Assessing relationships between discrimination and health: emphasis on measurement and methodology

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"Assessing Relationships Between Discrimination and Health: Emphasis on Measurement and Methodology"

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Assessing relationships between discrimination and health: emphasis on measurement and methodology

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Assessing relationships between discrimination and health: emphasis on measurement and methodology

Abstract

Research investigating relationships between discrimination and health has grown over the past two decades, establishing a body of evidence that documents the adverse health outcomes associated with inequitable systems. Efforts to strengthen the available evidence in this area have called for increased attention to measurement, mechanisms, and methodology. Specifically, prior work has called attention to the need for future research to focus on identifying experiences that are salient in regard to impacting health, evaluating hypothesized processes of embodiment, and utilizing methodological approaches to strengthen causal inference. These topics serve as the foundation of the present dissertation.

In Chapter 2, I conduct a systematic meta-analysis to estimate the mean correlation coefficient between self-reported discrimination and molecular biomarkers among studies that have operationalized discrimination using the Everyday Discrimination Scale. This analysis aims to (1) provide an understanding of how experiencing discrimination may become embodied to result in poor health and to (2) maximize cross-study comparability by only assessing those relationships among studies using the same measurement of discrimination. Examining relationships between discrimination and intermediate indicators of physiological wellbeing such as biomarkers allows for the assessment of indicators of inflammation, stress, and accelerated aging that have been associated with adverse mental and physical health outcomes.

Literature examining relationships between discrimination and blood pressure have been inconsistent, with some studies observing positive correlations between measures of

discrimination and elevated blood pressure and others finding null or inverse relationships. Differences in the associations between discrimination and blood pressure have also been observed by gender and indicators of socioeconomic status. Contributing to efforts to minimize threats to causal inference that could contribute to the differences in findings, such as measurement error and unmeasured confounding, I implemented instrumental variable (IV) estimation to assess the relationship between racial discrimination and blood pressure in Chapter 3. The analyses demonstrate that alternative methodological approaches, specifically IV, may be useful in accounting for potential measurement error and omitted variable bias. These findings contribute to a body of research that demonstrates the adverse effects of institutional discrimination on health and provide context for intervention.

Defined as accumulated “wear and tear” of physiologic systems due to exposure to chronic stress, allostatic load serves as a useful outcome to assess the system-wide impact of psychosocial stressors like discrimination. In much of the literature, allostatic load is evaluated as a summary index, however, this may obscure specific physiologic responses important to understanding the pathways through which discrimination contributes to adverse health outcomes. Using three measures of discrimination (i.e., everyday, lifetime, and appraised burden of discrimination), I assessed whether each form of discrimination operated distinctly or potentiated associations with other forms of discrimination (e.g., greater frequency of everyday discrimination and appraisal of discrimination as a significant burden) to heighten allostatic load. This investigation adds to the existing literature by identifying the extent to which the relationship between discrimination and allostatic load varied by measure used. Results from this analysis suggest distinct mechanisms through which everyday and major lifetime experiences or appraisals of discrimination contribute to allostatic load to impact mental and physical health outcomes.

Taken together, the findings from these three analyses provide guidance for future research, specifically regarding pathways through which discrimination may adversely impact

health, methodological approaches used, and the importance and theoretical implications of how discrimination is measured and utilized.

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1

Introduction

1.1. BACKGROUND

In the United States, racial and ethnic health inequities are pervasive.[1,2] There is a growing body of evidence that investigates racism as a driver of racial/ethnic health inequities, documenting the adverse effects associated with increased exposure to racism across domains.[2-6] In fact, addressing racism alongside other social determinants of health remains an objective of Healthy People 2030 in an effort to eliminate health inequities.[7] Racism impacts health through mutually supporting and adaptive mechanisms that traverse cultural, structural, and interpersonal domains to shape social hierarchies and value (or devalue) on the basis of race,[2-4] whether race is that perceived by others (e.g., socially assigned) or self-identified.[8,9] This hierarchy centers and equates whiteness (or the proximity to whiteness) to superiority over individuals categorized into other marginalized racial/ethnic groups, specifically Black, Indigenous, and Latinx populations.[10]

As a system, racism is predominantly thought to operate across three domains – cultural, structural, and interpersonal – to shape where and how marginalized racial and ethnic populations work, live, and exist.[4] Cultural racism refers to the day-to-day normalization of racial hierarchies, through means such as imagery, norms, and values.[4,10] Structural racism is typically defined as the interconnectedness of institutions (e.g., political, economic, legal) that shape the inequitable distribution of opportunities and resources available to marginalized racial/ethnic groups through interrelated and reinforcing laws, policies, and practices, while overdistributing

these resources among white populations.[2,11] Last, racism also operates interpersonally, which is often referred to as discrimination. Discrimination can be thought to exist as actions resulting in differential treatment that is perpetuated by individuals and social, economic, political and cultural institutions, typically to the benefit of the "dominant" group.[12] A subset of the aforementioned experiences – that individuals are aware of, often described as self-reported discrimination – are examined to estimate the relationship between discrimination and adverse health outcomes.[4,13-18] The present dissertation focuses on this pathway, with the overarching goal of examining the relationship between discrimination and health using multiple measures of self-reported discrimination, as well as proposing and implementing methodologies that strengthen our understanding of the relationships between discrimination and health. Though this work focuses on self-reported discrimination, it does so with full acknowledgement of the wide-reaching impacts that work evaluating and addressing the impacts of structural racism and institutional discrimination will have on the health and wellbeing of historically and presently oppressed groups.

Much of the discrimination literature focuses on self-reported experiences, with researchers predominantly examining racial or ethnic discrimination.[16] Evidence has also indicated that many socially marginalized groups report experiences of discrimination that adversely affect health and wellbeing.[3,5,16,19-21] Prior meta-analyses have provided evidence of the harmful effects of discrimination across mental health, physical health, and health behavior outcomes.[5,16,20] While prior meta-analyses have been insightful with regards to the relationships between discrimination and a range of health outcomes, many have used multiple measures of discrimination in their analyses – given that there is no established, "gold-standard" assessment of self-reported discrimination.[5,16,20,22] For example, a meta-analysis of studies examining the relationship between self-reported racism and health by Paradies et al. identified several instruments that were used to assess exposure to racism that varied in capturing direct or indirect exposure (e.g., vicarious racism), exposure timeframe, and number of items (e.g., one

item, nine or more).[5] The authors also found instrument-level characteristics (i.e., direct/indirect exposure to discrimination, timing, number of items, instrument used) to moderate the associations between self-reported racism and health outcomes, indicating that it may be useful to examine the associations between discrimination and health outcomes among studies using the same discrimination measure.

Identification of means to assess self-reported discrimination comprehensively remains an ongoing effort in the field.[4] Assessments of discrimination seek to capture the lived experiences of persons impacted, providing context and documentation of ills that extend beyond the scope of health – affecting a broader sense of fulfillment, wellbeing and self-expression. Existing discrimination measures capture aspects of the lived experience, including traumatic experiences (e.g., "experiences that are extreme, overwhelming, and often horrific in impact[23]"), large-scale, macro-stressors (e.g., media coverage of police killings and trials, restrictive immigration policies), major life experiences (e.g., being unfairly denied housing or employment), or chronic experiences (e.g., relatively minor, yet repeated differential treatment), with the bulk of the literature examining major and chronic experiences of discrimination.[23] Often posited as a stressor, discrimination affects health through numerous pathways, including activation of biological stress responses, adverse coping responses, but also social and economic deprivation, environmental injustices, targeted marketing of unhealthy products, inadequate or inaccessible medical treatment, disenfranchisement of people with a criminal record, and other social disadvantages.[13,24,25] While most stressful events do not affect health,[13] identifying salient experiences of discrimination that are likely to have implications for population health remains important for current and future work – in an effort to understand and intervene upon discriminatory processes that unfairly disadvantage some and unfairly advantage others.[26]

The present research focuses on examining the relationship between self-reported discrimination and health, with a focus on examining the role of measurement and methodology. Specifically, it (1) seeks to comprehensively quantify the relationship between discrimination

and several biological indicators of physiological functioning, across studies using the same measurement of discrimination; (2) proposes an instrumental variable approach to the examination of the relationship between racial discrimination and blood pressure as a means to address measurement concerns associated with observational studies; and (3) examines how multiple measures of discrimination, including appraisals of the burden of discrimination, contribute to allostatic load, an indicator of physiologic dysregulation.[27-29]

1.2. OVERVIEW

Paper 1 examines the overall association between discrimination and several biomarkers (i.e., cortisol, C-reactive protein, interleukin-6 (IL-6), telomere length) via a meta-analysis of studies that have used the Everyday Discrimination Scale.[30] Discrimination may affect physical and mental health through several biological pathways.[31,32] Given findings from the literature examining other forms of chronic stress, it has been posited that experiences of discrimination induce increased stress response,[31] dysregulation of inflammatory responses,[33] and accelerated cellular aging[32] which in turn affect morbidity and mortality.[33-35] Associations between psychosocial stress, including discrimination, and relevant biomarkers suggest that such measures may be plausible pathways through which discrimination contributes to mental and physical morbidity.[33,36] Comprehensively assessing the relationship between everyday discrimination and biomarkers provides an opportunity to further our mechanistic understanding of how chronic experiences of differential treatment become embodied, or “get under the skin”, to contribute to poor psychological and physiological health.[34,37] Prior systematic reviews and meta-analyses have focused on one particular form of discrimination (e.g., racial) and/or compare studies across multiple measures and outcomes. The present meta-analysis examined associations between discrimination and physiological indicators of stress, inflammation, and cellular aging while standardizing the assessment of discrimination. Through the identification of relevant empirical publications from several databases (i.e., Medline / PubMed (National Library

of Medicine / NCBI), PsycInfo (Ebsco) and Web of Science (Thomson Reuters)), the analysis provides deeper insight into the implications of discrimination for multiple biological indicators. Standardized measurement of discrimination results in more precise estimates of the relationship between discrimination and health and allows for stronger cross-study comparisons as it relates to strengths of associations, validity, and reliability.

Paper 2 explores the relationship between discrimination and blood pressure using an instrumental variable approach. Elevated blood pressure (BP) is an established risk factor for angina, stroke, and myocardial infarction[38]. Substantial inequities in elevated blood pressure have been documented among marginalized racial groups in the United States. Approximately 57% of non-Hispanic Black adults have elevated resting blood pressure or are on antihypertensive medication, compared to 44% of non-Hispanic white adults[39]. Several factors, including psychosocial stressors such as racial discrimination, have been examined as potential contributors to racial inequities in elevated blood pressure and hypertension status.[18,22,40,41] Many studies examining the relationship between discrimination and health have yielded mixed findings, which may reflect challenges to causal inference (e.g., residual confounding, measurement error).[42-46] The use of an instrumental variable approach allows the ability to address some of the commonly reported concerns related to confounding and measurement error in observational studies. Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, this paper compares estimates using IV and conventional linear regression analyses.

Paper 3 analyzes data from the Midlife in the United States (MIDUS) study to examine the role of experiences of everyday and lifetime discrimination, as well as appraised burden of discrimination with biomarker measurements used to operationalize allostatic load, its subscales, and the overall allostatic load score. Allostatic load, originally introduced by McEwen & Stellar, summarizes the hypothesized cumulative “wear and tear” on multiple physiologic systems induced by exposure to chronic stress.[29] As an overall score, allostatic load has been

shown to be associated with increased risk of cardiovascular disease, poorer cognitive functioning, and mortality.[27,28,47] Relationships between experiences of discrimination and elevated allostatic load have been documented, even after accounting for traditional risk factors (e.g., health behaviors) and sociodemographic covariates.[48-50] The seven subscales that comprise allostatic load provide insight into different physiological processes. Explicitly, they capture measures of stress response via sympathetic and parasympathetic nervous system and hypothalamic-pituitary-adrenal axis (HPA) axis activity, inflammation via several markers of inflammation (e.g., C-reactive protein), metabolic glucose and lipid profiles, and indicators of cardiovascular health. While representing allostatic load as the systems-wide impact of chronic stress on the body through the use of an overall summary score is useful, the operationalization of AL as a summary index may obscure specific physiologic responses important to understanding the pathways through which discrimination contributes to adverse health outcomes. This analysis builds on a body of research that calls for the examination of different measures to capture experiences of discrimination, including assessments capturing appraisal, timing, and severity[23]. Using a pooled, cross-sectional analysis, the paper assessed whether there were distinct pathways through which different measures of discrimination affect health. It also assessed whether interactions between multiple measures of experiences and appraisals of discrimination as well as between race/ethnicity and discrimination measures modified the relationship between discrimination and indicators of allostatic load.

This dissertation aims to address some of the methodologic challenges present in the literature examining the adverse associations between discrimination and health and well-being. Increased focus on the measurement and analytic approaches available to examine the health implications of discrimination not only strengthen our understanding of these relationships but bolster the ability to provide stronger evidence and points of intervention to rectify the social, economic, cultural, and individual-level practices that reify and reinforce social discrimination and inequity.

2

A Systematic Meta-Analytic Review of the Everyday Discrimination Scale and Biomarker Outcomes

2.1. ABSTRACT

Discrimination has consistently been associated with several adverse health outcomes. Similar to other psychosocial stressors, discrimination is thought to impact health through stress-related physiologic pathways including HPA axis activation, dysregulation of inflammation responses, and accelerated cellular aging. Given growing attention to research examining the biological pathways through which discrimination becomes embodied, this meta-analysis reviews literature examining relationships between self-reported discrimination and four biomarker outcomes (i.e., cortisol, C-reactive protein, interleukin-6, and telomere length) among studies that have used the Everyday Discrimination Scale. Twenty-four articles were eligible for inclusion, with several reporting on multiple outcomes. Discrimination was associated with elevated CRP levels (r = *0.13; 95% CI: 0.01, 0.24, k=9*), though not cortisol (*r = 0.05*; 95% CI: -0.06, 0.16, k = 9), IL-6 (r = *0.05*; *95% CI: -0.32, 0.42, k = 5*), or telomere length (*r = 0.03; 95% CI: -0.01, 0.07, k=6*). We identify several points of consideration for future research including addressing heterogeneity in

assessment of biomarker outcomes and the need for longitudinal assessments of relationships between discrimination and biomarker outcomes.

2.2. INTRODUCTION

The study of racial discrimination as a type of psychosocial stressor that could adversely affect health and could contribute to race/ethnic disparities in health has emerged as an area of research in the last two decades.[51] A recent review documented 29 reviews of the literature of discrimination and several health outcomes that were published between 2013 and 2019.[10] Most of the early research on the relationship between discrimination and health focused on mental health outcomes, indicators of health behavior, or self-reported measures of physical health.[13] However, as the field has grown, research has begun to elucidate the biological pathways through which societal and psychosocial stressors, like discrimination, are embodied to affect health.

In recent years, there has been discussion that discrimination, similar to other psychosocial stressors, may affect physical and mental health through several biological pathways.[31,32] Similar to other sources of chronic stress, researchers have posited that discrimination induces an increased HPA axis activation,[31] dysregulation of inflammatory responses,[33] and accelerated cellular aging.[32] Biomarkers associated with these pathways (e.g., cortisol, C-reactive protein, telomere length) have documented associations with increased morbidity and mortality.[33-35] Documented associations between psychosocial stress, including discrimination, and relevant biomarkers suggest multiple biological pathways through which discrimination contributes to mental and physical morbidities.[33,36] Indeed, closer examination of the relationship between everyday discrimination and biomarkers provides an opportunity to advance our mechanistic understanding of how chronic experiences of differential treatment become embodied or “get under the skin” to contribute to poor psychological and physiological

health.[34,37] The use of objective biomarkers also circumvents the issue of common source bias that may arise when both the exposure (discrimination) and health outcome are self-reported. However, a comprehensive assessment of the association between everyday experiences of discrimination and biomarkers of physiologic stress, inflammation, and accelerated aging has not been performed to date.

The Everyday Discrimination Scale, which captures minor experiences of unfair treatment, is one of the most widely used scales in the literature.[30] Everyday discrimination is associated with adverse mental and physical health outcomes.[3,5,16,19-21] In addition to the inequitable access to opportunities, resources, and power as a result of structural racism and institutional discrimination, self-reported experiences of discrimination have frequently been conceptualized as stressors that adversely affect health.[4,10,12-14,16,18,19,22,47,51] Such experiences have been associated with adverse mental and physical health outcomes and indicators.[13,14,16,18,51,52] These include depressive symptoms and psychological distress,[20,53] coronary artery calcification,[54] reduced sleep quality,[55] elevated E-selectin [56] and C-reactive protein (CRP)[57] levels, and several chronic health outcomes.[10,13,14,18,58]

Prior meta-analyses have examined the relationship between discrimination and health across multiple measures of discrimination and broader categories of health outcomes.[5,16,20] Studies assessing biological pathways are a small proportion of the total literature but are increasing in recent years. Since the publication of the most recent meta-analysis on discrimination[5] – specifically racial discrimination - literature assessing discrimination and biomarkers has grown. A recent systematic review of discrimination and systemic inflammation identified 28 articles published since 2009.[33] These measures have not been included in previous meta-analyses of the health implications of discrimination. Still, the strength of association is likely to vary according to the type of discrimination and instruments used to assess it. The Everyday Discrimination Scale (EDS) is a nine-item scale that captures the frequency by which individuals have experienced specific instances of discrimination including

items related to courtesy, respect, harassment, and others' perceptions of the respondent.[30] A sufficient number of studies have been conducted utilizing the EDS to permit a review of the association of discrimination with biomarkers (i.e., HPA axis, inflammation, and cellular aging). Accordingly, this paper sought to synthesize existing literature, provide deeper insight into methodological and measurement challenges, and identify future research directions.

2.2.1. STUDY OBJECTIVES

This systematic review and meta-analysis examined the relationship between experiences of discrimination and molecular biomarker outcomes, with quantitative focus on interleukin-6 (IL-6), CRP, cortisol, and leucocyte telomere length, among studies that have used the EDS. We characterized the existing body of literature that has included the EDS – highlighting study design and methodology, sample characteristics, operationalization of the EDS, and outcomes examined. We examined relationships between the EDS and individual biomarker measures of stress, inflammation, and cellular aging (e.g., telomere length) – to increase the comparability of findings across studies that have used the same assessment of exposure to discrimination.

Despite evidence that the associations between discrimination and health outcomes vary by type of discrimination and instruments used to assess experiences[5,22], this is the first meta-analysis to the authors' knowledge that examines the association of discrimination on stress-related biomarkers among studies that have used the same measure.

Specifically, the overarching research aims of the systematic review were to:

1. Meta-analyze associations between the EDS and stress-related biomarkers. We hypothesize that increased levels of discrimination have negative associations with biomarker measures (i.e., shorter telomere length; higher IL-6, CRP, and cortisol levels).

2. Descriptively map the mediators (e.g., smoking, excess drinking) of the associations between discrimination and molecular biomarkers across studies that have used the EDS. This provides context as to what factors have been considered as mediating variables in studies assessing discrimination and biomarker outcomes.

2.3. METHODS

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and criteria[59,60].

Search strategy. Studies discussing self-reported, everyday, or chronic discrimination in the context of identified health outcomes were identified by searching Medline / PubMed (National Library of Medicine / NCBI), PsycInfo (Ebsco) and Web of Science (Thomson Reuters). Controlled vocabulary terms (i.e., MeSH; Thesaurus of Psychological Index Terms) were included when available and appropriate. The search strategies were designed and executed by a research librarian (CM) at the Countway Library of Medicine. Publication date was limited to studies published in 1997 or later. No language restriction was applied. The exact search terms used for each of the databases are provided in the supplementary materials (Supplemental Table A.1). Reference lists of identified papers were examined for additional relevant articles for inclusion.

Inclusion criteria. For consideration of inclusion, studies must have used quantitative methodology reporting an estimate of the relationship between the EDS and a disease-related molecular biomarker (e.g., telomere length, IL-6).[32,61,62] As such, studies using qualitative methods were not included. All collection methods for molecular biomarkers were included (e.g.,

blood, saliva, hair, urine).[61] All study designs were eligible (i.e., cross-sectional, longitudinal, case-control, and experimental). Given that the EDS was first utilized in 1997,[30] studies were eligible for inclusion if published in 1997 or later.

Exclusion restrictions were not placed upon study populations, such that studies including participants from any age group, racial/ethnic/cultural identity, ability, and other sociodemographic factors were included.

***Exposure*.** Self-reported discrimination was measured using the EDS, which includes the frequency of self-reported discrimination in the respondent's day-to-day life.[30] The original scale includes nine-items: "In your day-to-day life, how often do any of the following things happen to you?" (1) You are treated with less courtesy than other people are; (2) You are treated with less respect than other people are; (3) You receive poorer service than other people at restaurants or stores; (4) People act as if they think you are not smart; (5) People act as if they are afraid of you; (6) People act as if they think you are dishonest; (7) People act as if they're better than you are; (8) You are called names or insulted; and (9) You are threatened or harassed. Responses for each item include "almost every day," "at least once a week," "a few times a month," "a few times a year," less than once a year," and "never". Respondents reporting "a few times a year" or more frequent experiences of discrimination as asked, "What do you think is the main reason for these experiences?" Participants are able to select one or more of the following attributions: (1) your ancestry or national origins; (2) your gender; (3) your race; (4) your age; (5) your religion; (6) your height; (7) your weight; (8) some other aspect of your physical appearance; (9) your sexual orientation; (10) your educational or income level.

A short form of the EDS was developed for the Chicago Community Adult Health Study (CCAHS)[63] in which respondents were asked: ""In your day-to-day life, how often have any of the following things happened to you?" (1) You are treated with less courtesy or respect than other people; (2) You receive poorer service than other people at restaurants or stores; (3)

People act as if they think you are not smart; (4) People act as if they are afraid of you; (5) You are threatened or harassed. The follow-up question and response categories of the shortened EDS are the same as the original. Other adapted versions of the scale were considered eligible for inclusion if they were not major adaptations beyond the original scope of the EDS (e.g., studies that created summary scores that joined the EDS with other measures or studies that only include one item from the EDS were not included).

Outcomes. All stress-related biomarker outcomes were eligible for inclusion. These included IL6, CRP, cortisol, DHEA (dehydroepiandrosterone, also DHEA-S), DNA methylation, E-selectin, fibrinogen, nerve growth factor, alpha amylase, HSP-70 (heat shock protein-70), HbA1c levels, and telomere length.

Several outcomes were only examined in one or two articles and were excluded from the meta-analysis but are included in our narrative synthesis of the findings (N=5). Studies that examined associations between the EDS and relevant outcomes but did not report sufficient data to ascertain the associations (or efforts to obtain additional information from study authors were not successful) were excluded from meta-analysis but were included in narrative/descriptive synthesis (N=1).

2.3.1. SCREENING

Search results were imported into Endnote X9, and duplicate entries were removed. The Endnote library was exported into Covidence[64], a web-based systematic review software. Two reviewers (JL, GM) independently conducted title and abstract screening to assess studies for eligibility (inter-reviewer reliability (κ) = 0.78, indicating good agreement).

Full texts of studies considered for inclusion were obtained. Discrepancies between reviewers regarding study inclusion was resolved by discussion with a third reviewer (HC) and/or consensus (JL, GM) [κ = 0.74]. The study selection process is outlined in full in Figure 2.1.

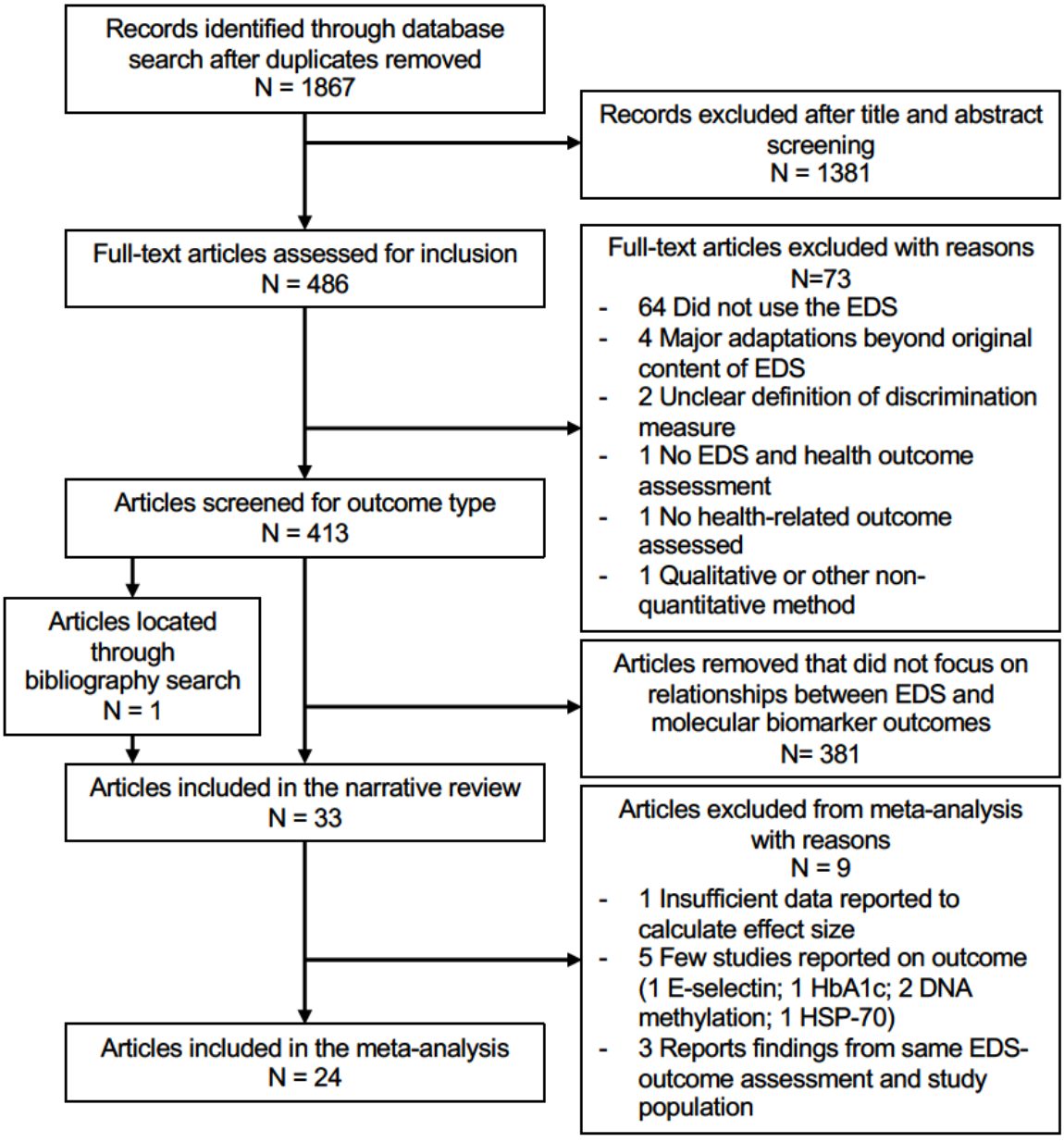

Figure 2.1. Study identification and selection process

2.3.2. DATA EXTRACTION AND ANALYSIS

Data from identified studies were independently extracted into an Excel document by one reviewer (JL) with another reviewer randomly checking 20% of the extracted data (HC). Inconsistencies were resolved by consensus and/or discussion with a third reviewer (GM). Extracted data included the information around the EDS (e.g., version used, operationalization) and biomarker assessed, demographic characteristics of participants (e.g., age, gender, educational attainment), study attributes (study design, location [country and region], period and duration of study (if relevant), sample size, most and minimally adjusted estimates, covariates adjusted for, psychometric properties of the scale (if assessed), mediators (if explicitly mentioned) and potential sources of bias (e.g., attrition, missing data). For articles using the same dataset to examine relationships with the same outcome, we extracted data from papers with the most information reported (e.g., both minimally and fully adjusted models reported). If multiple papers included the same amount of data, the earliest publication was included in the meta-analysis.

Minimally adjusted estimates include data from the least adjusted model reported or correlations between EDS and biomarkers. Fully adjusted estimates include data from the most adjusted model reported with all covariates included. Efforts were made to contact study authors for additional information; however, if only one estimate was available, it was used as both the minimally and most adjusted estimate.

Most studies reported beta coefficients. To incorporate beta coefficients into the present meta-analysis, we use a derived formula developed by Peterson and Brown.[65] After extracting over 1500 β and r values, the authors fit several models to assess the relationships between the two measures. They found that $r = 0.98\beta + 0.05\lambda$ yielded the best fit, where β is the coefficient reported and λ is an indicator variable that is 0 when β negative and 1 when β is positive[65]. After testing this efficacy of this formula against several alternatives including a “convenience” version

of the formula ($r = \beta + 0.05\lambda$), replacing *r* values with β values, and replacing missing *r* values with the mean of observed *r* values the authors found little difference between results from using the best fit model, replacing *r* values with corresponding β values, or using the convenience imputation formula. However, the authors note that this imputation is best used among β estimates within the interval of -0.50 to 0.50, given an observed tight joint distribution of β and *r* values in that range. Given that most estimates from eligible studies were within that range, we imputed *r* values from reported β values in eligible studies where *r* values were not reported using $r = 0.98\beta + 0.05\lambda$.

Estimates were coded such that greater experiences of discrimination are associated with poorer outcomes (negative for telomere length, positive for inflammation and stress biomarkers (e.g., IL-6)).

Weighted correlation sizes were calculated using inverse variance weighting, giving greater weight to studies with smaller variances (i.e., larger sample sizes). Random effects models were fit utilizing the minimally adjusted associations reported using the "metafor" package[66] available in R[67]. Random effect models essentially relax the assumption of fixed-effect models, which assume that there is one "true" effect estimated in all studies and that variations only occur due to chance (i.e., variations in samples)[68]. Random effects models instead assume a distribution of correlation sizes allowing there to be variations in the correlation size across studies, where factors beyond sampling variation may influence the association (e.g., age of sample).[68] Heterogeneity between studies was quantified using the I^2 – a measure that captures the percentage of total variability that is due to heterogeneity between studies. Cochran's Q test was conducted to test for heterogeneity. Forest plots are presented to illustrate study-specific and overall correlation sizes by outcome and 95% CIs. Sensitivity analyses included estimating the weighted correlation sizes using the most adjusted estimates reported in eligible articles.

Quality Assessment. Study quality was assessed in terms of potential for bias. Similar to Paradies et al.[5], we use sampling procedure, data type (e.g., cross-sectional, longitudinal), and instrument (i.e., full scale, short form), and covariates included in a narrative assessment of study quality. Funnel plots were created to illustrate potential publication bias and asymmetry was tested using Egger's tests.[69]

2.4. RESULTS

Database searches on 03/24/2020 yielded 2803 references, resulting in 1867 unique references for screening. Relevant outcomes were found in 33 articles included in the qualitative synthesis[70-102] and 24 studies were identified for inclusion in the quantitative synthesis of associations in the present study.[70-73,75,76,79-84,86,88,90,91,93,95,97-100,102,103] The number of studies excluded from the quantitative analysis, with reasons, are provided in detail in Figure 2.1. Overall descriptive data for the articles included in the quantitative assessment are summarized in Supplemental Table A.2**.**

Most studies were published between 2016 and March 2020, with all articles having publication dates between 2010 and 2020. Nearly all articles examined associations among populations in the United States, with one assessing associations among a sample in New Zealand. Nearly 38% of studies implemented representative sampling procedures, with 63% of studies reporting non-representative sampling methods. Many articles reported findings from cross-sectional analyses (75%) with the remainder being longitudinal (21%) or other (4%).

Sample sizes ranged from 49 to 12624, with a total sample of 36557 respondents included across all eligible studies. All articles reported some information on participant age (e.g., average age of population), race/ethnicity, and sex; however, two did not report the number of participants within each racial/ethnic group in the analytic samples. Articles mostly conducted analyses among adults (99% of the sample size), though populations under 18 were

included in three articles, yielding 419 young adult or adolescent participants to the total sample. One study did not report the age range of study participants to discern whether young adults (<18 years of age) could have been included in the study population. Data on participant educational attainment was reported in 18 studies.

The full version of the EDS was employed in most articles (N=16), with fewer using the short-form (N=5) or a modified version of the EDS (N=3). Attribution of experiences was assessed in only 6 studies, with most assessing attributions of experiences to both racial and non-racial reasons (N=4). The remaining two studies that captured attributions assessed only racial or non-racial attributions. Operationalization of the EDS remained fairly consistent across studies with most measuring experiences as the sum (N=10) or the average (N=10) of the frequency of experiences. Other means of operationalizing the EDS included a count of yes responses to experiences, dichotomizing beyond a certain threshold. How the measure was operationalized was unclear in one analysis. Among studies that examined the reliability of the EDS, it exhibited very good reliability using a Cronbach's alpha cutoff of greater than 0.80 in 17 of the 24 articles.

Cortisol and CRP were the most frequently assessed biomarker outcomes (N=9 and N=9 for respectively), followed by telomere length (N=6) and IL-6 (N=5). Approximately 17% (N=4) of articles reported associations between the EDS and multiple biomarker outcomes.

Table 2.1 presents the summary of study and sample characteristics by outcome. Weighted correlation sizes from the least adjusted associations reported between the EDS and each biomarker outcome are presented in Figures 2.2-2.5.

Table 2.1. Summary of study and sample characteristics by outcome (N=24 articles)

	Articles	Sample size (N) (median [range])	Age groups	Racial/ethnic groups	Study designs (%)
Cortisol	9	1205 (141 [41 – 293])	Adults (≥18): 6 Youth (<18): 2 Unclear: 1	N across 9 studies reporting = 1205 Black: 29.4% Latinx/Hispanic: 18.6% Asian: 7.7% White/European: 38.6% NH/PI/Māori: 1.5% Multiracial: 2.0% Other: 2.2%	Cross-sectional: 7 (77.8) Longitudinal: 1 (11.1) Other: 1 (11.1)
CRP	9	28409 (1054 [49 – 12624])	Adults (≥18): 8 Youth (<18): 1	N across 8 studies reporting = 21842 Black: 36.8% Latinx/Hispanic: 5.9% Asian: 2.1% White/European: 54.0% Other: 1.2%	Cross-sectional: 5 (55.6) Longitudinal: 3 (33.3) Other: 1 (11.1)
IL-6	5	7859 (99 [41 – 6567])	Adults (≥18): 5 Youth (<18): 0	N across 4 studies reporting = 1292 Black: 19.7% Latinx/Hispanic: 1.4% Asian: 0.5% White/European: 84.6% Multiracial: 0.9% Other: 0.6%	Cross-sectional: 5 (100) Longitudinal: 0 (0)
Telomere	6	6930 (683 [202 – 3868])	Adults (≥18): 6 Youth (<18): 0	N across 5 studies reporting = 6728 Black: 32.5% Latinx/Hispanic: 7.4% White: 60.1%	Cross-sectional: 5 (83.3) Longitudinal: 1 (16.7)

Across all analyzed outcomes, between study heterogeneity was high and statistically significant as measured by the I^2 and Cochran's Q test (**Table 2**). Results from the Q-test reject the null hypothesis of the "true" effect being the same across studies and only differing due to sampling variability.

Table 2.2. Between-study heterogeneity assessments by outcome

Outcome	I^2	Q statistic (p-value, df)
Cortisol	60.95%	19.83 (0.011, 8)
CRP	94.48%	71.84 (<0.001, 8)
IL-6	97.93%	47.01 (<0.001, 4)
Telomere length	39.51%	7.26 (0.202, 5)

2.4.1. CORTISOL

Nine studies were identified that examined relationships between discrimination and cortisol. Most frequently, the EDS was operationalized as the mean (N=4) or sum of frequencies (N=3). Another study used the count of yes responses, though one study did not clearly specify how the measure was operationalized. Studies included in the estimation of the mean correlation size were primarily cross-sectional (N=7) and conducted among adults (N=6). Black participants comprised nearly 29.4% of the cortisol study population, followed by Latinx/Hispanic (18.6%) and Asian (7.7%) participants; however, white participants (38.6%) comprised the largest proportion of the study population across all 9 studies. Native Hawaiian, Pacific Islander, or Māori, multiracial, and individuals categorized as "other" racial groups together comprised the remaining 5.7% of the pooled study population.

Assessments of cortisol varied across studies (Figure 2.2). Given the evidence of changes in cortisol levels throughout the day,[104,105] some studies assessed salivary cortisol by collecting multiple samples per day at different time points (≥4) over several days (≥3).[72,75,79,97] Others collected two saliva samples (morning and evening) over two consecutive days[93], three salivary samples in one day,[80] salivary samples before, during and after exposure to a stress task,[84] and the average of duplicate samples collected in one afternoon.[86] Another study

assessed cortisol concentration through hair cortisol, using 3 cm of hair closest to the scalp to assess retrospective cortisol levels.[82] In the main analysis, the reported assessment of cortisol levels varied, with articles assessing associations between the EDS and waking cortisol levels in five studies, baseline cortisol, average cortisol from one measurement, total daily cortisol, and hair cortisol concentration. Five studies reported both minimally and fully adjusted estimates, while the remaining reported only unadjusted (N=2) or adjusted (N=2).

The mean correlation coefficient for associations between EDS and cortisol was *r = 0.05* [95% CI: -0.06, 0.16, *k* = 9] (Figure 2.2A), suggesting no observed association with cortisol levels. Patterning in the direction of responses was observed, where larger studies showed null associations or negative associations while smaller studies typically had associations indicating greater cortisol levels with increased discrimination. Minimally adjusted models included four correlations and models that accounted for factors including age, race, sex or gender, BMI, socioeconomic indicators (i.e., household income, educational attainment, material deprivation), health behaviors (i.e., exercise, food, alcohol and caffeine consumption, cigarette use), daytime sleep, daily wake and sleep time, psychological factors (i.e., stress level, emotional stability), and medication (i.e., cortisol medication, other medication use) or medical history (i.e., C-section delivery).

Several studies reported estimates between the EDS and cortisol outcomes using the same measure (i.e., cortisol awakening response [CAR], waking levels). To minimize the impact of heterogeneity in the measurement of cortisol on the pooled estimate, we estimated mean correlation sizes for studies that examined the CAR[72,75,79,80,97] (defined as the change in cortisol from waking to a defined time period after waking) and waking cortisol levels[72,75,79,93,97].

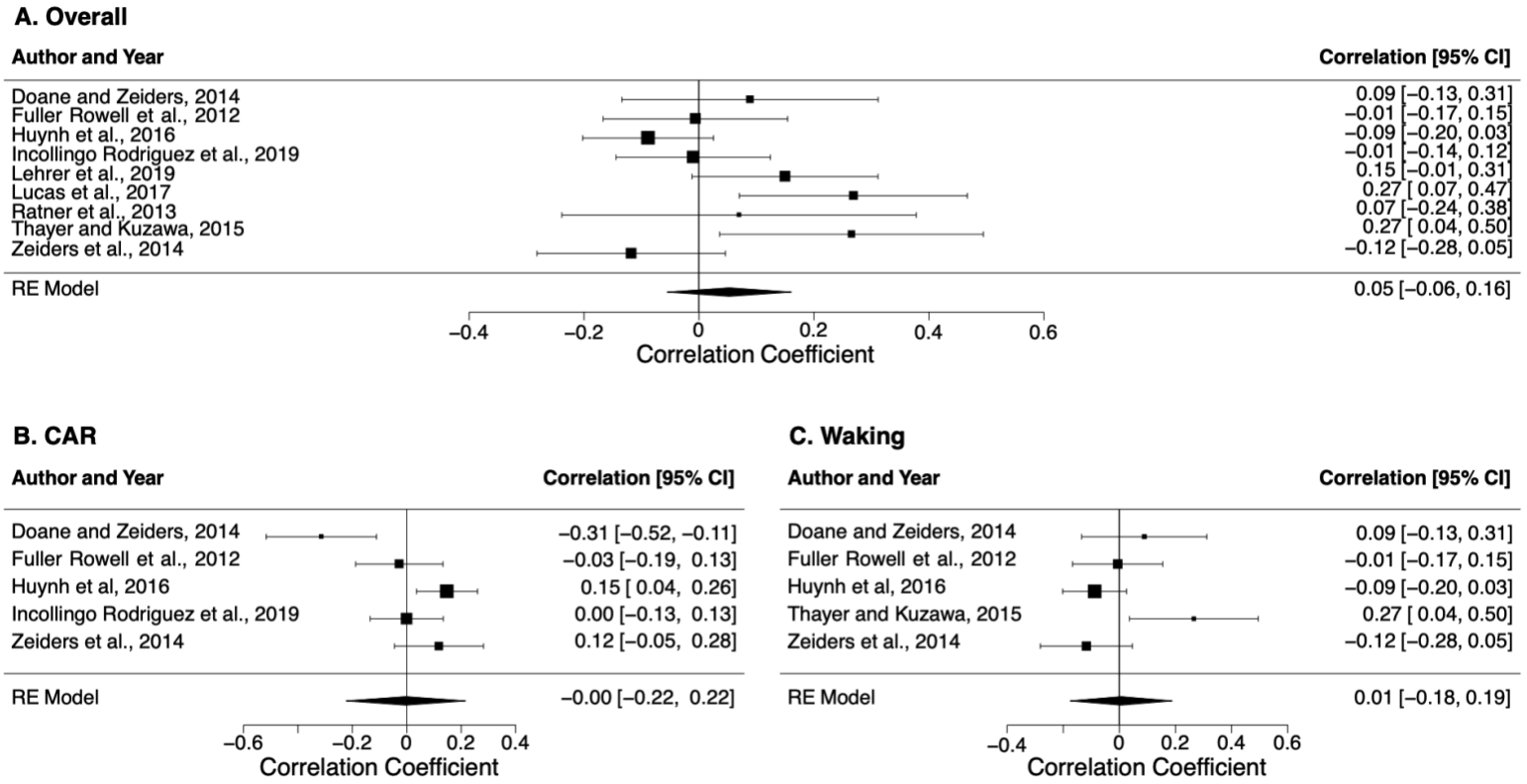

Figure 2.2. Associations between EDS and (a) all cortisol outcomes; (b) cortisol awakening response (CAR); and (c) waking levels (minimally adjusted)

Among studies that evaluated the relationship between the EDS and waking cortisol, the mean correlation size was *r = 0.01* (Figure 2.2C, *95% CI: -0.18, 0.19).* Whereas the mean correlation size among studies reporting associations between the EDS and CAR was *r = 0.00* (Figure 2.2B, *95% CI: -0.22, 0.22*). These findings may suggest that discrimination is not associated with cortisol levels, specifically waking and the cortisol awakening response. However, additional research, specifically longitudinal assessments and different measures of diurnal cortisol[106], is needed to understand these observations.

Sensitivity analyses were conducted using the most or fully adjusted estimates reported in each study. The mean correlation size did not differ greatly across fully adjusted estimates (*r=0.06; 95% CI: -0.06, 0.18)* compared to the minimally adjusted models. Associations between discrimination and CAR (*r = 0.02; 95% CI: -0.24, 0.29*) and waking cortisol (*r = 0.00; 95% CI: -0.19, 0.18*) remained null. Beyond covariates included in the minimally adjusted models, fully adjusted models also included factors such as psychological factors (i.e., neuroticism risk, public and private esteem), average hours of sleep, medication (i.e., contraceptive use), waist-to-hip ratio, and attributions of discrimination.

2.4.2. CRP

Among the nine eligible studies assessing the association between discrimination and CRP, the EDS was frequently implemented as the sum (N=4) or mean (N=4) of the frequencies of experiences of discrimination. One study operationalized the EDS as the sum of the experiences.[83] Eight studies reported the racial/ethnic breakdown of the analytic samples, with 37% identifying as Black, 6% as Latinx/Hispanic, 2% as Asian and 54% as white/European. A small percentage of participants were classified as “Other” race (1.2%). Most studies were cross-sectional in design (56%) and conducted among adult populations (N=8). CRP was assessed consistently, with most studies using blood/serum levels of CRP (N=8) and one using a measure of salivary CRP levels.

The pooled correlation size for the associations between discrimination and CRP was *r* = *0.13 [95% CI: 0.01, 0.24; k=9]*. Correlation sizes appear to be larger in smaller studies, though larger studies also show relationships between discrimination and CRP (Figure 2.3). Minimally adjusted models accounted for age, race/ethnicity, lifetime experiences of discrimination, measures of socioeconomic status (e.g., income, educational attainment, employment status), BMI and medications (e.g., statin use, hormone replacement therapy, anti-inflammatory use). Three articles reported solely adjusted associations,[70,88,95] though one only accounted for age, BMI and statin use in the adjusted estimate reported.[88]

Supplemental Figure A.2 illustrates the reported associations and mean correlation size using the most adjusted estimates reported. Marginally significant associations were observed [*r* = 0.10; 95% CI: 0.00, 0.19, *k* = 9]. Correlation sizes appear to be larger in studies with smaller populations, though larger studies also show evidence of an increase in CRP with increased report of discrimination. These associations remain considering the covariates included in the most adjusted models reporting these associations. One paper only reported a minimally adjusted association (correlation), however other articles accounted for factors such as race, age, sex, BMI, measures of socioeconomic status (e.g., financial strain, educational attainment, income), psychological factors (e.g., depressive symptoms, cynicism) and lifetime experiences of discrimination, health behaviors (e.g., physical activity, smoking, alcohol consumption), measures of physiological functioning (e.g., blood pressure, cholesterol and triglyceride levels, HbA1c, vital capacity, adiponectin), health conditions (e.g., heart attack, other vascular diseases, diabetes), and medications (e.g., statin use, anti-hypertensives, diabetes management medications). The similarities in mean correlation sizes from the most and minimally adjusted estimates reported suggest that the relationship between discrimination and CRP is robust to covariate adjustment and may not be strongly mediated by health behaviors (e.g., smoking, drinking).

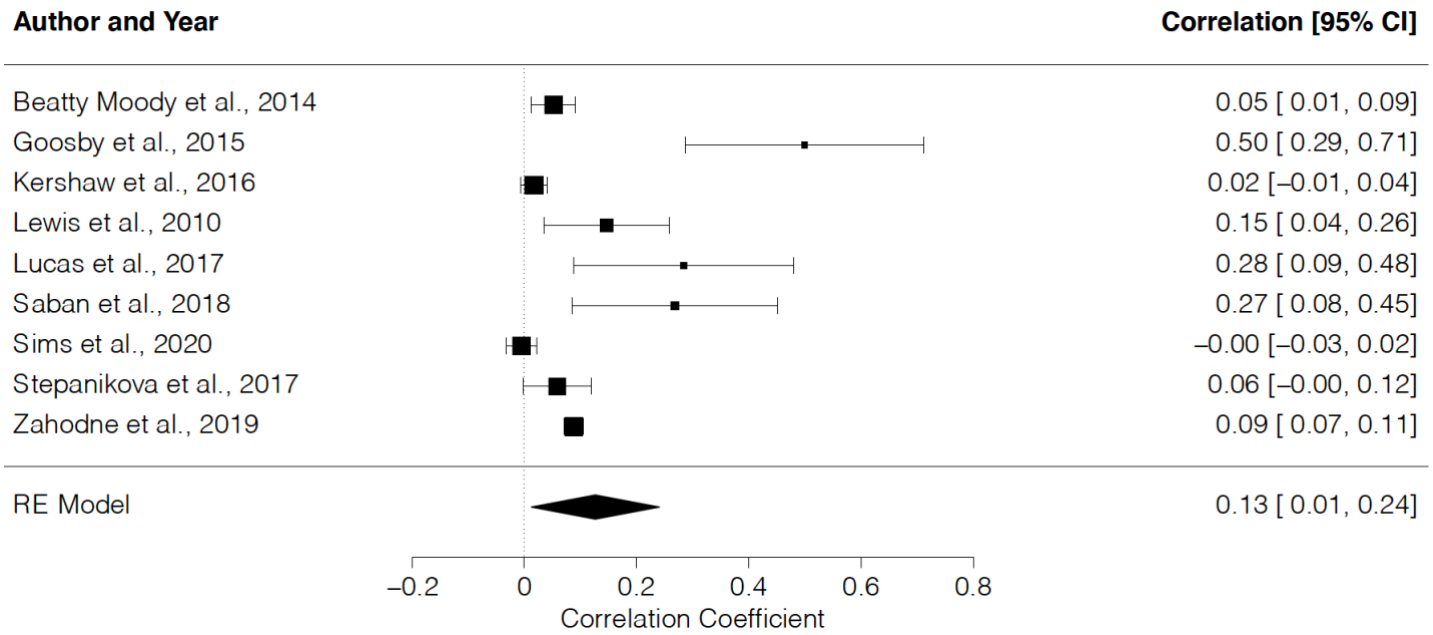

Figure 2.3. Associations between EDS and C-reactive protein (CRP, minimally adjusted)

2.4.3. IL-6

The EDS was operationalized as the sum of frequencies (N=3) or mean of frequencies (N=2) in the eligible studies. Among those reporting racial/ethnic breakdowns of the analytic samples (N=4), white/European participants comprised over 80% of the sample across studies. Measurement of IL-6 levels was captured through blood (N=3) or saliva (N=3). One study assessed both blood and salivary IL-6 levels, though only the adjusted association was reported for the blood IL-6 outcomes.[88] Eligible studies used in the meta-analysis were all cross-sectional in design and conducted among adult populations.

The mean weighted correlation size of discrimination on IL-6 suggests discrimination may not be correlated with elevated IL-6 levels (*r = 0.05*; 95% CI: -0.32, 0.42, k = 5; Figure 2.4A). Minimally adjusted estimates included an unadjusted correlation (N=1) and models (N=4) that accounted for factors such as race/ethnicity, gender, age, measures of socioeconomic status (i.e., income, educational attainment, employment status), medication use (i.e., anti-inflammatory, hormone replacement therapy), and time. Larger correlation sizes were observed among two smaller studies; however, the direction of associations was similar among the two larger studies suggesting that additional work assessing the relationship between discrimination and IL-6 is needed. One association went in the opposite direction, indicating an inverse relationship between discrimination and IL-6 levels.

Additionally, when assessed by measurement of IL-6 (i.e., plasma, salivary), we find the direction of the mean correlation size for the minimally adjusted estimates to be similar among both measures (*r = 0.03; 95% CI: -0.03, 0.09* and *r = 0.06; 95% CI: -0.99, 1.12* for plasma and salivary measures, respectively; Figure 2.4B and C) though the confidence interval is larger among studies using salivary measures of IL-6, possibly indicating greater variability in estimates derived from salivary samples. These assessments should be interpreted with caution given the small sample size for these assessments (k=3 for each) and one study reported only fully adjusted associations between discrimination and plasma IL-6 levels.

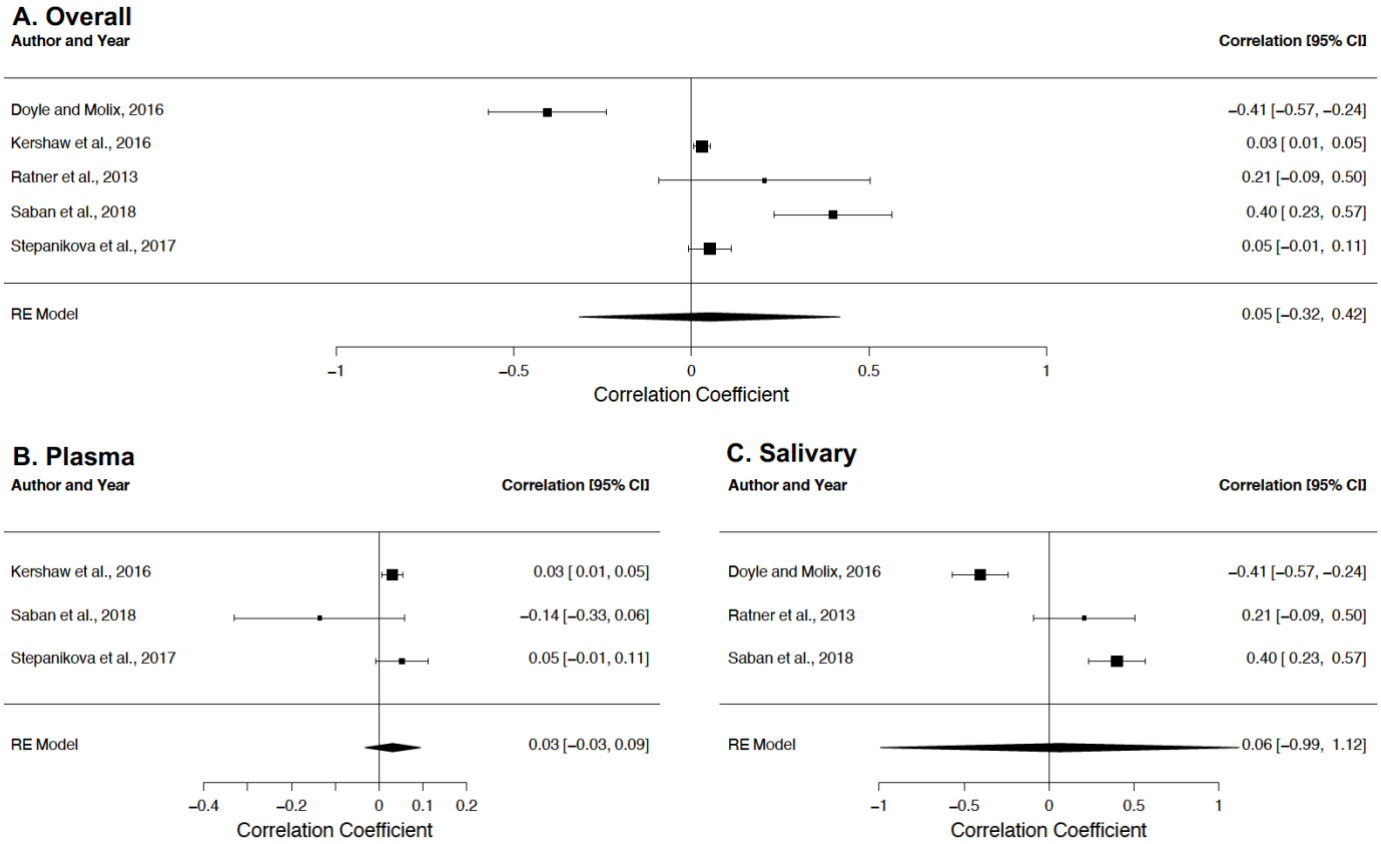

Figure 2.4. Associations between EDS and (a) interleukin-6 (IL-6) across all studies; (b) plasma samples; and (c) salivary samples (minimally adjusted)

Supplemental analysis of the most adjusted estimates reported resulted in a stronger correlation between increased experiences of discrimination and IL-6 levels [r = 0.07; 95% CI: -0.28, 0.42, k = 5], however, the confidence interval is wide and cross the null (Figure A.3). Examining the forest and tree plot, we observed null associations in studies of varying sample sizes (two, relatively large and one small), though the remaining two studies find lower and elevated IL-6 levels associated with increased discrimination. The observed null associations may be a function of covariates included in each model. In most adjusted models, several studies accounted for what could be potential mediators or moderators of the relationship between discrimination and IL-6 levels. Covariates included age, race, marital status, measures of socioeconomic status (i.e., income, employment status, educational attainment), psychological factors (i.e., measures of depression, anxiety, reactivity), perceived social status, reported childhood trauma, medication use (i.e., cholesterol, blood pressure, diabetes, hormone replacement), public and private esteem, BMI, and alcohol consumption.

Though not quantifiable in the present analysis given a limited number of studies, findings from individual studies suggest there may be differences by race/ethnicity, gender, and/or sexual orientation.[73,81] In a multi-ethnic sample of adult men and women, Kershaw et al. found differences in the direction and strength of associations between discrimination and IL-6 by gender. Increased experiences of everyday discrimination were inversely associated with IL-6 levels among men in the sample, while positive associations were observed for women.[81] Assessments of the association between everyday discrimination and IL-6 among a sample of gay men and lesbian women also found differences in the direction and magnitude of associations. Work by Doyle et al. found that increases in discrimination were associated with lower IL-6 levels among lesbian women, though with greater IL-6 levels among gay men.[73] Unadjusted correlation between the EDS and IL-6 from a study conducted among marginalized racial/ethnic groups of women (i.e., Black, Hispanic/Latina, and Afro-Latina) suggests there may be differences in the impact at the intersection of gender and race/ethnicity, however the sample

size was small, and the confidence interval was wide.[86] In a sample of Black and white women the unadjusted and adjusted analyses reported by Saban et al. indicated that increased exposure to discrimination was associated with greater salivary IL-6, though not blood measures.[88]

Mediators. One study explicitly assessed BMI as a potential mediator of the relationship between discrimination and IL-6 in a sample of men and women.[81] Among women, the authors found the positive relationship between everyday discrimination and IL-6 to be attenuated by BMI. However, the inability to establish temporality given the cross-sectional analysis does not provide insight as to whether BMI is subsequent to exposures to discrimination or whether may increase experiences of discrimination.[81]

2.4.4. TELOMERE LENGTH

Three of the six eligible studies operationalized the EDS as the sum of reported frequency of discrimination. Assessments also included the mean of frequency of experiences of discrimination (N=2) and a dichotomized assessment of if a respondent ever experienced everyday discrimination and attributed it to a personal characteristic (yes/no). The racial/ethnic breakdown of analytic samples were provided in 5 of the 6 studies, with white participants comprising 60% of the overall study populations. Black participants comprised approximately 33% of the overall sample size, followed by Latinx/Hispanic participants (7.4%). Asian, Native Hawaiian/Pacific Island, multiracial or “Other” racial/ethnic individuals were not represented in the studies eligible for inclusion. All eligible studies used quantitative polymerase chain reaction (qPCR) to assess and quantify telomere length, which is optimal for large studies given the small sample needed to replicate DNA and assess telomere length.[107] Additionally, all studies utilized leukocyte samples to ascertain telomere length. Three studies examined associations between discrimination and telomere length using the ratio of telomeric length of DNA to a

single-copy control gene (T/S ratio) which is correlated with telomere length,[98-100] while others converted the T/S ratio to kilobase or base pairs to compare differences in length.[71,76,102] Everyday discrimination was not associated with telomere length when minimally adjusted models were assessed (*r = 0.03; 95% CI: -0.01, 0.07, k=6)*. Examining the forest and tree plot, we observe that most studies indicate a null association, with larger studies finding discrimination to be associated with longer telomere length. Minimally adjusted estimates included unadjusted regression coefficients (N=2), estimates from an age-adjusted model (N=1), and two adjusted estimates that accounted for age, race, sex, measures of socioeconomic status (i.e., poverty-to-income ratio; educational attainment); and psychosocial stress (i.e., safety stress, physical environment and negative social interactions).

Supplemental analyses of fully adjusted estimates exhibited similar associations. The mean correlation size using the most adjusted estimates reported were not statistically significant [r = 0.02; 95% CI: -0.02; 0.06]. Models accounted for factors such as age, race, sex, measures of socioeconomic status (i.e., poverty-to-income ratio; educational attainment); and psychosocial stress (i.e., safety stress, physical environment, negative social interactions, perceived stress); psychological factors (i.e., depression, reaction type); smoking status; BMI; health conditions (e.g., diabetes, hypertension, myocardial infarction, cancer), Census region of birth; childhood health; lifetime substance use and physical activity.

Mediators. Two studies explicitly examined potential mediators of the relationship between discrimination and telomere length. Work by Liu and Kawachi assessed whether physical activity, smoking status, and having a BMI $\geq$ 30 kg/m^2 mediated the relationship between discrimination and telomere length.[99] The authors found evidence that suggested these factors mediate the relationship between everyday discrimination and telomere length, observing attenuated associations when these factors were included in regression analyses. Sullivan et al. examined whether depressive symptoms and perceived stress mediated the relationship between discrimination and telomere length.[102] The authors found that observed associations

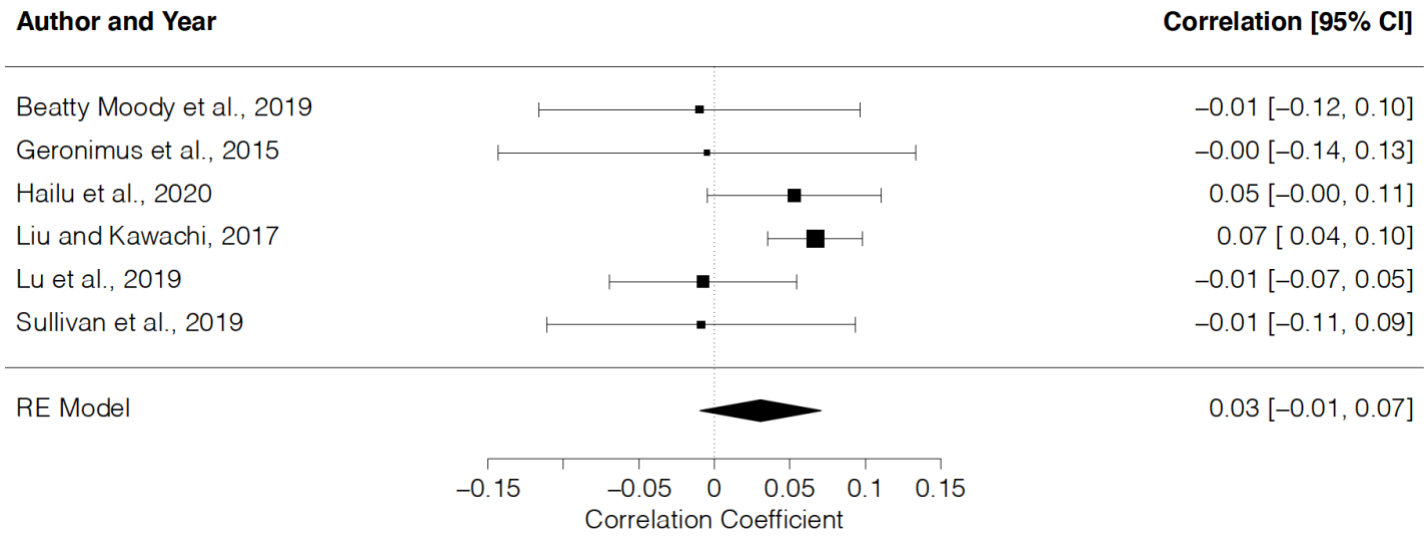

Figure 2.5. Associations between EDS and telomere length (minimally adjusted).

between everyday discrimination and telomere length among Black and white women remained after accounting for mediating variables, with correlation sizes remaining larger (i.e., shorter telomere length) for Black women; though no associations were observed among men.

Quality Assessment. The limited availability of longitudinal assessments of the relationship between the EDS and biomarker outcomes leaves us unable to assess the temporality of associations. Across all outcomes, most studies were cross-sectional (77.8%, 62.5%, 100%, and 100% for cortisol, CRP, IL-6 and telomere length respectively). Several studies utilized nonrepresentative sampling procedures (N=7, 6, 3, and 1 for cortisol, CRP, IL-6, and telomere length, respectively). This may raise concerns regarding potential bias such that correlation sizes may be estimated from samples that may not be generalizable, however they do provide context to the experiences of individuals from similar backgrounds (i.e., communities with similar sociodemographic characteristics). However, most studies assessing representative samples contributed greater weights to the estimated mean correlation size given the small variances across all outcomes. Most studies used the full EDS or short form (N= 8, 8, 4, 4), with few utilizing modified versions. Among studies reporting the Cronbach's alpha (N=19), α was greater than or equal to 0.70 suggesting acceptable or better internal consistency of the measure. Studies reporting adjusted models accounted for several socioeconomic, demographic, and health-related covariates that may confound the relationship between discrimination and biomarker outcomes. Adjusted models sometimes accounted for potential mediators of the relationship (i.e., perceived stress) that may have partially accounted for the effect of discrimination.

2.4.5. Assessment of Publication Bias

Funnel plots (Figure 2.6) and Egger's tests were used to evaluate the possibility of publication bias. Among studies that examined cortisol, eligible studies tended to have smaller

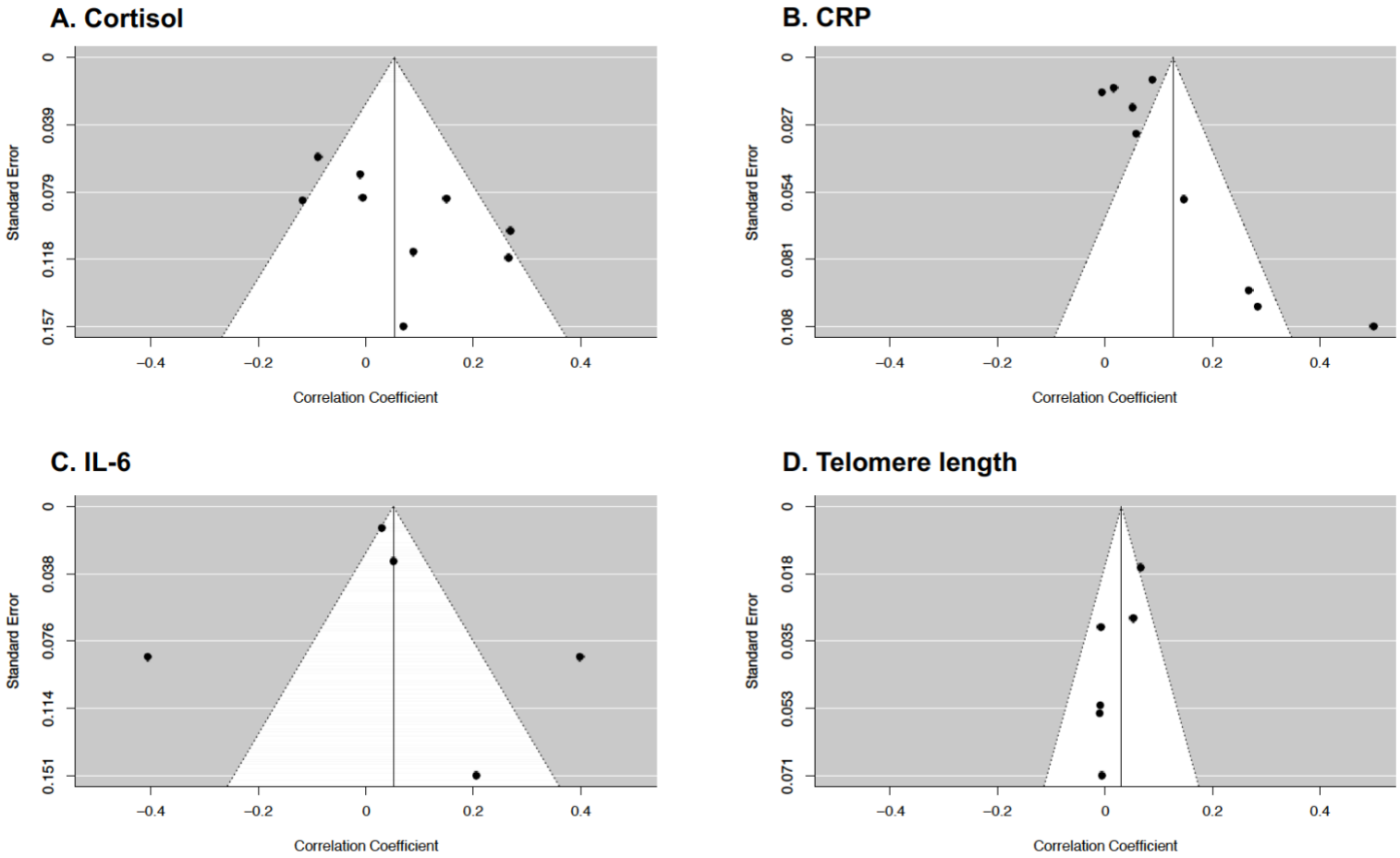

Figure 2.6. Funnel plots for A) cortisol; B) CRP; C) IL-6; and D) telomere length

standard errors, but eligible studies had positive, negative, and null associations. Results from the Egger's test to assess funnel plot asymmetry in funnel plots were not statistically significant ($t = 1.91$, $df = 7$, $p = 0.098$), suggesting that the funnel plot for cortisol is not imbalanced (i.e., no publication bias). Assessment of the funnel plot for CRP outcomes appears to be asymmetric. Eligible studies tend to have small standard errors or larger correlation sizes. Results from the Egger's test were statistically significant ($t = 4.92$, $df = 7$, $p = 0.002$), suggesting potential publication bias. Fewer studies examined IL-6 and telomere length. The funnel plot for IL-6 appears to be relatively symmetric, with eligible studies having variations in correlation size and standard error. One study was included that documented associations in the opposite direction for IL-6 (i.e., lower IL-6 levels for increased report of discrimination). Eligible studies examining telomere length had varying directions (i.e., null, and positive associations reported). The Egger's test for IL-6 was not statistically significant, suggesting that publication bias may not be a concern ($t = 0.30$, $df = 3$, $p = 0.785$); however, Egger's test for telomere length was significant ($t = -3.00$, $df = 4$, $p = 0.040$) indicating the possibility of publication bias. These results should be interpreted with caution as the Egger's test has limited power when used in a small sample of studies.

2.5. DISCUSSION

Though previous meta-analyses have examined the relationship between discrimination and several health outcomes, variations in the measurement of discrimination have made cross-study comparisons difficult. Evidence from meta-analysis by Paradies et al. suggests that the relationship between discrimination and health outcomes vary according to the measure of discrimination used.[5] This meta-analysis is the first to standardize the measure of discrimination to assess the association of discrimination and health by restricting the review to only studies that have used the Everyday Discrimination Scale. It is also the first to estimate the pooled

correlation coefficient across studies that have examined the relationship between discrimination and molecular biomarkers of stress, inflammation, and cellular aging.

Through a systematic search we were able to identify 24 articles eligible for quantitative assessment that provide context to the biological pathways through which reported experiences of discrimination become embodied. The findings of this meta-analysis are mixed. Among eligible studies, we found that the measurement of discrimination was fairly consistent with most studies operationalizing the EDS as the mean or sum of reported frequency (N=20). Our findings also suggest that increased self-report of discrimination is associated with higher CRP levels, but we did not observe statistically significant associations between discrimination and cortisol, IL-6 or telomere length. Additionally, one study that was eligible for inclusion, but sufficient data was not able to be obtained found null associations between discrimination and CRP levels in a sample of women from the Community Child Health Network study.[77]

Null associations between discrimination and cortisol and telomere measures were not surprising as neither of these biomarkers have been consistently associated with other types of stress. A recent meta-analysis of 16 studies examining racial discrimination and cortisol output found a null association.[108] We compare our findings to meta-analyses of other sources of psychosocial stress on biomarker outcomes. Our findings regarding cortisol are similar to conclusions from a meta-analysis by Fogelman and Canli that examined early life stress, which found null associations between early life stress and cortisol.[109] Contrary to our findings with discrimination and CAR, a meta-analysis of studies examining psychosocial factors (e.g., general life stress, fatigue/burnout) and the cortisol awakening response by Chida and Steptoe found varying associations depending on the stressor.[110] Positive associations were observed between the CAR and general life stress, for example, and negatively associated with fatigue and burnout.[110] Reviews and meta-analyses indicate associations between psychosocial stress (e.g., discrimination, stress tasks) and inflammatory markers.[33,111] A meta-analysis of studies examining self-reported psychological stress, using measures such as the Perceived Stress

Scale, and telomere length found evidence of a small decrease in telomere length with increased report of stress exposure.[36]

We noted three factors (1) heterogeneity in outcome measurement; (2) study design; and (3) sample demographics that could have contributed to our mixed findings. First, the observed findings between discrimination and cortisol, IL-6, and telomere length may be influenced by several factors related to outcome measurement. Specifically, eligible studies differed in their operationalization of biomarker outcomes. Among studies that examined cortisol, differences in both the number of samples captured and cortisol outcomes assessed (e.g., momentary cortisol, hair cortisol concentration) were observed. The use of hair cortisol in this analysis may contribute additional challenges given that hair samples provide insight into cortisol levels over a period ranging from several weeks to months.[112] Evaluating studies that used the same assessments of cortisol, we observed null associations between discrimination, lower waking cortisol levels, and the CAR. Given the variability in the measurement protocols for cortisol, differences in the number of samples taken and cortisol measures assessed in eligible studies could influence the mean correlation size estimated.[104] For example, cortisol levels fluctuate throughout the day, typically with higher levels at waking and lower during the evening.[104,105] Cortisol levels are also sensitive to the method of collection (i.e., blood, saliva) and typically require repeated sampling to establish an understanding of the cortisol trajectory.[104] Additionally, research has found that diurnal cortisol slopes, specifically having flatter diurnal slopes (e.g., CAR) provide insight into immunosuppressive and inflammatory responses.[106] Researchers have found associations between self-reported stress and flatter diurnal cortisol slopes, though few studies have examined discrimination and indices of diurnal slopes, with five identified in the present study. [72,75,79,80,97]

Among studies with markers of inflammation (i.e., IL-6, CRP) as outcomes, we found differences in how inflammation was assessed. Among studies that examined CRP, most utilized blood collections, though one examined saliva samples. Eligible studies captured IL-6

samples through blood (N=3) or saliva (N=3), with one study assessing both. While the mean correlation sizes across studies that used either measure where similar (*r = 0.03; r = 0.06*, plasma and saliva respectively), we observed a much wider confidence interval across studies using salivary assessments. This could reflect greater variability in salivary assessments of IL-6; however the intervals may also be wide given the limited number of studies available. These differences suggest points for consideration for future research, specifically in the means of assessment of inflammatory markers. Previous research has concluded that plasma and salivary samples of inflammatory biomarkers (i.e., IL-6, CRP) may not be strongly correlated, and that blood samples – though relatively invasive – are still preferred to salivary measures to assess systemic inflammation.[113,114]

Additionally, optimal assessments of telomere length are still being explored. All eligible studies used qPCR to assess telomere length which has several strengths that Montpetit et al. have summarized in great detail.[107] These strengths include that the method requires a small sample of DNA, is easily implemented in large studies, and has a reference of which to compare samples to. However, this method is sensitive to the quality of the DNA sample and the reference is not standardized which makes cross-study comparisons difficult.[107] Additionally, qPCR provides an estimate of the telomere amplification product (T) as compared to that of a reference single-copy gene (S).[107,115] This is used to create a T/S ratio that correlates with average telomere length, but does not yield a base pair estimate.[107] While qPCR has been widely accepted as an approach to assess telomere length, other techniques exist to determine telomere length.[107] These include flow-fluorescence in situ hybridization (FISH) and Southern blot, which is often referred to as the golden standard.[115] The FISH method is labor intensive and is likely not useful for large scale epidemiologic studies, additionally obtaining needed samples can be difficult given its' reliance on intact nuclei rather than DNA like qPCR and Southern blot.[107,115] Work by Aviv et al. found that the measurement error in qPCR analysis was greater than that of Southern blot, however both techniques yielded reproducible results (r >

0.90 for both).[115] Both qPCR and Southern blot measure comes with a set of tradeoffs. While Southern blot does provide an estimate of mean telomere length in kilobase pairs and does not require highly specialized equipment, the quality of the DNA sample is more important, and the amount of sample needed is greater than that of qPCR.[115] These differences in measurement across all four outcomes may have been contributors to the heterogeneity of findings and, as such, may cloud the interpretation of the estimated mean correlation coefficients. Observed differences in sample types and quality, frequency of measurement, as well as methodology implemented highlight a need for the identification of measures that accurately reflect biomarker levels and implement consistency in biomarker operationalization across studies.

Second, we found that the eligible studies were largely cross-sectional in design, with few longitudinal assessments of the relationship between discrimination and biomarker outcomes. The large representation of cross-sectional studies obscures the ability to establish temporal associations, inhibiting the assessment of directionality. Additionally, longitudinal assessment of experiences of discrimination affords opportunities to examine trajectories of experiences over time and the cumulative impacts of discrimination on biomarker outcomes. Several studies employed non-representative sampling, which may reflect populations that are more or less likely to report experiences of discrimination but provide insight into the experiences of individuals and communities with similar characteristics.[5] Priorities of future research on discrimination and health is more longitudinal assessments and representative sampling. Additionally, while the literature on discrimination and health is global,[10,116] assessments between discrimination and biomarkers that use the EDS are predominantly focused on the United States (N=23) and should be examined in other national contexts to assess comparability.

Last, differences in the strength of associations between discrimination and biomarker outcomes were observed among individual studies, though not quantitatively examined in the present analysis, which may be due attributable to sample demographics. Specifically, studies

that examined associations among marginalized groups observed different associations that what were estimated across studies. For example, Lehrer et al. found that everyday discrimination was associated with hair cortisol concentration among Black participants, though not whites.[82] Analysis among Black and white adults in the Mental Stress Ischemia Mechanisms and Prognosis Study (MIPS) by Sullivan et al. found greater effects of everyday discrimination on telomere length among Black and white women, with larger effect sizes among Black women.[102] No associations between everyday discrimination and telomere length were observed among Black or white men in the sample. Doyle et al. found that IL-6 levels were higher among gay men with increased report of discrimination with inverse associations observed among lesbian women.[73] Similar to other meta-analyses of discrimination, we found that white/European respondents comprised nearly 85% of the study populations overall, though this varied by biomarker. Assessments of effect modification by sex, race or ethnicity, and other social factors remain mixed in the literature. For example, a meta-analysis of the relationship between racial discrimination and cortisol found that neither age, race/ethnicity, sex, nor type of measure modified the observed mean correlation size.[108] Differential relationships among marginalized racial/ethnic, gender, or sexual orientation groups may be obscured in study populations where those groups are less represented and require further examination in future research.

CRP, cortisol, IL-6 and telomere length were frequently assessed outcomes from our search. However, in addition to studies in the meta-analysis, the narrative review revealed a broader range of biomarkers that could be included in future research. Friedman et al. found that everyday discrimination was associated with greater E-selectin levels, an indicator of inflammation response, among men, but not women in a sample of adults in the Midlife in the United States study (MIDUS).[74] Using data from a community sample of adults with poorly controlled Type 2 diabetes, Potter et al. found that everyday discrimination attributed to weight was associated with elevated HbA1c levels,[85] a measure of fasting blood glucose levels and an

indicator of glucose metabolism and regulation. Relationships between everyday discrimination and DNA methylation, an indicator of stress, were assessed in two studies.[89,94] Among a sample of Latina mothers, Santos et al. found that everyday discrimination was inversely associated with DNA methylation (less methylation with increased discrimination),[89] while van der Laan et al. found everyday discrimination to be positively associated with DNA methylation among participants in the Research on Obesity and Diabetes among African Migrants (RODAM) study.[94] Saban and colleagues examined the relationship between several social factors – including everyday discrimination – and heat shock protein-70 (HSP-70), another stress-related biomarker, in a small sample of Black and white women with atherosclerosis.[87] The authors did not observe an association between discrimination and HSP-70 levels, though this association should be examined in a larger study population. Additional inflammatory biomarkers have been identified in a recent review of the relationship between discrimination and inflammation.[33] Future research should examine relationships between discrimination and these understudied indicators of biological functioning.

Associations between discrimination and the identified biomarkers may differ other measures of discrimination are used (e.g., Experiences of Discrimination[117,118], Major Experiences of Discrimination Scale[30], Schedule of Racist Events[119]), though this should also accompany increased research examining discrimination and biomarker outcomes more generally. It is plausible that the observed differences in associations between self-reported racism and several health outcomes by instrument (and instrument characteristics) identified by Paradies et al. could extend to the assessment of associations between discrimination and biomarkers. Studies using the Experiences of Discrimination scale have found positive associations with IL-6 levels,[120] though null associations with telomere length.[121] Work examining the relationship between discrimination using the Schedule of Racist Events and cytokine levels (i.e., indicators of inflammation) found increased discrimination to be associated with elevated cytokines.[122,123] An eligible study also assessed associations between

discrimination and telomere length using the Major Experiences of Discrimination Scale finding null associations.[98] It seems that the direction of relationships are relatively consistent across measures, however these are comparisons to individual studies. Future research estimating the pooled correlation size between discrimination and biomarker outcomes across studies that use measures that capture different forms, severity, and specific attributions of discrimination would be insightful to characterizing how discrimination adversely impacts wellbeing prior to disease endpoints.

The present meta-analysis is not without its limitations. We only include findings from published manuscripts, which may differ from associations reported in unpublished works. Specifically, results from the Egger's test suggests publication bias among studies that assessed CRP and telomere length, though not for cortisol or IL-6. This may reflect a trend of not publishing null findings for CRP and may also reflect the need for more research on IL-6, telomere length, and cortisol given the smaller number of studies examined in the present analysis. We estimated mean correlation sizes from minimally adjusted associations reported in each article, however we also examine associations reported in most adjusted models in an effort to account for potential confounders of the association.

This study also has several strengths. It quantifies the relationship between discrimination and molecular biomarkers, which provide evidence for some of the pathways that discrimination may become embodied. We also examine the relationship among studies that use the same measure of discrimination, the EDS, thus increasing the comparability across studies. The EDS is a widely used measure in both domestic and international contexts. Full, abbreviated, or modified versions of the EDS are included in many major epidemiologic studies in the United States and elsewhere (See for example: [124-130]). The frequent inclusion of EDS in cross-national studies to examine the implications of discrimination on health allows for the systematic examination of the strength of associations between discrimination and health using a standardized exposure. Additionally, the utility of the EDS in accurately capturing experiences

of discrimination has been documented across a wide range of populations, with documented internal consistency and validity[52,131,132]. We also evaluate, where possible, the relationship between discrimination and biomarkers among studies that have utilized similar means of outcome assessment (i.e., CAR, waking cortisol, blood and salivary IL-6) in an effort to further increase the comparability across studies.

Overall, our results provide information on the relationships between discrimination and several molecular biomarkers. The number of studies was limited, but we did find associations consistent with discrimination having an adverse effect, though evidence is weak at this point. There is a need of research using a broader range of biomarkers to better characterize the relationships between discrimination and physiological indicators. This study identifies associations between discrimination and biological indicators that have been identified as possible precursors to adverse health outcomes using consistent measure of discrimination. We also provide considerations for future research utilizing biomarker outcomes in an effort to strengthen ongoing efforts.

3

Racial discrimination and blood pressure: an instrumental variable analysis

3.1. ABSTRACT

Experiences of racial discrimination are correlated with elevated blood pressure, although previous studies have not been uniformly consistent. Using data from Exam 4 of the Coronary Artery Risk Development in Young Adults (CARDIA) study, we examined the relationship between experiences of racial discrimination in institutional settings and blood pressure. We conducted an instrumental variable analysis using reflectance meter measurement of skin color as the instrument. Findings suggest that increased experience of racial discrimination is associated with increased systolic and diastolic blood pressure (β=2.23 mmHg; 95% CI: 1.85, 2.61; β=1.31; 95% CI: 1.00, 1.62, respectively). We also find that these effects are stronger among women and individuals in higher income households.

3.2. INTRODUCTION

Elevated blood pressure (BP) is an established risk factor for angina, stroke, and myocardial infarction[38]. Substantial inequities in elevated blood pressure have been documented among marginalized racial groups in the United States. Approximately 57% of non-Hispanic Black adults have elevated resting blood pressure or are on antihypertensive medication, compared to 44% of non-Hispanic white adults[39]. Several factors, including

psychosocial stressors such as racial discrimination, have been examined as potential contributors to racial inequities in elevated blood pressure and hypertension status[18,22,40,41].

Prior studies have documented positive associations between self-reported discrimination and elevated blood pressure or hypertension; however, findings have been inconclusive[18]. A recent meta-analysis by Dolezsar and colleagues found there to be no statistically significant relationship between combined measures of perceived racial discrimination and resting blood pressure; however, the analysis did find racial discrimination to be associated with hypertension status[22]. Additionally, the authors found measures that capture institutional dimensions of racial discrimination (e.g., experiences occurring in institutional settings such as housing) had strong positive associations with resting systolic and diastolic blood pressure.

Studies have also found heterogeneity in the associations between racial discrimination and health outcomes – for example, by gender – suggesting potential differences in the embodiment of experiences of discrimination[116,133]. Evidence from meta-analysis suggests that the association between racial discrimination and hypertension is stronger for men than women[22]. Differences in the report of racial discrimination by socioeconomic status (SES) have also been explored, though less is known[40]. Work by Kwate and Goodman found that SES, measured as years of education, was positively associated with reported racism[134], while Brondolo et al. reported that individuals with low SES reported greater lifetime stigmatization and threat, while individuals with higher SES reported more exposure to workplace discrimination[135]. Evidence thus far posits that stressors associated with SES may contribute to a positive association between racial discrimination and elevated blood pressure[116,118,136-138], though which populations are most impacted is not consistent. One study found evidence of varying effects of racial discrimination within strata of sex and class among Black participants in the CARDIA study[118]. Krieger and Sidney observed that Black women in higher occupational positions who reported 3 or more experiences of discrimination had higher systolic and diastolic

blood pressure than women in “working class” positions, however the opposite association was observed among men, though statistical tests of effect modification were not reported[118]. Researchers have called for more explicit examination and testing of relationships between socioeconomic status (SES) and perceived racial discrimination as they pertain to health outcomes[40].

Differences in the results of previous studies may partly reflect challenges to causal inference such as residual confounding and measurement error. For example, suppressing reactions to racial discrimination could be associated with under-reporting of experiences of discrimination *and* also associated with elevated blood pressure[118].

In the present analysis, we implemented an instrumental variable (IV) approach to identify the effect of racial discrimination on blood pressure and probability of hypertension within a sample of Black and white adults in the United States, hypothesizing that increased experiences of racial discrimination are associated with elevated blood pressure and greater probability of hypertension. We also investigate whether there is evidence of effect modification by gender, income, and educational attainment.

3.3. METHODS

3.3.1. DATA

We used publicly available data from the Coronary Artery Risk Development in Young Adults (CARDIA) study. CARDIA is a prospective cohort study of 5115 Black and white adults aged 18-30 at the time of baseline data collection (1985-86). The recruitment strategy and study design of the cohort have been summarized in further detail elsewhere[139,140]. The cohort was established to examine risk factors for clinical and subclinical cardiovascular disease, with participants recruited from four centers: Birmingham, AL (n=1179); Oakland, CA (n=1426); Chicago, IL (n=1109); and Minneapolis, MN (n=1402)[140]. Participants were recruited using

random-digit dialing from total communities or census tracts; however, in Oakland participants were randomly selected from a healthcare plan[140]. Sampling was stratified to obtain equal representation of individuals in each race (Black, white), age (18-24, 25-30), gender, and educational group (education ≤ 12, education > 12), with 51% of eligible contacted persons enrolling in the baseline survey. Retention of the surviving cohort during the follow-up examinations was 91%, 86%, 81%, 79%, 74%, 72%, 72% and 71% for Exams 2 through 9 (years 2, 5, 7, 10, 15, 20, 25, and 30 of the study).

Our primary analysis is based on data from Exam 4 (year 7, n = 4085), the year in which skin color was measured in cohort participants. Given the use of publicly available, de-identified data, this study was considered to be exempt by the Harvard School of Public Health Institutional Review Board.

3.3.2. MEASURES

Exposure – The exposure of interest was an instrument that captures experiences of racial discrimination in institutional settings that is derived from a prior instrument developed by Krieger[117,118]. Participants responded to a survey item inquiring about whether they "ever experienced discrimination, been prevented from doing something, or been hassled or made to feel inferior in any of the following seven situations" because of their race or color: at school; getting a job; at work; getting housing; getting medical care; from the police or in the courts; on the street or in a public setting. Responses were assessed as counts of experiences ranging from 0 to 7.

Primary and Secondary Outcomes – Our primary outcome is blood pressure – systolic and diastolic blood pressure captured with a random zero sphygmomanometer by trained technicians. Per CARDIA protocol, three measures were taken at 1-minute intervals with the average of the last two measures reported[141]. Secondary outcomes include hypertension

classification and change in blood pressure over time. Participants were categorized as having a diagnosis of hypertension (yes/no) following the American College of Cardiology/American Heart Association guidelines which define hypertension as systolic ≥ 130 mmHg or diastolic ≥ 80 mmHg[142]. CARDIA participants were also asked whether they were taking medications for high blood pressure. Responses of 'yes' were coded as having hypertension, even if their blood pressure was under control. Additionally, we assessed change in blood pressure (in continuous mmHg) from Exam 4 to Exam 5 (year 10).

3.3.3. INSTRUMENTAL VARIABLE ESTIMATION

To identify the causal effect of racial discrimination on blood pressure, we employ an IV analysis, specifically using a two-stage least squares (2SLS) linear model to estimate the local average treatment effect (LATE). IV analysis is useful in that it addresses issues related to unmeasured confounding reported in observational research. Using an instrumental variable analysis allows for the estimation of unbiased effects of the exposure (i.e., racial discrimination) on the outcome (i.e., blood pressure) even when there are unmeasured confounders, under a certain set of assumptions[143].

We used skin color (described below) as our instrument for experiences of racial discrimination. The key assumptions of our IV analysis include (1) relevance, i.e., the instrument (reflectance meter measure of skin color) is associated with the exposure (experiences of discrimination), (2) the exclusion restriction, i.e., the instrument (skin color) is only associated with the outcome through the exposure; and (3) marginal exchangeability, or that the instrument and the outcome have no shared causes after accounting for measured confounders[144,145]. A fourth assumption – homogeneity or monotonicity – is required to obtain and appropriately interpret the point estimate of the association[144]. The homogeneity assumption requires that skin color does not modify the association between discrimination and blood pressure among those

reporting discrimination (exposed) and those not reporting experiences of discrimination (unexposed) on the additive scale, and provides an estimate of the average treatment effect (ATE)[144,145]. Monotonicity is a more relaxed version of this assumption and solely requires that the instrument only affects the exposure (discrimination) unidirectionally for everyone[144]. However, if monotonicity is assumed, the estimated parameter that is identified is the average treatment effect among the compliers (or the LATE) instead of the ATE.

Our instrument is objectively measured skin color. CARDIA technicians collected data on skin color through the use of a reflectance meter during Exam 4. Assessments were taken on the inner upper arm, using blue, amber, and green filters[141]. Values range from 0 to 100, referring to the percentage of reflected light. Low values indicate low reflectance which is indicative of darker skin[141]. We used measurements from the blue filter as it yields the strongest instrument (i.e., highest F statistic), although prior studies found values between the three filters to be highly correlated and chose to use values from the amber filter[137,138]. Only the first assumption, relevance of the instrument, can be tested using an F test on the relationship between skin color and discrimination, referred to as the first stage of the IV model. We used the F statistic greater than 10 as the cutoff[146]. We performed the Wu-Hausman test which compares the ordinary least squares (OLS) estimate to the IV estimate. The null hypothesis is that both the OLS estimate and IV estimate are constant, and given that the OLS is more efficient, the OLS estimate should be used[147].

Covariates – In the OLS regression for the primary outcome (i.e., blood pressure), we included as covariates age (assessed continuously), gender (male; female), marital status (married; never married; widowed/divorced/separated/other), measures of socioeconomic status (SES), including educational attainment (≤ 12 years; > 12 years) and income (≤$24,999; $25,000 to $49,999; ≥$50,000) [148,149], and health insurance status. Additionally, we controlled for waist

circumference (cm), receipt of medication for hypertension (yes; no), as well as cigarette and alcohol consumption.

3.3.4. STATISTICAL ANALYSIS AND MODELS

All statistical analyses were conducted using R Statistical software[67]. The two-stage least squares (2SLS) approach was implemented using the "AER" package in R[150,151].

Analyses were conducted examining the overall association between racial discrimination and blood pressure. While the following models are written in the first and reduced stage format, the 2SLS approach was used to estimate the local average treatment effect (LATE) of racial discrimination on blood pressure, allowing for the estimation of corrected standard errors[150,151]. IV analysis essentially consists of two models, the "first stage" and "reduced form". The first stage is fit as:

$$\textbf{\textit{First stage}}: discrimination = \beta_0 + \beta_1 SC + \eta$$

Where SC = skin color and η = error term. This model regresses the predicted number of self-reported experiences of racial discrimination on skin tone (range: 0-100). The associated F-statistic in this stage provides support to the relevance assumption.

Blood pressure (in continuous mmHg) was then regressed on the predicted values of self-reported experiences of racial discrimination in the reduced form model, fit as below:

$$\textbf{\textit{Reduced form}}: BP = \beta_0 + \beta_1 \widehat{discrimination} + e$$

Where BP = blood pressure measures, $\widehat{discrimination}$ = the predicted values of self-reported experiences of discrimination from the first stage, and e = error term. β_1 yields the IV estimator of the effect of an increase in racial discrimination on blood pressure[143].

As a comparison to the IV model, we performed an OLS regression model to estimate the effect of discrimination on blood pressure, adjusting for the covariates listed in the section above. The fully adjusted model was fit as:

$$BP = \beta_0 + \beta_1 discrimination + \beta_c covariates + e_0$$

As secondary analyses, we examined effect modification of blood pressure outcomes by gender, education, and income. In our supplemental tables we report results from models that switched the outcome from continuous blood pressure (in mmHg) to the probability of receiving a diagnosis of hypertension and assessed the effect of discrimination on change in blood pressure from Exam 4 (year 7) to Exam 5 (year 10).

3.4. RESULTS

Sample characteristics are summarized in Table 3.1. The analytic sample was restricted to participants with data on experiences of racial discrimination, skin color, and blood pressure measures, resulting in 3876 eligible participants. Imputation of missing covariate variables was conducted using the built-in multivariate imputation by chained equations technique available in the "mice" package in R[152]. A total of 144 observations were missing some combination of covariate variables (3.72% of the analytic sample) with the greatest proportion missing data on income (1.37% missing) and educational attainment (1.41% missing), though these were the only two variables to exceed missingness of 1%. Imputations were conducted over 5 iterations, using proportional odds models for ordinal categorical variables (i.e., income, educational attainment) and polytomous logistic regression for nominal categorical variables (i.e., marital status). Binary categorical variables were imputed using logistic regression (i.e., high blood pressure medication (yes/no), drinking over the past year (yes/no)), while numeric variables were imputed using predictive mean modeling (i.e., waist circumference).

During Exam 4 of CARDIA, the average age of the sample was 32 years; ranging from 25 to 37 years. Approximately 48% of the sample was Black and 55% women. In the overall sample, the mean value of discrimination scores was 1.6 (range: 0 to 7), though approximately 46% of the

sample reported no experiences of discrimination and 80% of respondents reported 3 or fewer experiences. Average reports of racial discrimination were higher among Black participants (2.81) compared to white participants (0.50). Additionally, the average diastolic and systolic blood pressure measures were 69 mmHg and 109 mmHg, respectively. Differences between Black and white respondents' systolic and diastolic pressure were statistically significant ($p < 0.001$).

Results from the Wu-Hausman tests rejected the null hypothesis of the OLS and IV models being consistent, indicating a benefit in the use of IV analysis[153]. Table 3.2 presents the results from the instrumental and OLS models that examine the relationship between racial discrimination and blood pressure. To assess the relevance assumption (i.e., that skin color is associated with racial discrimination scores), we report both the beta coefficient for the relationship between skin color and discrimination (β= -0.10, 95% CI: -0.10, -0.09) and the F-statistic. Using the F-statistic and results from the test of weak instruments, we find that the reflectance meter measure of skin color has a strong association with racial discrimination scores (F-statistic: 1472.95, $p<0.001$). Using the IV estimate, we observed that each 1.0 unit increase in report of racial discrimination was associated with a 1.31 mmHg (95% CI: 1.00, 1.62) higher DBP. Similarly, the IV estimate showed increases in racial discrimination were associated with a 2.23 mmHg (95% CI: 1.85, 2.61) increase in systolic blood pressure. Table 3.2 also presents the unadjusted and adjusted OLS estimates of the effects of racial discrimination on blood pressure, respectively. Fully adjusted models suggest an increase in both diastolic and systolic blood pressure for each unit increase in reported racial discrimination (β = 0.21; 95% CI: 0.05, 0.36; β = 0.30; 95% CI: 0.12, 0.48, respectively).

Table 3.1 Summary data of the CARDIA sample (overall and by race)

	Overall	Black	White
N	3876	1865	2011
Race [n (%)]			
Black	1865 (48.1)	1865 (100)	-
White	2011 (51.9)	-	2011 (100)
Gender [n (%)]			
Female	2114 (54.5)	1071 (57.4)	1043 (51.9)
Male	1762 (45.5)	794 (42.6)	968 (48.1)
Age [m (sd)]	32.01 (3.57)	31.49 (3.73)	32.50 (3.34)
Diastolic BP [m(sd)]	69.38 (10.21)	70.95 (10.86)	67.92 (9.33)
Systolic BP [m(sd)]	108.75 (12.40)	111.32 (13.18)	106.36 (11.11)
Hypertension [n (%)]			
No	3234 (83.4)	1453 (77.9)	1781 (88.6)
Yes	642 (16.6)	412 (22.1)	230 (11.4)
Education [n (%)]			
≤ 12 years	1990 (51.3)	1228 (65.8)	762 (37.9)
> 12 years	1886 (48.7)	637 (34.2)	1249 (62.1)
Income [n (%)]			
≤ $24,999	1300 (33.5)	851 (45.6)	449 (22.3)
$25,000 to $49,999	1417 (36.6)	678 (36.4)	739 (36.7)
≥ $50,000	1159 (29.9)	336 (18.0)	823 (40.9)
Marital [n (%)]			
Married	1698 (43.8)	650 (34.9)	1048 (52.1)
Never married	1600 (41.3)	838 (44.9)	762 (37.9)
Wid/Div/Sep/Oth	578 (14.9)	377 (20.2)	201 (10.0)
Discrimination [m (sd)]	1.61 (2.00)	2.81 (2.15)	0.50 (0.93)
Waist circumference [m (sd)]	83.96 (14.07)	85.84 (14.68)	82.21 (13.25)
Antihypertensive medice [n (%)]			
No	3803 (98.1)	1813 (97.2)	1990 (99.0)
Yes	73 (1.9)	52 (2.8)	21 (1.0)
Tobacco Use – ever [n (%)]			
No	1596 (41.2)	858 (46.0)	738 (36.7)
Yes	2280 (58.8)	1007 (54.0)	1273 (63.3)
Alcohol Intake – past year [n (%)]			
No	693 (17.9)	455 (24.4)	238 (11.8)
Yes	3183 (82.1)	1410 (75.6)	1773 (88.2)

Abbreviations: n, number; BP, blood pressure; Wid/Div/Sep/Oth – Widowed/Divorced/Separated/Other

Effect modification by gender and SES

We used F-tests from OLS models to examine whether the effect of discrimination was modified by gender, income, and educational attainment. Interactions between discrimination x gender were significant for diastolic blood pressure (p=0.006), but not for systolic blood pressure (p=0.535) while interactions between discrimination x income were statistically

Table 3.2 Results instrumental and OLS models examining discrimination and blood pressure

Measure	Unadjusted OLS for skin color – discrimination assessment		IV	Unadjusted OLS for discrimination and blood pressure	Adjusted OLS for discrimination and blood pressure [A]
	Beta	F-statistic	IV estimate	Beta	Beta
Diastolic Blood Pressure	-0.10 (-0.10, -0.09)[B]	1472.95[B]	1.31 (1.00, 1.62)[B]	0.42 (0.26, 0.58)[B]	0.23 (0.08, 0.38)[C]
Systolic Blood Pressure			2.23 (1.85, 2.61)[B]	0.67 (0.48, 0.87)[B]	0.32 (0.15, 0.49)[B]

[A]: adjusted for educational attainment, income, marital status, gender, age at exam 4, waist circumference, alcohol and tobacco consumption, and antihypertensive medication status.
[B]: p <0.001; [C]: p<0.01; [D]: p<0.05

significant for both systolic (p=<0.001) and diastolic blood pressure (p=<0.001). Results are not reported for interactions between discrimination x education given the term was not statistically significant for either systolic or diastolic blood pressure (p=0.768 and p=0.050, respectively). Models stratified by gender are reported in Table 3.3, including the F-statistic of the first stage for each group (F-statistic: 654.40, p<0.001, 840.78, p<0.001 for female and male respondents respectively). The IV estimate for female respondents indicated that each increase in report of racial discrimination was associated with an increase in diastolic blood pressure by 2.22 mmHg (95% CI: 1.75, 2.70) and systolic blood pressure by 3.16 mmHg (95% CI: 2.57, 3.74). Fully adjusted OLS models suggest an increase in diastolic blood pressure (β = 0.27; 95% CI: 0.05,

0.47) associated with an increase in discrimination, however the association was not statistically significant for systolic blood pressure (β =0.17; 95% CI: -0.08, 0.41). Among males in the sample, the IV estimate suggests that increases in racial discrimination are associated with increases in diastolic and systolic blood pressure (β = 0.48; 95% CI: 0.08, 0.88 and β = 1.42; 95% CI: 0.95, 1.88). However, in fully adjusted OLS models, racial discrimination was only associated with increased systolic blood pressure among male respondents (β = 0.45; 95% CI: 0.19, 0.72).

Table 3.3 Results from instrumental and OLS models examining discrimination and blood pressure – stratified by gender

FEMALES	Unadjusted OLS for skin color – discrimination assessment		IV	Unadjusted OLS for discrimination and blood pressure	Adjusted OLS for discrimination and blood pressure [A]
Measure	Beta	F-statistic	IV estimate	Beta	Beta
Diastolic Blood Pressure	-0.09 (-0.09, -0.08)[B]	654.40[B]	2.22 (1.75, 2.70)[B]	0.61 (0.39, 0.83)[B]	0.30 (0.10, 0.50)[C]
Systolic Blood Pressure			3.16 (2.57, 3.74)[B]	0.69 (0.42, 0.95)[B]	0.21 (-0.03, 0.44)
MALES	Unadjusted OLS for skin color – discrimination assessment		IV	Unadjusted OLS for discrimination and blood pressure	Adjusted OLS for discrimination and blood pressure [A]
Measure	Beta	F-statistic	IV estimate	Beta	Beta
Diastolic Blood Pressure	-0.10 (-0.11, -0.10)[B]	840.78[B]	0.48 (0.08, 0.88)[D]	0.17 (-0.06, 0.39)	0.17 (-0.05, 0.38)
Systolic Blood Pressure			1.42 (0.95, 1.88)[B]	0.57 (0.31, 0.83)[B]	0.46 (0.20, 0.71)[B]

[A]: adjusted for educational attainment, income, marital status, age at exam 4, waist circumference, alcohol and tobacco consumption, and antihypertensive medication status.
[B]: p <0.001; [C]: p<0.01; [D]: p<0.05

Stratified results of the relationship between discrimination and blood pressure by income are reported in Table 3.4. Among participants making ≤$24,999, the IV estimates indicated that increases in racial discrimination were associated with 0.97 mmHg increases in diastolic blood pressure (95% CI: 0.23, 1.71) and 2.11 mmHg increases in systolic blood pressure (95% CI: 1.18, 3.03). No statistically significant relationship was observed between discrimination and blood pressure in fully adjusted OLS models. For respondents making $25,000 to $49,999, an increase in experiences of racial discrimination were associated with a 1.38 mmHg (95% CI: 0.91, 1.85) and 1.89 mmHg (95% CI: 1.31, 2.46) increase to diastolic and systolic blood pressure in IV models. The fully adjusted OLS estimate for the effects of discrimination on diastolic blood pressure were significant (β=0.23, 95% CI: 0.00, 0.46), as was the relationship for systolic blood pressure (β=0.39, 95% CI: 0.12, 0.66). The IV estimates for participants with household incomes of ≥$50,000 suggested increases in diastolic (β=1.29, 95% CI: 0.79, 1.79) and systolic (β=2.15, 95% CI: 1.55, 2.75) as a result of increased exposure to racial discrimination. Similarly, OLS models illustrated elevations in diastolic (β=0.55, 95% CI: 0.27, 0.83) and systolic (β=0.72, 95% CI: 0.39, 1.04) blood pressure due to racial discrimination.

Secondary analyses of the probability of having hypertension (Table B.3) and the change in blood pressure from Exam 4 to Exam 5 (Table B.4) are presented in supplementary tables. The IV estimate suggests that increases in experiences of racial discrimination are associated with a 5% increase (95% CI: 0.04, 0.06) in the probability of having hypertension. Fully adjusted OLS models suggest an 1% increase in the probability of having hypertension (95% CI: 0.00, 0.01). Examining changes in blood pressure from Exam 4 to 5, an increase in experiences of discrimination in Exam 4 was associated with a 0.68 mmHg (95% CI: 0.39, 0.96) increase in diastolic and 0.55 mmHg (95% CI: 0.19, 0.81) increase in systolic blood pressure.

Table 3.4 Results from instrumental and OLS models examining discrimination and blood pressure – stratified by income

≤$24, 999	Unadjusted OLS for skin color – discrimination assessment		IV	Unadjusted OLS for discrimination and blood pressure	Adjusted OLS for discrimination and blood pressure [A]
Measure	Beta	F-statistic	IV estimate	Beta	Beta
Diastolic Blood Pressure	-0.08 (-0.09, -0.07)[B]	246.16[B]	0.97 (0.23, 1.71)[D]	0.03 (-0.26, 0.32)	0.03 (-0.24, 0.29)
Systolic Blood Pressure			2.11 (1.18, 3.03)[B]	0.13 (-0.23, 0.48)	-0.02 (-0.33, 0.29)
$25,000 - $49,999	Unadjusted OLS for skin color – discrimination assessment		IV	Unadjusted OLS for discrimination and blood pressure	Adjusted OLS for discrimination and blood pressure [A]
Measure	Beta	F-statistic	IV estimate	Beta	Beta
Diastolic Blood Pressure	-0.10 (-0.11, -0.09)[B]	588.54[B]	1.38 (0.91, 1.85)[B]	0.39 (0.14, 0.64)[C]	0.23 (0.00, 0.46)[D]
Systolic Blood Pressure			1.89 (1.31, 2.46)[B]	0.65 (0.34, 0.95)[B]	0.39 (0.12, 0.66)[C]
≥$50,000	Unadjusted OLS for skin color – discrimination assessment		IV	Unadjusted OLS for discrimination and blood pressure	Adjusted OLS for discrimination and blood pressure A
Measure	Beta	F-statistic	IV estimate	Beta	Beta
Diastolic Blood Pressure	-0.11 (-0.12, -0.10)[B]	696.42[B]	1.29 (0.79, 1.79)[B]	0.88 (0.58, 1.19)[B]	0.55 (0.27, 0.83)[B]
Systolic Blood Pressure			2.15 (1.55, 2.75)[B]	1.17 (0.81, 1.54)[B]	0.72 (0.39, 1.04)[B]

[A]: adjusted for educational attainment, income, gender, marital status, age at exam 4, waist circumference, alcohol and tobacco consumption, and antihypertensive medication status.
[B]: p <0.001; [C]: p<0.01; [D]: p<0.05

3.5. DISCUSSION

Using an instrumental variable approach to account for potential threats to causal inference, we evaluated the relationship between experiences of racial discrimination, blood pressure, and hypertension. We found evidence of increased resting systolic and diastolic blood pressure, as well as increased probability of having hypertension, as a result of increased exposure to racial discrimination. We also found evidence of gender and household income as modifiers of the effects of racial discrimination on blood pressure. Specifically, we found the effect of racial discrimination on diastolic blood pressure to be stronger among women compared to men, but there were no gender differences in the effect of discrimination on systolic blood pressure. We also observed statistically significant interactions between discrimination score and household income – with greater effects on systolic and diastolic blood pressure among individuals in higher income households compared to those in households making less than $25,000.

Our findings are consistent with studies that have observed effects of racial discrimination on blood pressure and hypertension outcomes[18,40,41], specifically among those that have used measures of racial discrimination that capture institutional experiences of discrimination[22]. To combat issues regarding incomplete or unadjusted confounding and measurement error in the assessment of discrimination, our study uses an instrumental variable approach to examine the relationship between racial discrimination and blood pressure. Though evidence of the relationship between discrimination and blood pressure is inconsistent in studies, our findings suggest that alternative methodological approaches may be useful in further assessment.

Findings of effect modification by gender and household income require further exploration. Some studies have suggested differences in the report of racial discrimination among Black men and women, while others have suggested no differences[116,154]. Some work has found there to be similarities in the report of racial discrimination among Black men and

women, though the domains in which each group encountered discrimination varied[134,154]. While Black men are more likely to experience racial discrimination in encounters with police, for example, it has been noted that the educational domain is one area where Black women are more likely to encounter racial discrimination[134]. In qualitative analysis, Kwate and Goodman also found that many of the domains in which Black women are at risk may be unmeasured or unexplored in quantitative analyses (e.g., autonomy, sexuality)[134]. Studies examining effect modification of the relationship between racial discrimination and blood pressure or hypertension by gender have found discrepant findings[18]. However, a meta-analysis by Dolezsar et al. found there to be no differences in resting systolic or diastolic blood pressure among men compared to women except when the analysis was restricted to Black men and women[22]. In this subset of the population, the authors found evidence of higher resting diastolic blood pressure among Black men.

Similarly, variations in the report and effects of racial discrimination by socioeconomic standing (e.g., household income, educational attainment) are nuanced[116,135,155]. Some studies suggest that financial stressors among populations with lower socioeconomic status may exacerbate or amplify the stress associated with experiences of discrimination, while others identify that racial discrimination may be more harmful for persons of higher SES, though it appears that the measure of SES used may play a role[116]. Studies have found greater adverse effects of discrimination on health outcomes among individuals in high SES groups. One found that self-reported experiences of institutional discrimination in the workplace was associated with greater psychological distress among African Americans with occupations in higher socioeconomic positions (e.g., executives, lawyers)[156]. Hudson et al. also found that reports of racial discrimination increased with greater educational attainment and that experiences of racial discrimination were associated with poorer depression symptomology[157] and major depressive episode[158]. While evidence suggests that higher SES is associated with better health outcomes, studies suggest that benefits ascribed to increases in SES diminish for Black

people[159,160]. For example, some research has found that reports of institutional discrimination (e.g., occurring in educational or housing settings) increased with higher education and income among a sample of older Black adults[161]. Higher SES Black adults may have more exposure to overt and covert discrimination in the areas of housing (e.g., residential steering) and occupational settings (e.g., inequitable pay for similar levels of training and education), for exmple[162,163]. Our findings should also be considered in light of several studies documenting adverse effects of discrimination among low SES individuals as well[116]. While not observed in our analysis, the harms of institutional discrimination are also posited to be great for low SES individuals – likely through harms due to loss of opportunity in employment, environment and education quality, due to structural racism (e.g., residential segregation)[4,164]. Further research is needed to understand the mechanisms through which harmful social exposures (i.e., gendered racism, SES-based racism) become embodied, as well as the mechanisms by which gender and SES modify the adverse effects of racial discrimination (i.e., greater exposure to racial discrimination due to increased participation in contexts where racial marginalization occurs).

The principal strengths of our study are that it uses an instrumental variable approach to account for unmeasured confounding and measurement error, as well as objective measurement of blood pressure. That said, our findings should be interpreted with caution. Notably, our IV estimates were larger than the OLS estimates. This may have occurred because our IV estimation reduced measurement error in the assessment of discrimination. It is also possible that the discrepancy is due to the IV estimating the *local* average treatment effect (LATE), i.e., the IV estimate is the effect of exposure only for the population who were affected by the instrument (skin tone), whereas OLS estimates the average treatment effect across the entire population. On the other hand, we cannot reject the possibility that the exclusion restriction was violated, i.e., no direct path between the instrument and the outcome. For example, it has been proposed that skin color may directly affect blood pressure through variations in vitamin D levels.

Research has documented differences in vitamin D levels by skin color, such that individuals with darker skin tones have lower circulating vitamin D – indicative of lower vitamin D synthesis – following exposure to UV radiation compared to lighter-skinned persons[165,166]. In turn, studies have postulated insufficient levels of vitamin D to be a contributor to a wide variety of adverse health outcomes, including cardiometabolic disorders, suggesting a potential pathway through which skin tone causes increased blood pressure through lower vitamin D levels. However, empirical research on the correlation between lower vitamin D levels and elevated blood pressure (as well as whether vitamin D supplementation assists in lowering blood pressure) remains decidedly mixed[167-169]. The prevalence of vitamin D deficiency is widespread, with varying definitions that have not undergone an evidence-based evaluation to establish cut-points[170] – resulting in high rates being reported globally, including the United States[171]. Using a cutoff of <50 ng/mL to indicate vitamin D insufficiency, Parva et al. found no statistically significant differences in hypertension across sufficient and insufficient groups in the United States[172]. Additionally, evidence from meta-analysis of RCTs and cohort studies found no evidence of improved blood pressure outcomes through vitamin D supplementation[173]. Meta-analysis of Mendelian-randomized instrumental variable studies that examined the health effects of vitamin D found no evidence of a causal effect of vitamin D on several outcomes, including SBP, DBP, and risk of hypertension[174]. Given these findings and the inconclusive evidence in literature around vitamin D supplementation and blood pressure/hypertension, it seems unlikely that skin color affects blood pressure directly via vitamin D.

While our results must be interpreted with consideration of the assumptions of IV analysis, we document that increased exposure to institutional racial discrimination is associated with increased blood pressure, probability of hypertension, and greater change in blood pressure. We also demonstrate that alternative methodological approaches, specifically IV, may be useful in accounting for potential measurement error and omitted variable bias.

These findings contribute to a body of literature that demonstrates the adverse effects of institutional discrimination on health and provide context for intervention.

4

Associations Between Multiple Indicators of Discrimination and Allostatic Load Among Middle Aged Adults

4.1. ABSTRACT

Using data from the Biomarker Project of the Midlife in the United States study (MIDUS), we assessed the relationships between multiple measures of discrimination (i.e., everyday, lifetime, and appraised burden) and components of allostatic load. Quasi-Poisson models were fit to estimate prevalence ratios for each discrimination measure and high-risk quartiles across seven physiological systems (i.e., sympathetic; parasympathetic; HPA axis; inflammation; cardiovascular; metabolic glucose; and metabolic lipids) and overall allostatic load scores. We find that lifetime and everyday experiences, as well as appraised burden, of discrimination are associated with increased prevalence ratios of allostatic load subscale risk, with different patterns observed by measure of discrimination. Each measure was also associated with greater prevalence of higher overall AL scores. We did not find that interactions between the measures of discrimination or between the included measures and race/ethnicity modified the observed associations. In supplemental analyses, we found differences in associations with biomarkers used to assess allostatic load by measure of discrimination used. While AL summary scores provide insight into the cumulative impacts of discrimination on health, there

may be distinct mechanisms through which varying forms of discrimination contribute to allostatic load and, ultimately, poorer health. These unique pathways may be useful in identifying potential points of intervention.

4.2. INTRODUCTION

Experiences of discrimination have been linked to a broad range of adverse health outcomes, including physical and mental health[10,13,16,17]. There is growing interest in understanding the direct physiological effects of discrimination, e.g., chronic inflammation, and the mechanisms through which discrimination becomes embodied[15,33,47,175].

Self-reported discrimination refers to experiences differential and unfair treatment that individuals are able and willing to report.[4,10,176] Experiences of discrimination are hypothesized to affect wellbeing through numerous pathways, including the activation of biological stress responses (e.g., increased sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis activity, and down-regulation of parasympathetic nervous system activity), adverse coping responses (e.g., less health promoting behaviors), and depleted coping resources, that impact health outcomes[15,175]. Changes in health behavior in response to chronic stress – for examples excess drinking and tobacco use – appear to partially mediate the link between discrimination and health endpoints[10,177]. However, research has begun to use indicators of multisystem physiological dysregulation, such as allostatic load, to understand a fuller scope of the effects of discrimination.

The concept of allostatic load, originally introduced by McEwen & Stellar, summarizes the hypothesized cumulative “wear and tear” on multiple physiologic systems induced by exposure to chronic stress[29]. In turn, allostatic load is associated with increased risk for adverse health outcomes, including cardiovascular disease, poorer cognitive functioning, and mortality[27,28,47]. Experiences of discrimination are associated with higher allostatic load, even

after accounting for traditional risk factors (e.g., health behaviors) and sociodemographic covariates[48-50]. The seven subscales that allostatic load is comprised of provide insight into different physiological processes, specifically they capture measures of stress response via sympathetic and parasympathetic nervous system and hypothalamic-pituitary-adrenal axis (HPA) axis activity, inflammation via several markers of inflammation (e.g., C-reactive protein), metabolic glucose and lipid profiles, and indicators of cardiovascular health. While it is useful to conceptualize allostatic load as representing the systems-wide impact of chronic stress on the body, the operationalization of AL as a summary index may obscure specific physiologic responses important to understanding the pathways through which discrimination contributes to adverse health outcomes. It is plausible, for example, that the associations between discrimination and mental health could be mediated through one component of allostatic load, such as inflammation or HPA axis measures[178], but not dysregulation in lipid metabolism. Specific indicators used to create allostatic load summary scores can facilitate an enhanced understanding of physiological pathways underpinning the embodiment of experiences of discrimination.

4.2.1. MEASUREMENT OF DISCRIMINATION

In stress literature, distinctions are drawn between types of stressors such as acute, lifetime events (e.g., divorce, bereavement, job loss) and chronic, daily hassles (e.g., a traffic-heavy commute)[179]. Emphasis is also placed on identifying and evaluating the appropriate stress measure based upon the hypothesized relationship with the disease (or indicator of disease risk), in addition to considering practical issues (e.g., sampling) and the research question[179]. Illustrating the scope and range in impacts of measures of discrimination is of particular importance since all stressors may not equally contribute to or share plausible associations with the outcome. These distinctions are mirrored in discrimination research where major lifetime events of discrimination are referred to as acute, defined experiences (e.g., being denied or

receiving inferior quality medical care), compared to chronic or recurrent, stressors such as everyday differential treatment (e.g., being treated with less respect or courtesy)[23,180]. Though major lifetime events provide observable and more defined events to measure and provide context to the accumulated impact of discrimination over the lifecourse[23,179], they raise problems around statistical power given their infrequent occurrence. Additionally, issues may arise around the recall of major lifetime experiences, given that the exposure is sharply demarcated in time so that some people may omit experiences by the time they are asked. By contrast, chronic, everyday discrimination measures exposure to lower intensity, but persistent & frequent events. While issues pertaining to measurement and assessment remain[23], these experiences may be no less "toxic" in their effects. For example, someone might not have (yet) experienced a major discrimination event in their life, but still be exposed to daily inequitable treatment. This persistent exposure to negative experiences and differential treatment through everyday experiences has been a strong predictor of the onset and progression of health outcomes.

Although some studies have examined the number, chronicity, and frequency of experiences of discrimination, few have explored *appraisals* of experiences of discrimination and its implications for health-related outcomes. The conceptualization of discrimination as a stressor benefits from an understanding of appraisals of differential treatment, providing context to whether the individual considers experiences as being of "harm, threat, or challenge."[180] That is, capturing the appraisals related to the severity of experiences of discrimination provides some context relating to the subjective impact of experiences of discrimination on the respondent's wellbeing[181]. The inclusion of appraisals of experiences of discrimination in recent literature provides evidence that the additional consideration of burden and stress from discrimination are beneficial to understanding discrimination as a contributor to adverse health outcomes[44,182,183]. This evidence suggests that the inclusion of appraisals of burden may also be useful in understanding the implications of experiences of discrimination on wellbeing. In the present study, we operationalize discrimination using measures of everyday, lifetime, and

appraised burden of discrimination. Each form discrimination may operate distinctly and may potentiate existing associations with other forms of discrimination (e.g., greater frequency of everyday discrimination and appraisal of discrimination as a significant burden) to further contribute to greater allostatic load. These distinctions between everyday discrimination, lifetime discrimination, and the appraised burden of discrimination on allostatic load subscales has yet to be assessed.

The present analysis sought to understand patterning in relationships between multiple measures of discrimination and allostatic load subscales and overall allostatic load scores. In this paper, we examined associations between everyday and lifetime discrimination as well as the appraised burden of discrimination and allostatic load subscales. Given findings from previous literature, we also assessed whether burden of discrimination and race/ethnicity modify the association between everyday and lifetime discrimination with allostatic load. In post hoc analyses, we conducted linear regressions to evaluate relationships between reported experiences of major lifetime discrimination, everyday discrimination, appraised burden of discrimination and biomarkers used to assess each allostatic load subscale. We hypothesize that, individually, each measure of discrimination is associated with increased high-risk scores across seven physiologic indicators of allostatic load. Additionally, we also posit that effect modification will exist between each measure of discrimination, as well as between the individual measures and race/ethnicity.

4.3. METHODS

We use data from the Biomarker Substudy of the Midlife in the United States (MIDUS) Study for our analysis. MIDUS is a longitudinal study of a national probability sample of households in the 48 contiguous states with a telephone. Approximately 7,000 non-institutionalized U.S. residents aged 25 to 74 at the time of interview (1995) were included[184,185]. MIDUS I data includes

extensive measurement of sociodemographic and psychosocial factors. Additional detail regarding the sampling and data collection strategies of the MIDUS study are described elsewhere[185].

In Wave 2 (MIDUS II; data collected in 2004), MIDUS investigators added African American participants from Milwaukee, WI (n=592) in an effort to increase the racial diversity of the sample[185]. MIDUS II and the Milwaukee sample included measures captured in the initial assessment, however they also captured cognitive assessments, comprehensive biomarker assessments on a subsample of respondents, and neuroscience assessments on a subsample of respondents in the biomarker study. In 2011-14, MIDUS investigators included a Refresher study of approximately 3500 adults to replenish the original MIDUS I sample. Similar data were collected in this cohort as were collected in MIDUS II.

For the analyses, multiple measures of discrimination, including lifetime burden of discrimination are examined in relationship to allostatic load, using a merged data set of the biomarker data from MIDUS II (n=1255) and the MIDUS Refresher samples (n=863).

4.3.1. MEASURES

Experiences of discrimination. Experiences of discrimination were captured via self-administered questionnaires across two levels: (1) lifetime and (2) everyday. Items included in both measures are outlined in Supplemental Table C.1. Lifetime experiences of discrimination were captured across 11 events, with respondents answering how many times over the lifecourse they were discriminated against as a result of their “race, ethnicity, gender, age, religion, physical appearance, sexual orientation or other characteristics” in several areas (e.g., discouraged to seek higher education, denied a scholarship). Similar to previous MIDUS studies examining discrimination, responses for lifetime experiences of discrimination were coded as none (i.e., a response of 0 to all 11 items), 1–2 instances (i.e., a response greater than 0 to any 1-2 of the 11 items), and 3 or more[56].

Responses to experiences of everyday discrimination were also captured across 9 areas, including items related to being treated with less respect than others. For each item, respondents answered with the frequency of occurrence in their day-to-day life – 1 = often, 2 = sometimes, 3 = rarely, or 4 = never. Responses were reverse coded, such that 0 = never, 1 = rarely, 2 = sometimes, 3 = often and averaged. The mean of the frequency responses across the 9 items were used as the everyday discrimination score[44].

Burden of discrimination. Participants responded to two survey items inquiring: "Overall, how much has discrimination interfered with you having a full and productive life?" and "Overall, how much harder has your life been because of discrimination?" Potential responses included a lot, some, a little, and not at all. An overall measure of burden of discrimination was coded as low on both (i.e., reporting "a little" or "not at all" to both questions), high on both (i.e., "some" or "a lot" to both questions), or high on one (i.e., reporting "some" or "a lot" to either of the questions).

Allostatic load. Using information from 24 available biomarkers, MIDUS constructs variables related to allostatic load across seven physiological systems: (1) sympathetic nervous system (SNS) activity via overnight urinary epinephrine & norepinephrine measures; (2) parasympathetic nervous system (PNS) activity via heart rate variability data, including two **time-domain** measures: root-mean square difference of the successive R-R intervals (RMSSD) and standard deviations of R-R intervals (SDRR); and two **spectral frequency measures** (low and high frequency heart rate variability (LFHRV; HFHRV, respectively)); (3) HPA activity via salivary cortisol data and blood DHEA; (4) inflammatory markers via blood-level measures of interleukin-6 (IL-6), fibrinogen, C-reactive protein (CRP), E-Selectin, and intercellular Adhesion Molecule 1 (ICAM-1); (5) cardiovascular indicators via systolic blood pressure, pulse pressure, and pulse; (6)metabolic glucose via HbA1c, glucose, and insulin resistance; and (7) metabolic lipids via BMI, waist-to-hip ratio (WHR), triglycerides, and high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterols[185,186].

An overall allostatic load (AL) score was computed as the sum of the seven subscales (i.e., SNS, PNS, HPA, inflammation, cardiovascular, glucose and lipids), using a high-risk quartile defined for each subscale. Subscale scores were computed for respondents with at least half of the measured biomarkers for each subscale. Risk scores were created for each subscale ranging from 0 to 1 indicating the proportion of system indicators that fell into high-risk quartile ranges based on the sample distribution[186]. The overall AL score (range: 0–7) is a sum of the averaged subscale scores and was calculated where 6 of the 7 subscale scores were present. Further detailed descriptions of biomarker collection are available elsewhere[185]. Additional insight into variable creation for AL is available in supplemental materials from an analysis by Gruenewald and colleagues[186]. The primary outcomes of interest are average high-risk levels across each allostatic load subscale; however, the secondary outcome includes the overall AL score. Supplemental analyses include an outcomes-wide analysis of each of the 24 available biomarkers.

Covariates. Models included measures of socioeconomic status (including measures of education (high school or less; some college; college or more), income (total household income per year; $25,000 or less; >$25,000 to $40,000; >$40,000 to $55,000; >$55,000 to $70,000; >$70,000), and current employment status (employed [i.e., working now; self-employed]; retired; not working [i.e., unemployed; homemaker; students; on leave or disabled]), age, self-reported race [Black; Other; white], sex (male; female), wave of data collection (i.e., MIDUS II, Refresher, Milwaukee Refresher), and modifiable health behaviors[44]. Modifiable health behaviors include cigarette use (ever and current smoker status) and alcohol consumption (never, sometimes, and current (affirmative response to at least one drink in the past month))[44].

4.3.2. STATISTICAL ANALYSIS

Descriptive statistics of the overall sample (i.e., means and percentages) were calculated. Models were fit using quasi-Poisson regression. Baseline models assessed independent

associations between lifetime discrimination, everyday discrimination, and appraised burden and each allostatic load subscale and overall allostatic load scores. Two multivariable regression models were run, beginning with a model adjusted for age, sex, and race/ethnicity. The second model additionally accounted for additional covariates and potential mediators of the association (i.e., health behaviors and socioeconomic indicators).

All analyses were conducted using R Statistical Software[67]. Effect modification was assessed between race/ethnicity and each measure, as well as between measures of discrimination in fully adjusted models.

The analytic sample for each allostatic load measure varies. Missingness for each subscale and overall allostatic load scores are as follows (from most missing to least): parasympathetic nervous system (n=302; 14.3%); sympathetic nervous system (n=187; 8.8%); HPA axis (n=178; 8.4%); metabolic glucose (n=44; 2.1%); inflammation (n=36; 1.7%); metabolic lipids (n=26;1.2%); and cardiovascular (n=4; 0.2%). Overall AL scores were missing for 181 respondents in the sample (8.5%).

Sensitivity analyses. Sensitivity analyses were conducted to assess the robustness of findings to how measures of discrimination were coded. Everyday discrimination was assessed categorically, where respondents reporting 0 experiences were coded as none, the top quartile of experiences were coded as high, and non-zero responses in lower quartiles were coded as some. Lifetime discrimination was assessed as the count of experiences. Additionally, each burden appraisal was assessed individually to assess whether each item had unique relationships with the allostatic load subscales and overall allostatic load scores.

E-values were calculated to assess the robustness of the associations to potential unmeasured confounding[187]. The E-value is defined as “the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the treatment and outcome to fully explain away a specific treatment-outcome association, conditional on the

measured covariates"[187] with larger values indicating considerable unmeasured confounding would be necessary to explain away the observed outcome.

E-values were calculated for statistically significant findings from fully adjusted models using:

$$E - value = RR + \sqrt{RR\ X\ (RR - 1)}$$

Where RR = relative risk values greater than 1.[187] Prevalence ratios were used to calculate E-values.

4.3.3. SUPPLEMENTAL ANALYSES

To illustrate the potential differences in relationships between measures of discrimination and measures used to define the allostatic load scores, we employed an outcome-wide analysis[188] assessing relationships between everyday, lifetime, and burden of discrimination with each of the 24 biomarkers used to create allostatic load indicators. Utilizing an outcome-wide approach provides additional insight into the potentially different roles that each distinct measure of discrimination plays with the array of biomarkers used to compile allostatic load measures. Outcome-wide analytic approaches have been proposed to evaluate relationships between the same exposure and multiple outcomes where the relationship with each outcome may differ, offering additional guidance and specificity to public health recommendations[188]. Bonferroni correction was used to correct for multiple testing (p= [0.05/ (3*24)] = 0.0007). The conditional distribution of most biomarkers was skewed. As such, outcomes were log transformed, excluding systolic blood pressure, pulse, pulse pressure, HDL and LDL, and robust standard errors were used in linear regression models.

4.4. RESULTS

Overall sample descriptive statistics are provided in Table 4.1. The mean age of the overall sample was 53 years. Most participants were white (75.5%) and female (54.9%). Nearly 27% of respondents reported no everyday discrimination. Experiencing lifetime discrimination in three or more areas was reported by 18% of respondents and 40.9% appraised discrimination as both “some” or “a lot” of a burden to living a full and productive life and in making life harder.

Everyday discrimination and count of experiences lifetime discrimination were correlated (ρ=0.19, p<0.0001). Chi-square tests indicated that categories of lifetime discrimination and appraised burden were not independent of each other (χ^2 = 30.12, p<0.0001). One-way ANOVA was suggested positive relationships between everyday discrimination and categories of lifetime discrimination (F-statistic = 34.6, p<0.0001) and appraised burden (F-statistic = 551.7 p<0,0001).

Interactions between lifetime, everyday, and burden of discrimination were not statistically significant for any of the outcomes (p>0.05); nor was race/ethnicity an effect modifier of discrimination measures in fully adjusted models. Findings are reported for each measure. We place emphasis on findings from model 2 since model 3 also accounts for potential mediators between discrimination and physiologic markers.

4.4.1. EVERYDAY DISCRIMINATION

Among the full sample, increases in average frequency of everyday discrimination was associated with increased prevalence of high-risk scores in the parasympathetic nervous system (aPR: 1.14; 95% CI: 1.03, 1.27) and metabolic lipids subscales (aPR: 1.09; 95% CI: 1.03, 1.16) in models accounting for race, age, and sex (Table 4.2). Associations between everyday discrimination and PNS and metabolic lipids risk scores remained after accounting for potential mediators (i.e., health behaviors, SES measures). Increased everyday discrimination was also associated with higher allostatic load scores (aPR: 1.07; 95% CI: 1.03, 1.12).

Table 4.1 Summary data of the MIDUS samples (overall and by Wave)

	Overall	MIDUS 2	Milwaukee Refresher	MIDUS Refresher
N	2118	1255	117	746
Age [m (sd)]	53.02 (12.56)	54.52 (11.72)	45.86 (10.86)	51.62 (13.60)
Race [n (%)]				
Black	386 (18.4)	225 (18.1)	105 (89.7)	56 (7.6)
Other	128 (6.1)	37 (3.0)	6 (5.1)	85 (11.5)
White	1585 (75.5)	979 (78.9)	6 (5.1)	600 (81.0)
Sex [n (%)]				
Female	1163 (54.9)	713 (56.8)	78 (66.7)	372 (49.9)
Male	955 (45.1)	542 (43.2)	39 (33.3)	374 (50.1)
Employment Status [n (%)]				
Employed	1361 (69.4)	828 (69.6)	65 (62.5)	468 (70.2)
Retired	408 (20.8)	256 (21.5)	5 (4.8)	147 (22.0)
Not employed	191 (9.7)	105 (8.8)	34 (32.7)	52 (7.8)
Education [n (%)]				
High school or less	499 (23.6)	350 (28.0)	43 (36.8)	106 (14.2)
Some college	452 (21.4)	281 (22.4)	36 (30.8)	135 (18.1)
College or more	1163 (55.0)	621 (49.6)	38 (32.5)	504 (67.7)
Income [n (%)]				
≤ $25,000	421 (20.2)	266 (21.3)	49 (42.2)	106 (14.7)
$25,001 - ≤ $40,000	248 (11.9)	160 (12.8)	23 (19.8)	65 (9.0)
$40,001 - ≤ $55,000	230 (11.0)	155 (12.4)	13 (11.2)	62 (8.6)
$55,001 - ≤ $70,000	248 (11.9)	157 (12.6)	10 (8.6)	81 (11.2)
> $70,000	936 (44.9)	509 (40.8)	21 (18.1)	406 (56.4)
Smoking status [n (%)]				
Never	616 (29.1)	327 (26.1)	31 (26.5)	258 (34.6)
Sometimes	589 (27.8)	357 (28.4)	28 (23.9)	204 (27.3)
Prior	645 (30.5)	398 (31.7)	31 (26.5)	216 (29.0)
Current	268 (12.7)	173 (13.8)	27 (23.1)	68 (9.1)
Alcohol consumption [n (%)]				
Never	109 (5.1%)	63 (5.0)	8 (6.8)	38 (5.1)
Sometimes	619 (29.2)	408 (32.5)	38 (32.5)	173 (23.2)
Current	1390 (65.6)	784 (62.5)	71 (60.7)	535 (71.7)
Everyday discrimination [m (sd)]	0.89 (0.88)	0.45 (0.53)	0.62 (0.74)	1.67 (0.84)
Lifetime discrimination [n (%)]				
None	1077 (53.4)	632 (53.5)	42 (35.9)	403 (56.0)
1 to 2	576 (28.5)	335 (28.4)	42 (35.9)	199 (27.6)
3 or more	365 (18.1)	214 (18.1)	33 (28.2)	118 (16.4)
Burden of discrimination [n(%)]				
Low on both	682 (43.1)	603 (82.3)	79 (68.1)	0 (0.0)
High on one	253 (16.0)	50 (6.8)	10 (8.6)	193 (26.3)
High on both	647 (40.9)	80 (10.9)	27 (23.3)	540 (73.7)

Abbreviations: n, number; m, mean; sd, standard deviation

Table 4.2 Relationships between everyday discrimination and high-risk allostatic load subscales

Allostatic Load Subscale	Model 1[a]	Model 2[b]	Model 3[c]
SNS	1.00 (0.93, 1.07)	1.04 (0.94, 1.15)	1.04 (0.93,1.16)
PNS	1.03 (0.95, 1.11)	**1.14 (1.03, 1.27)**	**1.14 (1.02, 1.27)**
HPA Axis	0.96 (0.90, 1.03)	1.01 (0.92, 1.10)	0.97 (0.88, 1.07)
Inflammation	1.05 (1.00, 1.10)	1.04 (0.97, 1.11)	1.07 (0.99, 1.15)
Cardiovascular	1.03 (0.97, 1.09)	1.06 (0.98, 1.15)	1.06 (0.97, 1.15)
Metabolic Glucose	1.05 (0.99, 1.12)	1.06 (0.97, 1.16)	**1.11 (1.01, 1.22)**
Metabolic Lipids	1.03 (0.99 - 1.08)	**1.09 (1.03 - 1.16)**	**1.12 (1.05 - 1.20)**
Overall AL Score	1.01 (0.98 - 1.05)	**1.07 (1.03 - 1.12)**	**1.09 (1.04 - 1.14)**

[a]: unadjusted
[b]: adjusted for race (ref=Black), age, sex (ref=Female), and sample
[c]: adjusted for b and employment status, educational attainment, smoking and drinking status, and income

4.4.2. LIFETIME DISCRIMINATION

Compared to those who reported no lifetime discrimination, experiencing one to two and three or more experiences was associated with high-risk scores in the inflammation, metabolic glucose, and metabolic lipid subscales in unadjusted and partially adjusted models (Table 4.3). Experiencing lifetime discrimination in one to two areas was associated with increased inflammation (aPR: 1.14; 95% CI: 1.03, 1.27), metabolic glucose (aPR: 1.39; 95% CI: 1.21, 1.59), and metabolic lipids (aPR: 1.17; 95% CI: 1.06, 1.29) in partially adjusted models. With further adjustment, associations between one to two experiences of lifetime discrimination remained significant for metabolic glucose and metabolic lipids risk scores. In partially adjusted models, reporting three or more experiences of lifetime discrimination was associated with increased risk on the inflammation (aPR: 1.33; 95% CI: 1.17, 1.50), metabolic glucose (aPR: 1.44; 95% CI: 1.22, 1.69), and metabolic lipids subscales (aPR: 1.31; 95% CI; 1.16, 1.47). These associations remained unchanged after accounting for additional covariates and potential mediators.

Reporting both one to two (aPR: 1.10; 95% CI: 1.03, 1.17) and three or more (aPR: 1.17; 95% CI: 1.08, 1.27) experiences of lifetime discrimination was associated with higher allostatic load scores. Statistically significant associations between lifetime discrimination and SNS, PNS, HPA axis or cardiovascular risk scores were not observed, though estimates suggest increased prevalence of high risk.

Table 4.3 Relationships between lifetime discrimination and high-risk allostatic load score

Outcome	Category	Model 1[a]	Model 2[b]	Model 3[c]
SNS	None (ref)	--	--	--
	One to two	1.02 (0.88, 1.18)	1.04 (0.90, 1.20)	1.00 (0.86, 1.17)
	Three or more	0.81 (0.67, 0.97)	0.89 (0.74, 1.08)	0.84 (0.68, 1.03)
PNS	None (ref)	--	--	--
	One to two	0.92 (0.78, 1.08)	0.98 (0.83, 1.14)	0.98 (0.83, 1.16)
	Three or more	0.86 (0.70, 1.04)	1.07 (0.87, 1.30)	1.07 (0.86, 1.32)
HPA Axis	None (ref)	--	--	--
	One to two	0.92 (0.80, 1.05)	0.96 (0.84, 1.09)	0.97 (0.85, 1.12)
	Three or more	0.91 (0.78, 1.07)	1.04 (0.88, 1.21)	1.05 (0.88, 1.24)
Inflammation	None (ref)	--	--	--
	One to two	**1.19 (1.07, 1.32)**	**1.14 (1.03, 1.27)**	1.12 (1.00, 1.26)
	Three or more	**1.53 (1.37, 1.71)**	**1.33 (1.17, 1.50)**	**1.38 (1.21, 1.57)**
Cardiovascular	None (ref)	--	--	--
	One to two	1.05 (0.93, 1.19)	1.08 (0.96, 1.21)	1.05 (0.93, 1.19)
	Three or more	1.14 (1.00, 1.31)	1.15 (0.99, 1.32)	1.11 (0.95, 1.30)
Metabolic Glucose	None (ref)	--	--	--
	One to two	**1.38 (1.20, 1.58)**	**1.39 (1.21, 1.59)**	**1.40 (1.21, 1.61)**
	Three or more	**1.56 (1.34, 1.81)**	**1.44 (1.22, 1.69)**	**1.48 (1.25, 1.76)**
Metabolic Lipids	None (ref)	--	--	--
	One to two	**1.11 (1.01 - 1.23)**	**1.17 (1.06 - 1.29)**	**1.14 (1.03 - 1.26)**
	Three or more	**1.19 (1.06 - 1.33)**	**1.31 (1.16 - 1.47)**	**1.30 (1.15 - 1.47)**
Overall AL Score	None (ref)	--	--	--
	One to two	1.07 (1.00 - 1.15)	**1.10 (1.03 - 1.17)**	**1.09 (1.02 - 1.16)**
	Three or more	**1.14 (1.06 - 1.23)**	**1.17 (1.08 - 1.27)**	**1.16 (1.07 - 1.26)**

[a]: unadjusted
[b]: adjusted for race (ref=Black), age, sex (ref=Female), and sample
[c]: adjusted for a and employment status, educational attainment, smoking and drinking status, and income

4.4.3. BURDEN OF DISCRIMINATION

Relationships between the appraisals of burden of discrimination and allostatic load are presented in Table 4.4. Reporting “some” or “a lot” on both burden measures was associated with increased prevalence of high-risk inflammation scores in partially adjusted models (aPR: 1.31; 95% CI: 1.09, 1.57) and metabolic lipid scores (aPR: 1.24; 95% CI: 1.04, 1.47) compared

to those who reported “none” or “a little” on both. Associations between appraised burden and overall allostatic load scores were significant in partially adjusted models (aPR: 1.14; 95% CI: 1.01, 1.28) but were null once socioeconomic mediators and health behaviors were included.

Table 4.4 Relationships between burden of discrimination and high-risk allostatic load subscales

Outcome	Category	Model 1[a]	Model 2[b]	Model 3[c]
SNS	Low on both	--	--	--
	High on one	0.87 (0.69, 1.08)	0.86 (0.63, 1.16)	0.84 (0.60, 1.16)
	High on both	0.96 (0.82, 1.12)	0.97 (0.72, 1.30)	0.93 (0.67, 1.27)
PNS	Low on both (ref)	--	--	--
	High on one	1.02 (0.81, 1.27)	1.13 (0.82, 1.54)	1.24 (0.88, 1.71)
	High on both	0.98 (0.83, 1.17)	1.18 (0.87, 1.59)	1.28 (0.92, 1.74)
HPA Axis	Low on both (ref)	--	--	--
	High on one	0.91 (0.75, 1.11)	0.98 (0.74, 1.27)	0.98 (0.73, 1.29)
	High on both	0.86 (0.74, 1.00)	0.97 (0.74, 1.25)	0.90 (0.67, 1.19)
Inflammation	Low on both (ref)	--	--	--
	High on one	1.02 (0.87, 1.18)	1.12 (0.91, 1.36)	1.08 (0.87, 1.32)
	High on both	**1.14 (1.02, 1.27)**	**1.31 (1.09, 1.57)**	**1.24 (1.02, 1.50)**
Cardiovascular	Low on both (ref)	--	--	--
	High on one	1.09 (0.92, 1.29)	1.11 (0.88, 1.39)	1.13 (0.88, 1.43)
	High on both	1.09 (0.96, 1.24)	1.16 (0.93, 1.44)	1.17 (0.93, 1.46)
Metabolic Glucose	Low on both (ref)	--	--	--
	High on one	1.17 (0.97, 1.42)	1.12 (0.86, 1.45)	1.06 (0.80, 1.38)
	High on both	1.11 (0.96, 1.29)	1.10 (0.86, 1.40)	1.06 (0.82, 1.36)
Metabolic Lipids	Low on both (ref)	--	--	--
	High on one	1.03 (0.89 - 1.19)	1.19 (0.98 - 1.43)	1.15 (0.94 - 1.39)
	High on both	1.07 (0.96 - 1.19)	**1.24 (1.04 - 1.47)**	1.20 (1.00 - 1.43)
Overall AL Score	Low on both (ref)	--	--	--
	High on one	0.98 (0.89 - 1.08)	1.08 (0.95 - 1.22)	1.08 (0.95 - 1.23)
	High on both	1.00 (0.93 - 1.08)	**1.15 (1.02 - 1.30)**	1.13 (1.00 - 1.28)

[a]: unadjusted
[b]: adjusted for race (ref=Black), age, sex (ref=Female), and sample
[c]: adjusted for a and employment status, educational attainment, smoking and drinking status, and income

4.4.4. SENSITIVITY ANALYSES

When coded categorically, high everyday discrimination was associated with increased parasympathetic nervous system (aPR: 1.43; 95% CI: 1.12, 1.83), cardiovascular (aPR: 1.23; 95% CI: 1.03, 1.47), and metabolic lipids risk scores (aPR: 1.23; 95% CI: 1.06, 1.42), as well as overall AL score (aPR: 1.20; 95% CI: 1.08, 1.32) compared to respondents reporting no experiences (Supplemental Table C.2). Experiencing some everyday discrimination (compared

to none) was associated with increased metabolic lipids risk scores (aPR: 1.15; 95% CI: 1.04, 1.28) and increased allostatic load scores (aPR: 1.09; 95% CI: 1.02, 1.16), though the association between some everyday discrimination and allostatic load scores was attenuated after accounting for potential mediators (model 3).

Associations between count of experiences of lifetime discrimination and allostatic load remained similar to associations observed when experiences were assessed categorically (Supplemental Table C.3). Increased lifetime discrimination remained associated with increased inflammation, metabolic glucose, and metabolic lipid subscales and overall allostatic load scores in unadjusted and fully adjusted models.

Assessing burden of discrimination questions independently also revealed unique associations with allostatic load subscales and overall AL scores. Appraisals of discrimination as having interfered some or a lot in having a full and productive life were associated with increased inflammation subscale risk scores (aPR: 1.21; 95% CI; 1.06, 1.38; Supplemental Table C.4) and overall AL score (aPR: 1.10; 95% CI: 1.01, 1.20) compared to respondents who reported none or little interference, though no other associations were observed. Appraisals of life being some or a lot harder because of discrimination were associated with the prevalence of higher inflammation risk scores (aPR: 1.26; 95% CI: 1.05, 1.50; Supplemental Table C.5) and overall AL score in adjusted models (aPR: 1.13; 95% CI: 1.01, 1.27). Though both associations were no longer significant after accounting for socioeconomic factors and health behaviors.

Robustness of the observed associations between measures of discrimination and allostatic load subscale risk and overall scores to unmeasured confounding are presented in Supplemental Table C.6. These reflect the minimum association an unmeasured confounder would have to have with both the measure of discrimination and allostatic load outcome – beyond measured covariates – to explain away the observed associations from fully adjusted models.[187]

4.4.5. INDIVIDUAL BIOMARKERS USED TO COMPOSE ALLOSTATIC LOAD MEASURES

Post hoc analyses used an outcome-wide approach to understand differences in patterning of relationships between measures of discrimination and allostatic load subscales. Findings from these fully adjusted analyses are presented in supplemental tables (Supplemental Tables C.7- C.9). Relationships meeting the adjusted p-value level of significance to account for multiple testing ($p<0.0007$) are highlighted in red, while $p<0.05$ are highlighted in yellow.

Everyday discrimination was associated with lower HDL and average high-frequency heart rate variability, as well as higher E-selectin, pulse, insulin resistance, triglycerides, and LDL. Only the association between everyday discrimination and HDL was below the Bonferroni adjusted p-value ($p<0.0007$).

High levels of lifetime discrimination (3 or more experiences) were associated with lower HDL and elevated IL-6, fibrinogen, CRP, E-selectin, HbA1c, glucose, insulin resistance, BMI, WHR, triglycerides, and LDL levels ($p<0.0007$ for IL-6, CRP, insulin resistance, BMI, and triglycerides). Reporting one to two experiences of lifetime discrimination was associated with lower cortisol and greater E-selectin, ICAM-1, HbA1c, glucose, insulin resistance, BMI, and WHR ($p<0.0007$ for glucose and insulin resistance).

Appraisals of some or a lot on both burden of discrimination measures was associated with elevated CRP, E-selectin, pulse, insulin resistance, WHR, and triglycerides, while reporting some or high for one measure was associated with lower norepinephrine levels and higher pulse measures. None of the associations met statistical significance as defined by the adjusted p-value.

4.5. DISCUSSION

In this cross-sectional analysis of MIDUS participants we observed that relationships between discrimination and allostatic load subscales varied by the discrimination measure used

(Table 4.5). Most of the observed associations also remained after accounting for additional covariates and potential mediators between discrimination and physiologic markers. We extend the findings of previous literature that documented associations between discrimination and allostatic load using individual measures or composite scores of multiple measures of discrimination [48-50,189-191] by also noting that relationships between discrimination, individual physiologic markers, and allostatic load subscale risk scores vary by type of discrimination assessed and how measures are operationalized.

Everyday discrimination appears to have broader associations with short-term (e.g., PNS) as well as long-term physiological indicators (e.g., metabolic lipids). Adjusted models revealed that everyday discrimination was associated with greater risk scores in the parasympathetic nervous system (specifically vagal withdrawal, as indicated by the lower high frequency spectral power – see Suppl Table C.7), metabolic glucose (i.e., insulin resistance (HOMA-IR)), and metabolic lipids (i.e., BMI and triglyceride, HDL and LDL levels) subscales. No associations were observed for inflammation, and cardiovascular risk scores, however everyday discrimination was also associated with higher pulse and greater e-selectin levels (see Suppl Table C.7).

Table 4.5 Associations between measures of discrimination and allostatic load subscales and overall scores

	SNS	PNS	HPA	Inflammation	Metabolic Glucose	Metabolic Lipids	Cardiovascular	Overall AL
Everyday	Null	+	Null	Null	+	+	Null	+
Lifetime	Null	Null	Null	+	+	+	Null	+
Burden	Null	Null	Null	+	Null	+	Null	+

By contrast, lifetime and burden of discrimination were primarily associated with intermediate- and long-term physiological indicators – such as inflammation and metabolic glucose and lipids. Increased reports of lifetime discrimination were associated with higher risk scores for inflammatory markers (not only e-selectin, but also CRP, IL-6, fibrinogen, and ICAM-

1), metabolic glucose (i.e., HbA1c, glucose, and HOMA-IR), and metabolic lipid (i.e., BMI, WHR, and triglyceride, LDL and HDL levels) subscales compared to those reporting no experiences. Appraised burden of discrimination was associated with inflammation and metabolic lipid risk scores for individuals reporting appraised burden on both measures. These associations appear to be primarily through CRP, e-selectin, WHR, and triglyceride levels. The variations in associations by measures provide evidence of the criterion validity of each measure, where lifetime and appraised burden of discrimination capture the enduring impact of major events or appraised burden of discrimination on long-term health outcomes, while everyday discrimination captures the implications of broader, day-to-day exposures of stress.

Health behaviors (i.e., smoking and alcohol use) were included as potential mediators of associations between discrimination and allostatic load outcomes. Our findings were robust to these adjustments, including the outcome-wide assessments where measures of discrimination remained associated with several individual physiological markers. However, it is important to note that the included health behaviors and covariates do not represent the totality of variables that may mediate the effects of discrimination on indicators of allostatic load and allostatic load scores.

Additionally, we observed no interaction on the multiplicative scale between measures of discrimination or between individual measures and race/ethnicity and allostatic load. Previous work has found larger (though not statistically different) within-group associations between pervasive discrimination and allostatic load among African American respondents compared to whites when relative threshold categorization was used (e.g., high/low)[191]. Our findings may reflect 1) small samples of African American participants and participants that identified as "Other" racial/ethnic groups; 2) differences between general unfair treatment and racial or ethnic discrimination; or 3) that interactions between measures or race/ethnicity may occur on the additive scale.

In sensitivity analyses, we found that how we operationalize discrimination measures changes some of the observed associations for everyday discrimination and burden of discrimination measures. When everyday discrimination was assessed categorically, we found increased prevalence of high-risk scores among the parasympathetic nervous system, cardiovascular, metabolic glucose and metabolic lipids subscales among those in the top everyday discrimination quartile (i.e., high) compared to those reporting no experiences of everyday discrimination. In understanding what stressors result in adverse health outcomes, these findings suggest that there may be a threshold effect of everyday experiences of discrimination where these experiences may go beyond individual, collected, and structural resources available to mitigate the negative impacts of everyday differential treatment. Assessment of lifetime discrimination as a count of responses revealed consistent associations with increased high-risk scores in inflammation, metabolic glucose and metabolic lipid subscales. Evaluating each appraised burden measure independently revealed variations in associations with allostatic load subscales. Specifically, appraising discrimination as having interfered with living a full and productive life was associated with higher inflammation risk scores even after accounting for potential mediators, though both measures were associated with increased inflammation risk scores and overall AL scores in models omitting potential mediators (model 2). These findings, and results from the outcome-wide analysis, provide evidence of the importance of further consideration and theoretical guidance to how we operationalize discrimination measures when evaluating it as a stressor and/or contributor to health inequities.

4.5.1. Discrimination and Allostatic Load Scores

Our findings of positive associations between discrimination measures and overall allostatic load scores are supported by previous work. Three cross-sectional studies have found discrimination to be associated with allostatic load in samples of Indigenous Canadian, Puerto

Rican, and African American adults[48,189,190]. The analysis by Cuevas et al. yielded nuanced findings, however, with results indicating inverse relationships between everyday discrimination and allostatic load scores, while lifetime discrimination was associated with greater allostatic load in a sample of Puerto Rican adults in the Boston metro area[190]. Additionally, longitudinal work assessing the frequency of racist events among African American adolescents by Brody et al., the frequency of everyday discrimination among middle-aged women by Upchurch and colleagues, and weight discrimination among adults in the MIDUS sample by Vadiveloo and Mattei provide evidence of the persistent effects of discrimination on increased allostatic load[49,50,192]. Evidence of the adverse effects of pervasive discrimination, operationalized as the sum of tertiles across everyday, lifetime, and workplace discrimination, on allostatic load scores was observed in a recent analysis by Van Dyke et al. using MIDUS data[191]. When assessing the components of the summary score independently, Van Dyke et al. observed relationships between lifetime and everyday discrimination with allostatic load scores, though no associations were observed between workplace discrimination and allostatic load.

4.5.2. SUBSCALE-SPECIFIC FINDINGS

Subscale-specific findings provide empirical justification for the distinct associations between measures or types of discrimination and allostatic load subscales and components. Studies in this area that have examined the relationship between measures of discrimination and specific indicators have yielded similar findings. Specifically, we found no association between three measures of discrimination and SNS activity. Work by Wagner and colleagues which examined the physiological implications of lifetime exposure to racial discrimination using the Schedule of Racist Events scale observed no associations between discrimination and plasma norepinephrine levels[193]. Null associations between discrimination and epinephrine levels may reflect the differences between plasma and urinary assessments of epinephrine and norepinephrine and the timing of sample draws[194]. Depending on how the stressor is

conceptualized to impact SNS activity, plasma hormonal measures of SNS may reflect acute responses to stress, but require more invasive methods to capture that may influence levels (i.e., venipuncture), while urinary measures provide an opportunity for integrated assessments of measure SNS activity over a longer period of time[194,195].

Similar to our findings regarding everyday discrimination and increased risk of PNS dysregulation, prior research also found relationships between discrimination and parasympathetic nervous system activity[193,196]. Hill et al. found greater discrimination (summary score up to 17 using the Perceived Ethnic Discrimination Questionnaire-Community Version) to be associated with decreased high frequency heart rate variability (HRV) – one of the indicators used to calculate the parasympathetic nervous system risk score.[196] Adding to the literature, we also observed that associations between everyday discrimination and PNS activity was only seen for HFHRV in the outcome-wide analysis, though the items used to assess PNS activity were highly correlated (ρ: 0.46 – 0.84, all p-values <0.001). Although all measures used to assess PNS activity capture beat-to-beat alterations in heart rate (i.e., interval measures (RMSSD and SDRR); frequency measures (LFHRV and HFHRV)), different conclusions are able to be drawn depending on which is used[197,198]. Time domain measures (e.g., SDRR and RMSSD) do not tell us whether decreased HRV is due to sympathetic over-drive or vagal withdrawal. The advantage of spectral frequency analysis is that it allows us to pin down whether decreased HRV is due to parasympathetic activity to the heart (i.e., vagal withdrawal (high frequency domain)) versus sympathetic activity (low frequency)[198].

Our results indicated no associations between experiences and appraised burden of discrimination and HPA axis risk scores, though reporting one to two experiences of lifetime discrimination was associated with lower cortisol. Research has found inconsistent associations between discrimination and indicators of HPA axis dysregulation (i.e., cortisol, DHEAs)[199], with some studies reporting null findings[86] and others finding positive[200,201] or indirect associations[202]. A review by Busse et al. found that existing evidence suggests that a relationship exists

between discrimination and HPA axis activity, though variations in the direction of the relationship were observed in both experimental and observational studies, with some null findings reported[199]. Previous findings suggest that relationships between discrimination and HPA axis risk scores and indicators are sensitive to the timing of discrimination (i.e., acute, chronic) and may yield elevated changes to HPA axis activity or blunted responses[199].

Most studies examining associations between discrimination and inflammation markers have found increased experiences to be associated with greater inflammation, with CRP and IL-6 being the most frequently assessed biomarkers[33]. Similar to previous findings[33,203], we observed that lifetime discrimination is associated with increased levels of inflammatory risk scores with specific associations with IL-6, fibrinogen, CRP, E-selectin, and ICAM-1. We found no associations with everyday discrimination and overall inflammation risk scores, though increased experiences of everyday discrimination were associated with elevated E-selectin levels. Our findings are similar to an analysis of everyday and lifetime discrimination with inflammation markers by Stepanikova and colleagues, though their results differ slightly. The authors found lifetime discrimination to be associated with fibrinogen, E-selectin, and IL-6, but not with CRP and no associations between everyday discrimination and the above inflammation biomarkers[203].

Work by Van Dyke et al. found pervasive discrimination to be associated with inflammation, metabolic glucose and metabolic lipid subscales[191]. These results are similar to our findings regarding lifetime discrimination, though everyday discrimination was also associated with the metabolic glucose and metabolic lipid subscales and appraised burden with metabolic lipids risk scores. Among a sample of teens (16-18 years), Brody and colleagues found evidence of increased reports of racial discrimination to be associated with higher BMI and insulin resistance (HOMA-IR), both physiologic indicators used in the present analysis' metabolic lipids and glucose subscales, respectively[204].

Last, our findings regarding associations between discrimination and cardiovascular risk scores were consistently null across all measures. Our results are consistent with studies that have observed null associations between discrimination and cardiovascular outcomes[22]. However, the literature in this area remain mixed, with varying associations seen by operationalization of discrimination (e.g., implicit biases, internalized, interpersonal, institutional, domain-specific), gender, and type of outcome used to assess cardiovascular risk[18].

Calculated E-values for the observed findings (range: 1.40 to 2.24; the lowest possible E-value is 1) suggest that our findings may be robust to unmeasured confounding[205]. For example, an unmeasured confounder would have to have a prevalence ratio of 1.54 with everyday discrimination and prevalence of high-risk PNS scores to explain away the observed association beyond the included covariates. Potential factors that may be confounders include negative affect and neuroticism, though studies that have included these measures in assessing the effects of discrimination on health outcomes found associations to persist even after accounting for these factors[191,206,207].

This analysis is not without its limitations. First, given the cross-sectional design, the temporality of the associations between experiences and appraisals of discrimination and allostatic load markers is uncertain. However, the advantage of using biomarkers as the outcome is that reverse causality (i.e., values of biomarkers affecting self-reports of discrimination) as well as common-source bias seem less likely. While we capture major forms of institutional discrimination through items available in the lifetime discrimination measure, we only capture experiences of discrimination that people are able to recognize and are willing to report. This does not speak to forms of structural racism that exist and result in material, opportunity, and political deprivation whether or not an individual reported such experiences as discriminatory or harmful[2,13,24,25]. There is a growing body of evidence that larger, social factors such as structural racism, through interlinked and mutually reinforcing practices, policies, and patterns, directly and indirectly affect health and wellbeing[2]. Though we include appraised

burden of discrimination which provides some insight into the potential impacts and perceptions of discrimination as a barrier or hinderance without reliance on the report of or reaction to a specific experience, it still relies on self-report.

Also, while the MIDUS I sample is a nationally representative sample of US adults, the proposed analysis is a subsample of MIDUS participants – including the longitudinal (MIDUS II) and the Milwaukee samples. The overall percentage of Black respondents in the national MIDUS study were small and, as a result, most of the Black population in the MIDUS study was recruited in the Milwaukee sample. As such, it means that the Milwaukee sample is less representative, however the data provides insight into the experiences of Black Americans living in highly segregated cities. Researchers found that participants in the MIDUS II Biomarker Substudy were similar to participants in the full sample, except for higher levels of educational attainment, were less likely to smoke, and were more likely to use alternative therapies[185]. Additionally, small sample sizes of Black (n=386) and "Other" (n=128) individuals limits the power to capture interactions between race and discrimination measures; however, future work should assess whether interactions between multiple measures and race/ethnicity occur on the additive scale instead of multiplicative[208]. Additionally, future research should employ other considerations for modeling multiple experiences of marginalization and inequitable treatment[208].

Our analysis also has several strengths in that it adds to literature examining the impacts of racial discrimination by using and comparing the effects of multiple measures of discrimination on allostatic load subscales, individual biomarkers, and overall scores. These findings extend the existing body of literature by finding that associations between multiple measures of discrimination and allostatic load vary by measure used (i.e., everyday, lifetime, appraisals of burden) and subscale. This suggests that there may be distinct mechanisms through which frequent, though relatively minor and major lifetime experiences or appraisals of discrimination contribute to allostatic load and, ultimately, poorer mental and physical health

outcomes. These unique pathways may be useful in identifying potential points of intervention, though efforts should include rectifying harms from all forms of discrimination through institutional (e.g., policy) and cultural interventions (e.g., changes to norms)[2,4]. To further the understanding of pathways that drive relationships between individual measures of discrimination and allostatic load subscales, we employed an outcomes-wide analysis to capture specific indicators that shed light on the biological pathways through which multiple forms of discrimination may uniquely impact health. We also add to assessments of discrimination by capturing the appraisal of experiences of discrimination as a barrier to living a full life and making life harder, outside of reference to a specific event/experience. Last, we also identified that relationships between measures of discrimination and allostatic load outcomes can vary based on how discrimination is used in the analysis.

These findings provide points of focus for future research, specifically around the pathways through which discrimination adversely impacts health and the importance and theoretical implications of how discrimination is operationalized. While most stressful events do not affect health[13], identifying salient experiences of discrimination that are likely to have implications for population health remains important for current and future work – in an effort to understand and intervene upon discriminatory processes that unfairly disadvantage some and unfairly advantage others[26].

5

Conclusion

Results from these analyses provide points for interpersonal, structural, and policy intervention to mitigate the adverse impacts of discrimination on the health and wellbeing of marginalized groups. These papers also speak to the importance of theory and *a priori* guidance in data collection, operationalization of variables, and methodological choices. Using several approaches including meta-analysis, instrumental variable, and outcome-wide analysis, I explored the relationships between discrimination and biological measures of stress, inflammation, and accelerated cellular aging. I also investigated the utility of methodology in strengthening causal inference of discrimination and blood pressure and identified distinct associations between multiple measures of discrimination and indicators and subscales of allostatic load.

In Chapter 2, I estimated the pooled correlation coefficient across studies using the Everyday Discrimination Scale to explore associations between discrimination and molecular biomarkers. Findings from this analysis were mixed and dependent on the outcome assessed. Explicitly, we found that increased self-report of discrimination is associated with higher CRP levels, but not with cortisol, IL-6 or telomere length. This analysis identified several factors as potential contributors to heterogeneity in the observed associations (e.g., exposure assessment, sample demographics) and pays particular attention to the need for standardization in the assessments of biomarker outcomes. This issue is of most concern for measures of cortisol and telomere length, though it is also relevant for growing assessments of IL-6 and other biomarker

outcomes. Variations in assessment protocols, sample collection, and operationalization were observed across eligible studies. Measures of cortisol are heavily dependent on timing (e.g., morning, evening), sample collection (e.g., saliva, hair, plasma), and operationalization (e.g., change in cortisol, waking levels, momentary). Similarly, optimal means of obtaining samples for (i.e., cheek cell, leukocyte) and assessing (i.e., PCR, Southern blot) telomere length are still being explored. Sample collection is also of importance for IL-6 assessments. Overall, this analysis provides information on the relationships between discrimination and several molecular biomarkers using a consistent measure of discrimination. We also provide considerations for future research utilizing biomarker outcomes in an effort to strengthen ongoing efforts.

In Chapter 3, I focused on using instrumental variable analysis to strengthen causal inference in observational assessments of discrimination and health. I proposed reflectance meter measurement of skin color as an instrument and utilized available data from the CARDIA study to evaluate the relationships between discrimination, blood pressure, probability of hypertension, and change in blood pressure. This analysis found that increased report of racial discrimination was associated with elevated blood pressure, probability of hypertension, and changes in blood pressure across two waves. We also observed that associations were modified by gender and household income, with stronger associations observed among women compared to men and among individuals with higher household incomes. These findings provide impetus for structural interventions targeting institutional racial discrimination that contributes to inequitable access to resources such as housing and employment and unjust treatment from police or legal systems. The proposed instrument and analysis also provide evidence that IV may be a useful approach to account for potential measurement error and confounding allowing this approach to be extended to future research.

Finally, in Chapter 4, I demonstrated that lifetime and everyday experiences, as well as appraised burden, of discrimination are associated with increased prevalence ratios of allostatic load subscale risk, with different patterns observed by measure of discrimination, as well as

overall allostatic load scores. Results from this analysis did not identify interactions between the measures of discrimination or between the included measures and race/ethnicity. In an outcomes-wide assessment, we found further evidence of distinct mechanisms through which varying forms of discrimination contribute to allostatic load, and ultimately, poor health. These findings suggest areas of focus for future research, specifically assessments of embodiment of discrimination and the theoretical implications of how discrimination is operationalized. Identifying the implications of discriminatory processes that unfairly distribute advantage and disadvantage is crucial for improving population health and the development of policies and multilevel interventions to mitigate the occurrence and experience of discrimination.

Collectively, this body of work contributes to a body of literature that has documented discrimination as a driver of racial health inequities. Findings from this dissertation further our understanding of measurement and methodological approaches useful for examining how discrimination contributes to health inequities. Specifically, in Chapter 2 regarding the measurement of cortisol, IL-6, and telomere length. This was also observed in Chapter 4 as we parsed out relationships between multiple measures of discrimination and allostatic load. In addition, we provide evidence to the utility of methodology, applying meta-analysis in Chapter 2 and instrumental variable techniques in Chapter 3 to evaluate relationships between discrimination and physiologic indicators, suggesting considerations for future work that are useful to strengthening the available evidence. Last, our findings lend further credence to the inability to disentangle our bodies from the societies that we exist in and suggest that further efforts are needed to shift beyond documenting the consequences of discrimination, specifically racial discrimination, and the mutually reinforcing systems that drive it (i.e., racism) to encompass explicit institutions, policies, or cultural aspects that further perpetuate and worsen inequity.

Appendix A

Supplementary Materials for Chapter 2

Detailed search terms used for each database and results from sensitivity analyses estimating the weighted correlation sizes between discrimination and cortisol, CRP, IL-6 and telomere length using data from the most adjusted estimates reported in eligible articles are presented here.

Table A.1. Search terms used by database

Database	Search Terms
PubMed	("Social Discrimination"[Mesh] OR "Prejudice"[Mesh] OR discrimination[tiab] OR ((discriminate*[tiab] AND against[tiab]) AND ("Disabled Persons"[Mesh] OR "Overweight"[Mesh] OR "Ethnic Groups"[Mesh] OR "Continental Population Groups"[Mesh] OR "Minority Groups"[Mesh] OR "Sexual and Gender Minorities"[Mesh] OR "Homosexuality"[Mesh] OR African American*[tiab] OR ancestry[tiab] OR Asian[tiab] OR Asians[tiab] OR black[tiab] OR blacks[tiab] OR disabilities[tiab] OR disability[tiab] OR disabled[tiab] OR ethnic[tiab] OR ethnicity[tiab] OR hispanic*[tiab] OR Latinas[tiab] OR Latinos[tiab] OR mental illness*[tiab] OR mentally ill[tiab] OR minorities[tiab] OR national origin[tiab] OR Native American*[tiab] OR obese[tiab] OR obesity[tiab] OR race[tiab] OR racial[tiab] OR religion[tiab] OR religious[tiab] OR sexual orientation[tiab])) OR racist[tiab] OR racism[tiab] OR sexism[tiab] OR sexist[tiab] OR homophobia[tiab] OR homophobic[tiab] OR ageism[tiab] OR agism[tiab] OR ageist[tiab]) AND (daily discrimination[tiab] OR everyday[tiab] OR every day[tiab] OR chronic discrimination[tiab]) AND ("Surveys and Questionnaires"[Mesh:NoExp] OR "Health Surveys"[Mesh:NoExp] OR "Self Report"[Mesh] OR "Social Stigma"[Mesh] OR data[tiab] OR experience[tiab] OR experiences[tiab] OR experienced[tiab] OR measures[tiab] OR panel study[tiab] OR sample[tiab] OR scale[tiab] OR survey*[tiab] OR questionnaire[tiab] OR self report*[tiab] OR reported[tiab] OR perceived[tiab] OR perceptions[tiab] OR stigma[tiab] OR stigmatiz*[tiab])
Web of Science	discrimination OR racist OR racism OR sexism OR sexist OR homophobia OR homophobic OR ageism OR agism OR ageist OR ((discriminate* NEAR/0 against) AND (ancestry OR Asian OR Asians OR black OR blacks OR disabilities OR disability OR disabled OR ethnic OR ethnicity OR hispanic* OR Latinas OR Latinos OR "mental illness*" OR "mentally ill" OR minorities OR "national origin" OR "Native American*" OR obese OR obesity OR race OR racial OR religion OR religious OR "sexual orientation")) AND "daily discrimination" OR everyday OR "every day" OR "chronic discrimination" AND Data OR experience OR experiences OR experienced OR measures OR "panel study" OR sample OR scale OR survey* OR questionnaire OR "self report*" OR reported OR perceived OR perceptions OR stigma OR stigmatiz* AND "birth control" OR "blood pressure" OR "body mass" OR "physical activit*" OR "self esteem" OR "substance abuse" OR "substance use" OR alcohol* OR allostatic OR anthropometric* OR anxiety OR arterial OR biomarker* OR birth* OR BMI OR cardiovascular OR cigarette* OR contracept* OR coronary OR depression OR depressive OR diabetes OR disease* OR distress OR drug OR drugs OR exercise OR gestation* OR health OR healthcare OR hypertension OR illness* OR medical OR metabolic OR pain OR pregnancy OR risk OR sleep OR smoking OR stress OR suicid* OR symptom* OR telomere OR waist OR weight OR well being OR wellbeing

Table A.1. Continued from previous page

Database	Search Terms
PsycINFO	DE "Social Discrimination" OR DE "Age Discrimination" OR DE "Disability Discrimination" OR DE "Race and Ethnic Discrimination" OR DE "Sex Discrimination" OR DE "Prejudice" OR DE "Religious Prejudices" OR DE "Racism" OR DE "Sexism" OR [TITLE OR ABSTRACT OR KEY WORDS OR SUBJECTS]: discrimination OR ageism OR ageist OR agism OR homophobia OR homophobic OR racism OR racist OR sexism OR sexist OR [TITLE OR ABSTRACT OR KEY WORDS OR SUBJECTS]: (discriminate* AND against) AND DE "Disabled (Attitudes Toward)" OR DE "Mental Illness (Attitudes Toward)" OR DE "Physical Disabilities (Attitudes Toward)" OR DE "Sensory Disabilities (Attitudes Toward)" OR DE "Obesity (Attitudes Toward)" OR DE "Obesity" OR DE "Homosexuality (Attitudes Toward)" OR DE "Sexual Orientation" OR DE "Sexual Minority Groups" OR DE "Homosexuality" OR DE "Lesbianism" OR DE "Male Homosexuality" OR DE "Gender Nonconforming" OR DE "LGBTQ" OR DE "Transsexualism" OR DE "Transgender" OR DE "Transgender (Attitudes Toward)" OR DE "Racial and Ethnic Groups" OR DE "African Cultural Groups" OR DE "Arabs" OR DE "Asians" OR DE "Blacks" OR DE "Indigenous Populations" OR DE "Latinos/Latinas" OR DE "Romanies" OR DE "Minority Groups" OR DE "Sexual Minority Groups" OR [TITLE OR ABSTRACT OR KEY WORDS OR SUBJECTS] ancestry OR Asian OR Asians OR black OR blacks OR disabilities OR disability OR disabled OR ethnic OR ethnicity OR hispanic* OR Latinas OR Latinos OR "mental illness*" OR "mentally ill" OR minorities OR "national origin" OR "Native American*" OR obese[tiab] OR obesity[tiab] OR race OR racial OR religion OR religious OR "sexual orientation" AND TM "daily discrimination scale" OR [TITLE OR ABSTRACT OR KEY WORDS OR SUBJECTS OR FULL TEXT] "daily discrimination" OR everyday OR "every day" OR "chronic discrimination" AND DE "Questionnaires" OR DE "Self-Report" OR DE "Stigma" OR DE "Mental Health Stigma" OR [TITLE OR ABSTRACT OR KEY WORDS OR SUBJECTS] data OR experience OR experiences OR experienced OR measures OR "panel study" OR sample OR scale OR survey* OR questionnaire OR "self report*" OR reported OR perceived OR perceptions OR stigma OR stigmatiz*

Table A.2 Summary of study and participant characteristics (N=24 articles)

Study characteristics	No. of Articles (%)
Year of publication	
2010 – 2015	9 (37.5)
2016 – March 2020	15 (62.5)
Sample size	
≤ 300	14 (58.3)
> 300	10 (41.7)
Sampling procedure	
Representative	9 (37.5)
Non-representative	15 (62.5))
Study design	
Cross-sectional	18 (75.0)
Longitudinal	5 (20.8)
Other	1 (4.2)
Country	
United States	23 (95.8)
New Zealand	1 (4.2)
Version of EDS used	
Full scale	16 (66.7)
Short form	5 (20.8)
Modified	3 (12.5)
Attribution	
Racial	1 (4.2)
Non-racial	1 (4.2)
Both	4 (16.7)
Not assessed	18 (75.0)
Operationalization of EDS	
Sum of frequencies	10 (41.7)
Average of frequencies	10 (41.7)
Count of yes responses	2 (8.3)
Dichotomized (yes/no)	1 (4.2)
Not specified	1 (4.2)
EDS Cronbach Alpha	
$0.70 \leq \alpha < 0.80$	4 (16.7)
$0.80 \leq \alpha$	17 (70.8)
Not reported	3 (12.5)
Population Characteristics	**No. of Participants (%)**
Age of Population	
Adults (18 and older)	36074 (98.7)
Children, adolescents, teens	419 (1.1)
Not clearly specified	64 (0.2)
Sex	
Men	13662 (37.6)
Women	22693 (62.4)
Racial/ethnic groups	
Black	10503 (35.1)
Latinx/Hispanic	2012 (6.7)
Asian	565 (1.9)
Native Hawaiian/Pacific Islander/Māori	18 (0.1)
White/European	16455 (55.1)
Multiracial	36 (0.1)
Other	299 (1.0)

*****: some studies reported associations for more than one outcome

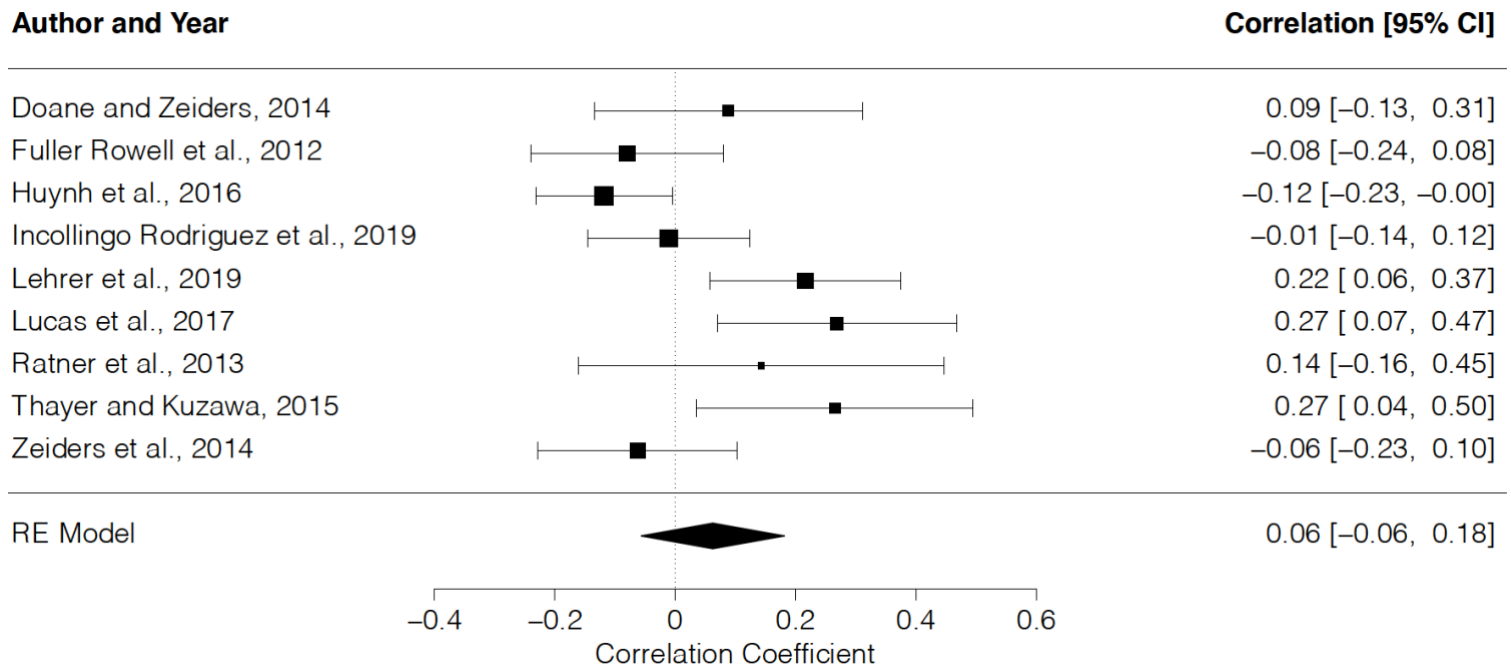

Figure A.1 EDS and (a) all cortisol outcomes; (b) cortisol awakening response (CAR); and (c) waking levels, most adjusted estimates

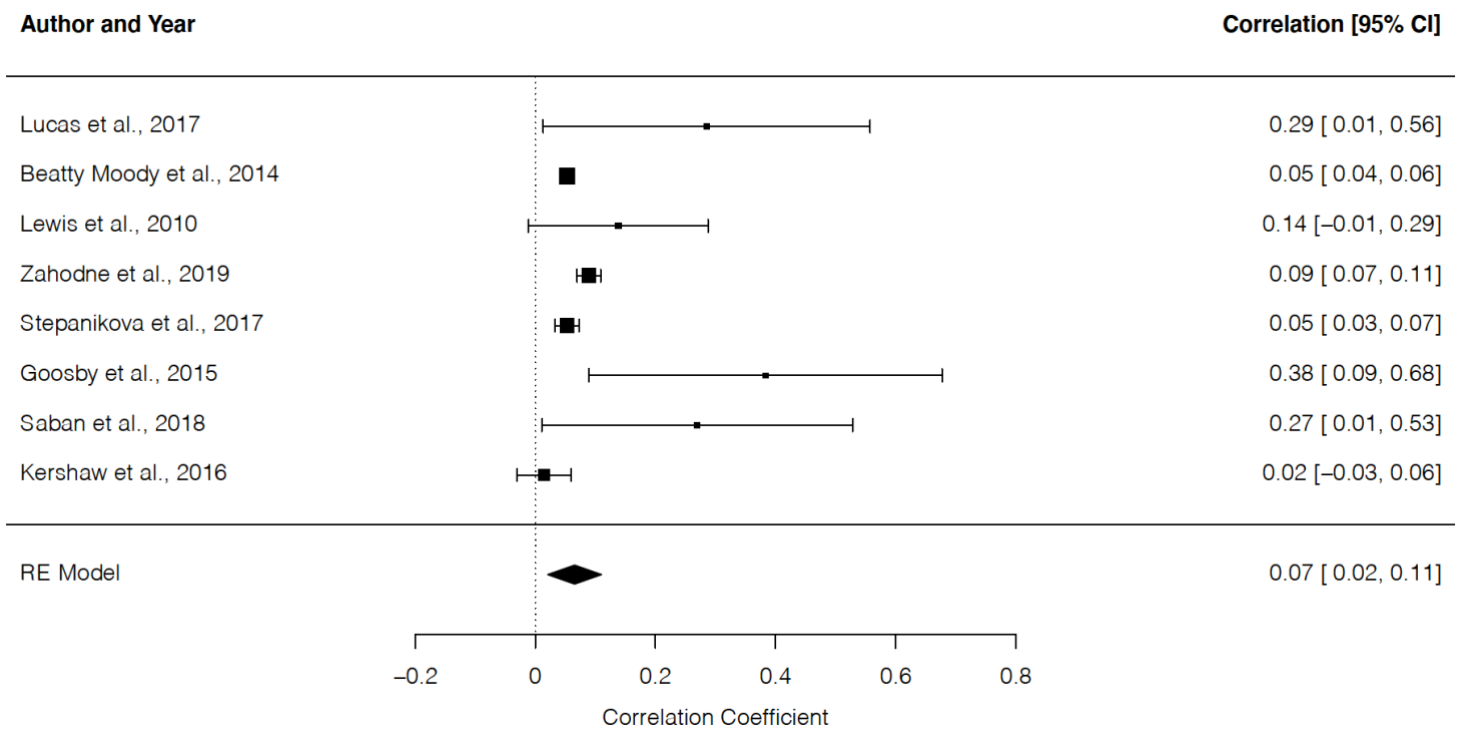

Figure A.2 EDS and CRP outcome, most adjusted estimates

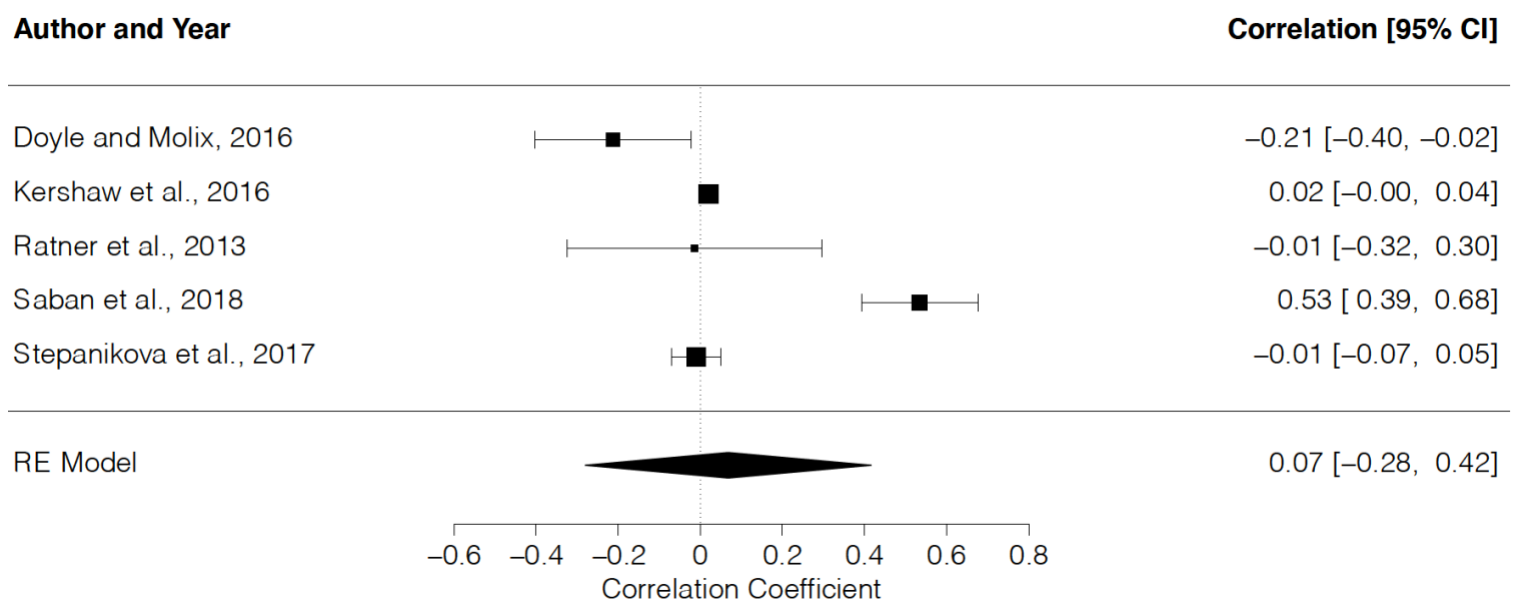

Figure A.3 EDS and IL-6, most adjusted estimates

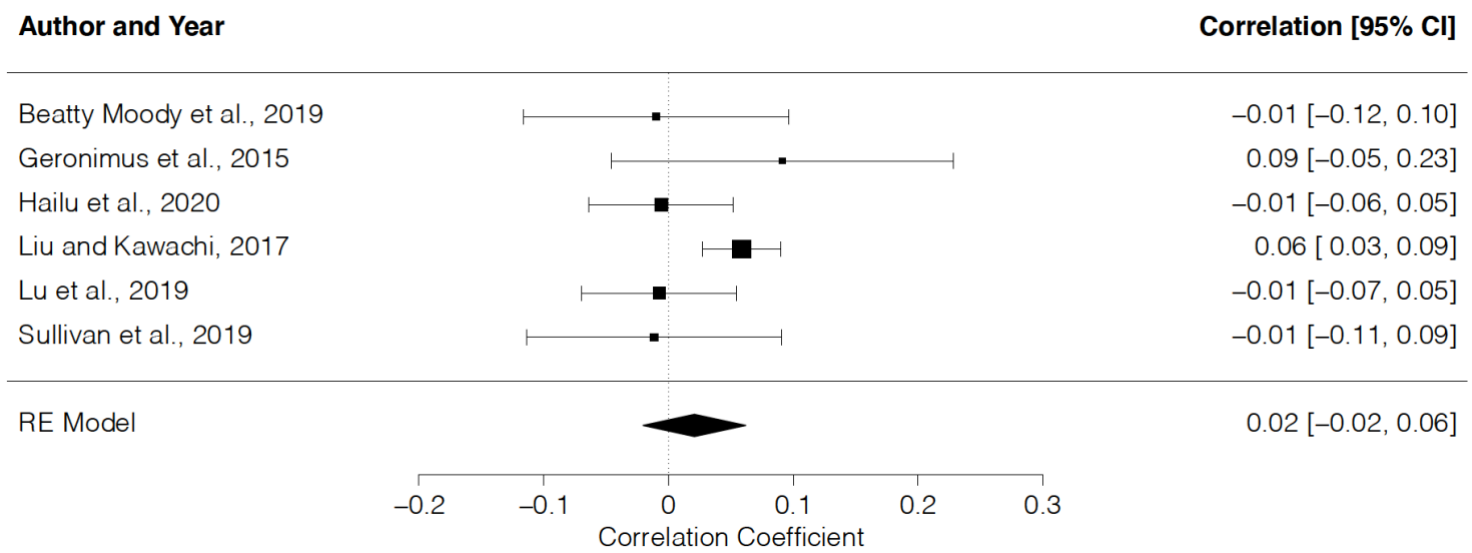

Figure A.4 EDS and telomere length, most adjusted estimates

Appendix B

Supplementary Materials for Chapter 3

Table B.1. Expanded IV Results and OLS estimates of the effect of racial discrimination on diastolic blood pressure

	Diastolic Blood Pressure		
	IV	**OLS**	**OLS** [A]
Discrimination	1.31 (1.00, 1.62)	0.42 (0.26, 0.58)	0.23 (0.08, 0.38)
Education			
≤ 12 years			Ref
> 12 years			-0.51 (-1.14, 0.12)
Income			
≤ $24,999			Ref
$25,000 to $49,999			0.00 (-0.73, 0.73)
≥ $50,000			-0.78 (-1.65, 0.08)
Marital Status			
Married			Ref
Never married			0.31 (-0.39, 1.00)
Wid/Div/Sep/Oth			1.50 (0.57, 2.42)
Gender			
Female			Ref
Male			2.67 (2.06, 3.28)
Age			0.29 (0.21, 0.38)
Waist circumference			0.20 (0.17, 0.22)
Alcohol intake – past yr			
No			Ref
Yes			-0.47 (-1.26, 0.32)
HBP medication			
No			Ref
Yes			15.00 (12.84, 17.15)
Tobacco Use – Ever			
No			Ref
Yes			-1.18 (-1.79, -0.58)

[A]: models adjusted for educational attainment, income, marital status, gender, age at exam 4, waist circumference, alcohol and tobacco consumption, and antihypertensive medication status.

Table B.2. Expanded IV Results and OLS estimates of the effect of racial discrimination on systolic blood pressure

	Systolic Blood Pressure		
	IV	**OLS**	**OLS** [A]
Discrimination	2.23 (1.85, 2.61)	0.67 (0.48, 0.87)	0.32 (0.15, 0.49)
Education			
≤ 12 years			Ref
> 12 years			-1.76 (-2.50, -1.03)
Income			
≤ $24,999			Ref
$25,000 to $49,999			-0.38 (-1.23, 0.48)
≥ $50,000			-0.84 (-1.85, 0.17)
Marital Status			
Married			Ref
Never married			1.51 (0.70, 2.33)
Wid/Div/Sep/Oth			3.20 (2.12, 4.28)
Gender			
Female			Ref
Male			5.44 (4.62, 6.05)
Age			0.08 (-0.02, 0.18)
Waist circumference			0.26 (0.23, 0.29)
Alcohol intake – past yr			
No			Ref
Yes			0.16 (-0.76, 1.08)
HBP medication			
No			Ref
Yes			18.49 (15.97, 21.00)
Tobacco Use – Ever			
No			Ref
Yes			-0.32 (-1.03, 0.39)

[A]: models adjusted for educational attainment, income, marital status, gender, age at exam 4, waist circumference, alcohol and tobacco consumption, and antihypertensive medication status

Table B.3. Results from instrumental and OLS models examining the relationship between racial discrimination and probability of hypertension

Measure	Unadjusted OLS for skin color – discrimination assessment		IV	Unadjusted OLS for discrimination and blood pressure	Adjusted OLS for discrimination and blood pressure [A]
	Beta	F-statistic	IV estimate	Beta	Beta
Hypertension	-0.005 (-0.006, -0.004)[B]	1472.95[B]	0.05 (0.04, 0.06)[B]	0.01 (0.01, 0.02)[B]	0.01 (0.002, 0.01)[C]

[A]: adjusted for educational attainment, income, marital status, gender, age at exam 4, waist circumference, alcohol and tobacco consumption
[B]: p <0.001; [C]: p<0.01; [D]: p<0.05

Table B.4. Results from instrumental models examining the relationship between racial discrimination at exam 4 and change in blood pressure from exam 4 (year 7) to exam 5 (year 10)

Measure	Unadjusted OLS for skin color – discrimination assessment		IV
	Beta	F-statistic	IV estimate
Δ in Diastolic Blood Pressure	-0.10 (-0.10, -0.09)[B]	1337.43[B]	0.68 (0.39, 0.96)[B]
Δ in Systolic Blood Pressure			0.50 (0.19, 0.81)[C]

[B]: p <0.001; [C]: p<0.01; [D]: p<0.05

Appendix C

Supplementary Material for Chapter 4

Scale items from the Everyday Discrimination Scale and Major Lifetime Discrimination Scale are provided. This section also presents results from sensitivity analyses to check the robustness of findings to how measures of discrimination were coded. Additionally, calculated E-values and outcomes from post-hoc outcome wide analyses are reported.

Table C.1. Measurement of Lifetime and Everyday Discrimination

Major Lifetime Discrimination – Responses are recorded as the number of times across the lifecourse

"How many times in your life have you been discriminated against in each of the following ways because of such things as your race, ethnicity, gender, age, religion, physical appearance, sexual orientation, or other characteristics?"

1. "You were discouraged by a teacher or advisor from seeking higher education."
2. "You were denied a scholarship."
3. "You were not hired for a job."
4. "You were not given a promotion."
5. "You were fired."
6. "You were prevented from renting or buying a home in the neighborhood you wanted."
7. "You were prevented from remaining in a neighborhood because neighbors made life so uncomfortable."
8. "You were hassled by the police."
9. "You were denied a bank loan."
10. "You were denied or provided inferior medical care."
11. "You were denied or provided inferior service by a plumber, care mechanic, or other service provider."

Everyday Discrimination – Responses are recorded as often, sometimes, rarely, never

"*How often on a day-to-day basis do you experience each of the following types of discrimination*?"

1. "You are treated with less courtesy than other people."
2. "You are treated with less respect than other people."
3. "You receive poorer service than other people at restaurants or stores."
4. "People act as if they think you are not smart."
5. "People act as if they are afraid of you."
6. "People act as if they think you are dishonest."
7. "People act as if they think you are not as good as they are."
8. "You are called names or insulted."
9. "You are threatened or harassed."

Respondents reporting discriminatory experiences also provided responses to the following:

"*What was the main reason for the discrimination you experienced? (If more than one main reason, check all that apply.)*"

- ☐ Your age
- ☐ Your gender
- ☐ Your race
- ☐ Your ethnicity or nationality
- ☐ Your religion
- ☐ Your height or weight
- ☐ Some other aspect of your appearance
- ☐ A physical disability
- ☐ Your sexual orientation
- ☐ Some other reason for discrimination

Table C.2. Sensitivity analyses of relationships between everyday discrimination quartiles and high-risk allostatic load scores

Outcome	Category	Model 1[a]	Model 2[b]	Model 3[c]
SNS	None	--	--	--
	Some	0.96 (0.83 - 1.11)	0.98 (0.85 - 1.14)	0.93 (0.79 - 1.09)
	High	0.96 (0.80 - 1.14)	1.02 (0.81 - 1.29)	0.98 (0.76 - 1.26)
PNS	None	--	--	--
	Some	1.05 (0.89 - 1.24)	1.14 (0.97 - 1.34)	1.13 (0.95 - 1.34)
	High	1.15 (0.95 - 1.39)	**1.43 (1.12 - 1.83)**	**1.42 (1.10 - 1.85)**
HPA Axis	None	--	--	--
	Some	1.04 (0.92 - 1.19)	1.06 (0.93 - 1.21)	1.03 (0.90 - 1.18)
	High	0.94 (0.79 - 1.10)	1.01 (0.82 - 1.24)	0.95 (0.76 - 1.19)
Inflammation	None	--	--	--
	Some	1.06 (0.95 - 1.18)	1.08 (0.96 - 1.21)	1.05 (0.93 - 1.18)
	High	1.12 (0.99 - 1.27)	1.09 (0.93 - 1.27)	1.15 (0.98 - 1.36)
Cardiovascular	None	--	--	--
	Some	0.98 (0.87 - 1.11)	1.05 (0.92 - 1.19)	1.03 (0.91 - 1.17)
	High	1.11 (0.96 - 1.27)	**1.23 (1.03 - 1.47)**	**1.23 (1.02 - 1.48)**
Metabolic Glucose	None	--	--	--
	Some	1.02 (0.89 - 1.18)	1.09 (0.94 - 1.26)	1.10 (0.95 - 1.28)
	High	1.15 (0.98 - 1.34)	1.18 (0.96 - 1.45)	**1.25 (1.01 - 1.55)**
Metabolic Lipids	None	--	--	--
	Some	1.10 (0.99 - 1.23)	**1.15 (1.04 - 1.28)**	**1.14 (1.03 - 1.27)**
	High	1.11 (0.98 - 1.25)	**1.23 (1.06 - 1.42)**	**1.28 (1.10 - 1.49)**
Overall AL Score	None	--	--	--
	Some	1.03 (0.97 - 1.11)	**1.09 (1.02 - 1.16)**	1.06 (1.00 - 1.14)
	High	1.06 (0.97 - 1.14)	**1.20 (1.08 - 1.32)**	**1.21 (1.09 - 1.34)**

[a]: unadjusted
[b]: adjusted for race (ref=Black), age, sex (ref=Female), and sample
[c]: adjusted for a and employment status, educational attainment, smoking and drinking status, and income

Table C.3. Sensitivity analyses of relationships between counts of lifetime discrimination experiences and high-risk allostatic load scores

Outcome	Model 1[a]	Model 2[b]	Model 3[c]
Sympathetic Nervous System	0.96 (0.93 - 1.00)	0.98 (0.95 - 1.02)	0.97 (0.93 - 1.01)
Parasympathetic Nervous System	0.97 (0.94 - 1.01)	1.02 (0.98 - 1.06)	1.01 (0.97 - 1.06)
HPA Axis	0.98 (0.95 - 1.01)	1.01 (0.97 - 1.04)	1.01 (0.97 - 1.05)
Inflammation	**1.08 (1.06 - 1.11)**	**1.05 (1.03 - 1.08)**	**1.06 (1.03 - 1.09)**
Cardiovascular	1.03 (1.00 - 1.06)	1.03 (1.00 - 1.06)	1.03 (1.00 - 1.06)
Metabolic Glucose	**1.08 (1.05 - 1.11)**	**1.06 (1.03 - 1.09)**	**1.07 (1.04 - 1.10)**
Metabolic Lipids	**1.04 (1.01 - 1.06)**	**1.05 (1.03 - 1.08)**	**1.05 (1.03 - 1.08)**
Overall AL Score	**1.03 (1.01 - 1.04)**	**1.03 (1.02 - 1.05)**	**1.03 (1.02 - 1.05)**

[a]: unadjusted
[b]: adjusted for race (ref=Black), age, sex (ref=Female), and sample
[c]: adjusted for a and employment status, educational attainment, smoking and drinking status, and income

Table C.4. Sensitivity analyses of relationships between discrimination interfering with life and high-risk allostatic load scores

How much has discrimination interfered with you having a full and productive life?				
Outcome	**Category**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
SNS	None/A little Some/A lot	-- 0.96 (0.82 - 1.11)	-- 1.02 (0.84 - 1.24)	-- 0.98 (0.79 - 1.21)
PNS	None/A little Some/A lot	-- 1.02 (0.87 - 1.20)	-- 1.17 (0.95 - 1.44)	-- 1.21 (0.96 - 1.51)
HPA Axis	None/A little Some/A lot	-- 0.86 (0.75 - 0.99)	-- 0.96 (0.81 - 1.15)	-- 0.89 (0.74 - 1.08)
Inflammation	None/A little Some/A lot	-- **1.15 (1.03 - 1.27)**	-- **1.21 (1.06 - 1.38)**	-- **1.17 (1.02 - 1.35)**
Cardiovascular	None/A little Some/A lot	-- 1.06 (0.94 - 1.19)	-- 1.06 (0.92 - 1.23)	-- 1.05 (0.89 - 1.23)
Metabolic Glucose	None/A little Some/A lot	-- 1.09 (0.95 - 1.25)	-- 1.04 (0.88 - 1.23)	-- 1.04 (0.87 - 1.24)
Metabolic Lipids	None/A little Some/A lot	-- 1.08 (0.98 - 1.19)	-- 1.13 (1.00 - 1.28)	-- 1.12 (0.98 - 1.27)
Overall AL Score	None/A little Some/A lot	-- 1.02 (0.95 - 1.09)	-- **1.10 (1.01 - 1.20)**	-- 1.08 (0.98 - 1.18)

[a]: unadjusted
[b]: adjusted for race (ref=Black), age, sex (ref=Female), and sample
[c]: adjusted for a and employment status, educational attainment, smoking and drinking status, and income

Table C.5. Sensitivity analyses of relationships between discrimination making life harder and high-risk allostatic load scores

How much harder has your life been because of discrimination?				
Outcome	**Category**	**Model 1[a]**	**Model 2[b]**	**Model 3c**
SNS	None/A little Some/A lot	-- 0.97 (0.84 - 1.12)	-- 1.03 (0.78 - 1.36)	-- 1.01 (0.74 - 1.35)
PNS	None/A little Some/A lot	-- 0.96 (0.82 - 1.13)	-- 1.00 (0.73 - 1.36)	-- 1.09 (0.79 - 1.50)
HPA Axis	None/A little Some/A lot	-- 0.90 (0.79 - 1.03)	-- 1.03 (0.80 - 1.32)	-- 1.01 (0.77 - 1.32)
Inflammation	None/A little Some/A lot	-- 1.09 (0.98 - 1.21)	-- **1.26 (1.05 - 1.50)**	-- 1.20 (0.99 - 1.44)
Cardiovascular	None/A little Some/A lot	-- 1.09 (0.97 - 1.23)	-- 1.21 (0.98 - 1.49)	-- 1.23 (0.98 - 1.52)
Metabolic Glucose	None/A little Some/A lot	-- 1.10 (0.96 - 1.26)	-- 1.08 (0.85 - 1.37)	-- 1.05 (0.82 - 1.33)
Metabolic Lipids	None/A little Some/A lot	-- 1.04 (0.94 - 1.14)	-- 1.17 (0.98 - 1.39)	-- 1.13 (0.95 - 1.35)
Overall AL Score	None/A little Some/A lot	-- 0.99 (0.93 - 1.06)	-- **1.13 (1.01 - 1.27)**	-- 1.13 (1.00 - 1.27)

[a]: unadjusted
[b]: adjusted for race (ref=Black), age, sex (ref=Female), and sample
[c]: adjusted for a and employment status, educational attainment, smoking and drinking status, and income

Table C.6. E-values for significant associations (model 2) between discrimination measures and allostatic load subscales risk scores and overall AL scores.

Measure	Outcome	E-value
Everyday Discrimination	**Parasympathetic Nervous System**	1.54
	Metabolic Lipids	1.40
	Overall AL Score	1.34
Lifetime Discrimination	**Inflammation**	
	One to two	1.54
	Three or more	1.99
	Metabolic Glucose	
	One to two	2.13
	Three or more	2.24
	Metabolic Lipids	
	One to two	1.62
	Three or more	1.95
	Overall AL Score	
	One to two	1.43
	Three or more	1.62
Burden of Discrimination	**Inflammation**	
	High on both	1.95
	Metabolic Lipids	
	High on both	1.79
	Overall AL Score	
	High on both	1.57

Table C.7. Outcome-wide analyses of everyday discrimination and biomarkers

Allostatic load subscale	Biomarker	Beta	SE	p-value
Sympathetic	Epinephrine	0.031	0.039	0.4229
	Norepinephrine	0.005	0.025	0.8350
Parasympathetic	Avg_SDRR	-0.028	0.018	0.1200
	Avg_RMSSD	-0.046	0.024	0.0570
	avg_LFHRV	-0.056	0.041	0.1683
	avg_HFHRV	-0.104	0.050	0.0370
HPA axis	cortisol	-0.036	0.027	0.1790
	DHEA	-0.033	0.023	0.1400
Inflammation	IL-6	0.040	0.026	0.1290
	Fibrinogen	0.013	0.008	0.0855
	CRP	0.053	0.045	0.2369
	E-selectin	0.048	0.017	0.0045
	ICAM	0.000	0.015	0.9850
Cardiovascular	SBP (normal)	0.252	0.590	0.6696
	Pulse (normal)	1.014	0.402	0.0117
	Pulse Pressure (normal)	-0.020	0.442	0.9638
Metabolic glucose	HbA1c	0.008	0.005	0.1317
	glucose	0.009	0.007	0.1724
	HOMA-IR	0.088	0.028	0.0013
Metabolic lipids	bmi	0.019	0.008	0.0119
	whr	-0.001	0.006	0.9065
	trig	0.047	0.019	0.0134
	HDL (normal)	-2.691	0.608	0.0000
	LDL (normal)	3.200	1.190	0.0072

Models were adjusted for race (ref=Black), age, sex (ref=Female), sample, employment status, educational attainment, smoking and drinking status, and income

Table C.8. Outcome-wide analysis of lifetime discrimination and biomarkers

Allostatic Load Subscale	Biomarker	Category	beta	se	p-value
SNS	Epinephrine	One to two	-0.015	0.051	0.7607
		Three +	-0.056	0.061	0.3588
	Norepinephrine	One to two	0.034	0.035	0.3310
		Three +	-0.053	0.045	0.2429
PNS	Avg_SDRR	One to two	0.020	0.025	0.4216
		Three +	0.000	0.033	0.9913
	Avg_RMSSD	One to two	-0.010	0.034	0.7652
		Three +	0.000	0.045	0.9915
	Avg_LFHRV	One to two	0.026	0.059	0.6603
		Three +	-0.020	0.075	0.7940
	Avg_HFHRV	One to two	-0.038	0.070	0.5841
		Three +	-0.011	0.091	0.9039
HPA Axis	Cortisol	One to two	-0.127	0.044	0.0036
		Three +	-0.072	0.052	0.1675
	DHEA	One to two	-0.039	0.036	0.2839
		Three +	-0.033	0.048	0.4934
Inflammation	IL-6	One to two	0.062	0.038	0.1025
		Three +	0.207	0.050	0.0000
	Fibrinogen	One to two	-0.003	0.013	0.8392
		Three +	0.041	0.015	0.0085
	CRP	One to two	0.104	0.064	0.1027
		Three +	0.377	0.081	0.0000
	E-selectin	One to two	0.067	0.029	0.0189
		Three +	0.099	0.036	0.0059
	ICAM-1	One to two	0.042	0.020	0.0360
		Three +	0.009	0.032	0.7767
Cardiovascular	SBP (normal)	One to two	0.099	0.905	0.9126
		Three +	0.100	1.105	0.9278
	Pulse (normal)	One to two	0.394	0.609	0.5177
		Three +	1.434	0.798	0.0725
	Pulse pressure (normal)	One to two	-0.184	0.684	0.7877
		Three +	-0.906	0.839	0.2805
Metabolic glucose	HbA1c	One to two	0.023	0.008	0.0036
		Three +	0.027	0.010	0.0078
	Glucose	One to two	0.046	0.010	0.0000
		Three +	0.038	0.013	0.0024
	HOMA-IR	One to two	0.188	0.042	0.0000
		Three +	0.306	0.055	0.0000

Allostatic Load Subscale	Biomarker	Category	beta	se	p-value
Metabolic lipids	BMI	One to two	0.028	0.012	0.0184
		Three +	0.071	0.015	0.0000
	WHR	One to two	0.012	0.005	0.0177
		Three +	0.026	0.008	0.0014
	Trig	One to two	0.048	0.029	0.0894
		Three +	0.149	0.036	0.0000
	HDL (normal)	One to two	-0.286	0.934	0.7595
		Three +	-2.677	1.174	0.0226
	LDL (normal)	One to two	3.176	1.931	0.1001
		Three +	6.527	2.381	0.0061

Models were adjusted for race (ref=Black), age, sex (ref=Female), sample, employment status, educational attainment, smoking and drinking status, and income. Reference group is “none”.

Table C.9. Outcome-wide analysis of burden of discrimination and biomarkers

Allostatic load subscale	Biomarker	Category	Beta	SE	p-value
SNS	Epinephrine	High on one	-0.087	0.110	0.4276
		High on both	-0.027	0.099	0.7843
	Norepinephrine	High on one	-0.162	0.068	0.0167
		High on both	0.017	0.059	0.7803
PNS	Avg_SDRR	High on one	-0.019	0.055	0.7309
		High on both	-0.015	0.052	0.7765
	Avg_RMSSD	High on one	-0.036	0.074	0.6256
		High on both	-0.026	0.070	0.7094
	Avg_LFHRV	High on one	-0.165	0.127	0.1932
		High on both	-0.092	0.122	0.4513
	Avg_HFHRV	High on one	-0.028	0.148	0.8492
		High on both	-0.026	0.137	0.8498
HPA Axis	Cortisol	High on one	-0.128	0.083	0.1260
		High on both	-0.053	0.076	0.4862
	DHEA	High on one	-0.014	0.082	0.8631
		High on both	-0.024	0.073	0.7380
Inflammation	IL-6	High on one	-0.007	0.076	0.9308
		High on both	0.109	0.073	0.1384
	Fibrinogen	High on one	0.018	0.024	0.4576
		High on both	0.046	0.023	0.0515
	CRP	High on one	0.099	0.126	0.4319
		High on both	0.316	0.119	0.0078
	E-selectin	High on one	0.075	0.052	0.1487
		High on both	0.098	0.049	0.0488
	ICAM-1	High on one	-0.026	0.065	0.6937
		High on both	-0.005	0.057	0.9351
Cardiovascular	SBP (normal)	High on one	-2.070	1.917	0.2802
		High on both	-2.207	1.782	0.2156
	Pulse (normal)	High on one	2.889	1.369	0.0349
		High on both	3.533	1.263	0.0052
	Pulse pressure (normal)	High on one	-1.865	1.437	0.1944
		High on both	-2.079	1.361	0.1266
Metabolic glucose	HbA1c	High on one	0.001	0.019	0.9660
		High on both	0.014	0.020	0.4743
	Glucose	High on one	0.018	0.024	0.4520
		High on both	0.029	0.025	0.2428
	HOMA-IR	High on one	0.059	0.089	0.5072

Allostatic load subscale	Biomarker	Category	Beta	SE	p-value
		High on both	0.181	0.089	0.0420
Metabolic lipids	BMI	High on one	0.023	0.025	0.3567
		High on both	0.041	0.024	0.0944
	WHR	High on one	0.019	0.011	0.0861
		High on both	0.021	0.010	0.0384
	Trig	High on one	0.089	0.056	0.1111
		High on both	0.131	0.053	0.0138
	HDL (normal)	High on one	1.587	1.911	0.4061
		High on both	-0.918	1.815	0.6133
	LDL (normal)	High on one	0.321	4.014	0.9363
		High on both	-0.627	3.656	0.8637

Models were adjusted for race (ref=Black), age, sex (ref=Female), sample, employment status, educational attainment, smoking and drinking status, and income

References

1. National Academies of Sciences, Engineering, and Medicine. The state of health disparities in the United States. In: Baciu A, Negussie Y, Geller A, Weinstein JN, eds. *Communities in action: pathways to health equity.* Washington (DC): National Academies Press (US); 2017.
2. Bailey ZD, Krieger N, Agénor M, Graves J, Linos N, Bassett MT. Structural racism and health inequities in the USA: evidence and interventions. *The Lancet.* 2017;389(10077):1453-1463.
3. Phelan JC, Link BG. Is racism a fundamental cause of inequalities in health? *Annual Review of Sociology.* 2015;41:311-330.
4. Williams DR, Lawrence JA, Davis BA. Racism and Health: Evidence and Needed Research. *Annual Review of Public Health.* 2019;40(1):105-125.
5. Paradies Y, Ben J, Denson N, et al. Racism as a determinant of health: a systematic review and meta-analysis. *PloS one.* 2015;10(9):e0138511.
6. Bailey ZD, Feldman JM, Bassett MT. How structural racism works—racist policies as a root cause of US racial health inequities. In: Mass Medical Soc; 2021.
7. Healthy People 2030, U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Social Determinants of Health. https://health.gov/healthypeople/objectives-and-data/social-determinants-health. Accessed April 9, 2021.
8. White K, Lawrence JA, Tchangalova N, Huang SJ, Cummings JL. Socially-assigned race and health: a scoping review with global implications for population health equity. *International journal for equity in health.* 2020;19(1):25.
9. Roth WD. Unsettled identities amid settled classifications? Toward a sociology of racial appraisals. *Ethnic and Racial Studies.* 2018;41(6):1093-1112.
10. Williams DR, Lawrence JA, Davis BA, Vu C. Understanding how discrimination can affect health. *Health Services Research.* 2019;54(S2):1374-1388.
11. Ford CL, Airhihenbuwa CO. Critical race theory, race equity, and public health: toward antiracism praxis. *American journal of public health.* 2010;100(S1):S30-S35.
12. Pager D, Western B, Bonikowski B. Discrimination in a Low-Wage Labor Market: A Field Experiment. *Am Sociol Rev.* 2009;74(5):777-799.
13. Williams DR, Mohammed SA. Discrimination and racial disparities in health: evidence and needed research. *J Behav Med.* 2009;32(1):20-47.
14. Lewis TT, Cogburn CD, Williams DR. Self-Reported Experiences of Discrimination and Health: Scientific Advances, Ongoing Controversies, and Emerging Issues. *Annual Review of Clinical Psychology.* 2015;11(1):407-440.
15. Lockwood KG, Marsland AL, Matthews KA, Gianaros PJ. Perceived discrimination and cardiovascular health disparities: a multisystem review and health neuroscience perspective. *Annals of the New York Academy of Sciences.* 2018;1428(1):170-207.
16. Pascoe EA, Smart Richman L. Perceived discrimination and health: a meta-analytic review. *Psychological bulletin.* 2009;135(4):531.

17. Williams DR, Neighbors HW, Jackson JS. Racial/ethnic discrimination and health: Findings from community studies. *American journal of public health.* 2003;93(2):200-208.
18. Lewis TT, Williams DR, Tamene M, Clark CR. Self-Reported Experiences of Discrimination and Cardiovascular Disease. *Curr Cardiovasc Risk Rep.* 2014;8(1):365-365.
19. Gilbert PA, Zemore SE. Discrimination and drinking: A systematic review of the evidence. *Social Science & Medicine.* 2016;161:178-194.
20. Pieterse AL, Todd NR, Neville HA, Carter RT. Perceived racism and mental health among black american adults: A meta-analytic review. *Journal of Counseling Psychology.* 2012;59(1):1-9.
21. Williams DR. Race and health: Basic questions, emerging directions. *Annals of Epidemiology.* 1997;7(5):322-333.
22. Dolezsar CM, McGrath JJ, Herzig AJ, Miller SB. Perceived racial discrimination and hypertension: a comprehensive systematic review. *Health Psychology.* 2014;33(1):20.
23. Williams DR. Improving the measurement of self-reported racial discrimination: Challenges and opportunities. 2016.
24. Krieger N. Methods for the scientific study of discrimination and health: an ecosocial approach. *American journal of public health.* 2012;102(5):936-944.
25. Krieger N. Ecosocial Theory of Disease Distribution: Embodying Societal & Ecologic Context. In: *Epidemiology and the People's Health: Theory and Context.* Oxford University Press; 2011:202-235.
26. Jones CP. Systems of power, axes of inequity: parallels, intersections, braiding the strands. *Medical care.* 2014;52:S71-S75.
27. McEwen BS. Allostasis and Allostatic Load: Implications for Neuropsychopharmacology. *Neuropsychopharmacology.* 2000;22(2):108-124.
28. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proceedings of the National Academy of Sciences.* 2001;98(8):4770-4775.
29. McEwen BS, Stellar E. Stress and the Individual: Mechanisms Leading to Disease. *Archives of Internal Medicine.* 1993;153(18):2093-2101.
30. Williams DR, Yu Y, Jackson JS, Anderson NB. Racial differences in physical and mental health: Socio-economic status, stress and discrimination. *Journal of health psychology.* 1997;2(3):335-351.
31. Clark R, Anderson NB, Clark VR, Williams DR. Racism as a stressor for African Americans: A biopsychosocial model. *American Psychologist.* 1999;54(10):805.
32. Epel ES. Telomeres in a life-span perspective: A new “psychobiomarker”? *Current Directions in Psychological Science.* 2009;18(1):6-10.
33. Cuevas AG, Ong AD, Carvalho K, et al. Discrimination and systemic inflammation: A critical review and synthesis. *Brain, behavior, and immunity.* 2020.
34. McEwen BS. Brain on stress: how the social environment gets under the skin. *Proc Natl Acad Sci U S A.* 2012;109 Suppl 2(Suppl 2):17180-17185.
35. McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *Eur J Pharmacol.* 2008;583(2-3):174-185.
36. Mathur MB, Epel E, Kind S, et al. Perceived stress and telomere length: A systematic review, meta-analysis, and methodologic considerations for advancing the field. *Brain, Behavior, and Immunity.* 2016;54:158-169.
37. Krieger N. Embodiment: a conceptual glossary for epidemiology. *Journal of Epidemiology & Community Health.* 2005;59(5):350-355.

38. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *The Lancet.* 2014;383(9932):1899-1911.
39. Ostchega Y, Fryar C, Nwankwo T, Nguyen DT. Hypertension prevalence among adults aged 18 and over: United States, 2017-2018. In: NCHS Data Brief, ed. Vol 364: National Center for Health Statistics; 2020.
40. Brondolo E, Rieppi R, Kelly KP, Gerin W. Perceived racism and blood pressure: A review of the literature and conceptual and methodological critique. *Annals of behavioral medicine.* 2003;25(1):55-65.
41. Cuffee YL, Hargraves JL, Allison J. Exploring the association between reported discrimination and hypertension among African Americans: a systematic review. *Ethnicity & Disease.* 2012;22(4):422-432.
42. Chae DH, Nuru-Jeter AM, Adler NE. Implicit racial bias as a moderator of the association between racial discrimination and hypertension: a study of Midlife African American men. *Psychosom Med.* 2012;74(9):961-964.
43. Mezuk B, Kershaw KN, Hudson D, Lim KA, Ratliff S. Job strain, workplace discrimination, and hypertension among older workers: The Health and Retirement Study. *Race and social problems.* 2011;3(1):38.
44. Sims M, Diez-Roux AV, Dudley A, et al. Perceived discrimination and hypertension among African Americans in the Jackson Heart Study. *Am J Public Health.* 2012;102 Suppl 2(Suppl 2):S258-S265.
45. Eliezer D, Townsend SS, Sawyer PJ, Major B, Mendes WB. System-justifying beliefs moderate the relationship between perceived discrimination and resting blood pressure. *Social Cognition.* 2011;29(3):303-321.
46. Cozier Y, Palmer JR, Horton NJ, Fredman L, Wise LA, Rosenberg L. Racial discrimination and the incidence of hypertension in US black women. *Annals of epidemiology.* 2006;16(9):681-687.
47. Goosby BJ, Cheadle JE, Mitchell C. Stress-related biosocial mechanisms of discrimination and African American health inequities. *Annual Review of Sociology.* 2018;44:319-340.
48. Ong AD, Williams DR, Nwizu U, Gruenewald TL. Everyday unfair treatment and multisystem biological dysregulation in African American adults. *Cultural diversity and ethnic minority psychology.* 2017;23(1):27.
49. Brody GH, Lei MK, Chae DH, Yu T, Kogan SM, Beach SR. Perceived Discrimination Among African American Adolescents and Allostatic Load: A Longitudinal Analysis With Buffering Effects. *Child development.* 2014;85(3):989-1002.
50. Vadiveloo M, Mattei J. Perceived Weight Discrimination and 10-Year Risk of Allostatic Load Among US Adults. *Ann Behav Med.* 2017;51(1):94-104.
51. Krieger N. Discrimination and health inequities. *International Journal of Health Services.* 2014;44(4):643-710.
52. Moomal H, Jackson PB, Stein DJ, et al. Perceived discrimination and mental health disorders: the South African Stress and Health study. *S Afr Med J.* 2009;99(5 Pt 2):383-389.
53. Schulz AJ, Gravlee CC, Williams DR, Israel BA, Mentz G, Rowe Z. Discrimination, symptoms of depression, and self-rated health among African American women in Detroit: results from a longitudinal analysis. *American journal of public health.* 2006;96(7):1265-1270.
54. Lewis TT, Everson-Rose SA, Powell LH, et al. Chronic exposure to everyday discrimination and coronary artery calcification in African-American women: the SWAN Heart Study. *Psychosom Med.* 2006;68(3):362-368.

55. Lewis TT, Troxel WM, Kravitz HM, Bromberger JT, Matthews KA, Hall MH. Chronic exposure to everyday discrimination and sleep in a multiethnic sample of middle-aged women. *Health Psychology.* 2013;32(7):810.
56. Friedman EM, Williams DR, Singer BH, Ryff CD. Chronic discrimination predicts higher circulating levels of E-selectin in a national sample: the MIDUS study. *Brain, behavior, and immunity.* 2009;23(5):684-692.
57. Lewis TT, Aiello AE, Leurgans S, Kelly J, Barnes LL. Self-reported experiences of everyday discrimination are associated with elevated C-reactive protein levels in older African-American adults. *Brain, behavior, and immunity.* 2010;24(3):438-443.
58. Gee GC, Spencer MS, Chen J, Takeuchi D. A nationwide study of discrimination and chronic health conditions among Asian Americans. *American Journal of Public Health.* 2007;97(7):1275-1282.
59. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine.* 2009;151(4):264-269.
60. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Jama.* 2000;283(15):2008-2012.
61. Broza YY, Zhou X, Yuan M, et al. Disease Detection with Molecular Biomarkers: From Chemistry of Body Fluids to Nature-Inspired Chemical Sensors. *Chemical reviews.* 2019;119(22):11761-11817.
62. Laterza OF, Hendrickson RC, Wagner JA. Molecular Biomarkers. *Drug Information Journal.* 2007;41(5):573-585.
63. Sternthal MJ, Slopen N, Williams DR. Racial disparities in health: how much does stress really matter? *Du Bois Review: Social Science Research on Race.* 2011;8(1):95-113.
64. Veritas Health Innovation. Covidence systematic review software. In: Veritas Health Innovation Melbourne, VIC; 2017.
65. Peterson RA, Brown SP. On the use of beta coefficients in meta-analysis. *Journal of Applied Psychology.* 2005;90(1):175-181.
66. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of statistical software.* 2010;36(3):1-48.
67. R Core Team. R: A language and environment for statistical computing. 2013.
68. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research synthesis methods.* 2010;1(2):97-111.
69. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj.* 1997;315(7109):629-634.
70. Beatty Moody DL, Brown C, Matthews KA, Bromberger JT. Everyday discrimination prospectively predicts inflammation across 7-years in racially diverse midlife women: Study of women's health across the nation. *Journal of Social Issues.* 2014;70(2):298-314.
71. Beatty Moody DL, Leibel DK, Darden TM, et al. Interpersonal-level discrimination indices, sociodemographic factors, and telomere length in African-Americans and Whites. *Biological Psychology.* 2019;141:1-9.
72. Doane LD, Zeiders KH. Contextual moderators of momentary cortisol and negative affect in adolescents' daily lives. *Journal of Adolescent Health.* 2014;54(5):536-542.
73. Doyle DM, Molix L. Minority stress and inflammatory mediators: Covering moderates associations between perceived discrimination and salivary interleukin-6 in gay men. *Journal of Behavioral Medicine.* 2016;39(5):782-792.
74. Friedman EM, Williams DR, Singer BH, Ryff CD. Chronic discrimination predicts higher circulating levels of E-selectin in a national sample: the MIDUS study. *Brain, Behavior, and Immunity.* 2009;23(5):684-692.

75. Fuller-Rowell TE, Doan SN, Eccles JS. Differential effects of perceived discrimination on the diurnal cortisol rhythm of African Americans and Whites. *Psychoneuroendocrinology.* 2012;37(1):107-118.
76. Geronimus AT, Pearson JA, Linnenbringer E, et al. Race-ethnicity, poverty, urban stressors, and telomere length in a Detroit community-based sample. *Journal of health and social behavior.* 2015;56(2):199-224.
77. Guardino CM, Dunkel Schetter C, Hobel CJ, et al. Chronic stress and C-reactive protein in mothers during the first postpartum year. *Psychosom Med.* 2017;79(4):450-460.
78. Guyll M, Matthews KA, Bromberger JT. Discrimination and unfair treatment: relationship to cardiovascular reactivity among African American and European American women. *Health Psychology.* 2001;20(5):315.
79. Huynh VW, Guan SA, Almeida DM, McCreath H, Fuligni AJ. Everyday discrimination and diurnal cortisol during adolescence. *Hormones and Behavior.* 2016;80:76-81.
80. Incollingo Rodriguez AC, Tomiyama AJ, Guardino CM, Dunkel Schetter C. Association of weight discrimination during pregnancy and postpartum with maternal postpartum health. *Health Psychology.* 2019;38(3):226-237.
81. Kershaw KN, Lewis TT, Diez Roux AV, et al. Self-reported experiences of discrimination and inflammation among men and women: The multi-ethnic study of atherosclerosis. *Health Psychology.* 2016;35(4):343-350.
82. Lehrer HM, Goosby BJ, Dubois SK, Laudenslager ML, Steinhardt MA. Race moderates the association of perceived everyday discrimination and hair cortisol concentration. *Stress.* 2020:1-9.
83. Lewis TT, Aiello AE, Leurgans S, Kelly J, Barnes LL. Self-reported experiences of everyday discrimination are associated with elevated C-reactive protein levels in older African-American adults. *Brain, Behavior, and Immunity.* 2010;24(3):438-443.
84. Lucas T, Wegner R, Pierce J, Lumley MA, Laurent HK, Granger DA. Perceived discrimination, racial identity, and multisystem stress response to social evaluative threat among African American men and women. *Psychosom Med.* 2017;79(3):293-305.
85. Potter L, Wallston K, Trief P, Ulbrecht J, Juth V, Smyth J. Attributing discrimination to weight: Associations with well-being, self-care, and disease status in patients with type 2 diabetes mellitus. *J Behav Med.* 2015;38(6):863-875.
86. Ratner KG, Halim ML, Amodio DM. Perceived stigmatization, ingroup pride, and immune and endocrine activity: Evidence from a community sample of black and latina women. *Social Psychological and Personality Science.* 2013;4(1):82-91.
87. Saban KL, Hoppensteadt D, Bryant FB, DeVon HA. Social determinants and heat shock protein-70 among African American and non-Hispanic white women with atherosclerosis: a pilot study. *Biological Research for Nursing.* 2014;16(3):258-265.
88. Saban KL, Mathews HL, Bryant FB, et al. Perceived discrimination is associated with the inflammatory response to acute laboratory stress in women at risk for cardiovascular disease. *Brain, Behavior, and Immunity.* 2018;73:625-632.
89. Santos HP, Jr., Nephew BC, Bhattacharya A, et al. Discrimination exposure and DNA methylation of stress-related genes in Latina mothers. *Psychoneuroendocrinology.* 2018;98:131-138.
90. Sims KD, Sims M, Glover LM, Smit E, Odden MC. Perceived Discrimination and Trajectories of C-Reactive Protein: The Jackson Heart Study. *American Journal of Preventive Medicine.* 2020;58(2):199-207.
91. Stepanikova I, Bateman LB, Oates GR. Systemic inflammation in midlife: Race, socioeconomic status, and perceived discrimination. *American Journal of Preventive Medicine.* 2017;52(1, Suppl 1):S63-S76.

92. Stepanikova I, Oates GR, Bateman LB. Does one size fit all? The role of body mass index and waist circumference in systemic inflammation in midlife by race and gender. *Ethnicity and Health.* 2017;22(2):169-183.
93. Thayer ZM, Kuzawa CW. Ethnic discrimination predicts poor self-rated health and cortisol in pregnancy: Insights from New Zealand. *Social Science and Medicine.* 2015;128:36-42.
94. van der Laan LC, Meeks KAC, Chilunga FP, et al. Epigenome-wide association study for perceived discrimination among sub-Saharan African migrants in Europe - the RODAM study. *Scientific Reports.* 2020;10(1):4919.
95. Zahodne LB, Kraal AZ, Sharifian N, Zaheed AB, Sol K. Inflammatory mechanisms underlying the effects of everyday discrimination on age-related memory decline. *Brain, Behavior, and Immunity.* 2019;75:149-154.
96. Zahodne LB, Kraal AZ, Zaheed A, Farris P, Sol K. Longitudinal effects of race, ethnicity, and psychosocial disadvantage on systemic inflammation. *SSM Popul Health.* 2019;7:100391.
97. Zeiders KH, Hoyt LT, Adam EK. Associations between self-reported discrimination and diurnal cortisol rhythms among young adults: The moderating role of racial–ethnic minority status. *Psychoneuroendocrinology.* 2014;50:280-288.
98. Hailu EM, Needham BL, Lewis TT, et al. Discrimination, social support, and telomere length: the Multi-Ethnic Study of Atherosclerosis (MESA). *Annals of Epidemiology.* 2020;42:58-63.e52.
99. Liu SY, Kawachi I. Discrimination and Telomere Length Among Older Adults in the United States. *Public Health Reports.* 2017;132(2):220-230.
100. Lu D, Palmer JR, Rosenberg L, et al. Perceived racism in relation to telomere length among African American women in the Black Women's Health Study. *Annals of Epidemiology.* 2019;36:33-39.
101. Pantesco EJ, Leibel DK, Ashe JJ, et al. Multiple forms of discrimination, social status, and telomere length: Interactions within race. *Psychoneuroendocrinology.* 2018;98:119-126.
102. Sullivan S, Hammadah M, Al Mheid I, et al. An investigation of racial/ethnic and sex differences in the association between experiences of everyday discrimination and leukocyte telomere length among patients with coronary artery disease. *Psychoneuroendocrinology.* 2019;106:122-128.
103. Goosby BJ, Malone S, Richardson EA, Cheadle JE, Williams DT. Perceived discrimination and markers of cardiovascular risk among low-income A frican A merican youth. *American Journal of Human Biology.* 2015;27(4):546-552.
104. Levine A, Zagoory-Sharon O, Feldman R, Lewis JG, Weller A. Measuring cortisol in human psychobiological studies. *Physiology & behavior.* 2007;90(1):43-53.
105. Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *The Journal of Clinical Endocrinology & Metabolism.* 1971;33(1):14-22.
106. Adam EK, Quinn ME, Tavernier R, McQuillan MT, Dahlke KA, Gilbert KE. Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. *Psychoneuroendocrinology.* 2017;83:25-41.
107. Montpetit AJ, Alhareeri AA, Montpetit M, et al. Telomere length: a review of methods for measurement. *Nurs Res.* 2014;63(4):289-299.
108. Korous KM, Causadias JM, Casper DM. Racial discrimination and cortisol output: A meta-analysis. *Social Science & Medicine.* 2017;193:90-100.
109. Fogelman N, Canli T. Early life stress and cortisol: A meta-analysis. *Horm Behav.* 2018;98:63-76.

110. Chida Y, Steptoe A. Cortisol awakening response and psychosocial factors: A systematic review and meta-analysis. *Biological Psychology.* 2009;80(3):265-278.
111. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain, behavior, and immunity.* 2007;21(7):901-912.
112. Iob E, Steptoe A. Cardiovascular Disease and Hair Cortisol: a Novel Biomarker of Chronic Stress. *Curr Cardiol Rep.* 2019;21(10):116-116.
113. Cullen T, Thomas AW, Webb R, Hughes MG. The relationship between interleukin-6 in saliva, venous and capillary plasma, at rest and in response to exercise. *Cytokine.* 2015;71(2):397-400.
114. Williamson S, Munro C, Pickler R, Grap MJ, Elswick RK. Comparison of Biomarkers in Blood and Saliva in Healthy Adults. *Nursing Research and Practice.* 2012;2012:246178.
115. Aviv A, Hunt SC, Lin J, Cao X, Kimura M, Blackburn E. Impartial comparative analysis of measurement of leukocyte telomere length/DNA content by Southern blots and qPCR. *Nucleic Acids Res.* 2011;39(20):e134-e134.
116. Paradies Y. A systematic review of empirical research on self-reported racism and health. *International Journal of Epidemiology.* 2006;35(4):888-901.
117. Krieger N. Racial and gender discrimination: risk factors for high blood pressure? *Social science & medicine.* 1990;30(12):1273-1281.
118. Krieger N, Sidney S. Racial discrimination and blood pressure: the CARDIA Study of young black and white adults. *American journal of public health.* 1996;86(10):1370-1378.
119. Landrine H, Klonoff EA. The schedule of racist events: A measure of racial discrimination and a study of its negative physical and mental health consequences. *Journal of Black Psychology.* 1996;22(2):144-168.
120. Giurgescu C, Engeland CG, Templin TN, Zenk SN, Koenig MD, Garfield L. Racial discrimination predicts greater systemic inflammation in pregnant African American women. *Appl Nurs Res.* 2016;32:98-103.
121. Chae DH, Nuru-Jeter AM, Adler NE, et al. Discrimination, racial bias, and telomere length in African-American men. *American journal of preventive medicine.* 2014;46(2):103-111.
122. Brody GH, Yu T, Miller GE, Chen E. Discrimination, racial identity, and cytokine levels among African-American adolescents. *Journal of Adolescent Health.* 2015;56(5):496-501.
123. Simons RL, Lei M-K, Klopack E, Zhang Y, Gibbons FX, Beach SRH. Racial Discrimination, Inflammation, and Chronic Illness Among African American Women at Midlife: Support for the Weathering Perspective. *Journal of Racial and Ethnic Health Disparities.* 2021;8(2):339-349.
124. Williams DR, Herman A, Kessler RC, et al. The South Africa Stress and Health Study: rationale and design. *Metab Brain Dis.* 2004;19(1-2):135-147.
125. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. *Journal of the American Medical Women's Association (1972).* 1995;50(2):56-58.
126. Heeringa SG, Connor JH. Technical description of the Health and Retirement Survey sample design. *Ann Arbor: University of Michigan.* 1995.
127. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: Objectives and Design. *American Journal of Epidemiology.* 2002;156(9):871-881.
128. Radler BT. The Midlife in the United States (MIDUS) Series: A National Longitudinal Study of Health and Well-being. *Open Health Data.* 2014;2(1):e3.
129. Jackson JS, Torres M, Caldwell CH, et al. The National Survey of American Life: a study of racial, ethnic and cultural influences on mental disorders and mental health. *Int J Methods Psychiatr Res.* 2004;13(4):196-207.

130. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. *Int J Epidemiol.* 2013;42(6):1640-1648.
131. Clark R, Coleman AP, Novak JD. Brief report: Initial psychometric properties of the everyday discrimination scale in black adolescents. *Journal of adolescence.* 2004;27(3):363-368.
132. Gonzales KL, Noonan C, Goins RT, et al. Assessing the Everyday Discrimination Scale among American Indians and Alaska Natives. *Psychol Assess.* 2016;28(1):51-58.
133. Lewis TT, Van Dyke ME. Discrimination and the health of African Americans: The potential importance of intersectionalities. *Current Directions in Psychological Science.* 2018;27(3):176-182.
134. Kwate NOA, Goodman MS. Racism at the intersections: Gender and socioeconomic differences in the experience of racism among African Americans. *American Journal of Orthopsychiatry.* 2015;85(5):397-408.
135. Brondolo E, Beatty DL, Cubbin C, et al. Sociodemographic variations in self-reported racism in a community sample of Blacks and Latino (a) s. *Journal of Applied Social Psychology.* 2009;39(2):407-429.
136. Borrell LN, Jacobs DR, Jr, Williams DR, Pletcher MJ, Houston TK, Kiefe CI. Self-reported Racial Discrimination and Substance Use in the Coronary Artery Risk Development in Adults Study. *American Journal of Epidemiology.* 2007;166(9):1068-1079.
137. Krieger N, Sidney S, Coakley E. Racial discrimination and skin color in the CARDIA study: implications for public health research. *American Journal of Public Health.* 1998;88(9):1308-1313.
138. Borrell LN, Kiefe CI, Williams DR, Diez-Roux AV, Gordon-Larsen P. Self-reported health, perceived racial discrimination, and skin color in African Americans in the CARDIA study. *Social science & medicine.* 2006;63(6):1415-1427.
139. Cutter GR, Burke GL, Dyer AR, et al. Cardiovascular risk factors in young adults: the CARDIA baseline monograph. *Controlled clinical trials.* 1991;12(1):1-77.
140. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *Journal of clinical epidemiology.* 1988;41(11):1105-1116.
141. CARDIA Steering Committee. *CARDIA Protocol, Year 7 Exam (1992 - 1993).* Birmingham, Ala: CARDIA Coordinating Center1992.
142. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary. *Journal of the American College of Cardiology.* 2018;71(19):2199.
143. Ertefaie A, Small DS, Flory JH, Hennessy S. A tutorial on the use of instrumental variables in pharmacoepidemiology. *Pharmacoepidemiology and drug safety.* 2017;26(4):357-367.
144. Labrecque J, Swanson SA. Understanding the assumptions underlying instrumental variable analyses: a brief review of falsification strategies and related tools. *Current epidemiology reports.* 2018;5(3):214-220.
145. Hernán M, Robins J. Instrumental variable estimation. In: *Causal Inference.* Boca Raton: Chapman & Hall/CRC; 2020.
146. Zhang Z, Uddin MJ, Cheng J, Huang T. Instrumental variable analysis in the presence of unmeasured confounding. *Ann Transl Med.* 2018;6(10):182-182.
147. Hausman J. Specification Tests in Econometrics. *Econometrica.* 1978;46(6):1251-1271.
148. Klonoff EA, Landrine H. Is skin color a marker for racial discrimination? Explaining the skin color-hypertension relationship. *J Behav Med.* 2000;23(4):329-338.

149. Cobb RJ, Thomas CS, Pirtle WNL, Darity Jr WA. Self-identified race, socially assigned skin tone, and adult physiological dysregulation: Assessing multiple dimensions of “race” in health disparities research. *SSM-population health.* 2016;2:595-602.
150. Kleiber C, Zeileis A, Zeileis MA. Package ‘AER’. https://cran.r-project.org/web/packages/AER/AER.pdf.
151. Kleiber C, Zeileis A. *Applied econometrics with R.* Springer Science & Business Media; 2008.
152. van Buuren S, Groothuis-Oudshoorn K, Robitzsch A, Vink G, Doove L, Jolani S. Package ‘mice’. *Computer software.* 2015.
153. Colonescu C. Random Regressors. In: *Principles of Econometrics with R.* The Economic Journal; 2016:165-172.
154. Brownlow BN, Sosoo EE, Long RN, Hoggard LS, Burford TI, Hill LK. Sex differences in the impact of racial discrimination on mental health among Black Americans. *Current psychiatry reports.* 2019;21(11):112.
155. Williams DR, John DA, Oyserman D, Sonnega J, Mohammed SA, Jackson JS. Research on discrimination and health: an exploratory study of unresolved conceptual and measurement issues. *American journal of public health.* 2012;102(5):975-978.
156. Forman TA. The social psychological costs of racial segmentation in the workplace: A study of African Americans' well-being. *Journal of Health and Social Behavior.* 2003:332-352.
157. Hudson DL, Neighbors HW, Geronimus AT, Jackson JS. Racial Discrimination, John Henryism, and Depression Among African Americans. *J Black Psychol.* 2016;42(3):221-243.
158. Hudson DL, Bullard KM, Neighbors HW, Geronimus AT, Yang J, Jackson JS. Are benefits conferred with greater socioeconomic position undermined by racial discrimination among African American men? *J Mens Health.* 2012;9(2):127-136.
159. Assari S. Blacks' Diminished Return of Education Attainment on Subjective Health; Mediating Effect of Income. *Brain Sci.* 2018;8(9):176.
160. Assari S. Diminished economic return of socioeconomic status for black families. *Social Sciences.* 2018;7(5):74.
161. Halanych JH, Safford MM, Shikany JM, et al. The association between income, education, and experiences of discrimination in older African American and European American patients. *Ethnicity & disease.* 2011;21(2):223-229.
162. Cole ER, Omari SR. Race, class and the dilemmas of upward mobility for African Americans. *Journal of Social issues.* 2003;59(4):785-802.
163. Iceland J, Wilkes R. Does socioeconomic status matter? Race, class, and residential segregation. *Social problems.* 2006;53(2):248-273.
164. Williams DR. Race, socioeconomic status, and health the added effects of racism and discrimination. 1999.
165. Xiang F, Lucas R, de Gruijl F, Norval M. A systematic review of the influence of skin pigmentation on changes in the concentrations of vitamin D and 25-hydroxyvitamin D in plasma/serum following experimental UV irradiation. *Photochemical & Photobiological Sciences.* 2015;14(12):2138-2146.
166. Jablonski NG. The evolution of human skin and skin color. *Annu Rev Anthropol.* 2004;33:585-623.
167. Jeong HY, Park KM, Lee MJ, Yang DH, Kim SH, Lee S-Y. Vitamin D and Hypertension. *Electrolyte Blood Press.* 2017;15(1):1-11.
168. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JPA. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ (Clinical research ed).* 2014;348:g2035-g2035.

169. He S, Hao X. The effect of vitamin D3 on blood pressure in people with vitamin D deficiency: A system review and meta-analysis. *Medicine.* 2019;98(19):e15284.
170. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium Food and Nutrition Board. *Dietary reference intakes for calcium and vitamin D.* Institute of Medicine;2011.
171. Shah D, Gupta P. Vitamin D Deficiency: Is The Pandemic for Real? *Indian J Community Med.* 2015;40(4):215-217.
172. Parva NR, Tadepalli S, Singh P, et al. Prevalence of Vitamin D Deficiency and Associated Risk Factors in the US Population (2011-2012). *Cureus.* 2018;10(6):e2741-e2741.
173. Zhang D, Cheng C, Wang Y, et al. Effect of Vitamin D on Blood Pressure and Hypertension in the General Population: An Update Meta-Analysis of Cohort Studies and Randomized Controlled Trials. *Preventing Chronic Disease.* 2020;17.
174. Meng X, Li X, Timofeeva MN, et al. Phenome-wide Mendelian-randomization study of genetically determined vitamin D on multiple health outcomes using the UK Biobank study. *International journal of epidemiology.* 2019;48(5):1425-1434.
175. Ong AD, Deshpande S, Williams DR. Biological Consequences of Unfair Treatment: A Theoretical and Empirical Review. In: Causadias JM, Telzer EH, Gonzales NA, eds. *The Handbook of Culture and Biology.* Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2017:279-315.
176. Banks KH. “Perceived” discrimination as an example of color-blind racial ideology’s influence on psychology. 2014.
177. Ahmed AT, Mohammed SA, Williams DR. Racial discrimination & health: Pathways & evidence. *Indian Journal of Medical Research.* 2007;126(4):318.
178. Berger M, Sarnyai Z. “More than skin deep”: stress neurobiology and mental health consequences of racial discrimination. *Stress.* 2015;18(1):1-10.
179. Cohen S, Kessler RC, Gordon LU. Strategies for measuring stress in studies of psychiatric and physical disorders. In: Cohen S, Kessler RC, Gordon LU, eds. *Measuring stress: A guide for health and social scientists.* New York, NY: Oxford University Press; 1995:3-26.
180. Lazarus RS. Theory-Based Stress Measurement. *Psychological Inquiry.* 1990;1(1):3.
181. Dohrenwend BP. Inventorying stressful life events as risk factors for psychopathology: Toward resolution of the problem of intracategory variability. *Psychological bulletin.* 2006;132(3):477-495.
182. Davis SK, Liu Y, Quarells RC, Din-Dzietham R. Stress-related racial discrimination and hypertension likelihood in a population-based sample of African Americans: the Metro Atlanta Heart Disease Study. *Ethnicity & disease.* 2005;15(4):585-593.
183. Pantesco EJ, Leibel DK, Ashe JJ, et al. Multiple forms of discrimination, social status, and telomere length: Interactions within race. *Psychoneuroendocrinology.* 2018;98:119-126.
184. Brim OG, Ryff CD, Kessler RC. The MIDUS national survey: An overview. *How healthy are we.* 2004:1-36.
185. Dienberg Love G, Seeman TE, Weinstein M, Ryff CD. Bioindicators in the MIDUS national study: protocol, measures, sample, and comparative context. *Journal of aging and health.* 2010;22(8):1059-1080.
186. Gruenewald TL, Karlamangla AS, Hu P, et al. History of socioeconomic disadvantage and allostatic load in later life. *Soc Sci Med.* 2012;74(1):75-83.
187. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Annals of internal medicine.* 2017.
188. VanderWeele TJ. Outcome-wide Epidemiology. *Epidemiology.* 2017;28(3).

189. Currie CL, Copeland JL, Metz GA, Chief Moon-Riley K, Davies CM. Past-Year Racial Discrimination and Allostatic Load Among Indigenous Adults in Canada: The Role of Cultural Continuity. *Psychosomatic medicine.* 2020;82(1):99-107.
190. Cuevas AG, Wang K, Williams DR, Mattei J, Tucker KL, Falcon LM. The Association Between Perceived Discrimination and Allostatic Load in the Boston Puerto Rican Health Study. *Psychosom Med.* 2019;81(7):659-667.
191. Van Dyke ME, Baumhofer NKi, Slopen N, et al. Pervasive discrimination and Allostatic load in African American and white adults. *Psychosomatic medicine.* 2020;82(3):316-323.
192. Upchurch DM, Stein J, Greendale GA, et al. A Longitudinal Investigation of Race, Socioeconomic Status, and Psychosocial Mediators of Allostatic Load in Midlife Women: Findings From the Study of Women's Health Across the Nation. *Psychosom Med.* 2015;77(4):402-412.
193. Wagner J, Lampert R, Tennen H, Feinn R. Exposure to discrimination and heart rate variability reactivity to acute stress among women with diabetes. *Stress and Health.* 2015;31(3):255-262.
194. Lundberg U. Catecholamines and Environmental Stress. *Allostatic Load Notebook.* 2003. https://macses.ucsf.edu/research/allostatic/catecholamine.php.
195. Lundberg U. Catecholamines. In: Fink G, ed. *Encyclopedia of Stress.* San Diego, CA: Academic Press; 2000.
196. Hill LK, Hoggard LS, Richmond AS, Gray DL, Williams DP, Thayer JF. Examining the association between perceived discrimination and heart rate variability in African Americans. *Cultural Diversity and Ethnic Minority Psychology.* 2017;23(1):5.
197. Singh N, Moneghetti KJ, Christle JW, Hadley D, Plews D, Froelicher V. Heart Rate Variability: An Old Metric with New Meaning in the Era of using mHealth Technologies for Health and Exercise Training Guidance. Part One: Physiology and Methods. *Arrhythm Electrophysiol Rev.* 2018;7(3):193-198.
198. Kawachi I. Heart Rate Variability. *Allostatic Load Notebook.* 1997. https://macses.ucsf.edu/research/allostatic/heartrate.php#allostasis. Accessed 03/16/2021.
199. Busse D, Yim IS, Campos B, Marshburn CK. Discrimination and the HPA axis: current evidence and future directions. *J Behav Med.* 2017;40(4):539-552.
200. Zeiders KH, Doane LD, Roosa MW. Perceived discrimination and diurnal cortisol: examining relations among Mexican American adolescents. *Hormones and behavior.* 2012;61(4):541-548.
201. Huynh VW, Huynh QL, Stein MP. Not just sticks and stones: Indirect ethnic discrimination leads to greater physiological reactivity. *Cultur Divers Ethnic Minor Psychol.* 2017;23(3):425-434.
202. Lee DB, Peckins MK, Miller AL, et al. Pathways from racial discrimination to cortisol/DHEA imbalance: protective role of religious involvement. *Ethn Health.* 2018:1-18.
203. Stepanikova I, Bateman LB, Oates GR. Systemic inflammation in midlife: race, socioeconomic status, and perceived discrimination. *American journal of preventive medicine.* 2017;52(1):S63-S76.
204. Brody GH, Yu T, Chen E, Ehrlich KB, Miller GE. Racial discrimination, body mass index, and insulin resistance: A longitudinal analysis. *Health Psychol.* 2018;37(12):1107-1114.
205. Chen Y, VanderWeele TJ. Associations of Religious Upbringing With Subsequent Health and Well-Being From Adolescence to Young Adulthood: An Outcome-Wide Analysis. *American Journal of Epidemiology.* 2018;187(11):2355-2364.

206. Smart Richman L, Pek J, Pascoe E, Bauer DJ. The effects of perceived discrimination on ambulatory blood pressure and affective responses to interpersonal stress modeled over 24 hours. *Health Psychology.* 2010;29(4):403.
207. Huebner DM, Nemeroff CJ, Davis MC. Do hostility and neuroticism confound associations between perceived discrimination and depressive symptoms? *Journal of Social and Clinical Psychology.* 2005;24(5):723-740.
208. Bauer GR. Incorporating intersectionality theory into population health research methodology: Challenges and the potential to advance health equity. *Social Science & Medicine.* 2014;110:10-17.