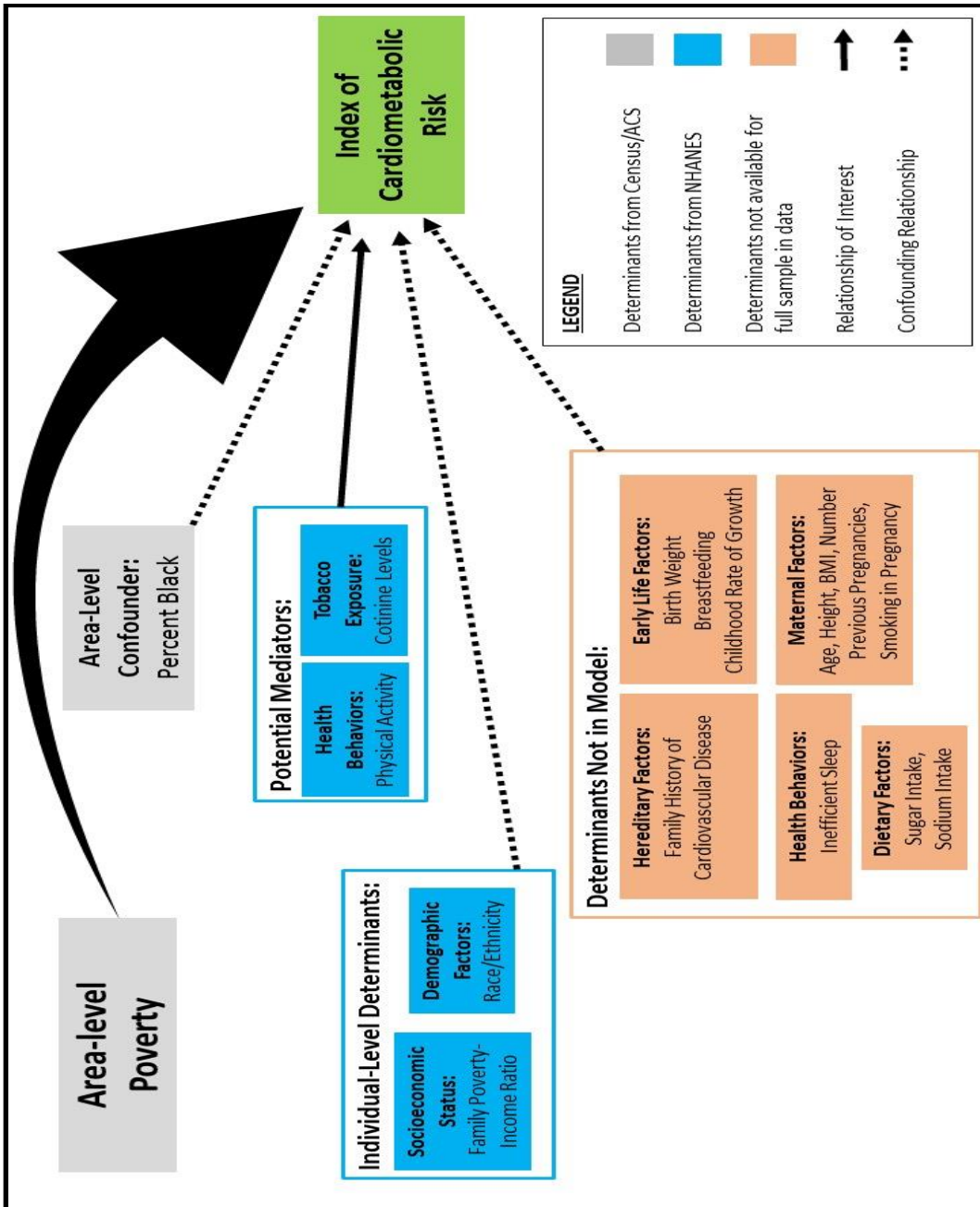**Figure 3. Association between area-level poverty and index of cardiometabolic risk: Overall sample**

Figure 3. Association between area-level poverty and index of cardiometabolic risk: Overall sample

Figure 4a. Assumption 1: Q-Q Plot and Histogram of Individual-Level Residuals: Initial Results
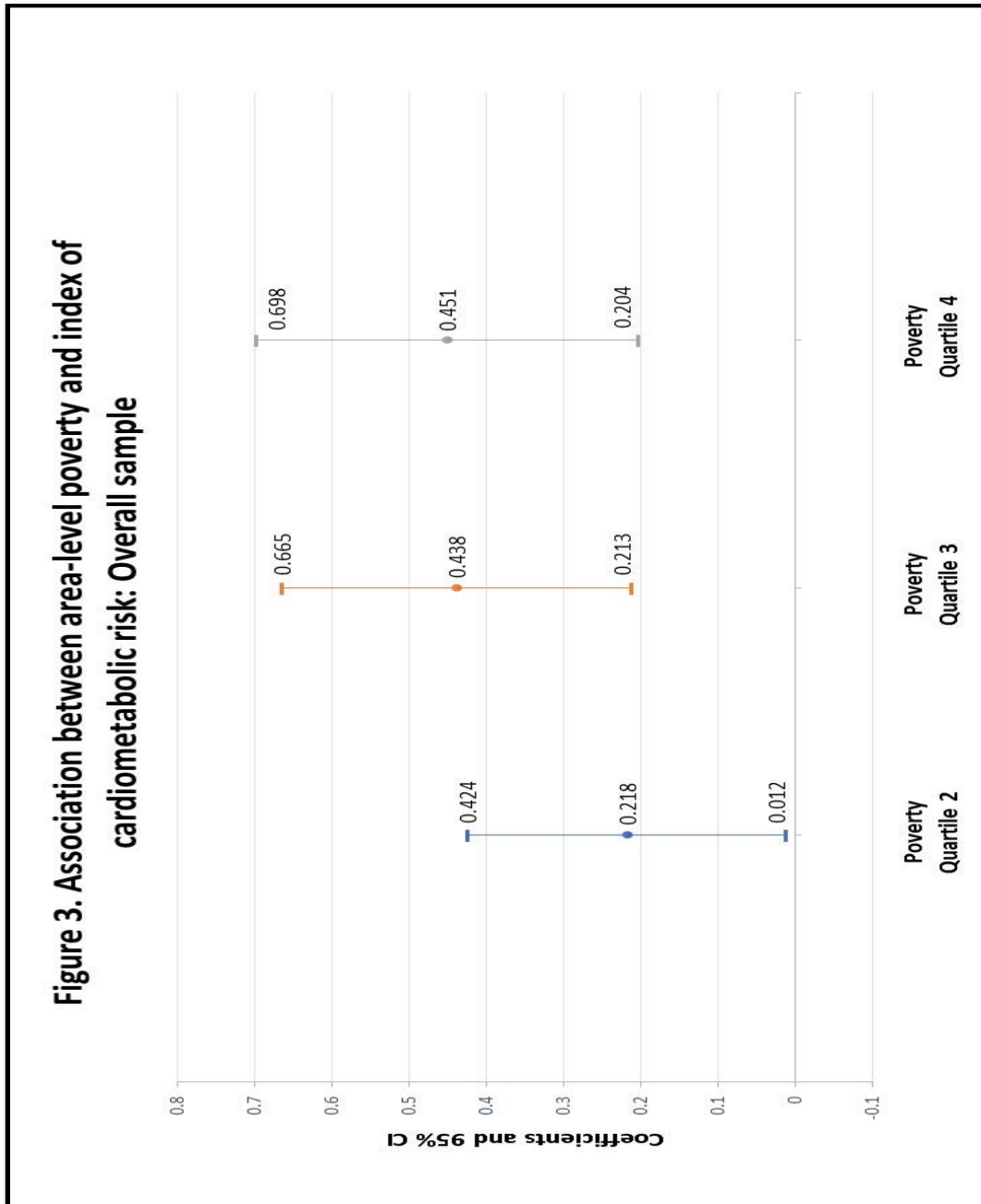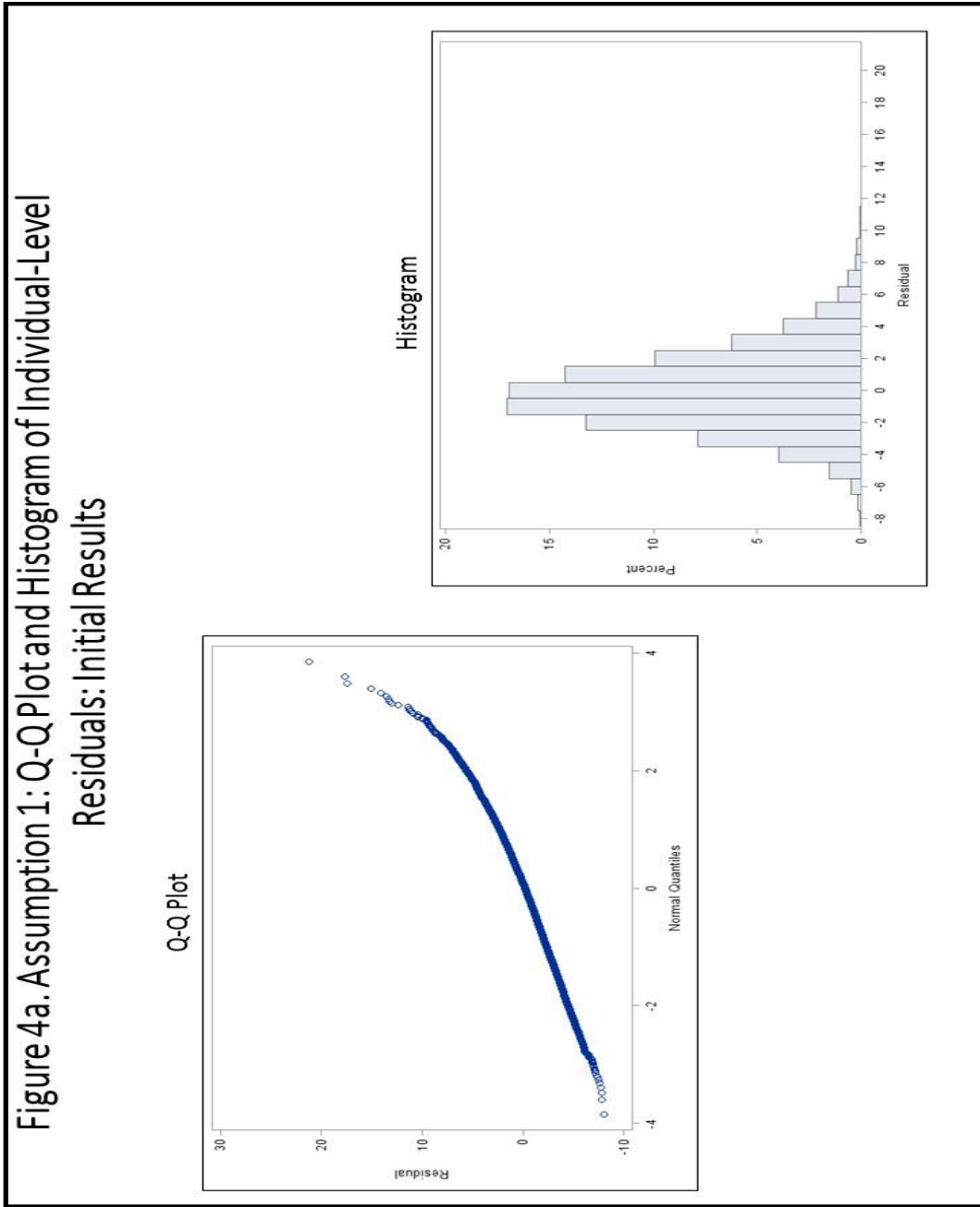

Figure 4a. Assumption 1: Q-Q Plot and Histogram of Individual-Level Residuals: Initial Results

Figure 4b. Assumption 1: Q-Q Plot and Histogram of Individual-Level Residuals: Deleted Observations
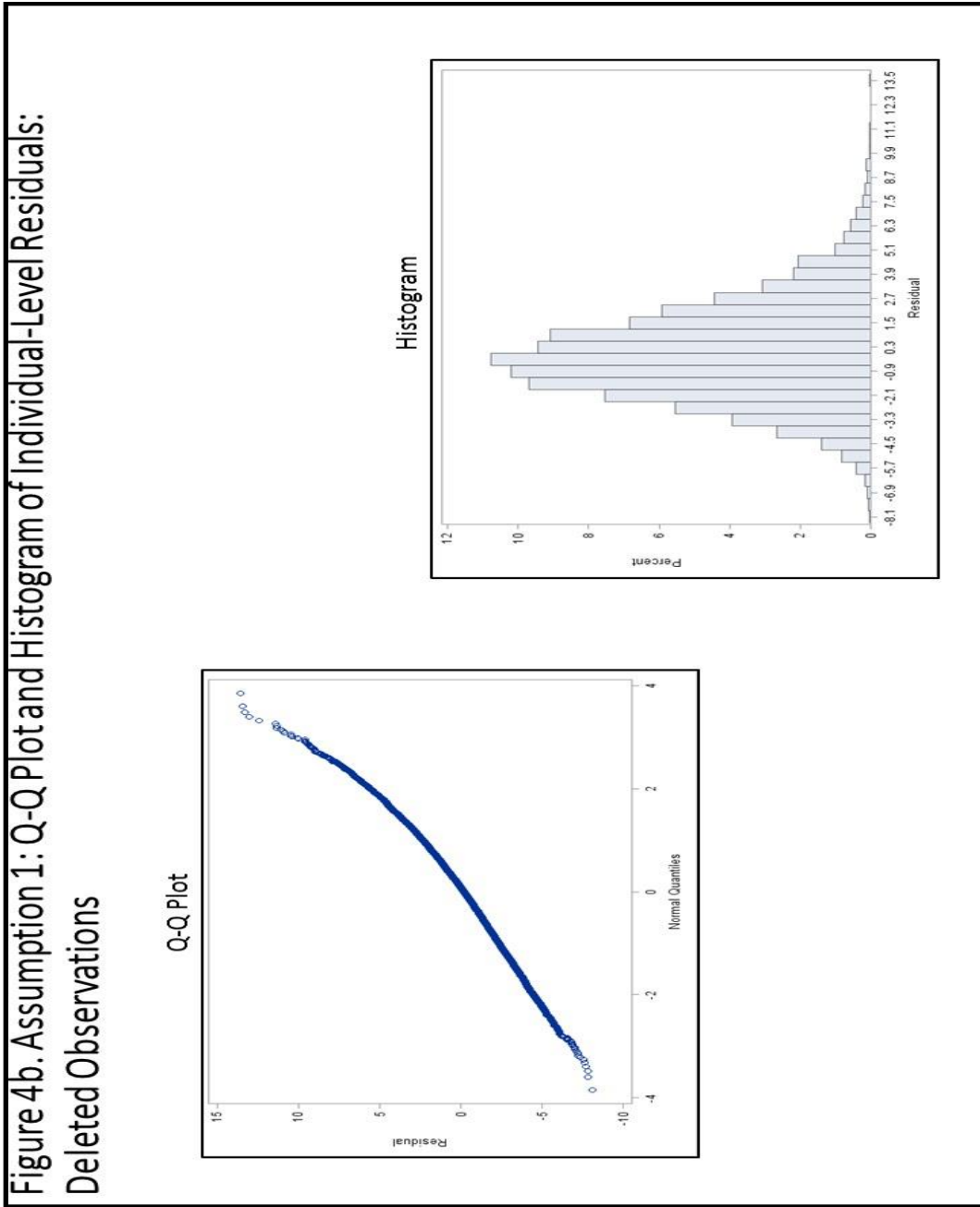
Figure 4c. Assumption 1: Individual-level residuals plotted against predicted values
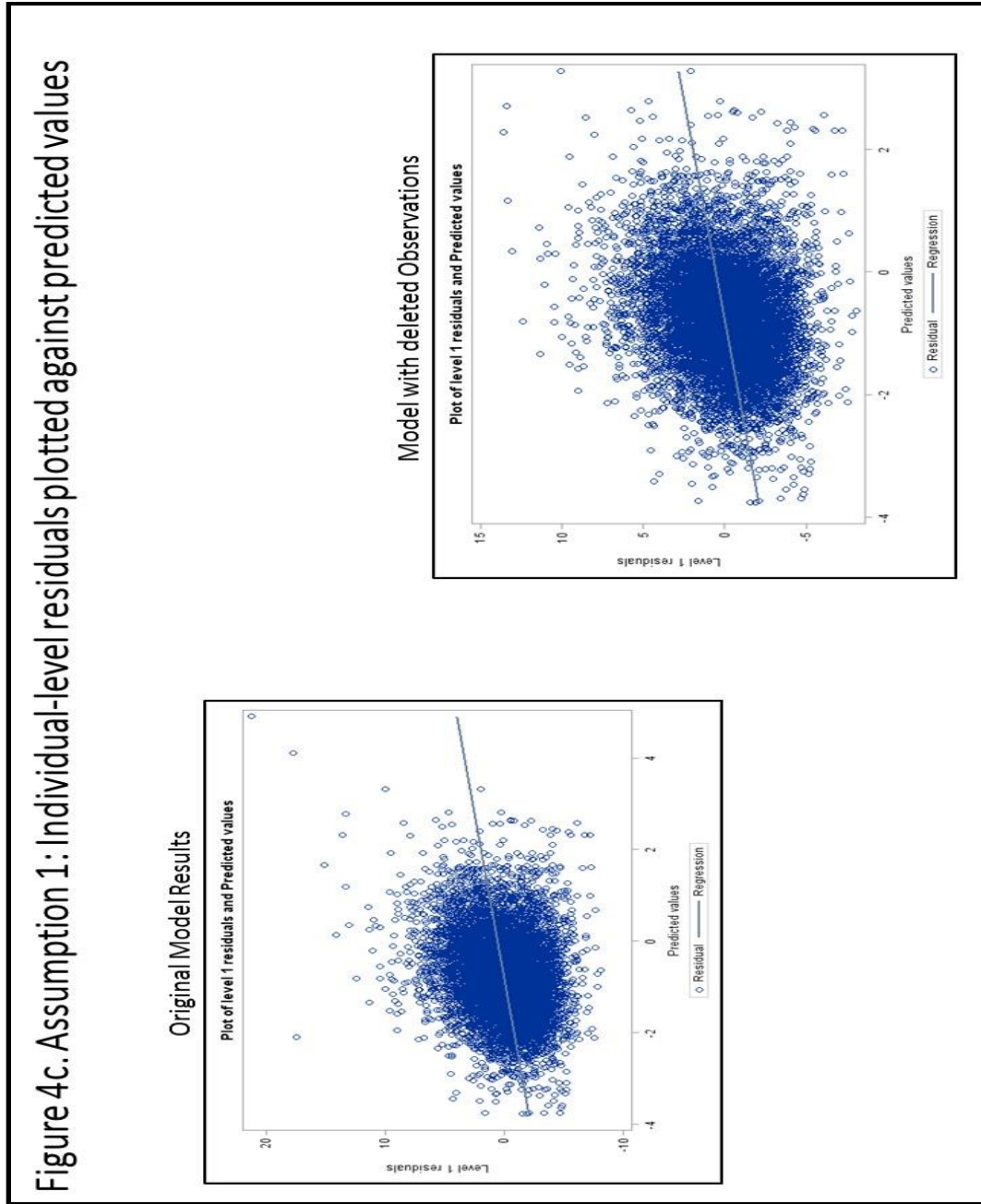
Figure 4d. Assumption 1: Individual-level residuals plotted against predicted values

Figure 4e. Assumption 2: Individual-level residuals plotted against individual-level predictors

Figure 4f. Assumption 2: Individual-level residuals plotted against individual-level predictors

Figure 4g. Assumption 3: Distribution of area-level residuals: Original Model
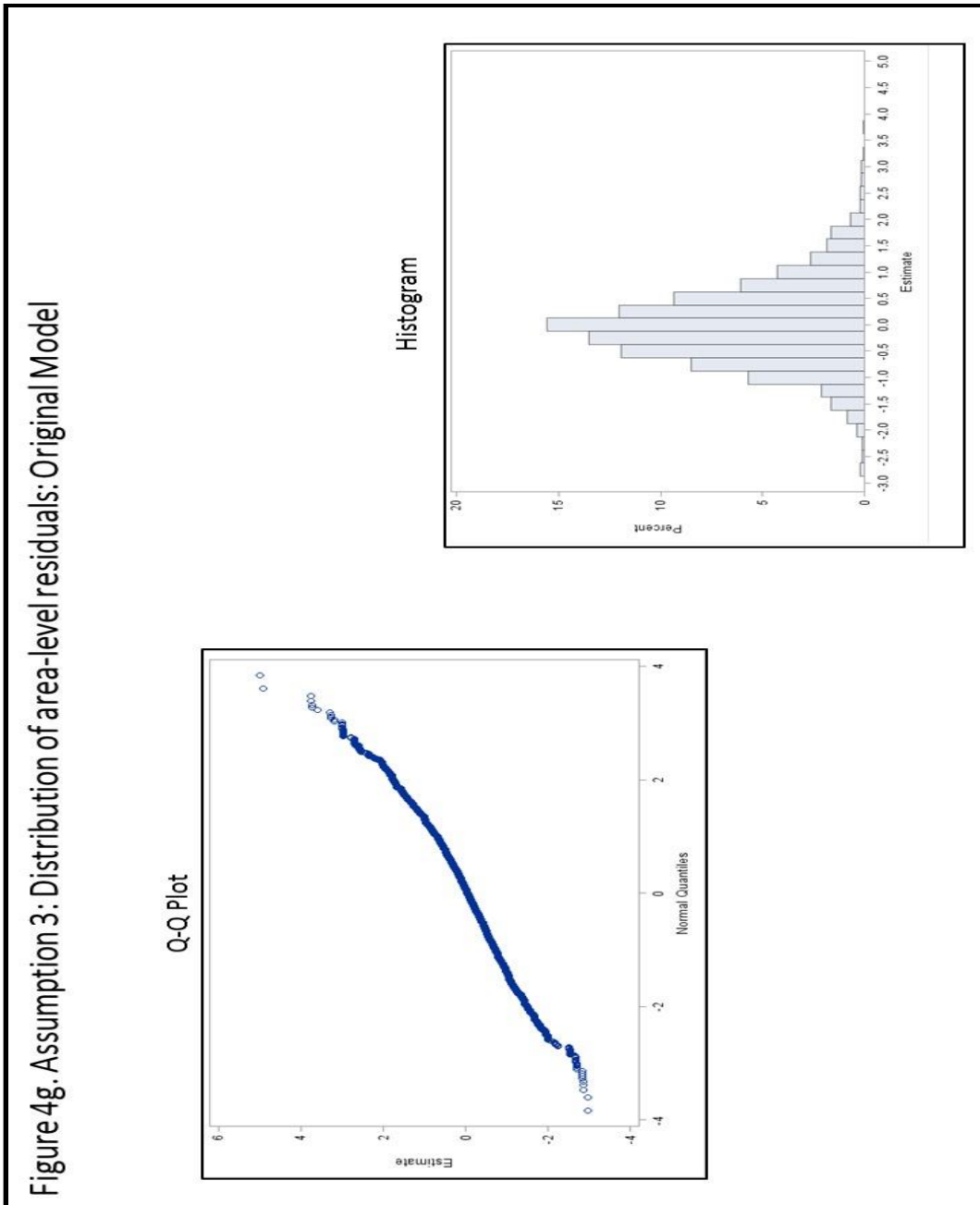
Figure 4h. Assumption 3: Distribution of area-level residuals: Deleted observations model

Figure 4h. Assumption 3: Distribution of area-level residuals: Deleted observations model
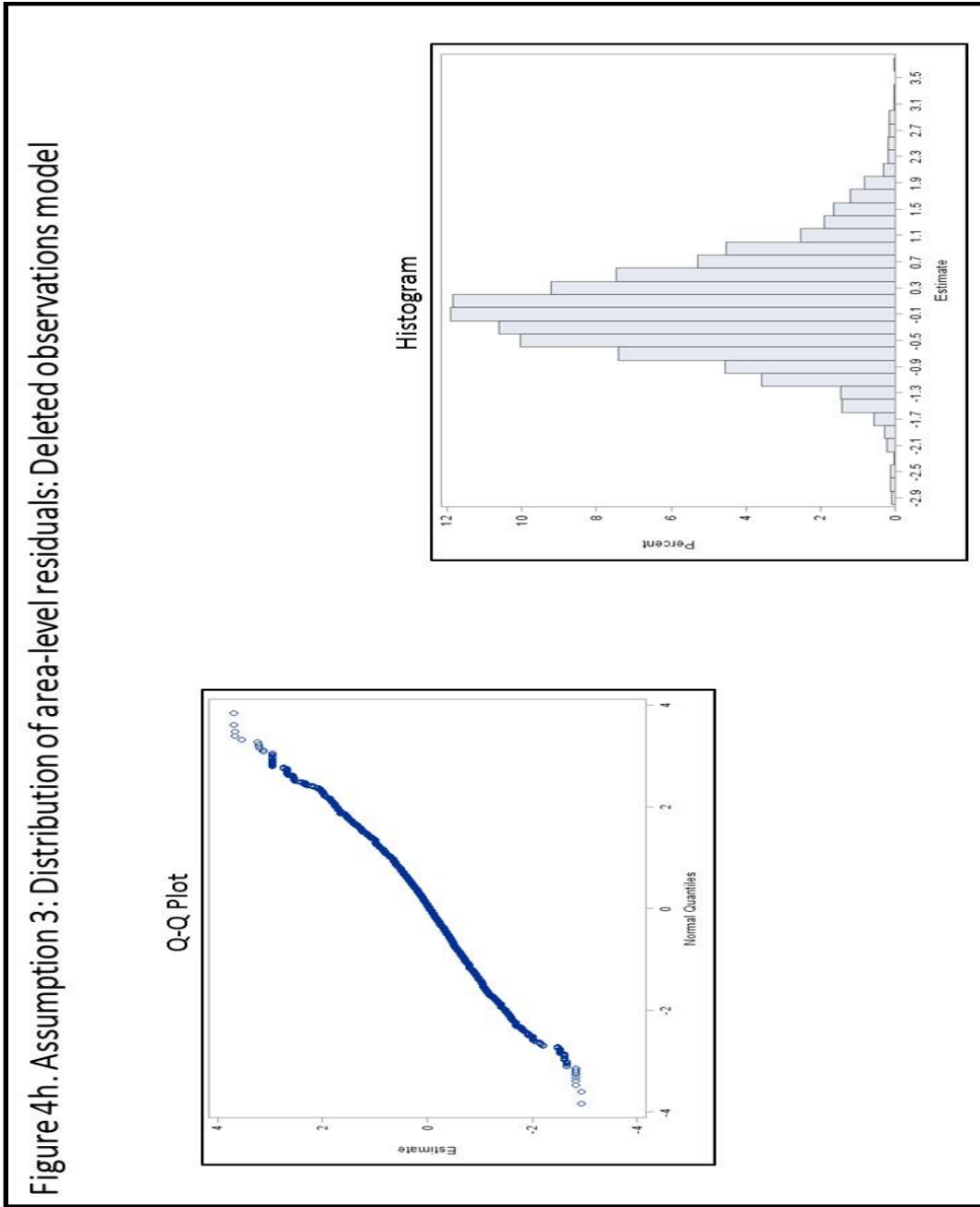
Figure 4i. Assumption 3: Plot of area-level residuals against predicted values
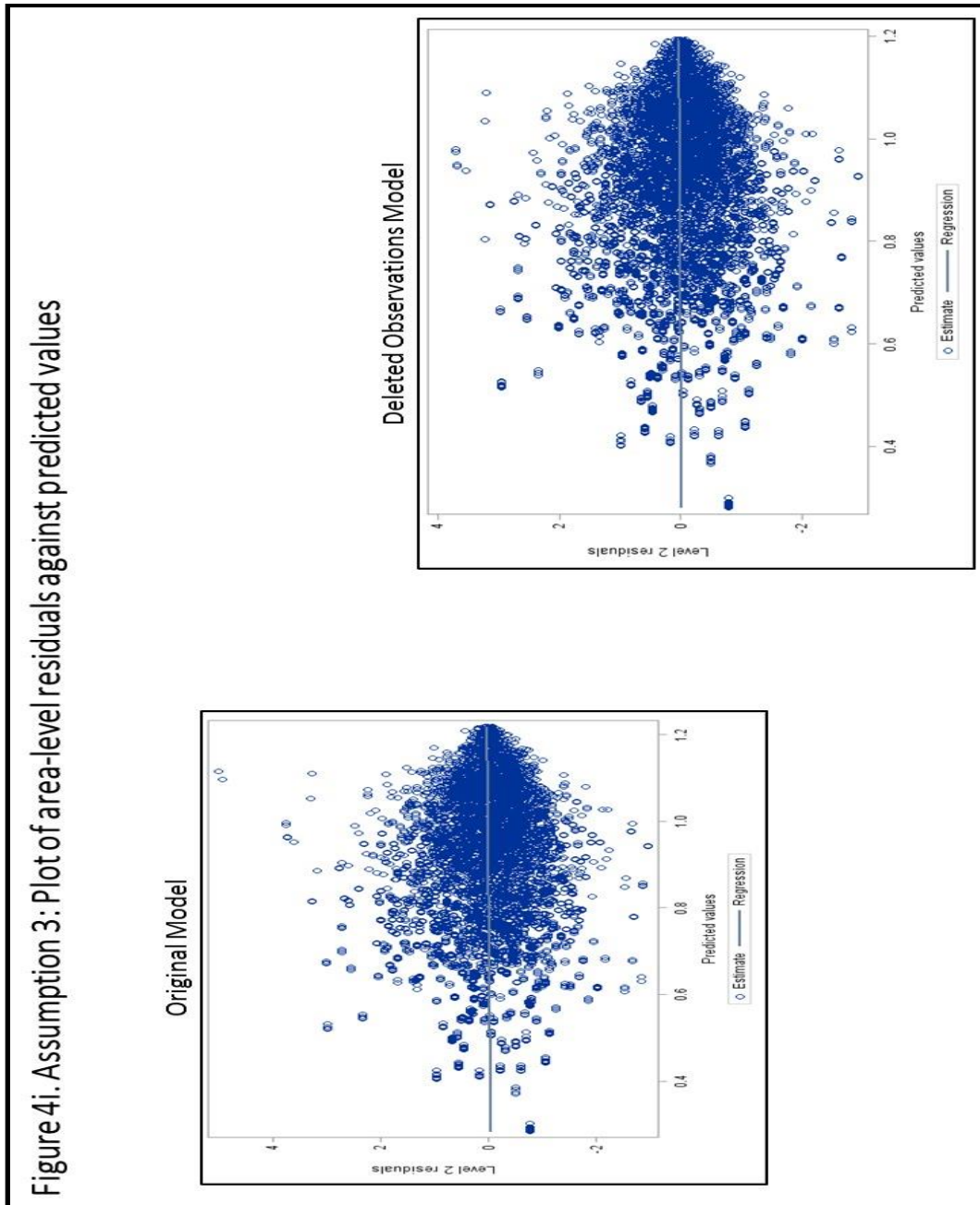
Figure 4j. Assumption 4: Plot of area-level residuals against area-level predictor variables

Figure 4j. Assumption 4: Plot of area-level residuals against area-level predictor variables
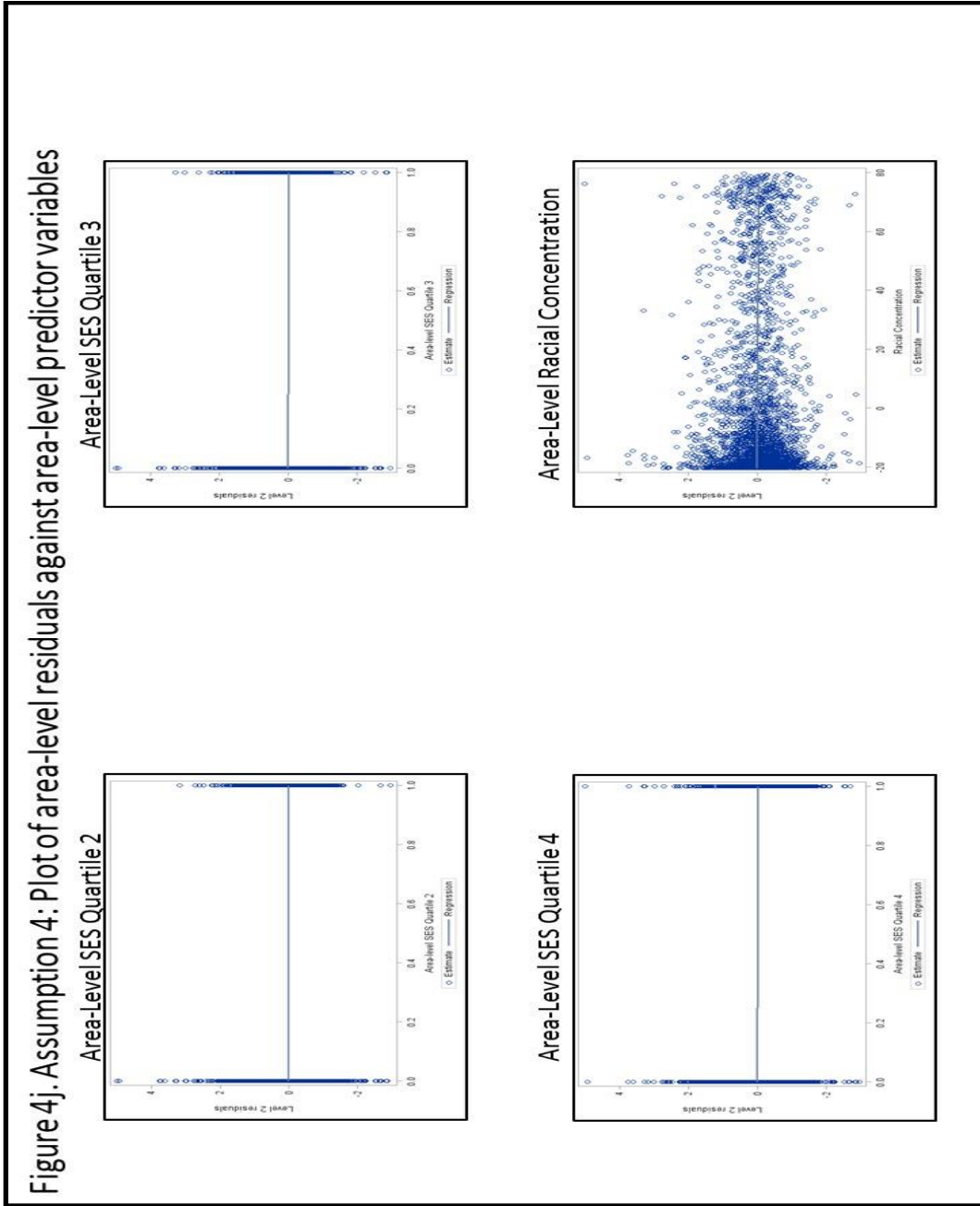
Figure 4k. Assumption 5: Individual-level residuals plotted against area-level residuals
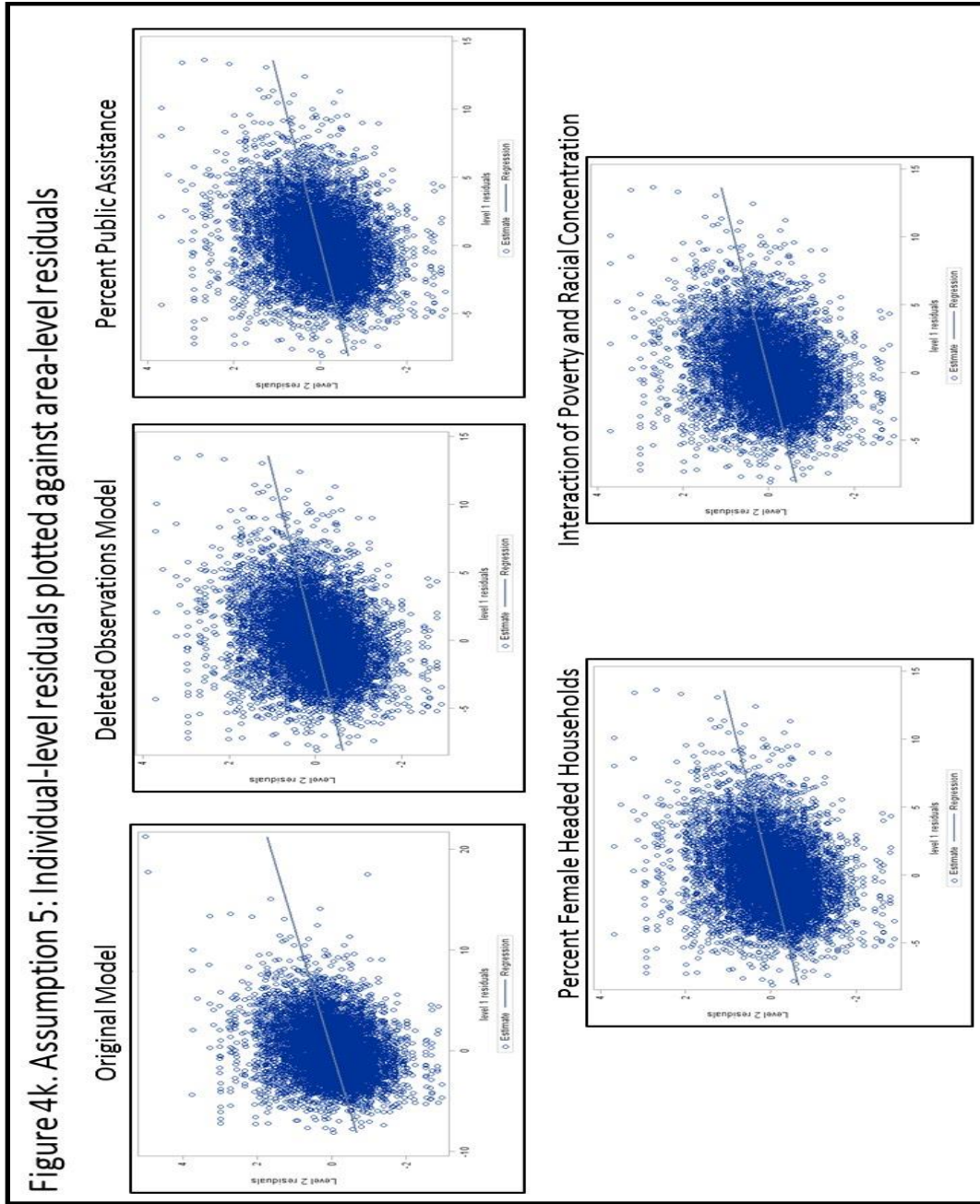
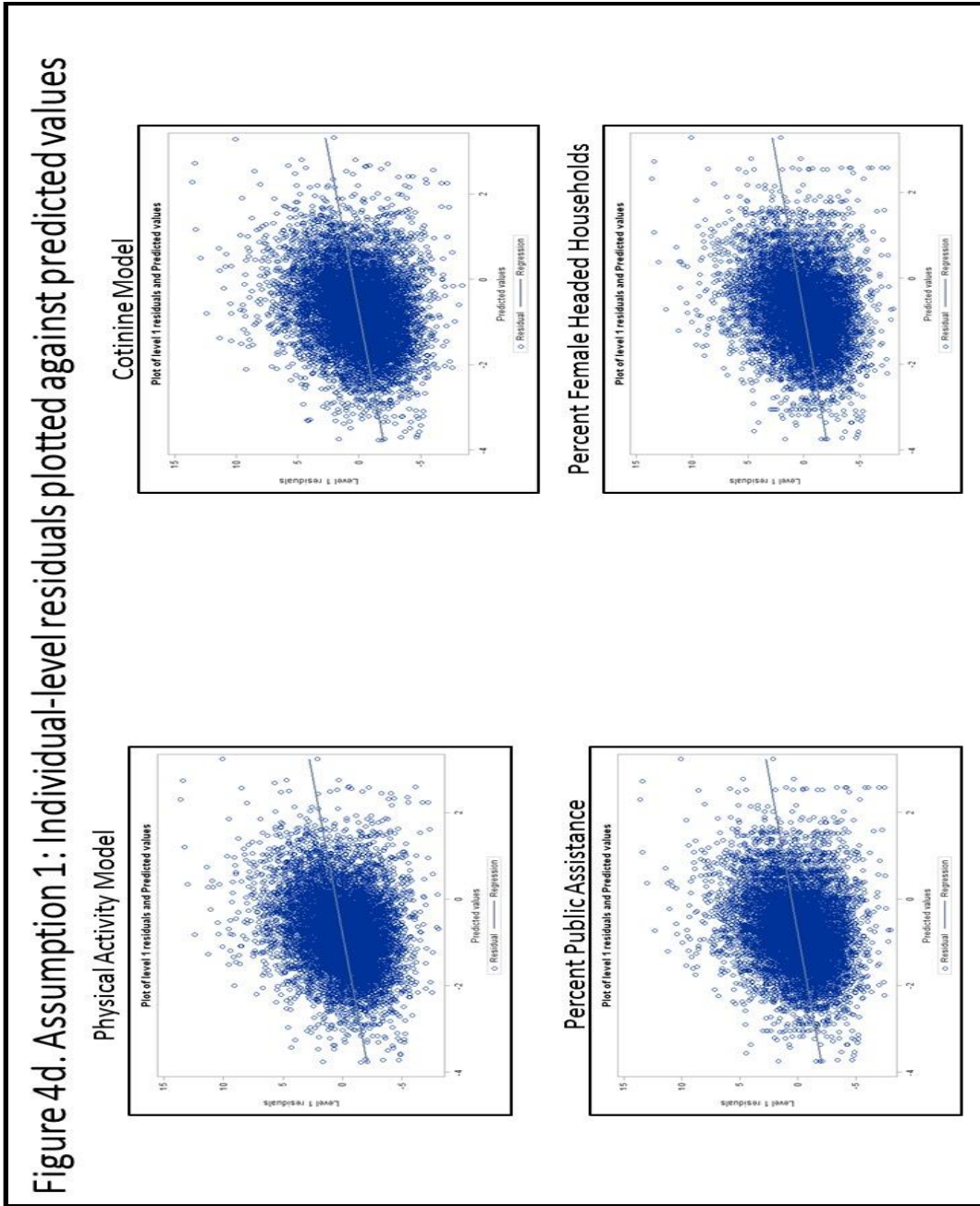**Figure 4l. Assumption 6: Plot of individual-level residuals against area-level predictor variables**
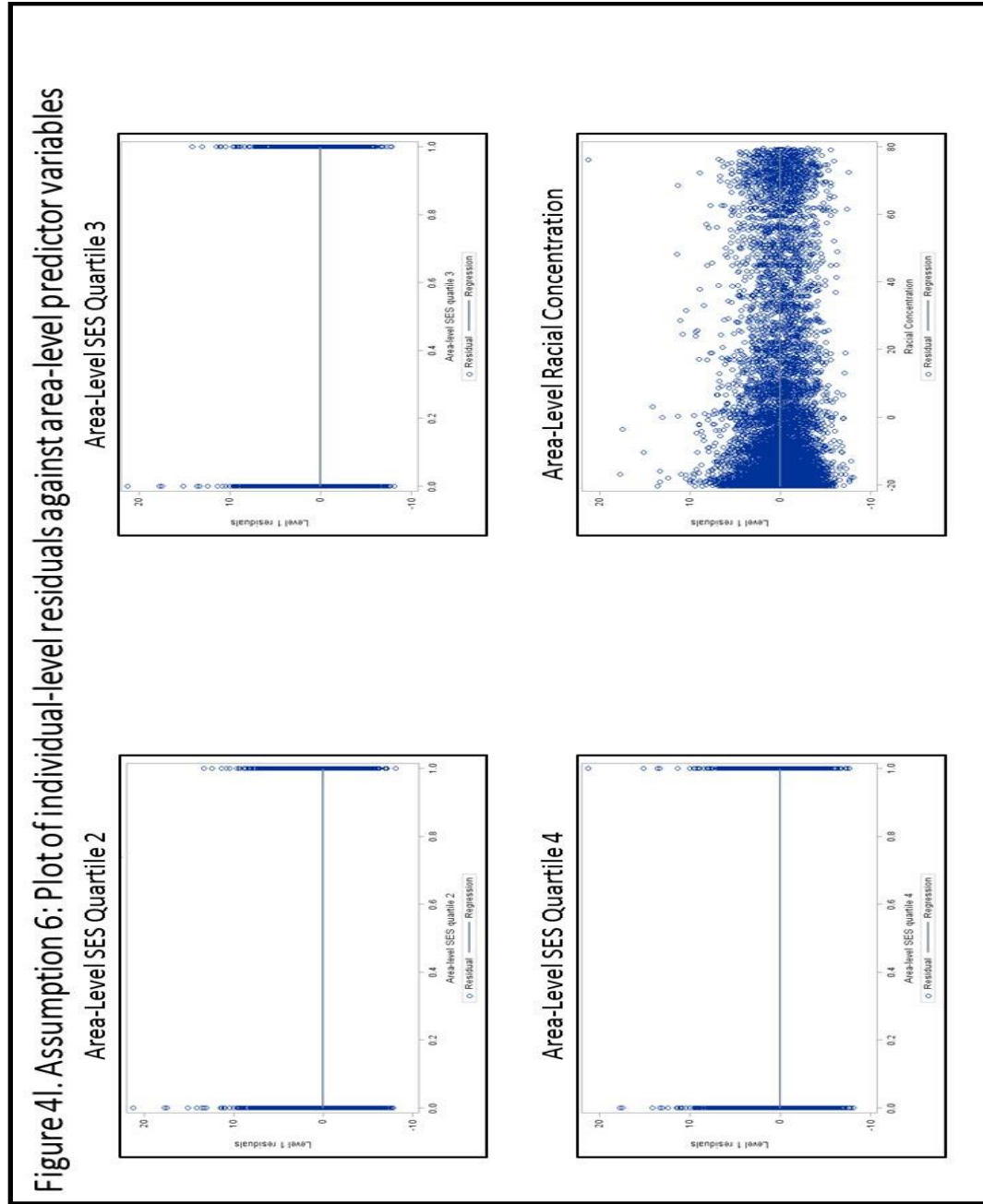
Figure 4m. Assumption 6: Area-level residuals plotted against individual-level predictors

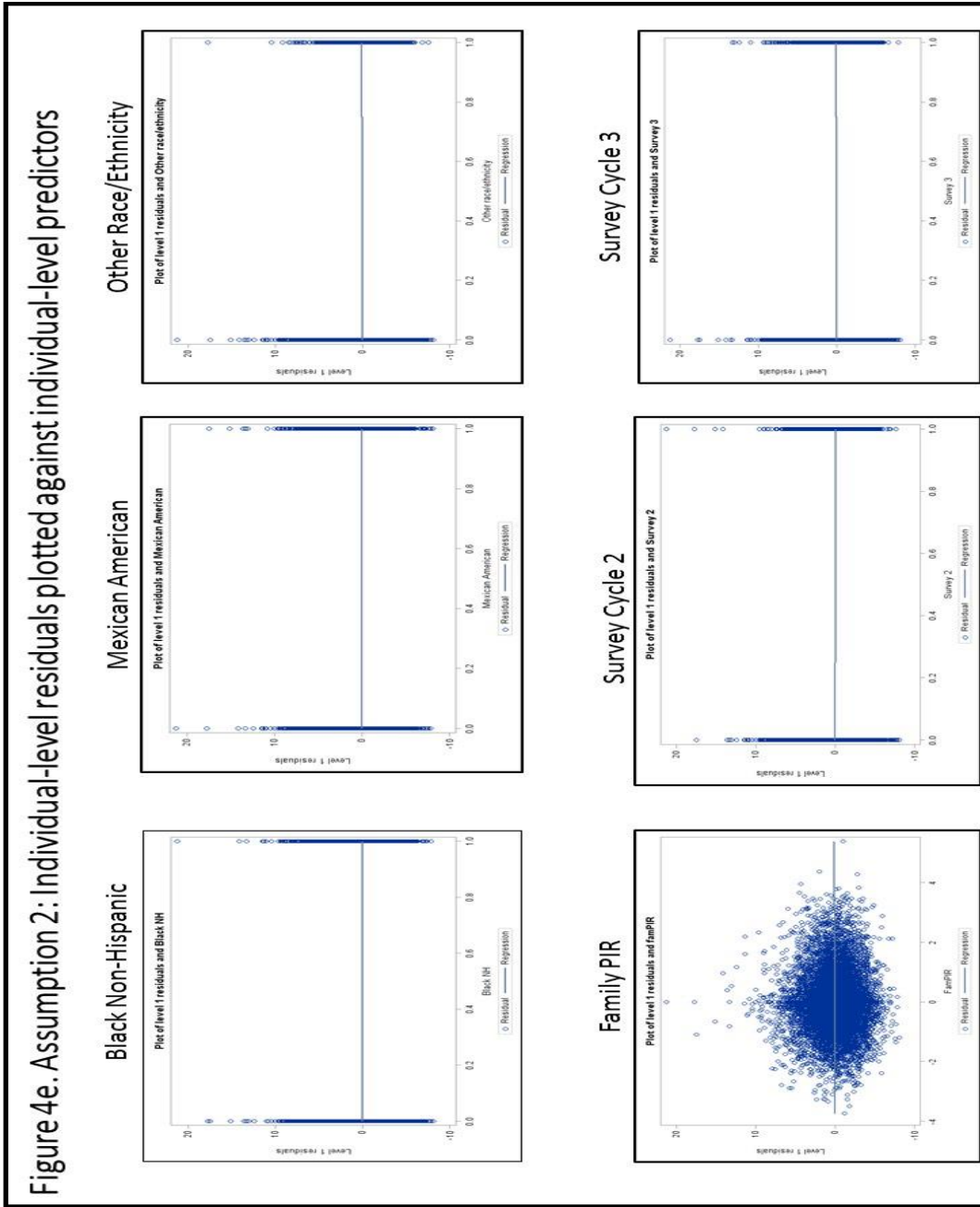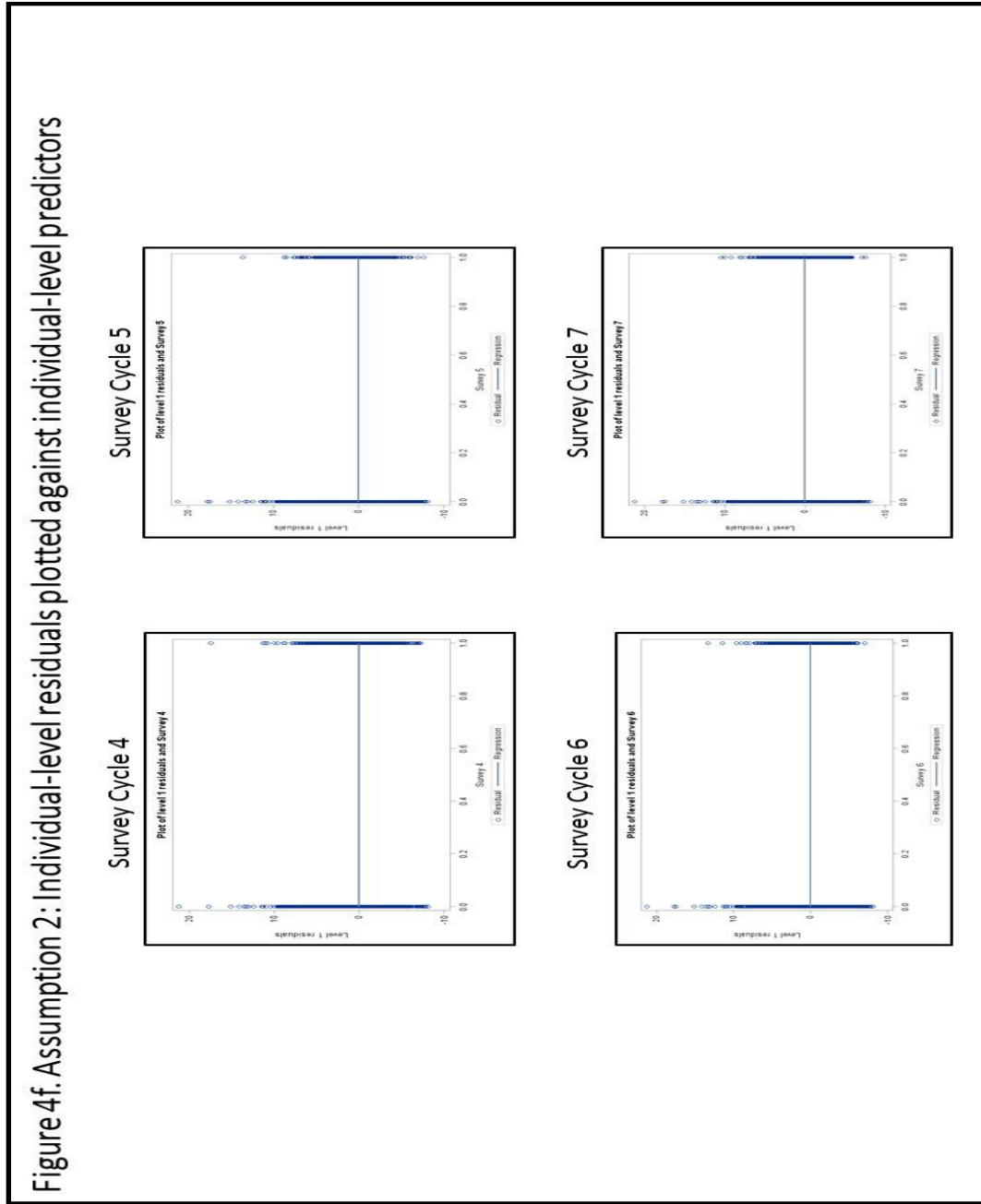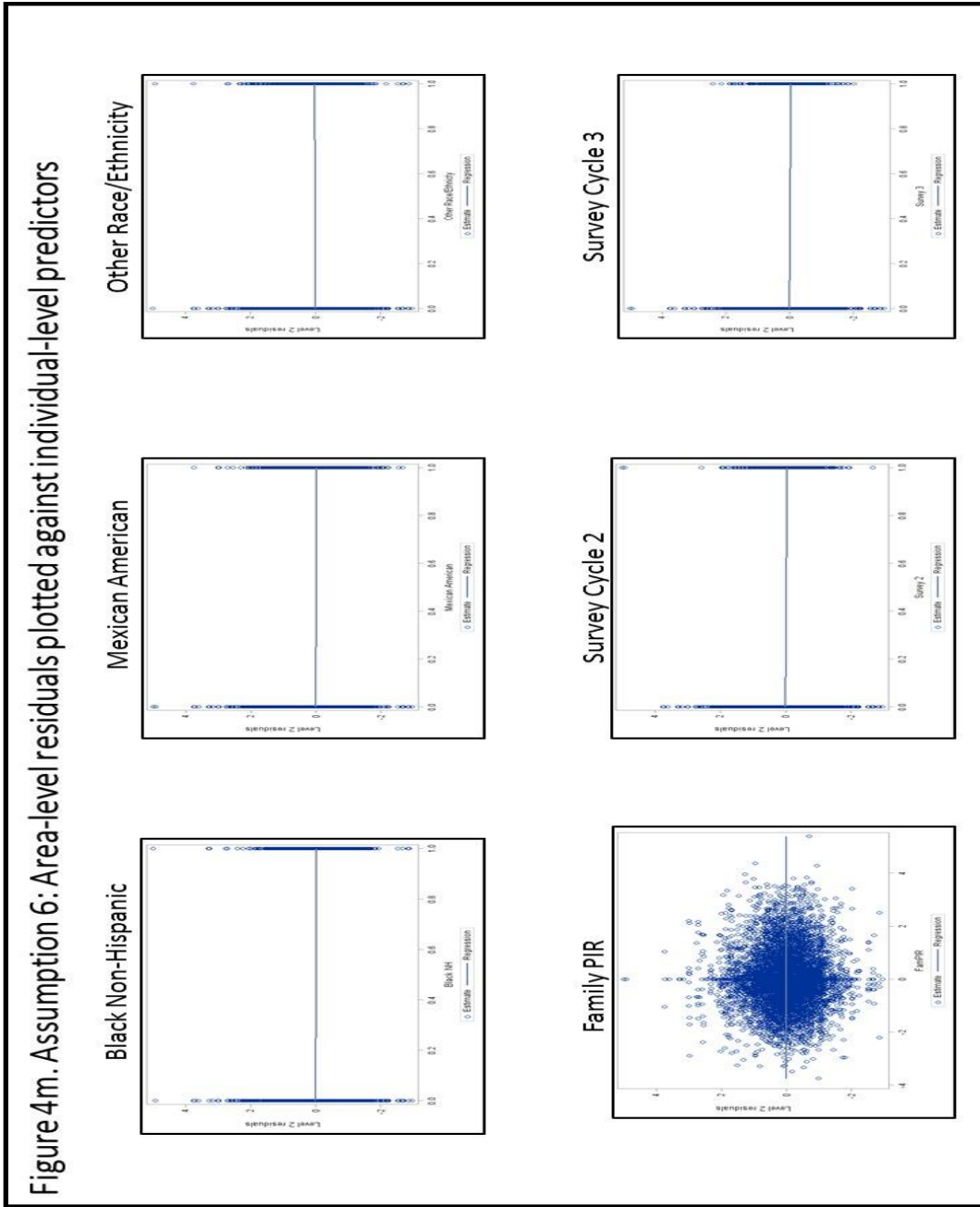**Figure 4n. Assumption 6: Area-level residuals plotted against individual-level predictors**

Figure 4n. Assumption 6: Area-level residuals plotted against individual-level predictors
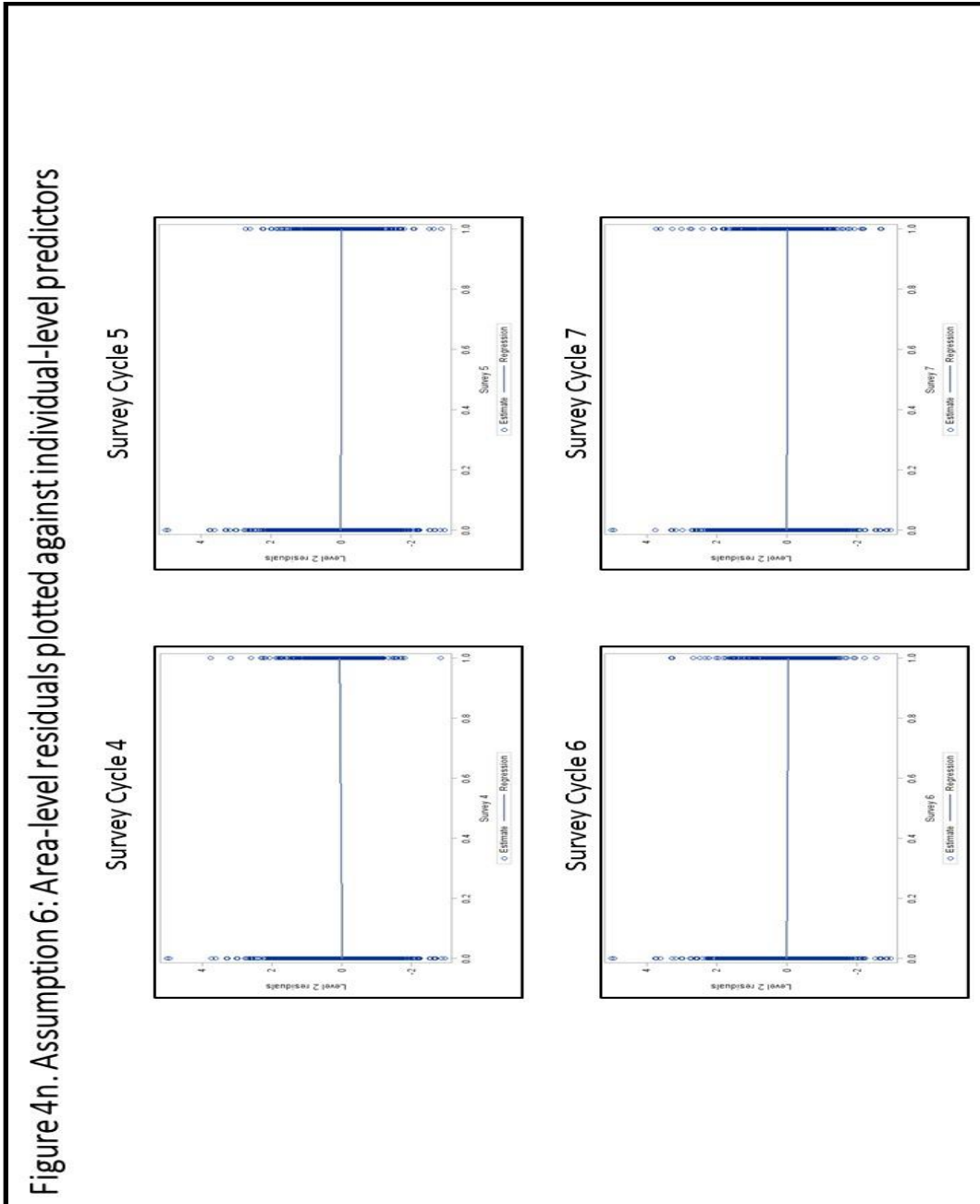
Appendix C. SAS Code

Appendix C.1. 14 Year Weight Sample SAS Code

```
if sddsrvyr=1 or sddsrvyr=2 then
        MEC14YR  = 2/7 * WTMEC4YR ; /* for 1999-2002 */

if sddsrvyr=3 or sddsrvyr=4 or sddsrvyr=5 or sddsrvyr=6 or sddsrvyr=7 then
        MEC14YR = 1/7 * WTMEC2YR ; /* for 2003-2012  */
```

Appendix C.2. Scaling Weights to Census Tracts Sample SAS Code

```
proc sort data = dataset;
by tract;
   run;
proc summary data = dataset;
  by tract;
  var MEC14YR;
  output out = intermediate
    uss = sumsqw
    sum = sumw
    n = nj;
  run;
data dataset;
  merge dataset intermediate;
    by tract;
  aw = MEC14YR/(sumw/nj);
  label aw = "Method A";
  bw = MEC14YR/(sumsqw/sumw);
  label bw = "Method B";
  run;
data dataset; set dataset; drop _freq_ sumsqw sumw nj _type; run;
```

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