Chronic Psychosocial Stress and Cardiometabolic Health: Variations in Measurement and Structural Determinants

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Epidemiological Science)
in the University of Michigan
2022

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Dedication

To Anton, Tatiana and Alexander who were there before the beginning.

Acknowledgements

This dissertation would not have come into being without the enduring support of many people. First and foremost, I would like to express my deepest gratitude to my Committee Chair, Bri, who has always believed in me more than I believed in myself. She generously and patiently guided me in every aspect of this work and beyond. Throughout the years, she has served as a role model of a researcher and empathetic leader. She included me in projects that both boosted my confidence as a researcher, and also pushed me to transform self-imposed limitations. Bri, I am forever grateful for your enduring mentorship.

I am thankful to the members of my Committee for their expertise, patience and continuous support. I thank Philippa for her uncanny capacity to instill confidence in her students through attentive presence, sincere engagement with research ideas, and unwavering support. I thank Bhramar for her feedback, which has always been on point, and has vastly improved the quality of this work. The ease with which she translates abstract theoretical models into concrete modelling decisions is truly inspirational. I thank Srijan for his thoughtful feedback, clinical insights, and also for asking questions that made me pause and rethink assumptions that otherwise would have been left unexplored. I thank Jon for his endless patience with me; whenever I was overwhelmed with complexity of challenges and modelling decisions, he would always remind me to start small and think possible.

I am indebted to the participants of the Richmond Stress and Sugar Study and the Healthy Aging in Neighborhoods of Diversity across the Lifespan Study for their participation and dedication to the pursuit of science, which made this dissertation possible.

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List of Abbreviations

ACASI=audio-computer assisted self-interview
ANS=autonomic nervous system
AUC=area under the curve
AUCg=area under the curve with respect to ground
AUGi=area under the curve with respect to increase
AL=allostatic load
BMI=body mass index
CDC=Centers for Disease Control and Prevention
CES-D=Center for Epidemiologic Studies Depression Scale
CI=confidence interval
CNS=central nervous system
CVD=cardiovascular disease
EHDIC=Exploring Health Disparities in Integrated Communities study
GED=general education diploma
GUTS=Generalized Unsafety Theory of Stress
HANDLS=Healthy Aging in Neighborhoods of Diversity across the Lifespan Study
HDL=high-density lipoprotein cholesterol
HIV/AIDS=human immunodeficiency virus/ acquired immunodeficiency syndrome
HbA1c=hemoglobin A1C
HPA-axis=hypothalamic pituitary adrenal axis
ICD=international classification of diseases code
IMT=carotid intima media thickness
IQR=interquartile range
IRB=Institutional Review Board
LMM=linear mixed models
Ln (Tri) =logarithm of the triglyceride
LMM=linear mixed model
LOESS=locally estimated scatter plot smoothing
MESA=Multi-Ethnic Study of Atherosclerosis
MESA=Multiethnic Study of Atherosclerosis study
MetS-Z=metabolic status severity z-score
MIDUS=Midlife in the United States study
MRV=medical research vehicle
NHB=non-Hispanic black
NHW=non-Hispanic white
NSES=neighborhood socioeconomic status
PS=Perceived Stress Scale
REML=restricted maximum likelihood
RSASS=Richmond Stress and Sugar Study
SAM=sympathetic adrenal medullary axis

SBP=systolic blood pressure
SES=socioeconomic status
SNS=sympathetic nervous system
SPT=Stress Process Theory
ToH=theory of habituation
TSST=Trier social stress test
VCU=Virginia Commonwealth University
WC=waist circumference

Abstract

There is growing recognition that chronic psychosocial stress may accelerate aging, increase risk of diseases, and contribute to health disparities. Variability across findings and methodological challenges limit our ability to examine chronic stress as a key mechanism driving health disparities at the population scale. In an effort to clarify some of these dimensions and methodological challenges, this dissertation (1) explored definitional and measurement-related issues around the construct of stress, and by employing uniquely positioned epidemiologic sources of data and life course analytical methods, (2) examined the impact of psychosocial stress on cardiometabolic health across structural and socioeconomic differences.

Aim 1 relied on quasi-experimental design features of the Richmond Stress and Sugar study (RSASS) to examine whether two common self-report measures of psychosocial stress reflect neurobiological stress response assessed by changes in salivary cortisol before and after an acute stress challenge. Adjusted linear spline mixed-effects models revealed that both perceived stress and domain-specific stress measures were inversely associated with neurobiological stress reactivity. Neighborhood SES, but not race/ethnicity, modified these associations.

In Aim 2, we applied a novel stress framework to examine associations between stress-related cognitive tendencies (i.e., vigilance and avoidant/adaptive stress coping) and metabolic risk in a prospective cohort from the Healthy Aging in Neighborhoods of Diversity across the Lifespan Study (HANDLS). Contrary to our expectations, vigilance was not associated with metabolic risk in any of our mixed-effects linear models, while both types of stress coping were

negatively associated with metabolic risk. Findings suggest that a higher level of engagement in any form of stress coping may be beneficial and help temper stress impact on metabolic health. Evidence for stress coping varied by race and lifecourse SES, suggesting that activation of a particular coping style may be context-specific and depend on the availability of psychosocial resources.

Aim 3 sought to clarify the role of stress as a contributor to type 2 diabetes incidence, with attention to inequities in diabetes risk. Two separate time-to-event analyses using data from RSASS and HANDLS showed that stress was not associated with incident diabetes, but the estimates of association were in the hypothesized direction and comparable across the studies. This was consistent across two distinct measures of stress: perceived stress and acute stress reactivity. Subgroup analyses in HANDLS revealed that compared to White adults with low levels of perceived stress, White adults with high stress and Black adults (both high and low stress) had higher diabetes incidence. Convergent results from two longitudinal samples underscored the importance of replicating evidence across studies with shared features and design, an effort that provides a more robust understanding of the substantive question than what could be obtained from a single cohort.

In sum, collective evidence generated from this work contributes toward efforts aimed at improving stress measures in population research and considering stress as a potentially modifiable factor of social health disparities.

Chapter 1 Introduction

1.1 Overview

Prior studies have repeatedly documented strong inverse relationships between socioeconomic status (SES) and cardiometabolic diseases (e.g., myocardial infarction, type 2 diabetes, stroke).[1,2] Similarly, despite advances in healthcare quality and access, racial and ethnic health disparities, especially around cardiometabolic disease, continue to emerge early and persist across the life course.[3–6] In the U.S., due to the history of slavery, structural racism and discriminatory practices that shaped social attitudes and normalized unequal access to socioeconomic resources (i.e., living conditions, social capital, etc.), SES, race and ethnicity are highly correlated.[7,8] This further translates into distinct structural and geographic patterning of health across the life course.[8–10] However, latest research suggests that racial disparities tend to be concentrated at the tail ends of the socioeconomic gradient, where a combination of other social and lifestyle factors contribute to unequal distribution of diseases.[11–13]

Targeting modifiable lifestyle factors (i.e., diet, exercise, smoking, and drinking alcohol) has been instrumental to reducing overall morbidity and mortality from cardiovascular and metabolic diseases.[10, 11] However, despite the extensive intervention efforts focused on health behaviors, disparities in prognosis and survival persist.[2] A recent multinational study (n=1,751,479) that combined 48 prospective cohorts from seven countries (mean follow-up 13.3 years) provides evidence that other mechanisms, besides individual behavior and health history, may contribute to the toxic effects of low SES on health disparities.[16] In this study, after

adjusting for known health and behavioral risk factors, including current smoking status, high alcohol use, and sedentary lifestyle, the association between low SES and mortality remained significant in a combined sample.[16] This finding was confirmed in a Finnish multicohort study (n=109,246), where after adjusting for individual risk factors, low SES was significantly associated with increased risk for 18 out of 56 health conditions.[17]

Psychosocial chronic stress has been proposed as a key mechanism that may explain the persistence of cardiometabolic health disparities across the social gradient of deprivation.[13,17–21] However, despite a large body of existing research, the exact role of stress remains incompletely understood.[22] Variability in the conceptualization and measurement of stress reflects the complexity of studying stress in relation to health, and also presents significant challenges in understanding the root of unexpected and inconsistent findings, particularly at the population scale.[22]

In an effort to clarify some of these dimensions and methodological challenges and contribute toward the understanding of how psychosocial stress processes impact cardiometabolic health over a life course, this dissertation pursued four main goals that cut across the three empirical studies: (1) in study 1 and 2, this dissertation explored heterogeneity in key conceptual and theoretical frameworks of psychosocial stress with respect to health; (2) guided by insights from the leading theories of stress, study 1 explores a range of definitional and measurement-related issues around the concept of stress, and tests the relations between various stress measures; (3) studies 2 and 3 contributed longitudinal evidence on the impact of stress on metabolic health, using two uniquely positioned epidemiologic sources of data and life course analytical methods, and (4) each of the three studies evaluated how variations in the ways

psychosocial stress is operationalized and measured shapes our understanding of the underlying mechanisms of structural and socioeconomic disparities in metabolic health.

Specifically, Chapter 1 provides a conceptual and theoretical background for the empirical studies conducted in this dissertation: it situates stress concepts and measures examined in this dissertation within a broader classification of stressors; briefly describes key neurobiological stress processes that are thought to mediate important links between stress and health; and offers an overview of the key stress theories that shaped empirical approaches. The chapter concludes with a brief summary of each of the substantive research studies that comprise the bulk of this dissertation. Chapter 2 relies on quasi-experimental design features of the Richmond Stress and Sugar study, to examine to what degree commonly used self-reported stress measures correspond to neurobiological stress response measured by changes in salivary cortisol before and after an acute stress challenge. The chapter further explores whether the associations between the examined measures vary by SES and race and ethnicity. Chapter 3 draws on the conceptual and analytic approaches from the life course epidemiology to explore evidence for longitudinal associations between stress-related cognitive tendencies (i.e., vigilance and stress coping) and metabolic risk severity. Using data from the Healthy Aging in Neighborhoods of Diversity across the Lifespan Study, this study further explores evidence for effect modification by race and ethnicity or life course socioeconomic mobility. Chapter 4 compares evidence from two distinct data sources on associations between self-reported perceived stress and incident diabetes. Chapter 5 presents a summary of findings and concludes by outlining future analytic steps and research directions.

1.2 Stress Classification: Concept and Measurement

In this dissertation, stress is conceptualized in terms of three broad, but interrelated categories that create a unifying stress classification, which facilitates the systematic examination of stress processes, consistent with key stress theories, and illustrates tensions between constructs of stress and their measurements in research.

   I.   *Stress Events.* This category encompasses distinct stress events that could be ascertained through self-report, historic or biographic records. These include stressors that are global events affecting many people at once (i.e., war), major life or traumatic events (i.e., loss, divorce, or house fire), and minor daily disturbances (i.e., flat tire on way to work). Global or traumatic events are generally regarded as inherently stressful due to their reverberating and long-lasting effects, although they occur with a relatively low frequency. However, whether minor everyday events are marked 'stressful' depends on the individual life circumstances, personality, one's ability to appraise their resources, or cope with the resulting consequences.[23] Both types of events are usually assessed in psychosocial stress surveys. Examples of some frequently used stress event measures in population studies include the "Daily Hassles scale"[24] that assesses commonplace disturbances and irritations (i.e., unpleasant interactions with friends or relatives), the 102-item "Psychiatric Epidemiology Research Stress Interview" that enumerates major life changes or traumatic events;[25] or chronic stress inventories that quantify individual stressful events in various life domains (i.e., relationship, employment, disability, etc.).[26] While these surveys are relatively easy to administer, some limitations of using stress checklists or inventories include recall bias, social desirability bias (i.e., individual or

cultural upbringing and the degree of social acceptability of reporting distress), and focus on stressors that are relevant for select participants or population groups.[22]

II. *Stress Adaptations*. The second stress category consists of a wide range of psychosocial and physiological adaptations to stressful experiences, which may occur over a short period or develop over time. Stress adaptations include subjective stress states (i.e., feelings of overwhelm or burn-out), and stress reactions: psychological or emotional (i.e., feelings of distress, anger, or fear), physical or somatic (i.e., increased heartbeat, perspiration, shortness of breath, gastrointestinal disturbances, or chronic pain and skin rashes), and neuroendocrine (i.e., hormonal fluctuations). Apart from the neuroendocrine reactions that are usually assessed by proxy measures of associated body fluids or tissues (i.e., salivary or hair cortisol), other mentioned stress reactions are ascertained through survey self-report. Examples include the "Perceived Stress Scale" [27] that measures the degree of overwhelm from uncontrollable stressors, various distress scales that assess challenges around managing a chronic condition such as "Diabetes Distress Scale,"[28] the "Somatic Stress Response Scale" [29] that measures somatic symptoms that may develop in encountering a short-term stressor. Long-lasting or severe experiences of psychological or somatic stress reactions can become a self-perpetuating source of stress and has been previously studied in relation to major psychiatric disorders, unexplained pain and chronic disease.[30]

III. *Background Stress*. The last stress category is the most elusive one to define and measure. It consists of the combined internal and external features of psychosocial environment that may elicit stress responses but may not be clearly or actively registered as a stressor by people experiencing them. This may partially be because of

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a degree of normalization or filtering that may happen due to chronic proximity with these experiences.[31] Examples may include external characteristics such as traffic noise and pollution or living in a neighborhood with high crime occurrence. These features could be approximated by geo-coding participants' addresses and linking administrative records on pollution or crime levels. However, such measures are often limited by their ability to assess stressors that are relevant for research participants.[22] Other key stressors that may be included in this category are psychosocial experiences of discrimination and injustice, or cognitive and emotional states such as anticipatory vigilance or feelings of loneliness and isolation. Although participants may self-report these stressors, for example, using discrimination[32] or vigilance scale[33], it remains unclear to what degree these chronic features are consciously regarded as stressors, and how these affect health outcomes.

1.3 Neurobiological stress mechanism

Acknowledging the underlying complexity of the neurobiological stress processes is a fundamental step toward understanding the link between stress and health. Biological stress response is governed by the autonomic (ANS) and central nervous systems (CNS) in concert with the endocrine system.[34] Upon experiencing an acute stressor, both the sympathetic adrenal medullary (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis activate simultaneously. The SAM axis is triggered by a complex dialogue between brain regions, sympathetic nervous system, and the adrenal medullas that begin to secrete epinephrine and norepinephrine, eliciting a state of the "flight or fight." [35,36] The SAM stress response is generally measured by monitoring blood pressure or heart rate and similar indices of neural activity (i.e., heart rate variability).[34]

The HPA is a negative feedback mechanism that downregulates neurobiological stress response through (1) activation of the glucocorticoid receptors in various brain regions (i.e., amygdala and hippocampus) and (2) release of neurochemicals (i.e., endorphins and dopamine) and hormones (mineral- and glucocorticoids, and aldosterone) that regulate base physical processes (i.e., metabolism, temperature).[37,38] The regulatory function of the HPA axis could be assessed within 15 to 40 minutes of experiencing a stressor by measuring circulating levels of hormones (i.e., cortisol) that normally change in response to stress-induced neurochemical and hormonal fluctuations.[35,39] Studies show that loss of sensitivity to hormonal changes in the HPA axis might lead to a state of continuously elevated or suppressed levels of cortisol, which has been implicated in metabolic dysfunction and decline in mental health.[18,40,41]

1.4 Stress dose-response

Whether 'stress' is defined in terms of events that in some way interfere with one's biological and psychological state or stress adaptations that occur as a results of stress experience, the dose or degree of stress response plays a pivotal role in understanding stress impact.

A simple dose-response model, commonly used in epidemiology and health sciences, suggests that with the increasing dose of harmful exposure, we expect to observe more severe effects on health or function (i.e., lead[42]). In the context of stress-health relationship, such a linear dose-response framework would suggest that any exposure to stress will yield harmful impact on health. Although this approach may appear to be crude, many stress surveys implicitly follow this framework, where stress exposure is ascertained by counting the number of stressful events experienced or assigning a score based on frequency or severity of reported stress. Subsequently derived stress summaries correspond to higher stress impact.

An alternative approach is to adopt a *hormetic* model that describes a "biphasic" or an inverted U-shaped dose-response, where at moderate doses a response is adaptive or stimulating, but becomes harmful or inhibitory at very low or high doses of exposure (see figure 1.1).[43] Such a non-linear model may be applicable to quantifying the impact of mild stressors or stress-induced states and responses. For example, consistent with the hormetic model, assessment of neurobiological stress response would suggest that a moderate reaction to a short-term stimulation reflects an adaptive stress responses, whereas extreme reactions (either too low or too high) signal an inefficient and dysregulated stress response.[44] Indeed, it is expected that repeated assessments of cortisol concentrations taken before and after an acute stress event will follow an inverted U-shaped curve, where a temporary spike in cortisol concentrations is expected to follow a gradual process of regulation.[45] Within this paradigm, a 'normal' stress response amounts to energy availability that comes from efficient activation of neural and metabolic processes.[46] Such functional efficiency provides necessary energy to ensure optimal performance, including during social encounters (i.e., presenting in front of a panel of evaluative judges), or solving a new and challenging problem. Elevated stress reactivity in response to an acute stress may then be considered normal or even beneficial, but only until a certain threshold or within a certain time frame beyond which stress becomes maladaptive. Understanding where and under what conditions that threshold might be crossed is one of the topics this dissertation explores.
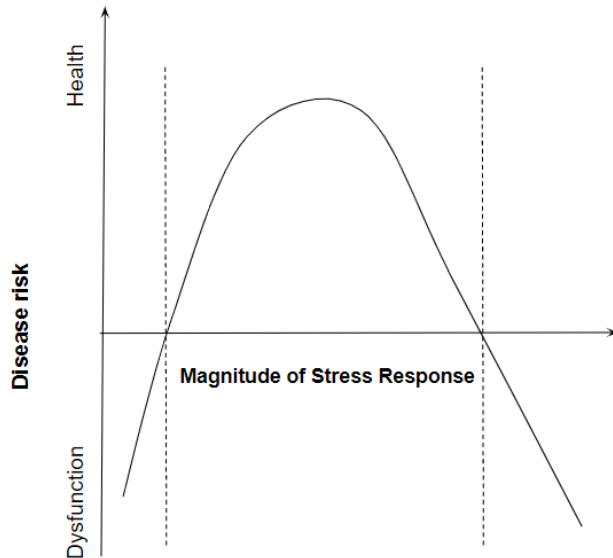
Figure 1-1. Schematic representation of hormetic model. Adapted from Calabrese and Baldwin, 2003.

The figure illustrates a conceptual relationship between the magnitudes of biological stress response to a laboratory stressor (x-axis) with respect to functional health status (y-axis). The dotted vertical lines represent hypothetical thresholds beyond which stress response becomes maladaptive. While the figure indicates the thresholds, these are not defined a-priori and represent an empirical question that the current study will explore with respect to metabolic health.

1.5 Theoretical Frameworks of Stress

Several theoretical frameworks of stress have informed the development of this dissertation research. In the following overview, I outline three key theoretical approaches that have guided specific aims explored in this dissertation. Each of these approaches emphasize distinct but interconnected stress aspects or mechanisms -- including stress physiology, cognitive salience of stress and psychosocial resources -- that jointly address the role of psychosocial stress as a determinant of vulnerability to chronic and communicable diseases.

1.5.1 Stress adaptation framework

The majority of epidemiologic evidence on the relationship between chronic stress and health is rooted in the stress adaptation framework originally formulated by physiologists Cannon and

Selye. [47,48] The underlying assumption of the adaptation framework is that 'stress' is a direct result of distinct events or temporary perturbations that disrupt an otherwise stable and stress-free internal environment and thus forces the body to activate innate defenses (i.e., neurobiological stress response). [47] In other words, the neurobiological stress mechanism acts as both an internal stress barometer and a switch that induces a cascade of neurochemical adaptations in response to stress (similar to an immune response to a skin burn or cut). Consistent with the hormetic model described above, abnormally high or low concentrations in stress biomarkers (i.e., glucocorticoids) may index a dysfunctional stress response. Under this framework, the focus is directed toward understanding what causes dysfunctions in the neurobiological stress mechanism and how they may relate to various health outcomes.

1.5.2 Allostatic Load

Situated within the framework of stress adaptation, the allostatic load (AL) model suggests that dysfunctions in the neurobiological stress mechanism may be caused by repeated stress experiences that may have been too severe or occurred too often and early in life. [49] Accordingly, repeated stressors lead to a gradual build-up of biological errors beyond that expected during 'normal' aging processes. [50] These errors are indexed by biomarkers across different physiological systems (i.e., neuroendocrine, immune, metabolic, and cardiovascular), which are further combined into a quantitative indicator of health decline, termed *allostatic load*. [49] AL is thus considered as a mediator between the dysfunction in biological stress mechanism and systemic biological damage that may be detrimental to health. [51–53]

AL is now a widely accepted marker of physiological dysregulation, and despite a heterogeneity of available AL measures, [54] research evidence consistently shows that increase in

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AL scores is associated with major disease outcomes, including cardiovascular disease, type 2 diabetes, arthritis, functional decline, mental illness, frailty, and mortality.[54–61]

1.5.3 Generalized Unsafety Theory of Stress

The Generalized Unsafety Theory of Stress (GUTS) is a relatively recent stress framework that highlights the role of cognitive salience and the interpretative mind in stress response, beyond the simple emphasis on stress physiology.[62,63] Specifically, GUTS posits that since neurobiological stress response is an evolutionary conserved physiological mechanism, it is not limited to being simply reactive to stressful stimuli, where it is likened to a light switch. Rather the stress response remains *continuously active,* but largely *outside of conscious awareness* (akin to temperature regulation or metabolism).[63] Furthermore, various cognitive processes are able to either increase and continuously perpetuate the stress response through a positive-feedback loop (e.g., vigilance, worry or rumination) or substantially reduce it through a negative-feedback mechanism when, for example, a sense of safety is perceived.[63] Although evidence from human studies is inconclusive, animal models have shown that maternal grooming during early development has been shown to positively affect memory and stress reactivity in rat pups, [64,65] and reduce vulnerability to cocaine and alcohol use.[66]

A direct implication of this functional interdependence is that the internal or external environments that may elicit a conscious or unconscious sense of contingency or insecurity (e.g., loneliness, financial instability, etc.) will promote chronic activation of the stress response. Importantly, such activation will occur even in the absence of major stressors or traumatic events. On the other hand, when the contextual cues or chronic stressors are removed, the activation of the stress response may still persist through stress-inducing cognitive tendencies

such as constant worry or rumination, which serve as a symptom of the internalized threat or previously experienced trauma.[63]

1.5.4 Stress Process Theory

Stress Process Theory (SPT) offers an integrative approach that describes (1) a dynamic interplay between isolated stress events and their proliferating effects on health and (2) highlights the importance of psychosocial environment.[20] Using multilevel systems perspective, SPT states that, when viewed in isolation, stress events (e.g., losing a job or a loved one) are not the key factors that contribute toward subsequent health declines.[20] Rather, the magnitude of stress impact largely depends on the psychosocial affordances available at the individual and group scales, including socioeconomic resources, quality of social relations, coping resources, and self-concepts (e.g., self-esteem). SPT posits that one of the main pathways through which stressful events increase vulnerability to disease is by indirect exacerbation of role strains and in the absence of psychosocial supports. In sum, the differences in socioeconomic and individual resources function as both pathways toward and amplifiers or buffers of harmful stress effects, and are thus instrumental to how stress experiences may impact individual well-being.[20] For example, perceived social support in adulthood has been shown to modify the negative effects of adverse childhood experiences on developing psychopathology in later life.[67] Similarly, higher quality of maternal care has been shown to facilitate secure attachments, foster positive reactions to novel stimuli, and reduced stress reactivity.[68,69]

In sum, as a sociologically informed framework, SPT situates the examination of stress-health link firmly within the framework of structural inequalities and psychosocial affordances. The emphasis on the reverberating effects of major life events further points to the importance of considering extended life trajectories and chronicity of life strains.

1.6 Specific Aims and Hypotheses

Informed by the intersections of the conceptual and theoretical frameworks reviewed above, the following dissertation aims to examine how various measures of stress contribute toward an understanding of the complex interplay between psychosocial stress and cardiometabolic health, with a particular focus on sociodemographic disparities.

Aim 1 examines whether common measures of psychosocial stress covary with the features of acute cortisol response to a laboratory stressor in a diverse cohort of adults at risk of type 2 diabetes from the Richmond Stress and Sugar Study (RSASS). Aim 1 further explores whether proxy indicators of neighborhood SES and race and ethnicity modify the associations between self-reported stress and neurobiological stress reactivity.

> *Hypotheses included:*
>
> *H 1.1*   Higher levels of self-reported stress will be associated with higher baseline cortisol and a blunted cortisol profile (i.e., weaker response, slower recovery) to the laboratory stress challenge.
>
> *H 1.2*   Compared to participants from high SES neighborhoods, individuals living in lower SES neighborhoods will self-report higher stress and have high baseline cortisol levels but exhibit blunted cortisol response to a laboratory stressor.

Aim 2 examines the longitudinal associations between stress-related cognitive tendencies -- vigilance and adaptive or avoidant stress coping -- and metabolic risk in the Healthy Aging in Neighborhoods of Diversity across the Lifespan (HANDLS), a racially and socioeconomically

diverse cohort of adults selected from a probability sample of Baltimore City neighborhoods.

Hypotheses included:

    H 2.1   Higher self-reported vigilance or avoidant coping will be associated with worse metabolic health at baseline and longitudinally, while higher levels of adaptive coping may be protective.

    H 2.2   Black adults will report higher vigilance or stress coping and will have worse metabolic risk, compared to White participants; adjusting for SES indicators will reduce these associations.

    H 2.3   Participants who experience lower life course SES (i.e., either persistently low or downwardly mobile) will report higher vigilance and avoidant stress coping and will have worse metabolic risk relative to those with higher life course SES.

Aim 3 examines whether self-reported perceived stress and HPA-axis stress reactivity were associated with incident type 2 diabetes in two prospective cohort samples used in aim 1 and 2 (i.e., RSASS and HANDLS).

Hypotheses included:

    H 3.1   Higher self-reported perceived stress and blunted cortisol response to acute stress will be associated with incident diabetes.

    H 3.2   Socioeconomic status, but not race, will modify the observed associations between stress and diabetes, such that low SES will be associated with higher perceived stress and incidence of diabetes.

Chapter 2 Psychosocial Stress and HPA Axis Stress Reactivity: Variations by Race and Socioeconomic Status among Adults at Risk of Diabetes

2.1 Introduction

Psychosocial stress has been widely hypothesized as a key mechanism underlying the systematic disparities in morbidity and mortality as a function of minority status and living in economically-disadvantaged environments. [70–72] Despite a large body of existing research, little agreement exists about which aspects of stressful experiences matter most for health, or which measurement tools for indexing stress may best capture these aspects. [73] This lack of clarity is due, in part, to the complexity of the interrelated psychological and biological processes that comprise a stressful experience, including recognition of events as stressors; appraisal of stressor characteristics, given past events and available resources; behavioral and neurobiological stress responses (i.e., the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis) and post-stress recovery. [22]

The complexity of stress processes poses major challenges in measuring psychosocial stress at the population scale. [74] With few exceptions, [75–78] most population surveys and epidemiologic studies either use proxy measures of stress (e.g., low socioeconomic status (SES)) or rely on self-report of stressful experiences (e.g., recall of negative life events or perceptions of current stressors). [73] Theoretically, the use of such self-report measures assumes that psychosocial stress is a conscious (and therefore *reportable*) experience, which necessarily relies on memory, self-awareness, and willingness to report and may thus result in spurious estimates of the stress and health relationship. [22] More fundamentally, limited empirical evidence shows

whether these self-report measures of stress reflect underlying neurobiological stress processes,[79] or whether these relationships are consistent across population subgroups. [80]

Several complementary frameworks provide conceptual guidelines for deriving testable hypotheses about how exposure to psychosocial stress may relate to the neurobiological stress response. McEwen (1998) posited that frequent and persistent exposure to stress over time is a key driver of *allostatic load (AL)*, a state of multi-system physiologic imbalance that results in rigidity (e.g., hyper or hyporeactivity) of the neurobiological stress response, often indexed by cortisol levels. [49,81]

Related, the mechanistic dual-process *Theory of Habituation (ToH)* synthesized by Thompson and Spencer (1966) describes how neurobiological stress responses may vary as a result of two co-occurring processes activated upon exposure to repeated stressors: habituation (i.e., attenuation of cognitive and neurobiological responses) and sensitization (i.e., exaggeration of these responses). [82] As such, ToH suggests that whether stressors are habituated or sensitized depends on stressors' characteristics (e.g., frequency, duration, intensity).[82] For example, severe or uncontrollable stressors may resist habituation and thus elicit persistently high levels of glucocorticoids. [36]

Finally, Brosschot (2017) recently proposed the *Generalized Unsafety Theory of Stress (GUTS),* a framework that pivots away from the common understandings of stress processes. [83] Instead of assuming that the neurobiological stress response is exclusively a short-term reaction to a stressor, GUTS describes it as an evolutionary-conserved mechanism that remains *continuously active,* but largely *outside of conscious awareness* (akin to temperature regulation or metabolism). [83] It follows that if the neurobiological stress response is largely unconscious, self-report measures of psychosocial stress (which necessarily rely on recall) may fail to reflect

essential processes. Furthermore, GUTS argues that if neurobiological stress mechanisms are continuously active, the processes most relevant to health are likely not those related to stressor perception or appraisal, but rather to cognitive disengagement (or, if we extend the logic to an acute stress experience, to the stage of neurobiological *recovery*) from the stressor. This understanding contrasts sharply with common approaches to measuring psychosocial stress that focus on quantifying the number, frequency, or intensity of stressful experiences.

These frameworks offer distinct interpretations for how psychosocial stress relates to health inequities. According to the AL model, disadvantaged groups will report higher psychosocial stress and, as a result, exhibit a dysregulated neurobiological stress response (either hyperreactivity or hyporeactivity). [81] In contrast, ToH predicts an interaction between stress processes and social disadvantage. Assuming that the pressures of severe or frequent stressors lead to both stress sensitization and habituation, disadvantaged groups may underreport habituated stressors (e.g., akin to living near a train track and tuning out the noise when a train goes by), while showing neurobiological hyperreactivity to acute short-term stress. [84] Finally, consistent with GUTS, disadvantaged groups will have an impaired ability to cognitively disengage and/or physiologically recover from a stressful encounter. [78] In sum, these stress frameworks offer complementary lenses for examining the associations between self-report stress and neurobiological stress response in the context of social disadvantage, with distinct implications for research and intervention.

The primary objective of this study is to examine the association between subjective assessments of psychosocial stress with HPA-axis reactivity to a laboratory stress challenge in a racially- and economically-diverse cohort of adults at risk of type 2 diabetes (hereafter, diabetes). The second objective is to explore whether structural conditions of inequality, such as

neighborhood SES and minority status, independently moderate the relationship between the subjective and neurobiological stress measures. Informed by the intersections of the theoretical frameworks reviewed above (see Figure 1S for a conceptual diagram), we generated two general hypotheses:

> 1) Higher levels of self-reported stress will be associated with higher baseline cortisol and a blunted cortisol profile (i.e., weaker response, slower recovery) to the laboratory stress challenge.

> 2) These relationship will be more pronounced among participants living in lower SES neighborhoods, after accounting for race/ethnicity. [9]

By comparing various approaches to measuring stress against each other (i.e., overall perceptions vs. specific domains vs. HPA-axis stress reactivity) we aimed to elucidate how these elements interconnect. Such clarification is critical to advancing population research on the impact of psychosocial stress as one of the key contributors to racial and socioeconomic health disparities.

2.2 Methods

Data

Data come from the Richmond Stress and Sugar Study (RSASS), a longitudinal cohort of adults at risk of diabetes. The study sample (n=125, at baseline) was recruited from the Virginia Commonwealth University (VCU) healthcare network located in Richmond, Virginia during 2016-2018. Specifics of study design and recruitment process are detailed elsewhere. [85] Briefly, a key feature of RSASS was recruitment of participants based on stratified sampling by neighborhood SES and race/ethnicity: 1) Non-Hispanic White (NHW) + high SES, 2) NHW + low SES, 3) Non-Hispanic Black (NHB) + high SES, and 4) NHB + low SES. This sampling design aimed to balance race/ethnicity and neighborhood SES in a manner that disentangles

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"race" from "place." [9,85] Participants were eligible if they were between 40 – 70 years old and had one or more of the following risk factors for diabetes: impaired glucose tolerance, elevated total glucose or HbA1c, hypertension, obesity, or history of gestational diabetes. [85] Study exclusion criteria included diagnosis of diabetes (type 1 or 2) or another serious medical condition, including Cushing's disease, cancer, or bipolar disorder. [85] Two participants did not provide salivary cortisol samples and were excluded from this analysis. Medical records were linked to the RSASS data.

The RSASS was approved by the VCU Institutional Review Board (IRB); all participants provided written informed consent. Analysis for this project was approved by the University of Michigan IRB.

Salivary Cortisol Response to Social Stress Challenge

The neurobiological stress response was measured by changes in salivary cortisol in response to the Trier Social Stress Test (TSST), a validated test for eliciting stress response in a laboratory setting. [86] Salivary cortisol has been shown to be a reliable measure of circulating cortisol. [87] The TSST consisted of two consecutive challenges, both performed in front of a panel of emotionally-reserved judges: a 5-minute speech about why they should be hired for their "dream job," followed by a 2-minute mental arithmetic task (subtracting 13 from 1,022). [85] To control for expected variations in diurnal cortisol levels, the TSST began around 5:00pm for all participants, who were asked to abstain from eating, smoking, or drinking alcohol five hours before the start of TSST procedure. In total, eight salivary cortisol samples were collected across two hours: two pre-TSST and six post-TSST, including four after the hypothesized peak at the fourth collection point (i.e., approximately 20 minutes after the completion of the TSST). Samples were stored at -20° C and processed in 27 batches using Enzyme Immunoassay

(Salimetrics LLC). Intra-assay coefficient of variation was 4.07%, which was within the manufacturer-reported range. [85]

Self-report Psychosocial Stress

The study used two measures of self-report psychosocial stress, common in population-based research: the Perceived Stress Scale [88] and a modified version of the Chronic Stress Scale, which we term domain-specific stress. [26] The 10-item Perceived Stress Scale assesses perceptions of overall stress within the last month (e.g., *in the last month, how often have you been upset because of something that happened unexpectedly?*). Item responses were recorded on a 5-point Likert scale ranging from *never (0)* to *very often (4)* (Cronbach's α=0.87 [95% CI: 0.84, 0.91]). To generate a total score, positively stated items were reversed, and all items were summed [observed range=3-23].

The 55-item domain-specific stress scale indexes ongoing stressful experiences across 12 life domains, including social and financial pressure, relationships and interactions, health and employment (see Table S1 for a detailed item description). Item responses were recorded on a 3-point Likert scale: *not true (0), somewhat true (1),* and *very true (2)* (Cronbach's α=0.85 [95% CI: 0.81, 0.89]). Not all participants were asked all questions (i.e., unemployed were not asked about work stress). To obtain the total score, missing values for non-applicable roles were set to zero; all items across 12 domains were summed [observed range=2-52].

We modeled the summary scores from the two measures in two ways. First, we median-centered and then scaled the continuous scores by their respective interquartile ranges, such that the mean difference between 25th and 75th quartiles of the empirical distribution would correspond to "low" and "high" self-reported stress. Second, for plotting, we also divided the continuous stress scores into three equally-sized empirical tertiles, corresponding to "low,"

"medium," and "high" stress. To test for linear trend between stress predictor and salivary cortisol, we used medians of stress tertiles, modelled as ordinal variables. [89]

Neighborhood SES and Race/Ethnicity

Participants' addresses were geocoded using geographic information system and linked to the 2010 Census to index area-level (hereafter *neighborhood*) SES. Details of constructing the composite measure are described elsewhere [85]. Briefly, a composite census tract measure was created using information on median household income, ownership and value of housing units. The neighborhoods were assigned as "high" and "low" SES based on the top and bottom tertiles of the composite SES index, respectively. [85] Race/ethnicity (coded as "NHW" and "NHB") was self-reported. Seven participants, who self-identified as neither NHW nor NHB, were coded as "Other." These latter participants were included in the main analyses and omitted when assessing the effect of race/ethnicity on the association between the stress measures.

Covariates

Information on sociodemographic factors was obtained from the baseline interview and included age (in years), sex (male, female), education (≤ high school, some college, ≥ college), and marital status (married/in relationship, separated/widowed, single/never married). These factors were previously shown to be important correlates of psychosocial stress and cortisol and were added to all the adjusted models. [90] Health behaviors and related factors (i.e., waist circumference, depression status, and medication use) may be regarded as confounders and/or mediators; [75] their influence was assessed in sensitivity analyses. Smoking status (never, past, current) and alcohol use (never/past, occasional, heavy/frequent) was measured by self-report. Participants reported any current medications on the day of the visit; medications were grouped into beta blockers, steroids, and glucocorticoids, each coded dichotomously (yes, no). Depression

diagnosis (yes, no) was obtained from medical records. Waist circumference (in centimeters) was measured by trained interviewers.

Statistical Analysis

We used locally estimated scatter plot smoothing (LOESS) curves to explore the shape of cortisol profile over eight assessments during the two-hour TSST for the full sample and stratified by race/ethnicity and neighborhood SES. The LOESS curves revealed a quadratic pattern of cortisol response. For all analyses salivary cortisol values were natural log-transformed.

We fit piecewise linear mixed models (LMM) with random intercepts and slopes to examine the relationships between self-reported stress and participant characteristics with salivary cortisol response to the TSST. Based on the exploratory work, two linear splines with a knot at 45 minutes since the start of the TSST (i.e., the 4th salivary collection) best captured the non-linear change in cortisol. Time splines were centered at time 1 to estimate baseline cortisol concentrations; each model was refit with time centered at time 4 to estimate cortisol concentrations at the peak. Satterthwaite-adjusted robust standard errors were used in all analyses to address heteroskedasticity in error variance and potential downward bias due to using cluster robust standard errors in smaller samples (R package *ClubSandwich*). [91]

All models included interactions with the time splines and IQR-scaled measures of self-reported stress, comparing participants with high (75th percentile) vs. low (25th percentile) stress scores. The empirical patterns of change before and after the peak at time 4 were interpreted as a rate of response and recovery respectively, consistent with prior research evidence: [86]

$$Log(cortisol)_{ij} = \beta_0 + \beta_1 Time_{ij} + \beta_2(Time_{ij} - 4) + \beta_3 Stress_i + \beta_4 Time_{ij} \times Stress_i + \beta_5(Time_{ij}$$
$$- 4) \times Stress_i + \beta_6^T X_i + b_{0i} + b_{1i} Time_{ij} + b_{2i}(Time_{ij} - 4) + \varepsilon_{ij}$$

where $Stress_i$ represents the self-reported stress scores scaled by their IQR. $\beta_1 Time_{ij}$ is the slope prior to peak at time 4, while $\beta_1 Time_{ij} + \beta_2(Time_{ij} - 4)$ is the slope after the peak. Parameters β_0 through β_6 are the fixed effects associated with the intercept, covariates and interaction terms. $Log(cortisol)_{ij}$ is the response for the ith participant at the *jth* time point, which assumes to differ from the population mean by a participant effect, represented by b_{0i}, b_{1i} and b_{2i} (random effects associated with the participant-specific intercept and linear effect of time) and a within-individual measurement error (ε_{ij}). X_i is a vector of individual-level covariates that include centered age, sex, race/ethnicity, education, marital status, and neighborhood SES.

As the primary goal of this analysis was to assess whether salivary cortisol response to the TSST varied as a function of self-reported stress scores, the null hypothesis of interest H₀: $\beta_3 = \beta_4 = \beta_5 = 0$. Each of the three random effects are assumed to be independent of the covariates, have a mean of zero and an auto-regressive within-individual correlation. The vector of errors is assumed to be independent of random effects and follow a multivariate normal distribution with mean zero and covariance matrix R_i(within-individual sources of variation in the responses).

To examine whether socioeconomic factors such as neighborhood SES or race/ethnicity modify the associations between stress measures, we sequentially added 3-way interaction terms to the fully adjusted LMM models (i.e., *stress × time × neighborhood SES* and *stress × time × race/ethnicity*). For example, the model with an interaction term for neighborhood SES was adjusted for race/ethnicity. Using R package *Emmeans*, we subsequently performed post-hoc multiple comparison analyses using Dunnett's correction for the family-wise error rate, designed to compare multiple groups to one referent. [92] Results are presented as percent differences in

predicted cortisol levels, compared to the following referent groups: high neighborhood SES at the 25th percentile of self-reported stress (henceforth referred to as *low stress*) and NHB at the 25th percentile of self-reported stress. All statistical analyses were performed in the R environment, version 4.0.5. A 2-sided P < 0.05 was considered statistically significant.

Sensitivity analyses

We tested the robustness of our results using a series of planned sensitivity analyses: (1) for measured confounding, we fit models additionally including depression diagnosis, smoking, alcohol use, waist circumference, and the use of three medication groups (i.e., steroids, beta blockers and glucocorticoids); (2) for unmeasured confounding, we calculated an approximate E-values for the main estimates and confidence intervals. [93] We also tested models excluding (3) extreme cortisol observations (< 1st or > 99th percentile) and (4) five participants whose medical chart indicated a recent diagnosis of diabetes. Finally, (5) we tested the inclusion of simultaneous interactions between time × self-reported stress × neighborhood SES and time × self-reported stress × race/ethnicity.

2.3 Results

Descriptive Analysis

The average age of the RSASS cohort was 57 years, and approximately half were female (49%), African American (48%), with a college degree or higher (54%), and 61% resided in a neighborhood of high socioeconomic status (SES) (Table 1). Summary scores for the perceived and domain-specific stress scales were moderately correlated (Spearman's r=0.62, p<0.001); the correlations between their individual items are shown in Supplemental Table S2. Compared to participants from low SES neighborhoods, those from high SES neighborhoods had lower

baseline concentration of salivary cortisol (0.06 vs. 0.08) and reported lower median domain-specific stress (16 vs. 20), but not perceived stress (16 vs. 16). Compared to NHW participants, NHB participants had higher baseline salivary cortisol (0.08 vs. 0.06 mg/L) and scored higher on both self-reported stress scales (perceived: 17 vs. 15 and domain-specific: 20 vs. 16). Participants reporting current smoking or heavy/frequent drinking had higher baseline cortisol compared to never or former/occasional users of these substances.

Self-report Stress and Salivary Cortisol Profile

Table 2 shows the salivary cortisol profile (baseline, rate of response, peak, and rate of recovery) associated with self-report stress measures expressed as percent differences. *Negative* percent differences in the rate of change from time 1 to 4 indicate *weaker response* to the TSST, and *positive* percent differences in the rate of change from time 4 to 8 indicate *slower recovery* from the TSST. Neither perceived stress nor domain-specific stress were significantly associated with baseline salivary cortisol concentrations. Controlling for age, gender, neighborhood SES, education and race/ethnicity, rate of response to the TSST was significantly associated with increase in perceived stress (-7.5%; 95% CI: -13.1% to -1.5% [P=0.017]), but was not significantly associated with domain-specific stress (-5.5%; 95% CI: -11.4% to +0.8% [P=0.083]). Salivary cortisol at peak (time 4) was 25.4% lower per IQR increase in perceived stress score (95% CI: -42.9% to -2.6% [P=0.032]) but was not significant for domain-specific stress (-17.4%; 95% CI: -36.7% to +7.8% [P=0.16]). Finally, for IQR increase in domain-specific stress we observed a +3.7% slower rate of recovery (95% CI: +0.6% to +7.0% [P=0.022]); this pattern was similar, but not statistically significant, for the perceived stress scale. The addition of interaction terms between time and race/ethnicity and neighborhood SES slightly attenuated the association between self-reported stress measures and salivary cortisol.

Figure 1 illustrates the cortisol response as a function of empirical tertiles of perceived stress (Panel A) and domain-specific stress (Panel B); Tables S3-S4 provide the respective estimates. Overall, these results are suggestive of a dose-response relationship between higher self-reported stress and monotonic decrease in cortisol during response (perceived: p for trend=0.024; domain-specific: p for trend=0.156) and recovery phases (perceived: p for trend=0.013; domain-specific: p for trend=0.005). However, only comparisons between the medians of the lowest and highest tertiles were statistically significant for both measures (Table S3).

Effect Modification by Neighborhood SES and Race/Ethnicity

Figure 2 summarizes how the associations between self-report stress and salivary cortisol vary by neighborhood SES (Panels A-B) and race/ethnicity (Panels C-D). Among those living in high SES neighborhoods, high (75th percentile) self-report stress was associated with weaker salivary cortisol response to the TSST (solid lines, Panels A-B). However, among those living in low SES neighborhoods, there was no association between self-report stress and cortisol response (dotted lines, Panels A-B). Corresponding patterns were observed for both self-report stress measures. In contrast, the associations between self-reported stress with salivary cortisol profile were not statistically different between NHW and NHB (Panels C-D). Tables S5-S6 provide the estimates for the figure from the SES- and race-stratified LMMs.

Sensitivity Analysis

Tables S7 through S11 show the results from the planned sensitivity analyses. As shown by Table S7 the associations between self-reported stress and salivary cortisol were largely unchanged with additional adjustments for smoking, drinking and waist circumference (Model 3), prescription medications (Model 4), or depression diagnosis (Model 5). Table S8 illustrates

that reported significant results (Table 2) may be relatively robust to unmeasured confounding, as indicated by moderate E-values for the point estimates and the lower limit of the confidence interval (min RR=1.37). Excluding observations with extreme cortisol observations (Table S9) or recent diabetes diagnosis (Table S10) yielded results consistent with the main analyses. Lastly, including simultaneous interactions between neighborhood SES and race/ethnicity with self-reported stress and time modestly attenuated model estimates, but did not impact the substantive findings (Table S11).

2.4 Discussion

The purpose of this study was two-fold. First, we aimed to quantify the associations between commonly used self-report measures of psychosocial stress with the neurobiological stress response as measured by HPA-axis reactivity to an acute laboratory stressor. Our second aim explored how conditions of structural and socioeconomic disadvantage, operationalized by low neighborhood SES and minority status, influenced the associations between these self-report stress measures and the neurobiological stress response.

With respect to our first aim, we found that these two self-report measures of perceived and domain-specific psychosocial stress had distinct, but generally congruent, associations with the neurobiological stress response. While neither measure was associated with baseline cortisol, high levels of perceived stress were consistently associated with lower cortisol response to, but not recovery from, the TSST. In contrast, high levels of domain-specific stress were associated with slower recovery from, but were not associated with the response to, the TSST. These discordances suggest that the two self-report measures examined in this analysis represent distinct but overlapping dimensions of subjective stress experiences: the perceived stress scale assesses a sense of being overwhelmed within the last month, and thus potentially indexes

dimensions of stress that are temporary and intense; while the domain-specific scale indexes

dimensions of stress that are typically prolonged but not necessarily a crisis. In our sample, the

domain-specific stress measure mostly reflected social and financial strains (i.e., living with debt,

interpersonal conflict).

Our results demonstrated that despite the underlying complexity of the neurobiological

stress response, the two widely-used subjective measures of psychosocial stress correlated with

neurobiological stress processes in a manner consistent with the three conceptual frameworks

highlighted earlier. [49,71,82,83] Specifically, the findings for the perceived stress suggested

attenuated sensitivity to glucocorticoids among participants reporting high levels of stress,

consistent with the ToH [94] and the AL frameworks. [49] The findings for the domain-specific stress

measure support the emphasis of GUTS on stress recovery (23) and further extend recent

evidence from the Multi-Ethnic Study of Atherosclerosis which demonstrated that individuals

with more ongoing stressors were unable to down-regulate neurobiological stress responses as

efficiently as those with fewer stressors. [78] Delayed recovery from acute stress has been

previously shown as an important marker of vulnerability to cardiovascular disorders. [95]

With respect to our second aim, we found that the association between self-reported

stress and neurobiological stress responses varied by neighborhood SES but not race/ethnicity.

For individuals living in low SES neighborhoods, self-reported stress was not associated with the

cortisol response profile, whereas among those from high SES neighborhoods higher levels of

self-reported stress was associated with a blunted response. These findings may suggest that the

examined self-report stress measures do not reflect physiologically relevant variation in stress

within socially disadvantaged contexts, here proxied by living in a low SES neighborhood.

Alternatively, they may point to the potentially non-additive effect of psychosocial stress on

neurobiology in socially disadvantaged environments, consistent with the ToH. [84] Finally, the small point estimates and overlapping confidence intervals offered limited evidence that the associations between self-report stress measures and cortisol profile differed by race/ethnicity, after accounting for neighborhood SES. These results contrasted with recent empirical findings that showed that minority status moderated associations between racial stressors (e.g., discrimination) and neurobiological stress reactivity. [96,97] Differences in sample age composition and stress measurements used might explain these discrepant findings. [90]

Our findings have implications for efforts aimed at refining the measurement of chronic psychosocial stress in population research and examining the mechanisms driving health disparities. According to the fundamental cause framework, health disparities are hypothesized to reflect a multi-level, developmental process in which distal factors (e.g., differential access to resources, here indexed by a minority status and neighborhood SES), become embodied via more proximal factors (e.g., the HPA-axis activity). [71,72] This physiological embodiment of disadvantage may, in turn, alter perceptions and appraisals of stressful experiences, thus influencing the ability of self-report measures to index meaningful variation in stress exposure. [98] Consistent with this interpretation, our results suggest that commonly used self-report stress measures might not be adequate for assessing stress among adults living in economically-disadvantaged neighborhoods. [99]

Findings should be interpreted considering study limitations. First, this was a cross-sectional study, therefore we cannot determine the temporal relationship between the self-reported stress measures and HPA-axis activity. The self-report measures of stress used in this study are not appropriate for considering questions of timescale (i.e., they cannot differentiate between past (but ongoing) vs. new sources of stress). The sample is comprised of middle-aged

adults at risk of diabetes, which limits our ability to generalize to other groups. Because of the relatively small sample, there is a possibility of type II error especially with respect to testing interactions; this also limited our ability to test additional interactions (i.e., biological sex). Finally, cortisol is only one aspect of the neurobiological stress response, which may be sensitive to other exposures that we could not account for (e.g., diet, environmental toxins, menstrual cycle phase or hormonal birth control, etc.).

This study also has several strengths. The TSST is a well-validated measure of HPA-axis stress reactivity, and it induced a robust cortisol response. Our racially and socioeconomically diverse sample reflects a population that is a focus of diabetes prevention efforts, which enhances the translation of our findings into practice. We conducted multiple sensitivity analyses that demonstrated the robustness of our findings. Lastly, the two-by-two study sampling frame approximately balanced participants across race and neighborhood SES was designed with considerations of moderating effects of SES and race/ethnicity.

In sum, this study contributes toward understanding the interrelationship between self-report assessments of psychosocial stress and the neurobiological stress response, particularly as they relate to mechanisms linking social (dis)advantage to health. [36,72] The use of theoretically-informed, and context-specific approaches toward measuring this complex construct may help reduce heterogeneity in study findings and accelerate progress toward understanding the links between chronic stress and health outcomes.

Table 2-1. Self-reported stress and baseline salivary cortisol by participant characteristics

Characteristics	No. (%)	Self-reported Stress Summary Score Perceived Median (IQR)	Domain-specific Median (IQR)	Salivary Cortisol (Time 1) (mg/L) (SC1) Median (IQR)
Overall	125	16 (10, 20)	18 (11, 27)	0.06 (0.04, 0.10)
Perceived Stress Empirical Tertiles				
[0, 13)	42 (34)	9 (7, 10)	11 (6, 16)	0.06 (0.04, 0.11)
[13, 19)	43 (34)	16 (14, 17)	21 (16, 26)	0.07 (0.05, 0.11)
[19, 36]	40 (32)	23 (20, 25)	28 (19, 40)	0.06 (0.04, 0.09)
Domain-specific Empirical Tertiles				
[2, 15)	43 (34)	10 (7, 14)	9 (6, 11)	0.06 (0.05, 0.11)
[15, 25)	41 (33)	17 (13, 19)	19 (16, 22)	0.06 (0.04, 0.09)
[25, 52]	41 (33)	20 (16, 25)	31 (27, 40)	0.06 (0.04, 0.11)
Age Groups				
40-49	17 (14)	16 (15, 21)	26 (19, 31)	0.05 (0.03, 0.09)
50-59	56 (45)	17 (13, 20)	22 (15, 30)	0.07 (0.05, 0.11)
60-71	52 (42)	13 (9, 19)	13 (8, 21)	0.06 (0.04, 0.09)
Sex				
Male	64 (51)	15 (10, 19)	20 (11, 27)	0.08 (0.04, 0.13)
Female	61 (49)	16 (11, 20)	17 (12, 27)	0.06 (0.04, 0.08)
Race and Ethnicity				
Non-Hispanic Black	60 (48)	17 (11, 20)	20 (15, 30)	0.08 (0.04, 0.12)
Non-Hispanic White	58 (46)	15 (9, 19)	16 (10, 25)	0.06 (0.04, 0.09)
Other [a]	7 (6)	19 (14, 20)	24 (23, 28)	0.06 (0.05, 0.06)
Education				
≤ High school	26 (21)	19 (14, 25)	23 (19, 32)	0.09 (0.06, 0.14)
Some college	32 (26)	16 (12, 18)	19 (9, 29)	0.08 (0.05, 0.10)
≥ College	67 (54)	13 (9, 19)	16 (11, 25)	0.06 (0.04, 0.08)
Marital Status				
Married/Partner	61 (49)	16 (11, 19)	16 (10, 26)	0.06 (0.04, 0.09)
Separated/Widowed	39 (31)	16 (9, 20)	19 (11, 28)	0.07 (0.04, 0.11)
Single/Never married	25 (20)	17 (13, 19)	22 (16, 27)	0.08 (0.05, 0.13)
Neighborhood SES				
Low	49 (39)	16 (12, 20)	21 (16, 27)	0.08 (0.05, 0.12)
High	76 (61)	16 (10, 20)	16 (9, 27)	0.06 (0.04, 0.09)
Waist circumference (cm) [c b]				
Female: < 88	20 (16)	12 (9, 19)	16 (11, 27)	0.06 (0.05, 0.07)
Female: ≥ 88	39 (31)	17 (13, 20)	18 (13, 26)	0.06 (0.04, 0.09)
Male: < 102	25 (20)	15 (9, 19)	18 (10, 25)	0.09 (0.05, 0.18)
Male: ≥ 102	36 (29)	16 (10, 17)	20 (11, 29)	0.06 (0.04, 0.11)
Smoking [c]				
Never	50 (40)	15 (9, 18)	17 (10, 23)	0.06 (0.04, 0.09)
Past	43 (34)	17 (11, 21)	20 (11, 28)	0.05 (0.04, 0.10)
Current	31 (25)	17 (11, 21)	23 (17, 32)	0.08 (0.05, 0.11)
Alcohol Use [d]				
Never/Past	43 (34)	16 (12, 19)	19 (13, 27)	0.06 (0.04, 0.09)
Occasional	68 (54)	16 (9, 20)	18 (10, 28)	0.06 (0.04, 0.08)
Heavy/Frequent	14 (11)	18 (13, 22)	17 (13, 26)	0.08 (0.05, 0.13)
Prescription Medications				
Beta Blockers				
Yes	16 (13)	16 (11, 20)	11 (9, 23)	0.08 (0.05, 0.13)
No	109 (87)	13 (9, 16)	19 (13, 27)	0.06 (0.04, 0.10)
Glucocorticoids				
Yes	8 (6)	16 (11, 20)	12 (9, 15)	0.04 (0.04, 0.08)
No	117 (94)	10 (9, 13)	19 (11, 27)	0.06 (0.04, 0.11)
Statins				
Yes	20 (16)	16 (11, 20)	19 (11, 30)	0.08 (0.05, 0.12)
No	105 (84)	15 (10, 19)	18 (11, 27)	0.06 (0.04, 0.10)
Depression Diagnosis [c]				
Yes	17 (14)	16 (10, 19)	22 (15, 41)	0.11 (0.09, 0.17)
No	106 (85)	19 (16, 24)	18 (11, 27)	0.06 (0.04, 0.09)

a. Combines Asian, Hispanic and Other categories due to limited sample size.
b. Cut-off determined based on the METS criteria.
c. Missing: waist circumference (n=5), smoking (n=1), depression diagnosis (n=2)
d. Occasional reflects > 2 drinks per occasion on > 15 days/month; frequent/heavy≥ 2 drinks on ≤ 15 days/month

Table 2-2. Change in salivary cortisol concentrations by self-reported stress (IQR)

Fixed Effects	Model 1a		Model 2a	
Salivary Cortisol	% Difference (95% CI)	*P-value*	% Difference (95% CI)	*P-value*
Perceived Stress				
Time 1: Baseline				
$\leq$ 20 vs. $\leq$ 10	-5.9 (-24.3, 17.0)	*0.58*	-6.3 (-24.8, 16.7)	*0.55*
nSES: low vs. high	6.6 (-21.0, 44.0)	*0.67*	22.5 (-11.3, 69.2)	*0.21*
Race/ethnicity: NHW vs. NHB	-18.1 (-36.7, 6.0)	*0.13*	-4.5 (-28.6, 27.6)	*0.75*
Time 1-4: Rate of Response				
$\leq$ 20 vs. $\leq$ 10	**-7.5 (-13.1, -1.5)**	***0.017***	**-6.4 (-11.8, -0.8)**	***0.027***
nSES: low vs. high	**--**	*--*	**-12.4 (-19.6, -4.5)**	***0.003***
Race/ethnicity: NHW vs. NHB	**--**	*--*	-2.0 (-10.5, 7.3)	*0.66*
Time 4: Peak*				
$\leq$ 20 vs. $\leq$ 10	**-25.4 (-42.9, -2.6)**	***0.032***	**-23.3 (-40.7, -0.7)**	***0.044***
nSES: low vs. high	6.6 (-21.0, 44.0)	*0.67*	-17.6 (42.0, 16.9)	*0.27*
Race/ethnicity: NHW vs. NHB	-18.1 (-36.7, 6.0)	*0.13*	-10.2 (-35.3, 24.6)	*0.51*
Time 4-8: Rate of Recovery				
$\leq$ 20 vs. $\leq$ 10	3.0 (-0.6, 6.8)	*0.10*	2.5 (-1.0, 6.2)	*0.16*
nSES: low vs. high	**--**	*--*	2.7 (-1.3, 6.8)	*0.19*
Race/ethnicity: NHW vs. NHB	**--**	*--*	**-4.9 (-8.5, -1.1)**	***0.013***
Domain-specific Stress	**Model 1b**		**Model 2b**	
Time 1: Baseline				
$\leq$ 27 vs. $\leq$ 11	-2.1 (-20.7, 20.9)	*0.84*	-1.6 (-20.5, 21.9)	*0.88*
nSES: low vs. high	7.7 (-20.3, 45.5)	*0.62*	23.6 (-10.5, 70.8)	*0.19*
Race/ethnicity: NHW vs. NHB	-18.3 (-37.2, 6.4)	*0.13*	-4.9 (-29.5, 28.1)	*0.74*
Time 1-4: Rate of Response				
$\leq$ 27 vs. $\leq$ 11	-5.5 (-11.4, 0.8)	*0.083*	-3.7 (-9.5, 2.4)	*0.22*
nSES: low vs. high	**--**	*--*	**-12.2 (-19.4, -4.4)**	***0.003***
Race/ethnicity: NHW vs. NHB	**--**	*--*	-2.6 (-11.4, 7.1)	*0.58*
Time 4: Peak*				
$\leq$ 27 vs. $\leq$ 11	-17.4 (-36.7, 7.8)	*0.16*	-12.2 (-32.5, 14.3)	*0.33*
nSES: low vs. high	7.7 (-20.3, 45.5)	*0.62*	-16.4 (-41.3, 18.9)	*0.31*
Race/ethnicity: NHW vs. NHB	-18.3 (-37.2, 6.4)	*0.13*	-12.2 (-37.3, 22.7)	*0.44*
Time 4-8: Rate of Recovery				
$\leq$ 27 vs. $\leq$ 11	**3.7 (0.6, 7.0)**	***0.022***	2.5 (-0.8, 5.9)	*0.14*
nSES: low vs. high	**--**	*--*	2.4 (-1.6, 6.6)	*0.23*
Race/ethnicity: NHW vs. NHB	**--**	*--*	**-4.4 (-8.1, -0.6)**	***0.025***

Models (M) 1a-b are adjusted for demographic characteristics: neighborhood SES [reference=high], race and ethnicity [reference=NHB], centered age, gender [reference=male], marital status [reference=married], and education level [reference $\geq$ college]. M2a-b: M1 + interaction terms for neighborhood SES x time splines, race and ethnicity x time splines.
Negative point estimates for rate of response reflects smaller increase in cortisol between each collection time; negative estimates for rate of recovery reflects larger decrease in cortisol.
*Estimates obtained from a separate model, where time was centered at the 4th time point.

Figure 2-1. Predicted salivary cortisol trajectories by self-reported stress tertiles during the Trier Social Stress Challenge.
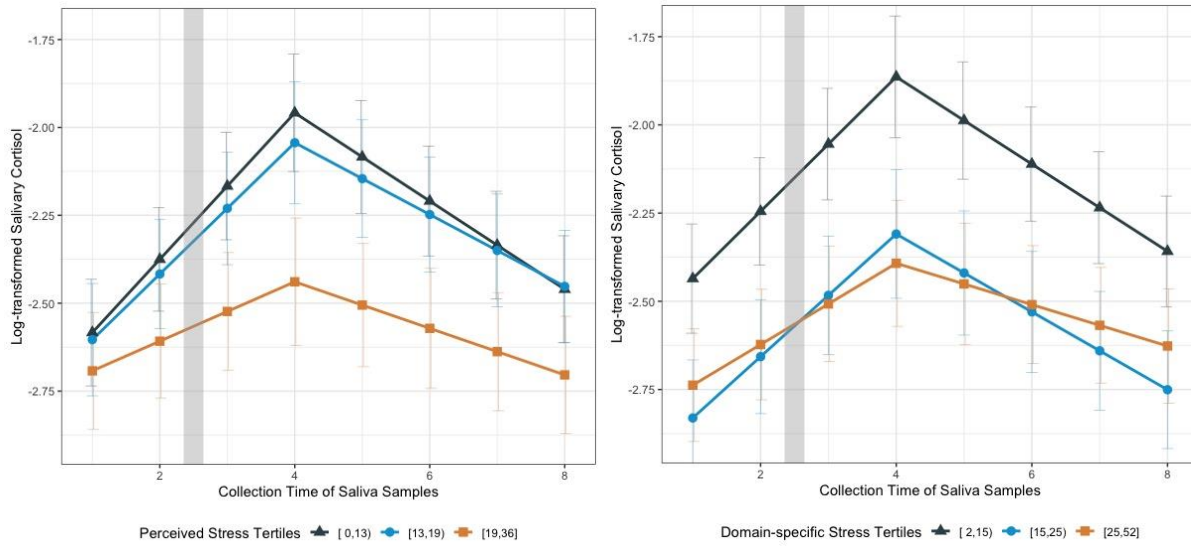
The figure illustrates how estimates of the log-transformed salivary cortisol (y-axis) change across eight collection time points (x-axis) by the empirical tertiles of self-reported stress, measured using the perceived (left panel) and domain-specific stress scales (right panel). Predicted trajectories and 95% confidence intervals were obtained by a post-estimation of marginal means, using linear mixed models with linear splines and Satterthwaite-adjusted robust standard errors. The gray vertical line between the collection times 2 and 3 indexes the timing of the Trier Stress Test. All models were adjusted for centered age, sex, marital status, education, neighborhood SES and race/ethnicity. See Tables S3 and S4 for corresponding estimates.

Figure 2-2. Predicted salivary cortisol trajectories during the Trier Social Stress Test (baseline Richmond Stress and Sugar Study, n=125) comparing scores at 75th vs. 25th percentiles of self-reported perceived
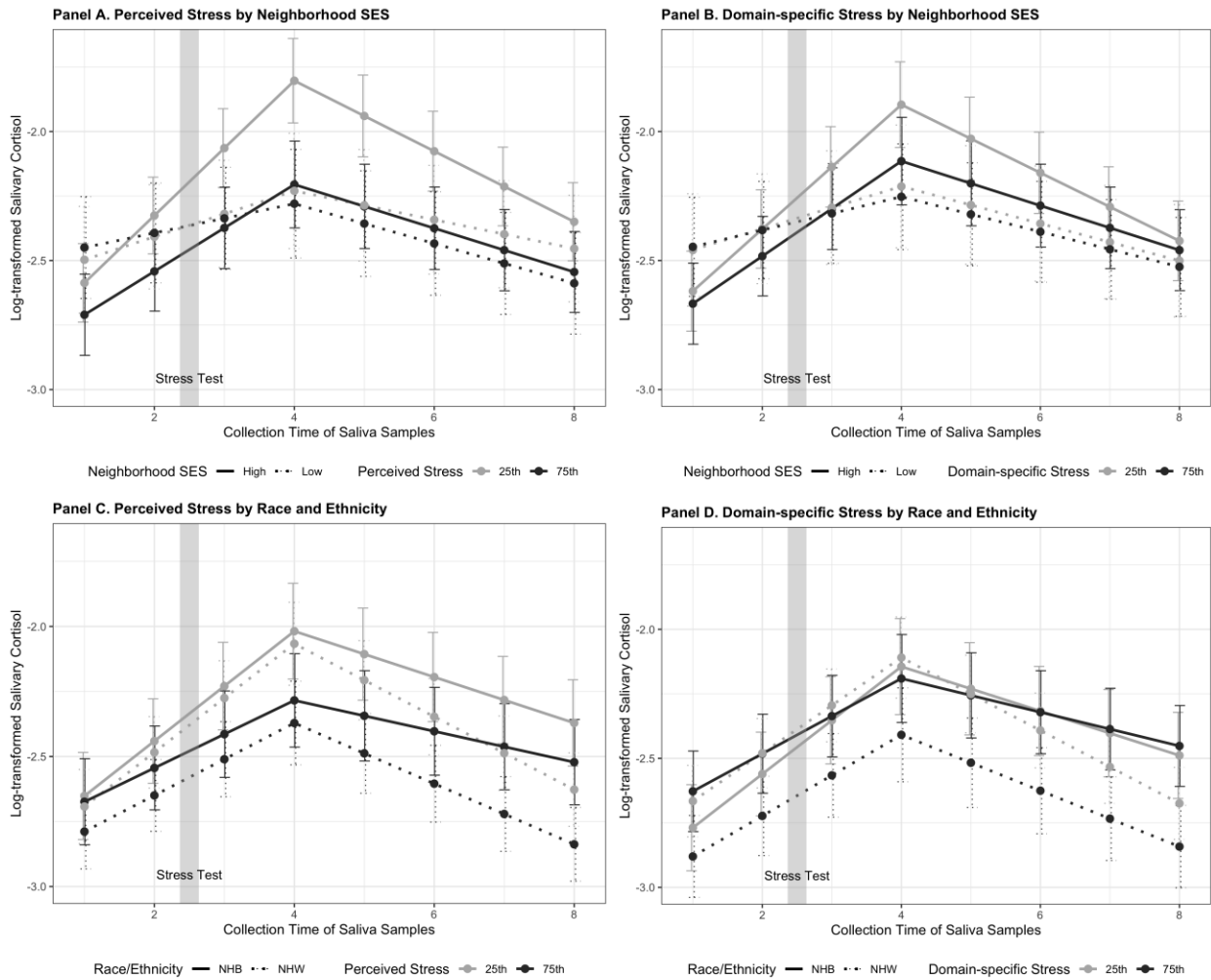
Predicted salivary cortisol trajectories during the Trier Social Stress Test (baseline Richmond Stress and Sugar Study, n=125) comparing scores at 75th vs. 25th percentiles of self-reported perceived [panels A and C] and domain-specific stress [panels B and C] by neighborhood SES (high vs low) [top row] and race/ethnicity (Non-Hispanic Black (NHB) vs. Non-Hispanic White (NHW)) [bottom row]. Predicted trajectories and 95% confidence intervals were obtained by a post-estimation of marginal means, using linear mixed models with linear splines and Satterthwaite-adjusted robust standard errors. The 75th and 25th percentiles correspond to scores 10 and 20 on the perceived stress scale, and 11 and 27 on the domain-specific scale. All models were adjusted for centered age, sex, marital status, and education. The model for interaction with neighborhood SES (reference=High) was adjusted for race/ethnicity; the model for interaction with race/ethnicity was adjusted for neighborhood SES. See Table S5 and Table S6 for corresponding estimates.

Supplemental Figure 2-1. Conceptual diagram: Stress Construct and Hypothesized Interrelationships between Chronic and Acute Stress, Perceptions and Physiology.

The figure illustrates how complex interrelationships between different sources of psychosocial stress, perceptual mechanisms, and conscious and unconscious processes may contribute toward participants' self-reports of stress and their physiological responses to stressors.

Supplemental Table 2-1. Domain-specific Chronic Stress Scale

Domain Name	Original Prompts*	No.	Questions
Pressure		1	You are trying to take on too many things at once.
		2	There is too much pressure on you to be like other people.
		3	Too much is expected of you by others.
Finances	The next few questions ask about money and finances.	4	You don't have enough money to buy the things you or your family need.
		5	You have a large amount of credit card debt or other loans.
		6	Your rent or mortgage is too much.
		7	You don't have enough money to take vacations.
		8	You don't have reliable transportation.
		9	You live "paycheck to paycheck".
		10	You are concerned that you aren't saving enough for retirement.
		11	You worry that your food will run out before you have money to buy more.
Job	The next few questions are about work.	12	You have more work to do than most people.
		13	Your supervisor is always monitoring what you do at work.
		14	You want to change jobs or career but don't feel you can.
		15	Your job often leaves you feeling both mentally and physically tired.
		16	You want to achieve more at work but things get in the way.
		17	You don't get paid enough for what you do.
		18	Your work is boring and repetitive.
Unemployed	The next few questions are about being out of work.	19	You are discouraged that you have not been able to find a job.
		20	You find it difficult to deal with the unemployment agency about your benefits.
		21	You feel pressure from your family to find a job quickly.
		22	You feel that you don't have the right training or experience to get the type of job you would like to have.
Disability**	The next few questions are about being on disability.	23	You are discouraged that you are not able to work.
		24	You feel it is difficult to deal with the social security agency about your disability benefits.
		25	You feel judged by others because you are on disability.
Partner	The next few questions are about your relationship with your partner or spouse.	26	You have a lot of conflict with your partner.
		27	Your relationship restricts your freedom.
		28	Your partner doesn't understand you.
		29	Your partner expects too much of you.
		30	Your partner doesn't show enough affection.
		31	Your partner is not committed enough to your relationship.
		32	Your partner isn't there for you when you need them.
Ex-partner	These next few questions are about your past relationships.	33	You have a lot of conflict with your ex-spouse.
		34	You don't see your children from a former relationship as much as you would like.
Children	The new few questions are about your children.	35	One or more of your children seems very unhappy.
		36	You feel your children don't listen to you.
		37	Your children's' behavior is a source of serious concern to you.
		38	One or more children do not do well enough at school or work.
		39	Your children don't help around the house.
		40	Your children spend too much time away from the house.
Social	The next few questions are about your social life.	41	You are alone too much.
		42	You feel left out of things.
		43	You don't have time to do the things that help you relax.
		44	You have a lot of conflict with members of your family.
Residence	These next few questions are about where you live currently.	45	You want to live farther away from your family.
		46	You would like to move but you cannot.
		47	Your family lives too far away.
		48	You don't have a stable place to live.
Family	The next few questions are about your family relationships.	49	Someone in your family or a close friend has a long-term illness or disability.
		50	You have a close family member who is in very bad health.
		51	Someone in your family has an alcohol or drug problem.
		52	You take care of a relative or friend almost every day, either by helping around the house or helping with their health care.
Interactions**	These next few questions are about your daily interactions with other people.	53	You feel you are treated with less respect than other people are.
		54	You feel that people act as if they think you are not smart.
		55	You feel that people act as if they are afraid of you.

*INTRODUCTORY PROMPT: Next, I'll describe some other situations that sometimes come up in people's lives. Some of these situations may not apply to you, and please be patient with me if I ask you questions that repeat things you've already told me. For each situation, I'd like you to tell me if these things are *Not true, somewhat true, or very true* for you at this time.

** Domain Items adopted from the Everyday Discrimination Scale (Williams DR, Yu Y, Jackson JS, and Anderson NB. Racial differences in physical and mental health. Socio-economic status, stress and discrimination. Journal of Health Psychology. 1997; 2:335–51).

Supplemental Table 2-2. Spearman Correlations: Domain-specific and Perceived Stress Domains

Domain-specific Stress					Perceived Stress							Domain Sum
	Upset	No Control	Stressed	Personal Problems	Not going right	Unable to cope	Irritations	Not on top of things	Angered	Difficulties	Perceived Sum	
Pressure	0.33**	0.38**	0.24**	0.37**	0.40**	0.53**	0.30**	0.39**	0.43**	0.57**	0.57**	0.57**
Finances	0.19*	0.23*	0.23**	0.20*	0.35**	0.20*	0.19*	0.31**	0.26**	0.37**	0.37**	0.68**
Job	-0.06	-0.01	0.15	-0.07	0.03	-0.06	0.07	0.02	0.10	-0.01	-0.01	0.21*
Unemployed	0.06	0.18*	0.09	0.05	0.08	0.20*	-0.12	0.02	0.12	0.12	0.13	0.27**
Disability	0.14	0.14	-0.02	0.02	0.11	0.06	0.12	0.10	-0.02	0.17	0.14	0.16
Partner	0.21*	0.26**	0.12	0.17	0.25**	0.14	0.08	0.25**	0.28**	0.22*	0.27**	0.33**
Ex-partner	0.11	0.09	0.13	0.14	0.09	-0.02	0.13	0.16	0.01	0.11	0.13	0.22*
Children	0.28**	0.15	0.17	-0.03	0.09	0.01	-0.07	0.01	0.09	0.07	0.11	0.38**
Social	0.30**	0.36**	0.30**	0.29**	0.48**	0.29**	0.39**	0.33**	0.38**	0.41**	0.51**	0.62**
Residence	0.18*	0.20*	0.19*	0.28**	0.24**	0.26**	0.15	0.19*	0.20*	0.24**	0.30**	0.49**
Family	0.30**	0.13	0.23**	0.14	0.20*	0.28**	0.07	0.22*	0.15	0.24**	0.27**	0.39**
Interactions	0.28**	0.24**	0.13	0.12	0.26**	0.15	0.14	0.20*	0.18*	0.22*	0.28**	0.48**
Domain Sum	0.45**	0.47**	0.43**	0.33**	0.55**	0.40**	0.31**	0.44**	0.43**	0.53**	0.62**	1
Perceived Sum	0.65**	0.76**	0.59**	0.63**	0.76**	0.68**	0.60**	0.78**	0.65**	0.80**	1	--

**P-value <0.1; *P-value<0.5

Supplemental Table 2-3. Salivary Cortisol at Baseline, Peak, and in Response/Recovery Rate during the Trier Social Stress Test by Perceived and Domain-specific Stress Tertiles.

Fixed Effects	Model 1a					Model 1b			
	Empirical Tertiles								
Salivary Cortisol Profile:	**Low** ≤33th	**Medium** >33th & <69th		**High** ≥69th		**Medium** >33th & <69th		**High** ≥69th	
Time 1-8		% difference (95% CI)	*P-value*	% difference (95% CI)	*P-value*	% difference (95% CI)	*P-value*	% difference (95% CI)	*P-value*
Perceived Stress Tertiles (PS)	≤12	>12 & <19		≥19		>12 & <19		≥19	
Time 1: baseline									
PS	[ref]	-4.9 (-32.7, 34.5)	*0.78*	-11.5 (-36.2, 22.9)	*0.46*	-7.0 (-33.3, 31.7)	*0.68*	-11.5 (-36.6, 23.3)	*0.46*
nSES: low vs. high	--	6.3 (-21.6, 44.1)			*0.69*	23.6 (-10.8, 71.4)			*0.20*
Race/ethnicity: NHW vs. NHB	--	-18.6 (-37.4, 5.8)			*0.12*	-5.1 (-29.3, 27.3)			*0.72*
Time 1-4: rate of response									
PS	[ref]	-2.1 (-12.7, 9.8)	*0.72*	**-11.7 (-20.1, -2.4)**	*0.02*	-0.6 (-9.9, 12.4)	*0.91*	**-9.8 (-17.8, -0.9)**	*0.03*
nSES: low vs. high	--	--	--	--	**--**	**-13.1 (-20.3, -5.3)**			*0.002*
Race/ethnicity: NHW vs. NHB	--	--	--	**--**	--	-2.4 (-10.9, 6.8)			*0.59*
Time 4: peak									
PS	[ref]	-10.7 (-38.8, 30.3)	*0.55*	**-38.9 (-59.3, -8.3)**	*0.02*	-5.2 (-34.6, 37.3)	*0.77*	**-35.0 (-56.2, -3.6)**	*0.03*
Time 4-8: rate of recovery									
PS	[ref]	2.4 (-1.9, 6.8)	*0.28*	**6.1 (1.0, 11.5)**	*0.02*	1.4 (-2.6, 5.5)	*0.50*	4.8 (-0.3, 10.1)	*0.06*
nSES: low vs. high	--	--	--	--	**--**	2.8 (-1.1, 6.8)			*0.16*
Race/ethnicity: NHW vs. NHB	--	--	--	**--**	--	**-4.7 (-8.3, -0.92)**			*0.02*
	Model 1b					**Model 2b**			
Domain-specific Stress Tertiles (DS)	≤14	>14 & <25		≥25		>14 & <25		≥25	
Time 1: baseline									
DS	[ref]	-31.8 (-53.6, 0.1)	*0.05*	-24.8 (-49.5, 12.1)	*0.16*	-32.3 (-54.2, 0.1)	*0.05*	-23.1 (-48.8, 15.5)	*0.20*
nSES: low vs. high	--	14.9 (-14.6, 54.7)			*0.35*	30.4 (-5.0, 79.0)			*0.10*
Race/ethnicity: NHW vs. NHB	--	-20.9 (-38.6, 1.9)			*0.07*	-8.5 (-31.5, 22.1)			*0.54*
Time 1-4: rate of response									
DS	[ref]	-1.7 (-12.3, 10.1)	*0.76*	-7.3 (-16.5, 2.9)	*0.15*	5.2 (-6.1, 17.9)	*0.37*	-4.5 (-14.1, 6.2)	*0.39*
nSES: low vs. high	--	--	--	--	--	**-14.1 (-21.8, -5.6)**			*0.002*
Race/ethnicity: NHW vs. NHB	--	--	--	--	--	-1.7 (-10.5, 8.0)			*0.72*
Time 4: peak									
DS	[ref]	**-35.3 (-57.1, -2.3)**	*0.04*	**-40.1 (-61.9, -5.9)**	*0.03*	-21.1 (-48.0, 19.9)	*0.26*	-32.9 (-57.1, 5.1)	*0.08*
Time 4-8: rate of recovery									
DS	[ref]	1.3 (-2.9, 5.7)	*0.53*	**6.7 (1.6, 12.1)**	*0.01*	-2.0 (-6.0, 2.2)	*0.34*	4.3 (-0.8, 9.6)	*0.10*
nSES: low vs. high	--	--	--	--	**--**	3.7 (-0.3, 7.9)			*0.07*
Race/ethnicity: NHW vs. NHB	--	--	--	**--**	--	**-4.6 (-8.2, -1.0)**			*0.02*

Supplemental Table 2-4. Predicted Mean Values of Log-transformed Salivary Cortisol by Self-reported Stress Tertiles.

Predicted Values	Empirical Stress Tertiles		
Cortisol Profile: Time 1- 8	Low $\leq 33^{th}$	Medium $>33^{th}$ & $<69^{th}$	High $\geq 69^{th}$
	Mean (SE)	Mean (SE)	Mean (SE)
Perceived Stress Tertiles	**≤ 12**	**>12 & <19**	**≥ 19**
Time 1: baseline	-2.55 (0.16)	-2.60 (0.17)	-2.67 (0.17)
Time 1-4: rate of response	0.21 (0.04)	0.19 (0.04)	0.08 (0.04)
Time 4: peak	-1.92 (0.18)	-2.04 (0.18)	-2.42 (0.19)
Time 4-8: rate of recovery	-0.13 (0.02)	-0.10 (0.02)	-0.07 (0.02)
Domain-specific Stress Tertiles	**≤ 14**	**>14 & <25**	**≥ 25**
Time 1: baseline	-2.44 (0.17)	-2.82 (0.18)	-2.72 (0.17)
Time 1-4: rate of response	0.19 (0.04)	0.17 (0.04)	0.12 (0.04)
Time 4: peak	-1.86 (0.18)	-2.30 (0.19)	-2.38 (0.19)
Time 4-8: rate of recovery	-0.12 (0.02)	-0.11 (0.02)	-0.06 (0.02)

Predicted means were obtained from LMM with linear splines for time and post-estimation of marginal means using *Emmeans* R package; these estimates are illustrated in figure 1. All covariates were set to their respective reference values or held at the mean and include: neighborhood SES (reference=High), race/ethnicity (reference=Non-Hispanic Black), mean age, sex (reference=Male), marital status (ref=Married/In a relationship), and education level (reference=4-year college or higher).

Supplemental Table 2-5. Interactions between neighborhood SES and race/ethnicity with self-reported stress at 25th% [Low] vs. 75th% [High]

Fixed Effects	Perceived Stress				Domain-specific Stress			
	Neighborhood SES % difference (95% CI) p-value		Race/Ethnicity % difference (95% CI) p-value		Neighborhood SES % difference (95% CI) p-value		Race/Ethnicity % difference (95% CI) p-value	
Salivary Cortisol	High n=76/608	Low n=49/392	NHW n=58/464	NHB n=60/480	High n=76/608	Low n=49/392	NHW n=58/464	NHB n=60/480
Baseline *(Time=1)*								
High (75th)	-11.6 (-34.2, 18.6) *0.63*	14.7 (-26.0, 77.7) *0.80*	-13.1 (-42.6, 31.8) *0.75*	-2.4 (-31.7, 39.4) *>0.99*	-4.7 (-29.5, 28.8) *0.96*	18.7 (-23.0, 83.1) *0.66*	-10.8 (-42.7, 38.6) *0.87*	14.5 (-15.5, 55.2) *0.58*
Low (25th)	[reference]	9.4 (-30.3, 71.7) *0.94*	-4.1 (-36.5, 44.9) *0.99*	[reference]	[reference]	17.3 (-27.6, 90.0) *0.76*	11.1 (-26.0, 66.6) *0.87*	[reference]
Rate of Response *(Time: 1-4)*								
High (75th)	-8.8 (-17.1, 0.2) *0.06*	**-18.5 (-28.1, -7.6)** ***0.001***	-7.0 (-18.9, 6.8) *0.45*	-7.8 (-18.2, 3.9) *0.25*	-5.5 (-13.7, 3.4) *0.32*	**-16.2 (-25.6, -5.5)** ***0.002***	-5.0 (-18.1, 10.3) *0.74*	-6.0 (-15.2, 4.1) *0.34*
Low (25th)	[reference]	**-15.8 (-26.6, -3.4)** ***0.01***	-0.3 (-13.0, 14.4) *>0.99*	[reference]	[reference]	**-14.7 (-26.2, -1.4)** ***0.03***	-2.2 (-14.7, 12.1) *0.96*	[reference]
Peak *(Time=4)**								
High (75th)	**-33.1 (-52.4, -6.0)** ***0.02***	-37.9 (-62.1, 1.6) *0.06*	-30.0 (-56.9, 13.8) *0.20*	-23.6 (-49.7, 16.1) *0.29*	-19.6 (-43.0, 13.3) *0.30*	-30.0 (-56.9, 13.7) *0.20*	-23.5 (-54.7, 29.4) *0.48*	-5.0 (-33.8, 36.3) *0.97*
Low (25th)	[reference]	-34.7 (-61.0, 9.1) *0.13*	-4.8 (-41.2, 54.1) *0.99*	[reference]	[reference]	-27.1 (-58.0, 26.5) *0.38*	-3.8 (-35.9, 68.0) *>0.99*	[reference]
Rate of Recovery *(Time: 4-8)*								
High (75th)	**5.3 (1.0, 9.9)** ***0.01***	**6.1 (0.4, 12.2)** ***0.03***	-2.8 (-8.4, 3.1) *0.51*	2.9 (-2.2, 8.3) *0.39*	**4.7 (0.6, 8.9)** ***0.02***	**6.6 (1.1, 12.4)** ***0.01***	-2.2 (-8.2, 4.2) *0.73*	2.1 (-2.1, 6.6) *0.52*
Low (25th)	[reference]	**8.4 (1.9, 15.4)** ***0.01***	-5.1 (-10.5, 0.7) *0.10*	[reference]	[reference]	6.2 (-0.5, 13.3) *0.08*	-5.4 (-10.7, 0.3) *0.07*	[reference]

Results show predicted estimates from piecewise LMM and post-hoc multiple comparison test, using Dunnett's adjustment. The components of the piecewise models were: 1) intercept reflecting either baseline at time 1 or peak at time 4, 2) rate of response (times from 1 to 4), and 3) rate of recovery (times from 4 to 8). Predicted estimates are presented as percent difference in cortisol values due to log-transformation of cortisol values. All models were adjusted for demographic characteristics: centered age, sex [reference=male], marital status [reference=married], and education level [reference ≥ college]. The model for interaction with neighborhood SES was adjusted for race/ethnicity [reference=NHB]; the model for interaction with race/ethnicity was adjusted for neighborhood SES [reference=high].

% differences reflect how groups differ in salivary cortisol concentrations compared to their reference group's baseline/peak or rate of response/recovery. Rate of response and recovery reflects percent change in the salivary cortisol between two collection times during the Trier Social Stress experiment. The time intervals were approximately uniform before the peak at time 3 (Intervals: 0-20 minutes, 20-30 minutes, and 30-45 minutes); the time intervals were uniform after the peak at time 3 (Intervals: 45-60 minutes, 60-75 minutes, 75-90 minutes, and 90-105 minutes). Negative percent difference for rate of response reflects smaller increase in cortisol; negative estimates for rate of recovery reflects larger decrease in cortisol.

* Estimates obtained from a separate model, where time was centered at the 4th time point.

Supplemental Table 2-6. Predicted mean values of Log-transformed Salivary Cortisol by Self-reported Stress at 25th (Low) vs. 75th (High) Percentiles and Neighborhood Socioeconomic Status or Race/Ethnicity

Predicted Values	Perceived Stress				Domain-specific Stress			
	Neighborhood SES Mean (SE)		Race/Ethnicity Mean (SE)		Neighborhood SES Mean (SE)		Race/Ethnicity Mean (SE)	
Cortisol Profile	High n=76/608	Low n=49/392	NHW n=58/464	NHB n=60/480	High n=76/608	Low n=49/392	NHW n=58/464	NHB n=60/480
Baseline *(Time=1)*								
High (75th)	-2.71 (0.16)	-2.45 (0.20)	-2.79 (0.14)	-2.67 (0.16)	-2.67 (0.16)	-2.45 (0.19)	-2.89 (0.16)	-2.64 (0.15)
Low (25th)	-2.59 (0.15)	-2.50 (0.21)	-2.69 (0.14)	-2.65 (0.16)	-2.62 (0.16)	-2.46 (0.22)	-2.67 (0.13)	-2.77 (0.16)
Rate of Response *(Time: 1-4)*								
High (75th)	0.17 (0.03)	0.06 (0.04)	0.14 (0.04)	0.13 (0.04)	0.18 (0.03)	0.06 (0.04)	0.16 (0.05)	0.15 (0.03)
Low (25th)	0.26 (0.03)	0.09 (0.05)	0.21 (0.04)	0.21 (0.04)	0.24 (0.03)	0.08 (0.05)	0.19 (0.04)	0.21 (0.04)
Peak *(Time=4)*								
High (75th)	-2.21 (0.17)	-2.28 (0.21)	-2.37 (0.16)	-2.28 (0.18)	-2.11 (0.17)	-2.25 (0.21)	-2.41 (0.18)	-2.20 (0.17)
Low (25th)	-1.80 (0.16)	-2.23 (0.22)	-2.06 (0.16)	-2.02 (0.18)	-1.90 (0.17)	-2.21 (0.24)	-2.11 (0.15)	-2.15 (0.18)
Rate of Recovery *(Time: 4-8)*								
High (75th)	-0.08 (0.01)	-0.08 (0.02)	-0.12 (0.02)	-0.06 (0.02)	-0.09 (0.01)	-0.07 (0.02)	-0.11 (0.02)	-0.07 (0.01)
Low (25th)	-0.14 (0.01)	-0.06 (0.02)	-0.14 (0.02)	-0.09 (0.02)	-0.13 (0.01)	-0.07 (0.02)	-0.15 (0.02)	-0.09 (0.02)

Results correspond to the Figure 2 and show predicted means of log-transformed cortisol at time 1 (baseline), time 4 (peak), and rate of change (time 1-time 4 and time 4-time 8), obtained from separate piecewise LMM with linear splines for time and post-estimation of marginal means using *Emmeans* R package. All models were adjusted for: mean-centered age, sex (reference=male), marital status (ref=married), and education level (reference=4-year college or higher). The model for interaction with neighborhood SES (reference=High) was adjusted for ethnic origin (reference=European American); the model for interaction with ethnic origin was adjusted for neighborhood SES (reference=High). Standard errors of the mean were estimated using Satterthwaite's degrees of freedom.

Supplemental Table 2-7. Salivary Cortisol at Baseline, Peak, and in Response and Recovery Rate during the Trier Social Stress Test by Interquartile Change in Perceived and Domain-specific Stress.

Fixed Effects Cortisol Profile Time 1-8	Model 1 % difference ¥ (95% CI)	p-value*	Model 2 % difference ¥ (95% CI)	p-value*	Model 3 % difference ¥ (95% CI)	p-value*	Model 4 % difference ¥ (95% CI)	p-value*	Model 5 % difference ¥ (95% CI)	p-value*
Perceived Stress Scale (PS: 25th vs. 75th percentile change)										
Baseline (Time=1)										
Intercept ‡	0.06 (0.05, 0.07)	--	0.07 (0.05, 0.10)	--	0.07 (0.05, 0.10)	--	0.07 (0.05, 0.10)	--	0.07 (0.05, 0.10)	--
<= 75th %	-2.7 (-20.8, 19.5)	0.79	-5.9 (-24.3, 17.0)	0.58	-11.1 (-28.3, 10.1)	0.27	-10.8 (-29.2, 12.4)	0.33	-11.4 (-29.8, 11.9)	0.30
*Rate** of Response (Time: 1-4)*										
Slope ‡‡	17.0 (12.1, 22.1)	--	17.0 (12.1, 22.1)	--	16.8 (11.9, 21.9)	--	16.6 (11.7, 21.7)	--	16.6 (11.7, 21.7)	--
<= 75th %	**-7.5 (-13.1, -1.4)**	**0.02**	**-7.5 (-13.1, -1.5)**	**0.02**	**-7.4 (-13.1, -1.4)**	**0.02**	**-8.4 (-14.0, -2.4)**	**0.01**	**-8.4 (-14.0, -2.5)**	**0.01**
Peak (Time=4)										
Intercept ‡	0.10 (0.09, 0.12)	--	0.12 (0.09, 0.16)	--	0.11 (0.08, 0.15)	--	0.11 (0.08, 0.17)	--	0.11 (0.07, 0.16)	--
<= 75th %	-22.9 (-40.2, -1.0)	0.05	**-25.4 (-42.9, -2.2)**	**0.03**	**-29.5 (-46.2, -7.5)**	**0.01**	**-31.4 (-48.2, -9.2)**	**0.01**	**-31.9 (-48.3, -10.2)**	**0.01**
*Rate** of Recovery (Time: 4-8)*										
Slope ‡‡	-9.2 (-11.0, -7.4)	--	-9.2 (-11.0, -7.4)	--	-9.2 (-10.9, -7.4)	--	-9.2 (-11.0, -7.3)	--	-9.4 (-14.0, -2.5)	--
<= 75th %	3.0 (-0.6, 6.8)	0.10	3.0 (-0.6, 6.8)	0.10	3.0 (-0.6, 6.8)	0.11	3.3 (-0.4, 7.1)	0.08	3.3 (-0.4, 7.2)	0.08
Domain-specific Stress Scale (CS: 25th vs. 75th percentile change)										
Baseline (Time=1)										
Intercept ‡	0.06 (0.05, 0.07)	--	0.07 (0.05, 0.10)	--	0.07 (0.05, 0.10)	--	0.08 (0.05, 0.11)	--	0.07 (0.05, 0.10)	--
<= 75th %	4.4 (-12.1, 24.1)	0.61	-2.1 (-20.7, 20.9)	0.84	-6.5 (-23.5, 14.2)	0.50	-1.1 (-21.1, 23.8)	0.92	-4.5 (-24.4, 20.5)	0.69
*Rate** of Response (Time: 1-4)*										
Slope ‡‡	18.1 (12.8, 23.6)	--	18.4 (13.1, 23.9)	--	18.1 (12.8, 23.6)	--	18.3 (13.0, 23.9)	--	18.3 (13.0, 23.9)	--
<= 75th %	-5.7 (-11.6, 0.6)	0.07	-5.5 (-11.4, 0.8)	0.08	-5.5 (-11.4, 0.7)	0.08	**-6.6 (-12.3, -0.5)**	**0.04**	**-6.6 (-12.3, -0.5)**	**0.04**
Peak (Time=4)										
Intercept ‡	0.10 (0.09, 0.12)	--	0.12 (0.09, 0.17)	--	0.12 (0.09, 0.16)	--	0.12 (0.08, 0.18)	--	0.11 (0.08, 0.17)	--
<= 75th %	-12.4 (-31.2, 11.7)	0.28	-17.4 (-36.7, 7.8)	0.16	-21.2 (-39.6, 2.8)	0.08	-19.4 (-39.1, 6.7)	0.13	-22.2 (-41.9, 4.3)	0.09
*Rate** of Recovery (Time: 4-8)*										
Slope ‡‡	-9.4 (-11.1, -7.8)	--	-9.8 (-11.4, -8.1)	--	-9.7 (-11.4, -8.0)	--	-9.8 (-11.5, -8.2)	--	-9.8 (-11.5, -8.2)	--
<= 75th %	**3.6 (0.5, 7.0)**	**0.03**	**3.7 (0.6, 7.0)**	**0.02**	**3.7 (0.6, 7.0)**	**0.02**	**4.2 (1.0, 7.5)**	**0.01**	**4.2 (1.0, 7.5)**	**0.01**
Variance Components	PS	DS	PS	DS	PS	CS	PS	CS	PS	CS
Within-person	0.06	0.05	0.06	0.06	0.06	0.07	0.07	0.07	0.07	0.07
Baseline	0.47	0.48	0.43	0.44	0.41	0.42	0.42	0.43	0.41	0.42
Peak	0.67	0.69	0.64	0.65	0.61	0.63	0.59	0.62	0.57	0.60
Increase	0.05	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.04	0.05
Decrease	0.005	0.007	0.005	0.004	0.005	0.004	0.004	0.004	0.004	0.004
Fit: AIC (DF)	785 (14)	785 (14)	778 (23)	778 (23)	764 (24)	766 (24)	756 (28)	758 (28)	753 (31)	755 (31)
N Obs./N Group	976/123		976/123		960/121		936/118		936/118	

Supplemental Table 2-8. Sensitivity analyses for unmeasured confounding using approximate E-value for continuous outcome

Outcome (Log mean cortisol)	Beta coefficient (SE) from MLM	Wald p-value	Sattertwaite-adjusted p-value	E-value estimate*	E-value for lower limit confidence interval
Perceived Stress Scale					
Baseline	-0.06 (0.10)	0.55	0.58	1.80	1
Rate of response (time 1-4)	**-0.08 (0.03)**	**0.02**	**0.02**	**2.01**	**1.38**
Peak	**-0.29 (0.12)**	**0.01**	**0.03**	**5.19**	**1.74**
Rate of recovery (time 4-8)	0.03 (0.01)	0.04	0.10	1.47	1.24
Domain-specific Stress Scale					
Baseline	-0.02 (0.10)	0.84	0.84	1.36	1
Rate of response (time 1-4)	-0.06 (0.03)	0.07	0.08	1.80	1.07
Peak	-0.19 (0.12)	0.11	0.16	3.41	1
Rate of recovery (time 4-8)	**0.04 (0.01)**	**0.01**	**0.02**	**1.58**	**1.37**

*E-value estimated using on-line calculator (https://www.evalue-calculator.com/evalue/). To estimate E-value, we assumed contrast of interest in exposure is 1 unit on a mean-centered exposure scale and used the estimated residual standard deviation (0.25). Beta estimates, standard errors, and p-values obtained from the model adjusted for centered age, race/ethnicity, neighborhood SES, sex, education and marital status.

E-value reflects the minimum amount of confounding needed to explain away the observed association. Higher E-value suggests a more robust estimate to unmeasured confounding. Specifically, E-value estimates the minimum strength of association on the risk ratio scale that unmeasured confounder(s) must have with the exposure and the outcome, conditional on the included covariates, to explain the observed exposure-outcome association (VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Annals of Internal Medicine. 2017; 167:268.).

Supplemental Table 2-9. Percent Differences in Salivary Cortisol by Interquartile Change in Self-reported Stress after Removing Outliers for the Outcome (1% on Both Ends of the Distribution) (n=966)

Fixed Effects	Model 1a		Model 2a	
Salivary Cortisol Profile: Time 1- 8	**Interquartile Change** $\leq 75^{th}$ vs. $\leq 25^{th}$		**Interquartile Change** $\leq 75^{th}$ vs. $\leq 25^{th}$	
	% difference (95% CI)	*P-value*	% difference (95% CI)	*P-value*
Perceived Stress (PS)				
Time 1: Baseline				
PS: ≤ 20 vs. ≤ 10	-6 (-24, 16)	*0.56*	-7 (-25, 16)	*0.53*
nSES: low vs. high	5 (-22, 41)	*0.74*	19 (-13, 62)	*0.27*
Race/ethnicity: NHW vs. NHB	-16 (-35, 8)	*0.17*	-4 (-27, 29)	*0.81*
Time 1-4: Rate of Response				
PS: ≤ 20 vs. ≤ 10	**-7 (-12, -1)**	***0.02***	**-6 (-11, -1)**	***0.03***
nSES: low vs. high	--	--	**-11 (-19, -3)**	***0.01***
Race/ethnicity: NHW vs. NHB	--	--	-2 (-10, 7)	*0.67*
Time 4: Peak				
PS: ≤ 20 vs. ≤ 10	**-25 (-42, -3)**	***0.03***	**-23 (-40, -1)**	***0.04***
nSES: low vs. high	5 (-22, 41)	*0.74*	-17 (-41, 17)	*0.28*
Race/ethnicity: NHW vs. NHB	-16 (-35, 8)	*0.17*	-9 (-34, 26)	*0.56*
Time 4-8: Rate of Recovery				
PS: ≤ 20 vs. ≤ 10	3 (-1, 7)	*0.10*	3 (-1, 6)	*0.16*
nSES: low vs. high	--	--	3 (-2, 6)	*0.26*
Race/ethnicity: NHW vs. NHB	--	--	**-5 (-9, -2)**	***0.01***
Domain-specific Stress (DS)	**Model 1b**		**Model 2b**	
Time 1: Baseline				
DS: ≤ 27 vs. ≤ 11	-1 (-20, 22)	*0.90*	-1 (-20, 23)	*0.95*
nSES: low vs. high	6 (-21, 42)	*0.69*	20 (-12, 63)	*0.25*
Race/ethnicity: NHW vs. NHB	-16 (-36, 9)	*0.18*	-4 (-28, 29)	*0.81*
Time 1-4: Rate of Response				
DS: ≤ 27 vs. ≤ 11	-6 (-11, 0.2)	*0.06*	-4 (-9, 2)	*0.16*
nSES: low vs. high	--	--	**-11 (-18, -3)**	***0.01***
Race/ethnicity: NHW vs. NHB	--	--	-3 (-11, 7)	*0.57*
Time 4: Peak				
DS: ≤ 27 vs. ≤ 11	-17 (-36, 7)	*0.15*	-12 (-32, 13)	*0.31*
nSES: low vs. high	6 (-21, 42)	*0.69*	-16 (-41, 19)	*0.32*
Race/ethnicity: NHW vs. NHB	-16 (-36, 9)	*0.18*	-11 (-36, 24)	*0.48*
Time 4-8: Rate of Recovery				
DS: ≤ 27 vs. ≤ 11	**4 (1, 7)**	***0.01***	3 (-1, 6)	*0.10*
nSES: low vs. high	--	--	2 (-2, 6)	*0.32*
Race/ethnicity: NHW vs. NHB	--	--	**-5 (-8, -1)**	***0.02***

Supplemental Table 2-10. Percent Differences in Salivary Cortisol by Interquartile Change in Self-reported Stress, after Removing 5 Participants with a Diagnosis of Diabetes, Based on Medical Records

Fixed Effects	**Model 1a**		**Model 2a**	
Salivary Cortisol Profile:	**Interquartile Change** $\leq 75^{th}$ vs. $\leq 25^{th}$		**Interquartile Change** $\leq 75^{th}$ vs. $\leq 25^{th}$	
Time 1- 8	% difference (95% CI)	*P-value*	% difference (95% CI)	*P-value*
Perceived Stress (PS)				
Time 1: Baseline				
PS: ≤ 20 vs. ≤ 10	-2 (-21, 22)	*0.84*	-3 (-22, 21)	*0.80*
nSES: low vs. high	10 (-19, 49)	*0.52*	26 (-9, 74)	*0.16*
Race/ethnicity: NHW vs. NHB	-20 (-39, 3)	*0.09*	-8 (-31, 24)	*0.59*
Time 1-4: Rate of Response				
PS: ≤ 20 vs. ≤ 10	**-9 (-14, -3)**	***0.01***	**-8 (-13, -2)**	***0.01***
nSES: low vs. high	--	--	**-13 (-21, -5)**	***0.002***
Race/ethnicity: NHW vs. NHB	--	--	-1 (-9, 9)	*0.91*
Time 4: Peak				
PS: ≤ 20 vs. ≤ 10	**-25 (-43, -1)**	***0.04***	-23 (-41, 0.3)	*0.05*
nSES: low vs. high	10 (-19, 49)	*0.52*	-18 (-43, 18)	*0.27*
Race/ethnicity: NHW vs. NHB	-20 (-39, 3)	*0.09*	-9 (-35, 27)	*0.57*
Time 4-8: Rate of Recovery				
PS: ≤ 20 vs. ≤ 10	3 (-1, 7)	*0.11*	3 (-1, 6)	*0.15*
nSES: low vs. high	--	--	3 (-1, 7)	*0.16*
Race/ethnicity: NHW vs. NHB	--	--	**-5 (-9, -2)**	***0.01***
Domain-specific Stress (CS)	**Model 1b**		**Model 2b**	
Time 1: Baseline				
DS: ≤ 27 vs. ≤ 11	1 (-18, 25)	*0.91*	2 (-18, 26)	*0.86*
nSES: low vs. high	11 (-18, 51)	*0.48*	27 (-8, 75)	*0.15*
Race/ethnicity: NHW vs. NHB	-20 (-39, 4)	*0.09*	-8 (-32, 25)	*0.60*
Time 1-4: Rate of Response				
DS: ≤ 27 vs. ≤ 11	**-7 (-12, -0.3)**	***0.04***	-5 (-10, 2)	*0.14*
nSES: low vs. high	--	--	**-13 (-20, -5)**	***0.002***
Race/ethnicity: NHW vs. NHB	--	--	-1 (-11, 8)	*0.76*
Time 4: Peak				
DS: ≤ 27 vs. ≤ 11	-17 (-37, 9)	*0.17*	-11 (-33, 16)	*0.37*
nSES: low vs. high	11 (-18, 51)	*0.48*	-17 (-42, 19)	*0.31*
Race/ethnicity: NHW vs. NHB	-20 (-39, 4)	*0.09*	-12 (-37, 25)	*0.48*
Time 4-8: Rate of Recovery				
DS: ≤ 27 vs. ≤ 11	**4 (1, 7)**	***0.02***	2 (-1, 6)	*0.15*
nSES: low vs. high	--	--	3 (-1, 7)	*0.20*
Race/ethnicity: NHW vs. NHB	--	--	**-5 (-9, -1)**	***0.01***

Supplemental Table 2-11. Interactions between Neighborhood SES or Race/Ethnicity with Self-reported Stress at 25th (Low) vs. 75th (High) Percentiles of Empirical Distribution.

	Perceived Stress				Domain-specific Stress			
Fixed Effects	**Neighborhood SES** % difference (95% CI) ‡ *p-value*		**Race/Ethnicity** % difference (95% CI) ‡ *p-value*		**Neighborhood SES** % difference (95% CI) ‡ *p-value*		**Race/Ethnicity** % difference (95% CI) ‡ *p-value*	
Cortisol Profile	High n=76/608	Low n=49/392	NHW n=58/464	NHB n=60/480	High n=76/608	Low n=49/392	NHW n=58/464	NHB n=60/480
Baseline *(Time=1)*								
High (75th)	-10 (-40, 35) 0.87	24 (-27, 108) 0.64	-17 (-47, 30) 0.62	-10 (-40, 34) 0.87	12 (-21, 60) 0.76	46 (-10, 135) 0.15	-12 (-46, 44) 0.86	12 (-21, 60) 0.77
Low (25th)	[reference]	15 (-28, 82) 0.82	-2 (-35, 48) >0.99	[reference]	[reference]	24 (-24, 100) 0.58	15 (-24, 73) 0.75	[reference]
Rate* of Response *(Time: 1-4)*								
High (75th)	-8 (-20, 5) 0.27	**-18 (-30, -5)** **0.01**	-10 (-22, 4) 0.22	-8 (-20, 4) 0.26	-7 (-17, 5) 0.35	**-18 (-29, -5)** **0.004**	-7 (-20, 10) 0.60	-7 (-17, 5) 0.34
Low (25th)	[reference]	**-15 (-26, -2)** **0.02**	-2 (-15, 12) 0.95	[reference]	[reference]	**-15 (-27, -2)** **0.03**	-6 (-17, 8) 0.61	[reference]
Peak *(Time=4)*								
High (75th)	-31 (-56, 10) 0.16	-33 (-63, 21) 0.25	-39 (-64, 2) 0.06	-31 (-56, 10) 0.15	-9 (-40, 38) 0.91	-20 (-54, 39) 0.64	-28 (-60, 27) 0.37	-9 (-40, 38) 0.91
Low (25th)	[reference]	-30 (-59, 19) 0.27	-9 (-43, 47) 0.94	[reference]	[reference]	-24 (-56, 33) 0.51	-3 (-40, 57) >0.99	[reference]
Rate* of Recovery *(Time: 4-8)*								
High (75th)	5 (-1, 11) 0.09	5 (-2, 12) 0.19	-3 (-8, 3) 0.51	3 (-2, 8) 0.39	3 (-2, 9) 0.32	4 (-2, 11) 0.25	-2.2 (-8.2, 4.2) 0.73	2.1 (-2.1, 6.6) 0.52
Low (25th)	[reference]	**7 (0.2, 14)** **0.04**	-5 (-10, 1) 0.10	[reference]	[reference]	5 (-2, 12) 0.26	-5.4 (-10.7, 0.3) 0.07	[reference]

Results show predicted estimates obtained from piecewise LMM with restricted maximum likelihood (REML) for the variance parameters and post-hoc multiple comparison tests, using Dunnett's adjustment. The separate components of each of the piecewise models were: 1) intercept reflecting either baseline at time 1 or peak at time 4, 2) rate of response (times from 1 to 4), and 3) rate of recovery (times from 4 to 8). Predicted estimates are presented as percent difference in cortisol values due to log-transformation of cortisol values. All models were adjusted for: mean-centered age, sex (reference=male), marital status (ref=married), and education level (reference=4-year college or higher). All models included simultaneous interactions with neighborhood SES and race/ethnicity.

‡ % differences reflect how groups differ in salivary cortisol concentrations compared to their reference group's baseline/peak or rate of response/recovery. Negative percent difference for rate of response indicate slower response due to smaller increase in cortisol per change in time between each collection, while negative percent difference for rate of recovery indicate faster recovery due to a more negative change in cortisol.

*Rate of response and recovery reflects percent change in the salivary cortisol between two collection times during the Trier Social Stress experiment. The time intervals were approximately uniform before the peak at time 3 (Intervals: 0-20 minutes, 20-30 minutes, and 30-45 minutes); the time intervals were uniform after the peak at time 3 (Intervals: 45-60 minutes, 60-75 minutes, 75-90 minutes, and 90-105 minutes).

Chapter 3 Vigilance, Stress Coping and Disparities in Metabolic Health Over the Life Course

3.1 Introduction

Exposure to stress and adversity has been proposed as one of the key mechanisms underlying health disparities. [5,20,100,101] In the public health literature, the stress-health link has been predominantly examined within the framework of stress adaptation, originally formulated by physiologists Cannon and Selye.[47,48] In this framework, the stress-health relationship is primarily mediated by the biological stress response, a neuroendocrine negative feedback system that maintains homeostasis in response to external stressors and threats.[47] Consistent with this seminal work, studies in humans and animals show that exposure to stress shapes the development of biological stress response through genes and environmentally-sensitive adaptations. [102–105] For example, repeated exposure to stressors reduces the sensitivity and efficiency of the biological stress response, resulting in neurobiological alterations that may lead to a wide range of adverse health outcomes (i.e., metabolic syndrome, heart disease, depression).[18,41,81,106,107]

However, these stress-related neurobiological processes work in tandem with complex cognitive and emotional processes that are also significantly impacted by chronic stress exposure. Growing research shows that chronic stress can induce substantial molecular and morphological changes in key brain regions (i.e., amygdala, prefrontal cortex), which process socially relevant events or emotional responses to threat, regulate executive function and memory.[108–112] Changes in these brain regions have been linked to the development of stress-

related cognitive tendencies (i.e., vigilance) that could themselves perpetuate a vicious stress-disease cycle.[33,113,114]

Stress-related cognitive tendencies such as vigilance and stress coping tap into a broader psychosocial construct of *emotion regulation*.[23,115–117] These cognitive tendencies function as adaptive mechanisms in response to short-term stress-evoking situations arising from the social environment.[23,115,118,119] For example, one may attempt to manage future stressors and broader social threats (i.e., experiences of racial discrimination) through the cognitive tendency of vigilance, often conceptualized in terms of an anticipatory orientation toward threat.[119] In contrast, the cognitive tendency of coping via suppression and avoidance (e.g., doing chores to think about a stressor less or saying "this isn't real") is a strategy that orients away from threat through cognitive and emotional disengagement.[120] Such stress-related cognitive tendencies may be effective for protecting health short-term and in certain situations (i.e., job-related vigilance), but over time and applied to a wide range of situations, these cognitions may become maladaptive and even harmful.[121,122] For example, vigilance after an exposure to violence or an acute illness, if not addressed, may develop into chronic anticipatory worrying and rumination; similarly, habitual avoidant coping may promote apathy and negative or invasive thoughts.[123–127]

A recently introduced model of stress, the Generalized Unsafety Theory of Stress (GUTS), centers cognitive tendencies as having a key role in regulating the biological stress response.[62,63] According to GUTS, while adaptive cognitive tendencies (e.g., active coping and reappraisal) help downregulate the neurobiological stress response, maladaptive cognitive tendencies (e.g., vigilance, avoidant coping or suppression) can perpetuate this neurobiological response even in the absence of external stressors or experiences.[63] In sum, the GUTS formulation emphasizes that cognitive and emotional processes play a key mediating role

between stress and disease by buffering or mitigating potential stress impact. However, they can also affect the neurobiological stress response independently from external stressors through a self-perpetuating process mediated by cognitive tendencies such as vigilance.[62]

A developing body of research has demonstrated mixed and sometimes unexpected results on how these cognitive tendencies may contribute to stress-related health disparities, especially with respect to variations by race and socioeconomic status (SES). For example, in the Exploring Health Disparities in Integrated Communities study (EHDIC), a sample of White and Black participants from an urban low-income area, LaVeist and colleagues found that Black participants reported higher vigilance, but lower depression, relative to White participants.[128] A recent study among Asian and Black Americans adults also found that experiences of vicarious racism or vigilance were positively associated with symptoms of depression and anxiety during the COVID-19 pandemic.[129]

Results further vary with respect to reported physical health outcomes. For example, using the EHDIC sample, Hines et al.,[130] found that both vigilance and race-related discrimination were associated with a lower odds of hypertension among White but not Black adults. However, in a sample of Chicago residents, vigilance was positively associated with hypertension among Black, but not White or Hispanic participants.[131] Another recent study found higher adaptive (i.e., reappraisal) and maladaptive (i.e., suppression) coping had respective inverse and positive associations with inflammation.[132] Several cross-sectional studies also report positive associations but only for specific subgroups: vigilance was associated with metabolic syndrome -- among participants with low childhood SES[133]; avoidant coping was associated with carotid intima media thickness (IMT) -- among older participants;[134] and expectations of racism and IMT -- among Black women.[135]

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Taken together, prior research shows that stress-related cognitive tendencies may interact with factors such as racial identity, SES, residing or growing up in disadvantaged environments, and experiencing unequal or hostile treatment due to racism-related expectations. Since cognitive tendencies may develop as a joint function of external circumstances, learned reactivity and innate tendencies, understanding how cognitive tendencies impact health may introduce a range of potentially modifiable points of intervention (i.e., social conditions, negative emotions, self-regulatory behaviors and stress coping).[136]

Present Study

Drawing on existing empirical research and motivated by the theoretical stress framework of GUTS, this study examines the longitudinal associations between stress-related cognitive tendencies - vigilance and adaptive or avoidant stress coping - and metabolic risk in the Healthy Aging in Neighborhoods of Diversity across the Lifespan Study (HANDLS), a racially and socioeconomically diverse cohort of community adults from Baltimore City, MD. Our second objective was to evaluate evidence for effect modification by lifecourse socioeconomic mobility and race and ethnicity.

We hypothesize that higher levels of vigilance or avoidant coping will be associated with worse metabolic health at baseline and longitudinally, while higher levels of adaptive coping may be protective. In addition, based on previous studies in this sample,[137–139] we expect that social factors including life course socioeconomic status and racial identity will modify the associations between cognitive tendencies and metabolic risk. Accordingly, we hypothesize that Black adults will report higher vigilance or stress coping and will have worse metabolic risk, compared to White participants; adjusting for SES indicators will reduce, but not eliminate these

associations. Likewise, we hypothesize that participants who experience lower life course SES will report higher vigilance and avoidant stress coping and will have worse metabolic risk relative to those with higher life course SES.

3.2 Methods

Study Population

The Healthy Aging in Neighborhoods of Diversity across the Lifespan (HANDLS) is a prospective cohort study of community adults residing in Baltimore, MD begun in 2004. Details on the study design and recruitment are described elsewhere.[140] Briefly, participants were selected from an area probability sample of thirteen Baltimore, MD census tracts, based on an intersection between age, sex, race, and neighborhood poverty status.[140] Non-Hispanic White (hereafter, White) and non-Hispanic Black or African American (hereafter, Black) adults were included into the study if they were between 30-64 years old at enrollment and able to give informed consent; individuals who were pregnant, being treated for cancer, or who had HIV/AIDS were ineligble.[140] The initial sample consisted of 1,042 Black adults and 493 White adults with a reported yearly income at or below 125% of the 2004 Federal poverty level for household size; the subsample with income above the poverty threshold (n=2,185) included 1,156 Black adults and 1,029 White adults. Of the total initial enrollment (n=3,720), about 73% (n=2,707) completed wave 1 laboratory and psychosocial examinations. Subsequent assessments were repeated every two to three years. This analysis uses data collected in wave 1, wave 3 (2009-2013, n=2,275) and wave 4 (2013-2017, n=2,174). Supplemental Tables 1 and 2 further details both cohort retention and sample sizes reflecting completeness of data on analytic variables.

HANDLS was approved by the Institutional Review Board (IRB) at the National Institute on Aging and all participants provided written informed consent. This analysis used only de-identified data and was determined to be exempt from human subjects' regulations by the University of Michigan IRB.

Measures

Stress-related Cognitive Tendencies: Vigilance and Reactive Stress Coping

Vigilance and stress coping were assessed via self-report using an audio-computer assisted self-interview (ACASI) at wave 1; stress coping was reassessed at wave 4. Vigilance was measured using a 6-item modified MacArthur Reactive Responding subscale, designed to assess self-regulatory tendencies to monitor contextual threat from the environment.[141] All items (e.g., "I am on guard in most situations," "I am always looking over my shoulder," or "I am pretty relaxed in most situations") were assessed on a 5-point Likert scale ranging from strongly agree to strongly disagree. Cronbach's α for the overall sample was α=0.58 [95% CI: 0.56, 0.60], and was appreciably lower for Black participants (α=0.46 [95% CI: 0.42, 0.49]) relative to White participants (α=0.71 [95% CI: 0.68, 0.73]). Items were reverse coded as needed and summed to create a total vigilance score, where the higher score corresponded higher vigilance (range: 6-30). Given the relatively low internal consistency of the vigilance scale in the sample, we further explored how median-dichotomized vigilance varied across participants' characteristics (Supplemental Table 4).

The multidimensional construct of psychosocial stress coping was measured by the Brief Cope scale.[142]Although the baseline scale included 28-items, the wave 4 assessment omitted 5 items, and thus the analysis of this measure was limited to the 23 items assessed at both wave 1 and 4. Participants evaluated the extent to which they usually use a behavior when "confronted

with a difficult or stressful event," with responses recorded on a 5-point scale ranging from "Not at all" to "A lot." Since the psychometric properties of the Brief Cope are typically sample-specific,[143] we used a combination of theory- and data-driven approaches to determine the subscales for analysis. We created two factors: *avoidant* and *adaptive* stress coping, using the hierarchical cluster analysis, where new clusters are formed when coefficients of reliability (alpha) and general factor saturation (beta) increase in the new cluster.[144] Avoidant coping (α=0.72 [95% CI: 0.71, 0.73]) included passive and suppressive tendencies (e.g., "I give up trying to deal with it" and "I refuse to believe that it has happened"). Adaptive coping (Cronbach's α=0.84 [95% CI: 0.83, 0.85]) included action-oriented tendencies (e.g., "I take action to try to make the situation better" or "I get emotional support from others"). Avoidant and adaptive coping were weakly correlated (baseline rho=0.01) (details are provided in Supplemental Table 3). We therefore modeled average scores for avoidant (range: 1-4) and adaptive (range: 1-3.8) coping simultaneously. This approach is consistent with the stress coping literature showing that although individuals may have a general tendency toward either adaptive or avoidant coping, both strategies may be used to cope with situational stressors.[23]

Metabolic risk

Metabolic risk was assessed using a metabolic status severity z-score (MetS-Z) based on five health indicators: waist circumference (WC, cm), HDL cholesterol (mg/dL), triglycerides (Tri, mg/dL), fasting glucose (mg/dL), and systolic blood pressure measurements (SBP, mmHg). These assessments were conducted at visit 1, 3 and 4. For systolic blood pressure, we used an average between right and left measurements, except for 45 participants at visit 1 and 27 participants at visit 3, for whom only one measurement was available. A small proportion of variable values (<1%) exceeded clinically plausible thresholds. After inspecting each outlier, we

set observations in fasting glucose, triglycerides, waist circumference > 99th percentile to the

value at the 99th percentile. In our sample, MetS-Z was strongly correlated with clinically

diagnosed diabetes and metabolic syndrome (Supplemental Table 5). Previous studies show that

MetS-Z severity was associated with a 3-fold increase in the odds of developing type 2 diabetes

over 36 year period among a younger sample, and an increased risk of coronary heart disease

among participants with type 2 diabetes.[145,146]MetS-Z was calculated using previously developed

and validated race- and sex-specific formulas among participants with a valid fasting status:[145,147]

- White Males: $-5.4559 + 0.0125 \times WC - 0.0251 \times HDL + 0.0047 \times SBP + 0.8244 \times ln(Tri) + 0.0106 \times Glucose$
- Black Males: $-6.3767 + 0.0232 \times WC - 0.0175 \times HDL + 0.0040 \times SBP + 0.5400 \times ln(Tri) + 0.0203 \times Glucose$
- White Females: $-7.2591 + 0.0254 \times WC - 0.0120 \times HDL + 0.0075 \times SBP + 0.5800 \times ln(Tri) + 0.0203 \times Glucose$
- Black Females: $-7.1913 + 0.0304 \times WC - 0.0095 \times HDL + 0.0054 \times SBP + 0.4455 \times ln(Tri) + 0.0225 \times Glucose$

Moderating variables: Race and Ethnicity and Lifecourse Socioeconomic Mobility

Race and ethnicity were self-reported. A 4-level life course indicator for *socioeconomic mobility*

was created from the cross-product of child and adult SES.[148]

For childhood SES, we followed a strategy developed using the Health and Retirement Study

that relies on retrospective recall to assess childhood SES.[149] The four indicators of childhood

environment, self-reported either at visit 1 or 4 (if any baseline indicators were missing) were:

maternal and paternal education (1=less than high school, 2=high school or diploma, 3=some

college or associate's degree, 4=4-year degree or above); at age 6 and 16, you were living

with/being raised by (0=don't know, 1=was raised by foster parents, grandparents or someone

else, 2=single (step)parents, 3=both (step)parents). To create the summary index of childhood

SES, we mean-standardized and then summed all the individual indicators with at least two non-

missing values, and then z-scored the composite score, where higher values reflect higher SES (range: -3.05, 2.89).

For adult SES, we used baseline indicators of annual adjusted household income (1= <125% of the 2004 federal poverty level, 2=income≥125%), education (1≤High School, 2=High School Diploma/GED, 3=Some college or associate's degree, 4=Bachelor's degree or above), house ownership (1=house owned/rented by friends/relatives, 2=rent, 3=own), and employment (1=Unemployed or disabled, 2=Student, homemaker or other, 3=Employed, 4=Retired or doesn't need/want job). To create the summary index of adult SES, we mean-standardized and then summed all the individual indicators with at least two non-missing values, and then z-scored the composite score, where higher values reflect higher SES (range: -2.05, 2.11). To create a 4-way cross-product indicator for socioeconomic mobility, we median dichotomized adult and childhood SES summaries to create high and low categories (Supplemental Table 6 for further details). The resulting categories of lifecourse SES were interpreted as: (1) stable high (high SES in childhood + high SES in adulthood), (2) persistently low (low SES in childhood + low SES in adulthood), (3) upwardly mobile (low SES in childhood + high SES in adulthood), and (4) downwardly mobile (high SES in childhood + low SES in adulthood).

Covariates

Information on the following sociodemographic factors was available at visit one: age (years), sex (male, female), and marital status (married, single, divorced/separated/widowed). Based on prior studies, these factors were explored as confounders for the associations between cognitive tendencies and metabolic health.[150,151] Health behaviors and related factors (i.e., depression status, and CVD medications) have been previously shown to be confounders and/or

mediators between stress and metabolic health; [152–154]their influence was assessed in sensitivity analyses. Indicators for substance use, including tobacco use (cigarette, pipes and cigars, coded as current vs. never/past)), illicit drug use (including opioids or stimulants, coded as current/past vs. never), and alcohol use (coded as current vs. never/past), were considered as both confounders and mediators. An indicator variable for CVD medications (any vs. none) was used to adjust for prescription medications taken for any of the following conditions: hypertension, heart disease, stroke, congestive heart failure, angina, hypercholesterolemia, and hypertriglyceridemia. An indicator variable for diabetes status was created based on self-reported diagnosis, diabetes medication use, or fasting glucose of >125 mg/dL. Finally, current depressive symptoms were measured with the 20-item Center for Epidemiologic Studies Depression Scale (CES-D), with positive items reverse-coded and then all items summed.

Statistical Analysis

 We fit linear mixed models (LMM) to estimate the longitudinal associations between the stress-related cognitive tendencies (vigilance and avoidant/adaptive coping) and MetS-Z across the three waves of study. Each LMM was fit with random intercepts and slopes, where each participant had a differing length of follow-up time. Linearity in continuous predictors was assessed using locally weighted smoothing functions. Temporal trends were modeled by including a variable for years of follow-up ($\beta_1 Time_{ij}$) natural spline for centered baseline age with three degrees of freedom($\beta_2 ns(Age)_{ij}$), and an interaction term between these two variables ($\beta_3 Time \; x \; ns(Age)_{ij}$), as shown by the equation below:

$$Y_{ij} = \beta_0 + \beta_1 Time_{ij} + \beta_2 ns(Age)_{ij} + \beta_3 Time \; x \; ns(Age)_{ij} + \beta_4 \; Cogntivie \; Tendencies_i + \beta_5^T X_i$$
$$+ \; b_{0i} + b_{1i} Time_{ij} + \varepsilon_{ij}$$

where $\beta_4 Cognitive\ Tendencies_i$ represents wave 1 vigilance or avoidant/adaptive coping

scores scaled by their interquartile range, yielding a comparison between the 75th and 25th

percentiles. Parameters β_0 through β_5 are the fixed effects associated with the intercept,

covariates, and interaction terms. Y_{ij} is the metabolic syndrome severity z-score calculated for

the ith subject at the jth time point, which assumes to differ from the population mean by a

subject effect, represented by b_{0i} and b_{1i} (random effects associated with the participant-specific

intercept and individual follow-up trajectories respectively), and a within-subject measurement

error (ε_{ij}). Mixed models are able to model missing at random data in level 1 outcomes, that is if,

conditional on observed data, missingness in outcome is unrelated to the probability of missing

values in covariates and outcomes or unknown random effects.[155] It is assumed that measurement

error and random effects are independently and interchangeably normally distributed; and are

also independent of each other. X_i is a vector of individual-level covariates that include sex, race,

socioeconomic mobility, marital status, and interactions between race x sex, sex x

socioeconomic mobility, and race x socioeconomic mobility. In the main analyses, our primary

predictors were cognitive tendencies, measured at wave 1 only. Separate models were fit for

vigilance and coping; for the latter, both avoidant and adaptive coping strategies were included

in the model simultaneously. In addition to allowing for individual metabolic health trajectories

over different durations of follow-up, we explored whether population metabolic health

trajectories differed by interquartile change in cognitive tendencies (i.e., time x cognitive

tendencies).

To explore the presence of effect modification by socioeconomic mobility and race,

multiplicative interaction terms were first added to separate fully adjusted LMM models. To

further explore the intersectional role of race and socioeconomic mobility, we also tested

interactions between cognitive tendency x race x socioeconomic mobility. Since the product term

time x coping and time x coping x race x socioeconomic mobility were statistically significant,

we also explored coping x time x socioeconomic mobility separately among White and Black

participants. A Wald test with a Kenward and Rogers[156] approximation for degrees of freedom

was used to test for significance of the interaction terms (R-package *pbkrtest,* version 0.5.1).

Including two- and three-way interactions with stress coping consistently showed model

improvement, however, this was not the case for any models with vigilance. To ease

interpretation of the multi-interaction models, we present these in a graphical format, illustrating

cognitive tendencies predicted at 25th and 75th percentiles by racial and socioeconomic mobility

groups, with covariates set to the mean or reference values.

All statistical analyses were performed in the R environment, version 4.0.5, and all p-

values refer to two-tailed tests at P < 0.05. All p-values were estimated with R-package *sjPlot*,

version 2.8.10, which uses conditional F-tests with Kenward-Roger approximation for the

degrees of freedom.[157]

Sensitivity Analysis

To test the robustness of our results, we conducted the following planned sensitivity analyses: (1)

we fit sequential models, additionally adjusting for a range of potential confounders or

mediators, including health behaviors (i.e., use of alcohol, drug and tobacco), CVD medications,

depressive symptoms; (2) diabetes diagnosis, as an indicator of more advanced metabolic

dysregulation, has been shown to impact cognition and serve as a significant source of stress

itself, thus modifying associations explored in this study.[158,159] Since about 26% of the baseline

sample had diabetes, we further fit fully-adjusted models to the subsamples, stratified by diabetes

status; (3) we repeated our primary analysis using the longitudinal (wave 1 and wave 4) measures of avoidant/adaptive coping; and (4) we used multiple imputation with chain equations to address concerns for bias associated with missing data in our exposure and covariates measured at visit 1. As illustrated by Supplemental Figure 1, the largest attrition (67%) occurred between baseline household sample and examination at visit 1, whereas new attrition at visit 3 and 4 comprised 33% and 23% of the total loss-to-follow-up. Supplemental Table 1-2 further offers details on the missingness for the main exposures and outcomes by key covariates and across all study visits. Imputation models for visit 1 exposures and covariates included outcome and correlates of exposure, covariates and missingness, determined based on prior knowledge and empirical examination of missing patterns in the data (Supplemental Table 1).[160]

3.3 Results

Table 1 shows baseline sample characteristics by race and socioeconomic mobility. Overall, Black and White participants were similar in terms of baseline age (mean: 48 years), sex, vigilance and avoidant coping scores; Black participants reported higher adaptive coping at the first visit. Compared to participants with high lifecourse SES or upward mobility, participants experiencing persistent poverty or downward mobility reported higher vigilance and avoidant coping and lower adaptive coping. These participants were younger and more likely to be non-married or identify as Black or African American; a larger percentage of these participants reported high depressive symptoms, current substance use, and a lack of health insurance.

We found inconsistent evidence for the association between cognitive tendencies and MetS-Z in the full sample. As shown in Table 2, change in interquartile range of vigilance score was not associated with MetS-Z at baseline or over the duration of follow-up. Table 3 shows that in fully adjusted models, comparing the 75th to 25th percentiles, avoidant and adaptive coping

were inversely associated with baseline MetS-Z ($\beta_{Avoidant}$=-0.11, 95% CI: -0.19, -0.04; $\beta_{Adaptive}$=-0.08, 95% CI: -0.15, -0.01); interactions with duration of follow-up suggested that these associations remained largely invariant over the study duration.

Concordant results across tables 2 and 3 demonstrated that metabolic health varied across racial and socioeconomic groups. On average, compared to Black adults with low lifecourse SES, Black participants experiencing downward mobility or White participants with low SES had significantly higher baseline MetS-Z. However, White adults who were upwardly mobile or had high life course SES had significantly lower average MetS-Z.

Effect modification by race and life course socioeconomic status

Associations between vigilance and MetS-Z did not significantly vary by indicators for race or socioeconomic mobility (Supplemental table 8). Supplemental table 9 illustrates associations between stress coping and expected MetS-Z by indicator for race and ethnicity (Model 1, coping x duration x race) or socioeconomic mobility (Model 2, coping x duration x SES). Results from model 1 demonstrate that White adults with low adaptive or avoidant coping had significantly higher baseline mean MetS-Z (β=1.05, 95% CI: 0.43, 1.68) relative to Black participants with similar levels of coping. However, higher levels of adaptive coping among White adults and higher avoidant coping among Black adults were associated with lower average baseline MetS-Z ($\beta_{adaptive}$=-0.39, 95% CI: -0.54, -0.24; $\beta_{avoidant}$=-0.18, 95% CI; -0.27, -0.08, respectively). Compared to Black adults with low stress coping, high avoidant coping was associated with an increase in MetS-Z for Black adults with each additional year of follow-up relative to White adults. Compared to participants with persistently low SES and low coping (Supplemental Table 9, Model 2), high avoidant coping was associated with significantly lower baseline MetS-Z

among those with low life course SES (β=-0.19, 95% CI: -0.31, -0.06), while high adaptive coping – among those with high life course SES (β=-0.21, 95 % CI: -0.41, -0.01).

The magnitude and direction of associations for the two subtypes of stress coping were generally concordant across race-stratified models (see Figure 1). Supplemental Table 10 shows that among Black adults with persistently low SES, reporting high vs. low avoidant coping was negatively associated with baseline MetS-Z (β=-0.29, 95 % CI: -0.44, -0.13); this was reversed for Black adults with high lifecourse SES (β=0.35, 95 % CI: 0.07, 0.62). Among White adults, compared to participants with low life course SES and low levels of coping, adults experiencing downward socioeconomic mobility had significantly higher average baseline MetS-Z if they reported low coping (β=2.09, 95 % CI: 0.55, 3.62), but lower MetS-Z if they reported higher adaptive coping (β=-0.51, 95 % CI: -0.91, -0.10). Over time, reporting high avoidant coping appeared to be protective for White adults with downward socioeconomic mobility or high SES, relative to Black adults with low lifecourse SES and low coping.

Sensitivity analyses

Results from our sensitivity analyses were generally consistent with the main findings, although some important variations existed. Adjustments for CVD medications or depressive symptoms further attenuated the coefficient for vigilance (Table 2, Models 4-5). The magnitude of the inverse association between avoidant coping and MetS-Z increased after adjusting for depressive symptoms (β=-0.17, 95% CI: -0.25, -0.09); the coefficient for adaptive coping was significantly attenuated (Table 3, Model 5). On the contrary, models further adjusted for substance use showed significant attenuation for avoidant coping (β=-0.06, 95% CI: -0.14, 0.01), but slight increase for adaptive coping (β=-0.09, 95% CI: -0.17, -0.01) (Table 3, Model 3). Supplemental Table 7 illustrates that adjusting for substance use and depressive symptoms

simultaneously further attenuated associations for both avoidant and adaptive coping ($\beta_{adaptive}$=-0.07, 95% CI: -0.15, 0.01; $\beta_{avoidant}$=-0.10, 95% CI; -0.18, -0.01), suggesting that the form of coping and their impact on metabolic health depended on the indicators for substance use and depression, but in the opposing directions. In models fitted to multiply imputed data (Supplemental Table 13, Model 1), or models using longitudinal measures of stress coping (Supplemental Table 11), we saw the significant inverse association with MetS-Z for adaptive and avoidant coping. In models stratified by diabetes status, cognitive tendencies were not significantly associated with MetS-Z (Supplemental Tables 12 and 13), while differences by demographic factors persisted only in the participants who did not have diabetes at baseline.

3.4 Discussion

The primary aim of this study was to examine whether the cognitive tendencies of vigilance and avoidant or adaptive coping were associated with metabolic risk longitudinally in a socioeconomically and racially diverse sample of urban adults. Overall, our results offer limited evidence that these cognitive tendencies are substantially related to metabolic risk.

Contrary to our expectations, we found that vigilance was not associated with metabolic risk overall, while both avoidant and adaptive stress coping showed modest inverse associations with metabolic risk. Following GUTS, the protective effect of higher engagement in any type of stress coping may be partially due to their role in maintaining the functionality of neurobiological stress response. The type of stress coping may depend on the changing contextual and individual factors.[20,161] For example, while adaptive coping that included task-oriented strategies (i.e., "take action to try to make the situation better" or "get help and advice from other people") may be relevant for addressing an actionable issue or a short-term stressor, avoidant coping that included such items as "refuse to believe that it has happened" or "use

alcohol or drugs to help me get through it" may help downregulate distress resulting from a non-controllable stressor. Sensitivity analyses helped clarify to what extent our findings may be attributed to cognitive aspects of stress coping, compared to engaging in actual behaviors such as drinking or experiencing depressive symptoms. In particular, we saw that substance use may partially explain the associations between avoidant coping and metabolic health and not adaptive coping; depressive symptoms may facilitate avoidant coping, while diminishing action-oriented coping with stress.

Second, we explored how associations between cognitive tendencies and metabolic risk varied as a function of race and socioeconomic mobility, a task the HANDLS cohort is uniquely positioned to undertake. We found some evidence for effect modification by race and socioeconomic mobility. For example, higher levels of adaptive coping were generally protective for metabolic health among White adults or those with high life course SES. However, high levels of avoidant coping were protective for Black adults or those experiencing persistent poverty. These differences generally reflected the observed sample differences in stress coping by socioeconomic mobility, where avoidant coping was more prevalent among participants with low SES, while participants with higher SES reported more adaptive coping strategies. Preferential use of avoidant coping among participants from disadvantaged backgrounds may further index disparities in high stress exposure but limited availability of psychosocial supports and other resources.[20,162] For example, in our sample, the protective role of higher levels of avoidant coping among Black participants with low SES might index emotional coping with pervasive experiences of discrimination, compounded by limited socioeconomic resources.[137,163] This is further consistent with a recent meta-analytic review that showed that avoidant coping promotes emotion regulation through "dissociation from internal and external reality."[164] Our

examinations of the intersection between race, SES and coping further illustrated that among Black participants, high avoidant coping was protective for those with persistently low SES, but harmful for those with high life course SES.

Our null findings regarding vigilance are at odds with a previous longitudinal study that showed positive association between worrying and the risk of nonfatal myocardial infarction and total coronary heart disease.[119] This might have been due in part to the challenges around ascertainment of the construct of vigilance through self-report. Following GUTS, vigilance may be hypothesized as a symptom of *internalized* threat due to past trauma and may be normalized or suppressed and unavailable for conscious recall, especially in the setting of a research study.[63] In addition, in our sample, the 6-item modified vigilance scale had an overall low reliability (Cronbach's alpha: 0.58), particularly among Black adults (alpha for White vs. Black adults: 0.71 vs. 0.46), which might have failed to reflect the underlying experiences of vigilance and sensitivity to threat relevant to Black adults in our sample.

Overall, our findings lend partial support of the GUTS stress theory that pose adaptive cognitive tendencies as buffers of stress impact, whereas maladaptive cognitions (i.e., vigilance or avoidant coping) – as elements that perpetuate chronic activation and subsequent dysfunction of neurobiological stress response and related physiological processes. Our results support buffering function of stress coping on metabolic risk. The illustrated parallels in protective functioning of adaptive and avoidant coping is generally consistent with the original stress and coping framework.[23] Although adaptive coping has been previously shown to be a preferred long-term strategy,[132] any form of coping may be beneficial and help dampen chronic stress impact on metabolic health.[23,165–167] The activation of a particular coping style may be context-specific[168]

and depend on the appraisal of the external demands and the availability of psychosocial resources.[23]

Our results further contribute to the evidence that disparities in metabolic health are socially stratified, where participants with low SES appeared to be most vulnerable.[154,169,170] Specifically, our results illustrate that on average, compared to upwardly mobile White adults, or those with high lifecourse SES, downwardly mobile participants and White participants with low lifecourse SES had substantially worse metabolic health at baseline and over the duration of the study. These differences were not explained by health or behavior risk factors or poor mental health but were further exacerbated by self-reports of low levels of any stress coping, particularly among those with downward socioeconomic mobility.

Limitations and strengths

The results of this study must be considered in the context of its limitations. First, since our primary analyses used measures of stress-related cognitive tendencies assessed at a single time point in adulthood, it is possible that individual components of metabolic risk and other measured or unmeasured factors (i.e., childhood trauma, family history, etc.) affected self-reports of cognitive tendencies. The use of a longitudinal measure of stress coping and additional adjustments in sensitivity analyses only partially addressed this concern. We also cannot discount that our findings with respect to stress coping might have been an artifact of empirical categorization of scale factors, whereas other combinations previously used in the current sample may have yielded different results.[171] Previous studies on physical and mental health disparities between Black and White adults often link vigilance or vigilant coping to experiences of discrimination and racism. Since our measures of vigilance or coping were not race- or SES-

specific, it is possible these failed to reflect chronic stressors or fundamental experiences relevant to the study sample.

The HANDLS sample is not representative of the U.S. population. However, its uniqueness may help detect socioeconomic heterogeneity within race groups, compared to what we see in nationally representative samples that may systematically miss important tail-end differences.[9,172] In our study, the unexpected difference in metabolic health between White and Black participants were mostly driven by differences in SES, which was possible to disentangle due to the sampling frame of HANDLS data.

Varying degrees of missingness were present in the study variables, thus posing potential concerns for selection bias due to non-response and informative attrition. Such differential sample selection, coupled with a large amount of missingness in the vigilance and coping scales, may have also negatively impacted the statistical power of the study. Examination of missing data patterns, usage of multilevel models and multiple imputation models for baseline exposures and covariates helped improve understanding of potential impact of bias.

The study's strengths included longitudinal design that afforded an opportunity to examine gradual changes in metabolic health over three study visits. The unique study design of HANDLS allowed for examination of health disparities by such key sociodemographic factors as race and lifecourse SES, whereas the latter was measured by combining indicators of childhood and adult SES. Finally, rich psychosocial and anthropometric data facilitated the use of a robust set of measured covariates, and an assessment of the metabolic syndrome severity z-score, a race- and gender-specific predictor of cardiometabolic risk.

In conclusion, this study demonstrated that socioeconomic disadvantage across the life course negatively affects metabolic health of both White and Black adults. The findings in this

study offered insights into how social processes that contribute toward these health disparities

may be further compounded by the absence or function of stress-related adaptations such as

cognitive tendencies.

Table 3-1. Baseline Sample Characteristics in a Full Sample and by Race and Ethnicity or Socioeconomic Mobility (col %)

	Full Sample	Racial Identity			Socioeconomic Mobility				
		White	Black	P-value	Stable Low	Downward	Upward	Stable High	P-value
	(n=3,720)	(n=1,522)	(n=2,198)		(n=1,103)	(n=605)	(n=947)	(n=1,002)	
Age in years (mean (SD))	48.27 (9.36)	48.34 (9.42)	48.22 (9.32)	0.716	47.94 (9.24)	46.97 (8.64)	49.42 (9.62)	48.24 (9.54)	<0.001
Black Adults, %	2198 (59.1)	--	--	--	751 (68.1)	383 (63.3)	616 (65.0)	439 (43.8)	<0.001
Below Poverty,[1] %	1535 (41.3)	493 (32.4)	1042 (47.4)	<0.001	821 (74.4)	443 (73.2)	124 (13.1)	121 (12.1)	<0.001
Female, %	2035 (54.7)	834 (54.8)	1201 (54.6)	0.952	633 (57.4)	300 (49.6)	528 (55.8)	540 (53.9)	0.016
Married, %	1690 (45.4)	812 (56.3)	878 (40.2)	<0.001	406 (36.9)	208 (34.4)	542 (57.4)	534 (54.5)	<0.001
Health Insurance (% No)	1213 (32.6)	441 (30.6)	772 (35.3)	<0.001	471 (42.8)	272 (45.0)	262 (27.8)	208 (21.2)	<0.001
Health & Behavior									
Current Alcohol (% Yes)	1490 (40.1)	654 (59.9)	836 (56.1)	0.005	401 (53.1)	243 (60.1)	380 (56.2)	446 (62.2)	0.003
Current Tobacco (% Yes)[2]	1291 (34.7)	526 (47.8)	765 (51.0)	0.009	493 (66.0)	247 (60.5)	262 (38.4)	264 (36.5)	<0.001
Current/Past Drugs (% Yes)[3]	697 (18.7)	233 (21.2)	464 (30.9)	<0.001	274 (36.6)	147 (36.2)	139 (20.3)	128 (17.7)	<0.001
CVD medications[4] (% Yes)	955 (25.7)	374 (33.1)	581 (37.5)	0.003	285 (36.8)	121 (28.6)	273 (39.1)	259 (34.9)	0.003
Diabetes[5] (% Yes)	481 (12.9)	193 (16.6)	288 (18.1)	0.007	142 (17.4)	84 (19.3)	129 (18.5)	117 (15.3)	0.336
CES-D[6] (median [IQR])	13 [6, 22]	13 [6, 24]	13 [6, 21]	0.272	17 [9, 27]	16 [8, 25]	10 [5, 18]	9 [4, 17]	<0.001
Cognitive Tendencies (mean (SD))									
Vigilance	17.61 (3.97)	17.48 (4.43)	17.70 (3.59)	0.194	18.29 (3.76)	18.17 (3.91)	17.22 (3.63)	16.83 (4.29)	<0.001
Stress Coping									
Adaptive (wave 1)	2.72 (0.64)	2.68 (0.63)	2.75 (0.64)	0.008	2.56 (0.64)	2.59 (0.65)	2.79 (0.62)	2.90 (0.59)	<0.001
Adaptive (wave 4)	2.48 (0.71)	2.52 (0.68)	2.45 (0.73)	0.047	2.30 (0.72)	2.36 (0.68)	2.50 (0.69)	2.69 (0.68)	<0.001
Avoidant (wave 1)	1.87 (0.50)	1.87 (0.47)	1.86 (0.52)	0.632	1.98 (0.54)	1.90 (0.55)	1.81 (0.48)	1.78 (0.43)	<0.001
Avoidant (wave 4)	1.64 (0.45)	1.68 (0.45)	1.61 (0.45)	0.003	1.73 (0.50)	1.67 (0.49)	1.59 (0.42)	1.57 (0.40)	<0.001
MetS-Z (mean (SD))[7]									
wave 1	0.28 (1.23)	0.46 (1.21)	0.14 (1.22)	<0.001	0.23 (1.26)	0.32 (1.40)	0.30 (1.15)	0.27 (1.16)	0.618
wave 2	0.33 (1.22)	0.42 (1.16)	0.27 (1.26)	0.009	0.32 (1.28)	0.42 (1.33)	0.36 (1.18)	0.28 (1.15)	0.364
wave 3	0.34 (1.21)	0.43 (1.10)	0.29 (1.28)	0.012	0.33 (1.30)	0.40 (1.42)	0.40 (1.14)	0.28 (1.03)	0.367

1. 125% Poverty Level for size-adjusted annual household income, calculated based on 2004 cut-off values.
2. Tobacco use includes self-reported smoking cigarettes, cigars or pipes.
3. Drugs include any reports of current or past use of stimulants or opioids.
4. CVD prescription medications included self-reported current medication use for the following conditions: hypertension, heart disease, stroke, congestive heart failure, angina, hypercholesterolemia, and hypertriglyceridemia.
5. Diabetes status was ascertained based on self-reported history of diagnosis, prescription medications for diabetes mellitus and/or having a fasting serum glucose of >125 mg/dL.
6. 20-item Center for Epidemiologic Studies Depression Scale (CES-D)
7. MetS-Z is metabolic syndrome severity z-score is a sex- and race-specific indicator of metabolic syndrome, calculated based on the formulae developed using a nationally representative U.S. population sample; scores were calculated among participants reporting fasting prior to blood collection.
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Table 3-2. Longitudinal associations between vigilance and metabolic risk severity z-score (MetS-Z) across median follow-up time of 4 [IQR=6.21] years

Fixed Effects	Model 1 Mean (95% CI)	P	Model 2 Mean (95% CI)	P	Model 3 Mean (95% CI)	P	Model 4 Mean (95% CI)	P	Model 5 Mean (95% CI)	P
Intercept	-0.07 (-0.42 – 0.28)	0.686	0.05 (-0.30 – 0.40)	0.784	0.23 (-0.14 – 0.60)	0.224	0.01 (-0.34 – 0.36)	0.952	0.05 (-0.31 – 0.40)	0.805
Vigilance (IQR)	0.03 (-0.04 – 0.10)	0.370	0.01 (-0.05 – 0.08)	0.736	0.03 (-0.04 – 0.09)	0.466	-0.01 (-0.08 – 0.05)	0.647	-0.01 (-0.08 – 0.06)	0.796
Duration	0.02 (-0.02 – 0.06)	0.297	0.02 (-0.02 – 0.06)	0.272	0.02 (-0.02 – 0.06)	0.255	0.02 (-0.02 – 0.06)	0.256	0.02 (-0.02 – 0.06)	0.272
Vigilance x duration	0.00 (-0.00 – 0.01)	0.229	0.00 (-0.00 – 0.01)	0.247	0.00 (-0.00 – 0.01)	0.215	0.00 (-0.00 – 0.01)	0.246	0.00 (-0.00 – 0.01)	0.253
Downward SM*	0.18 (0.03 – 0.33)	**0.020**	0.24 (0.01 – 0.47)	**0.044**	0.16 (-0.08 – 0.41)	0.182	0.24 (0.01 – 0.47)	**0.043**	0.25 (0.01 – 0.49)	**0.038**
Upward SM*	0.03 (-0.10 – 0.16)	0.681	0.00 (-0.19 – 0.19)	0.988	-0.11 (-0.31 – 0.09)	0.288	-0.03 (-0.21 – 0.16)	0.769	0.03 (-0.17 – 0.22)	0.778
Stable high SM*	-0.05 (-0.18 – 0.08)	0.426	0.08 (-0.13 – 0.29)	0.446	-0.01 (-0.23 – 0.21)	0.926	0.12 (-0.09 – 0.33)	0.252	0.10 (-0.11 – 0.32)	0.338
White adults	0.27 (0.17 – 0.37)	**<0.001**	0.40 (0.20 – 0.60)	**<0.001**	0.40 (0.19 – 0.61)	**<0.001**	0.55 (0.35 – 0.75)	**<0.001**	0.38 (0.18 – 0.58)	**<0.001**
Downward SM* x White adults	--		-0.06 (-0.37 – 0.25)	0.696	-0.02 (-0.34 – 0.31)	0.924	-0.08 (-0.39 – 0.22)	0.595	-0.05 (-0.36 – 0.27)	0.776
Upward SM* x White adults	--		-0.29 (-0.55 – -0.02)	**0.037**	-0.28 (-0.55 – 0.00)	0.052	-0.37 (-0.63 – -0.10)	**0.007**	-0.28 (-0.55 – -0.01)	**0.040**
Stable high SM* x White adults	--		-0.65 (-0.91 – -0.39)	**<0.001**	-0.58 (-0.85 – -0.31)	**<0.001**	-0.71 (-0.97 – -0.45)	**<0.001**	-0.63 (-0.89 – -0.36)	**<0.001**
σ^2	0.33		0.33		0.33		0.33		0.33	
$\tau_{00\,(id)}$	1.16		1.13		1.07		0.98		1.13	
$\tau_{11\,(id\,time)}$	0.00		0.00		0.00		0.00		0.00	
N Groups/N Obs.	2136/4797		2136/4797		1931/4343		2000/4491		2100/4723	
Marginal R^2 / Conditional R^2	0.042 / 0.786		0.063 / 0.786		0.080 / 0.778		0.130 / 0.778		0.062 / 0.785	

Results show estimates obtained from linear mixed effects models (LMM) with random intercepts and slopes and restricted maximum likelihood (REML) for the variance parameters. P-values were calculated using conditional F-test with Kenward-Roger approximation for the denominator degrees of freedom. P-values < 0.05 are bolded.

*Socioeconomic Mobility: Stable Low= Low childhood and adult SES or stable low; Downward= High childhood and Low adult SES or downwardly mobile; Upward=Low childhood and High adult SES or upwardly mobile; Stable High=High child and adult SES or stable high.

Model 1: interquartile change in vigilance, duration of follow-up, natural spline of centered baseline age with 3 degrees of freedom, interaction between spline for age and duration of follow-up, vigilance x duration of follow-up, sex (ref: women), marital status (ref: married/partnered), socioeconomic mobility (ref: stable low), race (ref: black).

Model 2: M1 + interactions between race and social mobility, race and sex, sex and socioeconomic mobility,

Model 3: M2 + alcohol, tobacco, and drug use

Model 4: M2 + use of prescription medications for cardiovascular conditions, including hypertension, heart disease, etc.

Model 5: M2 + depressive symptoms (CES-D)

Table 3-3. Longitudinal associations between stress coping and metabolic risk severity z-score across median follow-up time of 4 [IQR=6.21] years.

Fixed Effects	Model 1 Mean (95% CI)	P	Model 2 Mean (95% CI)	P	Model 3 Mean (95% CI)	P	Model 4 Mean (95% CI)	P	Model 5 Mean (95% CI)	P
Intercept	0.67 (0.28 – 1.05)	**0.001**	0.67 (0.28 – 1.07)	**0.001**	0.77 (0.36 – 1.19)	**<0.001**	0.47 (0.08 – 0.85)	**0.018**	0.60 (0.20 – 0.99)	**0.003**
Coping (IQR)*										
Avoidant	-0.12 (-0.19 – -0.04)	**0.002**	-0.12 (-0.19 – -0.04)	**0.002**	-0.06 (-0.14 – 0.01)	0.110	-0.08 (-0.15 – -0.01)	**0.027**	-0.17 (-0.25 – -0.09)	**<0.001**
Adaptive	-0.10 (-0.17 – -0.02)	**0.012**	-0.08 (-0.16 – -0.01)	**0.032**	-0.09 (-0.17 – -0.01)	**0.024**	-0.09 (-0.16 – -0.02)	**0.017**	-0.05 (-0.13 – 0.03)	0.185
Duration	-0.00 (-0.04 – 0.04)	0.943	-0.00 (-0.04 – 0.04)	0.953	0.01 (-0.03 – 0.05)	0.682	0.03 (0.01 – 0.06)	**0.005**	-0.00 (-0.04 – 0.04)	0.984
Avoidant x duration	0.01 (0.00 – 0.02)	**0.041**	0.01 (0.00 – 0.02)	**0.037**	0.01 (-0.00 – 0.01)	0.101	0.00 (-0.00 – 0.01)	0.256	0.01 (0.00 – 0.02)	**0.044**
Adaptive x duration	0.01 (-0.00 – 0.01)	0.229	0.00 (-0.00 – 0.01)	0.239	0.00 (-0.00 – 0.01)	0.366	0.00 (-0.01 – 0.01)	0.533	0.00 (-0.00 – 0.01)	0.259
Socioeconomic Mobility (SM)**										
Downward	0.18 (0.03 – 0.33)	**0.019**	0.22 (-0.00 – 0.45)	0.055	0.16 (-0.08 – 0.40)	0.187	0.23 (-0.00 – 0.46)	0.053	0.24 (0.00 – 0.47)	**0.046**
Upward	0.03 (-0.10 – 0.16)	0.670	0.01 (-0.18 – 0.20)	0.939	-0.09 (-0.29 – 0.11)	0.380	-0.02 (-0.20 – 0.17)	0.847	0.04 (-0.16 – 0.23)	0.715
Stable high	-0.06 (-0.20 – 0.07)	0.349	0.07 (-0.14 – 0.27)	0.526	-0.01 (-0.23 – 0.21)	0.941	0.10 (-0.11 – 0.31)	0.342	0.09 (-0.12 – 0.30)	0.404
White adults	0.26 (0.16 – 0.36)	**<0.001**	0.39 (0.19 – 0.59)	**<0.001**	0.41 (0.20 – 0.61)	**<0.001**	0.39 (0.18 – 0.59)	**<0.001**	0.36 (0.16 – 0.57)	**<0.001**
Downward SM x White adults	--		-0.04 (-0.35 – 0.27)	0.804	-0.00 (-0.32 – 0.31)	0.977	-0.06 (-0.36 – 0.24)	0.694	-0.02 (-0.34 – 0.29)	0.889
Upward SM x White adults	--		-0.30 (-0.56 – -0.03)	**0.028**	-0.30 (-0.57 – -0.02)	**0.033**	-0.36 (-0.62 – -0.10)	**0.007**	-0.29 (-0.55 – -0.02)	**0.035**
Stable high SM x White adults	--		-0.65 (-0.91 – -0.39)	**<0.001**	-0.60 (-0.87 – -0.33)	**<0.001**	-0.69 (-0.95 – -0.44)	**<0.001**	-0.62 (-0.88 – -0.36)	**<0.001**
σ^2	0.32		0.32		0.33		0.33		0.33	
$\tau_{00 \, (id)}$	1.15		1.12		1.06		0.97		1.12	
$\tau_{11 \, (id \, time)}$	0.00		0.00		0.00		0.00		0.00	
N Groups/N Obs.	2156/4843		2156/4843		1950/4387		2019/4535		2119/4767	
Marginal R^2 / Conditional R^2	0.045 / 0.787		0.066 / 0.787		0.081 / 0.779		0.134 / 0.780		0.068 / 0.786	

Results show estimates obtained from two sets of linear mixed effects models (LMM) with random intercepts and slopes and restricted maximum likelihood (REML) for the variance parameters. values were calculated using conditional F-test with Kenward-Roger approximation for the denominator degrees of freedom. P-values < 0.05 are bolded. *Adaptive and avoidant coping factors w modelled simultaneously. **Socioeconomic Mobility: Stable Low= Low childhood and adult SES or stable low; Downward= High childhood and Low adult SES or downwardly mobile; Upward=Low childhood and High adult SES or upwardly mobile; Stable High=High child and adult SES or stable high.
Model 1: interquartile change in adaptive/avoidant coping, duration of follow-up, natural spline of centered baseline age with 3 degrees of freedom, spline for age x duration of follow-up, coping duration of follow-up (Wald F-stat=2.89, p-value=0.06, Kenward-Roger approximation), sex (ref: women), marital status (ref: married/partnered), socioeconomic mobility (ref: stable low), race black). Model 2: M1 + interactions between race and social mobility, race and sex, sex and socioeconomic mobility. Model 3: M2 + alcohol, tobacco, and drug use Model 4: M2 + use of prescrip medications for cardiovascular conditions, including hypertension, heart disease, etc. Model 5: M2 + depressive symptoms (CES-D)

Figure 3-1. Predicted metabolic syndrome severity z-scores, comparing percentiles of stress coping
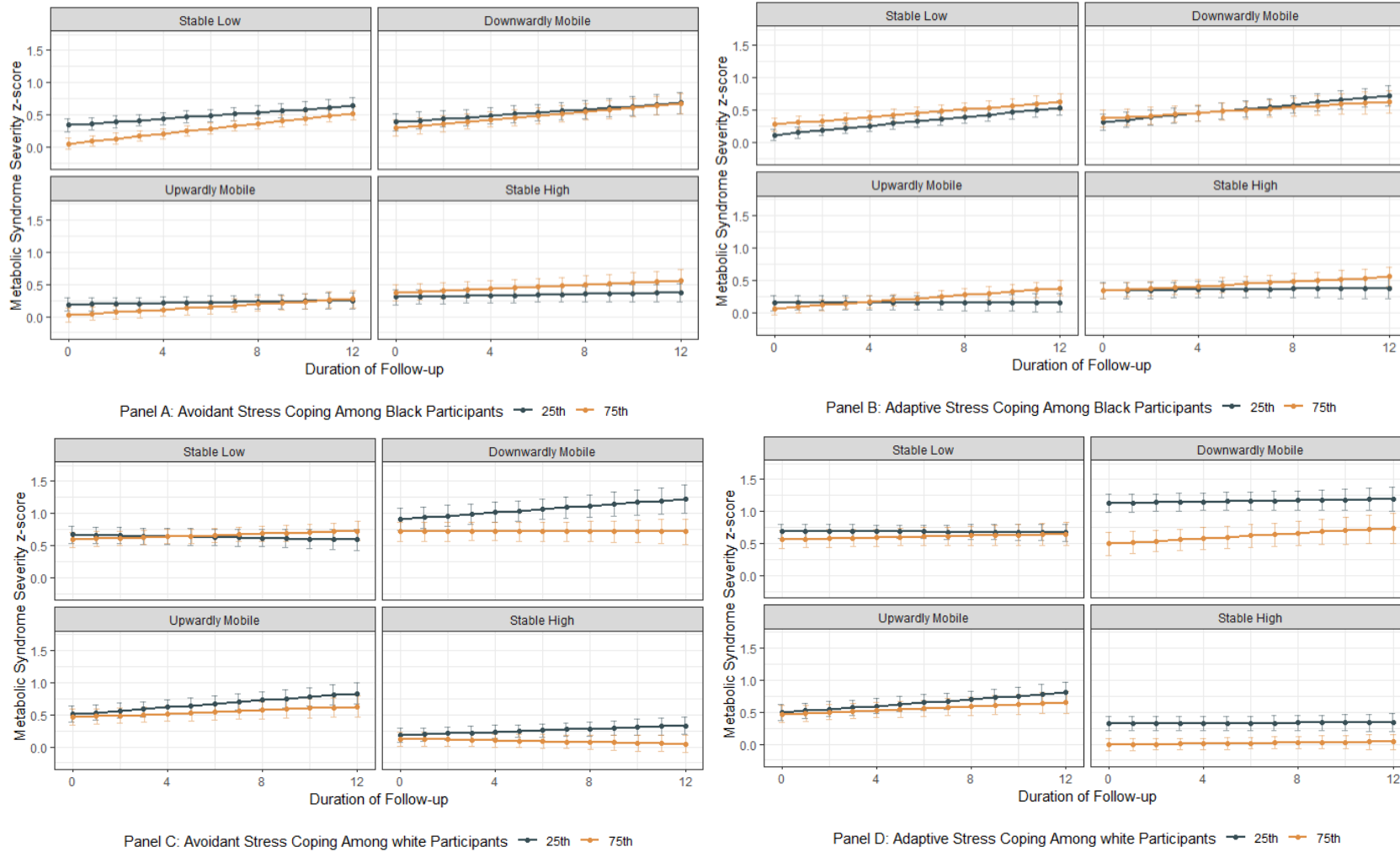
Predicted metabolic syndrome severity z-scores, comparing percentiles of avoidant stress coping (Panels A and B) and adaptive stress coping (Panels B and D) at 75th vs. 25th percentiles (orange vs. dark blue) by socioeconomic mobility (4 quadrants, starting from top left: Stable Low, Downwardly Mobile, Stable High, Upwardly Mobile) and duration of follow-up among White participants (Panel C and D) and Black participants (Panel A and B)). Predicted values were calculated by a post-estimation of marginal means, using values obtained from the linear mixed models. The 25th and 75th percentiles correspond to scores 2.3 and 3.2 for adaptive coping and 1.5 and 2.2 for avoidant coping. All models include time (indexed by study duration), natural spline for centered age with 3 degrees of freedom, age x time, sex (ref: female), sex x socioeconomic mobility, and sex x time. See Supplemental Table 10 for concordant estimates.

Supplemental Table 3-1. Participant characteristics by missingness in vigilance and stress coping at visit 1 (v1) **

	Overall	Vigilance			Stress Coping		
	n=3720	Non-missing, n=2265	Missing, n=1455	P-value	Non-missing, n=2285	Missing, n=1435	P-value
Age in years (mean (SD))	48.27 (9.36)	48.47 (9.19)	47.95 (9.61)	0.097	48.49 (9.19)	47.91 (9.60)	0.066
Black adults (%)	2198 (59.1)	1302 (57.5)	896 (61.6)	**0.014**	1314 (57.5)	884 (61.6)	**0.015**
Socioeconomic mobility (%)				0.174			0.13
Stable low	1103 (29.7)	668 (29.5)	435 (29.9)		676 (29.6)	427 (29.8)	
Downward mobility	605 (16.3)	359 (15.8)	246 (16.9)		360 (15.8)	245 (17.1)	
Upward mobility	947 (25.5)	570 (25.2)	377 (25.9)		575 (25.2)	372 (25.9)	
Stable high	1002 (26.9)	636 (28.1)	366 (25.2)		642 (28.1)	360 (25.1)	
Male (%)	1685 (45.3)	982 (43.4)	703 (48.3)	**0.003**	990 (43.3)	695 (48.4)	**0.003**
Married (% Yes)	1690 (45.4)	1016 (44.9)	674 (46.3)	0.430	1027 (44.9)	663 (46.2)	0.499
Health insurance (%)				0.262			0.196
No	1213 (32.6)	716 (31.6)	497 (34.2)		720 (31.5)	493 (34.4)	
Yes	2415 (64.9)	1491 (65.8)	924 (63.5)		1507 (66.0)	908 (63.3)	
Missing	92 (2.5)	58 (2.6)	34 (2.3)		58 (2.5)	34 (2.4)	
CVD medications (%)[2]				0.057			**0.035**
No	1723 (46.3)	1383 (61.1)	340 (23.4)		1397 (61.1)	326 (22.7)	
Yes	955 (25.7)	736 (32.5)	219 (15.1)		741 (32.4)	214 (14.9)	
Alcohol use (%)				**0.001**			**0.014**
Never/past	1091 (29.3)	838 (37.0)	253 (17.4)		849 (37.2)	242 (16.9)	
Current	1490 (40.1)	1211 (53.5)	279 (19.2)		1219 (53.3)	271 (18.9)	
Tobacco use (%)[1]				0.310			0.331
Never/past	1310 (35.2)	1052 (46.4)	258 (17.7)		1061 (46.4)	249 (17.4)	
Current	1291 (34.7)	1015 (44.8)	276 (19.0)		1025 (44.9)	266 (18.5)	
Use of stimulants or opioids (%)				0.076			0.074
Never	1903 (51.2)	1494 (66.0)	409 (28.1)		1508 (66.0)	395 (27.5)	
Past/current	697 (18.7)	570 (25.2)	127 (8.7)		575 (25.2)	122 (8.5)	
CES-D (median [IQR])[3]	13.00 [6.00, 22.00]	12.00 [6.00, 21.00]	15.00 [8.00, 24.00]	**<0.001**	12.00 [6.00, 21.00]	15.00 [8.00, 24.00]	**<0.001**
Died (%)	642 (17.3)	394 (17.4)	248 (17.0)	0.817	397 (17.4)	245 (17.1)	0.848
Fasted v1 (% Yes)	2678 (72.0)	2128 (94.0)	550 (37.8)	**<0.001**	2146 (93.9)	532 (37.1)	**<0.001**
Diabetes status (%)[4]				**0.033**			**0.029**
No diagnosis	1786 (48.0)	1444 (63.8)	342 (23.5)		1458 (63.8)	328 (22.9)	
Pre-diabetes	489 (13.1)	388 (17.1)	101 (6.9)		389 (17.0)	100 (7.0)	
Diabetes	481 (12.9)	363 (16.0)	118 (8.1)		367 (16.1)	114 (7.9)	
Vigilance (mean (SD))	17.61 (3.97)	17.61 (3.97)	--	--	17.61 (3.97)	--	--
Adaptive coping (mean (SD))	2.72 (0.64)	2.72 (0.64)	2.62 (0.70)	0.472	2.72 (0.64)	--	--
Avoidant coping (mean (SD))	1.87 (0.50)	1.87 (0.50)	1.82 (0.53)	0.685	1.87 (0.50)	--	--
Fasting MetS-Z v1 (mean (SD))[5]	0.28 (1.23)	0.25 (1.24)	0.38 (1.18)	0.054	0.25 (1.24)	0.39 (1.19)	**0.027**
Fasting MetS-Z v3 (mean (SD))	0.33 (1.22)	0.29 (1.19)	0.43 (1.31)	**0.032**	0.29 (1.18)	0.44 (1.31)	**0.012**
Fasting MetS-Z v4 (mean (SD))	0.34 (1.21)	0.32 (1.19)	0.40 (1.29)	0.241	0.32 (1.19)	0.41 (1.30)	0.164

1. Tobacco use includes self-reported smoking cigarettes, cigars or pipes.

2. CVD prescription medications included self-reported current medication use for the following conditions: hypertension, heart disease, stroke, congestive heart failure, angina, hypercholesterolemia, and hypertriglyceridemia.

3. 20-item Center for Epidemiologic Studies Depression Scale.

4. Diabetes status was ascertained based on self-reported history of diagnosis, prescription medications for diabetes mellitus and/or having a fasting serum glucose of >125 mg/dL.

5. MetS-Z is metabolic syndrome severity z-score.

Supplemental Table 3-2. Participant characteristics by missingness in metabolic syndrome severity z-score (MetS-Z) at visit 1 through 4 (v1-4) **

	MetS-Z visit 1			MetS-Z visit 3			MetS-Z visit 4		
	Non-missing, n=2498	*Missing*, n=1222	P-value	*Non-missing*, n=2024	*Missing*, n=1696	P-value	*Non-missing*, n=1892	*Missing*, n=1828	P-value
Age (mean (SD))	48.58 (9.26)	47.64 (9.52)	**0.004**	48.21 (9.01)	48.35 (9.76)	0.65	47.74 (8.88)	48.81 (9.80)	**<0.001**
Black adults (%)	1412 (56.5)	786 (64.3)	**<0.001**	1221 (60.3)	977 (57.6)	0.10	1158 (61.2)	1040 (56.9)	**0.008**
Socioeconomic mobility			**0.010**			**<0.001**			**0.014**
Stable low	739 (29.6)	364 (29.8)		587 (29.0)	516 (30.4)		579 (30.6)	524 (28.7)	
Downward mobility	378 (15.1)	227 (18.6)		295 (14.6)	310 (18.3)		274 (14.5)	331 (18.1)	
Upward mobility	638 (25.5)	309 (25.3)		541 (26.7)	406 (23.9)		502 (26.5)	445 (24.3)	
Stable high	707 (28.3)	295 (24.1)		582 (28.8)	420 (24.8)		521 (27.5)	481 (26.3)	
Male (%)	1076 (43.1)	609 (49.8)	**<0.001**	839 (41.5)	846 (49.9)	**<0.001**	778 (41.1)	907 (49.6)	**<0.001**
Married v1 (% Yes)	1136 (45.5)	554 (45.3)	0.931	926 (45.8)	764 (45.0)	0.832	876 (46.3)	814 (44.5)	0.329
Health insurance v1 (%)			**<0.001**			**0.031**			0.424
No	767 (30.7)	446 (36.5)		631 (31.2)	582 (34.3)		606 (32.0)	607 (33.2)	
Yes	1668 (66.8)	747 (61.1)		1349 (66.7)	1066 (62.9)		1242 (65.6)	1173 (64.2)	
Health[1] v1 (mean (SD))	43.77 (9.22)	43.76 (9.09)	0.973	44.13 (8.98)	43.32 (9.39)	**0.007**	44.20 (8.83)	43.31 (9.50)	**0.003**
CVD[2] medications v1 (%)			0.090			**0.031**			**<0.001**
No	1503 (60.2)	220 (18.0)		1148 (56.7)	575 (33.9)		1097 (58.0)	626 (34.2)	
Yes	855 (34.2)	100 (8.2)		596 (29.4)	359 (21.2)		532 (28.1)	423 (23.1)	
Alcohol use v1 (%)			0.501			**<0.001**			0.139
Never/past	960 (38.4)	131 (10.7)		679 (33.5)	412 (24.3)		648 (34.2)	443 (24.2)	
Current	1325 (53.0)	165 (13.5)		1011 (50.0)	479 (28.2)		929 (49.1)	561 (30.7)	
Tobacco[3] use v1 (%)[1]			**<0.001**			**<0.001**			**0.001**
Never/past	1189 (47.6)	121 (9.9)		899 (44.4)	411 (24.2)		835 (44.1)	475 (26.0)	
Current	1113 (44.6)	178 (14.6)		804 (39.7)	487 (28.7)		755 (39.9)	536 (29.3)	
Use of stimulants or opioids v1 (%)			**<0.001**			0.001			>0.99
Never	1719 (68.8)	184 (15.1)		1256 (62.1)	647 (38.1)		1164 (61.5)	739 (40.4)	
Past/current	582 (23.3)	115 (9.4)		446 (22.0)	251 (14.8)		426 (22.5)	271 (14.8)	
CES[4] v1 median [IQR]	13.00 [6.00, 22.00]	12.00 [6.00, 23.00]	0.742	12.00 [6.00, 21.00]	14.00 [7.00, 23.00]	**0.001**	12.00 [6.00, 22.00]	13.00 [6.00, 22.00]	0.124
Died (%)	402 (16.1)	240 (19.6)	**0.008**	225 (11.1)	417 (24.6)	**<0.001**	107 (5.7)	535 (29.3)	**<0.001**
Diabetes status[5] v1 (%)[4]			**<0.001**			**<0.001**			**<0.001**
No diagnosis	1562 (62.5)	224 (18.3)		1201 (59.3)	585 (34.5)		1141 (60.3)	645 (35.3)	
Pre-diabetes	467 (18.7)	22 (1.8)		332 (16.4)	157 (9.3)		296 (15.6)	193 (10.6)	
Diabetes	410 (16.4)	71 (5.8)		264 (13.0)	217 (12.8)		234 (12.4)	247 (13.5)	
Cognitive tendencies and MetS-Z (mean (SD))									
Vigilance	17.62 (4.01)	17.50 (3.60)	0.681	17.60 (4.08)	17.61 (3.75)	0.97	17.66 (4.06)	17.52 (3.81)	0.433
Adaptive coping	2.72 (0.64)	2.71 (0.65)	0.885	2.75 (0.64)	2.66 (0.63)	**0.002**	2.72 (0.63)	2.72 (0.65)	0.916
Avoidant coping	1.86 (0.50)	1.90 (0.52)	0.28	1.86 (0.50)	1.87 (0.50)	0.699	1.87 (0.51)	1.86 (0.48)	0.863
MetS-Z v1	0.28 (1.23)	--	--	0.22 (1.16)	0.39 (1.35)	**0.002**	0.23 (1.18)	0.36 (1.29)	**0.009**
MetS-Z v3	0.32 (1.19)	0.38 (1.34)	0.338	0.33 (1.22)	--	**--**	0.29 (1.15)	0.44 (1.41)	**0.016**
MetS-Z v4	0.35 (1.19)	0.31 (1.32)	0.576	0.31 (1.17)	0.45 (1.39)	**0.046**	0.34 (1.21)	--	--

1. Self-reported health assessed using 12-item short form health survey; higher values reflect better perceived health.
2. CVD prescription medications included self-reported current medication use for the following conditions: hypertension, heart disease, stroke, congestive heart failure, angina, hypercholesterolemia, and hypertriglyceridemia.
3. Tobacco use includes self-reported smoking cigarettes, cigars or pipes.
4. 20-item Center for Epidemiologic Studies Depression Scale.
5. Diabetes status was ascertained based on self-reported history of diagnosis, prescription medications for diabetes mellitus and/or having a fasting serum glucose of >125 mg/dL.

**Supplemental Tables 1-2 illustrate missingness in the study sample by exposure and outcome across three study visits. At visit 1, missingness in both vigilance and stress coping comprised 39% of the originally-recruited sample. Participants with missing exposure values were more likely to be black adults of male sex, report higher median depressive symptoms and were less likely to fast before the blood draw at visit 1. Finally, participants with missing assessment of stress coping had significantly higher MetS-z scores at visit 1 and 3, which may have resulted in the underestimation of the association between exposure and outcome of interest.

Of the original sample, 33% of participants had missing values for fasting metabolic syndrome severity z-score at visit 1, 46% -- at visit 3, and 49% -- at visit 4. Participants with missing outcome across 3 visits had similar values in most of the main exposure variables, except for adaptive stress coping, where participants with missing outcome at visit 3 had significantly lower mean adaptive coping.

Participants with missing outcome were younger at visit 1 and older at visit 4. Furthermore, at visit 1 and 4, missingness in the outcome was associated with race, sex, SES, health insurance, tobacco or drug use, and diabetes status, where higher proportion of black adults or those undergoing downward mobility had missing assessments. Across 3 visits, missingness in the outcome was associated with worse self-reported health, depression and likelihood of dying over the study follow-up. Finally, participants with missing outcome values at visit 3 or 4, had significantly higher mean MetS-Z at visit 1 or visit 3, respectively. The latter points to a possibility of selection bias, as those with worse metabolic health were not available at subsequent visits.

Supplemental Table 3-3. Description and psychometric properties of indices for stress-related cognitive tendencies.

Factor	Vigilance wave 1	Stress Coping wave 1		Stress Coping wave 4	
	Sum	Adaptive	Avoidant	Adaptive	Avoidant
n items/n obs.	6 items/n=2265	11 items/n=2285	10 items/n=2285	11 items/n=1820	10 items/n=1820
Cronbach's α	0.58 (0.56; 0.60)	0.84 (0.83; 0.85)	0.72 (0.71; 0.73)	0.87 (0.87; 0.88)	0.73 (0.72; 0.74)
Black adults	0.46 (0.42; 0.49)	0.84 (0.83; 0.85)	0.73 (0.72; 0.75)	--	--
White adults	0.71 (0.68; 0.73)	0.84 (0.83; 0.86)	0.71 (0.68; 0.73)	--	--
Mean (SD)	17.6 (3.97)	2.72 (0.64)	1.87 (0.5)	2.48 (0.71)	1.64 (0.45)
Median [Min; Max]	17 [6; 30]	2.73 [1; 4]	1.80 [1; 3.8]	2.45 [1; 4]	1.60 [1; 3.7]
Spearman Rho	--	0.01		0.17	
Spearman Rho (w1 & w4)	--	0.49	0.40	0.49	0.40

Supplemental Table 3-4. Baseline participants' characteristics by median-dichotomized vigilance scores.

	Vigilance	
	≤ **Median** n=1145	> **Median** n=1120
Age (mean (SD))	48.76 (9.14)	48.18 (9.24)
Black (%)	634 (55.4)	668 (59.6)
Below 125 % Poverty (%)	430 (37.6)	524 (46.8)
Men (%)	490 (42.8)	492 (43.9)
Marital Status (%)		
Single	344 (30.0)	338 (30.2)
Married/Partnered	532 (46.5)	484 (43.2)
Divorced/Separated	179 (15.6)	194 (17.3)
Widowed/Other	64 (5.6)	72 (6.4)
Socioeconomic Mobility (%)		
Stable Low	286 (25.0)	382 (34.1)
Downwardly Mobile	164 (14.3)	195 (17.4)
Upwardly Mobile	311 (27.2)	259 (23.1)
Stable High	373 (32.6)	263 (23.5)
Literacy (median [IQR])	45.00 [38.00, 49.00]	42.00 [37.00, 48.00]
Health Insurance (% Yes)	740 (64.6)	751 (67.1)
Self-reported Health (median [IQR])	48.00 [42.00, 52.00]	45.00 [35.00, 50.00]
ADL (% Yes)	95 (8.3)	156 (13.9)
Current alcohol use (% Yes)	599 (52.3)	612 (54.6)
Current tobacco use (% Yes)	488 (42.6)	527 (47.1)
Hypertension diagnosis (% Yes)	359 (39.5)	328 (46.8)
CVD prescription meds (% Yes)	351 (30.7)	385 (34.4)
CES-D (median [IQR])	9.00 [4.00, 17.00]	16.00 [8.00, 26.00]
Perceived Stress Score (median [IQR])	4.00 [2.00, 7.00]	6.00 [4.00, 8.00]
PTSD score (median [IQR])	6.00 [2.00, 12.00]	12.00 [5.00, 24.00]
Domestic Abuse (% Yes)	69 (6.0)	88 (7.9)
Sexual or Physical Assault (% Yes)	41 (3.6)	68 (6.1)
Recent ER use	357 (31.2)	383 (34.2)
MetS-Z (mean (SD))	0.23 (1.19)	0.28 (1.28)
Vigilance Sum Score (median [IQR])	15.00 [13.00, 16.00]	20.00 [19.00, 22.00]
Stress Coping (median [IQR])		
Adaptive	2.82 [2.36, 3.27]	2.64 [2.18, 3.09]
Avoidant	1.70 [1.40, 2.00]	1.90 [1.60, 2.30]

Caption: Compared to participants with vigilance below the sample median, those with above median vigilance level were more likely to be black (59.6% vs. 55.4%), low income (46.8% vs. 37.6%), with low literacy (42 vs 45), and worse self-reported physical (45 vs. 48) or mental health (16 vs. 9), higher perceived stress (6 vs 4) and PTSD (12 vs 6). No difference in vigilance levels was observed by a recent use of emergency, health insurance status, tobacco, alcohol or drug use, or experience of domestic abuse. Finally, participants with above median level of vigilance had higher avoidant (1.90 vs. 1.70), but lower adaptive stress coping (2.64 vs. 2.82).

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Supplemental Table 3-5. Baseline participant characteristics by indicators of metabolic health.

		Metabolic Syndrome*		Diabetes**		
	Overall (n=3720)	No (n=1908)	Yes (n=828)	No (n=1782)	pre-D (n=489)	Yes (n=481)
Age in years mean (SD)	48.27 (9.36)	47.83 (9.30)	50.61 (8.74)	47.24 (9.27)	50.38 (8.61)	52.54 (8.30)
Black (%)	2198 (59.1)	1169 (61.3)	395 (47.7)	1047 (58.6)	260 (53.2)	288 (59.9)
Below 125% Poverty	1535 (41.3)	777 (40.7)	336 (40.6)	749 (41.9)	184 (37.6)	202 (42.0)
Male (%)	1685 (45.3)	862 (45.2)	320 (38.6)	753 (42.2)	255 (52.1)	198 (41.2)
Self-reported health median [IQR]	47.00 [38.00, 51.00]	48.00 [40.00, 51.00]	43.00 [34.00, 50.00]	48.00 [40.00, 51.00]	46.00 [37.00, 51.00]	42.00 [32.00, 49.00]
MetS-Z mean (SD)	0.28 (1.23)	-0.25 (0.84)	1.41 (1.17)	-0.22 (0.81)	0.63 (0.74)	1.84 (1.55)

*The indicator of metabolic syndrome was calculated using the criteria from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III, based on the presence of 3 or more of the following components: waist circumference >102 cm in men or >88 cm in women; blood pressure ≥130/85 mmHg; fasting Glucose ≥110 mg/dL; triglycerides ≥150 mg/dL; and HDL cholesterol <40 mg/dL in men or <50 mg/dL in women.

**The indicator of the diabetes status includes diagnoses with both type 1 and type 2 diabetes and was based on self-reported diagnosis, diabetes medication use, or fasting glucose of >125 mg/dL.

Caption: The table illustrates face validity of the MetS-Z score. Compared to the indicator of diabetes status and traditional indicator of metabolic syndrome, we observe an expected increase in mean MetS-Z with the increase in metabolic disease severity.

Supplemental Table 3-6. Composition of the derived indicator of life course socioeconomic mobility.

	Socioeconomic Mobility			
	Stable Low	**Downward Mobility**	**Upward Mobility**	**Stable High**
	1103	605	947	1002
Adult SES z-score (mean (SD))	-0.93 (0.52)	-0.87 (0.53)	0.68 (0.49)	0.90 (0.56)
Household Income (Below 125 % Poverty)	821 (74.4)	443 (73.2)	124 (13.1)	121 (12.1)
Work Status				
Employed	321 (29.1)	190 (31.4)	734 (77.5)	815 (81.3)
Disabled	459 (41.6)	238 (39.3)	50 (5.3)	45 (4.5)
Unemployed	181 (16.4)	89 (14.7)	15 (1.6)	14 (1.4)
Retired/Other	139 (12.6)	87 (14.4)	145 (15.3)	106 (10.6)
Homeowner (% Yes)	110 (10.0)	76 (12.6)	581 (61.4)	649 (64.8)
Education				
<HS	636 (57.7)	296 (48.9)	202 (21.3)	108 (10.8)
HS/GED	374 (33.9)	228 (37.7)	378 (39.9)	260 (25.9)
Some college or more	87 (7.9)	79 (13.1)	364 (38.4)	612 (61.1)
Child SES z-score (mean (SD))	-0.73 (0.58)	0.67 (0.47)	-0.64 (0.58)	1.01 (0.75)
Mother's Education (%)				
<HS	566 (51.3)	68 (11.2)	554 (58.5)	97 (9.7)
HS/GED	216 (19.6)	296 (48.9)	176 (18.6)	453 (45.2)
Some college or more	19 (1.7)	90 (14.9)	24 (2.5)	289 (28.8)
Missing	302 (27.4)	151 (25.0)	193 (20.4)	163 (16.3)
Father's Education (%)				
<HS	475 (43.1)	120 (19.8)	494 (52.2)	179 (17.9)
HS/GED	147 (13.3)	262 (43.3)	111 (11.7)	370 (36.9)
Some college or more	14 (1.3)	56 (9.3)	15 (1.6)	269 (26.8)
Missing	467 (42.3)	167 (27.6)	327 (34.5)	184 (18.4)
Lived with both parents at age 6 (%)	556 (50.4)	560 (92.6)	527 (55.6)	914 (91.2)
Lived with both parents at age 16 (%)	228 (20.7)	450 (74.4)	284 (30.0)	773 (77.1)
Cumulative SES z-score (mean (SD))	-1.04 (0.48)	-0.18 (0.45)	0.08 (0.48)	1.18 (0.66)

Supplemental Table 3-7. Comparisons across models adjusted for substance use and depressive symptoms.

Fixed Effects	Model 1 Estimates	P-Value	Model 2 Estimates	P-Value	Model 3 Estimates	P-Value
Intercept	0.77 (0.36 – 1.19)	**<0.001**	0.60 (0.20 – 0.99)	**0.003**	0.71 (0.29 – 1.13)	**0.001**
Avoidant coping (IQR)	-0.06 (-0.14 – 0.01)	0.110	-0.17 (-0.25 – -0.09)	**<0.001**	-0.10 (-0.18 – -0.01)	**0.022**
Adaptive coping (IQR)	-0.09 (-0.17 – -0.01)	**0.024**	-0.05 (-0.13 – 0.03)	0.185	-0.07 (-0.15 – 0.01)	0.098
Follow-up duration (years)	0.01 (-0.03 – 0.05)	0.682	-0.00 (-0.04 – 0.04)	0.984	0.01 (-0.03 – 0.05)	0.639
Avoidant x duration	0.01 (-0.00 – 0.01)	0.101	0.01 (0.00 – 0.02)	**0.044**	0.01 (-0.00 – 0.02)	0.105
Adaptive x duration	0.00 (-0.00 – 0.01)	0.366	0.00 (-0.00 – 0.01)	0.259	0.00 (-0.01 – 0.01)	0.419
Socioeconomic mobility (SM) *						
Downward	0.16 (-0.08 – 0.40)	0.187	0.24 (0.00 – 0.47)	**0.046**	0.17 (-0.07 – 0.42)	0.167
Upward	-0.09 (-0.29 – 0.11)	0.380	0.04 (-0.16 – 0.23)	0.715	-0.07 (-0.27 – 0.13)	0.483
Stable High	-0.01 (-0.23 – 0.21)	0.941	0.09 (-0.12 – 0.30)	0.404	0.01 (-0.21 – 0.23)	0.935
White adults	0.41 (0.20 – 0.61)	**<0.001**	0.36 (0.16 – 0.57)	**<0.001**	0.38 (0.17 – 0.59)	**<0.001**
Downward SM x White adults	-0.00 (-0.32 – 0.31)	0.977	-0.02 (-0.34 – 0.29)	0.889	0.00 (-0.32 – 0.33)	0.980
Upward SM x White adults	-0.30 (-0.57 – -0.02)	**0.033**	-0.29 (-0.55 – -0.02)	**0.035**	-0.29 (-0.57 – -0.02)	**0.038**
Stable high SM x White adults	-0.60 (-0.87 – -0.33)	**<0.001**	-0.62 (-0.88 – -0.36)	**<0.001**	-0.57 (-0.85 – -0.30)	**<0.001**
Current alcohol	-0.18 (-0.28 – -0.07)	**0.001**	--		-0.17 (-0.27 – -0.07)	**0.001**
Current smoking	-0.20 (-0.31 – -0.10)	**<0.001**	--		-0.20 (-0.31 – -0.10)	**<0.001**
Current drug use	-0.14 (-0.26 – -0.02)	**0.021**	--		-0.15 (-0.27 – -0.02)	**0.019**
Depressive symptoms (CES-D)	--		0.01 (0.00 – 0.01)	**0.001**	0.01 (0.00 – 0.01)	**0.021**
σ^2	0.33		0.33		0.33	
τ_{00}	1.06		1.12		1.07	
τ_{11}	0.00		0.00		0.00	
N Groups/N Observations	1950/4387		2119/4767		1919/4321	
Marginal R^2 / Conditional R^2	0.081 / 0.779		0.068 / 0.786		0.082 / 0.779	

Results show estimates obtained from linear mixed effects models (LMM) with random intercepts and slopes and restricted maximum likelihood (REML) for the variance parameters. P-values were calculated using conditional F-test with Kenward-Roger approximation for the denominator degrees of freedom. P-values < 0.05 are bolded.

All models include time (indexed by duration of follow-up), natural spline for centered age with 3 degrees of freedom, age x time, sex (ref: female), marital status (ref: married), sex x race, and sex x socioeconomic mobility.

Model 1: + alcohol, tobacco, and drug use

Model 2: + depressive symptoms (CES-D)

Model 3: + alcohol, tobacco, and drug use, depressive symptoms (CES-D)

*Socioeconomic mobility (SM): Stable Low= Low childhood and adult SES or stable low; Downward= High childhood and Low adult SES or downwardly mobile; Upward=Low childhood and High adult SES or upwardly mobile; Stable High=High child and adult SES or stable high.

Supplemental Table 3-8. Interactions between sociodemographic factors and vigilance (75th vs. 25th percentile).

Fixed Effects	Model 1		Model 2		Model 3	
	Estimates	P-Value	Estimates	P-Value	Estimates	P-Value
Intercept	-0.10	0.621	0.04	0.874	0.24	0.428
	(-0.50 – 0.30)		(-0.44 – 0.52)		(-0.36 – 0.85)	
Vigilance (IQR)	0.06	0.171	0.02	0.721	-0.04	0.630
	(-0.03 – 0.14)		(-0.09 – 0.13)		(-0.19 – 0.12)	
Follow-up duration (years)	0.04	**0.003**	0.04	**0.003**	0.04	**0.003**
	(0.01 – 0.06)		(0.01 – 0.06)		(0.01 – 0.06)	
Socioeconomic mobility (SM) *						
Downward	0.24	**0.038**	0.23	0.530	-0.56	0.235
	(0.01 – 0.47)		(-0.49 – 0.95)		(-1.48 – 0.36)	
Upward	0.00	0.987	0.03	0.935	-0.23	0.579
	(-0.19 – 0.19)		(-0.60 – 0.66)		(-1.05 – 0.59)	
Stable High	0.09	0.381	0.09	0.765	-0.46	0.279
	(-0.11 – 0.30)		(-0.49 – 0.67)		(-1.31 – 0.38)	
White adults	0.69	**0.005**	0.39	**<0.001**	-0.09	0.846
	(0.20 – 1.17)		(0.20 – 0.59)		(-0.96 – 0.79)	
Downward SM x White adults	-0.07	0.660	-0.07	0.666	1.91	**0.010**
	(-0.38 – 0.24)		(-0.38 – 0.24)		(0.45 – 3.36)	
Upward SM x White adults	-0.30	**0.028**	-0.28	**0.040**	0.31	0.623
	(-0.57 – -0.03)		(-0.55 – -0.01)		(-0.93 – 1.55)	
Stable high SM x White adults	-0.70	**<0.001**	-0.67	**<0.001**	0.32	0.580
	(-0.96 – -0.44)		(-0.93 – -0.41)		(-0.82 – 1.47)	
Vigilance x White adults	-0.08	0.195	--		0.13	0.267
	(-0.20 – 0.04)				(-0.10 – 0.36)	
Vigilance x Downward SM	--		0.00	0.976	0.23	0.076
			(-0.19 – 0.19)		(-0.02 – 0.48)	
Vigilance x Upward SM	--		-0.01	0.925	0.06	0.577
			(-0.18 – 0.16)		(-0.16 – 0.29)	
Vigilance x Stable high SM	--		0.00	1.000	0.16	0.182
			(-0.15 – 0.15)		(-0.07 – 0.39)	
Vigilance x Downward SM x White adults	--		--		-0.53	**0.007**
					(-0.92 – -0.15)	
Vigilance x Upward SM x White adults	--		--		-0.16	0.352
					(-0.50 – 0.18)	
Vigilance x Stable high SM x White adults	--		--		-0.28	0.078
					(-0.59 – 0.03)	
σ^2	0.33		0.33		0.33	
τ_{00}	1.12		1.12		1.12	
τ_{11}	0.00		0.00		0.00	
N Groups/N Observations	2162/4870		2162/4870		2162/4870	
Marginal R^2 / Conditional R^2	0.063 / 0.786		0.063 / 0.786		0.066 / 0.786	

Results show estimates obtained from linear mixed effects models (LMM) with random intercepts and slopes and restricted maximum likelihood (REML) for the variance parameters. P-values were calculated using conditional F-test with Kenward-Roger approximation for the denominator degrees of freedom. P-values < 0.05 are bolded.

All models include time (indexed by duration of follow-up), natural spline for centered age with 3 degrees of freedom, age x time, sex (ref: female), sex x race, and sex x socioeconomic mobility.

Model 1: vigilance (IQR) x race (Wald F-stat=1.71, p-value=0.19, Kenward-Roger approximation)

Model 2: vigilance (IQR) x socioeconomic mobility (Wald F-stat=0.01, p-value>0.99, Kenward-Roger approximation)

Model 3: vigilance (IQR) x race x socioeconomic mobility (Wald F-stat=1.39, p-value=0.21, Kenward-Roger approximation)

*Socioeconomic mobility (SM): Stable Low= Low childhood and adult SES or stable low; Downward= High childhood and Low adult SES or downwardly mobile; Upward=Low childhood and High adult SES or upwardly mobile; Stable High=High child and adult SES or stable high.

Supplemental Table 3-9. Interactions between sociodemographic factors and stress coping (75th vs. 25th percentile).

Fixed Effects	Model 1		Model 2	
	Estimates	*P-Value*	*Estimates*	*P-Value*
Intercept	0.44 (0.01 – 0.88)	0.047	0.67 (0.12 – 1.22)	0.017
Stress Coping (IQR)				
Avoidant	-0.18 (-0.27 – -0.08)	<0.001	-0.19 (-0.31 – -0.06)	0.003
Adaptive	0.07 (-0.03 – 0.16)	0.162	0.00 (-0.13 – 0.14)	0.946
Duration of follow-up (years)	-0.00 (-0.05 – 0.04)	0.848	-0.00 (-0.06 – 0.06)	0.937
Avoidant x duration	0.01 (0.00 – 0.02)	0.003	0.01 (0.00 – 0.03)	0.035
Adaptive x duration	0.00 (-0.01 – 0.01)	0.590	0.00 (-0.01 – 0.02)	0.730
Socioeconomic mobility (SM) *				
Downward	0.23 (0.03 – 0.43)	0.021	0.45 (-0.40 – 1.30)	0.297
Upward	-0.11 (-0.27 – 0.06)	0.193	0.00 (-0.79 – 0.79)	0.998
Stable high	-0.21 (-0.38 – -0.04)	0.014	-0.07 (-0.88 – 0.75)	0.875
Downward SM x duration	--		0.05 (-0.04 – 0.15)	0.251
Upward SM x duration	--		-0.04 (-0.12 – 0.05)	0.380
Stable high SM x duration	--		0.01 (-0.08 – 0.10)	0.887
White adults	1.05 (0.43 – 1.68)	0.001	0.14 (0.01 – 0.27)	0.041
White adults x duration	0.03 (-0.04 – 0.10)	0.386	--	
Avoidant x White adults	0.11 (-0.04 – 0.26)	0.159	--	
Adaptive x White adults	-0.39 (-0.54 – -0.24)	<0.001	--	
Avoidant x Downward SM	--		0.08 (-0.12 – 0.29)	0.431
Avoidant x Upward SM	--		0.06 (-0.13 – 0.25)	0.545
Avoidant x Stable high SM	--		0.19 (-0.01 – 0.40)	0.060
Adaptive x Downward SM	--		-0.16 (-0.38 – 0.07)	0.174
Adaptive x Upward SM	--		-0.08 (-0.29 – 0.12)	0.417
Adaptive x Stable high SM	--		-0.21 (-0.41 – -0.01)	0.040
Avoidant x White adults x duration	-0.02 (-0.04– -0.00)	0.035	--	
Adaptive x White adults x duration	-0.00 (-0.02 – 0.02)	0.957	--	
Avoidant x Downward SM x duration	--		-0.01 (-0.04 – 0.01)	0.205
Avoidant x Upward SM x duration	--		-0.01 (-0.03 – 0.01)	0.567
Avoidant x Stable high x duration	--		-0.02 (-0.04 – 0.01)	0.154
Adaptive x Downward SM x duration	--		-0.01 (-0.03 – 0.02)	0.657
Adaptive x Upward SM x duration	--		0.02 (-0.01 – 0.04)	0.181
Adaptive x Stable high SM x duration	--		0.01 (-0.02 – 0.03)	0.608
σ^2	0.32		0.32	
$\tau_{00\ (id)}$	1.12		1.13	
$\tau_{11\ (id\ time)}$	0.00		0.00	
N Groups/N Observations	2156/4843		2156/4843	
Marginal R^2 / Conditional R^2	0.067 / 0.787		0.059 / 0.788	

Results show estimates obtained from linear mixed effects models (LMM) with random intercepts and slopes and restricted maximum likelihood (REML) for the variance parameters. All models include time (indexed by duration of follow-up), natural spline for centered age with 3 degrees of freedom, age x time, sex (ref: female), marital status (ref: married), sex x race and sex x socioeconomic mobility. P-values < 0.05 are bolded.

Model 1: adaptive coping (IQR) x race x time (Wald F-stat=0.004, p-value =0.95, Satterthwaite approximation); avoidant coping (IQR) x race x time (Wald F-stat=4.63, p-value =0.032, Satterthwaite approximation)

Model 2: adaptive coping (IQR) x socioeconomic mobility x time (Wald F-stat=0.73, p-value =0.54, Satterthwaite approximation); avoidant coping (IQR) x socioeconomic mobility x time (Wald F-stat=0.90, p-value =0.44, Satterthwaite approximation)

*Adaptive and avoidant coping factors were modelled simultaneously.

**Socioeconomic mobility: Stable Low= Low childhood and adult SES or stable low; Downward= High childhood and Low adult SES or downwardly mobile; Upward=Low childhood and High adult SES or upwardly mobile; Stable High=High child and adult SES or stable high.

Supplemental Table 3-10. Race-stratified models: stress coping by time, race and socioeconomic mobility.

Fixed Effects	Model 1 (White adults) Mean (95% CI)	P-value	Model 2 (Black adults) Mean (95% CI)	P-value
Intercept	0.93 (-0.03 – 1.89)	0.057	0.50 (-0.17 – 1.16)	0.143
Coping (IQR)*				
Avoidant	-0.08 (-0.29 – 0.12)	0.431	-0.29 (-0.44 – -0.13)	**<0.001**
Adaptive	-0.14 (-0.37 – 0.10)	0.249	0.16 (-0.00 – 0.33)	0.051
Duration	-0.03 (-0.14 – 0.07)	0.545	0.01 (-0.06 – 0.08)	0.695
Avoidant x duration	0.02 (-0.00 – 0.04)	0.098	0.01 (-0.00 – 0.03)	0.083
Adaptive x duration	0.01 (-0.02 – 0.04)	0.419	-0.01 (-0.02 – 0.01)	0.592
Socioeconomic Mobility (SM)**				
Downward	2.09 (0.55 – 3.62)	**0.008**	-0.05 (-1.06 – 0.96)	0.924
Upward	-0.57 (-1.93 – 0.79)	0.409	0.34 (-0.64 – 1.32)	0.494
Stable high	0.14 (-1.13 – 1.42)	0.824	-0.27 (-1.35 – 0.81)	0.622
Downward SM x duration	0.11 (-0.06 – 0.28)	0.217	0.04 (-0.07 – 0.15)	0.510
Upward SM x duration	0.14 (-0.01 – 0.29)	0.059	-0.12 (-0.23 – -0.02)	**0.023**
Stable high SM x duration	0.12 (-0.02 – 0.26)	0.082	-0.07 (-0.19 – 0.05)	0.255
Avoidant x Downward SM	-0.13 (-0.49 – 0.22)	0.461	0.20 (-0.06 – 0.45)	0.129
Avoidant x Upward SM	0.04 (-0.27 – 0.35)	0.813	0.12 (-0.12 – 0.37)	0.310
Avoidant x Stable high SM	0.02 (-0.29 – 0.32)	0.918	0.35 (0.07 – 0.62)	**0.013**
Adaptive x Downward SM	-0.51 (-0.91 – -0.10)	**0.014**	-0.11 (-0.38 – 0.16)	0.436
Adaptive x Upward SM	0.12 (-0.23 – 0.46)	0.508	-0.25 (-0.51 – 0.00)	0.053
Adaptive x Stable high SM	-0.21 (-0.51 – 0.09)	0.175	-0.17 (-0.46 – 0.11)	0.240
Avoidant x Downward SM x duration	-0.04 (-0.09 – -0.00)	**0.036**	-0.01 (-0.04 – 0.02)	0.575
Avoidant x Upward SM x duration	-0.03 (-0.06 – 0.00)	0.088	0.00 (-0.03 – 0.03)	0.930
Avoidant x Stable high SM x duration	-0.04 (-0.07 – -0.00)	**0.025**	-0.00 (-0.03 – 0.03)	0.801
Adaptive x Downward SM x duration	0.01 (-0.04 – 0.05)	0.782	-0.01 (-0.04 – 0.02)	0.658
Adaptive x Upward SM x duration	-0.02 (-0.05 – 0.02)	0.418	0.03 (0.00 – 0.06)	**0.022**
Adaptive x Stable high SM x duration	-0.01 (-0.04 – 0.02)	0.623	0.02 (-0.01 – 0.05)	0.241
σ^2	0.27		0.36	
$\tau_{00 \ (id)}$	1.09		1.09	
$\tau_{11 \ (id \ time)}$	0.00		0.00	
N Groups/N Observations	899/1973		1257/2870	
Marginal R^2 / Conditional R^2	0.097 / 0.811		0.068 / 0.769	

Results show estimates obtained from linear mixed effects models (LMM) with random intercepts and slopes and restricted maxi likelihood (REML) for the variance parameters. All models include time (indexed by duration of follow-up), natural spline for c age with 3 degrees of freedom, age x time, sex (ref: female), marital status (ref: married), sex x race and sex x socioeconomic m
P-values < 0.05 are bolded.
Model 1 (among White adults): adaptive coping (IQR) x socioeconomic mobility x time (Wald F-stat=0.53, p-value =0.66, Satterthwaite approximation); avoidant coping (IQR) x socioeconomic mobility x time (Wald F-stat=2.47, p-value =0.061, Satterthwaite approximation)
Model 2 (among Black adults): adaptive coping (IQR) x socioeconomic mobility x time (Wald F-stat=2.50, p-value =0.058, Satterthwaite approximation); avoidant coping (IQR) x socioeconomic mobility x time (Wald F-stat=0.16, p-value =0.92, Sattert approximation)

Supplemental Table 3-11. Results using longitudinal measures of stress coping (wave 1 and wave 4).

Coefficient	Model 1 Estimates	P-Value	Model 2 Estimates	P-Value	Model 3 Estimates	P-Value
Intercept	0.56 (0.22 – 0.91)	**0.001**	0.44 (0.06 – 0.83)	**0.023**	0.49 (0.02 – 0.97)	**0.042**
Avoidant (IQR)	-0.08 (-0.14 – -0.02)	**0.010**	-0.14 (-0.22 – -0.06)	**<0.001**	-0.16 (-0.26 – -0.06)	**0.003**
Adaptive (IQR)	-0.08 (-0.15 – -0.01)	**0.029**	0.02 (-0.07 – 0.11)	0.650	0.02 (-0.10 – 0.14)	0.748
Duration	0.00 (-0.04 – 0.04)	0.835	0.02 (-0.03 – 0.06)	0.411	0.00 (-0.05 – 0.06)	0.892
Avoidant x duration	0.01 (-0.00 – 0.01)	0.203	0.01 (-0.00 – 0.02)	0.129	0.01 (-0.00 – 0.03)	0.101
Adaptive x duration	0.00 (-0.00 – 0.01)	0.302	-0.00 (-0.01 – 0.01)	0.920	-0.00 (-0.02 – 0.02)	0.995
*Socioeconomic Mobility [ref: Stable Low] **						
Downward	0.23 (0.01 – 0.44)	**0.038**	0.22 (0.00 – 0.43)	**0.046**	0.24 (-0.50 – 0.98)	0.519
Upward	0.05 (-0.12 – 0.23)	0.557	0.02 (-0.16 – 0.19)	0.829	0.24 (-0.42 – 0.91)	0.476
Stable High	0.07 (-0.12 – 0.26)	0.464	0.03 (-0.16 – 0.22)	0.728	0.17 (-0.53 – 0.87)	0.642
Race [ref: Black]	0.36 (0.17 – 0.54)	**<0.001**	0.64 (0.11 – 1.18)	**0.019**	0.38 (0.19 – 0.56)	**<0.001**
Downward x White	-0.08 (-0.37 – 0.21)	0.602	-0.07 (-0.35 – 0.22)	0.657	-0.09 (-0.38 – 0.20)	0.533
Upward x White	-0.30 (-0.55 – -0.06)	**0.016**	-0.07 (-0.35 – 0.22)	0.657	-0.32 (-0.57 – -0.07)	**0.012**
Stable High x White	-0.62 (-0.86 – -0.39)	**<0.001**	-0.53 (-0.78 – -0.29)	**<0.001**	-0.66 (-0.90 – -0.42)	**<0.001**
Avoidant x White	--		0.12 (-0.00 – 0.25)	0.059	--	
Adaptive x White	--		-0.21 (-0.35 – -0.07)	**0.003**		
Duration x White	--		-0.04 (-0.11 – 0.03)	0.214	--	
Avoidant x Downward					0.11 (-0.07 – 0.29)	0.226
Avoidant x Upward					0.07 (-0.09 – 0.23)	0.420
Avoidant x Stable High	--		--		0.21 (0.04 – 0.38)	**0.015**
Adaptive x Downward	--		--		-0.12 (-0.33 – 0.10)	0.285
Adaptive x Upward	--		--		-0.14 (-0.32 – 0.05)	0.141
Adaptive x Stable High	--		--		-0.21 (-0.40 – -0.02)	**0.027**
Avoidant x Duration x White	--		-0.00 (-0.02 – 0.01)	0.705	--	
Adaptive x Duration x White	---		0.01 (-0.01 – 0.03)	0.188	--	
Downward x Duration	--		--		0.03 (-0.06 – 0.12)	0.490
Upward x Duration	--		--		-0.02 (-0.10 – 0.07)	0.699
Stable High x Duration	--		--		-0.01 (-0.10 – 0.08)	0.828
Avoidant x Downward x Duration	--		--		-0.02 (-0.04 – 0.01)	0.182
Avoidant x Upward x Duration	--		--		-0.01 (-0.04 – 0.01)	0.311
Avoidant x Stable High x Duration	--		--		-0.01 (-0.03 – 0.02)	0.490
Adaptive x Downward x Duration	--		--		0.00 (-0.03 – 0.03)	0.813
Adaptive x Upward x Duration	--		--		0.02 (-0.01 – 0.04)	0.188
Adaptive x Stable High x Duration	--		--		0.01 (-0.02 – 0.03)	0.570
σ^2	0.33		0.33		0.33	
τ_{00}	1.12		1.11		1.12	
τ_{11}	0.00		0.00		0.00	
N Groups/N Observations	2542/5017		2542/5017		2542/5017	
Marginal R^2 / Conditional R^2	0.060 / 0.780		0.064 / 0.780		0.064 / 0.780	

Estimates obtained from linear mixed effects models (LMM) with random intercepts and slopes and restricted maximum likelihood (REML) for the variance parameters. All models include time (indexed by duration of follow-up), natural spline for centered age with 3 degrees of freedom, age x time, sex (ref: female), marital status (ref: married), sex x race and sex x socioeconomic mobility. P-values < 0.05 are bolded.
**Socioeconomic Mobility: Stable Low= Low childhood and adult SES or stable low; Downward= High childhood and Low adult SES or downwardly mobile; Upward=Low childhood and High adult SES or upwardly mobile; Stable High=High child and adult SES or stable high.
Model 1: (adaptive coping (IQR)+avoidant coping (IQR)) x time
Model 2: (adaptive coping (IQR)+avoidant coping (IQR)) x time x race
Model 2: (adaptive coping (IQR)+avoidant coping (IQR)) x time x socioeconomic mobility

Supplemental Table 3-12. Fully adjusted model for vigilance and metabolic syndrome severity z-score in a full sample and stratified by diabetes status (from MI wide).

Fixed Effects	Model 1 Full Sample Mean (95% CI)	P-Value	Model 2 No Diabetes Mean (95% CI)	P-Value	Model 3 Pre-Diabetes Mean (95% CI)	P-Value	Model 4 Diabetes Mean (95% CI)	P-Value
Intercept	0.01 (-0.31 – 0.33)	0.950	-0.14 (-0.40 – 0.12)	0.278	0.66 (0.15 – 1.16)	**0.012**	2.45 (1.28 – 3.63)	**<0.001**
Vigilance (IQR)	0.03 (-0.04 – 0.09)	0.417	-0.01 (-0.06 – 0.04)	0.707	0.03 (-0.06 – 0.12)	0.567	0.02 (-0.19 – 0.22)	0.886
Duration	0.04 (0.00 – 0.07)	**0.037**	0.04 (0.01 – 0.07)	**0.006**	-0.03 (-0.11 – 0.05)	0.502	0.00 (-0.17 – 0.17)	0.987
Social Mobility** [ref: Stable Low]								
Downward	0.15 (-0.06 – 0.35)	0.159	-0.05 (-0.22 – 0.13)	0.593	-0.01 (-0.36 – 0.34)	0.953	0.39 (-0.30 – 1.08)	0.265
Upward	0.06 (-0.12 – 0.25)	0.520	0.01 (-0.15 – 0.17)	0.881	0.08 (-0.26 – 0.41)	0.649	-0.16 (-0.75 – 0.44)	0.609
Stable High	0.04 (-0.14 – 0.22)	0.640	-0.00 (-0.16 – 0.15)	0.985	-0.15 (-0.45 – 0.16)	0.347	-0.20 (-0.76 – 0.36)	0.490
Race [ref: Black]	0.29 (0.07 – 0.51)	**0.009**	0.25 (0.08 – 0.42)	**0.004**	0.15 (-0.20 – 0.49)	0.400	0.31 (-0.33 – 0.944)	0.340
Downward x White	-0.01 (-0.38 – 0.37)	0.971	0.05 (-0.19 – 0.30)	0.669	0.10 (-0.47 – 0.67)	0.737	-0.04 (-0.93 – 0.85)	0.930
Upward x White	-0.26 (-0.57 – 0.05)	0.101	-0.20 (-0.47 – 0.06)	0.133	-0.07 (-0.52 – 0.38)	0.755	-0.00 (-0.96 – 0.96)	0.995
Stable High x White	-0.52 (-0.79 – -0.25)	**<0.001**	-0.47 (-0.68 – -0.27)	**<0.001**	-0.16 (-0.55 – 0.24)	0.434	0.03 (-0.73 – 0.78)	0.946

After multiply imputing predictors and covariates using wide format, Rubin's rule was used to obtain estimates from linear mixed effects models (LMM) with random intercepts and slopes and restricted maximum likelihood (REML) for the variance parameters, fitted in 100 imputed datasets with 50 iterations each.

Model 1 shows results from the full sample (comparable to Model 2 in the Main Table 2), while Model 2-4 illustrate results from data stratified by diabetes status. All models additionally include study time duration, natural spline of centered baseline age with 3 degrees of freedom, interaction between spline for age and study time, sex (ref: women), marital status (ref: married/partnered), socioeconomic mobility (ref: stable low), race (ref: black), interactions between race and socioeconomic mobility, race and sex, sex and socioeconomic mobility. P-values < 0.05 are bolded.

**Social Mobility: Stable Low= Low childhood and adult SES or stable low; Downward= High childhood and Low adult SES or downwardly mobile; Upward=Low childhood and High adult SES or upwardly mobile; Stable High=High child and adult SES or stable high.

Supplemental Table 3-13. Fully adjusted model for stress coping and metabolic syndrome severity z-score in a full sample and stratified by diabetes status (from MI wide).

Fixed Effects	Model 1 Full Sample Mean (95% CI)	P-Value	Model 2 No Diabetes Mean (95% CI)	P-Value	Model 3 Pre-Diabetes Mean (95% CI)	P-Value	Model 4 Diabetes Mean (95% CI)	P-Value
Intercept	0.56 (0.20 – 0.92)	**0.003**	0.03 (-0.26 – 0.32)	0.862	1.12 (0.50 – 1.75)	**<0.001**	3.24 (2.05 – 4.43)	**<0.001**
Avoidant [IQR]	-0.07 (-0.14 – -0.00)	**0.038**	-0.05 (-0.10 – 0.01)	0.086	-0.08 (-0.19 – 0.03)	0.176	-0.07 (-0.30 – 0.16)	0.569
Adaptive [IQR]	-0.09 (-0.16 – -0.01)	**0.024**	-0.02 (-0.08 – 0.04)	0.452	-0.05 (-0.17 – 0.07)	0.417	-0.21 (-0.20 – 0.20)	0.073
Duration	0.01 (-0.02 – 0.05)	0.455	0.04 (0.01 – 0.07)	**0.022**	-0.06 (-0.16 – 0.05)	0.271	-0.04 (-0.22 – 0.14)	0.634
Avoidant x duration	0.01 (-0.00 – 0.02)	0.061	0.00 (-0.00 – 0.01)	0.181	0.02 (-0.00 – 0.04)	0.108	0.01 (-0.03 – 0.05)	0.524
Adaptive x duration	0.00 (-0.00 – 0.01)	0.389	-0.00 (-0.01 –0.01)	0.957	-0.00 (-0.02 – 0.02)	0.787	0.02 (-0.01 – 0.06)	0.183
Social Mobility **[ref: Stable Low]								
Downward	0.14 (-0.03 – 0.40)	0.181	-0.05 (-0.23 – 0.12)	0.551	-0.03 (-0.38 – 0.31)	0.863	0.41 (-0.28 – 1.09)	0.247
Upward	0.07 (-0.11 – 0.26)	0.488	0.01 (-0.15 – 0.17)	0.904	0.07 (-0.26 – 0.41)	0.663	-0.14 (-0.74 – 0.46)	0.650
Stable High	0.04 (-0.10 – 0.25)	0.640	-0.01 (-0.16 – 0.15)	0.946	-0.16 (-0.47 – 0.14)	0.296	-0.18 (-0.74 – 0.38)	0.524
Race [ref: Black]	0.29 (0.07 – 0.51)	**0.001**	0.25 (0.08 – 0.42)	**0.004**	0.13 (-0.22 – 0.48)	0.459	0.29 (-0.35 – 0.93)	0.369
Downward x White	0.01 (-0.36 – 0.38)	0.970	0.06 (-0.18 – 0.31)	0.604	0.11 (-0.46 – 0.68)	0.705	-0.07 (-0.96 – 0.83)	0.880
Upward x White	-0.27 (-0.58 – 0.04)	0.088	-0.20 (-0.47 – 0.06)	0.134	-0.07 (-0.52 – 0.37)	0.744	0.00 (-0.95 – 0.96)	0.996
Stable High x White	-0.52 (-0.79 – -0.25)	**<0.001**	-0.47 (-0.67 – -0.26)	**<0.001**	-0.14 (-0.54 – 0.26)	0.487	0.02 (-0.73 – 0.77)	0.958

After multiply imputing predictors and covariates using wide format, Rubin's rule was used to obtain estimates from linear mixed effects models (LMM) with random intercepts and slopes and restricted maximum likelihood (REML) for the variance parameters, fitted in 100 imputed datasets with 50 iterations each.

Model 1 shows results from the full sample (comparable to Model 2 in the Main Table 2), while Model 2-4 illustrate results from data stratified by diabetes status. All models additionally include study time duration, natural spline of centered baseline age with 3 degrees of freedom, interaction between spline for age and study time, sex (ref: women), marital status (ref: married/partnered), socioeconomic mobility (ref: stable low), race (ref: black), interactions between race and socioeconomic mobility, race and sex, sex and socioeconomic mobility. P-values < 0.05 are bolded.

**Social Mobility: Stable Low= Low childhood and adult SES or stable low; Downward= High childhood and Low adult SES or downwardly mobile; Upward=Low childhood and High adult SES or upwardly mobile; Stable High=High child and adult SES or stable high.

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Supplemental Figure 3-1. Missing data across all waves of follow-up.
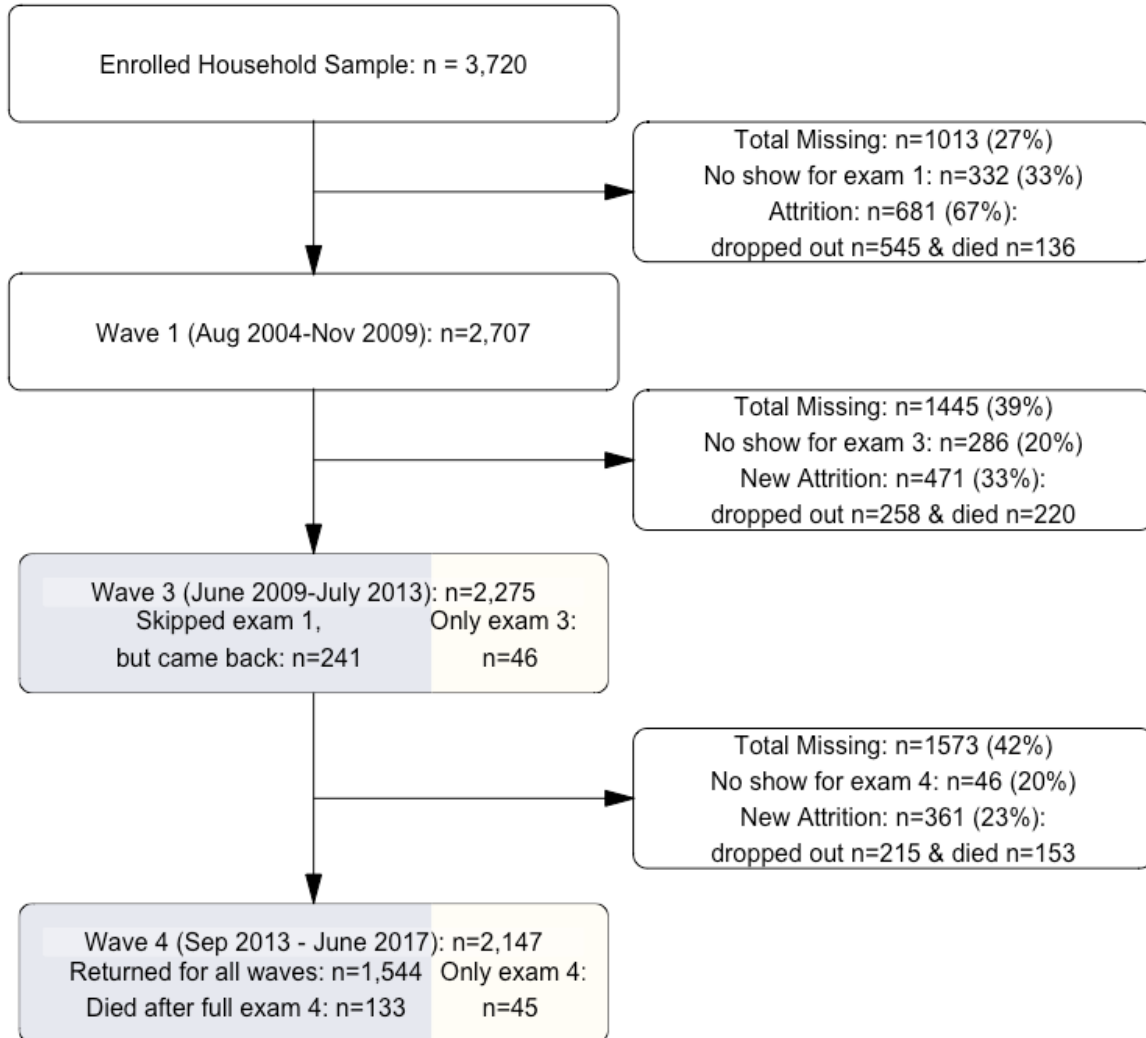
Varying degrees of missingness were present in the study variables at baseline and follow-up. In this figure, if participants had less than any five recorded values per examination, they were considered missing at that wave. Largest attrition occurred between the baseline household sample and the first wave or medical examination. Out of those, who missed wave 1 examination (n=1013), 681 (67 %) were lost to follow-up. Overall, 509 deaths occurred between baseline and wave 4; 133 participants died after wave 4. The missing pattern was non-monotone, such that 1544 participants returned for all three waves, some participants skipped one or two waves.

Supplemental Figure 3-2. Predicted metabolic syndrome severity z-scores comparing stress coping percentiles by socioeconomic mobility from race-stratified models.
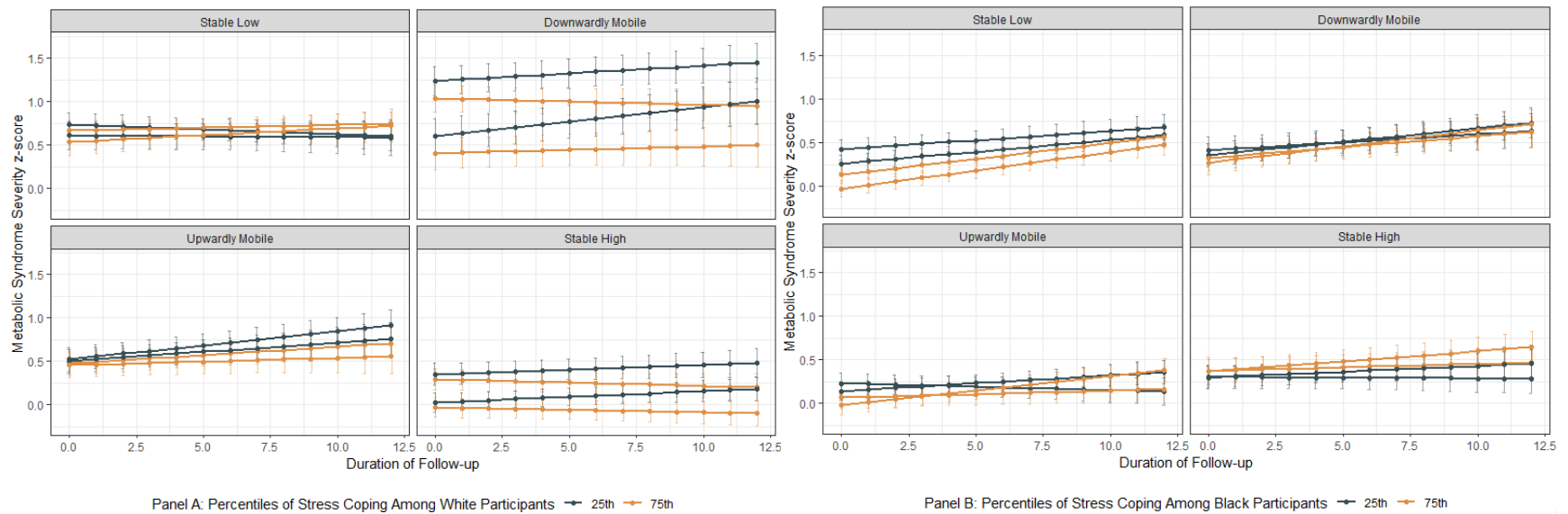
Predicted metabolic syndrome severity z-scores, comparing percentiles of both types of stress coping at 75th vs. 25th percentiles (orange vs. dark blue) by socioeconomic mobility (4 quadrants, starting from top left: Stable Low, Downwardly Mobile, Stable High, Upwardly Mobile) and duration of follow-up among White participants (Panel A) and Black participants (Panel B)). Predicted values were calculated by a post-estimation of marginal means, using values obtained from the linear mixed models. The 25th and 75th percentiles correspond to scores 2.3 and 3.2 for adaptive coping and 1.5 and 2.2 for avoidant coping. All models include time (indexed by study duration), natural spline for centered age with 3 degrees of freedom, age x time, sex (ref: female), and sex x socioeconomic mobility. See Supplemental Table 10 for concordant estimates.

Chapter 4 Psychosocial Stress and Incident Diabetes: Evidence from Parallel Analyses in Two Prospective Cohort Studies

4.1 Introduction

Type 2 diabetes (diabetes, hereafter) is a chronic multifactorial metabolic disorder, characterized by significant health and economic burden, and included among the ten leading causes of death in the United States.[173,174] A 2020 CDC report estimates that as much as 13% of the US adults (that is 34.1 millions of people) live with diabetes, of whom the hardest hit populations are certain racial and ethnic groups, including non-Hispanic Black and Hispanic or Latino adults.[175,176]

Stress as a potential risk factor for diabetes

The hypothesis that chronic stress may contribute to the etiology of diabetes through continuous activation of the hypothalamic pituitary adrenal (HPA) axis stress response was put forth at least in the early 1980s.[177,178] Chronic activation of the HPA-axis induces hyperglycemia, high circulating glucocorticoids, systemic inflammation, and other metabolic imbalances, all of which are also known risk factors for diabetes.[179] In the years since, extensive research efforts in biomedical sciences have largely supported the mechanistic link between dysregulated stress response and metabolic dysfunction using evidence from animal models.[180–182]

In this same vein, population-based health studies have examined the connections between psychosocial chronic stress and diabetes. However, evidence remains mixed due, in part, to a variety of ways stress has been operationalized and measured. For example, in a recent comprehensive review, Hackett & Steptoe (2017) argued that in large prospective cohort studies

diabetes risk is associated with a range of psychosocial stress factors, especially job stress, early life adversity and perceived general stress.[183] A different meta-analysis of 9 studies did not show statistically significant association between job-related psychosocial stress and risk of type 2 diabetes,[184] but a more recent pooled analysis of 13 prospective studies showed a significant association (HR: 1.15 (CI 1.06-1.25)).[185]

Cortisol as a physiologic mechanism underlying the hypothesized stress-diabetes relationship

Governed by nervous and endocrine systems, the innate biological stress mechanism regulates short-term responses to acute stress events and diurnal or cyclical responses to environmental changes (i.e., circadian rhythm or respiration cycles).[34] Since concentrations of cortisol, hormone formed from glucocorticoids in response to stress-induced neurochemical changes, are expected to fluctuate in response to both acute and diurnal perturbations, it is commonly used to measure the functionality of biological stress mechanism.[39]

Evidence from population studies using diurnal cortisol suggests that markedly elevated or reduced cortisol concentrations may indicate risk for metabolic dysregulation.[178,186,187]For example, using the Whitehall II study, Hackett et al. (2016) showed that blunted diurnal cortisol slope and higher bedtime cortisol was associated with an onset of type 2 diabetes.[188] In the Multiethnic Study of Atherosclerosis (MESA), longitudinal increase in body weight was linked to a gradual decline in diurnal cortisol output, independent of type 2 diabetes status.[189] However, there were no statistically significant associations found between fasting glucose and diurnal cortisol.[190]

Compared to diurnal cortisol, acutely-induced changes in cortisol may be a more informative indicator of the HPA-axis dysregulation and subsequently its role in linking stress and metabolic dysfunction.[186] For example, among people with type 2 diabetes, loneliness (as a

form of chronic stress) was inversely associated with acute stress reactivity to a mental stress task, [191] while dysregulated sleep was associated with blunted acute, but higher diurnal cortisol output.[192] However, in a recent systematic review, Turner et al. (2020) found that 2/3 of all reviewed studies (total n=263) report no evidence of association between baseline stress reactivity and health outcomes.[193] However, positive associations were found between acute cortisol reactivity and hypertension or carotid artery calcification, but null findings regarding increased adiposity or obesity.[193] Another systematic review focused on cortisol and obesity, found supportive evidence for positive association with the HPA-axis reactivity and obesity (BMI) or abdominal fat.[194]In a study comparing adults with and without diabetes, matched on sex, income and age, Steptoe et al. (2014) found that diabetes was associated with a blunted HPA (cortisol) stress reactivity to a laboratory stressor. Compared to the participants without diabetes, the group with diabetes had on average higher baseline cortisol and diurnal cortisol output, and also reported higher chronic stress and depressive symptoms.[53]

In sum, although the overall evidence remains inconclusive, a general pattern of findings suggests that incident diabetes may be associated with higher psychosocial stress burden and either higher or lower output of diurnal cortisol.[195] The evidence is less clear regarding the link between diabetes and the HPA-axis reactivity.[196]

Current study

This study pursued two main goals. First, we aimed to examine whether self-reported perceived stress and HPA-axis stress reactivity were associated with incident type 2 diabetes. Second, to explore these questions across distinct, but complementary data sources, we aimed to replicate our results in two prospective cohort studies (i.e., the Richmond Stress and Sugar study (RSASS) and the Healthy Aging in Neighborhoods of Diversity across the Lifespan study

(HANDLS)). RSASS and HANDLS share a common focus on understanding cardiometabolic

health disparities and have a similar sampling design but differ in terms of sample size and

duration of follow-up.

We hypothesize that higher self-reported perceived stress and blunted cortisol response to

acute stress will be associated with incident diabetes. We also hypothesize that socioeconomic

status, but not race, will modify the observed associations between stress and diabetes. Second,

considering a limited sample size in RSASS, we expected that we would be able to replicate the

magnitude and direction of main results, but not their statistical significance.

Convergence of evidence from two longitudinal studies that have shared design features,

but uncorrelated sources of measurement error and other biases may offer important

contributions to the growing body of research on the relationship between psychosocial stress

and diabetes.

4.2 Methods

Data

Study Population 1: The Healthy Aging in Neighborhoods of Diversity across the Lifespan

The Healthy Aging in Neighborhoods of Diversity across the Lifespan study (HANDLS) is a

prospective cohort of community adults residing in Baltimore City, Maryland begun in 2004.

Details on the study design and recruitment are described in Chapter 3 of this thesis and

elsewhere.[140] Briefly, participants were selected from an area probability sample of thirteen

Baltimore census tracts, based on an intersection between age, sex, race, and neighborhood

poverty status.[140] Inclusion criteria were self-identification as non-Hispanic Black or African

American (hereafter, Black) or non-Hispanic white (hereafter, White) race and ethnicity, aged

30-64 years old at enrollment, and able to give informed consent; individuals who were pregnant,

being treated for cancer, or who had HIV/AIDS were ineligble.[140] The initial sample consisted of n=3720 participants, where wave 1 laboratory and psychosocial examinations were conducted on n=2,707 (response rate=73%) using medical research vehicles (MRVs). Subsequent assessments were repeated every two to three years. This analysis uses data collected in wave 1, wave 3 (2009-2013) and wave 4 (2013-2017). Among the 3720 individuals, originally selected into the sample, 505 participants were missing information on outcome, while 1470 participants were missing the exposure, resulting in an analytic sample of 2247.

HANDLS was approved by the Institutional Review Board (IRB) at the National Institute on Aging and all participants provided written informed consent. This analysis used only de-identified data and was determined to be exempt from human subjects' regulations by the University of Michigan IRB.

Study Population 2: The Richmond Stress and Sugar Study

Richmond Stress and Sugar Study (RSASS) is a longitudinal cohort of adults at risk of diabetes. The baseline study sample (n=125) was recruited from the Virginia Commonwealth University (VCU) healthcare network located in Richmond, Virginia during 2016-2018. Specifics of study design and recruitment process are detailed in chapter 2 of this study and elsewhere [85]. Briefly, a key feature of RSASS was recruitment of participants based on stratified sampling by neighborhood SES and race and ethnicity: 1) Non-Hispanic White (hereafter, White) + high SES, 2) White + low SES, 3) Non-Hispanic Black (hereafter, Black) + high SES, and 4) Black + low SES. Participants were eligible if they were between 40 – 70 years old and had one or more of the following risk factors for diabetes: impaired glucose tolerance, elevated total glucose or HbA1c, hypertension, obesity, or history of gestational diabetes [85]. Study exclusion criteria included diagnosis of diabetes (type 1 or 2) or another serious medical

condition, including Cushing's disease, cancer, or bipolar disorder [85]. Medical records were linked to the RSASS data.

RSASS was approved by the VCU Institutional Review Board (IRB); all participants provided written informed consent. Analysis for this project was approved by the University of Michigan IRB.

Measures

Exposure: Perceived stress

Both HANDLS and RSASS used Perceived Stress Scale (PS) to assess current perceptions of general stress within the last month (e.g., *in the last month, how often have you been upset because of something that happened unexpectedly?*). [88] In RSASS, the 10-item PS scale was administered at all visits, in HANDLS, the 4-item PS scale was administered at visit 1 only (all 4 items were also in the 10-item version fielded in RSASS). Item responses were recorded on a 5-point Likert scale ranging from *never (0)* to *very often (4)*. To generate a total score, positively stated items were reversed, and all items were summed. See supplemental table 1 for details on each of the calculated scores.

In HANDLS and RSASS, we modeled the summary scores from the 4-item PS scale as a factor, after median-splitting the empirical distribution, such that participants with scores at or below the median were considered reporting "low" stress, while everyone with above median values were assigned to a "high" stress category. In RSASS, we also modeled the summary of the 10-item PS scale as continuous, scaled by their respective interquartile ranges, such that the mean difference between 25th and 75th quartiles of the empirical distribution would correspond to "low" and "high" self-reported stress.

Exposure: HPA-axis stress reactivity

In RSASS only, the neurobiological stress response was measured by changes in salivary cortisol in response to the Trier Social Stress Test (TSST), a validated test for eliciting stress response in a laboratory setting [86]. The TSST consisted of two consecutive challenges, both performed in front of a panel of emotionally-reserved judges: a 5-minute speech about why they should be hired for their "dream job," followed by a 2-minute mental arithmetic task (subtracting 13 from 1,022) [85]. In total, eight salivary cortisol samples were collected across two hours: two pre-TSST and six post-TSST, including four after the hypothesized peak at the fourth collection point (i.e., approximately 20 minutes after the completion of the TSST).

To create an indicator for biological stress response, we followed a strategy, developed by Lopez-Duran et al. (2014), where we assigned each participant into either responder or non-responder category, based on their cortisol response curve. Participants, who at their peak show at least 20% increase in cortisol concentration fro m the pre-TSST assessment, were assigned a responder status.[197] In a sensitivity analysis, we also calculated area under the curve (AUC) for cortisol with respect to ground (AUCg) and increase (AUCi).[198] AUCg is an estimate of the total cortisol secretion prior to the TSST test, which reflects the baseline circulating cortisol. AUCi capture the change in cortisol attributable to the acute stressor exposure; it is calculated by subtracting the AUCg from the total AUC over the entire TSST test.Two participants did not provide salivary cortisol samples and were excluded from this analysis.

Outcome: Diabetes Mellitus

In both RSASS and HANDLS, diabetes status (no vs. yes) was ascertained based on the following criteria: receiving a diagnosis by a healthcare provider (either self-report or medical records), taking diabetes medication (self-report), or using laboratory measures (i.e., fasting serum glucose $>$=126 mg/dL or glycated hemoglobin (A1c) >=5.6%).[199] In HANDLS, due to the

inclusion of the hemoglobin A1c as an additional indicator of the diabetes status, we screen-detected additional 37 cases and non-cases, whose outcome would have otherwise been set to missing. Thus, among the 3215 individuals with available information on outcome, a total of 307 (8.3%) participants developed diabetes during the follow-up time. In HANDLS, diabetes status refers to either type 1 or type 2 diabetes.

In RSASS, in addition to using self-reported data and laboratory values as described above, we linked the survey data to VCU medical records. The medical records included laboratory assessments (i.e., glucose) and diabetes diagnoses (ICD codes staring with E11). Among the 125 participants seen at baseline, 21 (17%) participants lost-to-follow up by the 6th months visit, and additional 36 (35%) – by the 12th months visit. Using medical records, information on diabetes status was recovered for 16 missing participants. Despite RSASS eligibility screener, 6 participants were censored, since their medical chart data indicated pre-existing diabetes.

Covariates

In both RSASS and HANDLS, information on sociodemographic factors was obtained from the baseline interview and included age (in years), sex (male, female), marital status (married/in relationship, separated/widowed, single/never married), education (less than high school, high school or GED, some college or higher), current employment (employed vs. unemployed/disabled/retired), and health insurance (yes, no).These factors were previously shown to be important common causes of psychosocial stress and cortisol and diabetes and were explored as key covariates.[90,200,201]

Indicators for race and ethnicity (White vs Black) and poverty status (above vs below 125 %) in HANDLS only and neighborhood socioeconomic status (high vs. low) in RSASS

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served as key features in stratified sampling design for respective studies and were additionally explored as effect modifiers.[202] Lifestyle behaviors and related factors (i.e., waist circumference, depression status, and medication use) have been previously shown to be confounders and mediators between stress and cardiometabolic risk; [75,203]their influence was assessed in sensitivity analyses. Smoking status (never/past or current) and alcohol use (never/past or current) were measured by self-report. Waist circumference (in centimeters) was measured by trained interviewers. Finally, hypertension status as a predictor of diabetes and medication use (i.e., steroids, beta blockers and glucocorticoids, each coded dichotomously (yes, no)) as a correlate of cortisol levels reflect participants' health status and were added to relevant models.[204,205]

In HANDLS, missing baseline values of the covariates were multiply imputed in a series of sensitivity analyses. In RSASS, for participants, whose outcome status was recovered from medical records, we carried the value of the time-varying covariates or predictors from the last observation.

Statistical Analysis

Initially, descriptive and exploratory univariate analyses using statistical summaries and data visualization were performed to examine patterns of missingness, variable distributions, outliers, and general characteristics.

Next, separately in each sample, we conducted parallel time-to-diabetes analyses using semi-parametric Cox models. Participant age was used as a time scale. Below is a general expression of a semi-parametric hazard function for the ith observation at time y_i for a participants at risk: $h(t|x_i) = h_0(t)\exp\left(\sum_{j=1}^{p} x_{ij}\beta_j\right)$, where $h_0(t) \geq 0$ is an unspecified

functional form of the baseline hazard, and $\exp\left(\sum_{j=1}^{p} x_{ij}\beta_j\right)$ is the relative rate of diabetes. Here, one unit increase in x_{ij} corresponds to an increase in $h(t|x_i)$ by a factor of $\exp(\beta_j)$; parameters $\beta = (\beta_1, \dots, \beta_p)^T$ are estimated by maximizing partial likelihood with respect to β.[206] For the purposes of conducting parallel analyses, we aimed to use similar analytical approaches in each sample. However, this common analytic approach was altered to address unique differences in sample design and data availability in each sample as detailed below.

Time-to-diabetes in HANDLS

To model time to diabetes onset as a function of baseline PS (4-item scale) and covariates, we started by fitting five sequential semi-parametric Cox proportional hazard models, assuming a counting process to adjust for delayed entry into the cohort. Participants who were lost-to-follow up or have not developed diabetes before the end of study follow-up (wave 4), were right-censored. In Cox models, predictors have a multiplicative effect on the hazard. The proportional-hazards assumption was examined using Schoenfeld residuals and log-minus log survival versus log survival curves, with no significant violations detected.

Model 1 included a dichotomous median-split indicator for perceived stress; Model 2 was adjusted for key demographic characteristics, including sex, race and ethnicity, baseline poverty status, education and employment status, as these factors could confound the association between stress and diabetes. In model 3, we excluded employment status, but further added health insurance status and hypertension to adjust for differential access to healthcare and health history. Model 4 was further adjusted for lifestyle indicators such as substance use and waist circumference (centered). Model 5 was adjusted for depressive symptoms, measured by CES-D scale. Based on the exploratory analyses using penalized splines, waist circumference and CES-

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D scores were fitted as continuous linear terms. Based on previous research, unique

characteristics included in model 4 and 5 were considered as potential confounders and/or

mediators, therefore model 3 was considered final. Finally, product terms were added to separate

fully adjusted models to test for effect modification by SES and race using Log Likelihood test.

We also examined effect modification by race and ethnicity on additive scale, where confidence

intervals were approximated by the delta method.[207]

Since outcome assessments occurred between follow-up examinations, the specific time

of diabetes onset was interval-censored. To address both interval censoring and left-censoring

(n=483), we fit the final model 3 as an accelerated failure time (AFT) model, assuming Weibull

distribution for logarithm of failure times: $\log(T_i) = X_i^T \beta + \sigma \varepsilon_i$, where $\sigma > 1$ is the variance (or

scale) of residual errors and ε_i is the error term that follows Weibull distribution:

$\varepsilon_i \sim Weibull(\mu_i, a)$ with mean $\mu_i = \exp\{X_i^T \beta\}$ and a shape parameter $a = \frac{1}{\sigma}$.

The choice of Weibull distribution was based on information criteria using AIC and the

empirical plot of log of a Kaplan-Meier estimate of the survivor function against logarithm of

time. Since the log-log of the survival function was approximately linear with the log of time, the

main assumption of a parametric accelerated failure time (AFT) model was satisfied.[208] Weibull

model is both an AFT model and proportional hazards model, therefore we can rewrite Weibull

conditional hazard function as: $h(t|X_i) = h_0(t)\exp\{X_i^T - a\beta_j\}$, where baseline hazard function is

$h_0(t) = ha(ht)^{a-1}$, and a is acceleration factor that defines monotonically increasing hazard

with accelerating survival time when $a > 1$.[208] Here a unit change in X_j corresponds to an increase

in $h(t|X_i)$ by a factor of $\exp(-a\beta_j)$. Adjusted survival plots for incident diabetes comparing

high vs. low stress, dichotomized at the median, and additionally by race and ethnicity were

created based on both parametric and semi-parametric estimates to illustrate absolute and relative survival.

Competing Risks and Missing Data

Among the right-censored participants (n=2425), 1608 (72%) were administratively censored and 817 (34%) were lost-to-follow-up, among which 303 participants died. In this study, we explored missing patterns in exposure, covariates and outcomes and addressed these through various sensitivity analyses. To address the role of missingness in the main exposure and covariates, we compared four sets of results from various imputation and combination methods that are known to generate different levels of bias.[209] Prior to imputation, we explored missing patterns by comparing characteristics by the missing status. To address potential concerns of informative censoring, we used available mortality data to explore the extent to which death as a competing risk may have biased our results from parametric or semi-parametric models that assume censored individuals to remain at risk of developing the outcome of interest after leaving the study. Further details and exploratory results are presented in the supplemental materials.

Time-to-Diabetes in RSASS

To explore whether time-varying self-reported stress and baseline acute stress reactivity were associated with incident diabetes, we fitted two sets of sequential Cox-proportional models, following a strategy detailed above. Given the limited sample size, all covariates were categorized into binary indicators; effect modification by race or neighborhood SES was not explored. Attrition over the study follow-up was partially mitigated by linking study data to medical records. Since the follow-up occurred over relatively short period of time (every 6

months), we addressed missingness in predictors and covariates by carrying forward the last value observed.

4.3 Results

Baseline characteristics in HANDLS and RSASS

Table 1 compares baseline participant characteristics in the full HANDLS sample (n=3720) and by median split perceived stress. In the full sample, median age was 49 years, 59% of participants were black, 65% had health insurance, and 41% reported household income below 125% poverty level. Compared to reporting median or below levels of stress (*low* hereafter), participants with above median (*high* hereafter) perceived stress tended to be younger and had a shorter length of follow-up. A larger percentage of participants with high stress lived below poverty, had lower education, were more likely to be uninsured, unemployed or disabled, were more likely to currently use tobacco and report higher depressive symptoms.

Tables 2 and 3 show baseline participant characteristics in the full RSASS sample (n=125) and by median-split 4-item perceived stress or cortisol response status, respectively. In the full sample, median age was 57 years, approximately half of the participants were black or female, over 80% had some form of health insurance, and 40% were from low neighborhood SES. Comparing high vs. low perceived stress groups or responder vs. non-responder status, no univariate differences were observed in terms of age, sex, race and ethnicity, marital status, alcohol use, waist circumference or systolic blood pressure. Table 2 shows that participants reporting high perceived stress had lower education, lower total cortisol levels, but higher cholesterol level and depression severity. Table 3 shows that compared to responders to acute stress challenge, participants assigned a non-response status, had lower education, and were

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more likely to be unemployed or disabled, reside in a low neighborhood SES, or report current tobacco use. Non-responders also reported higher perceived stress and depression severity.

Associations between stress and diabetes: HANDLS

Among the 2247 individuals with available information on exposure and outcome, 360 (16%) participants had a prevalent type 1 or type 2 diabetes; a total of 197 (8.8%) participants developed diabetes during a median study follow-up of 7 years (interquartile range: 3 to 8 years). Median-split perceived stress was not associated with incident diabetes in any of the models, with observed attenuation of the effect size after adjusting for the main demographic characteristics and other covariates (Table 4). Similar results were obtained when fitting parametric Weibull models (Table 5), cause-specific hazard models or multistate models (Supplemental Table 2).

Supplemental Tables 3-4 shows the results for testing effect modification by race and ethnicity, poverty level and education status on a multiplicative scale. While there was no evidence for effect modification by poverty or education level, the association between perceived stress and incident diabetes did vary by race (Figure 1). Supplemental table 5 displays results from both parametric and semi-parametric models, where effect modification by race and ethnicity is shown on additive and multiplicative scales. Since the hazard ratios were similar in both models, we will interpret estimates from the semi-parametric model. Compared to White adults with low stress, the expected hazard ratio for incident diabetes was 1.94 (95% CI: 1.20, 3.16) for Black adults reporting low stress and 1.70 (95 % CI: 1.03, 2.83) for Black adults reporting high stress. Although the hazard for White adults with high stress vs. low stress was 60% (95% CI: 0.92, 2.76) higher, 95% confidence intervals included unity. The size of

association and direction were comparable across parametric and non-parametric models. Results from models fit to multiply imputed datasets were generally consistent with the complete case analysis, showing slight increase in effect estimates for perceived stress (Supplemental table 5-6).

Associations between stress and diabetes: RSASS

Among the 125 individuals, 14 developed incident diabetes over a median study follow-up of 12 months (interquartile range: 7 to 13 months). Neither median-split perceived stress nor binary indicator of stress response was associated with incident diabetes in any of the models (Table 6 and 7). Similar results were obtained for continuous exposures for 10-item perceived stress (Stable 6) and AUC increase (Supplemental Table 7). All the estimates of associations were in the expected direction, whereas the HR for the association between perceived stress and diabetes tracked those obtained in HANDLS but were larger in magnitude. Simple power calculations using the *powerSurvEpiR* package revealed that if we were to assume that obtained HR=1.54 for perceived stress and HR=1.35 for cortisol response were true, the sample size of 526 and 3095, respectively, were needed to detect these associations, considering exposure and outcome distribution in the RSASS sample, at alpha value of 0.05 and power of 80%.

4.4 Discussion

This study sought to clarify the role of stress as a contributor to type 2 diabetes incidence, with attention to inequities in diabetes risk. To do so, we used data from two prospective cohort studies that have similar sampling frames appropriate for investigating stress as a contributor to diabetes disparities. Our results showed that stress was not significantly associated with diabetes, although the estimates of association were in the hypothesized direction. This null finding was

consistent across two distinct measures of stress: perceived stress and acute HPA-axis stress reactivity.

The null finding is in line with some, but not all, prior studies.[79,210,211] For example, in a 15-year follow-up of the Whitehall II cohort, psychological distress, assessed by the General Health Questionnaire, was not associated with incident diabetes in the sample overall. However, among the subset of participants who were at higher risk of diabetes, this measure of psychological distress was associated with two-times greater risk of diabetes.[212] In general, the inconsistent findings regarding the stress-diabetes relationship likely reflect systematic differences in the sample populations, variation in measures of psychosocial stress, differences in the frequency of stress assessments, differences in follow-up duration, as well as publication bias.[195,213,214]

In the HANDLS cohort we sought to explore how stress related to racial disparities in diabetes risk. We found that compared to White adults with low levels of stress, White adults with high stress and Black adults (both high and low stress) had higher diabetes incidence. However, when examining the relationship between stress and diabetes within each racial group, perceived stress was not significantly associated with diabetes among Black or White adults. These findings suggest some potential interpretations. First, the perceived stress measure may not adequately reflect the underlying stress experiences of the Black adults; indeed, the internal consistency of this measure was lower among Black vs. White adults (Cronbach's alpha: 0.56 vs. 0.71, respectively). As such, the observed differences between White adults with low stress and Black adults (both low and high stress) may reflect the insensitivity of this stress scale to index variation within non-White groups as it relates to diabetes risk. It may also be that factors such as experiences of interpersonal discrimination, historical and structural racism in policies, and processes that are correlated with self-reported race and ethnicity suppress the relationship

between perceived stress and diabetes risk. Finally, this analysis may have been underpowered to detect subgroup effects, particularly among the White participants with lower socioeconomic status as this group was underrepresented in the cohort.[140]

Replication is a central component of the scientific process, and it is through replication that fields move from isolated findings to shared knowledge.[215] A key strength of this study is its explicit focus on replication at various scales: first, it used two cohorts (HANDLS and RSASS) that were designed with similar goals (i.e., to understand social disparities in health) and had similar sampling frames (i.e., purposeful sampling by neighborhood SES and race). Second, it used measures that were conceptually similar (self-report stress and acute stress reactivity) and in some cases operationally identical (e.g., 4-item perceived stress scale) across those two cohorts. We also conducted parallel analyses in each cohort using analytic approaches (e.g., Cox and Weibull models) that each addressed different issues in the data. Parallel analyses demonstrate convergence of evidence across two longitudinal samples and provides a more robust understanding of the substantive question (i.e., *what is the relationship between stress and diabetes risk?*) than could be obtained from looking within a single cohort, with a single measure, and a single analytic approach. At the same time, parallel analyses also illustrate potential challenges around using different data sources that may include non-transferable populations, non-compatible measures, and different sources of bias requiring specific and non-replicable analytic approaches. Finally, parallel analysis provides an applied illustration of the conceptual and analytical strategies that build foundation for a future analytic approaches that may include direct data synthesis and integration.

Findings should be viewed considering study limitations. Although this study aimed to compare findings between two data samples, designed to reflect experiences of urban adults of

the Eastern U.S., neither datasets were representative, probability samples. Additionally, a combination of documented challenges in study recruitment[85,140] coupled with complex multi-stage sampling designs, may have yielded unique and non-comparable samples. Limitations in ascertainment of the outcome (i.e., inclusion of type 1 and 2 diabetes) and exposure (i.e., a short scale, administered at the first visit only) in HANDLS may have biased our results toward the null. Although RSASS sample contained the detailed assessments of stress experiences, the study was significantly underpowered due to a small number of cases and a relatively short follow-up period. Although estimates from the Weibull parametric models were similar to those obtained from the semi-parametric models, the magnitude of the Weibull estimates were attenuated despite the smaller confidence intervals. Although graphical assessments of the model fit were adequate, attenuation in the model coefficients may be due to a misspecification of the mean structure of the Weibull models. To address these limitations in both studies efforts were made to address potential concerns for bias due to attrition, by utilizing available information on mortality in HANDLS, multiply imputing missing data, and linking medical health records to RSASS data.

In conclusion, this internal replication study contributes toward elucidating the complex stress paradigm and its role in diabetes health disparities by examining the evidence from two uniquely positioned longitudinal cohort studies (i.e., HANDLS and RSASS). This study also lays a foundation for future planned efforts that include application of recently developed data integration techniques (i.e., either through Bayesian inference[216] or a combination of data synthesis and direct analytical derivations[217]) and reliance on larger external probability samples (i.e., MIDUS, MESA) to improve precision and accuracy of estimates from our non-probability samples.

Table 4-1. Baseline HANDLS sample: participant characteristics by medium-split perceived stress.

n (%) or median [IQR]	Overall sample	4-item Perceived Stress Median-Dichotomized		
	3720	Below/at (n=1135)	Above (n=1115)	p
Time on study (years)	6.95 [3.00, 8.00]	8.02 [5.59, 9.39]	7.41 [5.24, 9.09]	0.003
Perceived stress scale	5.00 [3.00, 8.00]	3.00 [1.00, 4.00]	8.00 [7.00, 9.00]	<0.001
Baseline age	48.70 [40.70, 55.90]	49.20 [41.45, 56.35]	48.40 [40.80, 55.45]	0.034
Black adults	2198 (59.1)	673 (59.3)	621 (55.7)	0.092
Below poverty[1]	1535 (41.3)	402 (35.4)	546 (49.0)	<0.001
Male sex	1685 (45.3)	506 (44.6)	468 (42.0)	0.228
Education				<0.001
<HS	1242 (33.4)	388 (34.2)	354 (31.7)	
HS/GED	1240 (33.3)	263 (23.2)	433 (38.8)	
College or higher	1142 (30.7)	457 (40.3)	296 (26.5)	
Missing	96 (2.6)	27 (2.4)	32 (2.9)	
Employment				<0.001
Employed	2059 (55.3)	704 (62.0)	537 (48.2)	
Unemployed/disabled	1091 (29.3)	254 (22.4)	385 (34.5)	
Retired/other	478 (12.8)	150 (13.2)	162 (14.5)	
Missing	92 (2.5)	27 (2.4)	31 (2.8)	
Marital Status				0.215
Partnered	1691 (45.5)	532 (46.9)	475 (42.6)	
Separated	802 (21.6)	251 (22.1)	257 (23.0)	
Single	1135 (30.5)	325 (28.6)	352 (31.6)	
Missing	92 (2.5)	27 (2.4)	31 (2.8)	
Health Insurance				0.002
Yes	2415 (64.9)	787 (69.3)	693 (62.2)	
No	1213 (32.6)	321 (28.3)	391 (35.1)	
Missing	92 (2.5)	27 (2.4)	31 (2.8)	
Hypertension status				0.863
No	1465 (39.4)	613 (54.0)	590 (52.9)	
Yes	1285 (34.5)	492 (43.3)	496 (44.5)	
Missing	970 (26.1)	30 (2.6)	29 (2.6)	
CES-Depression[2]	-2.16 [-9.16, 6.84]	-8.16 [-11.16, -2.16]	2.84 [-4.16, 12.84]	<0.001
Waist Circumference[3]	-1.92 [-12.92, 12.08]	-0.92 [-12.92, 11.08]	-2.92 [-14.92, 10.08]	0.187
Alcohol use				0.178
Current	1490 (40.1)	589 (51.9)	613 (55.0)	
Never/past	1091 (29.3)	426 (37.5)	406 (36.4)	
Missing	1139 (30.6)	120 (10.6)	96 (8.6)	
Tobacco Use[4]				<0.001
Never/past	1310 (35.2)	566 (49.9)	478 (42.9)	
Current	1291 (34.7)	458 (40.4)	550 (49.3)	
Missing	1119 (30.1)	111 (9.8)	87 (7.8)	
Outcome Status				--
Censored	1952 (52.5)	730 (64.3)	692 (62.1)	
Incident diabetes[5]	307 (8.3)	98 (8.6)	99 (8.9)	
Prevalent diabetes	483 (13.0)	184 (16.2)	176 (15.8)	
All-cause mortality	642 (17.3)	176 (15.5)	215 (19.3)	
Missing	505 (13.6)	2 (0.2)	1 (0.1)	

1.125% Poverty Level for size-adjusted annual household income, calculated based on 2004 cut-off values.
2. 20-item Center for Epidemiologic Studies Depression Scale (CES-D) summary score, mean-centered
3. Waist circumference, measured in centimeters, mean-centered.
4. Tobacco use includes self-reported smoking cigarettes, cigars or pipes.
5. Diabetes status was ascertained based on self-reported history of diagnosis, prescription medications for diabetes mellitus and/or having a fasting serum glucose of >125 mg/dL or hemoglobin A1c =>5.6%

Table 4-2. Baseline RSASS sample: participant characteristics by medium-split 4-item perceived stress.

n (%) or median [IQR]	Overall sample	4-item Perceived Stress Median-Dichotomized		
		Below/At (n=67)	Above (n=58)	p
Perceived stress (10-item)	16.00 [10.00, 20.00]	11.00 [8.00, 13.00]	20.00 [17.00, 24.00]	<0.001
Perceived stress (4-item)	5.00 [3.00, 7.00]	3.00 [2.00, 5.00]	7.00 [6.00, 9.00]	<0.001
AUC total[1]	0.54 [0.39, 1.05]	0.70 [0.43, 1.08]	0.46 [0.30, 0.87]	0.028
AUC increase[1]	0.06 [-0.04, 0.29]	0.07 [-0.07, 0.32]	0.06 [-0.01, 0.15]	0.994
Stress responder[1]	75 (60.0)	43 (64.2)	32 (55.2)	0.515
Baseline age	57.00 [52.00, 63.00]	59.00 [52.00, 65.00]	55.00 [51.00, 62.00]	0.122
Female sex	61 (48.8)	30 (44.8)	31 (53.4)	0.431
Black adults	60 (48.0)	32 (47.8)	28 (48.3)	0.825
High neighborhood SES	76 (60.8)	40 (59.7)	36 (62.1)	0.931
Education				0.08
<HS	26 (20.8)	9 (13.4)	17 (29.3)	
Some college	32 (25.6)	20 (29.9)	12 (20.7)	
College or higher	67 (53.6)	38 (56.7)	29 (50.0)	
Employment status				0.227
Full/part-time	66 (52.8)	39 (58.2)	27 (46.6)	
Unemployed/disabled	34 (27.2)	14 (20.9)	20 (34.5)	
Retired/other	25 (20.0)	14 (20.9)	11 (19.0)	
Marital status				0.687
Married/in partnership	61 (48.8)	35 (52.2)	26 (44.8)	
Divorced/separated	39 (31.2)	19 (28.4)	20 (34.5)	
Single	25 (20.0)	13 (19.4)	12 (20.7)	
Health insurance (Yes)	109 (87.2)	61 (91.0)	48 (82.8)	0.265
Tobacco use[2]				0.543
Never	50 (40.0)	29 (43.3)	21 (36.2)	
Past	43 (34.4)	23 (34.3)	20 (34.5)	
Current	31 (24.8)	14 (20.9)	17 (29.3)	
Alcohol use[3]				0.919
Never or past	43 (34.4)	24 (35.8)	19 (32.8)	
Occasional or moderate	68 (54.4)	36 (53.7)	32 (55.2)	
Frequent and heavy	14 (11.2)	7 (10.4)	7 (12.1)	
Depression [4]	5.00 [2.00, 11.00]	3.00 [2.00, 5.00]	9.00 [6.00, 12.00]	<0.001
Waist circumference (cm)	100.50 [86.75, 109.00]	99.00 [86.50, 108.00]	101.00 [87.00, 111.00]	0.855
Systolic blood pressure (mmHg)	132.00 [123.00, 143.00]	133.00 [123.00, 143.50]	131.00 [124.25, 143.00]	0.927
Total cholesterol (mg/L)	172.00 [144.00, 213.00]	165.00 [136.50, 201.00]	185.50 [153.25, 214.75]	0.041
HbA1c (%)	5.70 [5.50, 5.93]	5.70 [5.53, 5.90]	5.70 [5.50, 5.97]	0.624
Event status[5]				--
No diabetes	106 (84.8)	56 (83.6)	50 (86.2)	
Incident diabetes	14 (11.2)	8 (11.9)	6 (10.3)	
Diabetes prior to entry	5 (4.0)	3 (4.5)	2 (3.4)	

Missing: waist circumference (n=5), smoking (n=1), depression diagnosis (n=2)

1. AUC (area under the cortisol curve) and acute stress response status were calculated based on eight sample of salivary cortisol collected at baseline assessment before and after the administered laboratory stress challenge.

2. Tobacco use includes self-reported smoking cigarettes, cigars, pipes, or chewing tobacco.

3. Occasional reflects > 2 drinks per occasion on > 15 days/month; frequent/heavy≥ 2 drinks on ≤ 15 days/month

4. Depression severity was assessed with the Patient Health Questionnaire depression scale (PHQ-12), where symptoms related to sleep, eating and energy level were collapsed into one, such that the final score reflects a more common PHQ-9 scale.

5. Diabetes status was ascertained based on self-reported history of diagnosis, prescription medications for diabetes mellitus and/or having a fasting serum glucose of >125 mg/dL or hemoglobin A1c =>5.6%

Table 4-3. Baseline RSASS sample: participant characteristics by stress response.

n (%) or median [IQR]	Overall sample	Acute Stress Response[1]		
	125	Non-response (n=47)	Responder (n=75)	p
Perceived stress (10-item)	16.00 [10.00, 20.00]	18.00 [12.50, 21.00]	14.00 [10.00, 17.50]	0.024
Perceived stress (4-item)	5.00 [3.00, 7.00]	6.00 [4.00, 8.00]	5.00 [2.50, 6.00]	0.043
AUC total[1]	0.54 [0.39, 1.05]	0.47 [0.31, 0.80]	0.70 [0.41, 1.11]	0.035
AUC increase[1]	0.06 [-0.04, 0.29]	-0.06 [-0.12, 0.03]	0.13 [0.03, 0.50]	<0.001
Baseline age	57.00 [52.00, 63.00]	56.00 [52.00, 62.00]	59.00 [51.50, 64.00]	0.552
Female sex	61 (48.8)	24 (51.1)	36 (48.0)	0.886
Black adults	60 (48.0)	23 (48.9)	36 (48.0)	0.157
High neighborhood SES	76 (60.8)	20 (42.6)	55 (73.3)	0.001
Education				0.002
<HS	26 (20.8)	15 (31.9)	9 (12.0)	
Some college	32 (25.6)	15 (31.9)	16 (21.3)	
College or higher	67 (53.6)	17 (36.2)	50 (66.7)	
Employment status				0.009
Full/part-time	66 (52.8)	19 (40.4)	45 (60.0)	
Unemployed/disabled	34 (27.2)	20 (42.6)	13 (17.3)	
Retired/other	25 (20.0)	8 (17.0)	17 (22.7)	
Marital status				0.233
Married/in partnership	61 (48.8)	20 (42.6)	41 (54.7)	
Divorced/separated	39 (31.2)	18 (38.3)	18 (24.0)	
Single	25 (20.0)	9 (19.1)	16 (21.3)	
Health insurance (Yes)	109 (87.2)	39 (83.0)	68 (90.7)	0.329
Tobacco use[2]				0.001
Never	50 (40.0)	12 (25.5)	37 (49.3)	
Past	43 (34.4)	14 (29.8)	28 (37.3)	
Current	31 (24.8)	20 (42.6)	10 (13.3)	
Alcohol use[3]				0.644
Never or past	43 (34.4)	16 (34.0)	27 (36.0)	
Occasional or moderate	68 (54.4)	24 (51.1)	41 (54.7)	
Frequent and heavy	14 (11.2)	7 (14.9)	7 (9.3)	
Depression[4]	5.00 [2.00, 11.00]	7.00 [3.00, 12.00]	5.00 [2.00, 9.00]	0.016
Waist circumference	100.50 [86.75, 109.00]	100.50 [84.25, 109.75]	101.00 [88.75, 108.25]	0.808
Systolic blood pressure	132.00 [123.00, 143.00]	132.00 [125.00, 139.00]	133.00 [123.00, 147.50]	0.278
Total cholesterol	172.00 [144.00, 213.00]	172.00 [140.00, 212.50]	172.00 [154.00, 213.00]	0.833
HbA1c	5.70 [5.50, 5.93]	5.70 [5.50, 6.00]	5.70 [5.50, 5.90]	0.89
Rx beta blockers (Yes)	16 (12.8)	4 (8.5)	12 (16.0)	0.359
Rx statins (Yes)	20 (16.0)	8 (17.0)	11 (14.7)	0.926
Rx glucocorticoids (Yes)	8 (6.4)	1 (2.1)	7 (9.3)	0.234
Event status[5]				0.549
No diabetes	106 (84.8)	38 (80.9)	65 (86.7)	
Incident diabetes	14 (11.2)	6 (12.8)	8 (10.7)	
Diabetes prior to entry	5 (4.0)	3 (6.4)	2 (2.7)	

Missing: waist circumference (n=5), smoking (n=1), depression diagnosis (n=2)

1. AUC (area under the cortisol curve) and acute stress response status were calculated based on eight sample of salivary cortisol collected at baseline assessment before and after the administered laboratory stress challenge.

2. Tobacco use includes self-reported smoking cigarettes, cigars, pipes, or chewing tobacco.

3. Occasional reflects > 2 drinks per occasion on > 15 days/month; frequent/heavy≥ 2 drinks on ≤ 15 days/month

4. Depression severity was assessed with the Patient Health Questionnaire depression scale (PHQ-12), where symptoms related to sleep, eating and energy level were collapsed into one, such that the final score reflects a more common PHQ-9 scale.

5. Diabetes status was ascertained based on self-reported history of diagnosis, prescription medications for diabetes mellitus and/or having a fasting serum glucose of >125 mg/dL or hemoglobin A1c =>5.6%

Table 4-4. HANDLS: Cox-proportional hazard ratios for perceived stress and incident diabetes

Model (N Events)	Model 1 (n=197)			Model 2 (n=193)			Model 3 (n=187)			Model 4 (n=160)			Model 5 (n=186)		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Perceived stress [ref: <=Median]															
>Median	1.17	0.88, 1.55	0.3	1.06	0.79, 1.41	0.7	1.04	0.78, 1.40	0.8	0.99	0.72, 1.36	>0.9	0.88	0.64, 1.23	0.5
Sex [ref: Female]															
Male				0.90	0.67, 1.20	0.5	0.92	0.69, 1.24	0.6	0.93	0.67, 1.29	0.7	0.94	0.70, 1.26	0.7
Race [ref; White]															
Black				1.49	1.09, 2.05	**0.013**	1.41	1.02, 1.95	**0.036**	1.46	1.04, 2.06	**0.031**	1.46	1.06, 2.03	**0.022**
Poverty status [ref: Above]															
Below				0.98	0.72, 1.35	>0.9	1.05	0.77, 1.44	0.7	0.99	0.71, 1.39	>0.9	1.00	0.73, 1.37	>0.9
Employment status [ref: Employed]															
Unemployed/other				0.99	0.72, 1.35	>0.9									
Education [ref: HS/GED]															
<HS				1.46	1.03, 2.05	**0.032**	1.50	1.06, 2.12	**0.022**	1.56	1.07, 2.26	**0.020**	1.45	1.02, 2.05	**0.036**
some college or more				0.75	0.51, 1.09	0.13	0.75	0.51, 1.11	0.2	0.68	0.44, 1.05	0.082	0.76	0.51, 1.12	0.2
Health Insurance [ref: Yes]															
No							0.74	0.53, 1.03	0.077	0.78	0.54, 1.12	0.2	0.76	0.54, 1.06	0.10
Hypertension [ref: No]															
Yes							1.32	0.97, 1.80	0.076	1.19	0.83, 1.70	0.3	1.30	0.95, 1.77	0.10
Alcohol use [ref: Current]															
Never/past										0.86	0.62, 1.20	0.4			
Tobacco use [ref: Never/past]															
Current										1.37	0.97, 1.95	0.072			
Waist circumference										1.03	1.02, 1.04	**<0.001**			
CES-D score													1.02	1.00, 1.03	**0.017**

[1]HR = Hazard Ratio, CI = Confidence Interval,

Model 1: perceived stress median split

Model 2: model 1+baseline demographic characteristics: sex, race, 2010 poverty status, employment status+ level of education

Model 3: model 2-employment status+ health insurance+ hypertension diagnosis

Model 4: model 3+ lifestyle factors (alcohol and tobacco use, waist circumference)

Model 5: model 3+ depression score using CES-D

Table 4-5. HANDLS: Cox-proportional hazards model vs. parametric Weibull model: perceived stress

Characteristic	Model 1: Semi-parametric survival			Model 2: Parametric survival				
	Cox HR[1]	95% CI[1]	p-value	Weibull HR[1]	95% CI[1]	Weibull STR	95% CI[1]	p-value
Perceived stress (PS)								
<=Median	—	—		—	—	—	—	
>Median	1.04	0.78, 1.40	0.79	1.04	0.87, 1.24	0.99	0.96, 1.03	0.66
Sex								
Female	—	—		—	—	—	—	
Male	0.92	0.69, 1.24	0.59	0.90	0.76, 1.07	1.02	0.99, 1.06	0.25
Race								
White	—	—		—	—	—	—	
Black	**1.41**	**1.02, 1.95**	**0.036**	1.14	0.95, 1.37	0.97	0.94, 1.01	0.17
Poverty status								
Above	—	—		—	—	—	—	
Below	1.05	0.77, 1.44	0.74	**1.24**	**1.04, 1.50**	**0.96**	**0.92, 0.99**	**0.019**
Education								
<HS	**1.50**	**1.06, 2.12**	**0.022**	1.09	0.88, 1.34	0.98	0.94, 1.02	0.42
HS/GED	—	—		—	—	—	—	
some college or more	0.75	0.51, 1.11	0.15	0.84	0.68, 1.05	1.03	0.99, 1.08	0.13
Health Insurance								
Yes	—	—		—	—	—	—	
No	0.74	0.53, 1.03	0.077	**0.75**	**0.61, 0.92**	**1.06**	**1.02, 1.11**	**0.007**
Hypertension								
No	—	—		—	—	—	—	
Yes	1.32	0.97, 1.80	0.076	**1.65**	**1.32, 1.99**	**0.91**	**0.87, 0.94**	**<0.001**
Log Likelihood	-1059 (df=8)			-1224 (df=10)				
AIC	2135			2467				
Shape Parameter	—			5.02 (SE: 0.25)				

[1]HR = Hazard Ratio, CI = Confidence Interval, STR = Survival Time Ratio or acceleration factor
Model 1: Semi-parametric Cox-proportional hazards model, accounting for delayed entry through counting process
Model 2: Accelerated failure time model with Weibull distribution, accounting for left and interval censoring.
Interpretation for Weibull STR: compared to living above 125% of poverty level, living below the level may shorten time to diabetes by 4 %; having hypertension, shortens time by 9%, while having health insurance increases time by 6 %

Table 4-6. RSASS data: cox proportional hazards model: perceived stress median-split and incident diabetes.

Model (n events)	Model 1 (n=14)			Model 2 (n=14)			Model 3 (n=13)			Model 4 (n=14)		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Perceived Stress[2]												
At/Below Medium	—	—		—	—		—	—		—	—	
Above Medium	1.15	0.36, 3.68	0.8	1.54	0.43, 5.51	0.5	1.58	0.44, 5.69	0.5	2.79	0.60, 13.0	0.2
Sex												
Female				—	—		—	—		—	—	
Male				0.75	0.24, 2.34	0.6	0.77	0.24, 2.40	0.6	0.63	0.16, 2.53	0.5
Race and ethnicity												
White				—	—		—	—		—	—	
Black				2.99	0.85, 10.5	0.088	2.91	0.82, 10.3	0.1	2.49	0.65, 9.52	0.2
Neighborhood SES												
High				—	—		—	—		—	—	
Low				1.52	0.47, 4.93	0.5	1.31	0.32, 5.32	0.7	1.15	0.30, 4.36	0.8
College or higher												
Yes							—	—				
No							1.31	0.32, 5.38	0.7			
Alcohol use												
No										—	—	
Yes										0.12	0.03, 0.55	0.006
Waist circumference										0.97	0.94, 1.00	0.084

1. HR = Hazard Ratio, CI = Confidence Interval
2. 4-item perceived stress (time-varying)
Model 1: perceived stress
Model 2: model 1+ baseline neighborhood SES, sex, race and ethnicity
Model 3: model 2+ education
Model 4: model 2+ baseline alcohol use and centered waist circumference

Table 4-7. RSASS: Cox-proportional hazards models: acute stress response and incident diabetes.

	Model 1			Model 2			Model 3			Model 4			Model 5		
	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Stress Response															
Responder	—	—		—	—		—	—		—	—		—	—	
Non-responder	1.44	0.47, 4.35	0.5	1.35	0.41, 4.41	0.6	1.27	0.35, 4.57	0.7	2.94	0.49, 17.5	0.2	1.16	0.34, 3.90	0.8
Sex															
Female				—	—		—	—		—	—		—	—	
Male				0.78	0.25, 2.42	0.7	0.79	0.25, 2.49	0.7	1.79	0.37, 8.75	0.5	0.65	0.19, 2.20	0.5
Race															
White				—	—		—	—		—	—		—	—	
Black				2.47	0.72, 8.47	0.2	2.42	0.69, 8.42	0.2	2.45	0.57, 10.6	0.2	2.75	0.74, 10.2	0.13
NSES															
High				—	—		—	—		—	—		—	—	
Low				1.46	0.44, 4.85	0.5	1.33	0.33, 5.34	0.7	1.45	0.27, 7.71	0.7	2.74	0.61, 12.3	0.2
College or higher															
Yes										—	—				
No										0.70	0.09, 5.49	0.7			
Alcohol															
No										—	—				
Yes										0.06	0.01, 0.40	**0.004**			
Tobacco															
No										—	—				
Yes										0.70	0.09, 5.49	0.7			
Waist circumference										0.96	0.93, 1.00	0.059			
Any Rx															
No													—	—	
Yes													4.48	1.09, 18.3	**0.037**

[1] HR = Hazard Ratio, CI = Confidence Interval

Model 1: stress response status

Model 2: model 1+ baseline neighborhood SES, sex, race and ethnicity

Model 3: model 2+ education

Model 4: model 2+ current alcohol and tobacco use and centered waist circumference

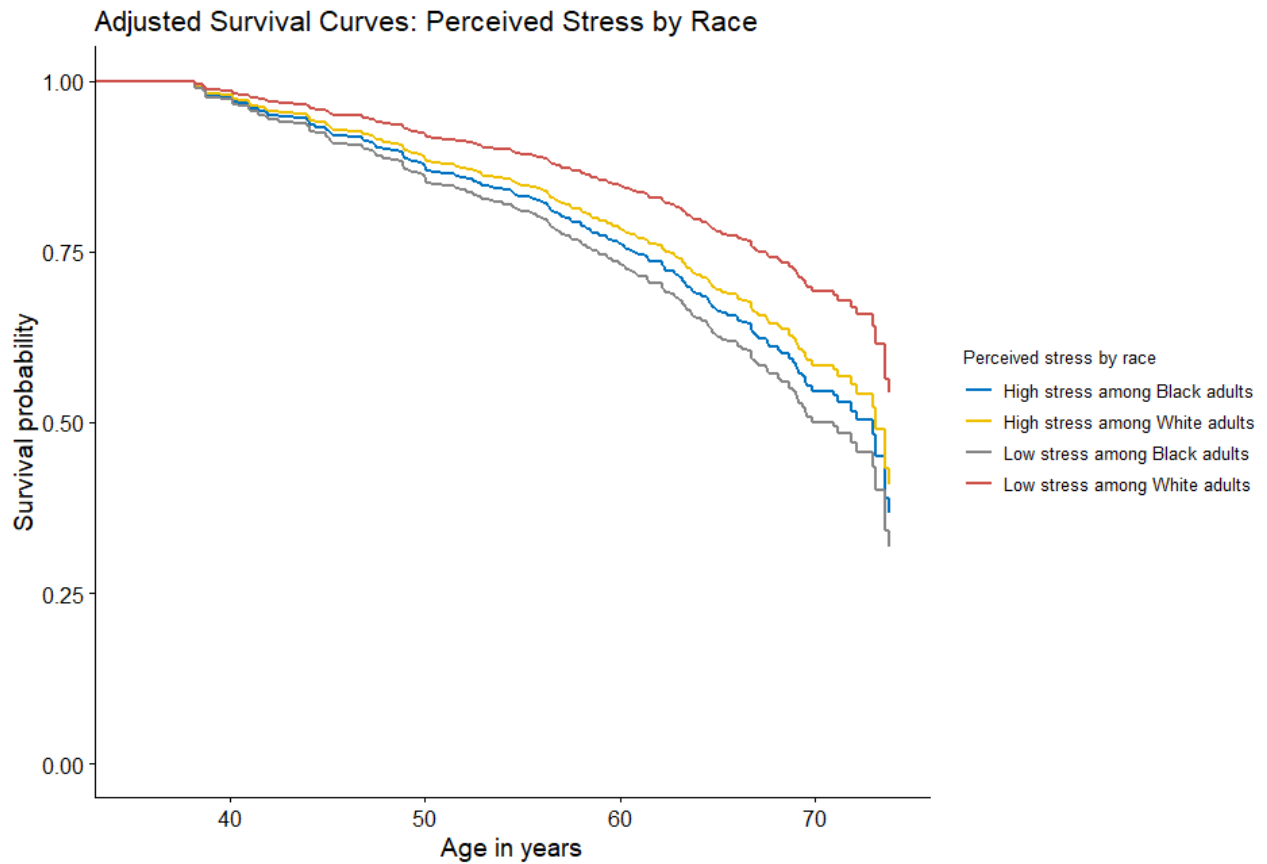Model 5: model 2+ self-reported prescription medications, including statins, beta blockers and glucocorticoids.

Figure 4-1. Adjusted survival curves obtained from Cox proportional hazards model.
The model was adjusted for sex, poverty level, health insurance and hypertension. Adjustment method: covariates in each subgroup were averaged after being balanced with respect to the full sample.

Supplemental Table 4-1. Perceived stress scale across HANDLS and RSASS.

Perceived Stress Scale N observations	Range	Cronbach's alpha (95 % Feldt CI)	Summary score median (IQR) / % missing	Summary score median (IQR)/ % missing
RSASS				
10-item, visit 1 (n=125)	0-36	0.88 (0.84, 0.91)	16 (10, 20)	--
10-item, visit 2 (n=109)	0-32	0.90 (0.87, 0.92)	14 (9, 20) / 17 %	15 (9, 20) / 2 %*
10-item, visit 3 (n=68)	0-30	0.87 (0.83, 0.90)	11 (8, 16) / 46 %	14 (9, 19) / 2 %*
4-item, visit 1 (n=125)	0-14	0.79 (0.72, 0.84)	5 (3, 7)	--
4-item, visit 2 (n=109)	0-14	0.80 (0.74, 0.85)	5 (2, 7) / 17 %	5 (2, 7) / 2 % *
4-item, visit 3 (n=68)	0-12	0.65 (0.54, 0.74)	4 (2, 5) / 46 %	4 (2, 7) / 2 % *
HANDLS				
4-item, visit 1 (n=2250)	0-16	0.62 (0.60, 0.64)	5 (3, 8) / 40 %	--
Among White adults (n=956)	0-16	0.71 (0.68, 0.73)	6 (3, 8)	--
Among Black adults (n=1294)	0-16	0.56 (0.55, 0.52)	5 (3, 8)	--

*Missing values for right-censored participants, whose outcome values were recovered through medical records, were carried forward from the last assessment.

Supplemental Table 4-2. Cause-specific and multistate hazard models for perceived stress and diabetes and death

Characteristic	Time to Diabetes (n event = 187)			Time to Death (n event = 253)			Transition to diabetes			Transition to death			Transition from diabetes to death		
	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Perceived stress (PS)															
<=Median	—	—		—	—		—	—		—	—		—	—	
>Median	1.60	0.92, 2.77	0.094	1.04	0.69, 1.57	0.8	1.01	0.76, 1.36	0.93	1.10	0.90, 1.36	0.35	0.54	0.05, 5.58	0.61
Race															
White	—	—		—	—		—	—		—	—		—	—	
Black	**1.95**	**1.20, 3.17**	**0.007**	0.86	0.59, 1.27	0.5	**1.43**	**1.05, 1.96**	**0.025**	0.92	0.75, 1.13	0.45	4.37	0.47, 40.94	0.20
Poverty status															
Above	—	—		—	—		—	—		—	—		—	—	
Below	1.05	0.76, 1.45	0.8	**1.42**	**1.08, 1.88**	**0.014**	0.99	0.72, 1.37	0.97	**1.44**	**1.14, 1.82**	**0.002**	**2.52**	**0.15, 43.08**	**0.52**
Sex															
Female	—	—		—	—		—	—		—	—		—	—	
Male	0.92	0.69, 1.24	0.6	**1.87**	**1.46, 2.41**	**<0.001**	0.94	0.71, 1.25	0.69	**1.70**	**1.38, 2.08**	**<0.001**	**1.37**	**0.47, 4.00**	**0.56**
Employment status															
Employed	—	—		—	—		—	—		—	—		—	—	
Unemployed	0.97	0.70, 1.34	0.8	**1.54**	**1.16, 2.04**	**0.003**	0.95	0.69, 1.31	0.77	**1.61**	**1.27, 2.05**	**<0.001**	**1.21**	**0.17, 8.77**	**0.85**
Education															
<HS	**1.51**	**1.06, 2.14**	**0.022**	1.00	0.75, 1.34	>0.9	**1.48**	**1.05, 2.08**	**0.027**	1.13	0.89, 1.44	0.32	0.28	0.89, 1.44	0.21
HS/GED	—	—		—	—		—	—		—	—		—	—	
some college or more	0.76	0.51, 1.12	0.2	0.74	0.53, 1.04	0.079	0.78	0.53, 1.13	0.19	0.77	0.58, 1.02	0.69	0.63	0.58, 1.02	0.78
Health Insurance															
Yes	—	—		—	—		—	—		—	—		—	—	
No	0.74	0.53, 1.04	0.079	1.28	0.98, 1.68	0.071	1.04	0.76, 1.43	0.79	1.16	0.93, 1.44	0.20	5.44	0.17, 173.56	0.34
Hypertension															
No	—	—		—	—		—	—		—	—		—	—	
Yes	1.33	0.98, 1.82	0.072	0.94	0.72, 1.22	0.6	0.81	0.58, 1.12	0.20	0.86	0.21, 3.58	0.04	0.86	0.21, 3.58	0.83

[1]HR = Hazard Ratio, CI = Confidence Interval

Time to death includes cases that occurred after participants dropped out, that is diabetes is treated here as a competing risk, because the purpose of this analysis is to conduct a sensitivity check among participants who dropped out. Based on these results, we see expected results, where male sex, poverty and unemployment are associated with a shorter time to death.

The regression coefficients are estimated by maximizing partial likelihood over the cause-specific time points. In other words, competing events are censored.

Supplemental Table 4-3. Multiplicative interactions: perceived stress and sociodemographic factors

Characteristic	Model 1 (n=187)			Model 2 (n=187)			Model 3 (n=187)		
	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Perceived stress (PS)									
<=Median	—	—		—	—		—	—	
>Median	1.59	0.92, 2.76	0.10	1.22	0.82, 1.82	0.33	1.47	0.87, 2.48	0.15
Sex									
Female	—	—		—	—		—	—	
Male	0.92	0.69, 1.24	0.60	0.93	0.69, 1.25	0.65	0.92	0.68, 1.23	0.56
Race									
White	—	—		—	—		—	—	
Black	1.94	1.20, 3.16	**0.007**	1.40	1.01, 1.94	**0.042**	1.41	1.02, 1.95	**0.036**
Poverty status									
Above	—	—		—	—		—	—	
Below	1.04	0.76, 1.41	0.81	1.25	0.82, 1.91	0.31	1.06	0.78, 1.44	0.72
Education									
<HS	1.50	1.06, 2.12	**0.022**	1.51	1.07, 2.13	**0.020**	2.10	1.27, 3.46	**0.004**
HS/GED	—	—		—	—		—	—	
some college or more	0.76	0.51, 1.12	0.17	0.76	0.51, 1.12	0.16	0.86	0.51, 1.48	0.60
Health Insurance									
Yes	—	—		—	—		—	—	
No	0.74	0.53, 1.04	0.08	0.74	0.53, 1.03	0.07	0.73	0.52, 1.03	0.07
Hypertension									
No	—	—		—	—		—	—	
Yes	1.33	0.97, 1.81	0.07	1.31	0.96, 1.79	0.09	1.30	0.95, 1.77	0.10
PS x Black	0.55	0.29, 1.04	0.07	—	—		—	—	
PS x Below poverty	—	—		0.72	0.40, 1.29	0.26	—	—	
PS x Education Status (<HS)	—	—		—	—		0.53	0.27, 1.04	0.07
PS x Education status (>=college)	—	—		—	—		0.77	0.35, 1.67	0.50

Model 1: perceived stress median split x race and ethnicity
Model 2: perceived stress median split x poverty status
Model 3: perceived stress median split x education level

Supplemental Table 4-4. HANDLS: effect modification by race and ethnicity: additive and multiplicative scale.

	Median-split Perceived Stress (4-item PS)				PS high vs low within strata of race and ethnicity
	Low		High		
	N with/without diabetes Prevalent: 282/851 Incident: 98/851	Cox HR (95% CI) Weibull HR (95% CI)	N with/without diabetes Prevalent: 275/839 Incident: 99/839	Cox HR (95% CI) Weibull HR (95% CI)	
Race and ethnicity: White	Prevalent: 86/374 Incident: 24/374	1.0	Prevalent: 120/373 Incident: 36/373	Cox HR (95% CI) 1.59 (0.92, 2.76) Weibull HR (95% CI) 1.38 (1.03, 1.85)	Cox HR (95% CI) 1.57 (0.89; 2.78) Weibull HR (95% CI) 1.30 (0.96, 1.76)
Race and ethnicity: Black	Prevalent: 196/477 Incident: 74/477	Cox HR (95% CI) 1.94 (1.20, 3.16) Weibull HR (95% CI) 1.43 (1.09, 1.87)	Prevalent: 155/466 Incident: 63/466	Cox HR (95% CI) 1.70 (1.03, 2.83) Weibull HR (95% CI) 1.27 (0.96, 1.69)	Cox HR (95% CI) 0.88 (0.62; 1.25) Weibull HR (95% CI) 0.91 (0.73, 1.13)
Measure of effect modification on additive scale: RERI (95% CI) = -0.83 (-1.97, 0.3); -0.54					
Measure of effect modification on multiplicative scale: ratio of Cox HR (95% CI): 0.55 (0.29, 1.04) ratio of Weibull HR (95% CI): 0.64 (0.45, 0.93)					
Models were adjusted for sex, race and ethnicity, education, poverty level, health insurance and hypertension status					

Supplemental Table 4-5. Cox HR for perceived stress using different multiple imputation strategies in HANDLS.

MI methods	High vs low perceived stress			
	Cox HR[1]	95% CI[1]	Weibull HR[1]	95% CI[1]
MICE, 100, Rubin[a]	1.09	0.84, 1.41	1.06	0.90, 1.25
MICE, stacking	1.09	0.87, 1.36		
MICE, 50, no exposure	1.06	0.80, 1.42	1.04	0.99, 1.10
SMCFC, 50	1.03	0.79, 1.34		

[1]HR = Hazard Ratio, CI = Confidence Interval from aemi-parametric Cox-proportional hazards model, accounting for delayed entry through counting process

a. Rubin's rule: 100 imputations, using both outcome and covariates, standard, using nelson aalen during imputations; we didn't impute outcome
b. Stacking
c. 100 imputations, using both outcome and covariates, standard, using nelson aalen during imputations; we didn't impute outcome. We didn't impute predictor, Rubin's rule
d. SMCFC

Supplemental Table 4-6. RSASS: Cox model: PSS10/IQR and incident diabetes

Characteristic	Model 1			Model 2			Model 3			Model 4		
	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
PSS10	1.18	0.57, 2.44	0.7	1.55	0.66, 3.67	0.3	1.54	0.65, 3.66	0.3	2.57	0.84, 7.91	0.10
sex												
Female				—	—		—	—		—	—	
Male				0.65	0.20, 2.14	0.5	0.66	0.20, 2.19	0.5	0.44	0.09, 2.09	0.3
Race												
White				—	—		—	—		—	—	
Black				2.99	0.86, 10.4	0.086	2.94	0.83, 10.4	0.093	2.47	0.65, 9.42	0.2
Neighborhood SES												
High				—	—		—	—		—	—	
Low				1.45	0.44, 4.74	0.5	1.31	0.32, 5.32	0.7	1.07	0.28, 4.12	>0.9
college												
Yes							—	—				
No							1.19	0.29, 4.85	0.8			
Current Alcohol												
No										—	—	
Yes										0.11	0.02, 0.50	**0.004**
Waist Circumference										0.98	0.95, 1.01	0.12

[1] HR = Hazard Ratio, CI = Confidence Interval

Model 1: perceived stress, scaled by interquartile range

Model 2: model 1+ baseline neighborhood SES, sex, race and ethnicity

Model 3: model 2+ education

Model 4: model 2+ baseline alcohol use and centered waist circumference.

Supplemental Table 4-7. RSASS: Cox model: AUC cortisol increase and incident diabetes

Characteristic	Model 1			Model 2			Model 3			Model 4			Model 5		
	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
AUC $_{increase}$	0.62	0.15, 2.59	0.5	0.61	0.14, 2.61	0.5	0.63	0.14, 2.78	0.5	0.52	0.05, 5.76	0.6	0.78	0.17, 3.56	0.7
Sex															
Female				—	—		—	—		—	—		—	—	
Male				0.78	0.26, 2.40	0.7	0.80	0.26, 2.47	0.7	1.42	0.33, 6.09	0.6	0.65	0.20, 2.16	0.5
Race															
White				—	—		—	—		—	—		—	—	
Black				2.58	0.77, 8.66	0.13	2.48	0.72, 8.57	0.2	2.47	0.53, 11.5	0.3	2.75	0.75, 10.0	0.13
SES															
High				—	—		—	—		—	—		—	—	
Low				1.36	0.40, 4.59	0.6	1.23	0.30, 4.99	0.8	1.34	0.22, 7.97	0.8	2.64	0.58, 12.0	0.2
College															
Yes							—	—							
No							1.22	0.29, 5.11	0.8						
Current Alcohol															
No										—	—				
Yes										0.06	0.01, 0.41	**0.004**			
Current Tobacco															
No										—	—				
Yes										1.55	0.18, 13.4	0.7			
Waist Circumference										0.97	0.94, 1.01	0.2			
Rx use															
No													—	—	
Yes													4.29	1.03, 17.8	**0.045**

[1] HR = Hazard Ratio, CI = Confidence Interval

Model 1: cortisol stress response, density increase in area under the curve

Model 2: model 1+ baseline neighborhood SES, sex, race and ethnicity

Model 3: model 2+ education

Model 4: model 2+ current alcohol and tobacco use and centered waist circumference

Model 5: model 2+ self-reported prescription medications, including statins, beta blockers and glucocorticoid

Chapter 5 Conclusions

5.1 Summary of Findings

There is growing recognition that chronic psychosocial stress may accelerate aspects of the aging process and increase risk of cardiometabolic diseases. Chronic stress is also hypothesized to contribute to the emergence and persistence of economic and racial/ethnic health disparities. However, conceptual variability and methodological challenges in extant research limit our ability to both understand the sources of inconsistencies across findings and integrate knowledge across different studies, which are critical elements of scientific investigation of chronic stress as a mechanism underlying health disparities at the population scale.[22]

In an effort to respond to these challenges, the primary goals of this dissertation were to: (1) explore heterogeneity in conceptual and theoretical frameworks of psychosocial stress with respect to health; (2) examine the interrelationship between commonly used measures of stress using self-report and stress biomarkers; (3) determine the impact of perceived psychosocial stress, stress-related cognitive tendencies, and neurobiological stress reactivity on metabolic health using longitudinal evidence from two distinct epidemiologic sources of data; and (4) evaluate how variations in the ways stress is operationalized and measured shapes our understanding of psychosocial stress as an underlying mechanism of racial and socioeconomic disparities in metabolic health.

In Chapter 2, we addressed an important gap in stress research on whether self-report measures of stress reflect underlying neurobiological stress processes. Self-report measures of stress are frequently the only measure of "chronic stress" included in population-based

epidemiologic studies. Because neurobiological stress processes are considered key mediators between psychosocial experiences and health outcomes, the knowledge on how stress self-report relates to neurobiological stress responses is critical to advancing population research on stress-health relationship. We also explored whether the associations between these measures were consistent across race and neighborhood SES, ascertained from administrative records.

This chapter used data from the Richmond Stress and Sugar Study (RSASS), a sample of adults at risk of type 2 diabetes. Self-report stress was operationalized using two common self-report scales: the 10-item Perceived Stress Scale and the 55-item Domain-specific stress scale. The neurobiological stress response was assessed by acute changes in salivary cortisol, induced by the Trier Social Stress Test (TSST), a validated laboratory stressor.

Our results showed that neither self-report measures of stress were associated with salivary cortisol assessed prior to the laboratory test. However, we found the two self-report stress measures correlated with neurobiological stress processes and were generally congruent in the magnitude and direction of the associations. Perceived stress was inversely associated with the cortisol response to the TSST, although the association with the recovery from the TSST was not statistically significant. Blunted cortisol response to a stress challenge has been previously linked to chronic and intense stress experiences that may contribute to a gradual loss of sensitivity to glucocorticoids, an index of a dysregulated neurobiological stress response.[49] The opposite pattern was observed for the domain-specific measure, where high levels of stress were associated with slower recovery from, but were not associated with the response to, the TSST. Delayed recovery from acute stress is also a recognized marker of dysregulation of neurobiological stress response and has been previously linked to cardiovascular disorders.[95]

Complementary results concerning the two self-report measures suggest that these reflect overlapping, but not identical dimensions of psychosocial stress process.

Neighborhood SES modified the association between self-reported stress and neurobiological stress responses. For individuals living in lower SES neighborhoods, self-reported stress was not associated with the neurobiological stress response, whereas among those from high SES neighborhoods higher levels of self-reported stress was associated with a blunted cortisol response.

These findings have important implications for population research, as our results suggest that commonly used self-report stress measures may have limited utility in assessing psychosocial stress among adults living in economically-disadvantaged neighborhoods. However, an alternative interpretation may suggest that the effect of psychosocial stress on neurobiology may be non-additive in the context of disadvantaged environments. Taken together, our findings suggest that although assessing psychosocial stress via self-report may be a viable research strategy, caution must be taken when using self-report measures in heterogeneous population samples.

In Chapter 3, we applied a novel theoretical stress framework to examine whether stress-related cognitive tendencies were prospectively associated with metabolic risk in a community-based cohort of adults from the Healthy Aging in Neighborhoods of Diversity across the Lifespan Study (HANDLS). Consistent with the stress-promoting and stress-buffering postulates of the Generalized Unsafety Theory of Stress (GUTS), we hypothesized that adaptive coping would be protective for metabolic health, whereas vigilance and avoidant coping – through negative interference with the self-regulatory stress processes – would be associated with higher

metabolic risk. Both sets of cognitive tendencies were assessed via self-report; for vigilance we used a modified 6-item MacArthur Reactive Responding scale designed to assess anticipatory threats from the environment, whereas stress coping strategies were ascertained with the 23-item Brief Cope scale. Two types of stress coping were examined: adaptive (i.e., "take action to try to make the situation better" or "get help and advice from other people") and avoidant (i.e., "refuse to believe that it has happened" or "use alcohol or drugs to help me get through it"). We also explored whether these cognitive tendencies contribute to disparities in metabolic health by examining effect modification by race/ethnicity and life course socioeconomic mobility.

Contrary to our expectations, we found that vigilance was not associated with metabolic health, while both types of stress coping were negatively associated with metabolic risk. These findings concerning coping strategies suggest that a higher level of engagement in any form of stress coping may be beneficial and help dampen chronic stress impact on metabolic health. Our findings with respect to the effect modification by race/ethnicity and life course SES suggest that the activation of a particular coping style may be context-specific[168] and depend on the appraisal of the stressor severity, other external challenges, and the availability of psychosocial resources.[23] For example, whereas reporting high avoidant coping was generally protective for participants with persistently low SES or/and Black adults, high adaptive coping appeared to be protective for White adults or those with high life course SES. In this study, adaptive coping included task-oriented strategies which may address an actionable issue or a short-term stressor, while avoidant coping included such dissociative strategies and may help downregulate distress resulting from non-controllable overwhelming stressors. To our knowledge, this is one of the few studies that examined whether such cognitive constructs as vigilance or stress coping may be associated with metabolic risk in a prospective cohort of adults followed for up to 13 years. Our

findings concerning stress coping were largely consistent with the buffering hypothesis of GUTS, although the form of coping and their impact on metabolic health depended on lifestyle factors and further varied by race and life course socioeconomic conditions. Our results further demonstrate that metabolic health disparities persist by race and SES, where participants with low life course SES who report low coping appear to be most vulnerable.

In Chapter 4, using data from both HANDLS and RSASS, we undertook two separate analyses to explore whether self-reported perceived stress, ascertained via a 4-item Perceived Stress scale, was associated with incident diabetes. In RSASS only, we also examined associations between the TSST stress reactivity and diabetes, while only in HANDLS, we examined evidence for effect modification by race and neighborhood poverty status. While the relationships between stress and diabetes incidence were not statistically significant in either sample, the direction of associations were as hypothesized and comparable across the cohorts. Issues related to differential sample selection, coupled with a large amount of missingness in the perceived scale (~30%), and may have negatively impacted the statistical power.

Our subgroup analyses in HANDLS revealed that compared to White adults with low levels of perceived stress, White adults with high stress and Black adults (both high and low stress) had higher diabetes incidence. Congruent with our findings in Chapter 2 and 3 that show limited reliability of self-report measures of stress construct among Black adults or adults with low SES, these results suggest that self-reported perceived stress scale may be insensitive to underlying variations in stress experiences among Black adults in our sample.

Overall, the results of this study demonstrate convergence of evidence from two longitudinal samples that have shared design features and a common focus on understanding

cardiometabolic health disparities. This evidence contributes toward elucidating the complex

stress paradigm, and illustrates potential challenges with relying on self-report stress measures

among Black participants to examine the role of stress in diabetes health disparities. This chapter

underscores the importance of replicating evidence across studies with shared features and

design, an effort that provides a more robust understanding of the substantive question that could

be obtained from a single cohort.

5.2 Strengths and Limitations

While this dissertation research offers several methodological and theoretical contributions to the

understanding of the role of psychosocial stress in cardiometabolic health disparities, these

contributions must be considered with respect to several important limitations.

First, across all studies, we relied on measures of stress that were assessed at a single time

point via self-report. The implications for timing of exposure assessment must be carefully

considered, especially when the influence of such exposures as psychosocial stress may depend

on life stage and other social circumstances and is further examined over a long follow-up.[218]

While results from Chapter 2 show that stress self-report may be potentially useful assessment

measure for evaluating stress experiences, particularly when other measures may not be feasible,

all three studies show evidence for considerable heterogeneity in the reliability of these measures

across racial and socioeconomic groups. These concerns are likely to result in an underestimation

of the associations between stress and cardiometabolic health overall and within population

groups.

Second, both the HANDLS and RSASS samples were not representative of the U.S.

population. Additionally, RSASS sample was comprised of a specialized population: adults who

were both considered at risk of type 2 diabetes and accessed healthcare facility which limits the generalizability of our findings. However, compared to what we see in nationally representative samples that may systematically underrepresent populations at the tail-end of the socioeconomic gradient, the purposeful sampling used to select participants for both RSASS and HANDLS facilitated assessment of socioeconomic heterogeneity within race groups. Differential selection due to loss to follow up in HANDLS may have biased associations if the exposure of interest influenced selection factors. These were partially addressed by comparing participants' characteristics for those lost to follow up and those with fully observed data.[219] In Chapter 3, we also fitted a series of multistate models to address concerns for differential selection due to death; findings for incident diabetes remained consistent with the main analyses. Finally, given that we relied on observational data, it is likely that residual confounding due to measures and unmeasured factors affected our results, which was partially addressed through a series of sensitivity analyses.

This dissertation also has several strengths. First, each of the empirical studies heavily relied on leading theoretical frameworks to guide analytic approaches and conceptual interpretations of our findings. Second, longitudinal analyses allowed for the examination of change in outcome of interest over time, which helped establish temporal ordering and strengthen inference. In Chapter 3, metabolic risk was operationalized by using race- and gender-specific formulas, while life course measure of socioeconomic mobility was created by combining a series of child and adult indicators of SES. Using these measures sensitive to variations across time and racial/ethnic differences strengthens inference in research focused on chronic health disparities. Finally, convergence of evidence across our empirical studies, where

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stress constructs were operationalized through distinct but complementary stress measures, further contributes information toward elucidating the link between stress and disease.

5.3 Public Health Significance and Future Directions

This dissertation makes a number of theoretical and methodological contributions to the field of social epidemiology. First, this work is a synthesis of several foundational stress theories and empirical studies that explore the role of psychosocial stress as a determinant of racial and socioeconomic health disparities. Building upon this research legacy, we conceptualized psychosocial stress as a multilevel process of biological and social mechanisms that jointly and systematically increase vulnerability to adverse health outcomes over the life course. Each dissertation chapter addresses a distinct element in this hypothesized stress process, whereas collectively they contribute toward a better understanding of the interrelationship between psychosocial and neurobiological pathways particularly as they relate to mechanisms linking social disadvantage to health. Furthermore, our racially and socioeconomically diverse samples reflect a population that is a focus of cardiometabolic prevention efforts, which enhances the translation of our findings into practice.

Second, our findings have implications for efforts aimed at refining the measurement of psychosocial stress in population research. Our empirical aims demonstrate that ascertaining psychosocial stress via self-report may be a useful assessment measure, particularly when other options may not be feasible due to concerns for participant burden or logistical challenges. However, our results also show the need for further development of new or refinement of existing stress measures. For example, in Chapter 3, we identified a potential challenge around ascertainment of the latent construct of vigilance through existing measures that rely on self-report and memory. Consistent with the GUTS theory used to frame the central research question

for this study, a state of heightened vigilance may be regarded as a symptom of internalized threat, developed after experiencing past trauma. Such internalization may affect memory integration and conscious recall, especially in the setting of a research study, thus limiting the utility of self-report measures. Measures focused on assessing physiological function (i.e., muscular stiffness, noise sensitivity or eye movement) may serve as a plausible complementary measure to cognitive assessments of vigilance.[220,221] However, further research is needed to differentiate between different constructs of vigilance (i.e., short-term cognitive effort of sustained attention, often required with completing job-related tasks vs. prolonged mental state of hypervigilance) and the corresponding relevance of neurophysiological correlates.[222–224]

In addition, all three empirical studies demonstrate that commonly used self-report stress measures may need further modifications for evaluating psychosocial stress in heterogeneous samples, especially among participants from low socioeconomic background or minority groups. For example, Chapter 2 showed that among participants residing in low SES neighborhoods, self-reported measures of stress failed to reflect variations in psychosocial stress exposure with respect to acute neurobiological stress response, while both Chapter 3 and 4 illustrate that, compared to White participants, self-reported measures of stress and vigilance had substantially lower reliability among Black adults. These results suggest that these measure might have failed to reflect the underlying stress experiences (i.e., race/ethnic discrimination) or variations in stress appraisal relevant to Black adults in our sample.[225,226] Future research efforts using a combination of qualitative and quantitative approaches must be directed toward developing theoretically informed and empirically grounded measures of stress experiences across diverse population groups. Such efforts may help reduce heterogeneity in study findings and accelerate progress toward understanding the links between stress and health outcomes.

Finally, comprehensive examinations of psychosocial stress as a key contributing factor in disease risk are often hampered by the lack of available population data with comprehensive measures of stress, including stress self-report (i.e., perceived stress or distress), stress biomarkers (i.e., stress hormones, inflammatory and oxidative stress markers), and exogenous measures of stress derived from administrative data that could index vulnerability to stress exposure (i.e., census-based indicators of disadvantage). This dissertation underscores the importance of replicating evidence across studies with shared features and design; it further lays a foundation for future efforts toward direct integration of multiple sources of data from specialized non-probability samples together with larger probability samples or cohorts followed over the life course. Such integration efforts are increasingly recognized as a viable alternative to one-sample analyses, as evidenced by methodological advances[227] and an availability of advanced data integration techniques (i.e., through Bayesian inference,[216] causal framework,[228] or a combination of data synthesis and direct analytical derivations).[217]

5.4 Conclusion

Taken together, this dissertation demonstrates that viewing chronic stress as a dynamic system comprised of interrelated processes offers a fruitful approach for research seeking to understand stress-health relationship. The convergence of complementary evidence in this dissertation supports the premise that chronic psychosocial stress plays an important role in cardiometabolic risk disparities and should be considered as a potentially modifiable mechanism linking social disadvantage to health.

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