

Cardiometabolic Risk and Resilience: Are Associations Between Childhood Socioeconomic Status and Midlife Cardiometabolic Health Buffered by Supportive Family Relationships?

by

Brianna Nicole Natale

Bachelor of Science in Psychology and Biology, Le Moyne College, 2016

Master of Science in Behavioral Science Research, Radboud University, 2018

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DIETRICH SCHOOL OF ARTS AND SCIENCES

This thesis was presented

by

Brianna Nicole Natale

It was defended on

July 22, 2020

and approved by

Karen A. Matthews, Distinguished Professor, Department of Psychiatry

Stephen B. Manuck, Distinguished Professor, Department of Psychology

Thesis Co-Advisor: Daniel S. Shaw, Distinguished Professor, Department of Psychology

Thesis Co-Advisor: Anna L. Marsland, Professor, Department of Psychology

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Brianna Nicole Natale, MS

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Childhood socioeconomic disadvantage is associated with greater risk for chronic inflammation and cardiometabolic disease at midlife. In addition, supportive family relationships have been shown to reduce the risk that early adversity typically poses on later adult health. However, prior research has not yet tested the mediating role of inflammation in the relationship between childhood socioeconomic status (SES) and cardiometabolic risk, nor has the family buffering hypothesis been applied to an understanding of the inflammation and cardiometabolic risk that accompanies low childhood SES. The aim of the current study was to determine whether the association between childhood socioeconomic disadvantage and risk for cardiometabolic disease in adulthood is mediated by adult inflammation and buffered by cohesive family relationships in a sample of healthy midlife adults. Participants were 1,785 healthy adults aged 30-54 (Adult Health and Behavior studies I & II) who retrospectively reported on childhood SES and family relationships and underwent a physiological assessment, primarily investigating circulating levels of inflammatory markers and cardiometabolic health. Associations between childhood SES, childhood family relationship quality, adult inflammation, and adult cardiometabolic risk were investigated using structural equation modeling, in which cardiometabolic risk was modeled as a second-order latent variable with adiposity, dyslipidemia, insulin resistance, and blood pressure as first-order components. As expected, individuals who reported socioeconomically disadvantaged backgrounds in childhood showed greater risk for cardiometabolic disease and higher circulating

levels of CRP and to a lesser extent IL-6 (marginally significant) at midlife than individuals who reported higher childhood SES. Findings also indicated that the relationship between childhood SES and adult cardiometabolic risk was partially explained by systemic inflammation, in particular by circulating levels of CRP. However, contrary to expectations, no evidence was found for the buffering of these socioeconomic health disparities by cohesive family relationships during childhood. Collectively, the current findings suggest that SES in early life has pervasive, long-lasting associations with inflammatory and cardiometabolic health in adulthood. The current study is among the first to find evidence that socioeconomic disparities in cardiometabolic risk may relate, in part, to the impact of systemic inflammation at midlife. Future work would benefit from prospective investigation of these relationships.

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1.0 Introduction

Cardiovascular disease, diabetes, and obesity continue to be leading causes of mortality in the United States (Benjamin et al., 2018). Moreover, socioeconomic disparities in cardiometabolic health in particular are well-documented, such that people of low SES are at greater health risk than their more socioeconomically advantaged peers (Langenberg, Kuh, Wadsworth, Brunner, & Hardy, 2006; Tamayo, Christian, & Rathmann, 2010; Schreier & Chen, 2013). SES reflects one's social and financial position and can be defined in a number of objective (e.g., education, income, material wealth) and subjective (e.g., perception of social standing relative to others) ways throughout the life course. Notably, this SES-related "health gap" has only widened over the past few decades (e.g., increases in life expectancy observed exclusively in people of higher SES), indicating that socioeconomic health inequality remains a pressing concern (Bor, Cohen, & Galea, 2017).

SES is broadly defined as one's social and economic standing within a community (American Psychological Association, 2019). However, based on its complex and multifaceted nature, there have been multiple theoretical perspectives and methods for characterizing SES. It is therefore not surprising that many different components of socioeconomic stratification have been established as proxies of the overarching construct of SES either individually or collectively. Educational attainment, household income, occupational prestige, and material wealth (i.e., home or vehicle ownership) are commonly used as indices of objective SES, while comparisons to others' perceived socioeconomic positions (i.e., ladder scales) are utilized to infer subjective SES. Overall, indicators of SES are moderately correlated and SES is relatively stable over the life course; however, variability in the magnitude of these correlations have been noted. Indeed, some

studies do not find significant associations between different indices of socioeconomic position, and the influence and interpretation of the different SES dimensions is not ubiquitous across populations (Shavers, 2007). For example, although moderately correlated ($r = 0.37$), higher levels of education do not always equate to higher income (Oakes & Rossi, 2003), and the interpretation of educational attainment varies substantially among countries, sexes, and generations. Shavers (2007) also notes that SES can fluctuate across the life course. Some people show stability in their socioeconomic positions (i.e., consistent SES from childhood onward), while others experience either upward or downward mobility (i.e., change SES from childhood to adulthood). Socioeconomic mobility in the United States has decreased both in comparison to likelihood of mobility in previous decades and other developed countries, however (Hertz, 2006). Altogether, the conceptualization of SES in the socioeconomic health disparities literature is diverse, meaning there is currently insufficient evidence to suggest that one measure of SES is superior to others in terms of its association with adult health outcomes. Consequently, some research focuses on particular measures of SES during discrete developmental periods, whereas other research aggregates multiple measures of SES across the lifespan.

1.1 Childhood SES and Cardiometabolic Health

Despite these discrepancies in the conceptualization of SES, studies have consistently shown modest yet significant relations between various objective indices of childhood SES and adult cardiometabolic health. Low childhood SES, as indexed by paternal occupation or education, has been retrospectively linked to risk for developing type 2 diabetes over a 34-year period (Maty, Lynch, Raghunathan, & Kaplan, 2008). Additionally, lower parental occupational status from birth

to 16 years of age has been associated with increased risk for type 2 diabetes- and cardiovascular disease-related mortality in a large ($N = 1,839,384$) prospective cohort (Lawlor, Sterne, Tynelius, Davey Smith, & Rasmussen, 2006). In conjunction with these clinically-oriented studies, many others have sought to discern the etiological trajectory of socioeconomic disparities in cardiometabolic health through the examination of preclinical outcomes.

Indeed, childhood SES has also been associated with a number of preclinical markers of risk for cardiometabolic disease. In this regard, considerable evidence shows that preclinical changes that presage the onset of cardiovascular and metabolic diseases begin as early as childhood (Shonkoff, Boyce, & McEwen, 2009; Miller & Chen, 2013). Metabolic syndrome is a well-established clustering of metabolic and cardiovascular risk factors (insulin resistance, dyslipidemia, central adiposity, and elevated BP) that develop during this preclinical period and increase risk for cardiometabolic disease, with the syndrome predicting risk for disease independently of its individual components (Ford, 2004; Alberti, Zimmet, & Shaw, 2005; Grundy, 2006; Sundström et al., 2006).

Research has revealed a robust inverse association of childhood SES with presence of metabolic syndrome and other preclinical indicators of cardiometabolic disease, with comparable evidence available from retrospective and prospective studies. A systematic review of childhood socioeconomic disadvantage and adult cardiovascular health reported that 31 out of 40 eligible studies (61% prospective) showed a relationship between low childhood SES and later risk for cardiovascular disease (Galobardes, Smith, & Lynch, 2006). Moreover, one sizable ($N = 2,250$) prospective study found that childhood family income assessed between 3 and 18 years of age was predictive of midlife metabolic syndrome and type 2 diabetes (Puolakka et al., 2016). Consistent with this finding, childhood SES, measured via retrospective report of parental education, was

associated with greater risk for metabolic syndrome in mid-adulthood (Miller et al., 2011). Despite the substantial amount of time separating childhood and midlife, childhood SES remained predictive of adult cardiometabolic risk even when controlling for adulthood SES (Puolakka et al., 2016) and upward socioeconomic mobility (Miller et al., 2011) in these studies.

Although the degree to which these associations are dependent on the developmental timing of adversity remains unresolved, prior research points to early life sensitivity to socioeconomic disadvantage (Larson et al., 2018; Kim, Evans, Chen, Miller, & Seeman, 2018). Early childhood, broadly defined as between birth to 8 years of age, represents a number of especially sensitive developmental periods (e.g., infancy, toddlerhood), characterized by heightened susceptibility to environmental influences, which can become biologically embedded and later manifest as altered immune function and enhance risk for an array of diseases (McDade, 2005; Shonkoff et al., 2009). Studies have been limited in their ability to identify distinct ages of vulnerability to environmental influences that confer risk for later cardiometabolic disease because of inconsistent metrics of childhood. However, when the earlier years of childhood were examined, socioeconomic disadvantage retrospectively recalled between ages 1 and 6 was linked to heightened inflammatory responses to acute stressors in midlife, independently of adult SES (Lockwood, John-Henderson, & Marsland, 2018). In this vein, prominent developmental health theories, namely Developmental Origins of Health and Disease (DOHaD) and Life Course Health Development (LCHD), posit that socioeconomic risk for adult cardiometabolic disease can be traced as far back as the first few years of life (Barker, 1990; Halfon & Hochstein, 2002). Therefore, the etiological importance of early life sensitivity has been maintained within these theories and sought to address the role of developmental timing of socioeconomic disadvantage (Hertzman, 2012).

1.2 Mechanisms of Association Between Childhood SES and Cardiometabolic Health

The persistent relationship between childhood SES and adult health is commonly explained by a number of behavioral and biological mechanisms, which delineate how SES can become biologically embedded at a young age and contribute to later cardiometabolic risk. Biological embedding mechanisms seek to explain the process by which life experiences can alter physiological processes and have enduring biological consequences (Miller, Chen, & Parker, 2011). Among candidate mechanisms proposed to contribute to the association between childhood SES and adult cardiometabolic risk are health behaviors (e.g., diet, exercise, and smoking status) and physiological function (e.g., sleep disturbances and altered biological responses to psychological stressors) (Cohen, Janicki-Deverts, Chen, & Matthews, 2010).

In terms of health behaviors, low childhood SES relates to poor diet and lack of exercise (i.e., risk for obesity), as well as later smoking from adolescence through adulthood, all of which increase the likelihood of midlife health problems, including cardiometabolic risk (Ferraro, Schafer, & Wilkinson, 2016). Meta-analyses that consider the role of body mass index (BMI) in the relationship between childhood SES and adult inflammation show that BMI does contribute to these associations (Liu et al., 2017; Pinto Pereira et al., 2019), although not entirely or consistently (Milaniak & Jaffee, 2019).

Similar to the biological embedding of socioeconomic disadvantage via health behaviors, low childhood SES also relates to changes in physiological function, as evidenced by poorer sleep quality and altered stress responsivity (Taylor, 2010; Irwin, Olmstead, & Carroll, 2016). Regarding stress responsivity, physiological systems that orchestrate biological responses to stress, particularly the sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) axes, have shown reactivity to acute stressors, especially in low SES individuals (Gallo &

Matthews, 2003). Furthermore, epigenetic changes, or alterations to DNA structure, have been observed across species in association with social disadvantage (Tung & Gilad, 2013). Certain epigenetic changes that accompany low childhood SES directly relate to biological stress responses, such as production of the HPA end product, cortisol. A primary example is the upregulation and downregulation of specific genes in individuals from low SES backgrounds, which ultimately increase cortisol secretion and promote glucocorticoid resistance in immune cells, incapacitating the typically anti-inflammatory effects of cortisol (Miller et al., 2009; Miller & Cole, 2010). These changes that are programmed early in development can result in heightened levels of systemic inflammation in addition to altered metabolic and cardiovascular functioning over time, all of which is believed to culminate in heightened risk for cardiometabolic disease (Gluckman, Hanson, Cooper, & Thornburg, 2008; Taylor, 2010; Miller & Chen, 2013).

1.3 Chronic Inflammation as a Proximal Mechanism Linking SES and Cardiometabolic Risk

Inflammation is the process by which the innate immune system responds to foreign substances and physical injury (Sompayrac, 2019). When confronted with a foreign antigen, macrophages become activated and start to produce and release pro-inflammatory cytokines, such as interleukin-6 (IL-6). These cytokines orchestrate a local inflammatory response that includes attracting leukocytes to the region and supporting an immune response designed to destroy pathogens. Pro-inflammatory cytokines also enter peripheral circulation where they initiate a systemic response to infection. This response includes stimulating liver cells to produce acute phase proteins, such as C-reactive protein (CRP). IL-6 and CRP play a crucial role in mounting

an inflammatory response by acting as signaling molecules which direct other immune cells to the infected site and contribute to the pathogen's destruction (Sompayrac, 2019). There are a number of different circulating markers of inflammation. Of these, IL-6 and CRP are the most widely used in research on inflammation because of their relatively long half-life and high likelihood of detection which allows for the quantification of individual differences (Gabay & Kushner, 1999). However, although IL-6 and CRP are commonly accepted as markers of inflammation, there are notable differences between the two. For instance, CRP is not subject to diurnal variation and has an established clinical range that is indicative of disease risk (Pearson et al., 2003). In contrast, IL-6 undergoes diurnal changes and is produced by a number of cell types (e.g., adipocytes and myocytes in addition to macrophages), making its circulating levels less solely immune-derived (Gudewill et al., 1992; Bauer et al., 1994; Kershaw & Flier, 2004).

Chronic systemic inflammation has been identified as an intermediary between the biological embedding mechanisms of early life disadvantage and long-term cardiometabolic risk. It is widely accepted that chronic systemic inflammation presages a host of cardiometabolic risk factors, including adiposity, insulin resistance, dyslipidemia, and blood pressure (Dandona, Aljada, & Bandyopadhyay, 2004; Marsland et al., 2010), and provides an index of altered metabolic functioning (Berens, Jensen, & Nelson, 2017). However, the direction of these effects remains unclear. Inflammation is a key component of the pathogenic processes that result in the accumulation of plaque in arteries and ultimately the development of atherosclerosis. Thus, inflammation contributes to the etiology of cardiovascular disease (Ellulu, Patimah, Khaza'ai, Rahmat, & Abed, 2017; Ruparelia, Chai, Fisher, & Choudhury, 2017). Inflammation also contributes to the development of insulin resistance and thus risk for metabolic disease (Black, 2003; Marsland et al., 2010). However, preclinical cardiometabolic disease conditions (e.g.,

atherosclerosis) and risk factors (e.g., adiposity) in and of themselves can contribute to increases in markers of systemic inflammation, making it difficult to infer directionality. In either case, even low-levels of chronic inflammation confer risk for future adverse cardiometabolic outcomes, including heart attack and stroke (Guarner & Rubio-Ruiz, 2015). Thus, empirical and theoretical evidence suggests that pro-inflammatory cytokines are a proximal biological mechanism linking low childhood SES to cardiometabolic risk.

Consequently, examination of cardiometabolic risk typically includes circulating levels of pro-inflammatory biomarkers, such as IL-6 and CRP (Marsland, McCaffery, Muldoon, & Manuck, 2010). Elevated levels of CRP have been observed in midlife adults who retrospectively reported lower childhood SES backgrounds, as indexed by level of parental educational attainment, compared to adults who reported higher childhood SES (Taylor, Lehman, Kiefe, & Seeman, 2006; Phillips et al., 2009). Similarly, IL-6 levels have been inversely related, although modestly, to retrospective reports of parental material wealth (e.g., home and vehicle ownership, number of rooms in home; Carroll, Cohen, & Marsland, 2011) and parental occupation (Chen, Miller, Kobor, & Cole, 2011) during childhood. Liu et al. (2017) conducted a systematic review and meta-analysis of 15 studies ($N = 43,629$), which showed that low childhood SES, largely based on retrospective reports, predicts higher levels of pro-inflammatory markers, specifically CRP, in adulthood. Adults from disadvantaged socioeconomic backgrounds during childhood, broadly defined, had 25% higher levels of circulating CRP than those whose childhood was more advantaged. This finding was replicated and shown to be independent of other forms of childhood adversity in a prospectively studied cohort (Pinto Pereira et al., 2019). A recent systematic review and meta-analysis by Milaniak and Jaffee (2019) showed a negative unadjusted correlation of $r = -0.09$ between childhood SES (i.e., parental education, occupation, and/or income) and later

inflammation across 15 longitudinal studies ($N = 43,972$) which included both prospective and retrospective reports of childhood SES. This association remained significant based on 20 additional studies ($N = 79,297$) that did adjust for demographic (e.g., age, sex, race) and/or health (e.g., BMI, smoking) covariates. Notably, this relationship was reduced to non-significance among the 11 studies ($N = 49,364$) controlling for SES in adulthood (Milaniak & Jaffee, 2019), likely reflecting the high stability of SES across the lifespan. However, low childhood SES remained predictive of heightened adult inflammation in 4 of the 11 studies and in the aforementioned studies that accounted for adulthood SES (Taylor et al., 2006; Phillips et al., 2009; Carroll et al., 2011; Liu et al., 2017; Pinto Pereira et al., 2019), suggesting that the association between childhood SES and adult inflammatory profiles independent of adult SES is equivocal in the current literature.

1.4 Moderators of Association Between Childhood SES and Cardiometabolic Health

Prior research indicates that some biological embedding mechanisms underlying associations between childhood SES and adult health outcomes are moderated by the quality of family relationships. The quality of the family environment has been quantified in a number of ways, including both positive and negative aspects of family relationships (Moos & Moos, 1981). Generally, positive dimensions include familial warmth, support, and cohesion, the latter of which is characterized by pleasant relationships, mutual helpfulness, and a sense of unity. In contrast, negative dimensions typically consist of conflict (i.e., criticism, anger, and fighting) and disorganization (i.e., lack of structure), and in extreme situations, maltreatment.

Harsh family environments, which are defined as being high in conflict and low in warmth and support, are consistently linked to altered biological stress responses, specifically altered SAM

and HPA functioning beginning in infancy, and unfavorable health behaviors, such as excessive drinking and smoking in adolescence (Repetti, Taylor, & Seeman, 2002). Additionally, children who grow up in harsh family environments have been proposed to develop pro-inflammatory phenotypes, as suggested by higher levels of pro-inflammatory markers in response to immune stimulation and greater resistance of immune cells to cortisol during adolescence (Miller & Chen, 2010). In more severe family environments, physical and/or cognitive neglect during childhood (e.g., lack of sufficient hygiene or supervision from the primary caregiver anytime between birth and 17.5 years of age) have predicted midlife cardiometabolic risk within a prospective study of individuals who were of low SES at the time of recruitment (Johnson et al., 2017). Furthermore, both low childhood SES and harsh family environments were retrospectively associated with increased metabolic risk in adulthood in a large ($N = 3,225$) community sample (Lehman, Taylor, Kiefe, & Seeman, 2005).

Conversely, positive family environments that are warm and cohesive have been shown to promote long-term health and buffer the risk for disease associated with early life disadvantage. Family relationships characterized by emotional support, encouragement, and acceptance are related to favorable health behaviors, including less drinking and smoking in adolescence, and less extreme biological responses to acute stressors in cross-sectional studies (Chen, Brody, & Miller, 2017). Parental caregiving quality in early life, particularly during infancy, is believed to affect the development of stress-response physiology, namely HPA axis regulation, through childhood (Loman & Gunnar, 2010). Caregiving behavior of a higher quality (e.g., greater contingent sensitivity and responsiveness) has been associated with lower HPA axis reactivity to psychosocial stressors in infancy (Gunnar & Quevedo, 2007) and attenuation of the prospective relationship between stress during early childhood and unfavorable adult health outcomes (Farrell, Simpson,

Carlson, Englund, & Sung, 2017). Research examining the combined influence of both positive and negative aspects of the family environment has found that greater amounts of retrospectively reported conflict relative to cohesion are related to earlier pubertal timing in women, which in turn has been associated with an earlier onset of cardiometabolic risk (Manuck, Craig, Flory, Halder, & Ferrell, 2011). Considering that approximately 50% of people who experience low childhood SES remain in good health through adulthood (Cohen, Doyle, Turner, Alper, & Skoner, 2004; Miller et al., 2011), focusing on potential protective factors, such as family warmth, support, and cohesion, has become imperative for understanding variability in health risk that associates with childhood socioeconomic disadvantage.

In light of these findings, the Developmental Stress Buffering Hypothesis posits that a greater amount of support, relative to conflict, within families could attenuate the association between childhood stress (e.g., low SES) and later physical health risk (Chen et al., 2017). Notably, the relative importance of specific aspects of supportive family relationships across developmental stages—from early childhood through adolescence—are taken into account. The hypothesis aptly notes that parent-child relationships are dynamic; thus, some of the most salient components of these relationships change throughout childhood and adolescence. For instance, parental proximity (i.e., physical closeness) in childhood and parental availability in adolescence are developmentally salient forms of support that have been proposed to buffer adverse health outcomes associated with early life adversity. Based on this theoretical perspective, Chen, Brody, and Miller (2017) propose that family relationships which are on the whole more supportive than conflictual throughout childhood and adolescence will likely lessen the health risks associated with several types of childhood adversity, including low SES. Consistent with this hypothesis, positive family environments have been found to moderate the direct relationship between retrospectively assessed

early life stress and risk for later cardiometabolic disease, such that higher levels were shown to significantly attenuate the magnitude of this association (Miller et al., 2011).

1.5 Current Study

To date, little research has tested the Developmental Stress Buffering Hypothesis with regard to positive and negative aspects of the family environment that might attenuate the cardiometabolic risk associated with low childhood SES. The majority of prior studies addressing aspects of the family environment that confer health promotion or risk have either focused solely on mother-child relationships (i.e., maternal warmth or caregiving behavior) or examined positive or negative family factors in isolation rather than contemporaneously. Therefore, the aim of the current study was to discern whether the quality of childhood family relationships moderates associations between childhood socioeconomic disparities and risk for inflammation and cardiometabolic disease among healthy midlife adults. It was hypothesized that childhood SES would predict adult cardiometabolic health, such that individuals who recall low childhood SES would show greater risk for cardiometabolic disease in midlife than people of higher childhood SES. Secondly, childhood SES was posited to be inversely related to circulating levels of inflammatory markers (i.e., IL-6 and CRP) in adulthood. Furthermore, IL-6 and CRP were individually hypothesized to mediate the relationship between childhood SES and adult cardiometabolic risk. Finally, it was predicted that greater amounts of family cohesion relative to conflict throughout childhood would attenuate associations between childhood SES and adult inflammatory and cardiometabolic health.

2.0 Method

2.1 Participants

A total of 1,785 adults between the ages of 30 and 54 were recruited for the Adult Health & Behavior (AHAB) project, which comprises a registry of behavioral and biological measurements for the study of individual differences. Participants were recruited studies via mass-mail solicitation in Allegheny County and neighboring southwestern Pennsylvania areas in two phases, termed AHAB I (2001-2005; $N = 1,295$) and AHAB II (2008-2011; $N = 490$). The current analyses combined participants from the two cohorts. General study exclusions for both samples included a reported history of atherosclerotic cardiovascular disease, chronic kidney or liver disease, cancer treatment in the preceding year, major neurological disorders, psychotic illness, systolic/diastolic blood pressure $\geq 180/110$ mmHg (AHAB I) or $\geq 160/100$ mmHg (AHAB II), and alcohol consumption >21 drinks/week (AHAB I) or ≥ 5 drinks 3-4 times/week (AHAB II). Also excluded were pregnancy and use of insulin, psychotropic, antiarrhythmic, and prescription weight-loss medications. Because additional exclusions in AHAB II included all other diabetic medications, antihypertensives, and lipid-lowering drugs, only AHAB I participants meeting these criteria as well were included in the current study. Further exclusions specific to AHAB II included shift-work schedules, use of fish-oil supplements, and AHAB II participants were all employed ≥ 25 hours/week. Thus, the eligible participants constituted a relatively healthy, community sample of midlife adults. Figure 1 depicts further eligibility criteria, which resulted in a final sample size of 1,359 for the current study.

2.2 Procedure

Participants were invited to the lab for multiple assessments over the course of the AHAB studies. The data utilized in the current study were collected in the first lab visit, with the exception of information about childhood SES which was collected from AHAB II participants during the third session. Otherwise, AHAB I and II did not differ from one another with regard to the collection or timing of measures currently being examined.

At session 1, participants were instructed to fast for 8 hours and abstain from exercise for 12 hours, alcohol for 24 hours, and nicotine for 1 hour prior to their morning lab visit. Upon arriving to the lab, participants completed questionnaires about childhood SES and family relationships, among others. Additionally, information about the participants' medical history and medication use was collected. If deemed eligible for further health assessment, participants' height, weight, and blood pressure were recorded and 40 mL of their blood was drawn. A portion of the blood sample was processed externally at the Heinz Nutrition Laboratory (University of Pittsburgh Graduate School of Public Health) to determine circulating lipid, glucose, and serum levels. The remaining sample was processed in house and aliquots of blood plasma were stored in a -80°C freezer for future analysis of IL-6 and CRP concentrations.

2.3 Materials

2.3.1 Childhood Socioeconomic Status (SES)

Childhood SES was retrospectively self-reported, in terms of parental education and occupation at 5 and 10 years of age, using the two-factor Hollingshead Index (Hollingshead, 1957). Parental education was reported as the highest level attained for both mothers and fathers, ranging from less than or equal to 8th grade to graduate degree. This was recorded on a 7-point scale, with greater scores representing a higher level of education. Similarly, parental occupation was stratified into categories based on occupational prestige which were rated on a 9-point scale, with higher scores indicating greater parental occupational status. The Hollingshead Index score was then calculated via the following formula: $(3 * Education) + (5 * Occupation)$, representing a composite weighted measure of highest level of education and occupational prestige for participants' parents during their childhood. This calculation was done using the highest parental score on each of these submeasures in instances when mothers and fathers had discrepant educational and occupational levels. The Hollingshead scores at ages 5 and 10 were averaged to construct the final childhood SES variable.

2.3.2 Family Relationships

Family relationships during childhood and early adolescence were retrospectively assessed via the Family Environment Scale (FES; Moos & Moos, 1981), which was previously shortened and altered to a Likert-scale format (Plomin & DeFries, 1985; McClearn, Pedersen, Nesselroade, & Bergeman, 1988). The modified FES contains 40 items which capture eight aspects (5 items

each) of the immediate family environment: cohesion, expressiveness, conflict, achievement orientation, cultural-intellectual orientation, active-recreational orientation, organization, and control. Participants rated the degree to which they agreed or disagreed with each item on a 5-point scale, with a greater score indicating strong agreement.

Only the cohesion and conflict subscales were used in the current study, both of which had strong internal consistency ($\alpha = .88$ and $\alpha = .83$, respectively) and have previously shown strong test-retest reliability, content validity, and construct validity (Moos, 1990). The cohesion subscale included items such as “When I was growing up, family members really helped and supported one another” and “When I was growing up, there was a feeling of togetherness in our family.” The conflict subscale contained items such as “When I was growing up, we fought a lot in our family” and “When I was growing up, people in our family often criticized each other.” The final family relationship score was created by subtracting the total conflict score from the total cohesion score, such that possible scores ranged from -20 to 20 and higher scores represented more cohesive family relationships.

2.3.3 Inflammation

Interleukin-6 (IL-6) levels were measured using a high-sensitivity quantitative sandwich enzyme immunoassay kit (R & D Systems) as per the manufacturer’s instructions. The standard range of this assay is 0.156 to 10 pg/mL. Notably, all samples were run in duplicate, and the intra- and inter-plate coefficients of variation (CVs) were <10%.

C-reactive protein (CRP) levels were determined using a particle-enhanced immunonephelometric assay. These assays were conducted within the Laboratory of Clinical Biochemistry Research at the University of Vermont with the BNII nephelometer from Dade

Behring (Newark, DE). The standard range of this assay is 0.175 to 1000 mg/L, and the intra- and inter-plate CVs ranged from 2.3% to 4.4% and 2.1% to 5.7%, respectively. IL-6 and CRP levels were each included in the models as distinct markers of inflammation.

2.3.4 Cardiometabolic Risk

The cardiometabolic risk variable was comprised of adiposity, blood lipid measures, insulin resistance measures, and blood pressure readings which formed a second-order latent variable in a manner consistent with previous studies (Marsland et al., 2010; Barber, Ringwald, Wright, & Manuck, 2019). Body mass index (BMI), waist circumference, triglycerides, high-density lipoproteins (HDL), glucose, insulin, systolic blood pressure, and diastolic blood pressure were used to create the latent cardiometabolic risk variable. Note that the concentration of high-density lipoproteins was reverse-scored and blood pressure measures were an average of two consecutive recordings.

2.3.5 Covariates

Participants' age, race, sex, and AHAB cohort were included as covariates. In addition to demographics, self-reported health behaviors and adult SES were accounted for. Adult SES was defined as participants' current Hollingshead Index score (i.e., composite measure of educational attainment and occupational prestige) to be consistent with the childhood SES measure. Health behaviors included self-reported smoking status (current smoker vs. former- or non-smoker), alcohol use (drinks per week in the past month), physical activity (kilocalories per week as determined by the Paffenbarger Physical Activity Questionnaire; Paffenbarger et al., 1993), and

sleep (average hours of sleep in the past week), which is also in line with prior work (Phillips et al., 2009) as all four adult health behaviors have been associated with both SES and cardiometabolic risk (Cohen et al., 2010; St-Onge et al., 2016; Du, Bruno, Dwyer, Venn, & Gall, 2017; Puolakka et al., 2018).

2.4 Statistical Analysis

2.4.1 Models

Two structural equation models were constructed in R to test the current hypotheses (R Core Team, 2016). The specified models were fit using the *sem()* function from the lavaan package to obtain MLR estimates and bias-corrected bootstrapped 95% confidence intervals, which were used to determine significance (Rosseel, 2012). First, the association between childhood SES and adult cardiometabolic risk, as potentially mediated by adult inflammation, was examined (Figure 2a). Second, family relationship quality was added as a potential moderator of the relationships between childhood SES and adult inflammation and cardiometabolic risk (Figure 2b). Note that in each model, cardiometabolic risk was constructed as a second-order latent variable with four first-order latent variable components (adiposity, dyslipidemia, insulin resistance, and blood pressure), while all other measures remained observed variables. Both models also had covariates introduced in a stepwise fashion: (1) age, race, sex, and AHAB cohort; (2) earlier covariates plus adult SES (Hollingshead score); and (3) earlier covariates plus health behaviors (smoking, alcohol use, physical activity, and sleep). All observed variables were regressed on the demographic covariates, and adult SES and health behavior covariates were included for each path within the overall

models. The direct (c), indirect ($a*b$), and total effects ($c+a*b$) of childhood SES on adult cardiometabolic risk were then estimated simultaneously for each model.

2.4.2 Sensitivity Analyses

Additionally, several sensitivity analyses were conducted following the main analyses. First, each model (six in total) was subsequently run excluding individuals who didn't grow up with both biological parents to test whether parental absence influenced the pattern of results. In a separate sensitivity analysis, all models were run examining childhood SES at ages 5 and 10 individually to test whether these separate time points distinctly predicted adult health outcomes. Next, if a significant correlation between IL-6 and CRP was observed in the main analyses, follow-up models were run using a composite measure of adult inflammation (i.e., average of the IL-6 and CRP z-scores) as the mediator. In another sensitivity analysis, adiposity was removed from the cardiometabolic risk latent variable to assess the contributions of this particular component to the pattern of results. Additionally, potential moderation by sex and race was examined to test whether associations between childhood SES and adult health differ between women and men or non-Hispanic Whites and Blacks. Another moderation sensitivity analysis investigated whether amount of family cohesion relative to conflict also moderates the relationship between inflammation and cardiometabolic risk. Finally, in the last sensitivity analysis, family cohesion and conflict were included separately as moderators to test the underlying assumption that their influences on risk and resilience are conjunctive and continuous rather than discrete and dichotomous.

3.0 Results

3.1 Descriptive Analyses

Prior to testing the models of interest, the univariate distributions and number of outliers for each variable were examined. Transformations were applied to variables that were skewed and/or kurtosed, including a logarithmic transformation for IL-6, CRP, triglycerides, glucose, insulin, and alcohol use, and a square root transformation for physical activity. Outliers (>3 SD above or below the mean) were also identified for all cardiometabolic risk observed variables and continuous health behavior covariates: BMI ($n = 18$), waist circumference ($n = 9$), triglycerides ($n = 25$), HDL ($n = 11$), glucose ($n = 15$), insulin ($n = 21$), systolic blood pressure ($n = 10$), diastolic blood pressure ($n = 9$), physical activity ($n = 7$), sleep ($n = 4$), and alcohol use ($n = 2$). All outliers were truncated at 3 SD via Winsorization (Dixon & Yuen, 1974).

Raw means and standard deviations for all observed variables are reported in Table 1 and further stratified by sex and race in Table 2. Participants retrospectively reported relatively advantaged socioeconomic backgrounds and childhood family relationships that were more cohesive than conflictual on average. However, mean reports of childhood SES differed by sex and race, such that men reported significantly higher childhood SES than women ($t(1311) = 3.56$, $p < 0.001$) and Whites reported significantly higher childhood SES than Blacks ($t(312) = 8.34$, $p < 0.001$). In terms of cardiometabolic health, on average, participants tended to be overweight, yet showed healthy metabolic and cardiovascular profiles at midlife. Although average IL-6 was not found to have significant sex or race differences, average CRP was significantly higher for women than men ($t(1354) = -2.61$, $p = 0.009$) and for Blacks than Whites ($t(299) = -4.05$, $p < 0.001$). In

addition, men had significantly more adverse cardiometabolic profiles on all measures than women, and Black participants showed more adverse cardiometabolic profiles on the adiposity and blood pressure measures than White participants.

Table 3 contains the Pearson correlations for all continuous variables as they were included in subsequent models (i.e., transformed and Winsorized when necessary). Childhood SES was found to correlate significantly with adult SES ($r = 0.26, p < 0.001$), family relationships ($r = 0.11, p < 0.001$), IL-6 ($r = -0.15, p < 0.001$), CRP ($r = -0.15, p < 0.001$), BMI ($r = -0.09, p = 0.002$), triglycerides ($r = -0.06, p = 0.04$), systolic blood pressure ($r = -0.12, p < 0.001$), diastolic blood pressure ($r = -0.12, p < 0.001$), and physical activity ($r = 0.08, p = 0.006$) in the expected directions. Note that childhood SES at ages 5 and 10 were highly correlated ($r = 0.92, p < 0.001$). Adult SES also showed weak yet significant correlations with all of these variables except BMI and triglycerides, and additionally was significantly correlated with sleep ($r = 0.11, p = 0.009$) and alcohol use ($r = 0.07, p = 0.023$). Family relationships had a positive correlation with glucose ($r = 0.05, p = 0.049$) but was not significantly correlated with any other cardiometabolic risk indicators or health behaviors. Conversely, IL-6 and CRP both showed significant positive correlations with all cardiometabolic risk indicators and negative correlations with physical activity. Likewise, cardiometabolic risk indicators were significantly and positively correlated with one another and negatively correlated with physical activity.

3.2 Formation of Cardiometabolic Risk Latent Variable

Cardiometabolic risk was modeled as a second-order latent variable using a confirmatory factor analysis, controlling for demographic covariates at the level of the observed variables

(Figure 3). The four first-order latent variables, adiposity, dyslipidemia, insulin resistance, and blood pressure, were each formed from two observed variables. Adiposity was constructed from BMI ($\lambda = 0.89$) and waist circumference ($\lambda = 0.86$); dyslipidemia was constructed from triglycerides ($\lambda = 0.67$) and HDL ($\lambda = 0.47$); insulin resistance was constructed from glucose ($\lambda = 0.43$) and insulin ($\lambda = 0.74$); and blood pressure was constructed from systolic ($\lambda = 0.74$) and diastolic ($\lambda = 0.79$) blood pressure. The first-order latent variables were then used to form the second-order cardiometabolic risk latent variable, with adequate factor loadings for adiposity ($\lambda = 0.78$), dyslipidemia ($\lambda = 0.72$), insulin resistance ($\lambda = 0.94$), and blood pressure ($\lambda = 0.49$). Notably, the cardiometabolic risk model met absolute and incremental goodness of fit criteria based on the CFI (0.99), RMSEA (0.04), and SRMR (0.01) indices (Kline, 2005).

3.3 Direct and Indirect Effects of Childhood SES on Cardiometabolic Risk

Next, path analyses (i.e., structural model) were conducted incorporating the cardiometabolic risk latent variable (i.e., measurement model) to test the direct and indirect effects of childhood SES on cardiometabolic risk in a single structural equation model (Figure 4). Again, model fit was good according to the CFI (0.96), RMSEA (0.05), and SRMR (0.03) indices, so parameter estimates were evaluated. The total effect, accounting for both the direct effect and total indirect effect of childhood SES on adult cardiometabolic risk, was significant ($\beta = -0.07$, CI [-0.040, -0.003], $p = 0.020$) in the final model adjusted for all covariates (Table 4). However, the direct association between childhood SES and adult cardiometabolic risk was non-significant in all steps of covariate adjustment (Table 4). Note that the direct effect of adult SES on cardiometabolic risk was also non-significant (Figures 6 and 7).

The indirect effects of childhood SES on adult cardiometabolic risk via IL-6 and CRP were also examined in the final model adjusted for all covariates (Table 4). For the IL-6 pathway, lower childhood SES was marginally associated with higher levels of adult IL-6 ($\gamma = -0.06$, CI [-0.007, 0.000], $p = 0.045$), and higher levels of IL-6 significantly predicted greater cardiometabolic risk ($\beta = 0.20$, CI [0.694, 1.301], $p < 0.001$). IL-6 was found to explain a marginally significant proportion of the relationship between childhood SES and cardiometabolic risk, as evidenced by its specific indirect effect ($\beta = -0.01$, CI [-0.007, 0.000], $p = 0.055$). A similar pattern of results was observed for the CRP pathway. Childhood SES was found to have a significant negative association with CRP in adulthood ($\gamma = -0.11$, CI [-0.012, -0.004], $p < 0.001$), and in turn, higher levels of CRP significantly predicted greater cardiometabolic risk ($\beta = 0.43$, CI [1.428, 1.965], $p < 0.001$). The specific indirect effect of CRP in the association between childhood SES and adult cardiometabolic risk was also significant ($\beta = -0.05$, CI [-0.021, -0.006], $p < 0.001$). In addition, the total indirect effect of the IL-6 and CRP pathways in the final model was significant ($\beta = -0.06$, CI [-0.026, -0.008], $p < 0.001$), indicating that considered together, markers of adult inflammation contribute to the association between childhood SES and cardiometabolic risk. Notably, the pattern of results did not change with the addition of adult health behavior covariates.

3.4 Moderation by Family Relationship Quality

Next, moderation of the associations between childhood SES and adult IL-6, CRP, and cardiometabolic risk by childhood family relationships was tested (Figure 5). In the moderated mediation model adjusted for demographic covariates and adult SES, family relationship quality was not found to have significant direct or moderating effects on either inflammatory mediator or

cardiometabolic risk (Table 5).

3.5 Sensitivity Analyses

When all models were tested again excluding individuals who experienced the absence of one or both biological parents prior to age 12 (i.e., not growing up in a two-parent household with both biological parents; $n = 256$), no differences emerged in the pattern of results (Figure 8). The significant indirect effect of CRP and total effect of childhood SES on adult cardiometabolic risk were retained.

Next, childhood SES was modeled using the retrospective reports at age 5 and age 10 separately, rather than a mean score, to determine whether socioeconomic disadvantage at either age distinctly predicts adult cardiometabolic risk (Figures 9 and 10). Childhood SES at age 5 was found to have a significant total effect on adult cardiometabolic risk in the model adjusted for all covariates ($\beta = -0.09$, CI $[-0.043, -0.007]$, $p = 0.007$), but the total effect on adult cardiometabolic risk was only marginally significant for childhood SES at age 10 ($\beta = -0.06$, CI $[-0.036, 0.000]$, $p = 0.052$).

A composite measure of adult inflammation (i.e., average of the IL-6 and CRP z-scores) was created to test mediation via a single inflammatory score because IL-6 and CRP were significantly correlated ($r = 0.37$) and contributed similarly to the association between childhood SES and adult cardiometabolic risk in the main analyses (Figure 11). Contrary to the prior findings, adult inflammation did not have a significant indirect effect, nor was it significantly predicted by childhood SES. However, there was a significant positive association between adult inflammation and adult cardiometabolic risk ($\beta = 0.16$, CI $[0.154, 0.790]$, $p = 0.004$), and the total effect of

childhood SES on adult cardiometabolic risk was significant too ($\beta = -0.07$, CI [-0.038, -0.003], $p = 0.020$). Furthermore, the direct effect of childhood SES on adult cardiometabolic risk became significant ($\gamma = -0.07$, CI [-0.037, -0.002], $p = 0.033$) when modeling the inflammatory markers together as a single indirect pathway.

In an additional sensitivity analysis, adiposity was modeled as a mediator rather than a component of cardiometabolic risk. In this model, adiposity was removed from the cardiometabolic risk second-order latent variable, and a composite measure of adiposity (i.e., average of the BMI and waist circumference z-scores) was added as a third potential mediator (Figure 12). To attain adequate model fit, the covariance between adiposity and both IL-6 and CRP were added. The resulting model fit according to the CFI (0.94), RMSEA (0.06), and SRMR (0.03) indices. The specific indirect effect of adiposity was marginally significant ($\beta = -0.03$, CI [-0.001, 0.000], $p = 0.068$). More specifically for adiposity, the association between childhood SES and adult adiposity was marginally significant ($\gamma = -0.05$, CI [-0.007, 0.000], $p = 0.066$), while adult adiposity showed a significantly strong positive relationship with adult cardiometabolic risk ($\beta = 0.67$, CI [0.155, 0.202], $p < 0.001$). In this model accounting for adiposity, IL-6, and CRP as potential mediators, only the CRP pathway was found to have a significant specific indirect effect on the association between childhood SES and adult cardiometabolic risk ($\beta = -0.02$, CI [0.000, 0.000], $p = 0.003$). The indirect effect of IL-6 was non-significant when introducing adiposity as a third potential mediator.

In terms of moderation, potential differences in results by sex and race were examined. First, sex- and race-specific versions of the cardiometabolic risk second-order latent variable were formed (Figures 13 and 14). These measurement models were not found to have metric invariance, meaning that the cardiometabolic risk factor loadings were significantly different between men

and women (χ^2 difference (7) = 26.54, $p < 0.001$) and between non-Hispanic Whites and Blacks (χ^2 difference (7) = 14.69, $p = 0.040$). Thus, further analyses using the full structural equation model are not comparable across sexes and races. However, within-group analyses were conducted by estimating the full structural equation model separately by sex and race. The total effect of childhood SES on adult cardiometabolic risk was significant for women ($\beta = -0.11$, CI [-0.064, -0.007], $p = 0.015$) but not men ($\beta = 0.01$, CI [-0.021, 0.024], $p = 0.895$), and for Whites ($\beta = -0.10$, CI [-0.045, -0.008], $p = 0.006$) but not Blacks ($\beta = 0.02$, CI [-0.060, 0.073], $p = 0.845$). The effect sizes for all pathways modeled separately by sex and race are shown in Figures 15 and 16, but it remains unclear whether these trends are significantly different between women and men and between Blacks and Whites because we were unable to directly compare the sex- and race-specific models.

Moderation of the association between inflammation and cardiometabolic risk by family relationship quality was also tested, but found to be non-significant. Finally, family cohesion and conflict were included separately as moderators of the relationships between childhood SES and IL-6, CRP, and cardiometabolic risk. Consistent with the main analyses, neither family cohesion nor family conflict were found to have significant direct or indirect effects on these adult health outcomes.

4.0 Discussion

The aim of this study was to determine whether the relationship between childhood socioeconomic disadvantage and risk for cardiometabolic disease in adulthood is mediated by adult inflammation and buffered by cohesive family relationships in a sample of healthy midlife adults. It was hypothesized that childhood SES would be inversely related to cardiometabolic risk and circulating levels of inflammatory markers, IL-6 and CRP. In line with these first two hypotheses, individuals from socioeconomically disadvantaged backgrounds in childhood showed greater risk for cardiometabolic disease and higher circulating levels of CRP and to a lesser extent IL-6 (marginally significant) at midlife than individuals who reported higher childhood SES. The third hypothesis was that adult IL-6 and CRP would partly explain the statistical inverse association between childhood SES and cardiometabolic risk. As expected, findings indicated that the relationship between childhood SES and adult cardiometabolic risk was partially explained (i.e., statistically mediated) by systemic inflammation, in particular by circulating levels of CRP. Low childhood SES was associated with higher levels of IL-6 and CRP at midlife, which in turn predicted greater concurrent risk for cardiometabolic disease. Lastly, it was hypothesized that greater family cohesion relative to conflict in childhood would moderate the relationships between childhood socioeconomic disadvantage and adult inflammation and cardiometabolic risk. However, contrary to expectations, no evidence was found for the buffering of these socioeconomic health disparities by cohesive family relationships during childhood.

Findings that low childhood SES is associated with heightened cardiometabolic risk in midlife are consistent with socioeconomic disparities in cardiometabolic health reported in prior work (Galobardes et al., 2006; Lawlor et al., 2006; Maty et al., 2008). Indeed, findings from both

retrospective and prospective studies indicate that childhood socioeconomic disadvantage (e.g., low parental education or family income) is associated with the metabolic syndrome at midlife (Miller et al., 2011; Puolakka et al., 2016). In addition to examining preclinical indicators of cardiometabolic risk, several other studies have found childhood SES to predict clinical cardiometabolic outcomes, namely type 2 diabetes (Maty et al., 2008; Puolakka et al., 2016) and cardiovascular-related mortality (Lawlor et al., 2006). Consistent with prior work (Puolakka et al., 2016; Liu et al., 2017; Pinto Pereira et al., 2019), the current findings show that the relationship between childhood SES and adult cardiometabolic risk was independent of demographics, adult SES, and adult health behaviors. In sum, although various indices of childhood SES and cardiometabolic risk have been examined, a negative association between childhood socioeconomic status and adult cardiometabolic risk is well-established and consistent with the current study's finding.

Childhood socioeconomic disadvantage also related to higher circulating levels of CRP, a well-established and reliable marker of systemic inflammation, in the current sample. This result is corroborated by previous empirical studies that show an inverse relationship between retrospectively reported parental educational attainment and midlife CRP (Taylor et al., 2006; Phillips et al., 2009). Notably, meta-analyses examining the link between childhood SES and CRP that have included both prospective and retrospective studies and a broader range of socioeconomic indices also find that adults from disadvantaged socioeconomic backgrounds during childhood have higher levels of circulating CRP than those of higher childhood SES (Liu et al., 2017; Pinto Pereira et al., 2019). In contrast, the relationship between childhood SES and adult IL-6 is more equivocal. While some studies show an inverse relationship between childhood SES and adult IL-6 (Carroll et al., 2011; Chen et al., 2011), others do not (Loucks et al., 2010;

Packard et al., 2011; Dich et al., 2015). In the current study, childhood SES and adult IL-6 showed the expected inverse relation in univariate analysis, but this association became attenuated to a marginal trend after accounting for covariates in multivariate analysis. The stronger and more consistent effects for CRP may relate to its greater stability across time and lack of diurnal variability (Pearson et al., 2003). Levels of IL-6 are also more reactive to environmental exposures, such as psychological stress (Marsland, Walsh, Lockwood, & John-Henderson, 2017) and likely more influenced by concurrent SES, which was demonstrated in the current study and in a recent meta-analysis (Milaniak & Jaffee, 2019).

Adult inflammation was found to explain a modest yet significant portion of the relationship between childhood SES and adult cardiometabolic risk, as evidenced by the indirect effect of CRP ($\beta = -0.05$) and a similar, though marginally significant, pattern for IL-6 ($\beta = -0.01$). The individual associations between childhood SES, inflammation, and cardiometabolic risk are consistent with prior research on the biological embedding of childhood disadvantage via pro-inflammatory phenotypes (McDade, 2005) and the role of inflammation in the pathogenesis of cardiometabolic risk (Dandona et al., 2004; Marsland et al., 2010). However, the current study is one of the first to demonstrate that adult inflammation may account for variance in the relationship between childhood SES and adult cardiometabolic risk. Although inflammation has been theorized to mediate associations between childhood adversity and adult cardiovascular disease (Slopen, Koenen, & Kubzansky, 2012), to our knowledge, mediation via inflammatory markers has not been tested before. In the current study, when considering both direct and indirect effects of childhood SES on adult cardiometabolic risk in a single model, only the indirect effect of childhood SES to adult cardiometabolic risk via CRP was significant, supporting the possibility that

childhood disadvantage contributes to physical health risk via levels of systemic inflammation in adulthood.

Notably, CRP showed a significant association with socioeconomic disparities in cardiometabolic health, while IL-6 only showed a marginal effect. This raises the possibility that CRP and IL-6 should be examined individually considering their distinct biological properties. As noted above, CRP shows greater diurnal stability than IL-6 (Gudewill et al., 1992; Bauer et al., 1994) and is produced by fewer cell types (Kershaw & Flier, 2004). For instance, in addition to being involved in the innate immune response, IL-6 is also secreted by adipose tissue, with approximately 30% of circulating IL-6 thought to originate from adipocytes and macrophages resident within adipose tissue (Mohamed-Ali et al., 1997; Wisse, 2004). Consequently, adiposity is often considered an important contributor to both systemic inflammation and cardiometabolic risk (Makki, Froguel, & Wolowczuk, 2013; Kahn, Wang, & Lee, 2019). Indeed, current sensitivity analyses considering adiposity as a mediator rather than a component of cardiometabolic risk found a strong association between adiposity and cardiometabolic risk, but childhood SES did not predict adult adiposity in the current sample. The current results support the possibility that CRP plays a role in socioeconomic disparities in cardiometabolic risk, possibly by providing a more reliable marker of systemic levels of inflammation. Although IL-6 and adiposity are also associated with cardiometabolic risk, their potentially mediating role in the relationship between childhood SES and adult cardiometabolic health is more ambiguous.

Considered together, the long-lasting direct and indirect associations between childhood SES and midlife cardiometabolic risk emphasize the importance of early life socioeconomic disadvantage in particular as a risk factor for cardiometabolic disease. Although adult SES, smoking status, and physical activity were significantly associated with circulating levels of

inflammatory markers and cardiometabolic health, relationships between childhood SES, inflammation, and cardiometabolic risk were largely independent of adult SES and health behaviors. The current results are consistent with prior empirical work and theoretical frameworks that suggest the biological embedding of socioeconomic adversity begins in childhood and its influence on cardiometabolic health extends into midlife (McDade, 2005; Shonkoff et al., 2009). Among other biological mechanisms, it has been proposed that early life adversity programs a pro-inflammatory phenotype, characterized by heightened circulating and stimulated levels of inflammation in childhood that persist throughout adolescence and into adulthood (Azad et al., 2012; Miller & Chen, 2013). To date, systematic reviews and meta-analyses examining early life adversity in relation to pro-inflammatory phenotypes prior to adulthood have acknowledged mixed findings in the literature; but, conclude that there is a modest positive association from infancy through adolescence (Slopen, Koenen, & Kubzansky, 2012; Kuhlman, Horn, Chiang, & Bower, 2019). Also in line with hypotheses that experiences in early childhood become embedded in the phenotype, the current study found that when childhood SES at ages 5 and 10 were modeled separately, only childhood SES at age 5 had a significant total effect on cardiometabolic risk. This suggests that socioeconomic disadvantage earlier in childhood (i.e., at age 5) might be driving the inverse association between childhood SES (i.e., average of SES at ages 5 and 10) and adult cardiometabolic risk in the current study, which future research might investigate more rigorously (i.e., prospectively) to elucidate the role of developmental timing of socioeconomic disadvantage.

Finally, inconsistent with the hypothesis that family relationships would buffer the risk for cardiometabolic disease associated with childhood socioeconomic disadvantage, the quality of childhood family relationships did not attenuate socioeconomic health disparities in the current sample. This finding does not align with the results of prior studies, which have shown that positive

aspects of family relationships (e.g., maternal warmth and sensitivity) buffer against the health risks typically associated with early socioeconomic disadvantage (Miller et al., 2011; Chen et al., 2017; Farrell et al., 2017). The lack of support for the Developmental Stress Buffering Hypothesis, proposed by Chen, Brody, and Miller (2017), in the current sample might be explained by differences between the current study and previous research in how family relationships are operationalized. Most prior research has examined parental characteristics, often maternal warmth or sensitivity, whereas our study used a measure of the entire nuclear family's relationships, including relationships with siblings and siblings' relationships with parents. It is possible that particular relationships within the family environment, namely parent-child relationships, are more closely related to biological development and biological embedding of adversity than others because of their proximal role in ensuring the child's early needs are met (e.g., providing nutrition and safety). The family environment measure used in the current study did not distinguish between biologically-salient developmental periods and developmentally-meaningful changes in family dynamics from birth through 18 years of age, which might have contributed to the lack of support for the buffering of socioeconomic health disparities via family relationships in the current sample.

4.1 Methodological Strengths and Limitations

The current study is among the first to test indirect effects of adult inflammation in the relationship between childhood SES and adult cardiometabolic risk, and the current findings are bolstered by a few key strengths. The large, community sample of relatively healthy midlife adults that were examined suggests that the current results are externally valid and generalizable to other non-clinical populations. Additionally, this study simultaneously examined CRP and IL-6 as two

distinct inflammatory mediators, which is theoretically important because they are often considered together but their circulating levels are not solely derived from the immune system (e.g., IL-6, but not CRP, is secreted by adipose tissue). Another methodological strength was the modeling of adult cardiometabolic risk as a second-order latent variable, which reduced the potential influence of measurement error in its estimation.

However, the current results should be interpreted in the context of a few methodological limitations. First, participants were asked to retrospectively report on their childhood SES and childhood family environment. Although some studies suggest that retrospective and prospective reports are similarly reliable and valid means of measuring nonspecific childhood adversities (Hardt & Rutter, 2004; McKenzie & Carter, 2009), it is widely accepted that retrospective reporting is subject to recall bias (Hardt & Rutter, 2004). Second, specific developmental periods were not captured in the current study, unlike prior work which has predominantly focused on experiences in infancy and other stages of early childhood (i.e., toddler and preschool periods) in relation to later health outcomes. Theoretical frameworks such as the Developmental Origins of Health and Disease posit that early family relationships have greater influence on health trajectories than those in later childhood and adolescence because of early life sensitivity to adversity and its biological costs (McDade, 2005; Shonkoff et al., 2009), including altered SAM and HPA responses to stress and the development of glucocorticoid resistant, pro-inflammatory phenotypes (Repetti et al., 2002; Miller et al., 2009; Miller & Chen, 2010; Miller & Cole, 2010). Third, the study's cross-sectional design did not allow for conclusions about the temporal nature of the relationships between adult inflammatory markers and cardiometabolic risk; therefore, mediation of socioeconomic disparities in cardiometabolic risk via CRP cannot be inferred. Rather, it is likely that associations between inflammation and risk for cardiometabolic disease at midlife

are bidirectional, such that inflammation presages cardiometabolic risk factors (Dandona et al., 2004; Marsland et al., 2010) but cardiometabolic risk factors and conditions (e.g., adiposity and atherosclerosis) also elicit an inflammatory response (Hansson, Robertson, & Söderberg-Nauclér, 2006).

4.2 Future Directions

While the current study adds to the prior literature on socioeconomic disparities in adult inflammatory and cardiometabolic health, more rigorous examinations of the long-term link between socioeconomic disadvantage and risk for cardiometabolic disease are needed. Future studies could approach the investigation of socioeconomic health disparities in a prospective manner to avoid the bias inherent in retrospective report and more accurately capture exposures at different developmental stages and their consequences for physical health in midlife. Such research could include repeated multi-method assessment of the family environment over time, permitting the examination of different family relationships as moderators during particular developmental stages, for example early childhood compared to adolescence, the latter age period a time when greater parent-child might be expected. Additionally, distinguishing between family relationships across developmental stages would allow future researchers to disentangle the relative importance of cohesive family environments in buffering socioeconomic health disparities across these stages.

In addition, further insight into the mediating role of inflammation could be gleaned by including a wider collection of inflammatory markers. To this end, future studies could use inflammatory panels to examine whether the patterns of association with childhood SES and midlife cardiometabolic risk seen with CRP is similar across other markers of inflammation, such

as IL-1 and tumor necrosis factor (TNF)- α . Cytokines such as TNF- α play a key role in the pro-inflammatory response, whereas IL-6 is involved in a wider range of immune processes, so research equipped to assess multiple inflammatory markers simultaneously could elucidate their relative contributions to the link between childhood socioeconomic disadvantage and adult cardiometabolic risk.

Finally, additional research is needed to better understand sex and race differences in cardiometabolic disease and its underlying risk factors. The current results indicate that cardiometabolic risk profiles (i.e., the degree to which individual components—adiposity, dyslipidemia, insulin resistance, and blood pressure—contribute to overall cardiometabolic risk) differed by both sex and race based on the variant factor loadings for cardiometabolic risk. Unique clustering of the metabolic syndrome components by sex (Kuk & Ardern, 2010) and race (Gurka, Lilly, Oliver, & DeBoer, 2014) has been previously reported, although the clinical implication of these differences remains unclear. Furthermore, although comparisons could not be made in the current study, it is quite possible that the effects of childhood SES on adult inflammation and cardiometabolic risk also differ by sex and race. To this end, we found that when examined separately by sex and race, childhood SES was predictive of adult cardiometabolic risk for women only and Whites only. While future studies are necessary to conduct between-group comparisons, the preliminary finding that socioeconomic disparities in cardiometabolic risk was evident for Whites but not Blacks is consistent with a broader literature that indicates racial health disparities are present irrespective of socioeconomic status (Braveman, Cubbin, Egerter, Williams, & Pamuk, 2010; Williams, Priest, & Anderson, 2016). It is possible that for Blacks, other forms of psychosocial adversity (e.g., personally experienced and institutionally pervasive racism) are stronger predictors of cardiometabolic risk than socioeconomic status (Phelan & Link, 2015). In

terms of sex differences in risk for cardiometabolic disease, prior work also corroborates the preliminary finding that women are especially susceptible to increased risk for the metabolic syndrome following socioeconomic disadvantage in childhood (Huang et al., 2019). Other research suggests that the relationship between early socioeconomic disadvantage and adult cardiometabolic risk is mediated by physical activity and diet for men, while these health behaviors do not explain the association for women (Lee, Tsenkova, Boylan, & Riff, 2018), alluding to the potential importance of health behavior intermediates for men in particular.

4.3 Conclusion

Collectively, the current findings suggest that SES in early life has pervasive, long-lasting associations with inflammatory and cardiometabolic health in adulthood, and that socioeconomic disparities in cardiometabolic risk may relate, in part, to the impact of systemic inflammation at midlife. More generally, these results allude to the importance of supporting low SES families to lessen children's risk for later inflammatory and cardiometabolic disease in adulthood. Considering the prevalence of cardiometabolic diseases and current socioeconomic disparities, such efforts could be vital for promoting life-long health.

5.0 Tables

Table 1. Descriptive Statistics for Raw Data

Variable	Total Sample (N=1,359)		AHAB I (N=969)		AHAB II (N=390)		p
	N	M (SD) or %	N	M (SD) or %	N	M (SD) or %	
Age	1,359	44.36 (6.89)	969	44.81 (6.72)	390	43.23 (7.17)	<0.001
Sex (% female)	1,359	52.24%	969	51.70%	390	53.59%	0.569
Race (% Blacks)	1,359	16.92%	969	16.82%	390	17.18%	0.937
Parents (% 2-parent family)	1,358	81.15%	969	82.15%	389	78.66%	0.159
<i>Socioeconomic Status</i>							
Mean Childhood SES	1,324	41.47 (13.39)	946	40.15 (13.17)	378	44.78 (13.38)	<0.001
Childhood SES at age 5	1,290	41.04 (13.69)	922	39.73 (13.39)	368	44.32 (13.89)	<0.001
Childhood SES at age 10	1,299	42.06 (13.65)	929	40.63 (13.45)	370	45.63 (13.52)	<0.001
Adulthood SES	1,356	43.76 (14.93)	969	41.67 (15.66)	387	48.99 (11.35)	<0.001
<i>Family Relationships</i>							
Cohesion	1,353	3.37 (8.07)	966	3.02 (8.18)	387	4.23 (7.73)	0.011
	1,353	17.67 (4.66)	966	17.47 (4.72)	387	18.18 (4.47)	0.010
Conflict	1,353	14.30 (4.33)	966	14.44 (4.42)	387	13.94 (4.08)	0.047
<i>Adult Inflammation</i>							
IL-6 (pg/mL)	1,352	2.13 (6.76)	964	2.52 (7.95)	388	1.16 (0.99)	<0.001
CRP (mg/L)	1,359	1.76 (1.95)	969	1.81 (1.96)	390	1.64 (1.90)	0.156

Table 1 (continued)*Adult Cardiometabolic Risk*

BMI (kg/m ²)	1,354	27.51 (5.43)	964	27.64 (5.56)	390	27.17 (5.08)	0.134
Waist Circumference (in)	1,358	36.26 (6.03)	968	36.39 (6.22)	390	35.95 (5.52)	0.199
Triglycerides (mg/dL)	1,352	119.45 (79.64)	963	122.71 (82.51)	389	111.37 (71.51)	0.012
HDL (mg/dL)	1,352	53.82 (14.31)	963	53.09 (14.06)	389	55.61 (14.79)	0.004
Glucose (mg/dL)	1,353	97.21 (16.38)	964	96.61 (18.01)	389	98.69 (11.26)	0.011
Insulin (μU/mL)	1,352	13.09 (6.90)	963	13.20 (7.02)	389	12.79 (6.57)	0.309
Systolic BP (mmHg)	1,356	116.50 (13.11)	969	116.90 (13.76)	387	115.47 (11.28)	0.049
Diastolic BP (mmHg)	1,356	76.85 (9.73)	969	78.62 (9.68)	387	72.41 (8.36)	<0.001

Adult Health Behaviors

Physical Activity (kcal/wk)	1,356	2,490.56 (1,912.85)	966	2,380.50 (1,796.26)	390	2,763.17 (2,153.27)	0.002
Sleep (hrs)	544	6.74 (0.95)	154	6.83 (0.88)	390	6.70 (0.97)	0.140
Smoking Status (% current)	1,324	16.62%	943	17.39%	381	14.70%	0.267
Alcohol Use (drinks/wk)	1,157	3.63 (6.63)	768	3.85 (7.45)	389	3.19 (4.57)	0.063

Table 2. Descriptive Statistics for Raw Data by Sex and Race

Variable	Black Women		White Women		Black Men		White Men	
	N	M (SD) or %	N	M (SD) or %	N	M (SD) or %	N	M (SD) or %
Age	140	44.84 (6.31)	570	44.58 (6.80)	90	44.22 (6.99)	559	44.04 (7.10)
Parents (% 2-parent family)	139	52.52%	570	87.72%	90	43.33%	559	87.66%
Socioeconomic Status								
Mean Childhood SES	125	35.16 (11.05)	565	41.34 (13.50)	81	34.99 (12.60)	553	43.98 (13.10)
Childhood SES at age 5	116	34.06 (11.17)	555	40.86 (13.77)	75	35.21 (13.21)	544	43.51 (13.41)
Childhood SES at age 10	115	36.57 (11.99)	561	41.69 (13.67)	76	35.01 (13.64)	547	44.57 (13.27)
Adulthood SES	140	39.72 (12.99)	568	43.36 (15.02)	90	31.58 (13.53)	558	47.15 (14.19)
Family Relationships	139	4.25 (7.54)	567	2.85 (8.79)	90	3.03 (6.81)	557	3.73 (7.58)
Cohesion	139	18.47 (4.38)	567	17.33 (5.04)	90	17.92 (4.14)	557	17.78 (4.37)
Conflict	139	14.22 (4.19)	567	14.48 (4.61)	90	14.89 (3.75)	557	14.04 (4.14)
Adult Inflammation								
IL-6 (pg/mL)	139	2.97 (8.57)	568	1.58 (1.79)	89	3.20 (8.28)	556	2.31 (8.85)
CRP (mg/L)	140	2.32 (2.12)	570	1.78 (2.04)	90	2.23 (2.37)	559	1.52 (1.67)
Adult Cardiometabolic Risk								
BMI (kg/m ²)	138	29.68 (6.74)	570	26.22 (5.46)	90	29.33 (5.91)	556	27.99 (4.56)
Waist Circumference (in)	140	36.40 (5.92)	569	33.08 (5.30)	90	39.41 (5.83)	559	38.96 (5.13)
Triglycerides (mg/dL)	139	87.85 (43.47)	568	102.02 (55.02)	90	114.93 (68.66)	555	145.93 (99.36)
HDL (mg/dL)	139	57.82 (13.24)	568	60.46 (14.38)	90	47.56 (11.30)	555	47.02 (11.04)
Glucose (mg/dL)	139	96.33 (13.32)	569	94.05 (14.83)	90	101.76 (27.61)	555	99.93 (15.53)
Insulin (μU/mL)	139	15.37 (8.90)	568	11.51 (5.43)	90	13.90 (7.51)	555	14.00 (7.22)
Systolic BP (mmHg)	140	120.31 (14.14)	568	111.42 (11.61)	90	122.54 (14.89)	558	119.73 (12.22)
Diastolic BP (mmHg)	140	78.11 (9.96)	568	73.62 (8.66)	90	81.06 (11.03)	558	79.14 (9.52)
Adult Health Behaviors								
Physical Activity (kcal/wk)	140	1,980.60 (1,968.92)	570	2,433.43 (1,892.56)	90	2,781.70 (2,351.91)	556	2,630.41 (1,816.82)
Sleep (hrs)	45	6.62 (1.19)	221	6.94 (0.91)	33	6.08 (1.20)	245	6.66 (0.84)

Table 2 (continued)

Smoking Status (% current)	139	24.46%	566	12.54%	88	46.59%	531	13.94%
Alcohol Use (drinks/wk)	123	1.63 (3.46)	477	2.48 (4.45)	77	3.91 (6.64)	480	5.24 (8.45)

Table 3. Correlations for Winsorized and Transformed Data

Variable	Correlations																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. Childhood SES	—																		
2. Adulthood SES	.26**	—																	
3. Family Relationships	.11**	.12**	—																
4. Family Cohesion	.10**	.11**	.91**	—															
5. Family Conflict	-.10**	-.11*	-.89**	.61**	—														
6. CRP	-.15**	-.08**	-.03	-.01	.04	—													
7. IL-6	-.15**	-.15**	-.03	-.02	.05	.37**	—												
8. BMI	-.09**	-.03	-.05	-.03	.07*	.43**	.32**	—											
9. Waist Circumference	-.04	-.02	-.01	-.00	.02	.37**	.32**	.85**	—										
10. Triglycerides	-.06*	-.01	.01	-.00	-.01	.24**	.18**	.33**	.43**	—									
11. HDL	.03	.00	-.03	-.03	.03	.18**	.19**	.31**	.40**	.42**	—								
12. Glucose	-.01	-.01	.05*	.06*	-.04	.12**	.13**	.31**	.40**	.29**	.17**	—							
13. Insulin	-.04	-.01	.02	.02	-.02	.31**	.22**	.52**	.54**	.38**	.33**	.35**	—						
14. Systolic BP	-.12**	-.07**	.04	.03	-.04	.19**	.18**	.36**	.43**	.27**	.17**	.22**	.29**	—					
15. Diastolic BP	-.12**	-.07*	.04	.02	-.04	.19**	.24**	.35**	.43**	.30**	.17**	.17**	.31**	.72**	—				
16. Age	-.15**	-.02	.09**	.04	-.12**	.02	.12**	.03	.09**	.11**	-.10**	.12**	.00	.18**	.17**	—			
17. Physical Activity	.08**	.10**	.00	-.01	-.01	-.11**	-.15**	-.16**	-.14**	-.14**	-.10**	-.09**	-.14**	-.06*	-.08**	-.02	—		
18. Sleep	.03	.11**	.02	.02	-.01	-.00	-.06	-.09*	-.16**	-.04	-.02	-.14**	-.16**	-.09*	-.08	-.08	.05	—	
19. Alcohol Use	.04	.07*	.01	.03	.01	-.05	-.02	-.06	.04	.09**	-.08**	.10**	-.09**	.07*	.04	.04	.09**	-.03	—

* $p < 0.05$, ** $p < 0.01$

Note. Pearson correlations were used for all variables, and calculations were based on pairwise deletion.

Table 4. Standardized Estimates for the Direct and Indirect Effects

	Model 1		Model 2		Model 3	
	<i>β</i> or <i>γ</i>	CI	<i>β</i> or <i>γ</i>	CI	<i>β</i> or <i>γ</i>	CI
Direct Effect						
Childhood SES → CMR	-0.01	[-0.020, 0.012]	-0.02	[-0.021, 0.012]	-0.02	[-0.021, 0.011]
Indirect Effect of IL-6						
Childhood SES → IL-6	-0.08	[-0.008, -0.001]	-0.06	[-0.007, 0.000]	-0.06	[-0.007, 0.000]
IL-6 → CMR	0.22	[0.775, 1.390]	0.22	[0.778, 1.394]	0.20	[0.694, 1.301]
Specific indirect effect (a1*b1)	-0.02	[-0.009, -0.001]	-0.01	[-0.008, 0.000]	-0.01	[-0.007, 0.000]
Indirect Effect of CRP						
Childhood SES → CRP	-0.12	[-0.013, -0.005]	-0.11	[-0.013, -0.004]	-0.11	[-0.012, -0.004]
CRP → CMR	0.43	[1.468, 2.015]	0.44	[1.468, 2.015]	0.43	[1.428, 1.965]
Specific indirect effect (a2*b2)	-0.05	[-0.022, -0.008]	-0.05	[-0.022, -0.007]	-0.05	[-0.021, -0.006]
Total Indirect Effect						
IL-6 & CRP ((a1*b1)+(a2*b2))	-0.07	[-0.029, -0.011]	-0.06	[-0.028, -0.009]	-0.06	[-0.026, -0.008]
Total Effect						
Direct & total indirect effects	-0.08	[-0.043, -0.005]	-0.08	[-0.042, -0.005]	-0.07	[-0.040, -0.003]

Note. Model 1 was adjusted for demographic covariates, Model 2 was additionally adjusted for adult SES, and Model 3 was further adjusted for adult health behaviors.

Table 5. Standardized Estimates for the Direct and Indirect Effects of Moderation Models

	Model 1		Model 2	
	<i>β</i> or <i>γ</i>	CI	<i>β</i> or <i>γ</i>	CI
Direct Effect				
Childhood SES → CMR	-0.01	[-0.020, 0.013]	-0.02	[-0.021, 0.012]
Family Relationship → CMR	-0.01	[-0.031, 0.023]	-0.01	[-0.032, 0.022]
SES x Family → CMR	-0.01	[-0.002, 0.002]	-0.01	[-0.002, 0.002]
Indirect Effect of IL-6				
Childhood SES → IL-6	-0.07	[-0.008, -0.001]	-0.06	[-0.007, 0.000]
Family Relationship → IL-6	-0.02	[-0.007, 0.003]	-0.02	[-0.007, 0.003]
SES x Family → IL-6	-0.02	[-0.001, 0.000]	-0.02	[-0.001, 0.000]
IL-6 → CMR	0.22	[0.774, 1.390]	0.22	[0.777, 1.394]
Specific indirect effect (a1*b1)	-0.02	[-0.009, -0.001]	-0.01	[-0.008, 0.000]
Indirect Effect of CRP				
Childhood SES → CRP	-0.11	[-0.013, -0.004]	-0.11	[-0.012, -0.004]
Family Relationship → CRP	-0.01	[-0.009, 0.005]	-0.01	[-0.008, 0.005]
SES x Family → CRP	-0.01	[-0.001, 0.000]	-0.00	[-0.001, 0.000]
CRP → CMR	0.43	[1.468, 2.017]	0.44	[1.469, 2.017]
Specific indirect effect (a2*b2)	-0.05	[-0.022, -0.007]	-0.05	[-0.022, -0.007]
Total Indirect Effect				
IL-6 & CRP ((a1*b1)+(a2*b2))	-0.07	[-0.029, -0.010]	-0.06	[-0.028, -0.009]
Total Effect				
Direct & total indirect effects	-0.08	[-0.042, -0.005]	-0.08	[-0.042, -0.004]

Note. Model 1 was adjusted for demographic covariates, Model 2 was additionally adjusted for adult SES, and Model 3 was further adjusted for adult health behaviors.

6.0 Figures

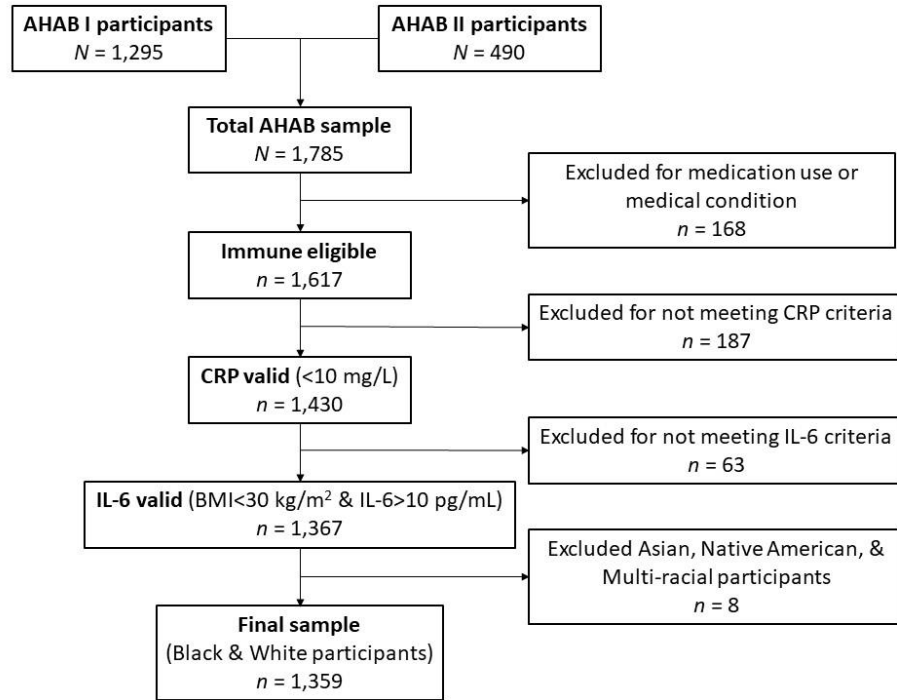
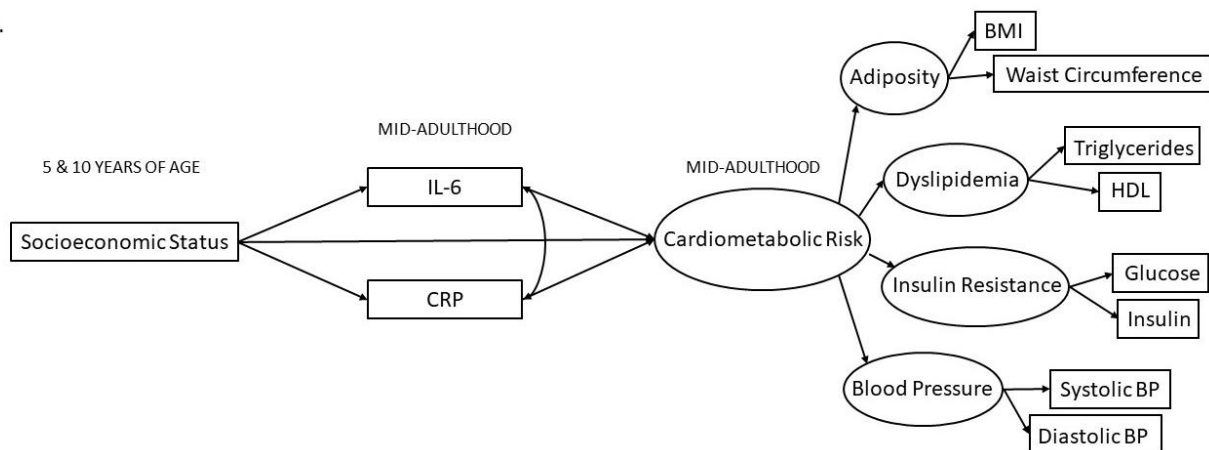


Figure 1. Flow chart of study inclusion and exclusion criteria.

A.



B.

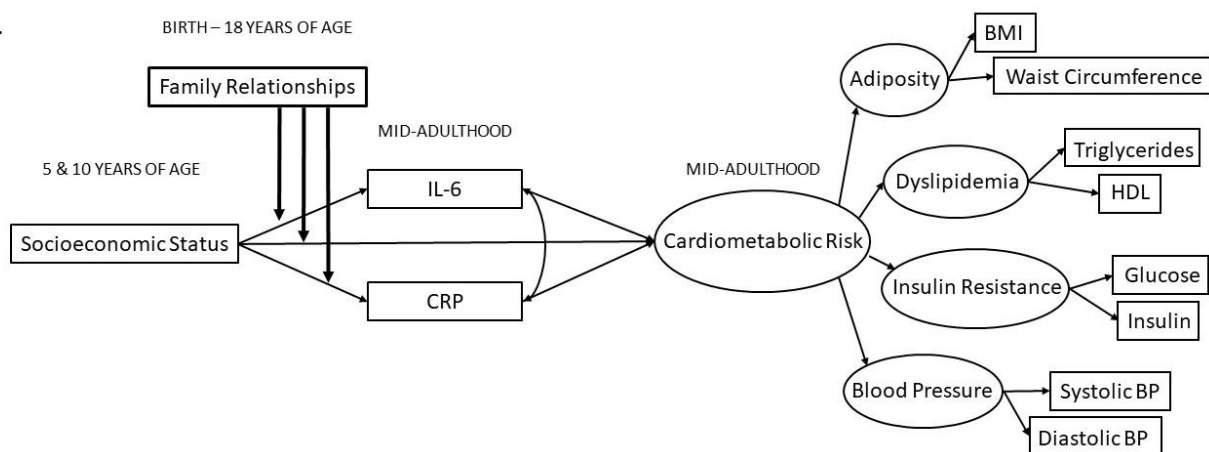


Figure 2. Simplified proposed models examining (a) multiple mediation and (b) moderated mediation.

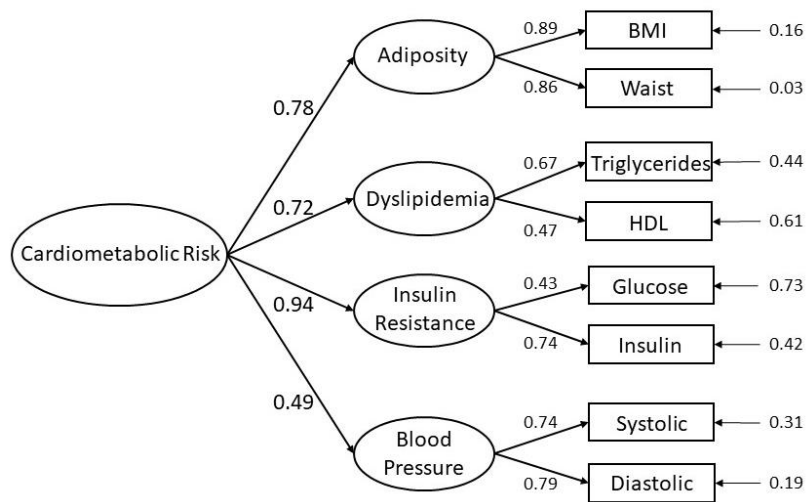


Figure 3. Cardiometabolic risk second-order latent variable adjusted for age, sex, race, and AHAB cohort at the level of the observed variables.

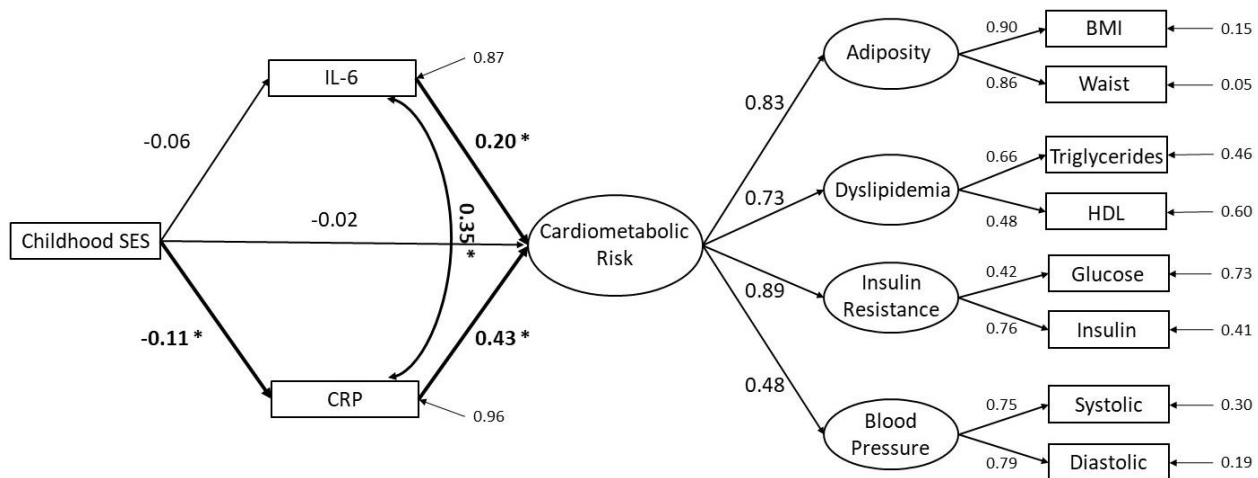


Figure 4. Direct and indirect effects of childhood SES on CMR via IL-6 and CRP, adjusted for demographic characteristics, adult SES, and adult health behaviors.

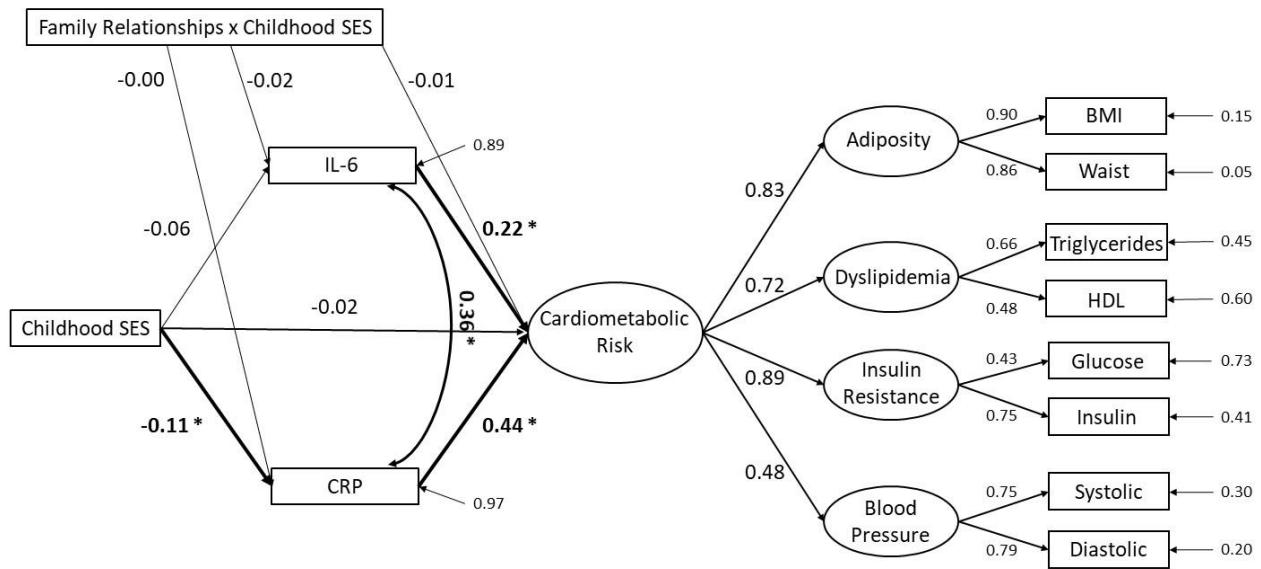


Figure 5. Childhood family relationships modeled as a moderator of the direct and indirect effects of childhood SES on CMR, adjusted for demographic characteristics and adult SES. Direct effect of family relationships on IL-6, CRP, and CMR not pictured for readability.

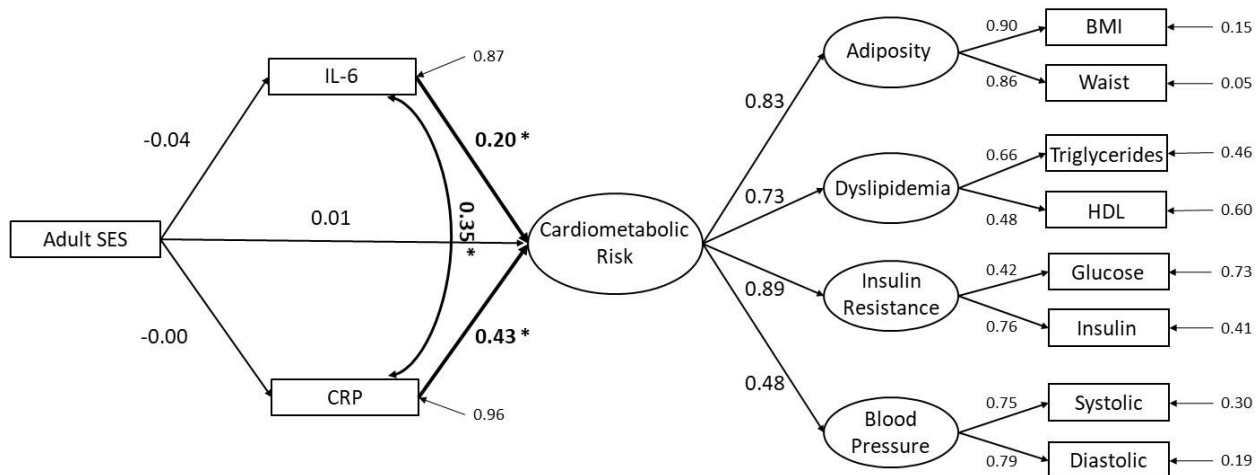


Figure 6. Direct and indirect effects of adult SES on CMR, adjusted for demographic characteristics, adult SES, and adult health behaviors.

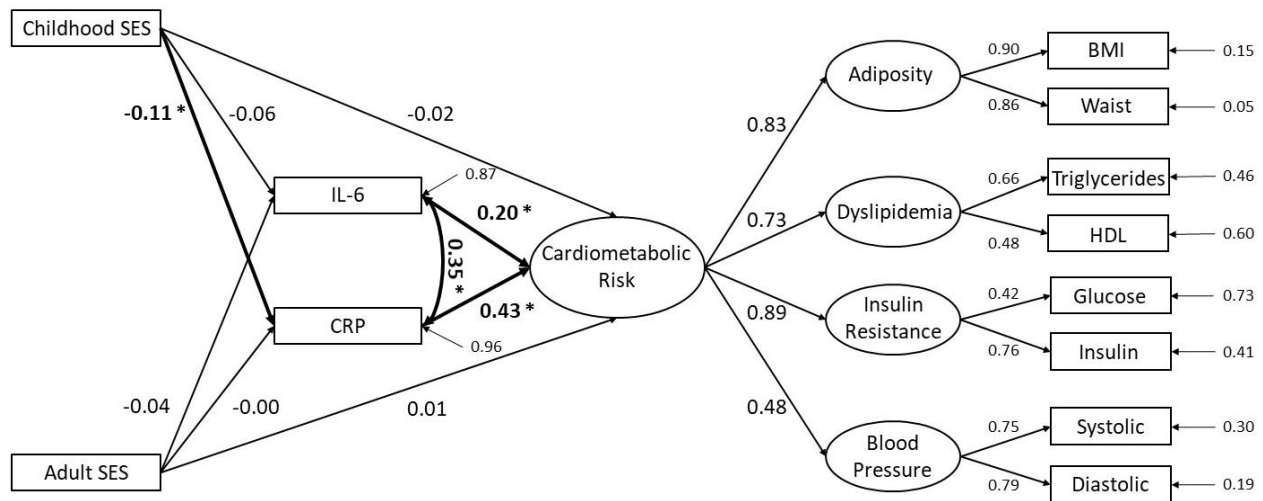


Figure 7. Childhood SES and adult SES pathways from the structural equation model (i.e., Figure 3 and Model 3 in Table 4) pictured together, accounting for demographic characteristics, adult SES, and adult health behaviors.

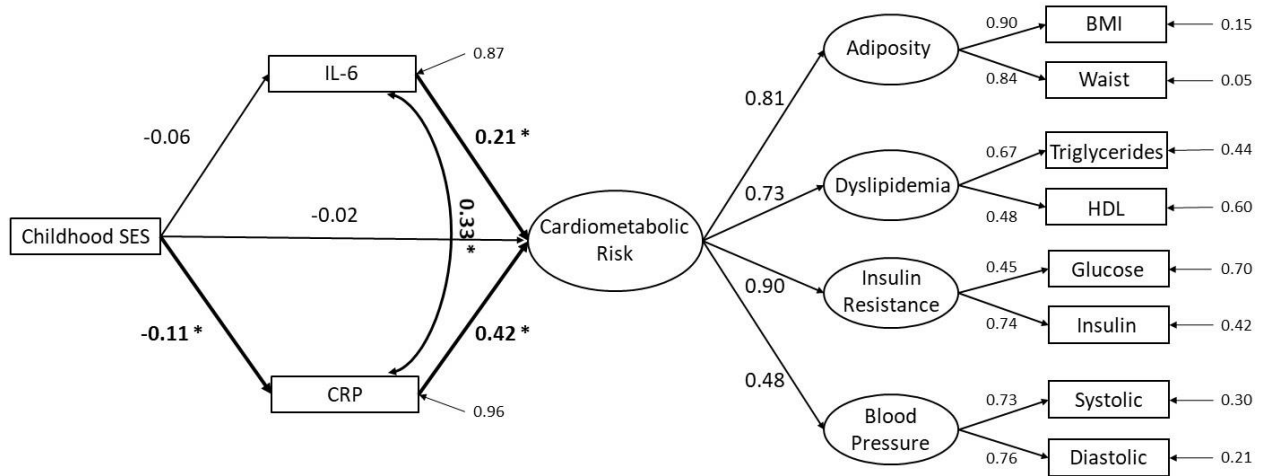


Figure 8. Model excluding those who experienced parental absence prior to age 12, adjusted for demographic characteristics, adult SES, and adult health behaviors.

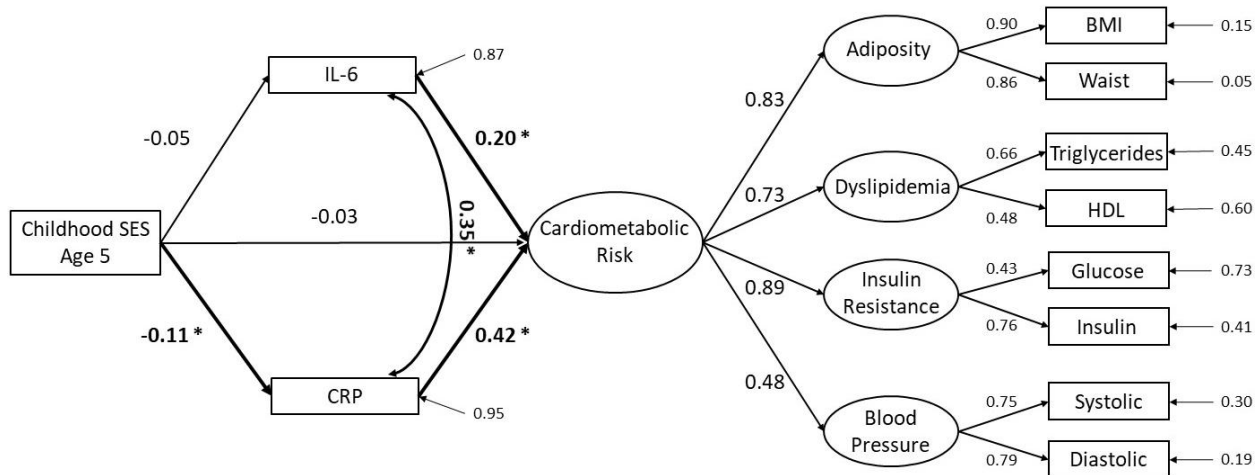


Figure 9. Direct and indirect effects of childhood SES at age 5 on adult CMR, adjusted for demographic characteristics, adult SES, and adult health behaviors.

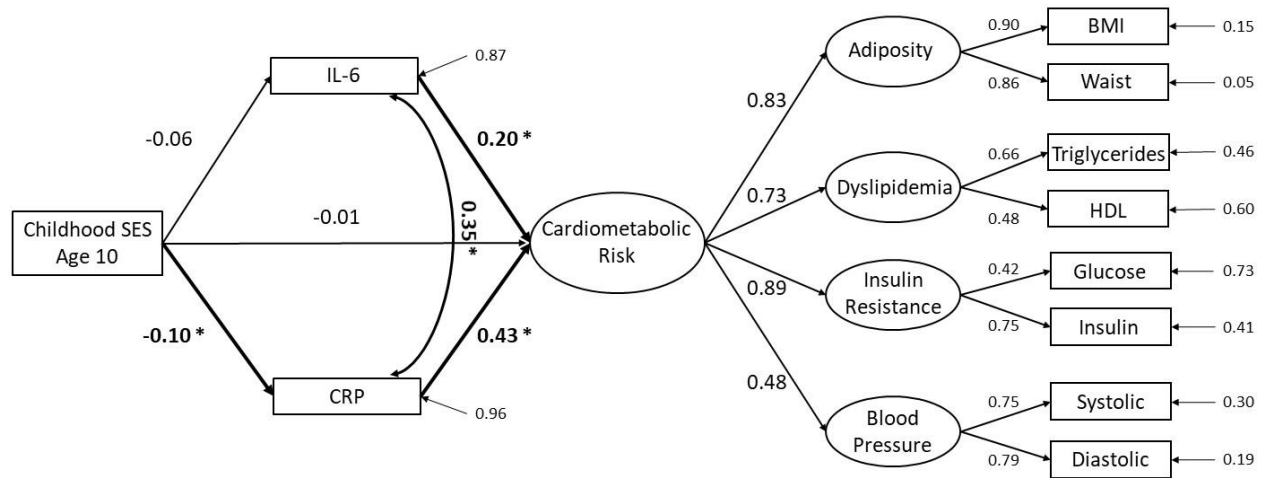


Figure 10. Direct and indirect effects of childhood SES at age 10 on adult CMR, adjusted for demographic characteristics, adult SES, and adult health behaviors.

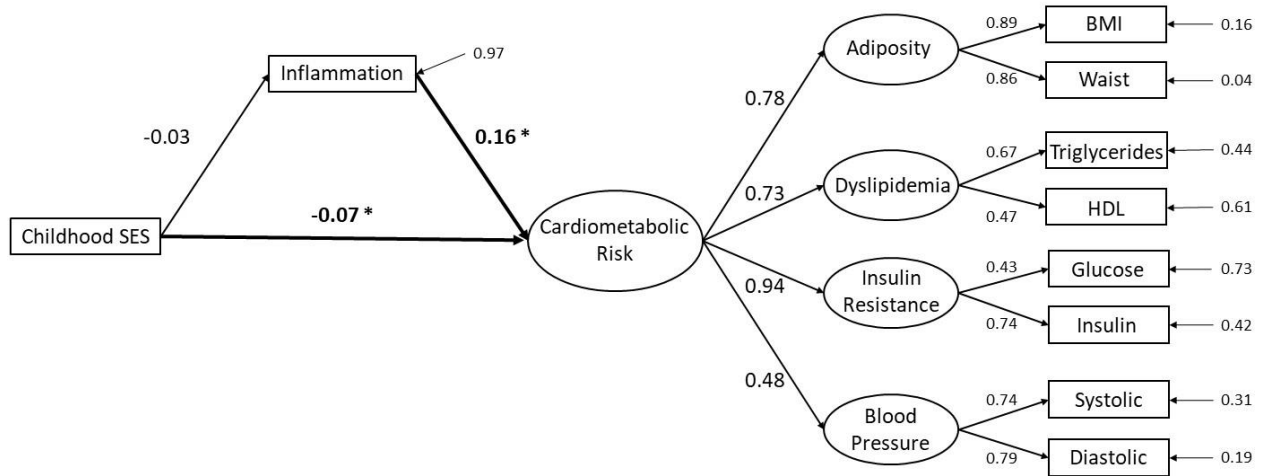


Figure 11. Indirect effect of childhood SES on adult CMR via a composite measure of adult inflammation (i.e., average of the IL-6 and CRP z-scores), adjusted for demographic characteristics, adult SES, and adult health behaviors.

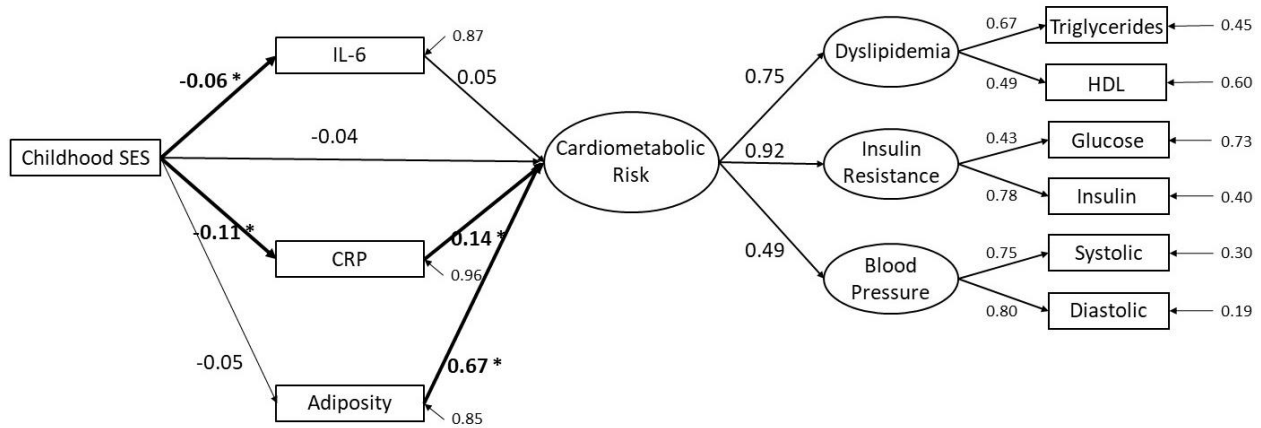


Figure 12. Indirect effect of childhood SES on adult CMR via a composite measure of adiposity (i.e., average of the BMI and waist circumference z-scores), IL-6, and CRP, adjusted for demographic characteristics, adult SES, and adult health behaviors. Covariance between mediators not pictured for readability: IL-6 and CRP (0.35^*), IL-6 and adiposity (0.30^*), CRP and adiposity (0.43^*).

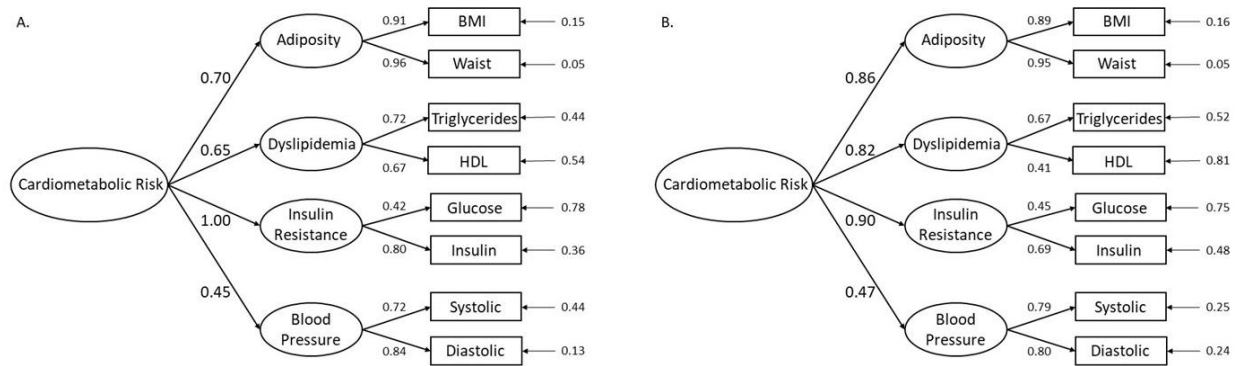


Figure 13. Sex-specific formation of the CMR second-order latent variable for (A) males (n = 649) and (B) females (n = 710). Both models were adjusted for age, race, and AHAB cohort at the level of the observed variables.

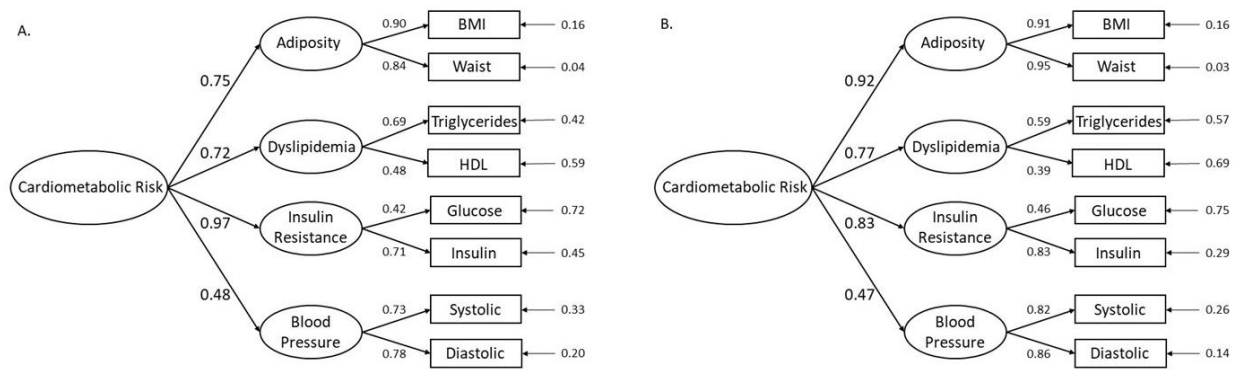


Figure 14. Race-specific formation of the CMR second-order latent variable for (A) Whites (n = 1129) and (B) Blacks (n = 230). Both models were adjusted for age, sex, and AHAB cohort at the level of the observed variables.

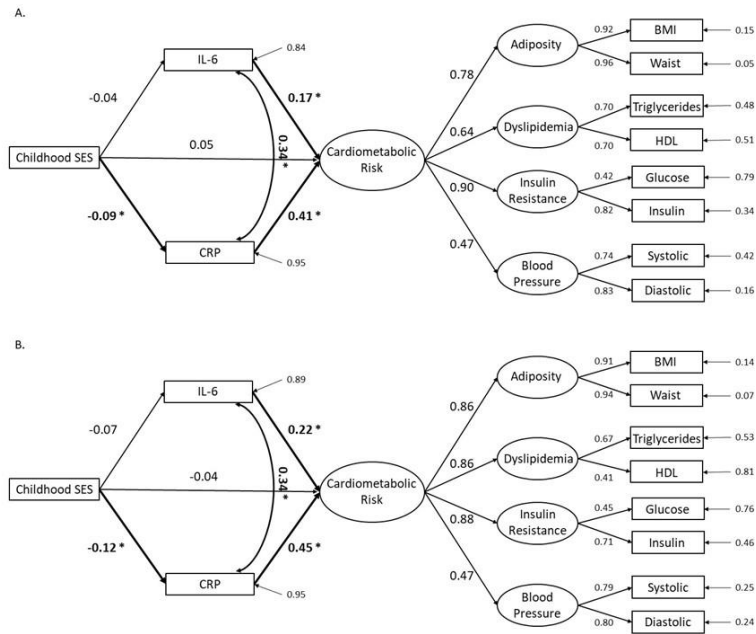


Figure 15. Sex-specific formation of the structural equation model for (A) males and (B) females, adjusted for demographic characteristics, adult SES, and adult health behaviors.

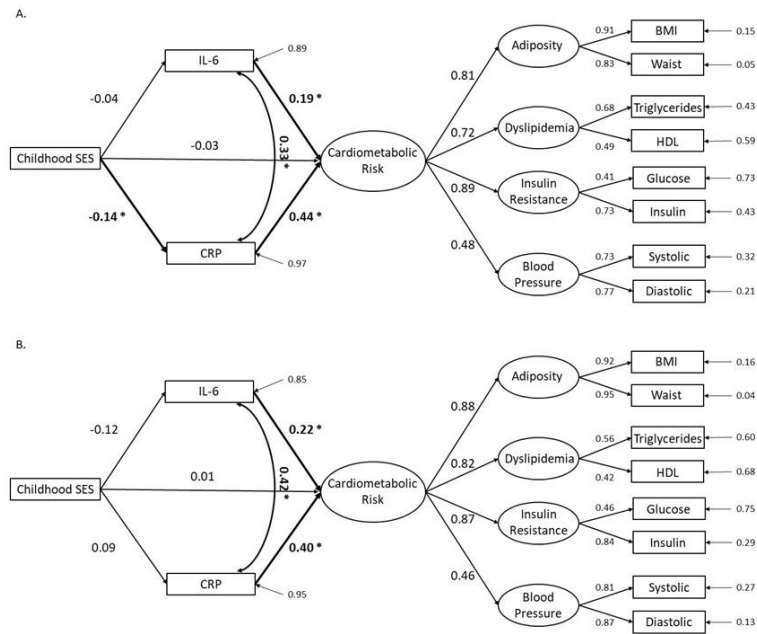


Figure 16. Race-specific formation of the structural equation model for (A) Whites and (B) Blacks, adjusted for demographic characteristics, adult SES, and adult health behaviors.

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