UNIVERSITY OF CALIFORNIA,
IRVINE

Multi-Systemic Biological Risk and its Association with Discrimination, Cancer Mortality, and All-Cause Mortality

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Epidemiology

by

Teofilia Y. Acheampong

Dissertation Committee:
Assistant Professor Andrew O. Odegaard, Chair
Assistant Professor Luohua Jiang
Associate Professor Argyrios Ziogas

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DEDICATION

To

Those close to me who have encouraged, supported and loved me through this process,
I thank you.
To my family, especially my mother, my guardian angel, I thank you so much for your unwavering effort to get me where I am.
I love you and thank you so much for your incessant prayers and support.

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CURRICULUM VITAE

TEOFILIA ACHEAMPONG
Address: 875 Boynton Ave, Bronx, NY
Email: Tacheam@gmail.com
Phone: (646)-643-0160

EDUCATION

June 2018, Doctor or Philosophy, Epidemiology, GPA: 3.82

University of California-Irvine, School of Medicine, Irvine, CA

Dissertation: The Multi-Systemic Biological Risk Index and its relationship to Discrimination, Cancer Mortality and All-Cause Mortality.

May 2013, Master of Public Health, GPA: 3.64

Hunter College, School of Public Health, New York, NY

Key Coursework: Community Health Education, Program Planning, Grant Writing & Funding, Epidemiology, Biostatistics, and Research Methods

Thesis: Implementing nutritional interventions in NYC communities and systematic program evaluations.

May 2008, Bachelor of Science, Public Health, GPA: 3.73, Cum Laude

Stony Brook University Stony Brook, NY

Key Coursework: Community Health Education, Epidemiology, Biostatistics, Research Methods, Ethics, and Bioinformatics, Biology, Physics, Statistics, Medical Sociology

EXPERIENCE

Research

6/2015-1/2016 Research Associate, ATHENA Health Network, UCI, School of Medicine, Irvine CA

- Designed and implemented periodic surveys.
- Managed data collection; including cleaning, coding and analyzing data.
- Conducted literature reviews.
- Contributed to proposals, posters and manuscripts.
- Coordinated clinician training of protocol across departments, as well as trained and mentored research assistants (UROP).

2011-2012 Research Assistant, Children's Museum of Manhattan, NY, NY

- Contribute to the development of training, interventions and research materials.
- Collected and analyzed evaluation survey results, utilizing statistical.

- Contributed to interpretation of study findings, written reports for stakeholders and posters.

Teaching

1/2017-Current Teaching Assistant UCI, School of Biological Sciences, Irvine, CA

- *Course*: (1) Biological and Scientific Writing, (2) Introduction to Biology II: Ecology & Evolution
- Holds office hours, and as needed studying sessions with students. Coach students individually to further improve writing performance and study design techniques.
- Proctor and grade exams; evaluate, provide feedback and grade mock journal article publications.
- Designed and led weekly discussions for 100+ students, in collaboration with lecture.
- Held office hours, and as needed studying sessions with students. Coached students individually to further improve performance on quizzes, labs, and exams.
- Proctored and graded exams.

SKILLS

- Experience acquiring IRB
- Software programs: MS Office Suite (Word, Excel, Publisher, PowerPoint), Endnote, Mendeley, SAS, STATA, Redcap.

PRESENTATIONS/PROJECTS:

- Acheampong, T. Isaac, L. PhD (2013). Informal daycare providers teach health curriculums with the support of professional development trainings. CUNY, CMOM, New York, NY, Presented during the CUNY School of Public Health's research poster symposium.
- Acheampong, T, (co-Dir.) Rivera, D., (co-Dir.). (2013). "I Speak Birth". CUNY, New York, NY. A documentary that explores some of the issues that plague women of color during their birthing experiences and the possible associated health outcomes. Debuted at CUNY School of Public Health Target's First Fridays Film Festival.
- Park, H., Acheampong, T, et. al. Association of periodontal disease and breast health in women undergoing screening mammography. [Abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16-20; New Orleans, LA. Philadelphia (PA): AACR; Cancer Res 2016;76(14 Suppl): Abstract nr 2599.
- UCI School of Medicine Diversity Week, (2016). Student National Medical Association (SNMA) Panelist for Session entitled: "Healthcare and the Plight of the Black Provider."
- Southern California NIOSH (CDC) Education and Research Center Pilot Project Training Program, UCLA Los Angeles, CA. "Occupational Exposures and Risk of Breast Cancer: The Singapore Chinese Health Study. Poster

Presentation.

- Acheampong, T, Odegaard, A. Multi-systemic Biological Risk and Cancer Mortality. [abstract]. In: Proceedings of the 10th Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved; 2017 Sep 25-28; Atlanta, GA. Philadelphia (PA): AACR; Cancer Res 2017;76(14 Suppl): Abstract nr A54. Awarded Minority in Cancer Research Fellow (Poster Presentation).

MANUSCRIPTS

- Acheampong, T., Odegaard, A., Yuan, J-M., Koh, WP., Jin, A. "Occupational Exposures and Risk of Breast Cancer: The Singapore Chinese Health Study. (Manuscript in Press).
- Acheampong, T., Ziogas, A., Jiang, L., Odegaard, A. Multi-Systemic Biological Risk and Cancer Mortality in a US Population: NHANES III. (Manuscript in Progress).
- Acheampong, T., Ziogas, A., Jiang, L., Odegaard, A. Associations between Discrimination and Multi-Systemic Biological Risk in Black and White Adults: The CARDIA Study. (Manuscript in Progress).
- Acheampong, T., Sims,M., Odegaard, A. Cumulative Biological Risk and All-Cause Mortality: The Jackson Heart Study (Manuscript in Progress).

AWARDS

- University of California-Irvine, Graduate Division. Faculty Mentor Program (FMP) Fellowship. Awarded: Honorable Mention. 2015
- Southern California NIOSH (CDC) Education and Research Center Pilot Project Training Program, UCLA Los Angeles, CA. "Occupational Exposures and Risk of Breast Cancer: The Singapore Chinese Health Study. Awarded maximum amount $15,000, AY 2015.
- 10th Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved; Awarded: Minority in Cancer Research Fellow. 2017

ABSTRACT OF THE DISSERTATION

The Multi-Systemic Biological Risk Index and its relationship to Discrimination, Cancer Mortality and All-Cause Mortality.

By

Teofilia Y. Acheampong

Doctor of Philosophy in Epidemiology

University of California, Irvine, 2018

Professor Andrew Odegaard, Chair

Multi-systemic biological risk (MSBR), a proxy for allostatic load, is a composite index of biomarkers that represent dysregulation due to responses to chronic external stress. Research suggests that long term or repeated stressful situations may adversely influence health. This provides the basis for a model that ties external stressors with physiological responses; in turn, this may influence incidence and prognosis of disease. This dissertation addresses several gaps in the literature. For one, while a few studies have linked a multi-systemic biological risk index with diabetes and cardiovascular disease, no research has examined an objective biological measure of stress with cancer outcomes. Therefore we examined the association between an index of MSBR with cancer mortality. Next, although previous research shows a positive association between MSBR and mortality, there are no studies that have accounted for major sources of chronic stress, which could potentially confound the association. Therefore, we examined the association between MSBR and all-cause mortality, and sequentially accounted for dimensions that are known to confound the association (demographic, socioeconomic and social support, lifestyle and health status, and discrimination experience), within an African-American cohort. Lastly, research demonstrates discrimination has important biological consequences, however, most are cross-sectional in nature and research regarding different types of discrimination has not been addressed. Therefore, we assessed the association between experienced discrimination due to gender, race, and socioeconomic position and MSBR. This dissertation provides evidence for the association between an index of MSBR and cancer mortality, particularly amongst overweight or obese participants in NHANES III. Furthermore, the association was mainly driven by the immune and cardiovascular domains. We also found a positive association between a higher MSBR index and risk for all-cause mortality; a stronger association was found in younger age groups. Furthermore, sequential adjustment for important dimensions of stress, demonstrated that each domain contributed to the association by attenuation of the point estimate, yet the association remained. Lastly, we found no association between changes in discrimination, and MSBR in the CARDIA cohort. This study provided novel data on the topic of discrimination, as we were able to examine discrimination and change with MSBR.

Epidemiology and social context

The German physician and pathologist Dr. Rudolf Virchow initiated the modern concept of pathology utilizing the cell theory to describe how disease affects the organs and tissues of the body.[1] He also advanced public health and social medicine, promoting the idea that disease is not purely biological, but can be initiated, spread, and intensified by social influences. He suggested that the typhus outbreak could've been prevented had it not been for poor living conditions.[1]

Dr. Virchow promoted social justice through social policies that attempted to combat poverty, and improve sanitation, occupational and housing conditions.[1] On a macro-scale the literature related to policy, from both national and international level governmental agencies, suggests that health practitioners recognize and take into account the poor social conditions of their patients.[2,3] From unsafe housing conditions and neighborhoods, food insecurity, mental health and victims of trauma, these are all social factors that undermine the health of a patient.[4–6] Moreover, the burden of adverse social factors disproportionately falls upon specific groups within the US. [7]

Up to date, the US has not fully adopted the ideas of Dr. Virchow regarding the integration of social factors and medicine; as a result, we continue to see the consequences that consist of systematic, reasonably preventable health differences negatively affecting socially disadvantaged groups,[8] reflected in our nations registries, reports and statistics regarding mortality and morbidity.[9–11] Currently, specific approaches and conceptual frameworks are needed to tackle the complex etiology of the differences in disease.

The Social Determinants of Health

Prominent health organizations such as The World Health Organization (WHO), the Centers for disease control (CDC) and Health People 2020 (10-year national objectives for improving the health of all Americans), have adopted social determinants of health (SDH) frameworks, utilizing it as a foundation to understand health inequities based on the social and physical conditions in which people, are born, grow, work and live.[12,13] The CDC utilizes the definition that describes the determinants as complex, integrated, and intersecting social structures and economic systems that are responsible for most health injustices. They further describe these social structures and economic systems to include the social environment, physical environment, health services, and structural and societal factors. Lastly, the social determinants of health are shaped by the distribution of money, power, and resources throughout local communities, nations, and the world.[14]

The conceptual framework that maps out the social determinants of health is a theory backed by a large body of peer-reviewed evidence contributed by the public health community, over the last three decades.[7,15] Moreover statistical methods have been used to elucidate how large of a role social factors can play in one's health and the estimated mortality in a population attributable to these factors.[7]

The WHOs global perspective describes that the SDH are "mostly responsible for health inequities - the unfair and avoidable differences in health

status seen within and between countries." Today, these determinants function as indicators and markers of complex social exposures and pathways by which societal circumstances or conditions influence health, physical function, quality-of-life, outcomes and risks. One's circumstance (i.e. social, economic, and physical) can occur in many types of settings (e.g., school, church, workplace, and neighborhood).[16,17] The relationship between one's environment, and health outcomes depends on both physical (i.e. exposure to toxic substances) and social (i.e. social norms and attitudes about subgroups, or exposure to crime and violence) determinants.[12] Healthy People 2020s social determinants of health are broadly grouped, as 4 key aspects that include: "(1) Economic Stability, (2) Education, (3) Social and Community Context, (4) Health and Health Care, and (4) Neighborhood and Built Environment."[12]

Although the Institute of Medicine, the CDC, the Surgeon General, and Healthy People 2020 have different descriptions of how to tackle the social determinants of health, they all describe the underlying factor or issue is historically linked to discrimination or exclusion by race or ethnicity, religion, socioeconomic status, gender, mental health, sexual orientation, or geographic location, or disability.[18–22] Thus far, in terms of the impact of social factors on the aforementioned key aspects, most studies very clearly show associations that depict a stepwise gradient pattern, with health and mortality improving as social position or resources increase.[15,23] Furthermore those historically excluded are disproportionately represented at the lower end of the gradient.

There are many examples of recent and historical events where institutions (governmental, academic, businesses, religious) and the individuals within them have played a role in the development and continued fostering of these barriers by social position. A mechanism by which this can happen is through discrimination against individuals, which can directly restrict socioeconomic acquisition; also, racial and economic segregation creates poor residential conditions which exacerbate exclusion and disparirites.[24] Discrimination can lead to reduced access to necessary goods and services, (i.e.: (1) employees or members of businesses deny services, (2) student attends public school with poor resources due to economic and racial segregation) and it also creates conditions that increase exposure to other conventional stressors (e.g. unemployment).[24] Furthermore, the internalization of discrimination based on race, skin color, sex, gender and social position can adversely affect health in a variety of ways.[24]For one, it can affect compliance with medical regimens based on the clinical care team and the patient.[24] It can also create adverse distress that can affect physiological systems such as cardiovascular, immune, and neuroendocrine domains; in turn this further shapes health behaviors[17]. Indeed, policy and laws that reduce social disadvantage can reduce health inequalities, for example, the health gap between blacks and whites narrowed in the decades after civil rights legislation (though the gap began to widen again after the 1980s after the modern war on drugs).[25] However when attempting to eliminate disparities, it also requires a societal shift in perspective and behavior amongst individuals.[12]

Conceptual Framework: Mechanisms by which social factors influence biological disturbances.: Eco-Social Theory and Embodiment

Eco-social theory is a multi-level epidemiological framework that attempts to integrate social and biological analyses as well as a dynamic, historical and ecological perspective to determinants of population distributions of disease and social inequalities in health.[16,26–28] The Eco-social theory asks a principal question of: "who and what is responsible for population patterns of health, disease, and wellbeing, as documented by the present, past, and ever-changing social inequalities in health?"[16] Dr. Nancy Kreiger, describes both persisting and changing distributions of disease as well as micro to macro factors from an epidemiological perspective.[16] Thus, Eco-social theory involves ideas around how population health is essentially generated and moved by social conditions that interact with biological processes at every spatiotemporal scale.[29,30] The core concepts for Eco-social theory include: (1) embodiment, a theory referring to how we literally incorporate, biologically, the social world in which we live, from in-utero to death.[16] Consequently, no aspect of our biology and clinical health can be fully understood without context and knowledge of historical, individual and societal ways of living.[16,29] In terms of mechanism (2) embodiment is carried out through (2a) the way society constructs and arranges power, economics and related patterns of production, consumption, and reproduction. Furthermore, it is carried out through (b) both the limitations and potential of our biology, as dictated by our species' evolutionary background, our ecological context, and individual histories (i.e.: biological and social development).[16,29] Krieger further deconstructs the

aforementioned mechanisms, stating that these mechanisms work through various, contemporaneous, and interacting pathways, involving adverse exposure to social and economic deprivation; exogenous hazards (e.g., toxic substances, pathogens, and hazardous conditions); social trauma (e.g., response to discrimination and other forms of mental, physical, and sexual trauma); targeted marketing of harmful commodities (e.g., tobacco, alcohol clusters, other licit and illicit drugs); inadequate or degrading health care; and degradation of ecosystems, (e.g., alienation of indigenous populations from their lands, and disproportionate placement of toxic brownfields and wastelands).”[29] In summary, there are many ways and levels to which social and environmental factors may harm health. Krieger further describes the (3) cumulative intersection of exposure, susceptibility, and resistance, with each factor and its distribution at multiple levels (i.e.: individual, neighborhood, regional or political jurisdiction, national, or international) and within multiple domains (i.e.: home, work, school), in relation to relevant ecological roles, and manifested in processes at multiple scales of time and space.[16,26,29] Furthermore, the process entails more than the simple formula of ‘‘phenotypes,’’ ‘‘genotypes,’’ and the ‘‘environment’’ causing ‘‘gene-environment’’ interactions. Genes do not interact with exogenous environments—only organisms can, resulting in embodied exposures that result in gene regulation and expression and, not simply gene frequency changes.[26,29] Lastly, (4) accountability and agency, is expressed in all pathways regarding institutions (government, business, religion, and public sector), communities, households, and individuals.

The importance of encouraging a theoretical approach in biomedical disciplines, who seek to include social context within its practice, is wrapped around the need for structural framework and mechanism,[31–33] where clinical studies and diagnosing of patients are looking to recognize "context-mechanism-outcome patterns" and provide a holistic explanation of how macro-social determinants, population health, and individual health are linked.[33] This framework allows epidemiologists to explore 'interpersonal mechanisms such as sexism, racism, heterosexism, able-ism, ageism, and classism.'[34]

Exposures over the lifespan.

Incorporated in the core concepts of eco-social theory, is the idea of accumulation of exposures through time. Commonly, the approach to clinical and observational studies involve exploring risk factors in a cross-sectional and/or contemporaneous manner, however the life-course approach to studying disease should be considered more often during study design. Taking into account latent, pathway and cumulative mechanisms, if not in the beginning of study design, but also, when interpreting the results of a data analysis, is important. The life-course literature describes latent consequences as early life exposures (in-utero or during important developmental periods during young adulthood) being "programmed", in such a way that may alter disease risk later in life. A classic example includes the use of Diethylstilbestrol (DES), a potent estrogen mimic, used from 1940-1970 to prevent miscarriages. Decades later, this hormone has been associated with a variety of documented adverse outcomes in the daughters of whom the women were

pregnant with at the time. This example displayed the consequences and basis of fetal exposure and subsequent adult disease for scientists across many disciplines. Pathway mechanisms refer to experiences that fix people onto trajectories that influence health and wellbeing over the lifespan. For example, a longitudinal study assessed if children exposed to adverse psychosocial experiences were at an increased risk for depression, elevated inflammation levels, and clustering of metabolic risk markers at age 32. They found that children who had experienced socioeconomic disadvantage, maltreatment or social isolation had elevated age-related-disease risks in adulthood.[35] Cumulative mechanisms refer to accumulation of advantage or disadvantage over the lifespan, which can be expressed through health status. Of course, one could have accumulated latent or pathway exposures as well.[36–38]

Therefore, embodiment is a process of biological characteristics as a result of humans engaging in their world.[16,26,29] Given this concept, the mission is to understand the many ways inequality becomes biologically embodied, over the life course and across generations, thereby creating health inequities .[16,26]

A Social Factor to Consider: Discrimination

Discrimination refers to "the process by which a member, or members, of a socially defined group is, or are, treated differently (especially unfairly) because of his/her/their membership of that group."[39] This unfair treatment arises from "socially derived beliefs each group holds about the other" and "patterns of dominance and oppression, viewed as an unequal distribution of power and privilege."[40] Predominant types of adverse discrimination are based on

race/ethnicity, gender, sexuality, disability, age, nationality, religion, and social class.[16]

Discrimination is a public health issue. According to the 2015 Stress in America Survey administered by the American Psychological Association, 70% of people who took the survey, report having experienced discrimination, with 61% reporting experiencing day-to-day discrimination, such as being treated with less courtesy or respect, and being threatened or harassed.[41] Furthermore, 76%, 74%, 72% and 81% of Black, Asian, Latino and American Indian/Alaska Natives (AI/AN) groups, report having experienced everyday discrimination.[41] About 31% of women cite gender as a reason for day-to-day discrimination, compared to just 8% of men.[41] People who say they have faced discrimination rate their stress levels higher, on average, than those who say they have not experienced discrimination.[41] In another recent study, they showed that expecting or anticipating prejudice leads to both psychological and cardiovascular stress responses. People may avoid situations where they expect or anticipate unfair or maltreatment, possibly missing out on educational and job opportunities.[42] Lastly, discrimination due to socioeconomic status (SES) (an aggregate concept that includes both resource-based and "prestige"-based measures)[16] is not a new idea, however studies have not been able to disentangle the effects of SES from social race constructs.[43–45] SES has been shown to predict disparities in health amongst both white and non-white populations; this also often accounts for much of the racial differences in health.[46] Previous studies have found significant inverse associations for the relationship

between socioeconomic position across the lifespan and increased inflammatory markers,[47] and chronic diseases. [48]

As a newly recognized SDH, many forms of perceived discrimination is associated with a plethora of negative health outcomes, including increased hypertension,[49] obesity,[50] inflammation,[51] birth outcomes,[52] heart disease,[53] other chronic health conditions and mortality.[54–56] Scientists in the field attribute these outcomes to two of many pathways by which discrimination can be can be executed.[55] One process involves a lack of access and positive interaction amongst those who experience discrimination with institutions that provide services and resources to improve quality of life, upward mobility and acquisition of wealth.[55] This includes the revelation of differences in health outcomes in health care facilities amongst non-whites, and women, even after controlling for insurance coverage, age, sex, income, comorbidities, and severity of illness.[57–61]

The second mechanism involves chronic exposure to stress due to internalizing discrimination. This contributes to weatherization of the body and mind, and incessant exposure may lead to dysregulation of multiple body systems given the pathophysiology of the stress response.[55,62–64]

Stress

Stress has been defined in many different ways within the literature and describing this dynamic biological phenomenon is challenging for many scientists. One definition, describes stress as the perception of one's "environmental demands or challenges that tax or exceed the adaptive capacity of an organism, resulting in biological and psychological changes that may be detrimental and place the

organism at risk for disease or disability.[65] There are also many different ways to organize stress theory. In particular, this dissertation project utilizes an allostatic load framework (multi-system biological risk) and focuses on response-oriented stress: the physical and biological response within the body due to exposure from the neuroendocrine system.

The physiological demand on the body when one must adapt, cope, or adjust,[66] can result in different outcomes that can be perceived as negative or positive events.[67–70] However, the biological, medical and mental health literature agrees that chronic, intense or continuous stress can take a toll on health.[71–73] Chronic or intense stressors can take many different forms for different individuals, including economic difficulties, immigration status, occupational stress, death of a spouse or child, family responsibilities or difficulties, neighborhood instability, and discrimination.[74]

Each individual's body makes an attempt to adapt to stressors, however this response is dependent on a combination of environmental, genetic, and developmental factors. [75] The inability to successfully respond to stressors exacts a toll on the body; repeated, or intense events may lead to disease; furthermore, recent research has revealed that, ancestrally (epigenetics) and in-utero through adolescence are extremely critical time periods for the development of the adaptive stress response, displaying differences in vulnerability and flexibility to stressors.[75]

Stress Response Physiology

Theoretically there are three areas of interest with regards to the functioning of the stress response; perceived threats can activate the nervous system, endocrine system, and immune system.

For context, neurological focus of emotion is in the limbic system of the brain. The limbic system is thought to play a major role in emotion and fear dynamics; largely responsible for detection and the biochemical reaction within the stress response used to restore homeostasis. A combination of studies show that the most agreed upon neural structures in this system consists of the hypothalamus, thalamus, pituitary gland, hippocampus and the amygdala. [76] The hypothalamus is responsible for many essential hormones that regulate temperature, thirst, hunger, sleep, detection of pain and pleasure, mood, sex drive, and the autonomic nervous system.[77–80] The primary function of the hypothalamus is homeostasis. The hypothalamus uses a set-range to standardize the body's systems, such as electrolyte and fluid balance, body temperature, and blood pressure. After receiving input from the body, it then makes the appropriate modifications if there is deviation. The mechanism by which the hypothalamus maintains homoeostasis is by secretion of hormones such as, growth hormone-releasing, corticotrophin-releasing, somatostatin, dopamine, oxytocin and vasopressin, into the blood, which in turn communicates to the pituitary gland.[75,76,81,82] In the face of a threat, the hypothalamus activates the autonomic nervous system, stimulates the secretion of adrenocorticotropic hormone, produces vasopressin, and then stimulates the thyroid to produce thyroxine.[76] In the diencephalon, the thalamus functions as a sensory relay station, sensing what humans hear see, taste, or touch, through nerves, all

while directing these messages to the appropriate areas within the cortex.[79,80,83] Anatomically curved around the thalamus is the hippocampus, which plays a role in forming new memories.[78,79,84] Lastly, the amygdaloid, within the telencephalon or the cerebral cortex, causes intense emotion such as aggression or fear once stimulated.[79,80] On the contrary, damaged tissue of the amygdala causes animals to behave tamely, and there is a docile calmness found in humans called a flatness of affect. [77]

The brain communicates with the rest of the body via signals sent through the spinal cord (CNS), working in collaboration with the peripheral nervous system (PNS), a tract of neural fibers.[77] The PNS can be divided into the sensory somatic nervous system and the autonomic nervous system.[76,83] The somatic system is a bidirectional path responsible for sensory and voluntary motor signals involving cranial nerves and the CNS. [77] Whereas the autonomic division transports impulses through the CNS, however its end goal is innervating the body's internal organs to keep them functions and maintain homeostasis.[77]

The ANS can be subdivided into two antagonistic branches, the sympathetic and the parasympathetic systems.[76,84] The ANS receives messages from parts of the CNS that process both endogenous and exogenous stimuli; this includes regulation by neural structures such as the hypothalamus, amygdala, hippocampus, and olfactory cortex.[79,80] The sympathetic and parasympathetic systems of the ANS each consist of 2 sets of nerve bodies, the preganglionic set which is located in the CNS, with connections to another set of ganglia outside the CNS, and the postganglionic set which has efferent fibers that go from the ganglia to effector

organs.[84,85] The SNS is catabolic, or controls energy expenditure; it activates the fight-or-flight response, using catecholamines, and the opposing system (PSN) is anabolic or it conserves energy mostly through the release of acetylcholine .[76,77,84]

The hypothalamus initiates activation of the sympathetic nervous system, causing the first and immediate response of the release of epinephrine and norepinephrine through sympathetic nerve endings. Then neural impulses from the hypothalamus descend through the spinal cord, to then send nerve signals that innervate the adrenal medulla to start the intermediate stress response.[76,83,84] The chemicals from the adrenal medulla take about 20-30 seconds longer to respond, and are able to last for 2-3 hours depending on the dose in the bloodstream.[76] The adrenal medulla consists of chromaffin cells that lie at the core of the adrenal gland. The adrenal glands produce steroids, amines, and two catecholamines of interest, norepinephrine (noradrenaline) and epinephrine (adrenaline) [86] Pheochromoblasts are responsible for catecholaminogenesis, as well as their secretion.[78,84] The catecholamines produce an increase in adrenergic tissue (receptor binding) activity in humans. [78,84] Both catecholamines work together to produce a quick physical reaction in the face of a threat. Typically the adrenal medulla secretes mostly epinephrine, and about 20% norepinephrine; under stress, about 300x the amount of epinephrine may be found in the blood in comparison to basal rate.[76] Specific outcomes observed in both humans and animal models as a result of activation of this axis in response to psychosocial stressor exposure are: increased arterial blood pressure, heart rate and cardiac output, blood flow to skeletal muscles, plasma free fatty acids, triglycerides, cholesterol, and decreased blood flow to kidneys,

gastrointestinal system, and skin. Prolonged exposure or dysfunction by way of hypersecretion or hypo secretion of these chemicals and subsequent effects can lead to a variety of increased risk such as hypertension, thrombosis, or arrhythmias.[84,87–89]

The brake for the sympathetic nervous system is the parasympathetic nervous system, and it releases acetylcholine, which results in a decrease in heart rate, dilation and muscle tension. [76,83] Both systems are partially active all the time, but only one system can dominate at a time (with some exceptions (i.e. blood vessels dominated by sympathetic system).[76]

The endocrine system's action is the final mechanism of the stress response and it is activated as a result of perceived *sustained* threat; therefore the goal of this system in the stress response is to extend energy release.[83] By utilizing hormones that its glands manufacture and secrete, it can regulate metabolic change throughout the body.[76]

For cascade begins with, neural impulses from the hippocampal which descend into the hypothalamus, promoting the secretion of corticotrophin –releasing factor (CRF).[78,84,85] The CRF stimulates the anterior pituitary to further release adrenocorticotropic- hormone (ACTH), into the blood. ACTH is carried through the blood until it reaches the target organ, the adrenal cortex, to stimulate the release of corticosteroids. [78,84,85],[76]

The corticosteroids of interest are: glucocorticoids (i.e.: cortisol) and mineralocorticoids (i.e.: aldosterone). The main function of aldosterone is to

regulate the reabsorption of sodium and the excretion of potassium by the kidneys to maintain volume and electrolyte balance in the plasma.[76] It does this by decreasing their excretion by the sweat glands and gastrointestinal tract, resulting in fluid retention.[78,84,85] Excessive activation of mineralocorticoids in human is associated with the development of Cushing's syndrome (hyperadrenocorticism), and high blood pressure.[84,85,89]

Glucocorticoids are biochemicals (cortisol being the primary hormone) that help to generate glucose in the blood stream. Through the process of gluconeogenesis in the liver (and sometimes the kidneys), the body can break down non-carbohydrates resulting in elevated plasma glucose, which, in turn, promotes the deposition of liver glycogen.[76,84,90] Increased hepatic gluconeogenesis and glycogenesis is the result of direct effects of glucocorticoids on the liver's gene expression, coding for enzymes to produce glucose and glycogen.[90] Typically, cortisol is known to suppress the inflammatory reaction to infectious or immunologic agents, inhibiting migration of leukocytes, and phagocytic activity. [90]

On the contrary, long term exposure results in an increase in white blood cells due to cytokine production and an influx from the bone marrow but a reduction of removal from the vascular system, causing atherosclerotic inflammation.[76,91,92] Prolonged or excess exposure also leads to a diabetic-like state due to the increase in plasma glucose, while low glucocorticoid concentrations lead to hypoglycemia, decreased glycogen stores, and hypersensitivity to insulin.[90] Glucocorticoids also decrease uptake of glucose in peripheral tissues to provide more glucose for glycogen formation in the liver, resulting in insulin resistance.[84]

In terms of the effects of glucocorticoids on lipid metabolism, cortisol is utilized for lipolysis, the mobilization and breakdown of fatty acids for energy. [84,90] It is also known to redistribute body fat in hyper-corticism and large doses of glucocorticoids lead to redistribution of fat to the upper trunk and face, along with simultaneous loss of fat in the limbs.[90,93]

In the intestine, glucocorticoids increase sodium and water retention and secrete potassium.[90,94] Cortisol increases gastric acid to the mucosa, and decreases the rate of gastric cell proliferation.[84,90,94] It is well established that high dose or long-term use of glucocorticoids may cause peptic ulceration or exacerbate existing ulcers.[89]

In terms of other hormones released, vasopressin, or antidiuretic hormone is used to regulate fluid loss by the urinary tract. It does this by modifying blood pressure, however during chronic stress many regulatory mechanisms become exhausted or dysfunctional, and increased secretion of vasopressin leads to hypertension.[76,95] Lastly, during the stress response, the hypothalamus releases thyrotropin-releasing factor (TRF) to the anterior pituitary; this stimulates the secretion of thyroid-stimulating hormone (TSH) into the blood. [84] TSH stimulates the thyroid gland to release triiodothyronine (T3) and thyroxine (T4).[89] These hormones are known to increase metabolism, heart rate, and have been associated with many hormonal imbalance disorders.[89]

Any stimulus that induces a stress response is referred to as a stressor, and in general there are two types typically studied: (a) psychosocial (b) biogenic. [96] In brief, biogenic stressors do not require cognitive appraisal to elicit a physical stress

response, because they have an intrinsic stimulant attribute. Examples are found in compounds such as caffeinated drinks, (i.e., coffee, tea) amphetamines, cocaine, as well as extreme heat or cold, all of which can directly trigger a physiological arousal without cognitive appraisal. On the other hand, psychosocial stressors mostly require a process of cognitive interpretation; in particular, they are processed within the brain and assigned meanings.[96–98] Furthermore affective integration refers to the intensity of a felt emotion while it is being interpreted. Therefore, the cognitive–affective complex represents how the stressors are ultimately perceived.[67,69,98] Hans Selye, (physician who proposed the definition of stress) once said, "It's not what happens to you that matters, but how you take it." Indeed, some stimuli leave less room for variation in terms of interpretation and are typically known to be more stressful for humans, (e.g., external threat to one's safety, grief, guilt, etc.). But even in these cases, many factors can play a role in the intensity or attenuation of the subsequent stress response. [96]

After the stimuli is interpreted, impulses are sent back to the limbic system [99] in which we may feel an emotion and prepare for the potential to trigger flight or fight. Impulses are also sent to the neo-cortex; these impulses are concerned with neuromuscular enhancement, where, the intention for action can be translated to motor activity, that is, these structures appear to trigger the multi-systemic stress response. [78] Hence, stress is a response to a stimulus; moreover, the stress response is a physiological mediator or link between a stressor and its target organ.[96]

The ways in which the stress response is linked to subsequent target-organ

disease is a multi-step process.[83] When a stimulus is deemed a threat, a combination of the nervous, neuroendocrine, and endocrine components of the stress response work together to activate, increase, or obstruct normal functioning of the organs in the human body to cope and restore homeostasis.[28,100–104] Target-organ systems mentioned included the cardiovascular system, lipid metabolism, glucose metabolism, the gastrointestinal system, and the immune system.[28,100–104] Typically, a sporadic stressful event that an organism can efficiently address is normal, adaptive and may improve the chances of survival.[100] However, if incessant activation or overstimulation of target organs and systems occur over the lifespan, or during critical developmental periods, various clinical symptoms may become prevalent due to systemic dysregulation, or exhaustion.[28,75,83,100–105]

Allostatic load theory & practical use of multi-systemic biological risk

The allostatic load (AL) theory describes over-activation of primary mediators such as the aforementioned stress hormones and pro- and anti-inflammatory cytokines that result in exhaustion and adverse effects on different organ systems.[106] These hormone levels (primary mediators) are increased in individuals who experience acute or chronic stress, and they are responsible for the immediate effects on cardiac, respiratory, vascular, and other organ.[107,108] Periodically, this dynamic process is pertinent and beneficial to survival.[108] However, the AL theory aligns with the biological stress response logic that there are consequences due to chronic, incessant, or prolonged activation of the HPA axis due to stress.[108] This approach is useful because it focuses on the effects of the neuroendocrine systems and their intersectional roles in homeostasis related to

regulatory processes of the body and managing external stressors.[100,108,109] Furthermore this theory includes how stress hormones and cytokines are linked to pathophysiologic processes such as elevated blood pressure, serum cholesterol, diabetes, and inflammation.[110–112] Therefore over the last 20 years, studies typically utilize sub-clinically relevant and streamlined markers from multiple interconnected systems, [62,113–116] and as expected AL composites have predicted the onset of chronic diseases related to cardiac disease, diabetes, and stroke and all-cause mortality.[117–120]

As a concept, allostasis is complementary to homeostatsis[121] encompassing what happens to the body while it attempts to maintain stability or homeostasis through change.[81,122] Operationally, the biological mechanism encompasses the response to psychological and physical threats to homeostasis (i.e., stressors), which consists of activating a network of mediators or chemical messengers via the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS).[76,106,108,121] Specifically, the autonomic nervous system responds to stress by activating the SNS and involves the downstream secretion of epinephrine and norepinephrine.[76,100,121–123] Furthermore, when a threat persists, the HPA responds by eventually secreting glucocorticoids such as cortisol, whose receptors are ubiquitous in the body and is involved with growth, metabolism and immune function.[76,100,121–123] The AL theory is a way to conceptualize health risks from a multi-systems perspective. As a result of the incessant failed attempts to adapt, the body continues to respond by secreting corticosteroids. The price paid for continuous exposure to excess hormones can be dysregulation of the stress response

at any step, and/or acquired resistance to hormones processing a feedback that results in hypo or hyper secretion, and an accumulation of physiological and somatic damage, experienced over the lifespan. All of which may exacerbate the disease risk of a patient or complicate their clinical status. AL summaries estimate wear-and-tear by using a composite of biomarkers representing neuroendocrine, cardiovascular, metabolic, and immune systems.[124].[63,108,117,125]

The factor structure of AL as a distinct model for dysregulation across multiple regulatory systems has provided a statistically significant good fit for data in previous studies.[110–112] This type of representation is especially valid for this analysis because the main outcome is the influence of this cascade on regulatory systems overtime, and not an actual snapshot of hormone chemistry labs.[62,113,116,126]

This approach is more efficient than self-report stressors because in research relating psychological factors to physical illness, patients typically re-evaluate their lives on the basis of their health state and might selectively recall their experience before disease diagnosis.

Epidemiology of the Trends of Mortality in the US.

In the US, age-adjusted mortality for the total US population hit a standstill in 2010 and increased slightly in 2015.[127,128] Mortality trends and causes of death in the US are strongly modified by age groups, sex and race ethnicity.

The percent distribution of the 10 leading causes of death, by age groups greater than 25 years of age in the US during 2014 included: Unintentional injury (28.2%), cancer (12.6%), heart disease (11.6%), suicide (11.2%), and homicide (5.7%) amongst those aged 25-44. [129] Amongst people from the ages of 45-64,

cancer (30.5), heart disease (20.8), unintentional injury (7.4), chronic liver disease and cirrhosis (4.1), and chronic lower respiratory diseases (4.0) are the main causes of death.[129] For those 65 and older, the leading causes of death are heart disease (25.5), cancer (21.5), chronic lower respiratory diseases (6.5), stroke (5.9), and Alzheimer's (4.8) are the top causes of death.[129] Lastly, in those above the age of 85, the profile changes slightly, and the prevalence of death due to cancer decreases dramatically (12.2), and heart disease (29.2), Alzheimer's (7.5), stroke (6.8) and chronic lower respiratory diseases (5.0) are the burden.[129]

In 2014, amongst white women aged 35-85, white men 55-85, black men 55-74, black women 35-74, malignant neoplasms are the #1 cause of death respectively.[130] Heart disease death is #1 for white males aged 45-54 and 85+, white women aged 85+, black males aged 35-54 and 75+, and black women aged 75+.[130] The other top causes of death for each sub group include: unintentional accidents, homicide, suicide, cerebrovascular disease, and chronic lower respiratory disease with differences in prevalence based on age and race ethnicity.[130]

A recent study published in Lancet by Shiels et al[127], performed an analysis utilizing death certificates from the US National Center for Health Statistics and denominator estimates from the US Census Bureau to create age-period-cohort models. They estimated yearly percent changes or trends, as well as excess age standardized deaths from the year 2000 to 2014.

From 1999 to 2014, premature mortality differentially changed based on age groups. Among white persons, mortality increased in men aged 25–32 years, 40–49 years, and 63–64 years.[127] Amongst white women increases were seen in those

aged 25–38 years, 40–50 years, and 62–64 years of age.[127] Premature mortality also increased for American Indians and Alaska Natives for most age groups.[127] The largest increases were seen in both in white and American Indians and Alaska Natives women aged 25–30 years. On the other hand, premature mortality declined across all age groups in Latino individuals (by up to 3·2% per year), black individuals (up to 3·9% per year), and Asians and Pacific Islanders (up to 2·6% per year). [127]

Besides the small changes in trends across 15 years, from 2011 to 2014, American Indians and Alaska Natives had the highest mortality across all age groups, and although the rates for premature mortality for black individuals have been improving, the rates for premature death are so high that this group carries the second highest mortality rate in the US.[127] Asians and Pacific Islanders had the lowest premature mortality across all age groups.[127]

Mortality due to accidental deaths and suicide increased in all age groups and both sexes, and contributed strongly to the increases in excess premature deaths from 2011 to 2014. [127] In comparison, decreases in all-cause mortality for 50 to 64 year old men and women were largely driven by declines in mortality caused by cancer and heart disease, resulting in 175,000 fewer deaths in white men and 135,000 fewer deaths in white women during 2000 to 2014.[127]

For Latinos, there were decreases in premature mortality for both men and women in all age groups, however the most were due to a decline in HIV deaths in 25 to 39 year old and 40 to 49 year old men, reductions in cancer deaths in 25 to 39 year old and 40 to 49 year old women, and decreases in heart disease deaths in 50 to

64 year old men and women.[127] These declines resulted in 76, 000 fewer deaths in men and 36, 000 fewer deaths in women from 2000 to 2014. [127]

Black individuals exhibited reductions in HIV deaths amongst 25 to 39-year-old and 40 to 49-year-old men and in 25 to 39 year old women, declines in cancer deaths in 40 to 49 year old women, and decreases in heart disease deaths in 50 to 64 year old men and women. Amongst those aged 25 to 64 years of age, 202, 000 deaths in men and 108, 000 deaths in women were prevented from 2000 to 2014. Nonetheless, mortality rates in both black men and women are still almost 1.5 times higher than that in white individuals. [127]

In Asians and Pacific Islanders, there were mortality decreases in men and women, all adult age groups, and the majority of the causes of death resulting in 17 000 fewer deaths in men and 17 000 fewer deaths in women from the ages of 25 to 64 from 2000 to 2014.[127]

Amongst American Indians and Alaska Natives, there were increases in mortality for all age groups, except 50 to 64 year old women.[127] Deaths rates in individuals aged 25 to 49 years increased for most major causes of death and this resulted in approximately 3000 more premature deaths in men and 3600 in women from 2000 to 2014. Most of the excess deaths in women were due to chronic liver disease and cirrhosis in all age groups. There were no decreases in heart disease death for those aged 25–49 years.[127]

The complexity of the top 5 morbidities, and the multiple factors contributing to the pathophysiology of these conditions have made prevention of premature death conceptually difficult to prevent and tackle. Furthermore, estimating which social, behavioral, or physical toxins may have been the primary reason for mortality in an individual has limitations. A study published in 2009 by Danaei et al,[131] estimated the influence of mortality due to modifiable risk factors. Their study found that, tobacco smoking and high blood pressure could be attributed to approximately 467,000 (95% confidence interval [CI] 436,000–500,000) and 395,000 (372,000–414,000) deaths in the US in 2005, accounting for about 20% of deaths in US adults.[131] Overweight–obesity and physical inactivity contributed approximately 216,000 (188,000–237,000) and 191,000 (164,000–222,000) deaths respectively, representing about 10% each. In terms of diet, high salt intake (102,000; 97,000–107,000), low dietary omega-3 fatty acids (84,000; 72,000–96,000), and high dietary trans fatty acids (82,000; 63,000–97,000) contributed the most to death in 2005.[131] About 90,000 (88,000–94,000) deaths from other cardiovascular diseases, cancers, liver cirrhosis, pancreatitis, alcohol use disorders, road traffic and injuries, and violence were attributable to alcohol consumption (although 26,000 (23,000–40,000) deaths from ischemic heart disease, ischemic stroke, and diabetes were deterred by current alcohol use). [131]

From 2005-2013, the CDC further verified that the aforementioned contributors are still prevalent and action toward reducing these contributors have shown limited improvement.[132] Smoking among adults remained stable at 25% and smoking among youth declined to15.7%.[132] Obesity rates remained level at 35% for

adults and 17% for youth.[132] They estimated that 21% of adults met the recommended levels of physical activity, the same for the last 3 years.[132] Hypertension and cholesterol increased to 46.3% and 29.5%, respectively.[132] The prevalence of people living with HIV who know their serostatus increased to 84.2%.[132] The number of incident hepatitis C cases and hepatitis C-associated deaths increased by an average of 6.4% and 6.0% per year.[132]

In 2011, researchers estimated the number of deaths attributable to social factors in the US using articles published between 1980 and 2007.[7] They obtained the estimates of the relation between social factors and adult all-cause mortality by calculating summary relative risk estimates of mortality, and using prevalence estimates for each social factor to calculate the population-attributable fraction for each social factor.[7] The study found that about 245,000 deaths in the United States in 2000 were attributable to low education, 176, 000 deaths were due to racial geographic segregation, 162,000 deaths were due to low social support, 133, 000 to individual-level poverty, 119, 000 to income inequality, and 39 000 to area-level poverty.[7] It was concluded that the approximate number of deaths due to social factors in the United States rivals numbers due to pathophysiological and lifestyle causes.[7] The discussion explains that stress may partially explain the link between social factors and mortality, however stress could not be addressed within this study, and future studies should assess this important pathway. [7]

Indeed, more recent studies show that these numbers may be an underestimation. Recently an analysis estimated annual life expectancy by county

from 1980 to 2014 and further assessed the proportion of variation in life expectancy explained by variation in socioeconomic and race/ethnicity factors, behavioral and metabolic risk factors, and health care factors.[11] The study found that socioeconomic and race/ethnicity factors, behavioral and metabolic risk factors, and health care factors explained 60%, 74%, and 27% of county-level disparity in life expectancy, respectively in the US.[11] When pooled, these factors explained 74% of this variation.[11] A majority of the association between socioeconomic and race/ethnicity factors and life expectancy was mediated through behavioral and metabolic risk factors.[11]

These analyses that assess contributors to chronic complex diseases, and subsequent premature death speak to a broader and more complex view of public health and medicine in understanding causes of mortality.

Survival is an important measure for directly and specifically assessing how much has been gained in the advancement in specific efforts (therapies) to improve cancer outcomes, however many scientist strongly believe that mortality rates remain the most important measure of our progress against fighting cancer.[133] Indeed, this strongly depends on the question being asked, however the interpretation of survival measures is biased by changes in screening and detection; specifically detecting cases that would not have clinically manifested into disease (over-diagnosis), or identifying cancers that are slow to develop (length bias).[134,135] Also, improved screening results in a lead-time bias, capturing earlier diagnosis, but not a change in when the death would occur.[135] Therefore, utilizing death rates

allows for the direct measurement of the burden of disease and/or death.[136] Furthermore when trends are assessed, death rates clearly highlight disparities of morbidity and mortality.

Cancer deaths are counted as the crude and absolute number of deaths in a specified population. Cancer death rates in the population are calculated as the number of deaths from cancer occurring in a particular group during a specified time period, and divided by the average number of persons alive during that period. Limitations in the interpretation of changes in mortality rates overtime can be biased by changes in disease classification, poor interpretation and completion of death certificates due competing causes of death.[136] For example, when cancer is present (the underlying disease or condition that preceded and caused the immediate cause of death) but not recognized during death examination, a death caused by some nonmalignant condition (i.e.: heart failure, the immediate cause of death) will be coded to that condition. Further misclassifications that influence the reliability of data on cancer type, (i.e.: confusing colon and rectal) and lastly there are limits to interpreting the relationships between competing causes of death, especially amongst diseases that share many risk factors.[136]

Cancer Risk and Cancer Mortality Epidemiology in the US and Globally

Currently, we are still identifying and elucidating the causes and promoters of cancer in humans. Although a small line of research suggests that random errors in DNA replication drive cancer risk,[137] the most common theory highlights that mutations are indeed a necessary but insufficient cause of cancer, and the driving theory regarding the etiology of cancer include additional mechanisms (the

hallmarks of cancer).[138] Cancer is complex, and it is likely to occur when several biological systems become dysfunctional.[139–141] Further, random occurrences of mutations are not equal to random occurrence or sporadic cancer incidence.[142,143],[144] Worldwide, patterns of the most common cancers develop differently in women, men, high income countries, low income countries, and change across time, ethnicity and geographic variation.

A recent study published regarding overall updates to cancer death statistics in the US and globally, utilizing data from the National Center for Health Statistics.[9] There were over 8.7 million deaths due to cancer around the world in 2015.[9] This caused about 208.3 million disability-adjusted life years (DALYs) in 2015, of which 96% came from years of life lost (YLLs) and 4% came from years lived with disability (YLDs).[145] Although cancer is the second leading cause of death in the US overall, when stratified it is the number one cause of death amongst 22 states,[146] amid Hispanic and Asian Americans,[147,148] among women aged 40-79 , and men aged 45-79.[149]

During 2017, it is projected that approximately 600,920 Americans will die from cancer; this is about 1,650 deaths per day.[150] Currently, the most common causes of cancer death are cancers of the lung and bronchus, colorectal, and prostate amongst men and lung and bronchus, breast, and colorectal in women. These 4 cancers account for 46% of all cancer deaths, with more than one-quarter resulting from lung cancer.[150]

From 1980 to 2014, there were a total of 19.5 million cancer deaths in the US.[9] Amongst the top cancer sites over the last 3 decades, there were 5,656,423

deaths due to tracheal, bronchus, and lung cancer; 2,484,476 deaths due to colon and rectum cancer; 1,573,593 deaths due to breast cancer; 1,157,878 deaths due to pancreatic cancer; 1,077,030 due to prostate cancer.[9] The decline in cancer mortality over the past 2 decades is the result of steady reductions in smoking as well as advances in early detection and treatment; this is seen mainly in the top 4 cancers (lung, breast, prostate, and colorectal).[150]

During the 20th century, the overall cancer death rates that increased mostly due to the tobacco epidemic, resulted in a cancer death rate peak in 1991 in the US of 215.1 per 100,000, and these rates have dropped by approximately 25% to 161.2 in 2014 due to the decreased prevalence of smoking. This decline is larger in men than in women, and resulted in approximately 2,143,200 fewer cancer deaths (1.4 million in men and 659,200 in women) than what would have been expected with peak rates.[149] Even so, within the Southern region of the US, about 40% of cancer deaths in men during 2014 was due to smoking.[151]

Researchers estimate that about 45% of cancer deaths in the US are due to modifiable risk factors including : high body mass index (BMI), low fruit and vegetable intake, lack of physical activity, infection, alcohol use, and tobacco use as previously mentioned.[152]

The percentage of adults that are overweight (BMI>25 kg m^{-2}) and obese (BMI>30 kg m^{-2}) has increased over the last 35 years.[153] A high BMI is associated with an increased risk of many non-infectious diseases, including cancer.[154,155] Around the world, the most common cancers related to excess adiposity are cancers of the: esophagus, gastric cardia, colorectal, gallbladder, pancreas, liver,

postmenopausal breast, ovary, endometrium, kidney and prostate.[156] The most commonly cited study regarding the burden of obesity on cancer death in the US was published in the New England Journal of Medicine in 2003 by Calle, et. al.[157] The study prospectively analyzed 900,000 US adults at baseline, which resulted in 57,145 deaths from cancer during 16 years of follow-up.[157] There were significant positive associations between a higher BMI and cancer death for cancers of the esophagus, colorectal, liver, gallbladder, pancreas, and kidney in cancers that men and women share.[157] In men alone, stomach and prostate cancers were observed and breast, uterus, cervix, and ovary were observed in women alone.[157] In conclusion, given the patterns and predictions of overweight and obesity at that time in the United States (US), excess weight could account for approximately 14% of all deaths from cancer in men and 20% in women.[157]

The relationship was also assessed in the Million Women Study, a prospective cohort study with 1.2 million women from the UK aged 50-64.[152] The study found increased relative risks of mortality for all cause cancer death due to increasing BMI while adjusting for age, location, socioeconomic status, age at first birth, parity, smoking status, alcohol intake, physical activity, years since menopause, and use of hormone replacement therapy.[158] The cancers that drove the association were likely, leukemia, multiple myeloma, kidney, ovary endometrium, postmenopausal breast, pancreas, and esophageal. [158]

Lastly, the Prospective Studies Collaboration published a study in Lancet, where they examined BMI and cause specific mortality by amalgamating data from 57 studies with 894, 576 participants, in Europe and North America. [158] There were

22,592 cancer deaths after 13 years of follow up (although the study excluded 5 years to limit reverse causality, leaving 8 years of follow up time). [159] For those with a BMI from 25–50 kg/m^2, cancer accounted for almost 60% as many deaths as vascular disease, but the association was not as strong.[159] BMI was associated with a 10% increased risk for cancer mortality, for each 5 kg/m2 higher BMI. In this study, liver, (HR 1.47 [1.26–1.71]), kidney (1.23 [1.06–1.43]), breast (1.15 [1.02–1.31] for pre and post-menopausal), endometrium (1.38 [1.08–1.77]), prostate (1.13 [1.02–1.24]), and large intestine (1.20 [1.12–1.28].[159]

For those with a BMI from 15–25 kg/m2, there was an inverse association with mortality from cancer as a whole, and this is likely because of strong inverse associations with the cancers related to smoking.[159]

Although it may seem intuitive to deduce that an increased risk for cancer may lead to an increase in cancer death, the interpretation of data regarding cancer death is not straightforward and the evidence carries large limitations that are currently being explored in the literature. It is not clear of whether or not associations are causal given the many-shared factors that lead to adiposity (i.e., diet quality, exercise), as well as a variety of metabolic disorders that adiposity imposes on the body. Furthermore, evidence from the literature has revealed an "obesity paradox",[160] where being overweight and obese category I has been associated with an improved survival compared with normal weight.[160,161] This paradox implicates 3 potential concepts: (1) Suggests that a measure of a single 'ideal weight' for a specific height may should be further assessed, (2) suggests that there are benefits to possessing a higher weight during older ages.[160,161] Lastly, (3)

epidemiologically, this could be due to uncontrolled confounding, temporality, or even collider bias, where results are strongly influenced by a confounder that has at least two sources common to the risk of the covariate and the outcome of interest, thereby influencing your results so much so that the association displayed is not necessary due to the exposure of interest (i.e., smoking and obesity).[160,161]

Another top contributor to cancer risk and therefore largely impacts cancer death rates globally are infections, where about 2.2 million (~15%) of cancer cases were attributable to infection in 2012.[162] IARC has identified ten infectious agents to be carcinogenic to humans (Group 1) which include: one bacterium called *Helicobacter pylori*, six viruses that include: hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV; types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), Epstein–Barr virus (EBV), human herpes virus type 8 (HHV-8), and human T-cell lymphotropic virus type 1 (HTLV-1), and 3 parasites: *Opisthorchis viverrini*, *Clonorchis sinensis*, and *Schistosoma haematobium*. [163]

Strongly correlated with socioeconomic development, cancer cases attributable to infection differ by country, ranging from approximately less than 4% in North America and some countries in west and north Europe up to about 50% in sub-Saharan Africa and Mongolia.[162] Almost 65% of infection-related cancers occurred in low human development index countries.[162]

H pylori, HPV, HBV, and HCV together were responsible for about 95% of new infection related cancers worldwide in 2012, with *H pylori and HPV* contributing the most in High and Very High Human Development Index countries such as the US (AF of new cancer cases due to HPV in the US= 1.1% for

men and 2.6% for women).[162] The burden of HPV-attributable cancer (mostly cervical cancer) was so excessive globally, it practically equated infectious-attributable cancer in men for all infections, making it that so that overall the numbers of cancers attributable to all infections were similar for both sexes.[162] Due to lack of vaccination and screening, almost half of the women diagnosed with cervical cancer will die from this cancer (~ 250,000), the majority of those deaths (>80%) are in low Human Development Index Countries. [164]

IARC has reviewed hundreds of epidemiological and animal studies over the last 30 years to examine the carcinogenicity of alcoholic drinks; each time the updated data and evaluation has confirmed that alcoholic beverages are indeed carcinogenic to humans (Group 1).[165] Tumors of the mouth, pharynx, larynx, esophagus, liver, colorectal, and female breast were all associated with alcohol consumption. Furthermore, the National Toxicology Program of the US Department of Health and Human Services reports that there is strong scientific evidence of a ”dose-response” association; after moderate drinking, the more alcohol consumed, the higher the risk for an alcohol-related cancer.[166]

A study published in the American Journal of Public Health in 2013 by Nelson et al,[167] provided current estimates of alcohol-attributable cancer mortality in the United States. Data was based on relative risks provided by meta-analyses published from 2000- 2009 as well as alcohol consumption data from the 2009 Alcohol Epidemiologic Data System, 2009 Behavioral Risk Factor Surveillance System, and the National Alcohol Survey in 2009–2010.[167] The results showed that alcohol consumption attributed to about 18,200 to 21,300 cancer deaths, or 3.2% to

3.7% of all US cancer deaths.[167] The majority of alcohol-attributable female cancer deaths were from breast cancer (56% to 66%), and alcohol-attributable cancer deaths in men were from upper airway and esophageal cancers (53% to 71%). [167]Lastly approximately 26% of alcohol-attributable cancer deaths were among those who consumed 20 grams or less of alcohol per day.[167]

Physical activity is an important component of metabolism.[168] While a decrease of physical activity may lead to cancer outcomes by way of excess weight and obesity, evidence also indicates that physical activity may reduce the risks of several cancers through other mechanisms, independent of obesity.[169] In a US sample population prospective study with 293,511 men and women, a higher pre-diagnosed physical activity level was associated with a lower risk of all-cancer mortality.[170] Specifically in comparison to those reporting rare or no physical activity, there was a lower risk starting from 7% to 11% for those reporting anywhere from 1 to 7 hours of physical activity. [170]

Over 35 years ago epidemiologists, Sir Richard Doll and Peto estimated that about 30–35% of cancer deaths in the US were associated with diet.[171] Estimating the burden and impact of ones diet on cancer mortality is complex and riddled with confounding due to its multifactorial interaction with the body, therefore it was also concluded that this percentage could be as low as 10% or as high as 70%. [171] Diet has been associated with at least 70% of colorectal cancer cases, however the majority of studies focus on the colorectum.[172,173] Still, positive associations were seen in epidemiological studies between consumption of red meat and non-indolent prostate cancers as well as cancers of the pancreas, breast and stomach.[172,173] A

component of the research considers carcinogens in cooked food and dietary fat; this is especially so for red processed (i.e.: curing, smoking, high temperature frying, grilling) meat where IARC has recently deemed it carcinogenic for humans.[173] Another component that may contribute to increased risks are due to excessive energy intake, characterized by rapid growth and quicker onset of menstrual cycles in childhood, as well as excess adiposity in adults, particularly for cancers of the colon and breast.[174]

According to WHO/IARC, about 19% of all cancers are attributable to environmental carcinogens (i.e.; agents, mixtures, and chemical exposures) including work setting, resulting in 1.3 million deaths annually.[175,176] In 2012 within the U.S., there were between 45,872 and 91,745 new cancer cases that were caused by past exposure in the workplace according to the CDC.[177] This is likely an underestimate, due to the fact that we are currently discovering new information about agents in the workplace that may cause cancer. [178]

In terms of trends and patterns of mortality in the US by age race and sex, an annual report completed and published by a collaboration of cancer health agencies including The American Cancer Society (ACS), Centers for Disease Control and Prevention (CDC), National Cancer Institute (NCI), and the North American Association of Central Cancer Registries (NAACCR) is being summarized for the epidemiology of cancer death trends in this dissertation. In terms of methodology, this report used data collected from death certificates by state and assembled into a national file. Furthermore, the International Classification of Disease (ICD) codes were used to identify underlying cause of death and they were further categorized

according to SEER causes of death recode to increase comparability between ICD versions. Lastly, age, sex, race, and ethnicity are based on information from medical records and death certificates.

For the duration of this dissertation, the social construct of race utilized in the US is categorized as white, black, Asian and Pacific Islander (API), American Indian/Alaska Native (AI/AN). Race by ethnicity based on Hispanic origin is categorized as non-Hispanic white (NHW), non-Hispanic black (NHB), non-Hispanic Asian and Pacific Islander (NHAPI), non-Hispanic American Indian/Alaska Native (NHAI/AN), and Hispanic (keeping in mind this category includes black and white participants).

By age group, for those younger than the age of 40, the leading causes of cancer death are due to brain cancer, leukemia, and female breast cancer before age 40 years. In 2013, lung cancer surpassed breast cancer as the leading cause of cancer death among women aged 40 to 59 years. Cervical cancer is the second leading cause of cancer death in women aged 20 to 39 years.

In terms of sex trends over the last 5 years, cancer death rates during the period 2010-2014 decreased for 11 of the 16 most common types of cancer in men and for 13 of the 18 most common types of cancer in women, including lung, colorectal, female breast, and prostate cancers. On the other hand, death rates increased for cancers of the liver, pancreas, and brain in men and for liver and uterine cancer in women. Adult height is positively associated with cancer incidence and death in both men and women, and has been hypothesized and estimated to account for one-third of the gender disparity in cancer risk.[179]

Currently, incidence and mortality rates are 20% and 40 % higher in men respectively; however, over the years, trends show that overall cancer incidence rates have decreased in men but stabilized in women during the period 1999-2013.

In general the disparity is potentially due to the disproportionate distribution of specific types amongst men.[150] For example, liver cancer, which is highly fatal, is 3 times higher in men than in women.[150] The largest sex disparities are for cancers of the esophagus, larynx, and bladder, for which incidence and death rates are about 4-fold higher in men.[150] This may be due to the disproportionate prevalence of alcohol consumption and smoking amongst men; the stabilization and increases in women may be due to the increase in the very same behaviors.[180,181] However, incidence rates are higher in women for cancers of the anus, gallbladder, and thyroid, cancer which are typically nonfatal.[150] On the other hand, melanoma incidence rates are about 60% higher in men and death rates are about double in men.[150] Women are typically diagnosed at an earlier stage, however men are also likely to have unfavorable prognostic indicators (i.e.; thick tumors, ulceration) and an older age at diagnosis. Furthermore, although hormonal influences are thought to play a role, women still fair better with advanced disease.[182]

By race ethnicity, in 2014, the cancer death rate has recently declined significantly, now resulting in a death rate that is about 15% higher in blacks than in whites.[150] The largest disparity is seen in men, likely due to prostate outcomes.[150] Many of the differences are due to the disproportionate burden of unequal access to high-quality health care.[150,183,184] This includes a lack of cancer prevention, early detection, timely diagnosis, and optimal treatment amongst minorities. However,

this gap is also narrowing rapidly, as a result of the Affordable Care Act, 11% of blacks, 16% of Latinos, and 7% of non-Hispanic whites were uninsured in 2015, down from 21%, 31% and 12%, respectively, in 2010.[185]

Cancer death rates among APIs, American Indians/Alaska Natives (AI/ANs), and Latinos are not comparable to the top 4 cancers in the US among non-Hispanic whites and blacks, however these groups have higher rates for cancers associated with infection.[150] AI/ANs in specific regions have the highest rates of kidney cancer, reflecting differences in the prevalence of renal cancer risk factors such as obesity and diet, smoking, alcohol consumption and hypertension.[150]

Overall, these changes and rates are disproportionate amongst populations and do not solely depend on the rate of mutations at the cellular level. Somatic mutations, related to environmental and behavioral factors such as tobacco, obesity, ultraviolet radiation and viruses are initiators and/or promoters and the prevalence of social determinant related factors are not distributed proportionately amongst the global population, however they are disseminated by social differentials. Therefore, cancer prevention strategies should proceed by tackling factors beyond the classic risk factors, including the whole system of an individual, both social and biological, and the intersection of the two, in order to estimate risk appropriately.

Literature Review: Hormonal and Immune Review

There are three areas of interest with regards to the functioning of the stress response; perceived threats can activate the nervous system, endocrine system, and immune system. Complementary to this, the allostatic load (AL) theory describes how prolonged or incessant exposure to stress hormones and cytokines are linked to

multiple interconnected systems including neuroendocrine, cardiovascular, metabolic, and immune systems.[63,108,117,124,125]

Physiologically, the endocrine system is closely integrated with the central and peripheral nervous systems as well as with the immune system. In brief review, the endocrine system utilizes feedback regulation where the sensitivity of target cells to hormonal action is due to "feed-back" from a specific endocrine organ the endocrine system is attempting to control. This loop can regulate ongoing secretion of a hormone negatively or positively.[186] Positive feedback enhances or continues stimulation of the original release stimuli (mostly common for gaining momentum i.e.: parturition).[186] Negative feedback inhibits or attenuates hormone release stimuli. This is how the endocrine system maintains a steady state or range; the key contributing hormones to regulating homeostasis include thyroid hormone, cortisol, parathyroid hormone, vasopressin, the mineralocorticoids, and insulin.[186]

Dysregulation of the endocrine system may symptomatically present in an inconsistent manner, influencing many organs and systems within the body due the ubiquitous nature of many hormone receptors.[186] Disorder can arise by both hormone deficiency and excess. Generally, hormone deficiency in a diseased state is due to the target tissues becoming resistant to the hormone's effects; therefore overproduction of the hormone begins due to the feedback loops that normally inhibit hormone synthesis and/or secretion, but they are also desensitized.[186] Dysfunctional hormone resistance that develops over time may come from a failure of receptor signaling and intracellular efficiency.[186] The converse would be hormone excess and/or overstimulation of hormone receptors due to endocrine

tumors, or disorder of hormone excess. Antibodies that bind to and activate the receptor for a particular hormone can mimic hormone excess.[186] This involves specific immunoglobulins binding to the receptor for the specified hormone, causing receptor activation, and thus secretion of the hormone regardless of the proper physiologic trigger for this event. [186]

This dissertation evaluates both animal lab studies and human epidemiological studies to review the biological mechanisms that bridges stress-related biological processes and disease in humans. Unfortunately, not all biological processes are easily assessed in large population studies due to sampling challenges, expenses, and ethical guidelines. Animal studies are used in science to control external factors and establish proof of principle relevant to humans especially because randomization to chronic stress is unethical. Through numerous pathways by which stress-related biological processes act, have been hypothesized and tested to understand the contribution of chronic stress to chronic morbidities such as cardiovascular disease and cancer etiology as well as overall mortality. The intersection of stress, immune, autonomic, cardiovascular, and metabolic processes are reviewed below.

Many markers of the immune system have been studied in relation to psychological stress; basic descriptions of immune components are described. There are two forms of response in defense of an external invasion. One is a nonspecific, innate system of immunity that is present at birth; the other is an adaptive system that is acquired and utilizes immunologic memory through the lifespan.[187] The skin, stomach acid, cough reflex, and mucosal barriers are some of

the first line of defense of the innate immune system.[187] Other factors, such as proteolytic enzymes, acute-phase proteins, cytokines and leukocytes, are additional layers of protection.[187] Toll-like receptors (TLR) that are found on macrophages, mast cells, and immature dendritic cells, identify patterns found in microbial proteins, DNA, RNA, and lipopolysaccharide (LPS), and this initiates inflammatory responses before an adaptive response.[187] The inflammatory response (inflammation) occurs when tissues are injured or damaged.[187] The damaged cells release chemicals including histamine, bradykinin, and prostaglandins.[187] These chemicals cause blood vessels to leak fluid into the tissues, causing swelling and attract phagocytes.[187] Foreign substances that can induce an immune response are called antigens or immunogens.[187] Immunogens can react with antigen-binding sites on antibody molecules or T-cell receptors.[187] Foreign agents that have breached the innate immune system may trigger the adaptive immune system.[187] It has specificity and memory for individual antigens creating a stronger defense. Triggering the adaptive immune system elicits a cascade of events initiating the activation of lymphocytes, the synthesis of antigen-specific antibodies (humoral immunity that are protein chemicals), and effector cells (cellular or cell-mediated immunity), and potentially the elimination of the foreign element.[187]

Effector cells derived from hematopoietic stem cells include mast cells, basophils, polymorphonuclear neutrophils, eosinophils, macrophages, monocytes, platelets, and lymphocytes.[187] Cytokines are proteins made by lymphocytes (lymphokine), monocytes (monokines), and leukocytes (interleukins), that affect the behavior of other cells through specific receptors.[187] Chemokines are a type of

cytokines that have chemo-attractant properties, inducing cells with the appropriate receptors to move toward the source of the chemokine.[187] Lymphocytes are able to identify specific antigens and they include B lymphocytes (from bone marrow) involved in humoral or antibody responses, T lymphocytes involved in cellular immune responses (from thymus) and natural killer cells.[188]

T lymphocytes are heterogeneous in terms of function. Helper-inducer T cells (CD4) help to amplify B-cell production of immunoglobulin and amplify T-cell (CD8)–mediated cytotoxicity. The two types of helper T cells are differentiated by their cytokine production and T-helper type 1 (TH_1) cells produce gamma-interferon (IFN-γ) and tumor necrosis factor-beta (TNF-β). T-helper type 2 (TH_2) cells produce interleukins 4, 5, 9, and 25, among others. Both helper types produce interleukin (IL)-2, IL-3, IL-10, IL-13. Cytotoxic or "killer" T cells are generated after mature T cells interact with certain foreign antigens. Cytotoxic T cells may kill their target through osmotic lysis, by secretion of TNF, or by induction of apoptosis. Mucosal dendritic cells regulate the generation of regulatory T cells. T_H-17 and T-regulatory cells (T_{REG}) are subsets of T cells, which modulate inflammatory responses through the secretion of regulatory cytokines. T_H-17 cells recruit neutrophils to sites of acute inflammation through secretion of IL-17. T_{REG} cells are inhibitory, suppressing activated T effector cells by their secretion of interleukin-10 and TGF-β cell$_{REG}$ cells modulate responses to antigen, thereby regulating homeostasis and tolerance versus inflammation, allergy, and autoimmunity. B-cell maturation proceeds in antigen-independent and antigen-dependent stages. All mature B cells bear surface immunoglobulin that is their

antigen-specific receptor. The major role of B cells is differentiation to antibody-secreting plasma cells, release of cytokines and also function as antigen-presenting cells. NK cells can kill a wide spectrum of target cells. Antibody-dependent cell-mediated cytotoxicity (ADCC) occurs when an organism or a cell is coated by antibody and suffers NK cell–destruction. Also, NK cells can destroy virally infected cells or tumor cells nonspecifically. Macrophages are involved in the ingestion, processing, and presentation of antigens for interaction with lymphocytes. In addition, they are effector cells for certain types of tumor immunity. Circulating monocytes are recruited to sites of inflammation where they mature into macrophages. Mast cells are basophilic staining cells found chiefly in connective and subcutaneous tissue. Neutrophils are granulocytes that consume and destroy foreign antigens and microbial organisms.[187,188]

Studies: The stress response and the immune system

Studies over the last few decades have revealed the various influences stress may have on the immune system. The stress response is directly and indirectly connected with the immune system in more than one way; this is because epinephrine, norepinephrine, and cortisol are able to bind to specific receptors on white blood cells and resulting in regulation of function and circulation.[189–191] Sympathetic nerve fibers are present in the bone marrow, thymus, spleen and lymph nodes.[191] In particular, almost all lymphocytes express adrenergic receptors, although there is differential sensitivity and quantity of receptors on lymphocytes, which may influence responsiveness to stress among specific cell groups.[190,192–194] For example, B cells have high density and lower affinity β_2-adrenergic receptors,

whereas NK cells have high-density and high- affinity, and T cells have the lowest concentration of receptors.[192,194–196] Once bonded with its ligand, β- adrenergic receptors signal for the activation of cyclic adenosine monophosphate (cAMP). Activation of β2-ARs when there are no physical immunogens increases pro-inflammatory cytokine production.[197–199] The catecholamines may mobilize hematopoietic stem cells out of bone marrow into circulation, moving to peripheral tissues and/or an area of injury to initiate inflammation.[200–202] Within the bone marrow SNS signaling stimulates the production of monocytes, granulocytes, and other immune cells, resulting in a pro-inflammatory shift in the immunoregulatory circulating pool of leukocytes.[200–202]

In general although systemic circulating glucocorticoids were traditionally known to be immunosuppressive, decades of updated and expanded research regarding this topic has revealed that they are in fact immunomodulating.[203–208] Glucocorticoids may reduce the number of circulating lymphocytes, monocytes, and eosinophils, mainly by increasing their movement out of circulation.[189,209] However conversely, they may also expand the number of circulating neutrophils by increasing their movement from the bone marrow to the bloodstream and simultaneously stopping their migration to an inflammatory location.[189,208,209] They are also shown to both promote and dampen neutrophil apoptosis.[189,208,209] The relationship between cortisol and the immune system is bidirectional where IL-1 stimulates the secretion of CRH and ACTH. Although traditionally used as an anti-inflammatory and/or immunosuppressive agent, glucocorticoids, especially at lower doses, also have stimulatory and permissive effects on the inflammatory response to

injury.[203,210] Determination of suppression or enhancement has yet to be fully elucidated however they may be related to dose, or whether or not the presence of glucocorticoids precedes challenge or trauma. One study showed that in macrophages activated by lipopolysaccharide and interferon-γ challenge (stress), a high dose of corticosterone inhibited the transcription of inflammatory genes, whereas a low doses of corticosterone enhance inflammatory gene expression.[211] In two murine studies, pro-inflammatory cytokine expression was enhanced when glucocorticoids were administered prior to lipopolysaccharide challenge (stress) but were attenuated when glucocorticoids were given after stress treatment.[203,212] Pathogen-associated molecular patterns or PAMPs detect microorganisms that are not associated with human cells, as well as DAMPs which are intracellular alarms that are activated when molecules are released from damaged tissues, and both are capable of initiating an inflammatory response. A study described rapid increases in circulating glucocorticoid concentrations triggered by physiological stress may play a role in the systemic warning system, by sensitizing cells to DAMPs, PAMPs and inflammatory cytokines.[206]

Indeed studies use different exposure compounds, and the effects due to physiologically induced endogenous glucocorticoids vs pharmacological or synthetic dose of glucocorticoids may influence the results of pathway studies.[85,101,195] Endogenous hormones at physiological concentrations can be immune-enhancing whereas endogenous hormones at pharmacological concentrations, and synthetic hormones, may be immunosuppressive.[85] Overall immunomodulation differs by duration (acute versus chronic) of stress, changes in

leukocyte distribution, the dose, the nature (endogenous versus synthetic) of glucocorticoid hormone exposure and the timing of stress or stress related hormone exposure.[85] This consideration falls in line with patterns of stress-related immune change and disease outcomes.[85,101,195]

Studies linking stress and the immune system in humans are substantial but results over the years have been equivocal. The first large-scale meta-analysis[195] regarding this topic assessed the effect sizes from 293 independent studies, reported in 319 separate articles in peer-reviewed journals. The total sample involved 18,941 individuals with a mean age of 34.8 years (*SD* = 15.9), ranging from (5-78) years of age, where most studies focused on young adults. In the average study almost half (42.8%) of the participants were female, and 84.8% focused on healthy adults. Acute laboratory stressors made of 29% of the studies while the chronic stressors section of this study made up about a fifth of studies utilized (*k* = 23; 7.8%).[195] The study revealed an increase related to natural immunity, specifically in the increase of the number of natural killer cells in circulation (*r* =.43, 95%CI .33-.51) although the test for heterogeneity were significant (p=.001), furthermore no other cells displayed strong significant differences from baseline.[195] For immune responses to chronic stress in healthy participants, none of the effect sizes for cell counts displayed a significant relationship.[195] However, all functional measures of the immune response displayed statistically significant negative effects on the immune system, (antibody to influenza after vaccination r=−.22, 95%CI −.33- −.11, natural killer cell cytotoxicity r= −.12, 95%CI −.20- −.01, cytokine production (IL2) r=−.21, 95%CI −.31-−.11), and the test for heterogeneity was non-significant (p-

values > .05).[195]

An update to this meta-analysis was conducted a few years later by Steptoe et al[213] on acute psychological stress in humans. The overall effect for IL-6 (r = 0.19, 95%CI .08-.30) and tests for heterogeneity were non-significant (p = 0.21).[213] For IL-1β (r = 0.58, 95%CI .30-.77) and tests for heterogeneity were not significant *(p* = 0.45), with less robust effects for C-reactive protein (*r* = 0.12, 95%CI -.18-.26) (*p* = 0.91).[213] The effects for TNF-α were not significant (*r* = 0.05, 95%CI -.10-.20).[213]

More recent human studies indicated that cell-mediated immune markers, including production and increase of activated T cells and NK cells were increased in maltreated children compared to healthy control children.[214] Another study revealed, higher childhood trauma questionnaire scores were positively associated with overall change in IL-6 response, as well as the maximum IL-6 concentration during the Trier Social Stress Test.[215]

A retrospective cohort study[216] (N=15,357) using longitudinal data from the Adverse Childhood Experiences Study (from 1995-1997 with follow up through 2005) developed an index that measured cumulative childhood traumatic stress (childhood physical, emotional, or sexual abuse; witnessing domestic violence; growing up with household substance abuse, mental illness, parental divorce, and/or an incarcerated household member). [216]The outcome was hospitalization for any of 21 selected autoimmune diseases (AD) and 4 immunopathology groupings: T-helper 1 (Th1) (e.g., idiopathic myocarditis); T-helper 2 (Th2) (e.g., myasthenia gravis); Th2 rheumatic (e.g., rheumatoid arthritis); and mixed Th1/Th2 (e.g.,

autoimmune hemolytic anemia). The fully adjusted sex-specific relationship between ACEs and the likelihood of hospitalization with any AD reported a statistically significant positive association (HR 2.1, 95%CI 1.4–3.2) for those with 2 or ≥3 ACEs compared with those with no ACE for women alone.[216] A test for linear trend revealed for every increase in the ACE Score, the probability of a first hospitalization with any AD increased 20% ($p < .001$) for women, 10% for men ($p < .05$),and the probability of a hospitalization with AD increased 20% for those aged 19 to 64 years ($p < .05$).[216]

Another longitudinal study by Takkouche et al[217], included an analytical sample of 1,149 participants aged 23-68 and 46% female. Participants completed a questionnaire assessing stressful life events, perceived stress, and negative and positive affect at baseline, they then periodically (every 10th week) self-reported common cold incidence.[217] After 1 year of follow up, and adjustment for gender, age and professional category, the common cold was associated with the 3rd (2.0 IRR, 95% CI 1.3-3.3) and 4th (2.8 IRR, 95% CI 1.7-4.6) quartile of increasing perceived stress.[217] The common cold was associated with the 2nd (1.7 IRR, 95% CI 1.0-2.8), 3rd (1.9 IRR, 95% CI 1.1-3.1) and 4th (2.0 IRR, 95% CI 1.2-3.3) quartile of increasing stressful events.[217] That being said some limitations that weakened the conclusions included high attrition and lack of adjustment covariates.

In general, regarding evidence the literature supports a positive association between psychological stress and immune related disorder, however there are some studies that have been null. Furthermore, the precision for some estimates have been poor.[85] Prospective studies aid in the issue of recall bias associated with cross-

sectional studies however assessment of outcomes may vary from study to study where self-report of a disorder is utilized and not adjudicated by a clinician.[85] Another issue is related to asymptomatic participants; for example, many may have an infection, however they may not overtly manifest well known symptoms of the disease, aiding in non-differential misclassification. On the same note, this may not be a huge limitation, where indolent disease may not aid in decreased quality of life.[85]

The Biological relationship between the stress response and the cardiovascular system

The cardiovascular system is made up of the heart and the channels of the vascular system that directs blood from the heart to all organs and tissues (via arteries and capillaries) as well as returns blood from these organs and tissues back to the heart (via veins).[218] The autonomic nervous system plays a key role in regulating cardiac function.[85] For example, AV node "ring" is regulated by nerve endings of the sympathetic and parasympathetic nervous system.[85,219] In particular, cholinergic nerve endings of the parasympathetic vagus nerve slow the ring rate of the SA node and, therefore heart rate, whereas sympathetic nerve endings secreting norepinephrine has an opposing effect.[85,219] Furthermore, catecholamines and cortisol secreted into circulation by the adrenal glands influence both the rate and force of cardiac contraction. [85,219]

When stimulated by the sympathetic nervous system, cardiac contractility, a component of myocardial performance, results in an increase in heart rate, change

in the speed of ventricular contractions, change in the force of these contractions, in contrast, parasympathetic stimulation can immediately slow the heart rate down. [219]

While the vascular system mainly directs blood to organs, it also functions as a pressure system that can smooth out the pulsating blood flow due to alternating contractions of the heart.[219] The arteries have elastic properties that may adjust to the high pressure associated with ventricular contraction, or the systolic blood pressure.[85,219] Meanwhile it also maintains a baseline or minimal pressure during relaxation, or the diastolic blood pressure reading. Loss of elasticity is a type of dysregulation observed along the pathophysiology of hypertension.[85]

The autonomic nervous system, as well as other processes, regulates vascular tone via both the endothelial cells and the layer of smooth muscle cells that surrounds the lumen.[219,220] The smaller arteries and arterioles are more muscular rather than elastic like the major arteries and this allows them to constrict or dilate, subsequently controlling blood flow to their respective capillary beds.[219,220] This involuntarily function is both locally and systemically controlled by metabolic needs related to overall levels or different types of activities.[219,220]

Regulation of circulation is executed via feedback loops that detect changes in circulatory function by monitoring chemical changes using chemoreceptors, and physical or pressure changes using baroreceptors, which include central nervous system feedback loops and circuits. Baroreceptor activation suppresses sympathetic activity and excitation of parasympathetic activity, together balancing blood pressure. [219,221]

Another component of vascular control is the renin–angiotensin–aldosterone system (RAAS), which regulates fluid volume and vascular resistance throughout the body. Sympathetic stimulation results in renin-secreting cells via $\beta_1$adrenoreceptors releases renin from the kidney that then leads to the formation of the hormone angiotensin II, which is a potent vasoconstrictor and participates in the increase in total peripheral resistance even in mild shock states.[222]Angiotensin II is the main product of the RAAS, and the primary hormonal factor controlling the production and secretion of aldosterone in the adrenal cortex and vasopressin by the pituitary; however, both hormones act on the kidneys to increase sodium and fluid retention.[85,222,223]

The aforementioned factors of the biological stress response that reasonably contribute to the pathophysiology of CHD when dysfunctional include raised blood pressure, insulin resistance, increased hemostasis, and endothelial dysfunction.[224,225]

Studies linking stress and cardiovascular disease.

The literature assessing the relationship between acute, chronic, and life event stress with cardiovascular events is saturated with strong consistent evidence for positive associations between these two concepts.[85,226] Epidemiological studies link chronic stress with increased risk of myocardial ischemia or infarction and cardiac wall abnormalities. High plasma norepinephrine levels are associated with increased risk of heart failure.[227–229] Takotsubo cardiomyopathy, described as a stress-related myocardial disorder, is characterized by the sudden weakening of the myocardium in response to acute stress.[230] Sympathetic nervous system hyperactivity alters cardiac wall contractility and increases apoptotic pathways in

cardiomyocytes, contributing to CVD development.[104,231,232] Stress also increases plaque rupture, leading to atherosclerosis [91] , likely via adrenergic signaling in platelets and well as inflammation. Furthermore every day or chronic stressors are also associated with poor health behaviors related to smoking, eating habits, indirectly leading to adverse cardiovascular outcomes.[224,233]

The INTERHEART study was a global case control study that examined several myocardial infarction risk factors; one study examined the association between chronic stress and risk of myocardial infarction in a sample of n=24,767 from 52 countries.[234] The study assessed stress with four questions about feeling irritable, anxiety, or as having sleeping difficulties as a result of conditions at work and at home, finances, or major life events in the past year. Additional questions assessed locus of control and symptoms of depression. The analysis was adjusted for age, gender, geographic region, smoking, diabetes mellitus, hypertension, ApoB:ApoA1 ratio, and obesity.[234] The study reported that those who indicated several events or permanent stress at work had an estimated 1.38 OR (95%CI 1.19–1.61) and 2.14 OR (95% CI 1.73–2.64) increased odds of myocardial infarction (MI) risk respectively and 9% population attributable risk (PAR).[234] Several events or permanent stress at home revealed 1.52 OR (95%CI 1.34-1.72) and 2.12 OR (95%CI 1.68-2.65) respectively and 8% PAR.[234] Unfortunately this retrospective analysis may be influenced by recall bias.

The Whitehall II study prospectively assessed the association between the effort-reward imbalance model and the job strain model with the risk of coronary heart disease in 10,308 people mean aged 35-55 from Great Britain over a mean of

5.3 years of follow up.[235] After adjustment for age, sex, study phase, employment grade level, negative affectivity, and coronary risk factors the study found that imbalance between both personal efforts (competitiveness, work-related over-commitment, and hostility) and rewards (poor promotion prospects and a blocked career) was associated with a 2.78 OR (95%CI 1.4-5.37) 3.55 OR (95% CI 1.42-8.90) and 3.14 OR (95%CI 1.72-5.71) fold higher risk of angina, ischemia or any coronary heart disease respectively.[235] Job strain and high job demands were not related significant; yet, low job control was associated with new disease.[235] The odds ratios for self-report low job control was 2.09 95%CI 1.29-3.37 and 2.04 95%CI 1.32-3.16 for angina and any coronary heart disease respectively.[235] The odds ratios for externally assessed low job control was 1.47 95%CI 1.77-2.02 and 1.57 95%CI 1.17-2.08 for angina and any coronary heart disease respectively.[235]

A study by Arnold et al,[236] assessed the association of chronic stress with adverse outcomes post-acute myocardial infarction (AMI). In a cohort of 4,204 AMI patients from 24 U.S. hospitals completed the globally known Perceived Stress Scale during hospitalization.[236] After adjustment for socio-demographic and clinical factors (including depressive symptoms), revascularization status, and GRACE (Global Registry of Acute Coronary Events) discharge risk scores, AMI patients with moderate/high stress had increased 2-year mortality compared with those having low levels of stress (1.42 HR, 95% CI 1.15 - 1.76).[236]

A recent longitudinal study utilized PET/CT to image the amygdala region of the brain to assess if its resting metabolic activity predicted risk of cardiovascular events.[91] The analytical sample was comprised of adults between the ages of 45-65

years of age, who underwent imaging during previous treatment.[91] Amygdala activity, bone-marrow activity, and arterial inflammation were assessed with validated methods.[91] After 3.7 years of follow up, amygdala metabolic activity was correlated with increased bone-marrow activity (**r**=0·47; p<0·0001), arterial inflammation (**r**=0·49; p<0·0001), and risk of cardiovascular disease events (HR 1.59 95% CI 1.27–1.98), after adjustment for age, smoking, hypertension, diabetes, dyslipidemia, and family history.[91] A secondary aim of this study cross-sectionally assess the relationship between perceived stress, amygdala activity, arterial inflammation, and C-reactive protein in a subset (n=13), and perceived stress was associated with amygdala activity (**r**=0·56; p=0·0485), arterial inflammation (**r**=0·59; p=0·0345), and C-reactive protein (**r**=0·83; p=0·0210).[91] That being said the sample size of this study therefore effect sizes should be interpreted with caution, and the participants are hospital based, contributing to selection bias.

Although the relationship between the topics of stress and cardiovascular outcomes provides strong consistent evidence, more studies regarding alternative pathways continue to accumulate in both experimental mechanistic studies and clinical studies in humans. However, other contributing factors to this relationship such as lifestyle are difficult to disentangle from this association while simultaneously aiding in disease.[233]

The biological relationship: stress hormones and metabolism

The hormones involved in chronic stress play an important role in more than one component of the metabolic process, including lipid and glucose mobilization and metabolism, directly and indirectly. Prolonged and excessive exposure of

corticosterone in the drinking water of mice subsequently leads to hyperglycemia, insulin resistance and dyslipidemia.[237,238] Feeding with a high-fat diet might exacerbate the effects of chronic administration of glucocorticoids, which is interesting considering that changes in eating behavior are a potential response to chronic stress in humans.[238] Conversely, removal of the adrenal gland in rodents sensitizes the brain to insulin, suggesting that the absence of circulating glucocorticoids improves insulin sensitivity.[239]

Animals that are adrenalectomized can function and live so long as food is provided, however once starvation commences, they are not able to move amino acids from muscle or serum protein, signifying that cortisol is important in this process.[239,240] A critical function of glucocorticoids are to release energy (i.e., glucose, fatty acids), so that it is available for mitochondrial oxidation in fight-or-flight conditions.[239,241,242] Therefore, glucocorticoids promote protein breakdown in the muscle, adipose tissue lipolysis, hepatic gluconeogenesis, and reduce glucose utilization.[242,243] All of these actions increase plasma glucose concentrations, and free fatty acid release from fat cells especially so in an insulin resistant state.[242,243] However, chronic or excessive glucocorticoids may lead to dyslipidemia (potentially age dependent in humans[244]), hyperglycemia and a diabetic-like state due to the increase in plasma glucose, and promotion of insulin resistance.[239,242,243,245,246] Glucocorticoids also decrease uptake of glucose in distant or limb tissues to provide more glucose for glycogen formation in the liver.[239,242] Large doses of glucocorticoids lead to redistribution of fat to the upper trunk, waist

and face.[93,242,245] It is theorized, that the mechanism is related to the differential density of glucocorticoid receptors in different organs or types of fat.[247]

The target organs involved in triglyceride metabolism (i.e., liver, adipose tissue) are heavily innervated by the sympathetic nervous system and are therefore at least partially neuronally controlled (by the hypothalamus). SNS hormones, epinephrine and norepinephrine are able to activate lipolysis,[85,248,249] stimulating free fatty acid secretion into circulation from fat depots. The catecholamines also cause IL-6 to be secreted from adipose tissue, [85,250] and promote a decrease in insulin sensitivity.[85,251,252]

Studies linking stress to metabolic disorders

The research regarding excessive or chronic stress and its influence on metabolic processes is relatively new and scarce with a large focus on job stress, depression and early life adversity.[85,253] Chronic stress is hypothesized to influence eating behavior, encouraging obesity and also promote obesity independent of eating behavior (potentially epigenetically), but above and beyond these traditional risk factors studies show that it may be an important risk factor for a several metabolic disorders.[85] Psychosocial stressors are able to activate and mobilize biological responses implicated in type 2 diabetes mellitus, involving the release of glucose and lipids into circulation, inflammatory cytokine expression and increased blood pressure.[253] Repeated or incessant exposure to these conditions within the body leads to chronic allostatic load, with a dysfunctional glucose metabolism and neuroendocrine feedback system as well as chronic low-grade inflammation.[85,253] A few observational studies are described below.

In the Whitehall II study, authors assessed the association between work stress and accumulation of components of the metabolic syndrome over 14 years. The study reports increased job stress was associated with greater risk of the metabolic syndrome 2.39 OR (95%CI 1.36-4.21) including obese individuals, and 2.29 OR (95%CI 1.27-4.12) excluding obese individuals.[254]

A study conducted in the Multi-Ethnic Study of Atherosclerosis, tested the contribution of psychosocial variables and their biological correlates to risk for metabolic syndrome among Latinos. In models fully adjusted for demographic and lifestyle and inflammatory variables, chronic stress had a 1.11 OR (95%CI 1.01-1.93), indicating that for each unit increase in chronic stress the risk of being diagnosed with metabolic syndrome increased by 11%. Once stratified by Latino group, the association for Mexican Americans 1.21 OR (95%CI 1.04-1.42), and Puerto Ricans 1.33 OR (95%CI 1.00-1.75) were significant.[255]

A prospective study by Hackett et al[256], utilized the Whitehall cohort to assess diurnal cortisol secretion at baseline and risk for T2D and impaired glucose metabolism over approximately 10 years of follow-up, in a sample of N= 3,270 men and women. Raised evening cortisol at baseline was predictive of incident T2D by the end of the study phase (OR, 1.18; 95% CI, 1.01-1.37) after adjustment for age, sex, smoking, grade of employment, BMI greater than 23, cardiovascular medication, history of CHD. [256]

A population-based study in Sweden explored incident cases of diagnosed diabetes over 35 years of follow-up in relation to self-perceived stress at baseline.

The study consisted of 7251 men from the Primary Prevention Trial Study, aged 47-56 years and absence of diabetes, coronary heart disease and stroke at baseline. They found a positive association between stress and diabetes, after adjusting for age, socio-economic status, physical inactivity, BMI, systolic blood pressure and use of anti-hypertensive medication (1.45 HR, 95% CI 1.20-1.75). [257]

Many of the observational studies support a positive association between type-2 diabetes and stress, but the magnitudes of the associations are not large, and many studies have reported null results (likely due to low sample sizes).[224,256]

A population-based study by Pyykkönen et al[258], utilized a random sample of 3,407 women and men aged 18–78 years from Western Finland. They explored associations between stressful life events, their accumulation, and metabolic syndrome as well as the individual components related to metabolic syndrome. [258] Models were fully adjusted for sex, age, alcohol consumption, current smoking status, regular exercise, level of education, and family history of diabetes.

The odds for having metabolic syndrome according to the ATP III criteria were significantly higher among participants who had experienced at least 2 stressful events in finance (ongoing financial strain, severe financial strain, threat of unemployment, or personal bankruptcy) 2.91 OR, (95%CI 1.75–4.89), or at least 3 stressful events 4.08 OR, (95% CI 1.66-10.66), and 2 events in family health (concern over own or child's ability to cope with stress) 1.65 OR, (95%CI 1.10-2.50).[258] Once stratified, different components of the metabolic syndrome were strongly correlated with some domains of stress, and weakly or not statistically associated at all for others.[258]

Overall the evidence from animal studies, experimental stress trials, and epidemiological studies shows that disturbances throughout several biological systems representing chronic allostatic load might be associated with chronic metabolic disorders over time.[253] Of course causal conclusions cannot be drawn from observational or murine studies, but the above accumulating evidence has linked various psychological stress factors with new onset T2DM after adjustment for lifestyle risk factors such as diet quality and obesity. Studies amongst those with comorbid psychological disorders and T2DM provides a clue of the potential long term severity of this relationship with increases the risk of early onset and progression of micro-vascular and macro-vascular complications and increased mortality.[259–261]

Review of tumor mechanisms and tumor environment (The Hallmarks of Cancer)

A natural component of development is the body's ability to balance growth; maintaining cell (rest and replication) division throughout life. [262]Although biologically and statistically speaking, cancer should be rare and random, the incidence of cancer is not sporadic and rare in the human population and this is due to the pattern of prevalence exposure to exogenous influences in the general population; this increases the probability of cancer risk throughout the lifespan.[262] Indeed, cancers are extremely diverse, this is some of the reason why it is incredibly complex to cure or understand mechanisms it uses to metastasize.[262] In terms of probability, successful cancers have a low chance of survival. In general, several perfectly timed genetically dysfunctional events provide the microenvironment that is permissive to tumor growth and mobility. .[262] Many cancers have self -sufficient

growth signaling, where either a mutation codes for a receptor that is always activated, not needing proteins (growth factors) to bind to subsequently activate it, or there are so many receptors present on the cell surface making the cancer hyper-sensitive to growth factor or the cancer may create its own growth factor.[262] Cancers are insensitive or evade anti-growth signals that are typically used during the cell cycle when a damaged DNS is detected in a cell; some of these tissues have a loss of function in their tumor suppressor proteins and some cancers gain function in their proto-oncogenes which could block the function of the tumor suppressor protein.[262] Another extremely efficient cell program is the ability of a cell to activate apoptosis when it detects that its DNA is damaged.[262] P53 is a vital protein, and its role entails detecting DNA damage or chromosome aberrations and halting the cell cycle to repair.[262] If repair is not possible then apoptosis is induced. [262] In most cancer cells, this protein has a mutated or missing gene, or it may be able to activate another protein that may inhibit its function, allowing the cancer to escape apoptosis. Many cancer cells are able to surpass the typical Hayflick limit by increasing the production of telomerase to lengthen the chromosomes ends or telomeres; this extends replicative capabilities and accumulating damaging mutations.[262] As a tumor begins to grow, surrounding cells become hypoxic or starved of oxygen.[262] This activates other transcription factors (HIF), which subsequently initiates the production of VEGF (an angiogenic growth factor), amongst other proteins.[262] The formation of new blood vessels, or angiogenesis, from endothelial cells begins to provide access to oxygen and nutrients; forcing normal local cells into participating in tumor development at a critical stage.[262] A

large component of tumor survival and subsequently death due to cancer,[262,263] is a tumors ability to release itself from the extracellular matrix, by expressing proteins that degrade the ECM, and molecules that don't allow binding to other cells, and promotes smooth migration to distant locations through blood vessels and the lymph system.[263]

In general as cancer cells evolve, there is selection for mutations over time, and accelerated accumulation of mutations by continued compromising of the aforementioned pathways of the genome, leading to tumor progression; this is sustained genome instability and mutations.[262] Also tumors promote chronic low grade inflammation by surrounding themselves with growth factors of the immune system through activation of NFκB in cancer cells and tumor associated macrophages, which amongst other roles, they may produce immunosuppressive molecules, allowing tumors to evade the immune system.[262] In terms of metabolism, cancer cells choose an inefficient pathway to acquire (much less) ATP, under anaerobic conditions; they do this because this pathway is quicker, and it also produces other molecules that are needed besides ATP for cell growth.[262] This includes up-regulation of glucose transporters, that increase glucose uptake and use in the cytoplasm through GLUT1 and HIF, as well as producing nucleosides and amino acids, which then produce macromolecules and organelles required for assembling new cells.[262] Cancer is a multistep process requiring many resources to thrive and grow over time. The aforementioned streamlined processes are common traits that help to distinguish successful cancer cells from normal cells, along with

chronic inflammation and a selective ancestry for mutations providing a foundation of genomic instability are strongly permissive environments in this process.

Researchers are only recently recognizing the large role of the Warburg affect in carcinogenesis. A review published by Cell, entitled "The Emerging Hallmarks of Cancer Metabolism"[139] organizes and develops the known cancer-associated metabolic changes into six hallmarks or traits. The first being dysregulated uptake of glucose and amino acids, then utilization of resourceful ways to acquire nutrients.[139] Next, tumor cells use new ways to acquire nutrients in harsh environments, which are mutations that have the ability to access inaccessible nutrient sources, increasing the quantity of nutrients.[139] Next cells may change the way nutrients are used by increasing carbon consumption and using glycolysis/TCA cycle factors for diverse biosynthesis and NADPH production to fuel ATP production.[139] At the same time, growth signaling increases the cellular demand for reduced nitrogen.[139] Then, abnormally activated growth signals may trigger the reprogramming of cancer cell metabolisms by directly transmitting the information regarding the cellular metabolic state to regulatory enzymes, some of which mediate epigenetic marks in metabolite-driven gene regulation.[139] Lastly, cancer cells control metabolic interactions within the microenvironment; this is done by signaling both a heterogenic pool of healthy, benign cells, along with immune system factors, to undertake necessary phenotypic changes for survival..[139]

The hypothesis is that this may be indirectly how stress may contribute to cancer outcomes. The relationship between stress and cancer has long been suspected, however the evidence regarding the complex relationship in

experimental and clinical studies have been weak and inconsistent. In general, the research base suggests that this mechanism is largely due to the immunosuppressive capabilities of the stress hormones. Only over the last decade have researchers changed their methodological approach [85] to show promising evidence regarding pathways by which the biological stress response could aid in the upkeep of a conducive environment.

Animal studies: Studies linking the biological stress response to carcinogenesis and progression.

Experimental pathway studies done with animal models have found that different forms of stress may influence the initiation, growth, and metastasis of some tumors. Murine models have shown that stress may exacerbate the progression of many cancers. These studies provide proof of principle for cancer cell proliferation, varied pathways for resistance to apoptosis, metastasis, angiogenesis, and cellular immune responses.[264] Further to this many of these studies have reversed tumor growth utilizing pharmacological drugs that are adrenergic antagonists, or β-blockers. Interestingly enough, these drugs are used to treat disorders, such as hypertension and arrhythmia and other ailments. RCTs and epidemiological studies have shown strong evidence for both progression-free and long-term survival for cancer patients utilizing β-blockers; however even more recent studies report that relapses are eminent[264] .

A study assessed the role of neuroendocrine activation by way of cage restraint, and breast cancer metastasis from the mammary gland to distant target tissues. Chronic stress had a little effect on growth of the primary tumor but

induced a 38-fold increase in metastasis to distant tissues including the lymph nodes and lung compared to controls (p=.04).[265] They also assessed the role of β2AR in stress-enhanced tumor progression, by treating stressed and control mice with the beta-adrenergic antagonist propranolol prior to tumor cell injection.[265] Propranolol treatment had no significant effect on metastatic burden in non-stressed control mice ($p = .08$), but completely blocked stress-enhanced metastasis in animals subject to chronic restraint stress ($p < .0001$); it also had no effect on primary tumor growth in the mammary fat pad for either stressed ($p = .73$) or non-stressed control animals ($p = .89$). [265]They also assessed if stress impacts macrophage infiltration into the mammary tumor; the effects increased mammary tumor infiltration of CD11b+F4/80+ macrophages by 53% (control vs. stress: 7.23 ± 0.49 % of live cells vs. 11.04 ± 1.22 %, $p = .013$).[265] Norepinephrine also increased expression of VEGF (3.2-fold, $p = .003$) and to determine if increased VEGF expression was adequate to regulate angiogenesis in vivo, they tracked primary tumor blood vessel density and found a 2.8-fold increase in stressed animals ($p < .001$).[265] Lastly treatment of stressed animals with the β-antagonist propranolol reversed the stress-induced macrophage infiltration and inhibited tumor spread to distant tissues. [265] Similar findings were found in a similar study examining β-AR density, signaling capacity, and functional responses to β-AR stimulation in four human breast adenocarcinoma cell lines.[266]

Another in vivo study examined stress and prostate cancer. In normal mice, the PI3K inhibitor is supposed to induce apoptosis in C42 prostate cancer

xenografts, however stress exposed mice or injection with adrenaline prevented induced apoptosis and sustained tumor growth.[267]

A recent study examined the impact of chronic stress on tumor development in a murine model of pancreatic cancer. Physiological stress response was demonstrated in stressed mice by the presence of elevated plasma levels of corticosterone (276.4 ± 20.6 ng/ml vs. 190.3 ± 18.1 ng/ml in control mice, $p = 0.0138$, $n = 6$), significantly elevated tyrosine hydroxylase (key enzyme in the production of catecholamines) (stressed mice 22.6% ± 0.7% vs. control mice 10.7% ± 2.1%, $p = 0.0052$, $n = 6$), and increased size of adrenal glands in stressed mice (seen via MRI 1.93 ± 0.04 mm **vs.** size of adrenals 1.48 ± 0.09 mm, $p = 0.02$, $n = 5$).[268] TGF-beta (growth factor signaling) in vitro was increased by 23.4% using catecholamines ($p < 0.012$) and in vivo employing chronic stress ($p < 0.001$).[268] After 5 weeks MRIs showed that the volumes of the tumors were (799 ± 143 mm^3 *vs.* 348 ± 76.3 mm^3, $p = 0.0061$) larger and median survival was reduced (52 days vs. 66 days in controls ($p = 0.0058$) n=18).[268] Tumors expressed more VEGF ($p = 0.0334$), had greater micro vessel densities ($p = 0.047$).[268] Furthermore, catecholamines increased proliferation in tumor cells by 18% ($p < 0.0001$) and migration by 78% ($p = 0.0348$) whereas the beta-blocker propranolol reduced these effects by 25% ($p < 0.0001$) and 53% ($p = 0.045$), respectively.[268] After being stressed the animals with tumors were treated with propranolol, and tumor volumes were reduced by 69% ($p = 0.0088$) and survival improved by 14% ($p < 0.0058$).[268]

Lastly, a study examined how catecholamines induced inflammation in ovarian tumors and promoted tumor metastasis. In human ovarian cancer samples from patients with known levels of depression as well as tumor NE levels, the researchers conducted a metabolite analysis. Metabolites that play a role in inflammation and tumor biology, Prostaglandin E2 (PGE2) and 6-keto prostaglandin F1 α (PGF2α), were elevated in tumors from those with high depression scores compared with those with low scores (PGE2: 2.38-fold increase, $P<0.05$; PGF2α: 2.03-fold increase, $P<0.05$).[269] The study showed that norepinephrine could activate beta2 adrenergic receptors and transcriptionally activate PTGS2 and PTGES via Nf-kB to produce PGE2.[269] The survival plots for patients with ovarian cancer, displayed combined expression of high PTGS2 and PTGES, displayed statistically significant decreased survival for overall (p=.005) and progression-free survival (p<.001). [269]

A clinical study utilized tissue microarrays from 481 patients with ovarian cancer and 4 without to investigate the association of tumor glucocorticoid receptor expression and patient outcome in ovarian cancer. [270] The study found that glucocorticoid receptor proteins were highly expressed in (39.0%) of tumors from patients who underwent surgery and adjuvant chemotherapy.[270] High glucocorticoid receptor expression was more common in serous tumors ($p < 0.001$), high-grade tumors ($p < 0.001$), and advanced stage tumors ($p = 0.037$).[270] Median progression free survival was significantly decreased in cases with high GR (20.4 months) compared to those with low GR (36.0 months, HR = 1.66, 95% CI 1.29–2.14, $p < 0.001$).[270] GR remained an independent prognostic factor for progression free

survival analysis that adjusted for age, histological cell type, grade, stage (early *versus* advanced), and the presence of gross residual disease after surgery.[270] However overall survival was not associated with GR status.[270]

In terms of initiation, the amount of studies are scarce. Thus far there are 2 hypotheses [200], regarding mechanisms related to DNA damage and inhibited p53. Several molecular pathways have been implicated in β-adrenergic inhibition of DNA damage repair; the first includes catecholamines activating both Gs–PKA and β-arrestin-mediated signaling pathways.[271] Gs–PKA-dependent signaling leads to the generation of reactive oxygen species and β-arrestin-1 facilitates AKT-mediated activation of MDM2 and also promotes MDM2 binding and degradation of p53, by acting as a molecular scaffold.[271] β-arrestin-1-dependent p53 degradation, results in impaired DNA checkpoint and repair mechanisms triggering DNA damage and then suppression of p53 levels respectively, together leading to accumulation of DNA damage.[271]

Another study assessed the mechanism by which chronic stress influences tumorigenesis in vivo. Typically, ionizing radiation induces carcinogenesis in mammals and P53 plays a direct role in preventing the replication of cells that are damaged by ionizing radiation.[272] In this study, male mice were subjected to periodic long-term physical restraint, inducing high corticosterone levels ($p<0.0001$ for relative corticosterone serum difference).[272] Unrestrained mice were treated with 4 Gy of ionizing radiation as controls (promoting tumor formation). Chronic restraint alone had no significant effect on the survival of $p53^{+/-}$ mice ($P = 0.92$), however it significantly reduced tumor latency in mice with IR (49wks vs. 38wks of

median survival age, p = 0.004).[272] Next researchers assessed if chronic restraint decreased p53 levels by measuring the mRNA levels of a group of well-known p53 target genes, shortly after IR exposure.[272] These genes were significantly lower in mice with chronic restraint versus mice without restraint by up to 50% (p=.041, p=.0042, p=.023 for p21, NOXA and Puma respectively).[272] Furthermore, in response to IR, p53+/+ mice with no restraint had significantly more apoptosis occur, vs p53+/+ mice with restraint (p=.017) (as a control, (<5%) of radiated cells died of apoptosis in *p53 knockout* mice). [272]Lastly the authors examine if the attenuation of p53 contributes to the promotion of chronic restraint on tumorigenesis. Using colorectal cancer cell lines with and without p53 (p53+/+ and p53-/-) mice were exposed to periodic restraint. Of course the growth rate of tumors in p53 knockout mice was faster than p53+/+ mice without restraint.[272] However in p53+/+ mice, tumor growth was significantly promoted amongst those with restraint vs non-restraint (p<.01) and the average tumor size was increased by 3.77mm^3 in mice with chronic restraint vs mice without restraint.[272]

Lastly, dysregulation of the Hippo pathway (onco-suppressor signaling that plays a role in cell growth, tissue homoeostasis and organ size) leads to abnormal activation of the transcription co-activator YAP which is known to promote tumorigenesis in several tissues.[273] A new study found that glucocorticoids are hormonal activators of YAP and activation the of glucocorticoid receptor leads to increase of YAP levels, transcriptional activity and expansion of chemo-resistant cancer stem cells *in vitro* and *in vivo*. [273] However glucocorticoids other than cortisol were used for this analysis.

Overall, in vivo and in-vitro stress response studies provide strong evidence regarding the relationship between catecholamines and glucocorticoids and progression of malignant tissue however extrapolation to humans is extremely limited.

Human studies linking the biological stress response and carcinogenesis and progression.

A meta-analysis conducted in 2008 assessed 165 longitudinal studies regarding the relationship between self-reported stress and cancer incidence, 330 studies examined survival, and 53 examined mortality.[274] The analysis chose studies with HR and RR and mostly adjustment for age, sex, smoking, alcohol consumption, body mass index, physical activity level, and socioeconomic status, and in the case of cancer populations, stage and treatment. The study reported an overall combined psychosocial stress HR of 1.06 (95% CI 1.02– 1.11, $P = 0.005$) for cancer incidence studies, however publication bias assessed by Egger's method was significant ($P < 0.10$), and the test for heterogeneity was also significant ($p<.001$).[274] Sub-analyses displayed that studies limited to a sample size ≥100,000 had a 1.21 HR (95%CI 1.09–1.34), emotional distress or poor quality of life, had a 1.13 HR (95%CI 1.05–1.22) and life-stress exposure was not significant 1.03 HR (95% CI 0.97–1.11). [274] When assessing risk for any cancer the analysis displayed a 1.20 HR (95%CI 1.09–1.32) however by breast cancer or colorectal cancer, the association was null, 0.99 HR (95%CI 0.92–1.06) and 1.00 HR (95%CI 0.89–1.11) respectively.[274] Lung cancer carried a 1.23 HR (95%CI 1.06–1.37), prostate had a 1.00 HR (95%CI 0.89–1.11), and thyroid carried a 0.66 HR (95%CI 0.55–0.81)

with no evidence for publication bias, or heterogeneity (p=.73).[274] Fully controlled covariates revealed a 1.07 HR (1.00–1.14), and no heterogeneity (p=.29).[274]

For the relationship between stress-related psychosocial factors and cancer survival, the study reported an overall combined psychosocial stress HR of 1.03 (1.02–1.04), p<. 001, however publication bias assessed by Egger's method was significant (*P* <0.10), and the test for heterogeneity was also significant (p<.001).[274] Sub-analyses displayed that studies that were fully controlled, had a 1.90 HR (95% CI 1.28–2.83), Life-stress exposure had a 1.15 HR (95%CI 1.06–1.24). [274] When assessing risk for any cancer the analysis displayed a 1.01 HR (95%CI 1.00–1.02).[274] Studies that assessed breast (1.13 HR, 95%CI 1.05–1.21), lung (1.17 HR, 95%CI 1.03–1.34), hepatobiliary (1.88 HR, 95%CI 1.07–3.30), and head and neck (1.58 HR, 95% CI 1.22–2.03) carried an increased hazard.[274] Colorectal cancer was null, 1.04 HR, 95%CI 0.84–1.30).[274]

For cancer mortality, interestingly, cancer mortality assessing any cancer type carried a 1.29 HR (95%CI 1.11–1.52), but by breast, colon, and lung, the hazards were null (small sample of studies for each).[274] In general the rest of the cancer mortality sub analyses displayed strong positive statistically significant associations with the strongest being 10+ years of follow-up 2.33 HR (p5%CI 1.63–3.33), and poor coping style 2.25 HR (95% CI 1.54–3.30) and the exception of fully-adjusted analyses carrying a null 1.15 HR (95%CI 0.95–1.40).[274] Overall effect sizes from over 600 studies suggest that stress-related psychosocial factors adversely influences cancer incidence, prognosis, and mortality, however there are substantial differences by stress type, and cancer type.[274] Also, all of these studies

utilized self-reported stress exposure which is subject to recall bias, and quantification of this variable it is hard to interpret due to its subjective nature. Furthermore there was presence of significant publication bias, which is likely to create a differential positive result bias therefore results should be interpreted with caution.[274]

The relationship between striking life events and primary breast cancer incidence in women was analyzed in another study. The analysis included seven studies of n= 99,807 women. The pooled OR for striking life events and breast cancer was 1.51 (95% CI 1.15 - 1.97, P = 0.003), severe striking life events and breast cancer the OR was 2.07 (95% CI 1.06 - 4.03), indicating that women with severe striking life events were at 2-fold greater risk of developing breast cancer.[275]

Very recently, researchers pooled data from 16 different cohorts, and assessed psychological distress and site-specific cancer mortality. There were a total of N=163, 363 men and women aged 16 or older at study induction, who were initially free of a cancer diagnosis, that provided self-reported psychological distress scores (based on the general health questionnaire, GHQ-12) and consented to health record linkage.[276] After 9.5 years and adjustment for age, sex, education, socioeconomic status, body mass index (BMI), and smoking and alcohol intake, relative to people in the least distressed group, death rates in the most distressed group were consistently raised for cancer of all sites combined (HR 1.32, 95% CI 1.18 to 1.48) and cancers not related to smoking (HR, 1.45, 95% CI 1.23 to 1.71), as well as carcinoma of the colorectal (HR 1.84, 95% CI 1.21 to 2.78), prostate (HR 2.42, 95% CI 1.29 to 4.54), pancreas (HR 2.76, 95% CI 1.47 to 5.19), esophagus

(HR 2.59, 95% CI 1.34 to 5.00), and for leukemia (3.86, 1.42 to 10.5).[276] Other studies have shown similar results.[277,278]

Overall, although animal models have shown strong evidence for direct pathways by which different components of the stress response may contribute to cancer progression, there are few well-done epidemiological studies that show increases in risk for cancer deaths or initiation. Many studies have null results, and some have modest increases.[85] Stress increases the secretion of cortisol, which may be directly and indirectly associated with an increase in weight gain, however many studies adjusted for BMI, no studies stratified this analysis by low and high weight, along with alcoholic drinkers and non-drinkers, or smokers or non-smokers.

Cancer progression and general excess death in different populations continues to increase. Potential reasons for the increase include an increasing number of different combinations of exposures, vulnerabilities, and underlying biology. However understanding and conceptualizing mechanisms of disease should be a dynamic process and there is still a need to better understand this throughout the life course; this is especially pertinent in the context of chronic disease and their relationship with nutritional, lifestyle and psychosocial factors, as well as genetic and epigenetic determinants of disease. Furthermore studies regarding whether such factors act cumulatively, interactively or individually, in predisposition and progression of cancer outcomes or overall excess disease are still developing. [85]

Psychosocial stressors, allostatic load and health

Multi-systemic biological risk is a clinically meaningful and practical surrogate of health risk used to express shared physiologic variance in multiple biological systems, based on the hypothesis that recurrent exposure to external stressors leads to progressive dysregulation.[111] As previously reviewed, the stress response has been linked to poorer cancer-related outcomes, in particular, abnormal cortisol rhythms or levels and elevated catecholamine's, (markers for prolonged stress response), have been linked to an increase risk of progression, recurrence and mortality in some human and murine models. However, studies that use biomarkers to interrogate the biology of cancer in different populations are sparse, albeit a practical way to assess key risk factors in different populations and the influence of physiologic stress and health outcomes. The allostatic load theory and similar proxies like multi-systemic biological risk capture the complex biological cascade that occurs in cardiovascular, metabolic, and immune domains in response to chronic environmental and psychosocial stress.[110,111] Previous research has demonstrated positive associations between higher indices of multi-systemic biological risk and declining cognition, physical function,[63,279] sleep apnea and insomnia,[280] telomere length,[281] and all-cause mortality.[119,279,282]

Other studies have explored other endpoints in relation to allostatic load. One assessed N=4,515 blacks and whites aged 35 to 64 years from the III National Health and Nutrition Examination Survey (1988–1994), and linked mortality data.[283] The researchers estimated sex-specific black-white disparities in cardiovascular/diabetes-related mortality and non-injury mortality, sequentially

adjusting for age, clinical conditions, socioeconomic status (SES), health behaviors, and then allostatic load.[283] For cardiovascular/diabetes-related mortality among women, the HR disparity amongst blacks versus whites after adjustment for other risk factors was 1.63 HR (95% CI, 0.96–2.75) and it decreased after adjustment for allostatic load to 1.15 HR; (95% CI, 0.70–1.88).[283] For non-injury mortality among women, the magnitude of the disparity after adjustment for other risk factors (HR, 1.43; 95% CI, 1.00–2.04) also decreased after adjustment for allostatic load (HR, 1.26; 95% CI, 0.90–1.78).[283] For men, disparities were attenuated but persisted after adjustment for allostatic load.[283]

Another study also used NHANES to explore all-cause and cause-specific mortality disparities by race, age (20–49 vs. 50+), and sex and poverty status.[284] For the young men above-poverty stratum, the socio-demographic-adjusted HR was 2.59, $p < 0.001$ was partially attenuated after adjustment for SES and other factors (full model HR = 2.08, $p = 0.003$).[284] Income, education, diet quality, allostatic load and self-rated health, were the main covariates that explained the non-Latino black (NLB) *vs*. non-Latino white (NLW) mortality difference and the Latino paradox was observed consistently among women above poverty.[284] NLBs had higher CVD-related mortality risk compared to NLW, which was explained by SES and lifestyle factors; however those factors did not explain excess risk among NLB for cancer-related death (fully adjusted HR = 1.41, 95 % CI: 1.02–2.75, $p = 0.044$).[284] Interestingly, those same factors explained the lower risk of cancer-related death among Mexican Americans (MA) compared to NLW, and CVD-related mortality risk became lower among MA compared to NLW upon

multivariate adjustment.[284]

Relationships between discrimination and health

As already reviewed, the potential physiological stress response may influence a wide array of biological systems; furthermore, whether or not people experiences a physical response will depend on, perception, past social and learning experiences, current resources and support. The pathways by which different people are subsequently influenced are extremely complex. Structural, institutional and individually perceived, experienced and documented forms of discrimination based on race, gender, or social class are well known aspects of our historical and current society. Attempting to be completely inclusive in citing the ways in which discrimination influences an individual and subsequently subgroups is simply impossible due to human complexity and conversely our crude methodologies. Racism, sexism, and social class issues are not the same for every sub group within these domains, and even more eminent, they are not the same at the intersections of these domains. No epidemiological study has been able to capture every niche and subsequent consequence or inequity of discrimination, although some researchers have greatly expanded the field. This dissertation attempts to address discrimination as related to the specific aims that addresses this topic.

There are very few studies that have assessed the health of those who experience gender-based discrimination even though the minority stress model suggests that sexual and gender minorities experience chronic stress as a result of their stigmatization.[285–288] A previous study assessed simultaneous race and gender

based discrimination, behavioral data to examine the independent and effect modification effects of both forms of discrimination in a sample of male and female Marine recruits (N = 1,516).[289] Both race and gender based discrimination had a strong and consistent negative impact on mental health symptoms (e.g., depression, anxiety), independent of gender and race. [289] Although women reporting high levels of gender based discrimination reported the highest levels of anxiety versus all other groups, men's anxiety levels changed more drastically as a function of level of gender based discrimination when compared to women.[289] Most interesting to note is that the interaction between race, gender, and levels of discrimination was only found with the objective physical fitness test scores but not with self-report measures.[289]

Another study explored the association between sexism and self-reported health, among women in Spain, a country with a strong patriarchal tradition.[290] They found that perceived sexism showed positive and consistent associations with four poor health outcomes (poor self-perceived health, poor mental health, injuries in the last 12 months, and smoking).[290] The strength of these associations increased with increasing scores for perceived sexism, and social class modified the patterns.[290]

A recent JAMA study executed an exploratory cross-sectional analysis using data from the Behavioral Risk Factors Surveillance System. The researchers examined 3 self-reported health outcomes including overall health status, limitation in any way in any activities because of physical, mental, or emotional problems, and serious difficulty concentrating, remembering, or making decisions because of

a physical, mental, or emotional condition.[291] Compared with cisgender adults, gender minority adults were younger, lower income, unemployed, uninsured; overweight had higher prevalence of unmet medical care due to cost, and reported depression.[291] In addition, gender minority adults were more likely less likely to be non-Hispanic white, married or living with a partner, have a minor child in the household, or be English speaking.[291] Adjusted for socioeconomic status, healthcare access, health conditions, and health behaviors the analysis estimated that gender minority adults were more likely to report poor or fair health (OR 1.30, 95% CI 1.09-1.56); difficulty concentrating, remembering, or making decisions (OR 1.56, 95% CI 1.27-1.93); and being limited in any way (OR 1.22, 95% CI 1.04-1.44).[291] Previous studies discuss the mental health impact of gender discrimination, where discrimination predicts psychological distress, anxiety, reproductive disorders, depression and maladaptive coping behaviors such as hard drug use.[292–297]

Health, and life expectancy in the US by socioeconomic correlates (an aggregate concept that includes both resource-based and "prestige"-based measures i.e., income and education) have only widened over the last 40 years despite the universal and strong evidence regarding socioeconomic status and health[16,298,299]

SES has been shown to predict disparities in health amongst both white and non-white populations; this also often accounts for some of the racial differences in health.[46] Previous studies have found significant inverse associations for the relationship between socioeconomic position across the lifespan and increased inflammatory markers,[47] chronic disease [300],allostatic load[301–303] and decreased life expectancy[10,299,304,305]

A large recent study in JAMA estimated the income level, time, and geographic variability in the relationship between income and life expectancy using income data in US from 1.4 billion tax records between 1999 and 2014. Using race- and ethnicity-adjusted life expectancy at 40 years of age, they first found that, higher income was associated with greater longevity through the entire income distribution, and the gap in life expectancy between the richest 1% and poorest 1% of individuals was 14.6 years (95% CI, 14.4 -14.8 years) for men and 10.1 years (95% CI, 9.9-10.3 years) for women. Next, they reported that inequality in life expectancy increased over time; specifically, from 2001 to 2014 life expectancy increased by 2.34 years for men and 2.91 years for women in the top 5% of the income distribution, and by 0.32 years for men and 0.04 years for women in the bottom 5% ($P < .001$ for the differences for both sexes). Life expectancy for low-income individuals was positively correlated with the local area fraction of immigrants ($r = 0.72$, $P < .001$), fraction of college graduates ($r = 0.42$, $P < .001$), and government expenditures ($r = 0.57$, $P < .001$).[10]

Another cross-sectional analysis was conducted using data on adults 40 to 79 years without cardiovascular disease at baseline within the National Health and Nutrition Examination Survey. The authors assess trends in 10-year groups of prevalence of cardiovascular disease and cardiovascular risk factors among US adults in different socioeconomic strata. Among adults with incomes at or below the federal poverty level, there was evidence of a stable trend in the percentage of adults with predicted absolute cardiovascular risk of 20% or more(14.9% [95% CI, 12.9%-16.8%] in 1999-2004; 16.5% [95% CI, 13.7%-19.2%] in 2011-2014; $P = .41$;

mean systolic blood pressure, 127.6 [95% CI, 126.1-129.0] mm Hg in 1999-2004; 126.8 [95% CI, 125.2-128.5] mm Hg in 2011-2014; P = .44; and smoking, 36.5% [95% CI, 32.1%-41.0%] in 1999-2004; 36.0% [95% CI, 31.1%-40.8%] in 2011-2014; P = .87) across survey years. However amongst adults in the high-income stratum, these variables decreased across survey years with ≥20% cardiovascular risk (12.0% [95% CI, 10.7%-13.3%] in 1999-2004; 9.5% [95% CI, 8.2%-10.7%] in 2011-2014; P = .003; systolic blood pressure, 126.0 [95% CI, 125.0-126.9] mm Hg in 1999-2004; 122.3 [95% CI, 121.3-123.3] mm Hg in 2011-2014; P < .001; and smoking, 14.1% [95% CI, 12.0%-16.2%] in 1999-2004; 8.8% [95% CI, 6.6%-11.0%] in 2011-2014; P = .001). There were no trend differences seen for diabetes.

A German study examined the influence of perceived income injustice on stress-associated diseases (diabetes, asthma, cardiopathy, stroke, hypertension and depression), taking into consideration duration. Data from N= 5,657 workers using survey responses from 2005-2013 and physician diagnosed new cases of disease starting from 2009-2013.[306] Fully adjusted models, stratified by gender and length of employment, estimated that income injustice over 5 years, predicted increased stress-related diseases for women (OR 1.64; 95% CI 1.17-2.30), and women working full-time (OR 2.43; 95% CI 1.54-3.84).[306] Men working full-time perceiving their income as unjust also showed an increased risk for stress diseases (OR 1.43; CI 1.03-1.98). [306]

The social science and medical literature, has theorized racism as a psychological stressor.[55] Up to date, there is consistent evidence for mental health as the strongest and most prevalent outcome of different types of

discrimination.[25,307] A meta-analysis was published in 2015 regarding the relationship between reported racism and mental and physical health outcomes. They used data from 293 studies that were mostly (89.8%) cross-sectional in nature, published between 1983 and 2013, and mostly (81.4%) in the U.S.[308] They used random effects models and mean weighted effect sizes and found that racism was associated with poorer mental health (negative mental health r = -.23, 95% CI [-.24,-.21], k = 227 including depression, anxiety, distress, psychological stress, negative affect, and post-traumatic stress; a decrease in positive mental health: r = -.13, 95% CI [-.16,-.10], k = 113 including self-esteem, life satisfaction, control and mastery, and wellbeing).[308] Racism was also associated with poorer general health (r = -.13 (95% CI [-.18,-.09], k = 30), and poorer physical health (r = -.09, 95% CI [-.12,-.06], k = 50). Age, sex, birthplace and education level did not moderate the effects of racism on health, however ethnicity significantly moderated the effect of racism on negative mental health and physical health where they found that the association between racism and negative mental health was significantly stronger for Asian American and Latino(a) American participants versus African American participants, and the association between racism and physical health was significantly stronger for Latino(a) American participants compared with African American participants.[308] Some of these findings regarding mental health were replicated and positive associations were estimated for some Asian American groups[309] and ethnic minorities in the UK.[310]

In terms of stress biological pathways, discrimination is accepted as a chronic stressor and experiences can be chronic or daily such as not being treated

with general respect at work or at school, receiving poor service, or being watched and followed at stores.[46],[26] A severe life experience could include one of violence, and harassment; the literature so far explains that it is more likely that accumulation of everyday or chronic exposure would contribute to biomarkers of disease, related to allostatic load, cortisol dysregulation, cardiovascular health and overall mortality. Chronic stressors, unlike everyday demands that we acutely overcome, can usually pervade a person's life; this forces a person to restructure their identity or social roles. Another feature of chronic stressors is their stability—the person either does not know whether or when the challenge will end or can be certain that it will never end. Examples of chronic stressors include suffering a traumatic injury that leads to physical disability, providing care for a spouse with severe dementia, or being a refugee forced out of one's native country by war

A recent and novel study, explored the ways in which externally sensitive biological systems coordinate in response to acute stress. Researchers used a social-evaluative stress task to investigate coordination among the autonomic nervous system, hypothalamic-pituitary-adrenal axis, and immune/ inflammatory system in a community sample of 85 healthy African American men and women in Detroit, MI.[311] Each participant provided 6 saliva samples in total (2 of each at baseline, event, and recovery phases of the stressor task, were assayed for cortisol, dehydroepiandrosterone-sulfate, salivary alpha-amylase, and salivary C-reactive protein.[311] Individual differences in perceived discrimination and racial identity were also measured and they utilized factor analysis to show that these biomarkers were initially dissociated before stressor exposure and then became aligned during

event and recovery phases into a biological stress responses (factor loadings ≥ .58).[311] Interestingly, the study captured responses related to interactions of perceived discrimination and racial identity; amongst those who strongly identified with their racial ethnic culture, highly perceived discrimination was associated with low hypothalamic-pituitary-adrenal axis activity at baseline (B's = .68–.72, $p < .001$), low stress mobilization during the task (B's = .46–.62, $p < .049$), and a robust inflammatory response (salivary C-reactive protein) during recovery (B's = .72–.94, $p < .002$).[311] Further differences on stress responses were reported by racial identity.

When assessing oxidative stress, and racial discrimination, fully adjusted models estimated positive significant associations with RBC oxidative stress (Beta = 0.55, $P < 0.05$) after adjustment for age, smoking, C-reactive protein level, and obesity.[312] When stratified by race, this association was only significant for black Americans (Beta = 0.36, $P < 0.05$) and not whites.[312]

Furthermore, a longitudinal study assessed self-reported racial discrimination amongst 160 African Americans aged 17-19 years predicted heightened cytokine levels at the age of 22 and if this association differed by positive racial identities.[313] After controlling for socioeconomic risk, life stress, depressive symptoms, and body mass index, racial discrimination (beta= .307; $p < .01$), racial identity (beta=.179; $p < .05$), and their interaction (beta= .180; $p < .05$) predicted cytokine levels (low vs high).[313] Those exposed to high levels of racial discrimination demonstrated elevated cytokine levels 3 years later and this association was not significant for young adults with positive racial identities.[313]

Another study assessed discrimination and allostatic load in 331 adolescents between the ages of 16 -18 years, along with exploration of covariates that may attenuate the association.[314] At age 18 emotional support was assessed, and allostatic load was assessed at age 20. Latent Growth Mixture Modeling identified two perceived discrimination classes: high and stable and low and increasing. Adolescents in the high and stable discrimination group displayed heightened AL even after adjustment for gender, depression, stress, SES and unhealthy behaviors at age 20 (b = 1.088, 95% CI (0.18, 2.00), $p < .05$) and the racial discrimination to allostatic load link was not significant for young adults who received high emotional support. [314]

A recent study examined the associations of major experiences of discrimination (unfair treatment in 6 situations) and everyday discrimination (frequency of day-to-day experiences of unfair treatment) with incident diabetes among N= 5,310 participants from the Multi-Ethnic Study of Atherosclerosis over 9.4 years.[315] Models were adjusted for demographic factors, depressive symptoms, stress, smoking, alcohol, physical activity, diet, waist circumference, and body mass index.[315] They found that major experiences of discrimination were associated with greater risk of incident diabetes when modeled continuously (for each additional experience of discrimination, hazard ratio = 1.09, 95% confidence interval: 1.01, 1.17) or categorically (for ≥2 experiences vs. 0, hazard ratio = 1.34, 95% confidence interval: 1.08, 1.66).[315] Similar patterns were observed when evaluating discrimination attributed to race/ethnicity but only amongst some associations for Chinese, Latino and non-Latino whites. [315]Everyday discrimination was not

associated with incident diabetes.[315]

The Black Women's Health Study assessed perceived racism in N=59,000 African-American women, over 16 years. Cox models estimated HRs for categories of everyday racism and lifetime racism (reporting ever treated unfairly due to race with respect to police, housing or work) and incident type 2 diabetes adjusting for age, cycle, marital status, socioeconomic status, education, family history of diabetes, physical activity, alcohol use and smoking status, with and without inclusion of terms for dietary patterns and adult BMI to assess moderation.[316] The results showed that compared with women in the lowest quartile of exposure, women in the highest quartile of exposure to everyday racism had a 31% increased risk of diabetes 1.31 HR, (95% CI 1.20-1.42) and women with the highest exposure to lifetime racism had a 16% increased risk 1.16 HR, 95% CI 1.05-1.27).[316] Mediation analysis estimated that diet did not attenuate this association; however BMI accounted for half of the association between either the everyday or lifetime racism measure and incident diabetes.[316] Similar results have been found in different ethnic populations for metabolic syndrome (South-Asian Surinamese, African Surinamese, and Moroccan participants (1.13 OR, 95% CI 0.99–1.30], 1.15 [1.00–1.32], and 1.19 [1.03–1.38], respectively after adjusting for potential confounders and mediators) and not in others (Ghanaian and Turkish participants).[317]

Persons reporting lifetime discrimination in ≥2 domains (versus none) had increased CVD risk, after adjustment for race/ethnicity and socio-demographic factors, behaviors, and traditional CVD risk factors (hazard ratio (HR) = 1.36, 95%

confidence interval (CI): 1.09, 1.70) and after control for chronic stress and depressive symptoms (HR = 1.28, 95% CI: 1.01, 1.60).[318] Reported discrimination in 1 domain was unrelated to CVD (HR = 1.05, 95% CI: 0.86, 1.30) and there were no differences by race/ethnicity, age, or sex.[318] In contrast, everyday discrimination interacted with sex (P = 0.03), and stratified models showed increased risk only among men (for each 1–standard deviation increase in score, adjusted HR = 1.14, 95% CI: 1.03, 1.27); controlling for chronic stress and depressive symptoms slightly reduced this association (HR = 1.11, 95% CI: 0.99, 1.25).[318] This study suggests that perceived discrimination is adversely related to CVD risk in middle-aged and older adults.

Although many of these studies show promising findings, discrimination predicting health outcomes have been mixed;[53,319–321] this is expected given the stress research explains that stress may lead to resistance,[322] or overcoming of challenge based on perception and resources, and subsequently improved health outcomes.

As separate isolated topics, the literature regarding perceived stress, physiologic measures of stress, discrimination, and subsequent disparities of health outcomes has demonstrated that lifetime stresses related to both racial/ethnic identity and poverty could potentially be associated with tumor biology and an attenuation of life span if time permits. The relationship of allostatic load or dysregulation of multiple organ systems as well as cancer outcomes as a consequence of cumulative lifetime stresses for minority, or populations living in poverty should be further explored.

Specific Aims

Discrimination is a public health issue.[41,323] Many groups in the United States have historically endured discrimination through pathways that deny basic human rights[324]. Race or skin color, sex, gender roles, disabilities, immigration status, and economic social class are the most common avenues for discrimination and lead to inequity in: employment, income and wealth, housing, education, criminal justice and health outcomes[324]. According to the most recent and recognized stress survey conducted in the US, 70% of people, report having experienced discrimination, with 61% reporting experiencing day-to-day discrimination, such as being treated with less courtesy or respect, and being threatened or harassed.[41] A body of evidence documents that long term stressful conditions take a toll on one's health, providing the basis for a model that ties external stressors with bio-physiological responses, which in turn influence incidence and prognosis of disease.[27] The concept of allostasis, maintaining stability through change, describes how we change in response to the environment or acute stress, producing hormones that aid in preserving homeostasis and promoting survival. However continuously responding to acute stress takes a toll on the body. Nonetheless, despite this theoretical model and documented evidence linking stress and disease outcomes, there are a few gaps in the literature. For one, although research demonstrates discrimination has important biological consequences, most studies are cross-sectional in nature, and research regarding different types of discrimination has not been addressed. Also, while a few studies have linked a multi-systemic biological risk index with diabetes and cardiovascular disease, no

research has examined an objective biological measure of stress with cancer outcomes. Next, previous research shows a positive association between MSBR and mortality, however there are no studies that have accounted for major sources of chronic stress, which could potentially confound the association.

The goal of this research is to examine if discrimination is associated with the physiological stress response utilizing the concept of allostatic load. Furthermore, this project will assess if allostatic load is associated with cancer and all- cause mortality. The research informing these hypotheses suggests that through neuroendocrine signaling, the stress of psychosocial factors may impact physiological health; experimental research suggests that they may further influence tumor biology through the same pathway.[104,274,325] Therefore it is hypothesized that an increase in discrimination predicts an increase in biological risk (allostatic load). Moreover, we expect that dysregulated clinical markers representing multi-systemic biologic risk (allostatic load) can increase the risk for cancer onset and mortality overtime.

Therefore, the following aims will be tested:

Aim 1 is to test if an index of multi-systemic biological risk (AL) is associated with cancer mortality. The hypothesis is that a higher allostatic load score will positively associate with increased risk of cancer mortality.

Aim 2 is to test if an index of multi-systemic biological risk (AL) is associated with all-cause mortality. The hypothesis is that a higher allostatic load score will positively associate with increased risk of all-cause mortality.

Aim 3 is to test if exposure to overall discrimination, as measured by a comprehensive discrimination index is associated with multi-systemic biological risk (AL). The hypothesis is that a high/increase in the comprehensive discrimination score cross-sectionally and over time (i.e. greater discriminatory experiences) predicts a high/increased allostatic load index score over 18 years.

This dissertation will make important contributions to the literature as it will assess if changes in discrimination is associated with higher levels of allostatic load over time in a potentially critical period for chronic disease development during young to early-middle age adulthood. Furthermore, it will be the first study to examine if allostatic load is associated with cancer outcomes. This research will have a high impact in the field since it utilizes populations that are approximately half black and white, thus informing the topic of black/white health disparities.

Study 1: Multi-Systemic Biological Risk and Cancer Mortality in a US Population

Introduction

Multi-systemic biological risk (MSBR) is a proxy for allostatic load, a metric of health risk that captures the complex biological cascade that occurs in cardiovascular, metabolic, and immune domains in response to chronic environmental and psychosocial stress.[111,326–328] The validity of this construct has been established by demonstrating common variance and statistical coherence between, prominent primary mediators of the stress response (e.g. stress related hormones), and secondary mediators reflecting the resulting biological alterations that accumulate over time.[111,112,126,329–331] Importantly, summary allostatic load

indices have demonstrated stronger prediction, or magnitude of association, with outcomes than with individual components that inform the calculation of the index.[330,332]

Previous research has demonstrated, inverse associations between allostatic load (representing greater MSBR) and cognitive function, as well as physical function. Also studies have shown positive associations between higher levels of allostatic load indices and cardiovascular disease, and mortality risk.[63,106,119] However, we are not aware of any studies that have examined an index of allostatic load with cancer outcomes. This is underscored by cancer being the second leading cause of death in the U.S. and globally, with shifting underlying contributors to this burden.[9,150,333] Thus, a prospective analysis examining the association of an index of MSBR with cancer mortality would address a major gap in the literature, giving credence to in vivo and in vitro studies of stress and cancer outcomes. Furthermore, it may also have clinical utility for cancer prediction, as the index relies upon commonly measured biomarkers to address this gap. In this study, we examined the association between an index of MSBR and cancer mortality utilizing the NHANES III study, a representative sample of the U.S. from 1988 to 1994. We hypothesized that a higher score on the index was positively associated with cancer mortality.

Methods

Study Population

The NHANES III is a complex, multistage clustered probability sample conducted by the National Center for Health Statistics (NCHS); it represents the US non-institutionalized population from 1988 to 1994. Detailed descriptions of all

NHANES III data collection, and analytical guidelines are available elsewhere.[334] In brief, demographic characteristics, medical, family history, dietary and lifestyle factors, including smoking history, alcohol consumption, and physical activity, was collected at study entry from participants through a structured household interview. Physical examinations (including anthropometric measurements), and blood samples were collected within mobile examination centers.[334]

Analytical population

The initial sample size of NHANES III included 33,994 participants. Participants were excluded for reporting an age of 20 years or less (n=15,169), pregnancy (n=231), a history of cancer (n=777) at baseline, and only completed a modified home examination (n=396). Furthermore, participants who died from cancer at baseline (n=5), were missing follow-up time (n=1722), fasting time (n=10), or at least one of the biomarkers included in the AL index (n=2,010) were also excluded, leaving a final study sample of (n=13,674) participants. All participants within NHANES III provided written informed consent, and the NHANES study was approved by National Center for Health Statistics (NCHS) Institutional Review Board.

Exposure assessment

The MSBR index is based on an aggregate score of seven biomarkers used to represent the overall extent of physiological dysregulation across multiple systems, or allostatic load. Our operationalization of allostatic load was similar to other studies that have used NHANES to investigate multi-systemic biological risk.[120,335,336] The domains and biomarkers for the index include: cardiovascular

(pulse rate, blood pressure), metabolic (Homeostasis model assessment ($HOMA_{IR}$), triglycerides, and waist circumference), and immune (white blood cell count, C-reactive protein) domains.

Participants were asked to fast at least 6 hours for venous blood sample collections depending on time of lab appointment. Therefore the amount of hours fasted was ascertained from each participant prior to lab draws and included as a covariate in all models.[337] Detailed specimen collection, processing instructions, and laboratory procedures are discussed in the Manual for Medical Technicians (U.S. DHHS, 1996) and the NHANES III Laboratory Procedures reference manual.[337] Homeostasis model assessment ($HOMA_{IR}$) was used to estimate insulin resistance according to the formula: fasting serum insulin level (μU/mL) × fasting plasma glucose level (mmol/L)/22.5, where the higher the $HOMA_{IR}$ value the more insulin resistant the individual[338]

Covariates

Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, and Mexican American. Participants who did not identify as belonging to 1 of these categories ("other") were not analyzed separately but were included in the overall estimates. Other covariates included age, sex, current tobacco use (cotinine level >10ng/mL[339]or self-report current smoker), years of education (less than 12 years/ greater than 12 years), health insurance (yes/no), and average alcoholic drinks per week. Body mass index (BMI) was calculated by the formula weight (kg)/height $(m)^2$, and further categorized as underweight for a BMI under 18.5, normal or healthy weight as 18.5 – 24.9, overweight as 25.0 – 29.9, and obese as 30.0 and

above.[340] Geographic urbanization classification was based on USDA Rural/Urban continuum codes, where urban includes central or fringe counties in metro areas that have a population of 1 million or more.[341] Within NHANES III, duration of physical activity was not ascertained however participants were asked how many times in the previous month did they engage in several types of activities. Each participants physical activity was assigned an intensity value by NHANES (metabolic equivalent tasks [METs]) which represents the ratio of the energy expenditure of the activity to the basal metabolic rate.[342] We therefore measured physical activity by: (Number of times engaged in specific physical activity in previous month x MET assignment)/ 4 weeks). Then participants were classified as physically active for greater than 15 METS per week, moderately active for 9-15 METS per week, and little to no physical activity for less than 9 METS per week.[342,343] Diet as a confounder was estimated by calculating the Healthy Eating Index from the NHANES III dietary intake data. This provides a measure of overall quality of an individual's diet; by alignment with Dietary Guidelines recommendations.[344] A score represents the sum total of ten diet components (grain, fruit, vegetables, dairy and meat food groups; intake of dietary fats, saturated fats, cholesterol, and sodium; and a variety score) and individuals who consumed the recommended number of servings received a maximum score of 10; a zero was assigned to any food group where no items from that category were consumed (range: 0-100).[344] Medication for type 2 diabetes, high blood pressure, and high cholesterol were also assessed.

Case ascertainment

Mortality status for the NHANES III survey participants was ascertained primarily through probabilistic record matching with the National Death Index (NDI). The NDI is a NCHS database of all U.S. deaths since in 1979.[345] The updated 2011 linked mortality files are superior to previous linkages of NCHS surveys linked to the NDI due to the use of additional sources (i.e. Social Security) of demographic mortality information to determine vital status.[345] Person-months of passive follow-up were calculated from the examination date through the date of cancer death or end of study period on 31 December 2011. Underlying causes of death were identified through the International Classification of Diseases, Ninth Revision and Tenth Revision (ICD-9 codes until 1998 and ICD-10 codes for deaths after 1998). Final cause of deaths that happened before 1999 were re-coded into comparable ICD-10-based underlying cause of death groups. The primary outcome of this study was all cancer-specific death (ICD-10: C00-C97).[345] Only aggregate information on leading causes of death is available in the public 2011 mortality follow-up, therefore cancer specific analyses are not possible. [345]

Statistical Analysis

NHANES III utilizes a complex survey design. To take this into account, we utilized the appropriate variables for the design effects of stratification and clustering. Furthermore, estimates were weighted to adjust for the differential probabilities of sampling and non-response, to represent the total civilian, non-institutionalized US population. Stata utilizes Taylor Series Linearization for calculating standard errors and 95%CI for means and percentages. Study characteristics were described by the MSBR index, using means and standard errors

for continuous variables and percentages for categorical variables. Cox proportional hazard regressions were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations between the multi-systemic biological risk index and overall cancer mortality. The proportional hazards assumption was assessed by creating interaction terms between biological risk index, all covariates and follow-up time and no evidence of a violation was detected.

Participants were assigned a score for each biomarker informed by either clinical cut points or based upon evidence in the literature indicating a threshold of risk for disease (Table 1). Each blood marker within each domain was assigned a value of either a 0 (no risk indicated or decreased risk), 1(moderate), or 2 (high). The value for each marker was then aggregated to a final index for each participant. For this index, a higher score represents a higher presence of dysregulation (range 0-14).

Table1. Score assignment for each biological measurement

Measurement	Score = 0	Score=1	Score = 2	References
Pulse Rate (Beats/Min)	<=60	60-99	>= 100	[346,347]
Blood Pressure (mm/Hg)	<120/80	120-139/80-89	>=140/90mm/ Hg or hypertension medication	[347–349]
Homa-IR	<2.6	>=2.6-4.65	>4.65 or diabetes diagnosis	[350–352]
Triglycerides	<150 mg/dL	150 to 199 mg/dL	> 200 mg/dL	[353]
Waist Circumference	< 94 cm (M), or < 80 cm (W),	94 - 102 cm (M) or 80-88 cm (W)	>102 cm (M) or >88 cm (W)	[354]
White Blood Cell Count	1500-4500 cells/mcL	4500-11,000 cell/mcL	>11,001 cells/mcL or <1500	[355–357]

C-Reactive Protein	<=.21mg/dL	>.21-1mg/dL	>1 mg/dL	[358]

We built four models to provide statistical inference. Model 1 included demographic variables (age, sex, race and ethnicity. Model 2 included variables from model 1 plus socio-economic variables (education, health insurance, geographic urbanization). Model 3 includes variables from model 2 plus lifestyle variables (physical activity, current tobacco use, the healthy eating index, alcoholic drinks per week and medication use). Finally, model 4 adjusted for all variables previously mentioned and BMI categories. All models adjusted for fasting status. We tested for effect measure modification by age, sex, race, and BMI. Stratified results were presented if there was evidence of effect modification. We assessed tests for trend by including the index modeled as a continuous variable in the Cox models.

About 87% of the observations had complete data for all the variables relevant to this study. We utilized multiple imputation using chained equations, which uses a sequence of univariate imputation methods with fully conditional specification (FCS) of prediction equations to generate 20 imputed datasets for the estimation of 7 covariates (healthy eating index (missing=3%), education (missing=.5%), health insurance (missing=5%), alcoholic drinks per week (missing=20%), physical activity (missing=21%), and BMI (missing=.05%)) using all other relevant complete variables within the analysis.[359–361] We conducted a sensitivity analysis utilizing complete cases only and the results did not differ in any material way from the imputed analysis. Therefore, the entire analysis was carried out with imputed estimates.

We utilized both statistical software, SAS 9.4 and STATA 10, for survey specific commands that allow for inclusion of the appropriate weight, strata, and primary sampling unit variables as recommended in the NHANES III Analytical Guidelines.

Results

The total person-years of follow-up among the 13,674 study participants were 232,826.6 (mean follow-up duration of 17.9 years) and 6.2% (n=852) of the study population died due to malignant neoplasms during this time period. The mean age at baseline was 44.4 (SE .49) years. Table 2. displays participant characteristics across quartiles of the MSBR index. Compared to quartile 1, participants from quartile 2-4 were older, slightly more female, less educated, less likely to have health insurance, less physically active, and had higher average BMIs.

Table 2. Baseline Characteristics of Participants According to Quartiles of Baseline Multi-Systemic Biological Risk (n = 13,674), NHANES III, 1994-1998

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Score Range	(0-4)	(5-7)	(7-8)	(9-14)
	(n=4,753)	(n=3,842)	(n=2,920)	(n=2,159)
Median Age (IQR 25-75)	35 (27-47)	45 (32-65)	53 (37-68)	58 (43-69)
	Mean (SE) or %	Mean (SE) or %	Mean (SE) or %	Mean (SE) or %
Sex (% Female)	46.6	51.5	53.5	59.5
% Non-Latino White	78.0	75.5	74.4	75.5
% Non-Latino Black	9.8	10.6	10.6	11.4
% Mexican American	4.3	5.1	6.2	6.2
% Other	7.8	8.7	8.6	6.9
% High school or	48.0	60.0	67.7	74.6

less				
% Without health insurance	19.1	22.2	25.2	27.0
% Within urban area	51.8	50.0	47.2	40.7
% Physically active	70.6	65.3	55.4	46.7
% Currently smoking	31.9	35.3	32.4	28.6
Average diet score (HEI)	63.7 (.36)	63.3 (.35)	63.5 (.54)	64.6 (.55)
Average alcoholic drinks/week	4.4 (.19)	4.0 (.27)	3.1 (.30)	2.7 (.38)
Average BMI	23.4 (.07)	26.6 (.11)	29.8 (.11)	32.6 (.24)
% Using >=1 medication	3.2	12.7	24	50.8

Table 3 presents HRs for cancer mortality by quartiles of the MSBR index. There was a graded, positive association between higher index scores and risk for cancer mortality after adjustment for all covariates [Model 4: HRq1=1.26, 95% CI: (0.93-1.70), HRq2=1.56, 95% CI: (1.13-2.17), HRq3=1.64, 95% CI: (1.06-2.52), p.Trend=.013]. To inform the interpretation of the main index results, we also assessed the association between the individual domains (inflammatory, metabolic, and cardiovascular) and risk for cancer mortality, shown in Table 4. In fully adjusted models we observed a positive association between the immune domain [HR per SD increase in score=1.21, 95% CI: (1.07-1.37)] and the cardiovascular domain [HR per SD increase in score=1.19, 95% CI: (1.00-1.41)]. However, there was no association found between the metabolic domain [HR per SD increase in score=1.00, 95% CI: (0.94-1.07)] and cancer mortality.

Table 3. HR and 95% CI of Cancer Mortality Risk According to Quartiles of Multi-Systemic Biological Risk (n = 13,674), NHANES III, 1994-1998

MSBR Index Groups	Cancer deaths (n=852)/ Total Population (n=13,674)	HR (95%CI) Model 1: Demographics	HR (95%CI) Model 2: + SES	HR (95%CI): Model 3: +Lifestyle	HR (95%CI): Model 4: +BMI
Quartile 1	183/4,753	Ref	Ref	Ref	Ref
Quartile 2	250/3,842	1.25 (0.90-1.75)	1.23 (0.89-1.70)	1.17 (0.85-1.60)	1.26 (0.93-1.70)
Quartile 3	245/2,920	1.54 (1.16-2.04)	1.46 (1.11-1.93)	1.44 (1.08-1.92)	1.56 (1.13-2.17)
Quartile 4	174/2,159	1.71 (1.20-2.43)	1.59 (1.13-2.25)	1.55 (1.09-2.20)	1.64 (1.06-2.52)
P. Trend		<.0001	0.002	0.004	.013
*Covariates: fasting status, (1) age, sex, ethnicity, (2) education, health insurance coverage, urbanization, (3) HEI scores, physical inactivity, smoking status, alcoholic drinks per week, medication, and (4) BMI categories.					

Table 4. HR and 95% CI of Cancer Mortality Risk According to Domain Specific Index of Multi-Systemic Biological Risk (Per unit) (n = 13,674), NHANES III, 1994-1998

Domains of MSBR (Cancer deaths n=852)	HR (95%CI) Model 1: Demographics	HR (95%CI) Model 2: + SES	HR (95%CI): Model 3: +Lifestyle	HR (95%CI): Model 4: +BMI
Inflammation Index	1.33 (1.20-1.48)	1.32 (1.18-1.46)	1.22 (1.08-1.38)	1.21 (1.07-1.37)
Metabolic Index	1.00 (0.95-1.06)	0.99 (0.94-1.05)	1.01 (0.96-1.07)	1.00 (0.94-1.07)
Cardiovascular Index	1.23 (0.98-1.45)	1.21 (1.03-1.43)	1.19 (1.01-1.41)	1.19 (1.00-1.41)
*Covariates: fasting status, (1) age, sex, ethnicity, (2) education, health insurance coverage, urbanization, (3) HEI scores, physical inactivity, smoking status, alcoholic drinks per week, medication, and (4) BMI categories.				

Analyses used to determine if there was effect measure modification by race, sex, and age displayed no evidence of interaction between MSBR index and those covariates. However, the interaction between the MSBR index and BMI was significant (P=0.02). Therefore, we fitted the models after stratifying by overweight status (BMI > 25). Among overweight participants (BMI>25), fully

adjusted models displayed strong positive associations between a higher index score and risk for cancer mortality [HRq2=1.54, 95% CI: (0.92-2.60), HRq3=2.36, 95% CI: (1.41-3.95), HRq4=2.35, 95% CI: (1.31-4.22), p.Trend=.002] compared to quartile 1 (Table 5). However, no association was found amongst those with BMI ≤25 (Table 5).

Table 5. HR and 95% CI of Cancer Mortality Risk According to Quartiles of Multi-Systemic Biological Risk stratified by BMI (<=25 vs >25) NHANES III, 1994-1998

MSBR Index Groups		HR (95%CI) Model 1: Demographics	HR (95%CI) Mode 2: + SES	HR (95%CI): Model 3: +Lifestyle
BMI <= 25 (n=5,441)				
Quartile 1	144/ 3,381	Ref	Ref	Ref
Quartile 2	124/ 1,452	1.41 (0.94-2.11)	1.34 (0.90-2.00)	1.23 (0.83-1.83)
Quartile 3	43/ 448	1.12 (0.70-1.79)	1.06 (0.68-1.67)	1.01 (0.63-1.61)
Quartile 4	16/160	2.02 (0.85-4.78)	1.73 (0.76-3.96)	1.56 (0.65-3.79)
P. Trend		0.07	0.11	0.31
BMI > 25 (n=8,226)				
Quartile 1	39/1,371	Ref	Ref	Ref
Quartile 2	126/2,388	1.68 (0.99-2.88)	1.68 (0.98-2.87)	1.54 (0.92-2.60)
Quartile 3	202/2,469	2.63 (1.58-4.38)	2.54 (1.52-4.25)	2.36 (1.41-3.95)
Quartile 4	158/1,998	2.73 (1.53-4.91)	2.61 (1.46-4.68)	2.35 (1.31-4.22)
P. Trend		<.0001	<.0001	0.002

*Covariates: fasting status (1), age, sex, ethnicity, (2) education, health insurance coverage, urbanization, (3) HEI scores, physical inactivity, smoking status, alcoholic drinks per week, medication.

Table 6. HR and 95% CI of Cancer Mortality According to Domains of Multi-Systemic Biological Risk (Per unit) stratified by BMI (<=25 vs >25), NHANES III, 1994-1998

	HR (95%CI) Model 1: Demographics	HR (95%CI) Model 2: + SES	HR (95%CI): Model 3: +Lifestyle
BMI <= 25 (Cancer deaths n=327/Total (n=5,441)			
Inflammation Index	1.32 (1.05-1.66)	1.29 (1.02-1.61)	1.14 (0.91-1.44)
Metabolic Index	0.99 (0.86-1.15)	0.98 (0.84-1.13)	1.00 (0.86-1.17)
Cardiovascular Index	1.19 (0.94-1.51)	1.15 (0.92-1.45)	1.12 (0.88-1.42)
BMI> 25 (Cancer deaths n=525/Total n=8,226)			
Inflammation Index	1.33 (1.14-1.57)	1.33 (1.13-1.56)	1.26 (1.06-1.49)

Metabolic Index	1.04 (0.96-1.14)	1.04 (0.96-1.13)	1.04 (0.96-1.14)
Cardiovascular Index	1.26 (0.97-1.63)	1.25 (0.96-1.61)	1.22 (0.94-1.60)
*Covariates: fasting status (1), age, sex, ethnicity, (2) education, health insurance coverage, urbanization, (3) HEI scores, physical inactivity, smoking status, alcoholic drinks per week, medication			

Discussion

This study provides new evidence for the strong association between an index of MSBR, (a proxy for allostatic load), and cancer mortality in the NHANES III population. Additionally, the association was stronger in participants who were overweight or obese. The association of the overall index was mainly driven by the immune and cardiovascular domains, as they were also positively associated with cancer mortality as well.

Theoretically, allostatic load is often used to explain the biological "wear and tear"[62] taken on by the body after prolonged activation of primary markers in the autonomic nervous system (ANS) and the hypothalamic- pituitary- adrenal (HPA) axis.[63,100,362] Chronic stress (repeated or prolonged) can be deleterious for most physiological systems that are continuously exposed to stress hormones.[362,363] Many epidemiological studies have suggested an elevated risk for heart disease, [224,234,364] immune dysfunction,[195,203] and metabolic disorders.[253,257,365]

Several studies have investigated the association between allostatic load and overall mortality using NHANES III data. A study by Borrell et al, investigated the association between a multi-systemic biological risk or an allostatic score and all-cause mortality risk.[366] This study found that after adjustment for age, gender,

race/ethnicity, education, and income, mortality rates were 88% [HR=1.88, 95% CI (1.56, 2.26)] higher for participants with the highest allostatic load score.

Another recent study assessed if allostatic load predicts all-cause mortality and cause specific mortality within a nationally representative sample of the Scottish population.[282] This analysis included shorter follow up time, and a limited number of relevant covariates (sex, age and deprivation). In the fully-adjusted model, higher allostatic load was associated with an increased risk for mortality but only after 10 years [HR = 1.08, 95% CI (1.01 to 1.16); p = 0.026], and not within the 5 year follow up group.[282] Moreover, allostatic load was not associated with any of the specific causes of death over the 5 or 10 year follow up period, including cancer death, in this population.[282]

This study assessed risk for cancer death alone, however due to well known risk factors for cancer mortality as well as stress, we sequentially adjusted for factors related to socioeconomic status (degree of urbanization as there are documented differences for rates of survival based on this covariate[9,367,368], education, health insurance), lifestyle factors (current tobacco use, physical activity, current use of medications, diet variety, and number of alcoholic drinks per week). The association between the MSBR index and risk for cancer death remained above and beyond adjustment for these important confounders. However, BMI was an effect modifier, and the association was much stronger in overweight and obese participants.

Studies regarding stress and cancer outcomes have been equivocal. Although animal experiments have shown strong positive associations,[87,264,269,270,369]

human studies suffer from a variety of biases leading to inconsistent evidence.[274,276–278] Furthermore, the complex nature of the perception of stress, makes assessment of this exposure difficult in humans.[84,370]

The scientific literature in this field hypothesize that the stress response may influence the immune and the cardiovascular system.[200,202,203,224] In general they posit that stress may be permissive by way of immunomodulation or conducive by aiding in alterations of the tumor microenvironment.[87,204,264,325,369,371]

This is the first study to assess a multi-systemic biological risk index and cancer mortality in a multi-ethnic US population. This analysis may be especially useful to the research area of cancer prevention, as the index relies upon commonly measured pre-clinical biomarkers. Moreover, a noteworthy contribution of this paper was further assessment of whether an individual domain would be a stronger predictor for cancer mortality risk, versus the entire index. Elucidating which domains are relevant in the association between multi-systemic biological risk and cancer death can help hone in on the appropriate preventative measures to take earlier on in the life course regarding chronic stress. Another strength would be that this includes over 13,000 participants, linked to the national death index with 23 years of follow up, which is an appropriate time frame for follow up of cancer outcomes. The study also contains detailed standardized lab data as well as relevant and detailed standardized questionnaires for which confounders could be tightly adjusted for.

There are limitations that warrant further consideration. First, we utilized a "one -point in time measurement" of the multi-systemic biological risk index;

repeated measures of biomarker from several time periods would allow us to account for time-varying changes of the index. Next, the biological markers utilized to create an AL index in this study were restricted to availability in NHANES. Also, our analytical sample is a subset of the original cohort due to missing data. Although we imputed relevant covariates, participants were excluded if they had missing data on follow up time, fasting time, or at least one of the biomarkers included in the AL index. Furthermore, only aggregate information on leading causes of death is available in the public 2011 mortality follow-up, therefore cancer specific analyses were not possible. However, currently, it is understood that the most cancer death would occur among those diagnosed with aggressive, advanced, or metastatic disease, which is relevant to assess in contrast to indolent or localized cancers. Therefore, assessment of the relationship between exposure to high risk markers and cancer mortality maybe useful for understanding the general biology and relevant pathways of the early stages of an aggressive cancer. Also, there are well recognized limitations to the use of a 24-h dietary recall to calculate an HEI score and we therefore cannot rule out misclassification of participants with respect to HEI status. Physical activity was assessed as activity done in the last month. Although this is may be useful marker for pattern of behavior, it is not likely a true representation of a physically fit individual. Other inherent limitations of the NHANES include, recall bias, non-validated diagnoses, and the inability to stratify on racial/ethnic groups due to sample size and study design.

In the practical sense, allostatic load is operationalized as a metric of health risk used to express shared physiologic variance in multiple biological systems.[81,122] We utilized the MSBR index to represent pre-clinical exposure to secondary damaging effects on multiple systems.[126,279] Our results suggest that, by way of immune and cardiovascular risk factors, the MSBR index strongly predicts increased cancer mortality risk, specifically amongst overweight and obese individuals. The use of the MSBR index, a measure of AL, may potentially be relevant for understanding new directions for relevant pathways regarding disease risk. In particular the metric may be useful for guiding researchers towards relevant pathways by which factors may influence physiological functioning and harbor environments conducive to aggressive cancer outcomes.[111,314,372,373] It may also have clinical utility, where this index may be a useful practical screening tool for high-risk individuals, highlighting early points to intervene and potentially prevent premature death, particularly amongst overweight and *obese individuals.*

Study 2: Multi-systemic Biological Risk and All-Cause Mortality: The Jackson Heart Study

Introduction

Multi-systemic Biological Risk (MSBR) is a proxy for allostatic load, a metric of health risk that captures the complex biological cascade that occurs in neuroendocrine, metabolic, autonomic and immune domains in response to chronic environmental and psychosocial stress.[111,326–328] MSBR is a significant risk factor for the major sources of morbidity and mortality across populations.[63,119,282,374,375] Indeed, many forms of chronic stress have been documented to influence MSBR via

direct and indirect mechanisms across the lifespan.[102,195,254,376–378] Chronic stress may indirectly influence MSBR by producing unhealthy behaviors such as smoking, excess alcohol intake, unhealthy eating habits and failure to exercise.[366,373,379] Furthermore, lack of social support is also associated with chronic stress.[380,381] Other research suggests that chronic stress directly impacts MSBR and disease risk via a physiological "weathering" response;[55,62,91] impacting cardiovascular,[102,382]metabolic,[253,254,258] and immune domains.[195,203]

Most studies that have examined the relationship between stress and health related outcomes utilized self-reported stress.[195,278,307,364] Conversely, there is a burgeoning body of evidence that has examined biomarker indices of allostatic load with disease and mortality endpoints.[119,282,283,375] Generally, these studies show a positive association between allostatic load and morbidity/mortality, and that allostatic load levels partially explain racial disparities observed in disease and mortality outcomes.[283,284,375] However, a gap in this research is that previous studies have not been able to account for major sources of chronic stress such as low social support and multiple dimensions of discrimination, which could potentially confound the allostatic load-mortality association.

Therefore, to address this gap we examined the association of MSBR (allostatic load) with all-cause mortality in an African-American cohort. We hypothesized that a higher MSBR score would be associated with higher mortality risk during follow up, and sequential adjustment for dimensions of stress would lead to a sequential attenuation of the association.

Methods

Study Population

The Jackson Heart Study (JHS) is a prospective, community-based, cohort study that examines the etiology of cardiovascular disease (CVD) in African Americans. A total of 5,306 (women, n = 3,371; men, n = 1,935) participants aged 20-95 were enrolled from the Jackson, Mississippi metropolitan area between 2000 and 2004. Further details of the study design, recruitment and data collection are reported elsewhere.[383] Briefly, demographic characteristics, behavioral and lifestyle, as well as clinical information and laboratory values were collected during a home interview and onsite clinical examination at baseline. There were 2 follow-up visits: examination 2 (2005-2008) and examination 3 (2009-2013). The analytic sample for this study utilized data available from baseline and was restricted to participants with complete data on all biomarkers included in the MSBR index (n=4,139). Furthermore, final models were restricted to 3,942 participants who completed the assessment of the burden of lifetime discrimination.

All data collection procedures were approved by the institutional review boards of Jackson State University, Tougaloo College and the University of Mississippi Medical Center, and all JHS participants provided informed consent. The IRB of the University of California, Irvine reviewed and approved the use of the data for this analysis.

Exposure Assessment

The MSBR index utilized the same measures and methods as previous studies examining this index as an exposure variable in the JHS.[301,384] Sex stratified Z-scores for each biomarker were averaged within each biological domain to create

sub-index scores. The sub index scores were then summed to create the overall MSBR index with higher scores indicating higher MSBR.[384] This standardized formulation allows the weight of each biomarker to be different depending on its deviation from the sample's mean. Specifically, the index included the following domains: neuroendocrine (cortisol, ug/dL); metabolic (glycosylated hemoglobin A1c [%]; total cholesterol–high density lipoprotein cholesterol ratio [mg/dL]; waist circumference [cm]); autonomic (systolic blood pressure [SBP] [mmHg]; diastolic blood pressure [DBP] [mmHg]; heart rate [beats/min]); and immune (C-reactive protein [mg/dL]; white blood cell count [th/cmm]). Skewed distributions were log transformed prior to standardization. The summed standardized total MSBR index was ranked to create quintiles to assess for threshold effects. Details on the measurement of all biomarkers included in the score were assessed using standard laboratory procedures and are reported in previous JHS-related research.[385]

Outcome Ascertainment

The primary outcome was all-cause mortality during follow up. Identification and reporting of mortality in the JHS has been previously described.[386] Briefly, mortality status and data were generated from annual follow-up interviews, the National Death Index, and physician and coroner reports reviewed by a medical record abstraction unit. All statuses were adjudicated by trained clinical staff. Participants were censored at the date of death, loss to follow-up, or the end of follow-up (December 31, 2014).

Covariates

Demographic and socioeconomic data collected included age, sex, family income, educational attainment, and health insurance status. Specifically, family income was assessed by 11 categories ranging from <$5000 to >$100,000 that were collapsed into 4 categories (low, lower-middle, upper-middle, and high) accounting for family size and poverty level. Educational attainment responses (less than or equal to high school, some college, and college or more) was collapsed into 2 categories (college education or greater or less than college education). Physical activity was assessed with an 18-item self-report questionnaire modified from the Kaiser Physical Activity Survey and validated against an accelerometer.[387] Dietary information was ascertained using a Food Frequency Questionnaire validated for use in the JHS sample.[388] The data from the physical activity questionnaire and the food frequency questionnaire were categorized into poor, intermediate and ideal physical activity or nutrition levels based on the American Heart Association Life's Simple 7 guidelines. The criteria for physical activity was scored: two points for moderate-intensity activity ≥150 min/week or vigorous-intensity activity ≥75 min/week or combination. One point for moderate-intensity activity 1-149 min/week or vigorous-intensity activity 1-74 min/week or combination of moderate- and vigorous-intensity activity 1-149 min/week, and zero for no physical activity. The criteria for nutrition scored: two points for at least 4 of the following 5 components (based on 2000-kcal diet): fruits and vegetables ≥4.5 cups/day, fish >3.5 oz. twice per week, sodium <1500 mg/day, sugary beverages <450 kcal/week, or whole grains ≥3 servings per day. One point for 2–3 components, and zero for 0-1 components. Other covariates included smoking status (current, former, past),

alcohol consumption (grams per week), sleep (average number of hour per night), health insurance status (yes or no). We created an abbreviated comorbidity index by assigning 1 point for each of the following prevalent comorbid conditions: CVD, diabetes, hypertension and stroke. We then dichotomized the variable to comorbidity (no=1 vs. one or more=1). The same method used to create the disease index was used for medication history. Medication classifications included: all anti-hypertensives (including beta-blockers, and calcium channel blockers), statins, diabetes medications, and anti-arrhythmias. We then dichotomized the variable into no medications versus at least 1. Body mass index (BMI) was measured using anthropometric data collected by trained staff and defined as weight (kg)/height $(m)^2$. Perceived social support was assessed with a 16-item version of the Interpersonal Support Evaluation List. This is a measure of perceived access to four types of support: tangible, emotional, belonging and self-esteem. A sum score was created from the responses ranging from 16 (low support) to 80 (high support).[389,390]

Perceived every day, lifetime, and burden of lifetime discrimination were assessed utilizing the Jackson Heart Discrimination Instrument from exam 1, which measures the occurrence, frequency, attribution, and coping responses to everyday, lifetime, and burden of lifetime discrimination.[391] The everyday discrimination measure was adopted from the Williams' Everyday Discrimination scale[392] and the Cronbach's alpha within JHS indicated excellent internal consistency ($\boldsymbol{\alpha} = 0.88$). Participants were asked questions such as: "How often on a day-to-day basis do you have the following experiences: You are treated with less

courtesy. You are treated with less respect. You receive poorer service than others at restaurants." Participants' responses range from ("several times a day") to ("never"). Responses were averaged (1 = "never" to 7 = "several times a day") and the total score (range 1-7) was transformed into z scores.[377]

Lifetime discrimination was adopted from the Krieger scale[286,393] and it had good internal consistency within JHS ($\alpha = 0.78$). Participants provided a yes/no answer when asked about events of unfair treatment over their lifetime across domains including: school, acquiring a job, and at place of employment. The sum of their responses was used as the score ranging from 0 (no unfair treatment) to 9 (greater unfair treatment),[3] and the score was then transformed into *z* scores.

Burden of discrimination was assessed for participants who reported "yes" for at least one instance of lifetime discrimination. Questions asked, "When you have had experiences like these over your lifetime, would you say they have been very stressful, moderately stressful, or not stressful? (4, 2.5 1)", "Overall how much has discrimination interfered with you having a full and productive life? Would you say a lot, some, a little, or not at all?", and "Overall, how much harder has your life been because of discrimination? Would you say a lot, some, a little, or not at all?" A mean score was created from the responses ranging from 1 (low burden) to 4 (greater burden) and the score was then z-scored.

Statistical Analysis

Baseline sample characteristics were presented by MSBR quintiles using percentages for categorical variables and means with standard deviations for continuous variables. Cox proportional hazard regressions models were used to

estimate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for associations between the MSBR index and all-cause mortality. The proportional hazards assumption was assessed by creating interaction terms between MSBR, all covariates and follow-up time and no evidence of a violation was detected.

To examine the statistical impact of adjustment for different domains of confounders, we utilized a sequential regression approach with adjustment for confounders in each domain. Model 1 adjusted for age and sex (basic demographics). Model 2: Model 1 + education, income, health insurance status and the social support score (domains of social support). Model 3: Model 2 + physical activity, diet quality, hours of sleep, smoking, alcohol intake, comorbidities, medication use), and BMI (lifestyle/ health status).[49] Model 4: Model 3 + discrimination (everyday, lifetime, and burden).

We tested for effect modification for age group (Median, >54 vs <=54), sex, smoking, health insurance status, income, BMI (<=25 vs >25), any alcohol use, and stress from burden of discrimination by including a term for the interaction between the exposure score and the aforementioned covariates into each of the fully adjusted models. Sensitivity analyses assessed the association amongst those taking at least 1 medication versus no medication. We also assessed the association amongst those with at least 1 disease versus no diseases.

Missing data

Multiple imputations for missing data were used to impute missing values of covariates in this analysis. We utilized multiple imputation using chained equations (MICE), which uses a sequence of univariate imputation methods with fully

conditional specification (FCS) of prediction equations to generate 20 imputed datasets for the estimation of 14 covariates [education (n=15), income (n=656), health insurance (n=17), social support score(n=956), physical activity (n=4), nutrition (n=399), smoke (n=37), alcohol (n=149), hours of sleep (n=23), BMI (n=1), everyday discrimination score (n=69), lifetime discrimination score (n=148), burden of discrimination (n=10), medication history (n=89)] using all other relevant complete variables within the analysis.[360,361] The parameter estimates from each imputed data set (m=20), were estimated using the Stata MI estimate command. Sensitivity analyses were performed to compare estimates from the original data and the imputed data. The analysis utilizing complete participant data versus the imputed dataset were not materially different; therefore, we utilized the imputed results. All statistical analyses were performed using SAS version 9.4 and STATA 14.

Results

Of the 4,193 participants included in the analysis there were 536 deaths during 47,939 person-years of follow up. The mean age of participants was 55.3±12.8 years. Table 5 displays participant characteristics according to quintiles of the MSBR index. Compared to quintile 1, participants from quintile 2-5 were older, had higher average BMIs, a greater proportion with a high school degree or less, lower income, and higher prevalence of a history of smoking. They were also less likely to have health insurance and be physically active.

Table 7 reports the results from the Cox proportional hazard regression models for the association between quintiles of the MSBR index and all-cause

mortality. After adjustment for demographic, socioeconomic, lifestyle and health status, and discrimination related variables, higher MSBR was associated with an increased risk of all-cause mortality (HR per SD increase in MSBR = 1.20, 95% CI: [1.13-1.27]). Further, examining the MSBR index by quintiles displayed a graded association for all-cause mortality, across quintiles 2-5 compared to quintile 1.

Table 7: Baseline Characteristics of the Jackson Heart Study Participants, by quintiles of MSBR index (n=4,193)

Quintile # Z-score range Sample size	Quintile 1 (-5.52 to -1.56) (n=838)	Quintile 2 (-1.55 to -0.54) (n=839)	Quintile 3 (-0.53 to 0.30) (n=839)	Quintile 4 (0.31 to 1.45) (n=839)	Quintile 5 (1.46 to 10.73) (n=838)
Median Age (IQR 25-75)	48.3 (40.8-59.8)	53.7 (44.5-63.4)	54.7 (45.0-64.6)	56.9 (47.2-65.3)	58.2 (48.3-64.9)
Characteristics	% or Mean (SD)				
Sex (female)	63.4	62.5	64.6	63.5	64.4
<=High school	25.2	34.7	35.5	41.1	46.4
Upper middle/affluent	68.5	65.2	63.1	56.4	52.1
No health insurance	12.3	12	11.9	15.5	16.9
Not physically active	36	43.9	49.5	53.6	56.9
Current smoker	9.1	9.9	11.8	15.9	16.6
Past smoker	14.4	17.4	19.1	20	18.7
Never smoker	76.5	72.7	69.1	64.1	64.7
Poor diet quality	58.4	57.9	60.5	57.1	53.8
Average grams of alcohol /week	29.3 (5.5)	29.5 (3.3)	26.1 (3.1)	38.4 (4.6)	44.4 (5.9)
Average BMI	27.9 (.17)	30.4 (.22)	32.3 (.25)	33.5 (.27)	35.0 (.28)
Average social score (16-80)	51.0 (.22)	50.8 (.22)	51.1 (.23)	51.8 (.23)	51.1 (.25)
Hours of sleep/night (1-18)	6.4 (.05)	6.4 (.05)	6.4 (.05)	6.5 (.05)	6.5 (.05)
% At least 1 medication	9.7	12.2	18.7	21.0	27.0
% At least 1 morbidity	29.7	45.5	56.6	64.6	75.6
Discrimination scores					
Every day (0-6)	1.2 (.03)	1.1 (.04)	1.1 (.03)	1.1 (.04)	1.1 (.04)
Lifetime (0-9)	3.2 (.08)	3.0 (.08)	2.9 (.07)	2.9 (.08)	2.8 (.07)
Burden (1-4)	2.0 (.04)	1.9 (.04)	2.0 (.04)	2.0 (.04)	2.0 (0.4)
Stress (% yes)	64.2	61.6	64.0	65.0	62.4

Table 8. Hazard Ratio and 95% CI of All-Cause Mortality According to Quintiles of Multi-Systemic Biological Risk Index (MSBR): The Jackson Heart Study

MSBR Quintiles	Cases (n=536) /Total (n=4,193)	HR 95% CI Model 1	HR 95% CI Model 2	HR 95% CI Model 3	Cases (n=398)	HR 95% CI Model 4

					/Total (n=3,415)	
Quintile 1	48/838	Ref	Ref	Ref	37/688	Ref
Quintile 2	75/839	1.27 (0.89-1.83)	1.21 (0.84-1.75)	1.11 (0.77-1.61)	51/667	0.98 (0.64-1.51)
Quintile 3	95/839	1.51 (1.07-2.14)	1.49 (1.05-2.11)	1.31 (0.92-1.86)	66/683	1.20 (0.79-1.81)
Quintile 4	140/839	2.22 (1.60-3.09)	2.09 (1.50-2.90	1.77 (1.26-2.49)	102/692	1.59 (1.08-2.36)
Quintile 5	178/838	2.90 (2.10-3.99)	2.72 (1.97-3.75)	2.24 (1.59-3.15)	142/685	2.19 (1.48-3.23)
Per SD	536/4,193	1.25 (1.19-1.30)	1.23 (1.18-1.29)	1.20 (1.14-1.26)	398/3,415	1.20 (1.13-1.27)

*Model 1: age and sex. Model 2: model 1 and also education, income, health insurance status and the social support score. Model 3: model 2 and also physical activity, HEI score, smoking, alcohol, comorbidities, medication, BMI, average number of hours of sleep. Model 4: model 3 and also dimensions of discrimination (everyday, lifetime, and burden) limited to n=3,415 who completed the discrimination index.

Analyses used to determine the presence of effect measure modification by sex, smoking, health insurance status, income, BMI, and alcohol use provided no evidence that the results differed by those measures. However, there was evidence that the magnitude of the estimate was stronger within the younger age group when the population was stratified by the median age. In the model adjusted for all noted confounders the positive association between a higher MSBR index score and risk for mortality in participants who were 54 years of age or less is presented in Table 9 (HR per SD MSBR = 1.28, 95% CI: [1.13-1.44]). There was also a positive association between a higher index score and risk for mortality amongst those who were greater than 54 years of age presented in Table 9 (HR per SD MSBR = 1.18, 95% CI: [1.11-1.26]).

Table 9. Hazard Ratio and 95% CI of All -Cause Mortality According to Quintiles Multi-Systemic Biological Risk Index (MSBR) amongst participants age 54 or less at baseline: The Jackson Heart Study

MSBR Quintiles	Cases (n=86) /Total (n=2,071)	HR 95% CI Model 1	HR 95% CI Model 2	HR 95% CI Model 4	Cases (n=69) /Total (n=1,795)	HR 95% CI Model 4
Quintile 1	8/540	Ref	Ref	Ref	8/459	Ref

Quintile 2	11/425	1.59 (0.64-3.97)	1.53 (0.61-3.82)	1.49 (0.60-3.74)	8/361	1.13 (0.42-3.04)
Quintile 3	13/402	1.99 (0.82-4.81)	1.90 (0.78-4.60)	1.60 (0.65-3.97)	10/355	1.24 (0.47-3.23)
Quintile 4	18/368	2.95 (1.28-6.80)	2.70 (1.17-6.26)	2.24 (0.94-5.38)	13/321	1.56 (0.62-3.95)
Quintile 5	36/336	6.60 (3.05-14.3)	5.63 (2.58 -12.27)	4.05 (1.74-9.41)	30/299	3.19 (1.31-7.74)
Per SD	86/2,071	1.36 (1.24-1.48)	1.37 (1.21-1.45)	1.26 (1.14-1.40)	69/1,795	1.28 (1.13-1.44)

*Model 1: age and sex. Model 2: model 1 and also education, income, health insurance status and the social support score. Model 3: model 2 and also physical activity, HEI score, smoking, alcohol, comorbidities, medication, BMI, average number of hours of sleep. * Model 4: model 3 and also dimensions of discrimination (everyday, lifetime, and burden) limited to n=3,415 who completed the discrimination index.

Sensitivity analyses assessing estimates for participants who reported any medication use versus none, any comorbidities versus none, and those who reported that the burden of discrimination was stressful versus not stressful displayed estimates that did not significantly differ between sub-groups.

Table 10. Hazard Ratio and 95% CI of All-Cause Mortality According to Quintiles of Multi-Systemic Biological Risk (MSBR) amongst participants age 55 or greater at baseline: The Jackson Heart Study

MSBR Quintiles	Cases (n=450) /Total (n=2,122)	HR 95% CI Model 1	HR 95% CI Model 2	HR 95% CI Model 4	Cases (n=329) /Total (n=1,620)	HR 95% CI Model 4
Quintile 1	40/298	Ref	Ref	Ref	29/229	Ref
Quintile 2	64/414	1.22 (0.82-1.81)	1.10 (0.74-1.64)	1.01 (0.67-1.50)	43/306	0.90 (0.56-1.46)
Quintile 3	82/437	1.42 (0.97-2.07)	1.36 (0.93-1.99)	1.22 (0.83-1.79)	56/328	1.16 (0.73-1.83)
Quintile 4	122/471	2.11 (1.47-3.02)	1.92 (1.34-2.75)	1.63 (1.13-2.36)	89/371	1.50 (0.97-2.32)
Quintile 5	142/502	2.48 (1.75 -3.53)	2.30 (1.62-3.28)	1.93 (1.34-2.79)	112/386	1.97 (1.28-2.32)
Per SD	450/2,122	1.22 (1.16-1.29)	1.21 (1.15-1.27)	1.18 (1.11-1.24)	329/1,620	1.18 (1.11-1.26)

*Model 1: age and sex. Model 2: model 1 and also education, income, health insurance status and the social support score. Model 3: model 2 and also physical activity, HEI score, smoking, alcohol, comorbidities, medication, BMI, average number of hours of sleep. Model 4: model 3 and also dimensions of discrimination (everyday, lifetime, and burden) limited to n=3,415 who completed the discrimination index.

Discussion

In this analysis of a large population-based cohort of African Americans, there was a strong, positive association between a higher MSBR index (proxy for allostatic load) and risk for all-cause mortality during follow-up. Sequential adjustment for dimensions that are known to confound the association (demographic, socioeconomic and social support, lifestyle and health status, and discrimination experience), demonstrated that each domain contributes to the association by the attenuation of the point estimate with each adjustment. However, the strong association remained.

Multi-systemic biological risk is a composite index representing the underlying biological relationship between chronic stress due to social, economic, and environmental disadvantage and burden of disease.[301,384,394] Previous research has demonstrated inverse associations between higher levels of allostatic load indices and cognition, sleep, physical function, socioeconomic status, disadvantaged neighborhoods, and increased risk for cardiovascular outcomes and mortality.[63,106,107,374,384,395] This analysis shows that an index of MSBR may potentially serve as a practical prediction tool for mortality, and preventive measures may be taken to reduce this risk.

Several studies have investigated the association between allostatic load and overall mortality. Borrell et al, investigated the association between a MSBR index and all-cause mortality risk using the national multi-ethnic NHANES III data.[375] This study found that after adjustment for age, sex, race/ethnicity, education, and income, mortality rates were 88% higher for participants with the highest score for

allostatic load. However, this study slightly differs in their formulation of the MSBR score because the index did not include the stress hormone cortisol.

A study by Duru, et. al, used NHANES III data to estimate unadjusted cardiovascular/diabetes-related mortality and non-injury mortality due to sex and race.[283] They then sequentially added risk factors including: (1) age/ clinical conditions, (2) socioeconomic status variables, (3) health behaviors, and finally (4) allostatic load, with a hypothesis that these adjustments would explain the basic model results. For black women versus white women, the magnitude of the disparity for non-injury mortality decreased from 43% greater risk to a 26% risk after adjustment for all domains including allostatic load. For men, disparities were attenuated but persisted after adjustment for allostatic load. This study suggests that allostatic load burden partially explains higher mortality among Black Americans, independent of SES and health behaviors.

The MSBR index, as a proxy for allostatic load, aims to explain the underlying relationship between external chronic stressors and health. The statistical modeling approach we used was constructed to provide insight into this theory. We did observe that adjustment for each of the major domains did lead to modest attenuation of the estimates providing some evidence for this theory. However, the overall strong association between the MSBR index and mortality, regardless of statistical modeling, suggests that a higher MSBR is a strong risk factor for mortality regardless of the underlying cause of the elevated risk factors.

There are several limitations to this study. The biomarker measurement of allostatic load in epidemiological studies is not uniform and is based on the availability of data across studies, making them somewhat of a challenge to compare. We utilized markers that were representative of the major domains, however, we were limited to only cortisol from the neuroendocrine domain. Also, although we imputed relevant covariates which strengthened the statistical power of this analysis, some participants were excluded if they had missing data on at least one of the biomarkers included in the exposure index. Furthermore, the use of biomarkers, which represent complex etiologies, as a simple proxy of dysfunction, is a limitation. Our results align with theoretical frameworks and empirical evidence that suggest secondary measures of biological chronic stress may be an important contributor to mortality outcomes. However, the potential for residual confounding cannot be ruled out, and future studies in this field are needed to further validate these concepts. Finally, this study was conducted in a single metropolitan area which limits its generalizability to other African American populations.

There are important strengths to note. The JHS is the largest prospective cohort assessing clinical risk factors in African Americans. This study includes detailed psychosocial instruments, and as well as strong characterization of complex social and economic factors central to the theory of allostatic load and MSBR. This analysis adds to a body of research that examines the ways by which MSBR, as a proxy for chronic external stressors, leads to poor health outcomes including premature mortality, specifically amongst African American adults of all ages. The use of this MSBR index, a measure of AL, has been useful for understanding

disparities regarding disease risk in previously mentioned studies. Disentangling the complex relationship between race and other social factors is likely strongly biased and confounded within observational studies with multiple race/ethnicities. However, this study examines other important contributors to disparities in mortality, while restricting the design for race, providing a stronger basis for inference into this question.

In conclusion, we observed a strong, positive association between MSBR, a measure of allostatic load, and risk for mortality in adults after an average follow up of 14 years. This analysis suggests that the commonly measured biomarkers that are used to characterize MSBR may also have clinical utility. This tool may serve as a practical screening tool for high-risk individuals, highlighting targeted and early points to intervene and potentially prevent premature death, particularly amongst individuals burdened by stress from discrimination, low income, and lack of social support. Future research carrying out formal prediction analyses will better inform this topic.

Study 3: Perceived Discrimination and Multi-System Biological Risk: The CARDIA Study

Introduction

A substantial body of evidence indicates that perceived discrimination is an important risk factor for mental and physical health.[396,397] Discrimination can lead to poor health by direct and indirect mechanisms. Indirectly, discrimination may prompt unhealthy behaviors such as smoking, excess alcohol intake, unhealthy

eating habits and failure to exercise.[366,373,379] Directly, discrimination can cause acute and chronic stress, which can be deleterious for most physiological systems that are exposed to stress hormones.[362,363] A metric fundamental to the stress response is multi-systemic biological risk (MSBR), a proxy for allostatic load, that captures the complex biological cascade that occurs amongst the autonomic, metabolic, and immune domains in response to chronic environmental and psychosocial stress.[111,326–328]

Indeed, research demonstrates discrimination has important biological consequences.[29,42,55,398] One documented effect in response to the chronic stress derived from discrimination has been described as "physiological weathering".[62] However, most studies that have examined the association between self-reported discrimination and health are cross-sectional in nature and have not looked at objective clinical measures of health status as outcomes,[307] although a few have examined individual markers part of typical MSBR scores[315,393,399,400]. Furthermore, research assessing the relationship between different types of discrimination, and MSBR has not been addressed. Therefore, the aim of this study was to assess the association between experienced discrimination due to gender, race, and socioeconomic position and MSBR. We hypothesized a higher number of discrimination experiences, and an increase in the number of perceived experiences of discrimination over time was positively associated with MSBR.

Methods

Study Population

CARDIA is a multicenter prospective study that focuses on the etiology of cardiovascular risk development in young adulthood. From 1985–86, a total of 5,115 individuals were recruited from four study communities within the United States. This included: Chicago, Illinois; Minneapolis, Minnesota; Birmingham, Alabama; and Oakland, California.[401] A stratified random sampling procedure was used to attain a balanced number of participants at each center by gender, race/ethnicity (Black, White), age (18–24 and 25–30 years), and education (high school degree or less, some college or more).[401] Follow up examinations were done at years 2, 5, 7, 10, 15, 20, 25, and 30. The institutional review boards for each site approved this study with all procedures followed in accordance with institutional guidelines and informed consent was obtained from each participant. Further details regarding study design, eligibility requirements, and recruitment are available elsewhere.[402] This analysis used data collected in year 7 (1992–93), year 15 (2000–01), and year 25 (2010–11). Follow-up rates at year 7, year 15, and year 25 were 81%, 74%, and 72%, respectively.

Exposure Measurement

At years 7, 15, and 25 participants were asked about their experiences of discrimination with the Experiences of Discrimination (EOD) instrument.[403,404] The EOD instrument asked, "Have you ever experienced discrimination, been prevented from doing something, or been hassled or made to feel inferior in any of the following situations because of your: race or skin color, gender, or socioeconomic position (SEP)". The yes or no question was asked within seven domains including: at school, getting a job, at work, getting housing, getting medical care, on

the street or in a public setting, and from the police or in the courts. The gender section did not include a domain regarding the police or in the courts, and instead of experiencing gender discrimination while "getting housing", the question asked if you have experienced gender discrimination "at home." At years 15 and 25, the phrase "been prevented from doing something" was dropped from the discrimination instrument and the domain "from the police or in the courts' was replaced with "at home," for all three types of discrimination. Also, experiencing gender discrimination while "getting housing" was added to the section related to gender. As indicated by Cronbach's alpha, the reliability of the EOD Index for racial/ethnic discrimination was 0.82 for all participants, 0.79 for black participants, and 0.66 for white participants in CARDIA.[404]

This analysis focused on discrimination due to race or color, gender, and socioeconomic position (SEP) or social class. To characterize discrimination, a summary scale was created as the sum score of answers to the respective discrimination questions (for each question, 0 points were given to those who answered "No", 1 point for those who answered "Yes"). At year 7, the race and color survey, as well as the SEP survey scores ranged from 0-7; the gender survey scores ranged from 0-6. Lastly, all survey scores ranged from 0-7 at years 15 and 25. Therefore, at year 7, the total sum scores ranged from 0-20, and at years 15 and 25 the total sum scores ranged from 0-21. Overall number of experiences of discrimination was the sum of all discrimination scores for each participant. The overall discrimination measure was then ranked into quartiles and modeled as a categorical predictor. We also modeled the assigned ranked quartiles continuously

with increasing values indicating higher frequency of experiencing discrimination across time. The sub-discrimination domains were ranked into tertiles.

Outcome measurement

The markers included to construct the MSBR index in this analysis were clinical measures most commonly utilized for allostatic load and uniformly available at year 7, 15, and 25 of the Cardia study. The metabolic domain was defined by (Homeostasis model assessment [$HOMA_{IR}$] calculated as fasting glucose (mmol/L) × insulin (mU/L)/22·5, triglycerides [mg/dL], and waist circumference); the autonomic domain was defined by (systolic blood pressure, diastolic blood pressure, and pulse rate [beats/min]); and the immune domain by (c-reactive protein). In each domain Z-scores for each biomarker were averaged to create sub-index scores. The sub index scores were summed to create the overall MSBR index with higher scores indicating higher MSBR. Skewed distributions were log transformed prior to standardization. All measures were z-scored separately for males and females. All biomarkers utilized in the score were assessed using standard laboratory procedures and are discussed in detail in previous published work from the CARDIA study.[381]

Covariates

Demographic covariates included race, sex and the baseline enrollment center of the four study communities. Time varying covariates included: age, current smoking status (reported presently smoking at least five cigarettes per week almost every week), alcohol consumption (milliliters of wine, beer, and liquor consumed in a week), education (high school or less, some college or college

graduate, graduate degree), and household income ($24,999 or less, $25,000-50,000, $50,000 or more), disease status (history of cardiovascular disease or diabetes, or high blood pressure, or cancer), medication history (history of cholesterol lowering medications or hypertension medications) . Body mass index (BMI) was calculated by the formula weight (kg)/height $(m)^2$ and was evaluated using a standardized protocol for measuring height and weight. Physical activity was measured with the CARDIA physical activity questionnaire.[405] An intensity score was computed by multiplying reported frequency of engagement in 13 different exercise and recreational activities by the intensity of the activity. The CARDIA Diet History questionnaire was used to assess dietary intake at baseline, and years 7 and 20. The A Priori Diet Quality Score, an index of diet quality based upon evidence linking food groups with health, from years 7 and 20 was used for this analysis.[406,407]

Statistical Methods

We calculated race and gender stratified descriptive statistics for study covariates by follow up year (7, 15, 25) and number of overall discrimination experience quartiles. Cross-sectional regression models were used to calculate parameter estimates and 95% confidence intervals to estimate the relationship between the overall discrimination index and MSBR for year 7, year 15, and year 25. Models were also stratified by discrimination type and were limited to those with complete data at all three time points. Then we utilized a fixed-effects regression approach to calculate parameter estimates and 95% confidence intervals to estimate the association of within-person changes in discrimination with within-

person changes in MSBR from year 7 to year 15 and then from year 15 to year 25. Models were specified with an unstructured covariance structure for correlated errors. Time-varying covariates, including age, alcohol consumption, BMI, smoking status, disease status, medication use, income, and physical activity, were included in the models to adjust for changes of MSBR due to potential confounding over time. Furthermore, models were adjusted for field center, diet score and year 7's (low, medium or high) discrimination score for year 15 to 25. The discrimination experience variables were ranked and modeled by category of discrimination to observe within person changes in MSBR. Lastly, we conducted a sensitivity analyses to investigate only participants with low discrimination at baseline and changes in MSBR from years 7 to 15 and years 15 to 25.

Results

Descriptive characteristics according to levels of discrimination experiences at year 7, 15, and 25 are presented in Table 9. Black women had the highest average MSBR. Amongst black women, across all three time points, those who reported more experiences of discrimination engaged in more physical activity, had higher income, higher education, lower medication use and higher amounts of alcohol consumption. White women who reported higher discrimination also reported higher physical activity, alcohol intake and were more likely to have higher education. However white women who reported lower income reported higher experienced discrimination. Similar to black women, black men who reported higher discrimination experiences had higher income, physical activity levels, and higher consumption of alcoholic beverages. Lastly white men who reported higher

discrimination were more likely to report lower education, lower income, higher physical activity, and higher consumption of alcoholic beverages. The mean (SD) overall discrimination score for all three time points is shown in Table 11; in general, experiences in discrimination decreased with time.

Table 11. Characteristics of Study Participants by Overall Discrimination Quartiles and Follow Up year, Coronary Artery Risk Development in Young Adults, United States, 1991-2011

	Year 7			
Discrimination Quartile Range and Sample Size	(0) n=577	(1-2) n=502	(3-6) n=539	(7-20) n=400
Discrimination Index, mean (SD)	0 (0)	1.5 (.5)	4.2 (1.1)	10.5 (3.1)
MSBR Z-Score, mean (SD)	-0.27 (1.8)	-.29 (1.9)	-.27 (1.9)	0.04 (1.8)
Age, mean (SD)	32.4 (3.4)	32.7 (3.6)	32.2 (3.6)	32.2 (3.6)
Alcohol intake, mean (SD) ml/week	70.7 (110.5)	60.0 (102.0)	68.9 (132.6)	69.0 (141.6)
BMI, mean (SD)	26.4 (5.3)	25.9 (5.7)	26.7 (5.7)	27.3 (6.4)
Physical activity, mean (SD) exercise units	345.8 (268.5)	325.6 (260.9)	341.9 (259.1)	353.2 (303.6)
Diet Score, mean (SD)	67.3(12.6)	68.8 (11.3)	68.3 (12.5)	65.9 (11.5)
Income (% >$50,000 per year)	42.11	39.19	30.97	21
Education (% high school or less)	22.7	20.03	22.44	23.75
% Female	37.44	62.41	64.2	63
% Black	20.8	29.46	45.74	79.5
Smoking status (% current smoker)	17.85	17.42	26.7	29.5
%Disease (at least 1)	2.25	3.48	4.55	3.75
% Medications (at least 1)	1.39	1.45	1.99	1.5
	Year 15			
Discrimination Quartile Range and Sample Size	(0) n=705	(1-2) n=475	(3-5) n=409	(6-21) n=429

Discrimination Index, mean (SD)	0 (0)	1.4 (0.5)	3.8 (0.8)	9.7 (3.6)
MSBR Z-Score Mean, (SD)	-.36 (1.9)	-0.23 (1.8)	-0.08 (1.9)	0.16 (1.9)
Age, mean (SD)	40.6 (3.3)	40.3 (3.6)	40.3 (3.6)	40.1 3.6)
Alcohol intake, mean (SD) ml/week	79.8 (147.2)	74.7 (147.5)	65.7 (137.0)	58.6 (110.2)
BMI, mean (SD)	28.0 (6.3)	28.2 (6.4)	28.7 (7.0)	29.6 (6.8)
Physical activity, mean (SD) exercise units	366.5 (289.8)	351.2 (265.6)	345.7 (280.0)	343.3 (287.0)
Income (% >$50,000 per year)	71.77	67.79	67.24	50.82
Average Diet Score between year 7 and year 20, mean (SD)	70.1 (11.3)	70.6 (10.9)	70.1 (11.6)	67.0 (10.9)
Education (% high school or less)	19.29	15.16	14.91	22.61
% Female	44.26	58.11	66.26	61.77
% Black	80.43	71.58	50.61	23.78
Smoking status (% current smoker)	14.89	17.05	18.34	22.38
%Disease (at least 1)	3.12	3.16	4.16	3.26
% Medications (at least 1)	7.8	7.58	7.82	9.32
	Year 25			
Discrimination Quartile Range and Sample Size	(0) (n=1,046)	(1-2) (n=423)	(3-5) (n=275)	(6-21) (n=274)
Discrimination Index, mean (SD)	0 (0)	1.4 (0.5)	3.8 (0.8)	9.8 (3.7)
MSBR Z-Score Mean, (SD)	-0.29 (1.9)	-0.07 (2.1)	-.11 (1.9)	0.29 (2.0)
Age, mean (SD)	50.5 (3.4)	50.2 (3.7)	50.3 (3.5)	50.0 (3.6)
Alcohol intake, mean (SD) ml/week	91.7 (152.5)	77.3 (159.0)	69.8 (120.1)	63.5 (131.0)
BMI, mean (SD)	29.4 (6.7)	30.1 (7.2)	30.1 (7.5)	31.6 (7.6)
Physical activity, mean (SD) exercise units	360.0 (289.5)	333.7 (263.4)	318.2 (270)	332.6 (264.1)
Diet Score, mean (SD)	72.0 (12.9)	72.0 (12.6)	71.3 (12.3)	68.5 (12.1)
Income (% >$50,000 per year)	76.86	69.74	69.45	54.74

Education (% high school or less)	17.3	17.02	16.36	25.55
% Female	48.57	64.07	64	61.68
% Black	24.28	40.9	55.64	81.02
Smoking status (% current smoker)	12.24	12.29	15.64	16.79
%Disease (at least 1)	17.21	19.15	16.36	24.45
% Medications (at least 1)	31.26	31.44	33.09	39.05

Table 12. Follow-up Examination Characteristics of Study Participants by Race/Sex and Year. Coronary Artery Risk Development in Young Adults, United States, 1991-2011

Year 7 Characteristics	Black Woman n=499				White Woman n=625			
Overall Discrimination, Mean (SD)	5.64 (4.84)				2.88 (2.81)			
Overall Discrimination Quartile (Range)	(0) n=80	(1-2) n=87	(3-6) n=146	(7-21) n=186	(0) n=136	(1-2) n=218	(3-6) n=205	(7-17) n=66
MSBR, mean (SD)	0.37 (1.9)	0.78 (2.1)	0.48 (1.8)	0.22 (1.8)	-0.58 (2.0)	-0.69 (1.7)	-0.99 (1.6)	-0.34 (1.7)
Age, mean (SD)	31.0 (3.9)	32.1 (3.9)	31.8 (3.9)	31.6 (3.7)	32.6 (3.3)	32.9 (3.2)	33.0 (3.2)	33.1 (3.2)
Alcohol intake, mean (SD) ml/week	13.3 (30.3)	32.2 (78.1)	41.7 (104.7)	32.3 (68.7)	39.1 (66.3)	44.8 (68.0)	52.0 (67.4)	42.8 (76.3)
BMI, mean (SD)	29.4 (7.5)	29.8 (7.7)	29.0 (7.3)	28.5 (7.7)	25.5 (6.1)	24.1 (4.9)	24.3 (4.7)	25.0 (5.0)
Diet Score, mean (SD)	57.5 (11.5)	63.0 (9.6)	61.8 (10.5)	65.0 (11.0)	71.4 (11.5)	73.1 (10.3)	75.6 (11.2)	75.2 (9.8)
Physical activity, mean (SD) exercise units	173.6 (184.3)	183.4 (171.0)	228.9 (205.2)	244.8 (243.5)	249.4 (192.9)	301.0 (231.1)	323.1 (220.5)	368.7 (295.9)

Income (% >$50,000 per year)	12.5	16.79	16.67	16.13	43.38	51.83	40.49	21.21
Education (% high school or less)	35	33.33	28.77	21.51	27.21	16.97	12.2	10.61
Smoking status (% current smoker)	21.25	28.47	25	26.88	17.65	14.22	21.46	19.7
Disease (% with at least 1)	2.5	2.92	4.17	5.38	2.21	5.05	2.93	3.03
Medications (% with at least 1)	2.5	2.92	4.17	1.08	0.47	0.92	0.49	0

Year 15	Black Woman n=499				White Woman n=625			
Overall Discrimination, Mean (SD)	5.29 (4.87)				2.18 (2.67)			
Overall Discrimination Quartiles (Range)	(0) n=87	(1-2) n=85	(3-5) n=135	(6-21) n=192	(0) n=225	(1-2) n=191	(3-5) n=136	(6-15) n=73
MSBR, mean (SD)	0.74 (1.6)	0.62 (2.0)	0.30 (1.86)	0.41 (1.9)	-0.8 (1.9)	-0.6 (1.7)	-0.7 (1.8)	-0.3 (1.8)
Age, mean (SD)	39.6 (3.7)	39.4 (4.0)	39.7 (3.9)	39.7 (3.8)	40.8 (3.3)	40.9 (3.1)	40.9 (3.4)	41.4 (2.9)
Alcohol intake, mean (SD) ml/week	34.3 (158.3)	27.6 (64.4)	35.4 (73.4)	34.2 (68.5)	55.1 (82.0)	63.4 (93.7)	54.8 (79.7)	50.4 (78.3)
BMI, mean (SD)	32.2 (7.6)	32.9 (7.7)	31.4 (8.5)	31.0 (7.4)	26.6 (7.0)	26.5 (6.5)	25.7 (5.0)	27.8 (7.1)
Diet Score, mean (SD)	60.4 (9.4)	64.0 (8.5)	65.9 (10.0)	65.9 (10.1)	74.5 (10.3)	75.9 (10.0)	77.3 (10.3)	76.9 (9.5)

Physical activity, mean (SD) exercise units	216.2 (225.9)	210.6 (202.7)	214.9 (184.8)	245.9 (234.2)	328.9 (295.2)	322.1 (235.2)	354.9 (241.3)	382.2 (252.0)
Income (% >$50,000 per year)	28.74	49.41	48.15	47.92	79.56	76.96	79.41	54.79
Education (% high school or less)	42.53	23.53	23.7	17.19	15.56	11.52	5.15	10.96
Smoking status (% current smoker)	18.39	22.35	20	24.48	15.11	12.04	15.44	10.96
Disease (% with at least 1)	3.45	4.71	3.7	4.17	4	2.09	6.62	0
Medications (% with at least 1)	20.69	15.29	14.81	12.5	4.44	2.62	2.21	2.74

Year 25	Black Woman n=499				White Woman n=625			
Overall Discrimination, Mean (SD)	3.73 (4.62)				1.37 (2.36)			
Overall Discrimination Quartiles (score range)	(0) n=161	(1-2) n=113	(3-5) n=93	(6-21) n=132	(0) n=347	(1-2) n=158	(3-5) n=83	(6-18) n=37
MSBR, mean (SD)	0.73 (1.8)	0.87 (1.8)	0.50 (1.8)	0.52 (2.0)	-0.7 (1.9)	-0.7 (2.0)	-1.0 (1.7)	-0.50 (2.1)
Age, mean (SD)	49.6 (3.7)	49.3 (4.1)	49.5 (1.8)	50.1 (3.8)	50.8 (3.3)	51.1 (3.2)	51.1 (3.3)	50.8 (2.8)
Alcohol intake, mean (SD) ml/week	23.7 (47.0)	37.9 (96.0)	27.0 (64.6)	52.1 (121.4)	75.3 (100.9)	72.0 (98.3)	81.3 (117.5)	36.9 (62.9)
BMI, mean (SD)	34.1 (8.1)	33.5 (7.3)	32.7 (7.9)	33.1 (8.4)	28.0 (7.3)	28.0 (7.6)	28.1 (7.3)	29.0 (6.5)
Diet Score, mean (SD)	63.8 (11.3)	66.5 (11.2)	66.7 (10.4)	70.2 (11.4)	77.1 (12.1)	78.5 (11.9)	80.7 (10.5)	75.2 (11.7)

Physical activity, mean (SD) exercise units	209.1 (232.8)	200.1 (166.2)	214.4 (204.9)	253.7 (222.5)	338.2 (271.8)	337.4 (239.3)	296.0 (208.6)	385.7 (270.8)
Income (% >$50,000 per year)	45.34	51.33	61.29	47.73	84.44	76.58	81.93	67.57
Education (% high school or less)	31.68	20.35	20.43	21.97	12.1	10.76	6.02	13.51
Smoking status (% current smoker)	19.25	17.7	18.28	17.42	10.66	5.7	9.64	13.51
Disease (% with at least 1)	21.74	24.78	20.43	28.79	18.44	18.35	10.84	27.03
Medications (% with at least 1)	48.45	38.94	41.94	44.7	21.61	24.68	20.48	10.81

Year 7 Characteristic	Black Men n=303				White Men n=591			
Overall Discrimination, Mean (SD)	6.16 (4.69)				1.28 (2.01)			
Overall Discrimination Quartile (Range)	(0) n=40	(1-2) n=42	(3-6) n=89	(7-20) n=132	(0) n=321	(1-2) n=155	(3-5) n=99	(7-15) n=16
MSBR, mean (SD)	0.2 (1.8)	-0.2 (1.8)	0.0 (2.0)	-0.2 (1.8)	-0.3 (1.7)	-0.3 (2.0)	-0.1 (1.8)	-0.4 (1.4)
Age, mean (SD)	31.0 (3.8)	31.1 (3.8)	31.0 (3.9)	31.1 (3.8)	32.8 (3.1)	33.0 (3.2)	32.0 (3.2)	31.8 (3.9)
Alcohol intake, mean (SD) ml/week	85.5 (115.4)	77.8 (138.6)	92.1 (173.8)	77.8 (138.6)	96.5 (127.9)	89.0 (130.7)	123.0 (196.3)	120.0 (220.6)

BMI, mean (SD)	27.3 (5.2)	26.8 (5.4)	27.8 (4.9)	26.8 (5.4)	26.0 (4.0)	25.9 (4.2)	26.3 (3.6)	25.7 (3.2)
Diet Score, mean (SD)	55.2 (11.9)	58.9 (9.4)	60.7 (10.5)	58.9 (9.4)	69.6 (11.3)	68.5 (11.0)	69.9 (10.3)	72.1 (15.9)
Physical activity, mean (SD) exercise units	484.7 (393.0)	470 (358.2)	460.9 (328.8)	470.1 (358.2)	412.2 (262.0)	400.9 (268.5)	440.3 (256.0)	522.3 (297.0)
Income (% >$50,000 per year)	12.5	21.43	30.34	27.27	52.65	47.1	35.35	25
Education (% high school or less)	45	23.81	30.34	31.82	14.95	15.48	23.23	37.5
Smoking status (% current smoker)	37.5	14.29	25.84	36.36	14.64	16.77	21.21	43.75
Disease (% with at least 1)	5	0	4.49	1.52	1.87	2.58	7.07	6.25
Medications (% with at least 1)	0	0	3.37	3.03	1.25	0.65	2.02	0

Year 15	Black Men n=303				White Men n=591			
Overall Discrimination, Mean (SD)	5.57 (4.81)				1.20 (2.09)			
Overall Discrimination Quartiles (Range)	(0) n=51	(1-2) n=50	(3-5) n=67	(6-21) n=135	(0) n=342	(1-2) n=149	(3-5) n=71	(6-17) n=29
MSBR, mean (SD)	-0.2 (1.9)	0.0 (1.9)	0.5 (2.0)	0.1 (1.9)	-0.4 (1.8)	-0.3 (1.7)	-0.2 (1.9)	-0.2 (1.8)

Age, mean (SD)	39.5 (3.6)	38.9 (4.0)	39.6 (3.7)	40.0 (3.6)	40.9 (3.1)	40.5 (3.5)	40.7 (3.1)	39.8 (3.2)
Alcohol intake, mean (SD) ml/week	91.5 (137.8)	72.9 (146.4)	98.3 (192.5)	89.4 (148.8)	105.9 (171.9)	116.8 (213.9)	113.2 (216.0)	97.4 (146.7)
BMI, mean (SD)	28.5 (7.0)	29.2 (5.0)	30.4 (6.1)	28.9 (5.6)	27.7 (4.7)	27.4 (4.1)	27.7 (4.8)	28.2 (4.3)
Diet Score, mean (SD)	60.9 (9.1)	61.2 (7.9)	62.5 (10.7)	62.2 (8.7)	71.0 (10.5)	70.7 (10.1)	71.6 (9.7)	73.1 (9.7)
Physical activity, mean (SD) exercise units	413.8 (329.6)	410.8 (340.0)	470.8 (329.9)	439.4 (336.5)	422.5 (277.8)	448.7 (264.5)	458.5 (340.2)	443.6 (236.9)
Income (% >$50,000 per year)	54.9	56	73.13	50.37	80.12	70.47	74.65	62.07
Education (% high school or less)	41.18	26	16.42	36.3	12.57	11.41	15.49	24.14
Smoking status (% current smoker)	31.37	26	16.42	28.15	11.4	17.45	22.54	10.34
Disease (% with at least 1)	1.96	6	1.49	2.22	2.63	2.68	2.82	10.34
Medications (% with at least 1)	1.96	8	10.45	8.89	7.6	9.4	2.82	6.9

Year 25	Black Men n=303	White Men n=591
Overall Discrimination, Mean (SD)	3.97 (4.5)	0.67 (1.58)

Overall Discrimination Quartiles (score range)	(0) n=93	(1-2) n=60	(3-5) n=60	(6-21) n=90	(0) n=445	(1-2) n=92	(3-5) n=39	(6-14) n=15
MSBR, mean (SD)	0.2 (1.9)	0.3 (1.8)	0.2 (2.0)	0.4 (1.8)	-0.5 (1.8)	-0.3 (2.1)	-0.2 (1.9)	-0.5 (2.1)
Age, mean (SD)	49.8 (3.8)	48.9 (3.8)	49.7 (3.6)	49.9 (3.6)	50.8 (1.8)	50.8 (3.2)	51.0 (3.2)	48.3 (2.8)
Alcohol intake, mean (SD) ml/week	96.1 (215.5)	76.6 (138.4)	94.4 (148.7)	89.3 (163.3)	128.3 (182.0)	135.3 (267.3)	109.8 (149.5)	73.6 (97.7)
BMI, mean (SD)	30.2 (6.7)	31.3 (5.9)	30.1 (7.4)	30.8 (6.4)	28.7 (4.6)	28.6 (5.2)	28.6 (5.0)	30.1 (5.7)
Diet Score, mean (SD)	63.1 (10.9)	63.8 (10.2)	64.7 (10.2)	63.4 (11.6)	72.9 (12.0)	72.7 (10.6)	72.8 (10.8)	70.7 (12.1)
Physical activity, mean (SD) exercise units	349.7 (279.2)	364.1 (334.8)	453.8 (358.1)	413.4 (293.6)	433.8 (299.7)	471.5 (272.5)	404.3 (258.5)	411.1 (214.5)
Income (% >$50,000 per year)	62.37	71.67	61.67	58.89	85.39	79.35	74.36	60
Education (% high school or less)	39.78	31.67	25	34.44	11.46	14.13	15.38	33.33
Smoking status (% current smoker)	17.2	21.67	21.67	17.78	9.89	10.87	12.82	13.33
Disease (% with at least 1)	12.9	18.33	16.67	18.89	15.51	14.13	17.95	13.33
Medications (% with at least 1)	37.63	36.67	40	43.33	31.24	30.43	28.21	33.33

The cross-sectional analysis was first limited to participants with complete data at each time point (Table 13.), then we further limited the analysis to complete data at all time points (n=2018). Results from the multivariate linear models, displayed no associations for all groups between the overall cross-sectional relationship between self-reported experiences of discrimination and MSBR z-scores at year 7, year 15 and year 25 (Table 13, 14 and 15.) Parameter estimates by sub-discrimination domains were similar. The fixed effect analysis was partitioned into two parts: change from year 7 to year 15 and change from year 15 to year 25. The first analysis was limited to participants with complete data from year 7 to 15 (n=2,898), and second was limited to complete data from years 15 to 25 (n=2,174). Fixed effect regression models estimating changes from year 7 to year 15 in the discrimination score were not associated with changes in MSBR z-scores (Table 16.) Similar results were found in the models estimating differences from year 15 to year 25. In general, analyses that assessed the overall discrimination score stratified by type of discrimination also showed no associations with change in MSBR (Table 17.). Trends in adjusted means were assessed and there was no evidence for any statistical trends (Table 18. and Supplemental Table 19). Sensitivity analyses investigating change amongst only participants with low discrimination at baseline and changes in MSBR were similar to the main results (data not shown).

Table 13. Multivariate Parameter Estimates for the Association Between Self-Reported Experiences of Discrimination and MSBR Z-Score, by race/ethnicity–gender group: the CARDIA study (1991–2011).

	Black Women			White Women			Black Men			White Men		
		(95%CI)			(95%CI)			(95%CI)			(95%CI)	
Year 7	β	LB	UB	β	LB	UB	β	LB	UB	β	LB	UB

Overall	-0.01	-0.03	0.01	0.01	-0.02	0.04	0.00	-0.02	0.02	0.01	-0.03	0.05
Race	-0.03	-0.08	0.01	0.11	0.01	0.20	0.02	-0.04	0.07	0.01	-0.09	0.12
Gender	-0.01	-0.07	0.04	-0.01	-0.06	0.04	0.00	-0.07	0.06	-0.01	-0.10	0.09
SES	-0.01	-0.06	0.04	0.01	-0.06	0.08	0.00	-0.06	0.06	0.03	-0.06	0.11
Year 15												
Overall	-0.01	-0.03	0.01	0.03	0.00	0.06	0.01	-0.02	0.03	0.01	-0.04	0.05
Race	-0.02	-0.07	0.03	0.11	0.00	0.21	0.05	-0.02	0.11	0.03	-0.09	0.15
Gender	-0.01	-0.06	0.04	0.04	-0.01	0.10	-0.01	-0.07	0.06	0.02	-0.08	0.11
SES	-0.01	-0.07	0.04	0.04	-0.04	0.12	0.00	-0.06	0.06	0.00	-0.09	0.09
Year 25												
Overall	-0.02	-0.04	0.00	0.00	-0.04	0.04	0.02	-0.01	0.05	-0.01	-0.08	0.05
Race	-0.05	-0.10	0.00	0.01	-0.12	0.13	0.04	-0.03	0.11	-0.08	-0.25	0.09
Gender	-0.03	-0.10	0.03	-0.02	-0.10	0.05	0.05	-0.03	0.14	0.02	-0.15	0.18
SES	-0.07	-0.13	-0.01	0.05	-0.05	0.14	0.01	-0.07	0.09	-0.02	-0.16	0.11

*Sample size for Year 7: Black women n=941, White women n=983, Black men n=690, White men n=940. *Sample size for Year 15: Black women n=810, White women n=901, Black men n=548, White men n=836. *Sample size for Year 25: Black women n=716, White women n=769, Black men n=434, White men n=677.

Table 14. Multivariate Parameter Estimates for the Association Between Self-Reported Experiences of Discrimination and MSBR Z-Score, by race/ethnicity–gender group: the CARDIA study (1991–2011). (Limited to complete data at all three time points n=2,018)

	Black Women			White Women			Black Men			White Men		
		(95%CI)			(95%CI)			95%CI)			(95%CI)	
	β	LB	UB	β	LB	UB	β	LB	UB	β	LB	UB
Overall												
Year 7	0.00	-0.11	0.12	0.02	-0.09	0.14	-0.02	-0.18	0.13	0.03	-0.10	0.16
Year 15	-0.01	-0.03	0.02	0.04	0.00	0.08	0.01	-0.05	0.06	0.01	-0.05	0.06
Year 25	-0.01	-0.04	0.02	-0.01	-0.05	0.04	0.02	-0.02	0.05	-0.01	-0.08	0.06
Sub-domains												
Racial												
Year 7	0.00	-0.15	0.14	0.14	-0.01	0.29	-0.02	-0.24	0.19	-0.01	-0.18	0.16
Year 15	-0.04	-0.10	0.03	0.20	0.06	0.34	0.09	0.00	0.17	0.03	-0.13	0.18
Year 25	-0.02	-0.08	0.05	0.01	-0.14	0.16	0.03	-0.05	0.11	0.03	-0.05	0.11
Gender												

Year 7	0.06	-0.10	0.22	0.00	-0.15	0.15	-0.07	-0.27	0.12	-0.16	-0.36	0.04
Year 15	-0.01	-0.07	0.06	0.05	-0.02	0.12	-0.01	-0.09	0.07	-0.01	-0.12	0.11
Year 25	0.00	-0.08	0.07	-0.05	-0.13	0.03	0.09	-0.01	0.18	0.02	-0.16	0.19
SEP												
Year 7	0.02	-0.12	0.16	0.03	-0.11	0.18	-0.06	-0.24	0.11	0.10	-0.06	0.26
Year 15	-0.01	-0.08	0.06	0.03	-0.07	0.14	0.02	-0.06	0.11	0.01	-0.09	0.11
Year 25	-0.05	-0.12	0.03	0.04	-0.07	0.15	0.01	-0.08	0.10	-0.01	-0.16	0.14

Table 15. Adjusted Means of Multi-System Biological Risk Index, (95% CI) by Overall Discrimination Experiences for year 7, 15, and 25, by race/ethnicity–gender group: the CARDIA study (1991–2011).

	Black Women			White Women			Black Men			White Men		
		(95%CI)			(95%CI)			(95%CI)			(95%CI)	
	Mean	LB	UB	Mean	LB	UB	Mean	LB	UB	Mean	LB	UB
Year 7												
1	0.74	0.14	1.35	0.58	-0.05	1.21	1.03	0.18	1.89	1.48	0.93	2.02
2	1.14	0.55	1.73	0.84	0.23	1.46	0.95	0.08	1.81	1.51	0.94	2.07
3	0.98	0.43	1.54	0.50	-0.12	1.12	0.91	0.15	1.66	1.57	1.01	2.14
4	0.88	0.32	1.44	0.95	0.26	1.63	0.94	0.18	1.70	1.44	0.62	2.26
Year 15												
1	1.02	0.63	1.40	-0.18	-0.57	0.20	0.78	0.15	1.41	0.05	-0.28	0.38
2	0.92	0.53	1.31	0.00	-0.40	0.39	0.83	0.21	1.46	0.21	-0.14	0.57
3	0.72	0.36	1.07	0.14	-0.27	0.55	1.12	0.52	1.71	0.17	-0.25	0.60
4	0.99	0.68	1.29	0.09	-0.38	0.56	0.99	0.46	1.53	0.11	-0.44	0.65
Year 25												
1	0.81	0.55	1.08	-0.39	-0.63	-0.14	0.64	0.27	1.01	-0.05	-0.31	0.20
2	1.12	0.83	1.42	-0.41	-0.68	-0.13	0.43	0.01	0.85	0.06	-0.29	0.41
3	0.90	0.59	1.22	-0.62	-0.96	-0.28	0.57	0.18	0.95	0.16	-0.30	0.63
4	0.90	0.64	1.16	-0.34	-0.80	0.11	0.73	0.39	1.06	-0.53	-1.24	0.19

Table 16. Fixed Effects Parameter Estimates for the Association of Overall Self-Reported Experiences of Discrimination and Change in MSBR Z-Score, by race/ethnicity–gender group: the CARDIA study (1991–2011)

	Black Women			White Women			Black Men			White Men		
	β	(95%CI)		β	(95%CI)		β	(95%CI)		β	(95%CI)	
		LB	UB		LB	UB		LB	UB		LB	UB
Years (7-15)	-0.04	-0.10	0.02	0.06	0.00	0.13	0.01	-0.06	0.09	0.02	-0.05	0.10
Years	0.04	-0.04	0.11	0.02	-0.06	0.10	0.02	-0.08	0.11	-0.01	-0.10	0.09

(15-25)												

All Models adjusted for year, center*year, age, milliliters of alcohol per week, BMI, smoking status, disease status, medication status, income status, education, physical activity. Year 15 to 25 models additionally adjusted for Year 7 discrimination score.

Table 17. Fixed Effects Parameter Estimates for the Association of Sub-Domain Self-Reported Experiences of Discrimination and Change in MSBR Z-Score, by race/ethnicity–gender group: the CARDIA study (1991–2011)

	Black Women			White Women			Black Men			White Men		
	β	(95%CI)		β	(95%CI)		β	(95%CI)		β	(95%CI)	
Sub-domains		LB	UB		LB	UB		LB	UB		LB	UB
Racial												
(7-15)	-0.07	-0.16	0.01	0.10	-0.01	0.21	0.04	-0.07	0.15	-0.03	-0.14	0.07
(15-25)	0.06	-0.04	0.15	0.08	-0.04	0.20	0.05	-0.08	0.18	0.06	-0.07	0.19
Gender												
(7-15)	-0.04	-0.12	0.05	0.06	-0.02	0.14	-0.04	-0.14	0.06	0.05	-0.06	0.16
(15-25)	0.02	-0.07	0.12	-0.01	-0.10	0.08	0.00	-0.12	0.13	-0.02	-0.16	0.11
SEP												
(7-15)	0.00	-0.08	0.08	0.02	-0.07	0.11	0.06	-0.03	0.16	0.04	-0.05	0.14
(15-25)	0.06	-0.04	0.17	-0.03	-0.16	0.09	0.00	-0.14	0.13	-0.07	-0.22	0.07

All Models adjusted for year, center*year, age, milliliters of alcohol per week, BMI, smoking status, disease status, medication status, income status, education, physical activity. . Year 15 to 25 models additionally adjusted for Year 7 discrimination score.

Table 18. Adjusted Mean Change in Multi-System Biological Risk Index, (95% CI) by Overall Discrimination Experiences for year 7, 15, and 25, by race/ethnicity–gender group: the CARDIA study (1991–2011)

	Black Women			White Women			Black Men			White Men		
		(95%CI)			(95%CI)			(95%CI)			(95%CI)	
	Mean	LB	UB	Mean	LB	UB	Mean	LB	UB	Mean	LB	UB
Year (7-15)												
1	0.97	0.73	1.21	-0.51	-0.77	-0.24	0.43	0.10	0.76	-0.13	-0.33	0.08

2	1.05	0.83	1.27	-0.33	-0.59	-0.08	0.39	0.09	0.70	-0.04	-0.26	0.17
3	0.82	0.60	1.03	-0.36	-0.63	-0.10	0.53	0.23	0.83	-0.06	-0.31	0.19
4	0.92	0.72	1.13	-0.31	-0.60	-0.01	0.45	0.17	0.73	-0.11	-0.44	0.21
Year (15-25)												
1	0.63	0.41	0.85	-0.63	-0.82	-0.45	0.36	0.06	0.66	-0.13	-0.32	0.06
2	0.75	0.54	0.96	-0.57	-0.77	-0.37	0.47	0.17	0.78	-0.25	-0.48	-0.03
3	0.75	0.54	0.95	-0.53	-0.74	-0.31	0.48	0.19	0.77	-0.25	-0.52	0.03
4	0.78	0.59	0.98	-0.66	-0.93	-0.39	0.46	0.20	0.72	0.06	-0.33	0.45
All Models adjusted for year, center*year, age, milliliters of alcohol per week BMI, smoking status, disease status, medication status, income status, education, physical activity. Year 15 to 25 models additionally adjusted for Year 7 discrimination score.												

Table 19. Adjusted Mean Change in Multi-System Biological Risk Index, (95% CI) by Sub-Domain Discrimination Experiences for year 7, 15, and 25, by race/ethnicity–gender group: the CARDIA study (1991–2011).

	Black Women			White Women			Black Men			White Men		
		(95%CI)			(95%CI)			(95%CI)			(95%CI)	
	Mean	LB	UB	Mean	LB	UB	Mean	LB	UB	Mean	LB	UB
Racial (7-15)												
1	1.02	0.80	1.24	-0.44	-0.68	-0.19	0.42	0.10	0.74	-0.09	-0.29	0.11
2	0.96	0.74	1.19	-0.23	-0.50	0.04	0.38	0.07	0.69	-0.07	-0.29	0.15
3	0.88	0.68	1.08	-0.37	-0.71	-0.03	0.48	0.21	0.76	-0.22	-0.52	0.07
Racial (15-25)												
1	0.65	0.45	0.85	-0.46	-0.70	-0.22	0.35	0.07	0.64	-0.12	-0.40	0.17
2	0.77	0.55	0.99	-0.33	-0.60	-0.06	0.35	0.01	0.68	-0.23	-0.56	0.11
3	0.76	0.58	0.95	-0.35	-0.65	-0.04	0.45	0.19	0.72	0.10	-0.25	0.45
Gender (7-15)												
1	0.94	0.73	1.15	-0.46	-0.72	-0.20	0.49	0.20	0.77	-0.11	-0.30	0.09
2	0.99	0.79	1.20	-0.35	-0.60	-0.10	0.43	0.14	0.73	-0.07	-0.29	0.15
3	0.87	0.66	1.08	-0.34	-0.61	-0.08	0.41	0.11	0.71	0.01	-0.30	0.32
2	0.74	0.54	0.93	-0.64	-0.84	-0.44	0.60	0.32	0.88	-0.42	-0.68	-0.15
3	0.73	0.53	0.92	-0.59	-0.81	-0.38	0.42	0.14	0.69	-0.05	-0.42	0.31
SEP (7-15)												
1	0.94	0.74	1.14	-0.40	-0.65	-0.16	0.41	0.13	0.69	-0.11	-0.30	0.09
2	0.90	0.67	1.13	-0.31	-0.58	-0.03	0.42	0.10	0.73	-0.01	-0.25	0.23
3	0.95	0.73	1.17	-0.40	-0.69	-0.10	0.54	0.25	0.83	-0.06	-0.32	0.20
SEP (15-25)												
1	0.72	0.54	0.90	-0.54	-0.74	-0.35	0.42	0.15	0.68	-0.01	-0.23	0.20
2	0.79	0.57	1.00	-0.41	-0.64	-0.19	0.39	0.07	0.71	-0.18	-0.43	0.08
3	0.85	0.61	1.09	-0.78	-1.08	-0.47	0.42	0.10	0.74	-0.03	-0.40	0.34

All Models adjusted for year, center*year, age, milliliters of alcohol per week BMI , smoking status, disease status , medication status, income status , education, physical activity . Year 15 to 25 models additionally adjusted for baseline discrimination score.

Discussion

Overall, we found no association between discrimination or changes in discrimination, and MSBR in the CARDIA cohort.

This study provides novel data on the topic of discrimination and objectively measured health risk factors, as we were able to examine discrimination and change in discrimination with MSBR. A previous CARDIA study assessed whether a change in self-reported experiences of racial/ethnic discrimination predicts changes in waist circumference and body mass index over time using a fixed-effects regression over eight years. They found that increased discrimination was associated with an increase in waist circumference and an increase in body mass index was among Black women only.[408] Another study by Kershaw et al., examined the cross-sectional relationship of lifetime and everyday discrimination with inflammation, specifically interleukin-6 and CRP. [409] They found that higher levels of discrimination measures were associated with higher IL-6 in women only, however associations were attenuated after adjustment for BMI.

The Black Women's Health Study analyzed data from n=59,000 African-American women to examine the association between everyday racism and lifetime racism and self-reported incident type 2 diabetes, after 16 years of follow up.[316] After adjustment for confounders, compared with women in the lowest quartile of

exposure, those in the highest quartiles had a 31% and 16% increased risk of diabetes due to everyday and lifetime racism.[316] Furthermore, in a mediation analysis they found that BMI accounted for half of the association between the racism measure and incident diabetes.[316] Of note, this same cohort conducted another study that found no association between perceived experiences of racism and all-cause mortality[319]. This study adds to this body of research by assessing both black and white participants, change in the exposure over time, as well as expanding domains of discrimination assessed to socioeconomic position and gender discrimination, which provides stronger inference for all domains assessed since there was very little racial discrimination reported in white participants in CARDIA.

Previous studies in CARDIA have documented that racial discrimination may influence both healthy and unhealthy behaviors in both black and white participants.[366] In this study, those who reported high levels of discrimination were more likely to report higher physical activity. It was theorized that these behaviors may serve as a coping mechanism to help buffer or reduce the stress of discrimination.[366] We also observed that black participants who reported high levels of discrimination also reported higher education and income versus those who experienced less discrimination.[366] For white participants we observed the opposite, lower education and income. Both groups reported higher alcoholic intake. Thus, it was speculated that in the same way individuals may engage in unhealthy behaviors such as smoking or excessive alcohol consumption to cope with discrimination, many individuals may also utilize resources to reduce stress and engage in healthy

behaviors, including exercise.

This study examined if there was an association between increased experiences of discrimination and MSBR, above and beyond health behaviors. Therefore, we adjusted for measured health behaviors associated with increases in MSBR over time as time varying covariates. Multi-system biological risk is a composite index representing the underlying biological relationship between chronic stress and burden of disease.[301,384,394] Previous research has demonstrated inverse associations between higher levels of allostatic load indices and cognition, sleep, physical function, socioeconomic status, disadvantaged neighborhoods, and increased risk for cardiovascular outcomes and mortality.[63,106,107,374,384,395] This analysis used this tool versus self-reported stress as an objective measure of stress; this may provide a clinically meaningful assessment of overall health where preventive measures may be taken to reduce this risk.

Of note, the use of longitudinal panel data allowed us to investigate whether changes in self-reported experiences of discrimination were associated with changes in MSBR while controlling for time varying confounders. Although models were sex and race stratified, utilizing a fixed-effects regression model potentially reduces bias further, as this approach focuses on within-person variation. This therefore provides control for both measured and unmeasured time-invariant covariates.[409]

There are also several limitations to note. The biomarker measurement of allostatic load in epidemiological studies is not uniform and appears to be based on the availability of data across studies, making them somewhat of a challenge to compare. Although a fixed effect modeling approach was used, there may still be

residual confounding by unmeasured time-varying factors. Also, although retention rates in CARDIA are high especially for a longitudinal study of this size, attrition over time could bias our results, particularly when utilizing a complete case analysis. Furthermore, the exclusion of CARDIA participants due to missing data on at least one of the biomarkers may have influenced our results. The Cronbach's alpha for the EOD index was much lower for White women and men, therefore this may have decreased the ability to detect meaningful associations in this group. Also, the instrument does not specify a time frame of the discrimination experience except "lifetime,", which requires assumptions for the analysis of change in discrimination experiences; and could also reflect evolving views of life experiences related to discrimination rather than new experiences over time. Lastly, a simple measure of biomarkers in relation to social constructs such as discrimination may not capture the complex influence as a potential stressor of different biologic systems.

In conclusion, the findings of this study demonstrate no association between discrimination, changes in the number of experiences of discrimination and MSBR. Furthermore, it does not support the hypothesis that increased self-reported experiences of discrimination are associated with increased MSBR in a cross-sectional or prospective manner. Future research with more specific assessment of discrimination time periods, and nature of the discrimination within each domain will inform this topic; as well as more granular analyses that examine the impact of discrimination on modifiable factors of health (i.e. psychosocial, lifestyle choices, and clinical).

Conclusions and Public Health Significance

Both psychosocial stress and disease can jointly work together to influenced biological vulnerability and premature mortality. However, identifying high risk individuals and preventative use of resources, social support and healthy health behaviors may be useful for reducing stress related health outcomes and may influence the course of chronic diseases.

Studies regarding stress and health, in human studies are difficult to execute; they also suffer from a variety of biases leading to inconsistent evidence. Furthermore, the complex nature of the perception of stress, makes assessment of this exposure difficult in humans. In the practical sense, allostatic load is operationalized as a metric of health risk used to express shared physiologic variance in multiple biological systems.[81,122] We utilized the MSBR index to represent pre-clinical exposure to secondary damaging effects on multiple systems. Our results suggest that, by way of immune and cardiovascular risk factors, the MSBR index strongly predicts increased cancer mortality risk, specifically amongst overweight and obese individuals in the NHANES III. We also observed a strong, positive association between MSBR, and risk for mortality in adults after an average follow up of 14 years in the JHS cohort. In conclusion, the findings of this study demonstrate no association between discrimination, changes in the number of experiences of discrimination and MSBR. Lastly, the findings of the CARDIA study demonstrate no association between discrimination, changes in the number of experiences of discrimination and MSBR. Furthermore, it does not support the hypothesis that increased self-reported experiences of discrimination are

associated with increased MSBR in a cross-sectional or prospective manner. Future research with more specific assessment of discrimination time periods, and nature of the discrimination within each domain will inform this topic; as well as more granular analyses that examine the impact of discrimination on modifiable factors of health (i.e. psychosocial, lifestyle choices, and clinical). Therefore, the use of the MSBR index, a measure of AL, may potentially be relevant for elucidating relevant pathways regarding disease risk. In particular the metric may be useful for guiding researchers towards relevant pathways by which factors may influence physiological functioning and harbor environments conducive to aggressive cancer outcomes. It may also have clinical utility, where this index may be a useful practical screening tool for high-risk individuals, highlighting early points to intervene and potentially prevent premature death, particularly amongst those at high risk amongst young age groups as well as overweight and obese individuals.

Understanding and including the social context of an individual while assessing their health may improve upon aspects of the social determinants health, which so strongly dictate health and quality of life. Therefore, the integration of social factors that may influence health-related behaviors and health status by the promotion of well-known positive lifestyle changes and the development of prevention strategies that influence relevant communities. Furthermore, innovative research strategies that examines the complexity of the social determinants of health are strongly needed.

.References

1. Schultz M. Rudolf Virchow. *Emerg Infect Dis*. 2008;14(9):1480-1481.

doi:10.3201/eid1409.086672.

2. Koo D, O 'carroll PW, Harris A, Desalvo KB. An Environmental Scan of Recent Initiatives Incorporating Social Determinants in Public Health. In: *An Environmental Scan of Recent Initiatives Incorporating Social Determinants in Public Health*. National Academy of Medicine; 2016. https://nam.edu/wp-content/uploads/2016/06/An-Environmental-Scan-of-Recent-Initiatives-Incorporating-Social-Determinants-in-Public-Health.pdf. Accessed April 13, 2017.
3. Medicine I of. *Vital Signs: Core Metrics for Health and Health Care Progress*. Washington, D.C.: National Academies Press; 2015. doi:10.17226/19402.
4. Fiscella K, Tancredi D, Franks P. Adding socioeconomic status to Framingham scoring to reduce disparities in coronary risk assessment. *Am Heart J*. 2009;157(6):988-994. doi:10.1016/j.ahj.2009.03.019.
5. Seligman HK, Bolger AF, Guzman D, Lopez A, Bibbins-Domingo K. Exhaustion Of Food Budgets At Month's End And Hospital Admissions For Hypoglycemia. *Health Aff*. 2014;33(1):116-123. doi:10.1377/hlthaff.2013.0096.
6. Varkey AB, Manwell LB, Williams ES, et al. Separate and Unequal. *Arch Intern Med*. 2009;169(3):243. doi:10.1001/archinternmed.2008.559.
7. Galea S, Tracy M, Hoggatt KJ, Dimaggio C, Karpati A. Estimated deaths attributable to social factors in the United States. *Am J Public Health*. 2011;101(8):1456-1465. doi:10.2105/AJPH.2010.300086.
8. Braveman PA, Kumanyika S, Fielding J, et al. Health disparities and health equity: the issue is justice. *Am J Public Health*. 2011;101 Suppl 1(S1):S149-55.

doi:10.2105/AJPH.2010.300062.

9. Mokdad AH, Dwyer-Lindgren L, Fitzmaurice C, et al. Trends and Patterns of Disparities in Cancer Mortality Among US Counties, 1980-2014. *JAMA*. 2017;317(4):388. doi:10.1001/jama.2016.20324.
10. Chetty R, Stepner M, Abraham S, et al. The Association Between Income and Life Expectancy in the United States, 2001-2014. *JAMA*. 2016;315(16):1750. doi:10.1001/jama.2016.4226.
11. Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, et al. Inequalities in Life Expectancy Among US Counties, 1980 to 2014. *JAMA Intern Med*. 2017;177(7):1003. doi:10.1001/jamainternmed.2017.0918.
12. Secretary's Advisory Committee on Health Promotion and Disease Prevention Objectives for 2020. Healthy People 2020: An Opportunity to Address the Societal Determinants of Health in the United States. Annual Review of Public Health. http://www.healthypeople.gov/2010/hp2020/advisory/SocietalDeterminantsHealth.htm. Published July 2010. Accessed November 18, 2016.
13. Healthy People 2020 USD of H and HS. Determinants of Health. https://www.healthypeople.gov/2020/about/foundation-health-measures/Determinants-of-Health. Published 2017. Accessed June 28, 2017.
14. World Health Organization: Geneva. Closing the gap in a generation: health equity through action on the social determinants of health. In: *Final Report of the Commission on Social Determinants of Health.* Geneva: World Health Organization; 2008.

15. Braveman P, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. *Public Health Rep*. 2014;(Suppl 2):19-31. http://www.ncbi.nlm.nih.gov/pubmed/24385661. Accessed December 21, 2016.

16. Krieger N. A glossary for social epidemiology. *J Epidemiol Community Health*. 2001;55(10):693-700. doi:10.1136/JECH.55.10.693.

17. Adler NE, Glymour MM, Fielding J. Addressing Social Determinants of Health and Health Inequalities. *JAMA*. 2016;316(16):1641. doi:10.1001/jama.2016.14058.

18. Healthy People 2020. U.S. Office of Disease Prevention and Health Promotion. *Determinants of Health*. Washington (DC); 2017. https://www.healthypeople.gov/2020/about/foundation-health-measures/Determinants-of-Health.

19. The Surgeon General. *Priorities: National Prevention Strategy- Elimination of Health Disparities*. https://www.surgeongeneral.gov/priorities/prevention/strategy/elimination-of-health-disparities.html.

20. Centers for Disease Control and Prevention. National Center for Health Statistics. *NCHHSTP Social Determinants of Health. Definitions*.; 2014.

21. Institute of Medicine (US) Committee on Cancer Control in Low- and Middle-Income Countries. *Cancer Control Opportunities in Low- and Middle-Income Countries.* (Sloan FA GH, ed.). Washington, DC: National Academies Press (US); 2007.

22. Smedley BD (Ed), Stith AY (Ed), Nelson AR (Ed). *Unequal Treatment:*

Confronting Racial and Ethnic Disparities in Health Care. National Academies Press; 2003. http://psycnet.apa.org/psycinfo/2003-02632-000. Accessed May 5, 2017.

23. Black D, Whitehead M. *Inequalities in Health : The Black Report : The Health Divide*. (Peter Townsend and Nick Davidson, ed.). Penguin; 1988.

24. Williams DR, Mohammed SA. Discrimination and racial disparities in health: evidence and needed research. *J Behav Med*. 2009;32(1):20-47. doi:10.1007/s10865-008-9185-0.

25. Williams DR, Mohammed SA. Racism and Health II: A Needed Research Agenda for Effective Interventions Reducing the Health Effects of Racism: Improving Socioeconomic Opportunities. *Am Behav Sci*. 57(8):1200-1226. doi:10.1177/0002764213487341.

26. Krieger N. Methods for the scientific study of discrimination and health: an ecosocial approach. *Am J Public Health*. 2012;102(5):936-944. doi:10.2105/AJPH.2011.300544.

27. Krieger N. Discrimination and health inequities. In: Berkman LF, Kawachi I, Glymour MM, eds. *Social Epidemiology*. ; 2014:615.

28. Miller G, Chen E, Cole SW. Health Psychology: Developing Biologically Plausible Models Linking the Social World and Physical Health. *Annu Rev Psychol*. 2009;60(1):501-524. doi:10.1146/annurev.psych.60.110707.163551.

29. Krieger N. Ecosocial Theory of Disease Distribution. In: *Epidemiology and the People's Health: Theory and Context*. Oxford Scholarship Online; 2011. doi:10.1093/acprof:oso/9780195383874.001.0001.

30. Krieger N, Whitmarsh I. The Science and Epidemiology of Racism and Health: Racial/Ethnic Categories, Biological Expressions of Racism, and the Embodiment of Inequality — an Ecosocial Perspective. In: *What's the Use of Race? : Modern Governance and the Biology of Difference*. MIT Press; 2010:303.

31. Scambler G, Scambler S. Theorizing health inequalities: The untapped potential of dialectical critical realism. *Soc Theory Heal*. 2015;13(3-4):340-354. doi:10.1057/sth.2015.14.

32. Collins C, McCrory M, Mackenzie M, McCartney G. Social theory and health inequalities: Critical realism and a transformative activist stance? *Soc Theory Heal*. 2015;13(3-4):377-396. doi:10.1057/sth.2015.13.

33. Wemrell M, Merlo J, Mulinari S, Hornborg A-C. Contemporary Epidemiology: A Review of Critical Discussions Within the Discipline and A Call for Further Dialogue with Social Theory. *Sociol Compass*. 2016;10(2):153-171. doi:10.1111/soc4.12345.

34. Ng E, Muntaner C. A Critical Approach to Macrosocial Determinants of Population Health: Engaging Scientific Realism and Incorporating Social Conflict. *Curr Epidemiol Reports*. 2014;1(1):27-37. doi:10.1007/s40471-013-0002-0.

35. Danese A, Moffitt TE, Harrington H, et al. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Arch Pediatr Adolesc Med*. 2009;163(12):1135-1143. doi:10.1001/archpediatrics.2009.214.

36. Power C, Hertzman C. Social and biological pathways linking early life and adult disease. *Br Med Bull*. 1997;53(1):210-221. http://www.ncbi.nlm.nih.gov/pubmed/9158295. Accessed April 13, 2017.

37. Hertzman C. The biological embedding of early experience and its effects on health in adulthood. *Ann N Y Acad Sci*. 1999;896:85-95. http://www.ncbi.nlm.nih.gov/pubmed/10681890. Accessed April 13, 2017.

38. Halfon N, Hochstein M, Lynch J, Hallqvist J, Power C. Life course health development: an integrated framework for developing health, policy, and research. *Milbank Q*. 2002;80(3):433-79, iii. doi:10.1111/1468-0009.00019.

39. Jary D, Jary J. *Collins Dictionary of Sociology*. Collins; 2005.

40. Marshall G, Barthel-Bouchier DL. *The Concise Oxford Dictionary of Sociology*. Oxford University Press; 1994.

41. American Psychological Association. *Stress in America: The Impact of Discrimination*.; 2016. www.stressinamerica.org. Accessed November 21, 2016.

42. Sawyer PJ, Major B, Casad BJ, Townsend SSM, Mendes WB. Discrimination and the Stress Response: Psychological and Physiological Consequences of Anticipating Prejudice in Interethnic Interactions. *Am J Public Health*. 2012;102(5):1020-1026. doi:10.2105/AJPH.2011.300620.

43. Ren XS, Amick BC, Williams DR. Racial/ethnic disparities in health: the interplay between discrimination and socioeconomic status. *Ethn Dis*. 1998;9(2):151-165. http://www.ncbi.nlm.nih.gov/pubmed/10421078. Accessed November 22, 2016.

44. Williams DR, Mohammed SA, Leavell J, Collins C. Race, socioeconomic

status, and health: complexities, ongoing challenges, and research opportunities. *Ann N Y Acad Sci*. 2010;1186:69-101. doi:10.1111/j.1749-6632.2009.05339.x.

45. ADLER NE, OSTROVE JM. Socioeconomic Status and Health: What We Know and What We Don't. *Ann N Y Acad Sci*. 1999;896(1):3-15. doi:10.1111/j.1749-6632.1999.tb08101.x.

46. WILLIAMS DR. Race, Socioeconomic Status, and Health The Added Effects of Racism and Discrimination. *Ann N Y Acad Sci*. 1999;896(1):173-188. doi:10.1111/j.1749-6632.1999.tb08114.x.

47. Loucks EB, Pilote L, Lynch JW, et al. Life course socioeconomic position is associated with inflammatory markers: The Framingham Offspring Study. *Soc Sci Med*. 2010;71(1):187-195. doi:10.1016/j.socscimed.2010.03.012.

48. Loucks EB, Lynch JW, Pilote L, et al. Life-Course Socioeconomic Position and Incidence of Coronary Heart Disease: The Framingham Offspring Study. *Am J Epidemiol*. 2009;169(7):829-836. doi:10.1093/aje/kwn403.

49. Dolezsar CM, McGrath JJ, Herzig AJM, Miller SB. Perceived racial discrimination and hypertension: A comprehensive systematic review. *Heal Psychol*. 2014;33(1):20-34. doi:10.1037/a0033718.

50. Stepanikova I, Baker EH, Simoni ZR, et al. The Role of Perceived Discrimination in Obesity Among African Americans. *Am J Prev Med*. 2017;52(1):S77-S85. doi:10.1016/j.amepre.2016.07.034.

51. Stepanikova I, Bateman LB, Oates GR. Systemic Inflammation in Midlife: Race, Socioeconomic Status, and Perceived Discrimination. *Am J Prev Med*. 2017;52(1):S63-S76. doi:10.1016/j.amepre.2016.09.026.

52. Mustillo S, Krieger N, Gunderson EP, Sidney S, McCreath H, Kiefe CI. Self-reported experiences of racial discrimination and Black-White differences in preterm and low-birthweight deliveries: the CARDIA Study. *Am J Public Health*. 2004;94(12):2125-2131. doi:10.2105/AJPH.94.12.2125.

53. Dunlay SM, Lippmann SJ, Greiner MA, et al. Perceived Discrimination and Cardiovascular Outcomes in Older African Americans: Insights From the Jackson Heart Study. *Mayo Clin Proc*. 2017;92(5):699-709. doi:10.1016/j.mayocp.2017.01.024.

54. Gee GC, Spencer MS, Chen J, Takeuchi D. A nationwide study of discrimination and chronic health conditions among Asian Americans. *Am J Public Health*. 2007;97(7):1275-1282. doi:10.2105/AJPH.2006.091827.

55. Cockerham WC, Hamby BW, Oates GR. *The Social Determinants of Chronic Disease*. Vol 52.; 2017:S5-S12. doi:10.1016/j.amepre.2016.09.010.

56. Barnes LL, de Leon CFM, Lewis TT, Bienias JL, Wilson RS, Evans DA. Perceived discrimination and mortality in a population-based study of older adults. *Am J Public Health*. 2008;98(7):1241-1247. doi:10.2105/AJPH.2007.114397.

57. Yancy CW, Wang TY, Ventura HO, et al. The Coalition to Reduce Racial and Ethnic Disparities in Cardiovascular Disease Outcomes (credo). *J Am Coll Cardiol*. 2011;57(3):245-252. doi:10.1016/j.jacc.2010.09.027.

58. Cooke CR, Nallamouthu B, Kahn JM, Birkmeyer JD, Iwashyna TJ. Race and Timeliness of Transfer for Revascularization in Patients With Acute Myocardial Infarction. *Med Care*. 2011;49(7):662-667.

doi:10.1097/MLR.0b013e31821d98b2.

59. Cavender MA, Rassi AN, Fonarow GC, et al. Relationship of Race/Ethnicity With Door-to-Balloon Time and Mortality in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction: Findings From Get With the Guidelines-Coronary Artery Disease. *Clin Cardiol*. 2013;36(12):749-756. doi:10.1002/clc.22213.

60. Popescu I, Vaughan-Sarrazin MS, Rosenthal GE. Differences in Mortality and Use of Revascularization in Black and White Patients With Acute MI Admitted to Hospitals With and Without Revascularization Services. *JAMA*. 2007;297(22):2489. doi:10.1001/jama.297.22.2489.

61. Lafata JE, Karter AJ, O'Connor PJ, et al. Medication Adherence Does Not Explain Black-White Differences in Cardiometabolic Risk Factor Control among Insured Patients with Diabetes. *J Gen Intern Med*. 2016;31(2):188-195. doi:10.1007/s11606-015-3486-0.

62. Geronimus AT, Hicken M, Keene D, Bound J. "Weathering" and Age Patterns of Allostatic Load Scores Among Blacks and Whites in the United States. *Am J Public Health*. 2006;95(5):826-833. doi:10.2105/AJPH.2004.060749.

63. Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS. Price of adaptation--allostatic load and its health consequences. MacArthur studies of successful aging. *Arch Intern Med*. 1997;157(19):2259-2268. http://www.ncbi.nlm.nih.gov/pubmed/9343003. Accessed November 18, 2016.

64. Mauss D, Jarczok MN, Fischer JE. The streamlined Allostatic Load Index: a

replication of study results. *Stress*. 2016;19(6):553-558. doi:10.1080/10253890.2016.1219718.

65. Cohen S, Kessler RC, Underwood LG. *Measuring Stress : A Guide for Health and Social Scientists*. Oxford University Press; 1997.

66. Nevid JS, Rathus SA, Greene B. *Abnormal Psychology in a Changing World*.

67. Lazarus RS, Folkman S. *Stress, Appraisal, and Coping*. Springer Pub. Co; 1984.

68. Lazarus RS, Cohen JB. Environmental Stress. In: *Human Behavior and Environment*. Boston, MA: Springer US; 1977:89-127. doi:10.1007/978-1-4684-0808-9_3.

69. Lazarus RS, S. R. Progress on a cognitive-motivational-relational theory of emotion. *Am Psychol*. 1991;46(8):819-834. doi:10.1037/0003-066X.46.8.819.

70. Cohen F, Matarazzo JD. Coping. In: *Behavioral Health : A Handbook of Health Enhancement and Disease Prevention*. Wiley; 1984:1292.

71. Vorvick LJM, Zieve, David. MD M, Ogilvie, Isla P, A.D.A.M Editorial team. Stress and your health. Medline Plus, U.S. National Library of Medicine. doi:10.1016/j.pop.2008.07.011.

72. Ahmed SM, Lemkau JP HP. Textbook of family medicine. In: Rakel RE, Rakel D, eds. 8th ed. Elsevier/Saunders; 2011:1169.

73. National Institute of Mental Health. Adult Stress— Frequently Asked Questions. https://www.nimh.nih.gov/health/publications/stress/stress_factsheet_ln_142898.pdf. Accessed November 18, 2016.

74. Bulatao RA, Anderson NB, National Research Council (U.S.). Panel on Race E. *Understanding Racial and Ethnic Differences in Health in Late Life : A Research Agenda*. National Academies Press; 2004.

75. Tsigos C, Kyrou I, Kassi E, Chrousos GP. *Stress, Endocrine Physiology and Pathophysiology*. MDText.com, Inc.; 2000. http://www.ncbi.nlm.nih.gov/pubmed/25905226. Accessed July 14, 2017.

76. Seaward B. *Managing Stress*. Jones & Bartlett; 2013.

77. Kandel ER. *Principles of Neural Science*. https://www.mhprofessional.com/9780071390118-usa-principles-of-neural-science-fifth-edition-group. Accessed April 14, 2017.

78. Everly GS, Lating JM. The Anatomy and Physiology of the Human Stress Response. In: *A Clinical Guide to the Treatment of the Human Stress Response*. New York, NY: Springer New York; 2013:17-51. doi:10.1007/978-1-4614-5538-7_2.

79. Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL. *Bradley's Neurology in Clinical Practice*. 7th ed. 9780323287838; 2015. https://www.us.elsevierhealth.com/bradleys-neurology-in-clinical-practice-2-volume-set-9780323287838.html. Accessed April 14, 2017.

80. Arslan O. *Neuroanatomical Basis of Clinical Neurology*. Parthenon Pub. Group; 2001.

81. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. *Horm Behav*. 2003;43(1):2-15. http://www.ncbi.nlm.nih.gov/pubmed/12614627. Accessed November 18, 2016.

82. ThyagaRajan S, Priyanka HP. Bidirectional communication between the neuroendocrine system and the immune system: relevance to health and diseases. *Ann Neurosci*. 2012;19(1):40-46. doi:10.5214/ans.0972.7531.180410.

83. Everly, GS, Lating JM. *A Clinical Guide to the Treatment of the Human Stress Response*. New York, NY: Springer New York; 2013. doi:10.1007/978-1-4614-5538-7.

84. Fink G. *Stress Science : Neuroendocrinology.* Elsevier Science; 2009.

85. Contrada R, Baum A. *The Handbook of Stress Science: Biology, Psychology, and Health*. New York NY: Springer Pub.; 2011. doi:10.1002/9781118083222.

86. Fink G, ed. *Stress Science : Neuroendocrinology*. Academic Press; 2010. https://books.google.com/books?hl=en&lr=&id=HJwqWQhQELMC&oi=fnd&pg=PR1&dq=stress+science+neuroendocrinology&ots=onrJ6X070_&sig=Ff0ogaFElSRVGqNZwVpFs1UjtRY#v=onepage&q=stress science neuroendocrinology&f=false. Accessed March 19, 2017.

87. Jenkins FJ, Van Houten B, Bovbjerg DH. Effects on DNA Damage and/or Repair Processes as Biological Mechanisms Linking Psychological Stress to Cancer Risk. *J Appl Biobehav Res*. 2014;19(1):3-23. doi:10.1111/jabr.12019.

88. Selye H. *Stress in Health and Disease.* Elsevier Science; 1976.

89. Kumar V, Abbas AK, Aster JC, Perkins JA. *Robbins and Cotran Pathologic Basis of Disease*.

90. McKay LI, Cidlowski JA. Physiologic and Pharmacologic Effects of Corticosteroids. In: Kufe DW, Pollock RE, Weichselbaum RR et al., ed. *Holland-Frei Cancer Medicine*. 6th ed. Hamilton: BC Decker.

91. Tawakol A, Ishai A, Takx RAP, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. 2017;389(10071):834-845. doi:10.1016/S0140-6736(16)31714-7.

92. Molina P, ed. Endocrine Integration of Energy and Electrolyte Balance. In: *Endocrine Physiology*. 4e ed. New York: McGraw-Hill; 2013. http://accessmedicine.mhmedical.com/content.aspx?sectionid=42540510&bookid=507&jumpsectionID=42541760&Resultclick=2#57308397. Accessed July 18, 2017.

93. Rimsza ME. Complications of corticosteroid therapy. *Am J Dis Child*. 1978;132(8):806-810. http://www.ncbi.nlm.nih.gov/pubmed/356588. Accessed July 14, 2017.

94. Cushman P, Jr. Glucocorticoids and the gastrointestinal tract: current status. *Gut*. 1970;11(6):534-539. http://www.ncbi.nlm.nih.gov/pubmed/4317169. Accessed July 14, 2017.

95. Fink G, Antoni FA. Chapter 9 – Vasopressin as a Stress Hormone. In: *Stress: Neuroendocrinology and Neurobiology*. ; 2017:97-108. doi:10.1016/B978-0-12-802175-0.00009-7.

96. Everly GS, Lating JM. The Concept of Stress. In: *A Clinical Guide to the Treatment of the Human Stress Response*. New York, NY: Springer New York; 2013:3-15. doi:10.1007/978-1-4614-5538-7_1.

97. Lazarus RS, S. R. Cognition and motivation in emotion. *Am Psychol*. 1991;46(4):352-367. doi:10.1037/0003-066X.46.4.352.

98. Michael W. Eysenck MTK, ed. Cognition and Emotion. In: *COGNITIVE*

PSYCHOLOGY: A STUDENT 'S HANDBOOK. Philadelphia: Taylor and Francis Inc; 2000. http://www.psypress.co.uk/ek5/resources/pdf/chap18.pdf. Accessed April 13, 2017.

99. Cullinan WE, Herman JP, Helmreich DL, Watson Jr. SJ. *A Neuroanatomy of Stress*. Lippincott Williams & Wilkins Publishers; 1995. http://psycnet.apa.org/index.cfm?fa=search.displayRecord&uid=1995-98620-001. Accessed April 14, 2017.

100. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med*. 1993;153(18):2093-2101. http://www.ncbi.nlm.nih.gov/pubmed/8379800. Accessed November 18, 2016.

101. Cohen S, Janicki-Deverts D, Doyle WJ, et al. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci U S A*. 2012;109(16):5995-5999. doi:10.1073/pnas.1118355109.

102. Lagraauw HM, Kuiper J, Bot I. Acute and chronic psychological stress as risk factors for cardiovascular disease: Insights gained from epidemiological, clinical and experimental studies. *Brain Behav Immun*. 2015;50:18-30. doi:10.1016/j.bbi.2015.08.007.

103. Everly GS, Lating JM. The Link from Stress Arousal to Disease. In: *A Clinical Guide to the Treatment of the Human Stress Response*. New York, NY: Springer New York; 2013:53-65. doi:10.1007/978-1-4614-5538-7_3.

104. Nagaraja AS, Sadaoui NC, Dorniak PL, Lutgendorf SK, Sood AK. SnapShot: Stress and Disease. *Cell Metab*. 2016;23(2):388-388.e1. doi:10.1016/j.cmet.2016.01.015.

105. Entringer S, Kumsta R, Hellhammer DH, Wadhwa PD, Wüst S. Prenatal exposure to maternal psychosocial stress and HPA axis regulation in young adults. *Horm Behav*. 2009;55(2):292-298. doi:10.1016/j.yhbeh.2008.11.006.

106. Juster R-P, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev*. 2010;35(1):2-16. doi:10.1016/j.neubiorev.2009.10.002.

107. Seeman T, Epel E, Gruenewald T, Karlamangla A, McEwen BS. Socio-economic differentials in peripheral biology: Cumulative allostatic load. *Ann N Y Acad Sci*. 2010;1186(1):223-239. doi:10.1111/j.1749-6632.2009.05341.x.

108. McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. *Dialogues Clin Neurosci*. 2006;8(4):367-381. http://www.ncbi.nlm.nih.gov/pubmed/17290796. Accessed November 18, 2016.

109. Seeman TE, McEwen BS. Impact of social environment characteristics on neuroendocrine regulation. *Psychosom Med*. 1995;58(5):459-471. doi:10.1097/00006842-199609000-00008.

110. Booth T, Starr JM, Deary I. Modeling multisystem biological risk in later life: Allostatic load in the lothian birth cohort study 1936. *Am J Hum Biol*. 2013;25(4):538-543. doi:10.1002/ajhb.22406.

111. Wiley JF, Gruenewald TL, Karlamangla AS, Seeman TE. Modeling Multisystem Physiological Dysregulation. *Psychosom Med*. 2016;78(3):290-301. doi:10.1097/PSY.0000000000000288.

112. McCaffery JM, Marsland AL, Strohacker K, et al. Factor Structure Underlying Components of Allostatic Load. Oresic M, ed. *PLoS One*.

2012;7(10):e47246. doi:10.1371/journal.pone.0047246.

113. Kaestner R, Pearson JA, Keene D, Geronimus AT. Stress, Allostatic Load and Health of Mexican Immigrants. *Soc Sci Q*. 2009;90(5):1089-1111. doi:10.1111/j.1540-6237.2009.00648.x.

114. Doamekpor LA, Dinwiddie GY. Allostatic Load in Foreign-Born and US-Born Blacks: Evidence From the 2001–2010 National Health and Nutrition Examination Survey. *Am J Public Health*. 2015;105(3):591-597. doi:10.2105/AJPH.2014.302285.

115. Duong MT, Bingham BA, Aldana PC, Chung ST, Sumner AE. Variation in the Calculation of Allostatic Load Score: 21 Examples from NHANES. *J Racial Ethn Heal Disparities*. June 2016:1-7. doi:10.1007/s40615-016-0246-8.

116. SEPLAKI C, GOLDMAN N, GLEI D, WEINSTEIN M. A comparative analysis of measurement approaches for physiological dysregulation in an older population. *Exp Gerontol*. 2005;40(5):438-449. doi:10.1016/j.exger.2005.03.002.

117. Salazar CR, Avlund K, Morse DE. Abstract W P126: Allostatic Load Predicts Stroke Mortality Risk in Older Danes: Findings From the 1914 Glostrup Aging Study. *Stroke*. 2014;45(Suppl 1).

118. Mattei J, Demissie S, Falcon LM, Ordovas JM, Tucker K. Allostatic load is associated with chronic conditions in the Boston Puerto Rican Health Study. *Soc Sci Med*. 2010;70(12):1988-1996. doi:10.1016/j.socscimed.2010.02.024.

119. Karlamangla AS, Singer BH, Seeman TE. Reduction in Allostatic Load in Older Adults Is Associated With Lower All-Cause Mortality Risk: MacArthur Studies of Successful Aging. *Psychosom Med*. 2006;68(3):500-507.

doi:10.1097/01.psy.0000221270.93985.82.

120. Levine ME, Crimmins EM. A comparison of methods for assessing mortality risk. *Am J Hum Biol*. 2014;26(6):768-776. doi:10.1002/ajhb.22595.

121. Sterling P, Eyer J. Allostasis: A New Paradigm to Explain Arousal Pathology. 1988.

122. McEwen BS, Wingfield JC. What is in a name? Integrating homeostasis, allostasis and stress. *Horm Behav*. 2010;57(2):105-111. doi:10.1016/j.yhbeh.2009.09.011.

123. McEwen B, Nasveld P, Palmer M, Anderson R. *Allostatic Load: A Review of the Literature*.; 2012. http://www.dva.gov.au/sites/default/files/files/consultation and grants/healthstudies/allostatic/allostatic.docx. Accessed December 4, 2016.

124. Berger M, Sarnyai Z. "More than skin deep": stress neurobiology and mental health consequences of racial discrimination. *Stress*. 2015;18(1):1-10. doi:10.3109/10253890.2014.989204.

125. McEWEN BS, SEEMAN T. Protective and Damaging Effects of Mediators of Stress: Elaborating and Testing the Concepts of Allostasis and Allostatic Load. *Ann N Y Acad Sci*. 1999;896(1):30-47. doi:10.1111/j.1749-6632.1999.tb08103.x.

126. Gallo LC, Fortmann AL, Mattei J. Allostatic load and the assessment of cumulative biological risk in biobehavioral medicine: challenges and opportunities. *Psychosom Med*. 2014;76(7):478-480. doi:10.1097/PSY.0000000000000095.

127. Shiels MS, Chernyavskiy P, Anderson WF, et al. Trends in premature mortality in the USA by sex, race, and ethnicity from 1999 to 2014: an analysis

of death certificate data. *Lancet*. 2017;389(10073):1043-1054. doi:10.1016/S0140-6736(17)30187-3.

128. Ma J, Ward EM, Siegel RL, Jemal A. Temporal Trends in Mortality in the United States, 1969-2013. *JAMA*. 2015;314(16):1731. doi:10.1001/jama.2015.12319.

129. Heron M. *Deaths:Leading Causes for 2014*. Vol 65. Hyattsville; 2016. https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_05.pdf. Accessed August 9, 2017.

130. National Center for Health Statistics. LCWK2. Deaths, percent of total deaths, and death rates for the 15 leading causes of death in 10-year age groups, by race and sex: United States, 2014. 2014. https://www.cdc.gov/nchs/data/dvs/lcwk2_2014.pdf. Accessed August 10, 2017.

131. Danaei G, Ding EL, Mozaffarian D, et al. The Preventable Causes of Death in the United States: Comparative Risk Assessment of Dietary, Lifestyle, and Metabolic Risk Factors. Hales S, ed. *PLoS Med*. 2009;6(4):e1000058. doi:10.1371/journal.pmed.1000058.

132. Johnson NB, Hayes LD, Brown K, Hoo EC, Ethier KA. CDC National Health Report: Leading Causes of Morbidity and Mortality and Associated Behavioral Risk and Protective Factors—United States, 2005–2013. *MMWR Surveill Summ* . 2014;63:3-27. https://www.cdc.gov/healthreport/publications/compendium.pdf. Accessed August 11, 2017.

133. Welch HG, Schwartz LM, Woloshin S. Are Increasing 5-Year Survival Rates Evidence of Success Against Cancer? *JAMA*. 2000;283(22):2975.

doi:10.1001/jama.283.22.2975.

134. DICKMAN PW, ADAMI H-O. Interpreting trends in cancer patient survival. *J Intern Med*. 2006;260(2):103-117. doi:10.1111/j.1365-2796.2006.01677.x.

135. Croswell JM, Ransohoff DF, Kramer BS. Principles of Cancer Screening: Lessons From History and Study Design Issues. *Semin Oncol*. 2010;37(3):202-215. doi:10.1053/j.seminoncol.2010.05.006.

136. Extramual Committee To Assess Measures of Progress Against Cancer. Measurement of progress against cancer. *J Natl Cancer Inst*. 1990;82(10):825-835. http://www.ncbi.nlm.nih.gov/pubmed/2332901. Accessed July 20, 2017.

137. Tomasetti C, Li L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science (80-)*. 2017;355(6331):1330-1334. doi:10.1126/science.aaf9011.

138. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell*. 2011;144(5):646-674.

139. Pavlova NN, Thompson CB. The Emerging Hallmarks of Cancer Metabolism. *Cell Metab*. 2016;23(1):27-47. doi:10.1016/j.cmet.2015.12.006.

140. Stewart TJ, Abrams SI. How tumours escape mass destruction. *Oncogene*. 2008;27(45):5894-5903. doi:10.1038/onc.2008.268.

141. Park J, Morley TS, Kim M, Clegg DJ, Scherer PE. Obesity and cancer--mechanisms underlying tumour progression and recurrence. *Nat Rev Endocrinol*. 2014;10(8):455-465. doi:10.1038/nrendo.2014.94.

142. Greenman C, Stephens P, Smith R, et al. Patterns of somatic mutation in human cancer genomes. *Nature*. 2007;446(7132):153-158.

doi:10.1038/nature05610.

143. Kan Z, Jaiswal BS, Stinson J, et al. Diverse somatic mutation patterns and pathway alterations in human cancers. *Nature*. 2010;466(7308):869-873. doi:10.1038/nature09208.

144. Kelly-Irving M, Delpierre C, Vineis P, al. et, Lin G, Henry K. Beyond bad luck: induced mutations and hallmarks of cancer. *Lancet Oncol*. 2017;18(8):999-1000. doi:10.1016/S1470-2045(17)30520-X.

145. Fitzmaurice C, Allen C, Barber RM, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015. *JAMA Oncol*. 2017;3(4):524. doi:10.1001/jamaoncol.2016.5688.

146. Heron M, Anderson RN. Changes in the Leading Cause of Death: Recent Patterns in Heart Disease and Cancer Mortality. *NCHS Data Brief*. 2016;(254):1-8. http://www.ncbi.nlm.nih.gov/pubmed/27598767. Accessed July 20, 2017.

147. Torre LA, Sauer AMG, Chen MS, Kagawa-Singer M, Jemal A, Siegel RL. Cancer statistics for Asian Americans, Native Hawaiians, and Pacific Islanders, 2016: Converging incidence in males and females. *CA Cancer J Clin*. 2016;66(3):182-202. doi:10.3322/caac.21335.

148. Siegel R, Naishadham D, Jemal A. Cancer statistics for Hispanics/Latinos, 2012. *CA Cancer J Clin*. 2012;62(5):283-298. doi:10.3322/caac.21153.

149. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin*. February 2017. doi:10.3322/caac.21395.

150. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*.

2017;67(1):7-30. doi:10.3322/caac.21387.

151. Lortet-Tieulent J, Goding Sauer A, Siegel RL, et al. State-Level Cancer Mortality Attributable to Cigarette Smoking in the United States. *JAMA Intern Med*. 2016;176(12):1792. doi:10.1001/jamainternmed.2016.6530.

152. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin*. 2018;68(1):31-54. doi:10.3322/caac.21440.

153. Di Cesare M, Bentham J, Stevens GA, et al. Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. 2016;387(10026):1377-1396. doi:10.1016/S0140-6736(16)30054-X.

154. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. *J Obes*. 2013;2013:291546. doi:10.1155/2013/291546.

155. Odegaard AO, Pereira MA, Koh W-P, et al. BMI, All-Cause and Cause-Specific Mortality in Chinese Singaporean Men and Women: The Singapore Chinese Health Study. Vitzthum VJ, ed. *PLoS One*. 2010;5(11):e14000. doi:10.1371/journal.pone.0014000.

156. Freisling H, Arnold M, Soerjomataram I, et al. Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: meta-analysis of individual participant data of seven prospective cohorts in Europe. *Br J Cancer*. 2017;116(11):1486-1497. doi:10.1038/bjc.2017.106.

157. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. *N*

Engl J Med. 2003;348(17):1625-1638. doi:10.1056/NEJMoa021423.

158. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*. 2007;335(7630):1134. doi:10.1136/bmj.39367.495995.AE.

159. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373(9669):1083-1096. doi:10.1016/S0140-6736(09)60318-4.

160. Lennon H, Sperrin M, Badrick E, Renehan AG. The Obesity Paradox in Cancer: a Review. *Curr Oncol Rep*. 2016;18(9):56. doi:10.1007/s11912-016-0539-4.

161. Arnold M, Leitzmann M, Freisling H, et al. Obesity and cancer: An update of the global impact. *Cancer Epidemiol*. 2016;41:8-15. doi:10.1016/j.canep.2016.01.003.

162. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Heal*. 2016;4(9):e609-e616. doi:10.1016/S2214-109X(16)30143-7.

163. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Biological Agents, No.100B. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Lyon: International Agency for Research on Cancer; 2012.

164. Oh J-K, Weiderpass E, Xu LL, Zhang YN, Qiang HQ, Tommasino M. Infection and cancer: global distribution and burden of diseases. *Ann Glob Heal*. 2011;80(5):384-392. doi:10.1016/j.aogh.2014.09.013.

165. Baan R, Straif K, Grosse Y, et al. Carcinogenicity of alcoholic beverages. *Lancet Oncol*. 2007;8(4):292-293. doi:10.1016/S1470-2045(07)70099-2.

166. National Toxicology Program. *14th Report on Carcinogens: Alcoholic Beverage Consumption*. http://ntp.niehs.nih.gov/go/roc. Accessed July 27, 2017.

167. Nelson DE, Jarman DW, Rehm J, et al. Alcohol-attributable cancer deaths and years of potential life lost in the United States. *Am J Public Health*. 2013;103(4):641-648. doi:10.2105/AJPH.2012.301199.

168. Warburton DER, Nicol CW, Bredin SSD. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174(6):801-809. doi:10.1503/cmaj.051351.

169. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body Fatness and Cancer — Viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375(8):794-798. doi:10.1056/NEJMsr1606602.

170. Arem H, Moore SC, Park Y, et al. Physical activity and cancer-specific mortality in the NIH-AARP Diet and Health Study cohort. *Int J cancer*. 2014;135(2):423-431. doi:10.1002/ijc.28659.

171. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst*. 1981;66(6):1191-1308. http://www.ncbi.nlm.nih.gov/pubmed/7017215. Accessed August 1, 2017.

172. Anand P, Kunnumakkara AB, Kunnumakara AB, et al. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res*. 2008;25(9):2097-2116. doi:10.1007/s11095-008-9661-9.

173. Bouvard V, Loomis D, Guyton KZ, et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol*. 2015;16(16):1599-1600.

doi:10.1016/S1470-2045(15)00444-1.

174. Willett WC. Diet and cancer. *Oncologist*. 2000;5(5):393-404. doi:10.1634/THEONCOLOGIST.5-5-393.

175. World Health Organization. *Environmental and Occupational Cancers*. World Health Organization; 2011. http://www.who.int/mediacentre/factsheets/fs350/en/. Accessed August 1, 2017.

176. Takala J. Eliminating occupational cancer. *Ind Health*. 2015;53(4):307-309. doi:10.2486/indhealth.53-307.

177. Centers for Disease Control and Prevention. *U.S. Cancer Incidence Statistics: An Interactive Atlas.* https://nccd.cdc.gov/DCPC_INCA/. Accessed August 1, 2017.

178. National Institute for Occupational Safety and Health Division of Surveillance, Hazard Evaluations and FS. NIOSH Workplace Safety and Health Topic. Centers for Disease Control and Prevention. Cancer Policy. https://www.cdc.gov/niosh/topics/cancer/. Published 2015. Accessed August 1, 2017.

179. Walter RB, Brasky TM, Buckley SA, Potter JD, White E. Height as an Explanatory Factor for Sex Differences in Human Cancer. *JNCI J Natl Cancer Inst*. 2013;105(12):860-868. doi:10.1093/jnci/djt102.

180. Ryerson AB, Eheman CR, Altekruse SF, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer*. 2016;122(9):1312-1337. doi:10.1002/cncr.29936.

181. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific

cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015;112(3):580-593. doi:10.1038/bjc.2014.579.

182. Joosse A, Collette S, Suciu S, et al. Sex Is an Independent Prognostic Indicator for Survival and Relapse/Progression-Free Survival in Metastasized Stage III to IV Melanoma: A Pooled Analysis of Five European Organisation for Research and Treatment of Cancer Randomized Controlled Trials. *J Clin Oncol*. 2013;31(18):2337-2346. doi:10.1200/JCO.2012.44.5031.

183. Bach PB, Schrag D, Brawley OW, Galaznik A, Yakren S, Begg CB. Survival of Blacks and Whites After a Cancer Diagnosis. *JAMA*. 2002;287(16):2106. doi:10.1001/jama.287.16.2106.

184. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J Clin*. 54(2):78-93. http://www.ncbi.nlm.nih.gov/pubmed/15061598. Accessed August 1, 2017.

185. Barnett J VM. *Health Insurance Coverage in the United States: 2015*. Washington D.C.; 2016.

186. Jameson J, ed. *Harrison's Endocrinology*. 2nd ed. New York, NY: McGraw-Hill; 2010.

187. Murphy K, Weaver C. *Janeway's Immunobiology*. Garland Science; 2016. https://books.google.com/books?id=GmPLCwAAQBAJ&lr=&source=gbs_navlinks_s. Accessed August 18, 2017.

188. Barrett KE, Barman SM, Boitano S RJ, ed. Blood as a Circulatory Fluid & the Dynamics of Blood & Lymph Flow. In: *Ganong's Medical Physiology Examination & Board Review* . New York: McGraw-Hill.

https://vpn.nacs.uci.edu/+CSCO+00756767633A2F2F6E70707266667A727176707661722E7A757A727176706E792E70627A++/content.aspx?bookid=2139&sectionid=160313914#1142556305. Accessed September 5, 2017.

189. Bellinger DL, Lorton D. Autonomic regulation of cellular immune function. *Auton Neurosci*. 2014;182:15-41. doi:10.1016/j.autneu.2014.01.006.

190. Ader R. *Psychoneuroimmunology*. Elsevier/Academic Press; 2007. https://books.google.com/books?id=9gYIHhaHDWsC&dq=Ader,+Felten,+%26+Cohen,+2001&source=gbs_navlinks_s. Accessed September 6, 2017.

191. Felten SY, Felten DL. Neural-immune interactions. *Prog Brain Res*. 1994;100:157-162. http://www.ncbi.nlm.nih.gov/pubmed/7938514. Accessed September 6, 2017.

192. Sanders VM, Baker RA, Ramer-Quinn DS, Kasprowicz DJ, Fuchs BA, Street NE. Differential expression of the beta2-adrenergic receptor by Th1 and Th2 clones: implications for cytokine production and B cell help. *J Immunol*. 1997;158(9):4200-4210. http://www.ncbi.nlm.nih.gov/pubmed/9126981. Accessed September 6, 2017.

193. Fan X, Wang Y. β2 Adrenergic receptor on T lymphocytes and its clinical implications. *Prog Nat Sci*. 2009;19(1):17-23. doi:10.1016/j.pnsc.2008.10.001.

194. Sanders VM. The beta2-adrenergic receptor on T and B lymphocytes: do we understand it yet? *Brain Behav Immun*. 2012;26(2):195-200. doi:10.1016/j.bbi.2011.08.001.

195. Segerstrom SC, Miller GE. Psychological Stress and the Human Immune System: A Meta-Analytic Study of 30 Years of Inquiry. *Psychol Bull*.

2004;130(4):601-630. doi:10.1037/0033-2909.130.4.601.

196. ANSTEAD MI, HUNT TA, CARLSON SL, BURKI NK. Variability of Peripheral Blood Lymphocyte Beta-2-Adrenergic Receptor Density in Humans. *Am J Respir Crit Care Med*. 1998;157(3):990-992. doi:10.1164/ajrccm.157.3.9704071.

197. Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. *Brain Behav Immun*. 2013;30:S41-S47. doi:10.1016/j.bbi.2012.06.015.

198. Tomozawa Y, Yabuuchi K, Inoue T, Satoh M. Participation of cAMP and cAMP-dependent protein kinase in β-adrenoceptor-mediated interleukin-1β mRNA induction in cultured microglia. *Neurosci Res*. 1995;22(4):399-409. doi:10.1016/0168-0102(95)00922-G.

199. Tan KS, Nackley AG, Satterfield K, Maixner W, Diatchenko L, Flood PM. β2 adrenergic receptor activation stimulates pro-inflammatory cytokine production in macrophages via PKA- and NF-κB-independent mechanisms. *Cell Signal*. 2007;19(2):251-260. doi:10.1016/j.cellsig.2006.06.007.

200. Cole SW, Nagaraja AS, Lutgendorf SK, Green PA, Sood AK. Sympathetic nervous system regulation of the tumour microenvironment. *Nat Rev Cancer*. 2015;15(9):563-572. doi:10.1038/nrc3978.

201. Méndez-Ferrer S, Lucas D, Battista M, Frenette PS. Haematopoietic stem cell release is regulated by circadian oscillations. *Nature*. 2008;452(7186):442-447. doi:10.1038/nature06685.

202. Heidt T, Sager HB, Courties G, et al. Chronic variable stress activates hematopoietic stem cells. *Nat Med*. 2014;20(7):754-758. doi:10.1038/nm.3589.

203. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol*. 2017;17(4):233-247. doi:10.1038/nri.2017.1.

204. Sorrells SF, Sapolsky RM. An inflammatory review of glucocorticoid actions in the CNS. *Brain Behav Immun*. 2007;21(3):259-272. doi:10.1016/j.bbi.2006.11.006.

205. Wiegers GJ, Reul JM. Induction of cytokine receptors by glucocorticoids: functional and pathological significance. *Trends Pharmacol Sci*. 1998;19(8):317-321. http://www.ncbi.nlm.nih.gov/pubmed/9745359. Accessed August 17, 2017.

206. Busillo JM, Cidlowski JA. The five Rs of glucocorticoid action during inflammation: ready, reinforce, repress, resolve, and restore. *Trends Endocrinol Metab*. 2013;24(3):109-119. doi:10.1016/j.tem.2012.11.005.

207. van de Garde MDB, Martinez FO, Melgert BN, Hylkema MN, Jonkers RE, Hamann J. Chronic Exposure to Glucocorticoids Shapes Gene Expression and Modulates Innate and Adaptive Activation Pathways in Macrophages with Distinct Changes in Leukocyte Attraction. *J Immunol*. 2014;192(3):1196-1208. doi:10.4049/jimmunol.1302138.

208. Dhabhar FS, Malarkey WB, Neri E, McEwen BS. Stress-induced redistribution of immune cells—From barracks to boulevards to battlefields: A tale of three hormones – Curt Richter Award Winner. *Psychoneuroendocrinology*. 2012;37(9):1345-1368. doi:10.1016/j.psyneuen.2012.05.008.

209. Scheiermann C, Kunisaki Y, Frenette PS. Circadian control of the immune system. *Nat Rev Immunol*. 2013;13(3):190-198. doi:10.1038/nri3386.

210. Carroll TB, Aron DC, Findling JW, Tyrrell B. Glucocorticoids and Adrenal Androgens. In: David G. Gardner DS, ed. *Greenspan's Basic & Clinical Endocrinology*. 9th ed. New York: McGraw-Hill; 2011. http://accessbiomedicalscience.mhmedical.com/content.aspx?bookid=380&sectionid=39744049. Accessed September 6, 2017.

211. Lim H-Y, Müller N, Herold MJ, van den Brandt J, Reichardt HM. Glucocorticoids exert opposing effects on macrophage function dependent on their concentration. *Immunology*. 2007;122(1):47-53. doi:10.1111/j.1365-2567.2007.02611.x.

212. Frank MG, Miguel ZD, Watkins LR, Maier SF. Prior exposure to glucocorticoids sensitizes the neuroinflammatory and peripheral inflammatory responses to E. coli lipopolysaccharide. *Brain Behav Immun*. 2010;24(1):19-30. doi:10.1016/j.bbi.2009.07.008.

213. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain Behav Immun*. 2007;21(7):901-912. doi:10.1016/j.bbi.2007.03.011.

214. Bielas H, Jud A, Lips U, Reichenbach J, Landolt MAA. Increased number of activated T cells in lymphocyte subsets of maltreated children: Data from a pilot study. *J Psychosom Res*. 2012;73(4):313-318. doi:10.1016/j.jpsychores.2012.08.003.

215. Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between Plasma IL-6 Response to Acute Stress and Early-Life Adversity in Healthy Adults. *Neuropsychopharmacology*. 2010;35(13):2617-

2623. doi:10.1038/npp.2010.159.

216. Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB. Cumulative childhood stress and autoimmune diseases in adults. *Psychosom Med*. 2009;71(2):243-250. doi:10.1097/PSY.0b013e3181907888.

217. Takkouche B, Regueira C, Gestal-Otero JJ. A cohort study of stress and the common cold. *Epidemiology*. 2001;12(3):345-349. http://www.ncbi.nlm.nih.gov/pubmed/11338315. Accessed September 6, 2017.

218. Mohrman DE, Heller LJ. Overview of the Cardiovascular System. In: Mohrman DE HL, ed. *Cardiovascular Physiology* . 8th ed. New York: McGraw-Hill Medical; 2014. http://accessmedicine.mhmedical.com/content.aspx?bookid=843&sectionid=48779649. Accessed September 6, 2017.

219. Mohrman DE, Heller LJ. Cardiovascular Function in Pathological Situations. In: Mohrman DE HL, ed. *Cardiovascular Physiology*. 8th ed. New York: McGraw-Hill Medical; 2014. http://accessmedicine.mhmedical.com/content.aspx?bookid=843&sectionid=48779659. Accessed September 6, 2017.

220. Kibble JD, Halsey CR. Cardiovascular Physiology. In: Kibble JD HC, ed. *Medical Physiology: The Big Picture* . New York: McGraw-Hill Medical; 2014. http://accessmedicine.mhmedical.com/content.aspx?sectionid=75576461&bookid=1291&Resultclick=2#1106601952. Accessed September 6, 2017.

221. Barrett KE. Cardiovascular Regulatory Mechanisms. In: Barrett KE, Barman SM, Boitano S RJ, ed. *Ganong's Medical Physiology Examination & Board*

Review . New York: McGraw-Hill Medical. http://accessmedicine.mhmedical.com/content.aspx?bookid=2139&sectionid=160314139#1142556528. Accessed September 6, 2017.

222. Kotchen TA. Hypertensive Vascular Disease. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J LJ, ed. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill Medical; 2014. http://accessmedicine.mhmedical.com/content.aspx?sectionid=79743947&bookid=1130&jumpsectionID=98723486&Resultclick=2#1120806836. Accessed September 6, 2017.

223. Muñoz-Durango N, Fuentes C, Castillo A, et al. Role of the Renin-Angiotensin-Aldosterone System beyond Blood Pressure Regulation: Molecular and Cellular Mechanisms Involved in End-Organ Damage during Arterial Hypertension. *Int J Mol Sci*. 2016;17(7):797. doi:10.3390/ijms17070797.

224. Steptoe A, Kivimäki M. Stress and cardiovascular disease. *Nat Rev Cardiol*. 2012;9(6):360-370. doi:10.1038/nrcardio.2012.45.

225. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet*. 2007;370(9592). doi:10.1016/S0140-6736(07)61305-1.

226. Grippo AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. *Stress*. 2009;12(1):1-21. doi:10.1080/10253890802046281.

227. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Edema of cardiac origin. Studies of body water and sodium, renal function,

hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. *Circulation*. 1989;80(2):299-305. http://www.ncbi.nlm.nih.gov/pubmed/2752558. Accessed August 24, 2017.

228. Grassi G. Sympathetic Neural Activity in Hypertension and Related Diseases. *Am J Hypertens*. 2010;23(10):1052-1060. doi:10.1038/ajh.2010.154.

229. Chatterjee K. *Cardiology : An Illustrated Textbook*. Jaypee Brothers Medical Publisher; 2013. https://books.google.com/books/about/Cardiology.html?id=7DhFdgp3rfkC. Accessed August 24, 2017.

230. Lakdawala N, Stevenson L, Loscalzo J. Cardiomyopathy and Myocarditis. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J LJ, ed. *Harrison's Principles of Internal Medicine*. 19th ed. New York: McGraw-Hill ; 2014. http://accessmedicine.mhmedical.com/content.aspx?sectionid=79743046&bookid=1130&jumpsectionID=98722686&Resultclick=2#1120805864. Accessed August 24, 2017.

231. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The Sympathetic Nervous System in Heart Failure. *J Am Coll Cardiol*. 2009;54(19):1747-1762. doi:10.1016/j.jacc.2009.05.015.

232. Olivetti G, Abbi R, Quaini F, et al. Apoptosis in the Failing Human Heart. *N Engl J Med*. 1997;336(16):1131-1141. doi:10.1056/NEJM199704173361603.

233. Steptoe A, Kivimäki M. Stress and Cardiovascular Disease: An Update on Current Knowledge. *Annu Rev Public Health*. 2013;34(1):337-354. doi:10.1146/annurev-publhealth-031912-114452.

234. Rosengren A, Hawken S, Ôunpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):953-962. doi:10.1016/S0140-6736(04)17019-0.

235. Bosma H, Peter R, Siegrist J, Marmot M. Two alternative job stress models and the risk of coronary heart disease. *Am J Public Health*. 1998;88(1):68-74. http://www.ncbi.nlm.nih.gov/pubmed/9584036. Accessed August 23, 2017.

236. Arnold S V., Smolderen KG, Buchanan DM, Li Y, Spertus JA. Perceived Stress in Myocardial Infarction. *J Am Coll Cardiol*. 2012;60(18):1756-1763. doi:10.1016/j.jacc.2012.06.044.

237. Fransson L, Franzén S, Rosengren V, Wolbert P, Sjöholm Å, Ortsäter H. β-Cell adaptation in a mouse model of glucocorticoid-induced metabolic syndrome. *J Endocrinol*. 2013;219(3):231-241. doi:10.1530/JOE-13-0189.

238. Karatsoreos IN, Bhagat SM, Bowles NP, Weil ZM, Pfaff DW, McEwen BS. Endocrine and Physiological Changes in Response to Chronic Corticosterone: A Potential Model of the Metabolic Syndrome in Mouse. *Endocrinology*. 2010;151(5):2117-2127. doi:10.1210/en.2009-1436.

239. McKay LI, Cidlowski JA, McKay L, Cidlowski J, McKay LI, Cidlowski JA. Physiologic and Pharmacologic Effects of Corticosteroids. In: Kufe DW, Pollock RE, Weichselbaum RR et al., ed. *Holland-Frei Cancer Medicine*. 6th ed. Hamilton: BC Decker; 2003. https://scholar.google.com/scholar_lookup?oi=gsb80&title=Physiologic and Pharmacologic Effects of Corticosteroids&publisher=BC

Decker&year=2003&author=Lorraine I. McKay&author=John A. Cidlowski&lookup=0&hl=en. Accessed August 24, 2017.

240. KAPLAN SA, SHIMIZU CSN. Effects of Cortisol on Amino Acids in Skeletal Muscle and Plasma. *Endocrinology*. 1963;72(2):267-272. doi:10.1210/endo-72-2-267.

241. Lecocq FR, Mebane D, Madison LL. The Acute Effect of Hydrocortisone on Hepatic Glucose Output and Peripheral Glucose Utilization*. *J Clin Invest*. 1964;43(2):237-246. doi:10.1172/JCI104908.

242. Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism. *Endocrinol Metab Clin North Am*. 2014;43(1):75-102. doi:10.1016/j.ecl.2013.10.005.

243. Macfarlane DP, Forbes S, Walker BR. Glucocorticoids and fatty acid metabolism in humans: fuelling fat redistribution in the metabolic syndrome. *J Endocrinol*. 2008;197(2):189-204. doi:10.1677/JOE-08-0054.

244. Choi HK, Seeger JD. Glucocorticoid use and serum lipid levels in US adults: The third national health and nutrition examination survey. *Arthritis Rheum*. 2005;53(4):528-535. doi:10.1002/art.21329.

245. Filipsson H, Monson JP, Koltowska-Häggström M, Mattsson A, Johannsson G. The Impact of Glucocorticoid Replacement Regimens on Metabolic Outcome and Comorbidity in Hypopituitary Patients. *J Clin Endocrinol Metab*. 2006;91(10):3954-3961. doi:10.1210/jc.2006-0524.

246. Adam TC, Hasson RE, Ventura EE, et al. Cortisol is negatively associated with insulin sensitivity in overweight Latino youth. *J Clin Endocrinol Metab*.

2010;95(10):4729-4735. doi:10.1210/jc.2010-0322.

247. Miller LK, Kral JG, Strain GW, Zumoff B. Differential binding of dexamethasone to ammonium sulfate precipitates of human adipose tissue cytosols. *Steroids*. 1987;49(6):507-522. http://www.ncbi.nlm.nih.gov/pubmed/3453560. Accessed August 24, 2017.

248. Morimoto C, Kameda K, Tsujita T, Okuda H. Relationships between lipolysis induced by various lipolytic agents and hormone-sensitive lipase in rat fat cells. *J Lipid Res*. 2001;42(1):120-127. http://www.ncbi.nlm.nih.gov/pubmed/11160373. Accessed September 6, 2017.

249. Nakamura J. Protein kinase C attenuates β-adrenergic receptor-mediated lipolysis, probably through inhibition of the β1-adrenergic receptor system. *Arch Biochem Biophys*. 2006;447(1):1-10. doi:10.1016/j.abb.2006.01.011.

250. Keller P, Keller C, Robinson LE, Pedersen BK. Epinephrine infusion increases adipose interleukin-6 gene expression and systemic levels in humans. *J Appl Physiol*. 2004;97(4):1309-1312. doi:10.1152/japplphysiol.00284.2004.

251. Guilherme A, Pedersen DJ, Henchey E, et al. Adipocyte lipid synthesis coupled to neuronal control of thermogenic programming. *Mol Metab*. 2017;6(8):781. doi:10.1016/j.molmet.2017.05.012.

252. Nguyen NLT, Barr CL, Ryu V, Cao Q, Xue B, Bartness TJ. Separate and shared sympathetic outflow to white and brown fat coordinately regulates thermoregulation and beige adipocyte recruitment. *Am J Physiol - Regul Integr Comp Physiol*. 2017;312(1). http://ajpregu.physiology.org/content/312/1/R132.long. Accessed September 6,

2017.

253. Hackett RA, Steptoe A. Type 2 diabetes mellitus and psychological stress — a modifiable risk factor. *Nat Rev Endocrinol*. 2017;13(9):547-560. doi:10.1038/nrendo.2017.64.

254. Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. *BMJ*. 2006;332(7540):521-525. doi:10.1136/bmj.38693.435301.80.

255. Ortiz MS, Myers HF, Dunkel Schetter C, Rodriguez CJ, Seeman TE, Lahey B. Psychosocial Predictors of Metabolic Syndrome among Latino Groups in the Multi-Ethnic Study of Atherosclerosis (MESA). Oresic M, ed. *PLoS One*. 2015;10(4):e0124517. doi:10.1371/journal.pone.0124517.

256. Hackett RA, Kivimäki M, Kumari M, Steptoe A. Diurnal Cortisol Patterns, Future Diabetes, and Impaired Glucose Metabolism in the Whitehall II Cohort Study. *J Clin Endocrinol Metab*. 2016;101(2):619-625. doi:10.1210/jc.2015-2853.

257. Novak M, Björck L, Giang KW, Heden-Ståhl C, Wilhelmsen L, Rosengren A. Perceived stress and incidence of Type 2 diabetes: a 35-year follow-up study of middle-aged Swedish men. *Diabet Med*. 2013;30(1):e8-e16. doi:10.1111/dme.12037.

258. Pyykkönen A-J, Räikkönen K, Tuomi T, Eriksson JG, Groop L, Isomaa B. Stressful life events and the metabolic syndrome: the prevalence, prediction and prevention of diabetes (PPP)-Botnia Study. *Diabetes Care*. 2010;33(2):378-384. doi:10.2337/dc09-1027.

259. Park M, Katon WJ, Wolf FM. Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. *Gen Hosp Psychiatry*. 2013;35(3):217-225. doi:10.1016/j.genhosppsych.2013.01.006.

260. van Dooren FEP, Nefs G, Schram MT, Verhey FRJ, Denollet J, Pouwer F. Depression and Risk of Mortality in People with Diabetes Mellitus: A Systematic Review and Meta-Analysis. Berthold HK, ed. *PLoS One*. 2013;8(3):e57058. doi:10.1371/journal.pone.0057058.

261. Hofmann M, Köhler B, Leichsenring F, Kruse J. Depression as a risk factor for mortality in individuals with diabetes: a meta-analysis of prospective studies. *PLoS One*. 2013;8(11):e79809. doi:10.1371/journal.pone.0079809.

262. Hanahan D, Weinberg RAA, Pan KH, et al. *Hallmarks of Cancer: The next Generation*. Vol 144. Arnold Constable, London, UK; 2011:646-674. doi:10.1016/j.cell.2011.02.013.

263. Steeg PS. Tumor metastasis: mechanistic insights and clinical challenges. *Nat Med*. 2006;12(8):895-904. doi:10.1038/nm1469.

264. Eng JW-L, Kokolus KM, Reed CB, Hylander BL, Ma WW, Repasky EA. A nervous tumor microenvironment: the impact of adrenergic stress on cancer cells, immunosuppression, and immunotherapeutic response. *Cancer Immunol Immunother*. 2014;63(11):1115-1128. doi:10.1007/s00262-014-1617-9.

265. Sloan EK, Priceman SJ, Cox BF, et al. The Sympathetic Nervous System Induces a Metastatic Switch in Primary Breast Cancer. *Microenviron Immunol*. 2010;70(18). doi:10.1158/0008-5472.CAN-10-0522.

266. Madden KS, Szpunar MJ, Brown EB. β-Adrenergic receptors (β-AR) regulate

VEGF and IL-6 production by divergent pathways in high β-AR-expressing breast cancer cell lines. *Breast Cancer Res Treat*. 2011;130(3):747-758. doi:10.1007/s10549-011-1348-y.

267. Hassan S, Karpova Y, Baiz D, et al. Behavioral stress accelerates prostate cancer development in mice. *J Clin Invest*. 2013;123(2):874-886. doi:10.1172/JCI63324.

268. Partecke LI, Speerforck S, Käding A, et al. Chronic stress increases experimental pancreatic cancer growth, reduces survival and can be antagonised by beta-adrenergic receptor blockade. *Pancreatology*. 2016;16(3):423-433. doi:10.1016/j.pan.2016.03.005.

269. Nagaraja AS, Dorniak PL, Sadaoui NC, et al. Sustained adrenergic signaling leads to increased metastasis in ovarian cancer via increased PGE2 synthesis. *Oncogene*. 2016;35(18):2390-2397. doi:10.1038/onc.2015.302.

270. Veneris JT, Darcy KM, Mhawech-Fauceglia P, et al. High glucocorticoid receptor expression predicts short progression-free survival in ovarian cancer. *Gynecol Oncol*. 2017;146(1):153-160. doi:10.1016/j.ygyno.2017.04.012.

271. Hara MRM, Kovacs JJJ, Whalen EJE, et al. A stress response pathway regulates DNA damage through β2-adrenoreceptors and β-arrestin-1. *Nature*. 2011;477(7364):349-353. doi:10.1038/nature10368.

272. Feng Z, Liu L, Zhang C, et al. Chronic restraint stress attenuates p53 function and promotes tumorigenesis.tle. *Proc Natl Acad Sci*. 2012;109(18). doi:10.1073/pnas.1203930109.

273. Sorrentino G, Ruggeri N, Zannini A, et al. Glucocorticoid receptor signalling

activates YAP in breast cancer. *Nat Commun*. 2017;8:14073. doi:10.1038/ncomms14073.

274. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Clin Pract Oncol*. 2008;5(8):466-475. doi:10.1038/ncponc1134.

275. Lin Y, Wang C, Zhong Y, et al. Striking life events associated with primary breast cancer susceptibility in women: a meta-analysis study. *J Exp Clin Cancer Res*. 2013;32(1):53. doi:10.1186/1756-9966-32-53.

276. Batty GD, Russ TC, Stamatakis E, Kivimäki M. Psychological distress in relation to site specific cancer mortality: pooling of unpublished data from 16 prospective cohort studies. *BMJ*. 2017;356. http://www.bmj.com/content/356/bmj.j108/peer-review. Accessed September 3, 2017.

277. Hamer M, Chida Y, Molloy GJ. Psychological distress and cancer mortality. *J Psychosom Res*. 2009;66(3):255-258. doi:10.1016/j.jpsychores.2008.11.002.

278. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimäki M, Batty GD. Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *BMJ*. 2012;345. http://www.bmj.com/content/345/bmj.e4933. Accessed September 3, 2017.

279. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc Natl Acad Sci U S A*. 2001;98(8):4770-4775. doi:10.1073/pnas.081072698.

280. Chen X, Redline S, Shields AE, Williams DR, Williams MA. Associations of

allostatic load with sleep apnea, insomnia, short sleep duration, and other sleep disturbances: findings from the National Health and Nutrition Examination Survey 2005 to 2008. *Ann Epidemiol*. 2014;24(8):612-619. https://www.sciencedirect.com/science/article/pii/S1047279714001951. Accessed September 5, 2017.

281. Ahrens KA, Rossen LM, Simon AE. Relationship Between Mean Leucocyte Telomere Length and Measures of Allostatic Load in US Reproductive-Aged Women, NHANES 1999-2002. *Paediatr Perinat Epidemiol*. 2016;30(4):325-335. doi:10.1111/ppe.12277.

282. Robertson T, Beveridge G, Bromley C. Allostatic load as a predictor of all-cause and cause-specific mortality in the general population: Evidence from the Scottish Health Survey. Abe T, ed. *PLoS One*. 2017;12(8):e0183297. doi:10.1371/journal.pone.0183297.

283. Duru OK, Harawa NT, Kermah D, Norris KC. Allostatic load burden and racial disparities in mortality. *J Natl Med Assoc*. 2012;104(1-2):89-95. http://www.ncbi.nlm.nih.gov/pubmed/22708252. Accessed September 4, 2017.

284. Beydoun MA, Beydoun HA, Mode N, et al. Racial disparities in adult all-cause and cause-specific mortality among us adults: mediating and moderating factors. *BMC Public Health*. 2016;16(1):1113. doi:10.1186/s12889-016-3744-z.

285. Molix L. Sex differences in cardiovascular health: does sexism influence women's health? *Am J Med Sci*. 2014;348(2):153-155. doi:10.1097/MAJ.0000000000000300.

286. Krieger N. Racial and gender discrimination: risk factors for high blood

pressure? *Soc Sci Med*. 1990;30(12):1273-1281. http://www.ncbi.nlm.nih.gov/pubmed/2367873. Accessed November 18, 2016.

287. Institute of Medicine (US) Committee on Lesbian, Gay, Bisexual and THI and RG and O. *The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding*. National Academies Press (US); 2011. https://www.ncbi.nlm.nih.gov/books/NBK64809/?report=reader. Accessed September 7, 2017.

288. Hatzenbuehler ML, Pachankis JE. Stigma and Minority Stress as Social Determinants of Health Among Lesbian, Gay, Bisexual, and Transgender Youth. *Pediatr Clin North Am*. 2016;63(6):985-997. doi:10.1016/j.pcl.2016.07.003.

289. Foynes MM, Shipherd JC, Harrington EF. Race and gender discrimination in the Marines. *Cult Divers Ethn Minor Psychol*. 2013;19(1):111-119. doi:10.1037/a0030567.

290. Borrell C, Artazcoz L, Gil-González D, Pérez G, Rohlfs I, Pérez K. Perceived Sexism as a Health Determinant in Spain. *J Women's Heal*. 2010;19(4):741-750. doi:10.1089/jwh.2009.1594.

291. Streed CG, McCarthy EP, Haas JS. Association Between Gender Minority Status and Self-Reported Physical and Mental Health in the United States. *JAMA Intern Med*. 2017;177(8):1210. doi:10.1001/jamainternmed.2017.1460.

292. Ro A, Choi K-H. Effects of gender discrimination and reported stress on drug use among racially/ethnically diverse women in Northern California. *Womens Health Issues*. 2010;20(3):211-218. doi:10.1016/j.whi.2010.02.002.

293. Zucker AN, Landry LJ. Embodied Discrimination: The Relation of Sexism

and Distress to Women's Drinking and Smoking Behaviors. *Sex Roles*. 2007;56(3-4):193-203. doi:10.1007/s11199-006-9163-3.

294. Klonoff EA, Landrine H, Campbell R. Sexist Discrimination may account for well-known gender differences in psychiatric symptoms. *Psychol Women Q Russo Green*. 2000;2450(35):93-99. https://pswccp06.hs.uci.edu:9091/servlet/com.trend.iwss.user.servlet.sendfile?downloadfile=IRES-1928242270-C2BB2BC0-7034-7005-285. Accessed September 7, 2017.

295. Moradi B, Subich LM. A Concomitant Examination of the Relations of Perceived Racist and Sexist Events to Psychological Distress for African American Women. *Couns Psychol*. 2003;31(4):451-469. doi:10.1177/0011000003031004007.

296. Patel V, Kirkwood BR, Pednekar S, et al. Gender Disadvantage and Reproductive Health Risk Factors for Common Mental Disorders in Women. *Arch Gen Psychiatry*. 2006;63(4):404. doi:10.1001/archpsyc.63.4.404.

297. Gonzales G, Przedworski J, Henning-Smith C, L T, DP T, J B. Comparison of Health and Health Risk Factors Between Lesbian, Gay, and Bisexual Adults and Heterosexual Adults in the United States. *JAMA Intern Med*. 2016;176(9):1344. doi:10.1001/jamainternmed.2016.3432.

298. Saez E. Striking it richer: The evolution of top incomes in the United States (Updated with 2014 preliminary estimates). *Econ Dep UC Berkeley*. 2015. http://eml.berkeley.edu/~saez/saez-UStopincomes-2015.pdf. Accessed September 7, 2017.

299. Chetty R, Stepner M, Abraham S, et al. The Association Between Income and Life Expectancy in the United States, 2001-2014. *JAMA*. 2016;315(16):1750. doi:10.1001/jama.2016.4226.

300. Odutayo A, Gill P, Shepherd S, et al. Income Disparities in Absolute Cardiovascular Risk and Cardiovascular Risk Factors in the United States, 1999-2014. *JAMA Cardiol*. 2017;2(7):782. doi:10.1001/jamacardio.2017.1658.

301. Hickson DA, Diez Roux A V, Gebreab SY, et al. Social patterning of cumulative biological risk by education and income among African Americans. *Am J Public Health*. 2012;102(7):1362-1369. doi:10.2105/AJPH.2011.300444.

302. Lipowicz A, Szklarska A, Malina RM. Allostatic load and socioeconomic status in Polish adult men. *J Biosoc Sci*. 2014;46(2). doi:10.1017/S0021932013000345.

303. Merkin SS, Karlamangla A, Diez Roux A V, Shrager S, Seeman TE. Life Course Socioeconomic Status and Longitudinal Accumulation of Allostatic Load in Adulthood: Multi-Ethnic Study of Atherosclerosis. doi:10.2105/AJPH.2013.

304. Mode NA, Evans MK, Zonderman AB. Race, Neighborhood Economic Status, Income Inequality and Mortality. Olson DR, ed. *PLoS One*. 2016;11(5):e0154535. doi:10.1371/journal.pone.0154535.

305. Marmot MG, Smith GD, Stansfeld S, et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet (London, England)*. 1991;337(8754):1387-1393. http://www.ncbi.nlm.nih.gov/pubmed/1674771. Accessed September 7, 2017.

306. Boscher C, Arnold L, Lange A, Szagun B. Die Last der Ungerechtigkeit. Eine

Längsschnittanalyse auf Basis des SOEPs zum Einfluss subjektiv wahrgenommener Einkommensgerechtigkeit auf das Risiko einer stressassoziierten Erkrankung. *Das Gesundheitswes*. May 2017. doi:10.1055/s-0043-107876.

307. Pascoe EA, Smart Richman L. Perceived Discrimination and Health: A Meta-Analytic Review. *Psychol Bull*. 2009;135(4). doi:10.1037/a0016059.

308. Paradies Y, Ben J, Denson N, et al. Racism as a Determinant of Health: A Systematic Review and Meta-Analysis. Hills RK, ed. *PLoS One*. 2015;10(9):e0138511. doi:10.1371/journal.pone.0138511.

309. Li M. Discrimination and Psychiatric Disorder Among Asian American Immigrants: A National Analysis by Subgroups. *J Immigr Minor Heal*. 2014;16(6):1157-1166. doi:10.1007/s10903-013-9920-7.

310. Wallace S, Nazroo J, Bécares L. Cumulative Effect of Racial Discrimination on the Mental Health of Ethnic Minorities in the United Kingdom. *Am J Public Health*. 2016;106(7):1294-1300. doi:10.2105/AJPH.2016.303121.

311. Lucas T, Wegner R, Pierce J, Lumley MA, Laurent HK, Granger DA. Perceived Discrimination, Racial Identity, and Multisystem Stress Response to Social Evaluative Threat Among African American Men and Women. *Psychosom Med*. 2017;79(3):293-305. doi:10.1097/PSY.0000000000000406.

312. Szanton SL, Rifkind JM, Mohanty JG, et al. Racial Discrimination Is Associated with a Measure of Red Blood Cell Oxidative Stress: A Potential Pathway for Racial Health Disparities. *Int J Behav Med*. 2012;19(4):489-495. doi:10.1007/s12529-011-9188-z.

313. Brody GH, Yu T, Miller GE, Chen E. Discrimination, Racial Identity, and Cytokine Levels Among African-American Adolescents. *J Adolesc Heal*. 2015;56:496-501. doi:10.1016/j.jadohealth.2015.01.017.

314. Brody GH, Lei M-K, Chae DH, Yu T, Kogan SM, Beach SRH. Perceived discrimination among African American adolescents and allostatic load: a longitudinal analysis with buffering effects. *Child Dev*. 2014;85(3):989-1002. doi:10.1111/cdev.12213.

315. Whitaker KM, Everson-Rose SA, Pankow JS, et al. Experiences of Discrimination and Incident Type 2 Diabetes Mellitus: The Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Epidemiol*. 2017;186(4):445-455. doi:10.1093/aje/kwx047.

316. Bacon KL, Stuver SO, Cozier YC, Palmer JR, Rosenberg L, Ruiz-Narváez EA. Perceived racism and incident diabetes in the Black Women's Health Study. *Diabetologia*. August 2017:1-5. doi:10.1007/s00125-017-4400-6.

317. Ikram UZ, Snijder MB, Agyemang C, et al. Perceived Ethnic Discrimination and the Metabolic Syndrome in Ethnic Minority Groups. *Psychosom Med*. 2017;79(1):101-111. doi:10.1097/PSY.0000000000000350.

318. Everson-Rose SA, Lutsey PL, Roetker NS, et al. Perceived Discrimination and Incident Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2015;182(3):225-234. doi:10.1093/aje/kwv035.

319. Albert MA, CF de L, TT L, et al. Perceptions of Race/Ethnic Discrimination in Relation to Mortality Among Black Women. *Arch Intern Med*. 2010;170(10):896. doi:10.1001/archinternmed.2010.116.

320. Williams DR, Neighbors HW, Jackson JS. Racial/ethnic discrimination and health: findings from community studies. *Am J Public Health*. 2008;98(9 Suppl):S29-37. http://www.ncbi.nlm.nih.gov/pubmed/18687616. Accessed September 5, 2017.

321. Taylor TR, Williams CD, Makambi KH, et al. Racial Discrimination and Breast Cancer Incidence in US Black Women: The Black Women's Health Study. *Am J Epidemiol*. 2007;166(1):46-54. doi:10.1093/aje/kwm056.

322. Tugade MM, Fredrickson BL, Burchett D, Udumyan R, Montgomery S, Fall K. Resilient individuals use positive emotions to bounce back from negative emotional experiences. *J Pers Soc Psychol*. 2004;86(2):320-333. doi:10.1037/0022-3514.86.2.320.

323. American Psychological Association. Discrimination: What it is, and how to cope. Psychology Help Center . doi:10.1037/a0016059.

324. WHO Health and Human Rights Publication Series. *WHO's Contribution to the World Conference against Racism, Racial Discrimination, Xenophobia and Related Intolerance: Health and Freedom from Discrimination.* Geneva: World Health Organization; 2001. http://www.who.int/gender-equity-rights/knowledge/hhr-publication-series/en/. Accessed January 12, 2017.

325. Green McDonald P, O'Connell M, Lutgendorf SK. Psychoneuroimmunology and cancer: a decade of discovery, paradigm shifts, and methodological innovations. *Brain Behav Immun*. 2013;30 Suppl(0):S1--9. doi:10.1016/j.bbi.2013.01.003.

326. Seeman T, Gruenewald T, Karlamangla A, et al. Modeling multisystem

biological risk in young adults: The Coronary Artery Risk Development in Young Adults Study. *Am J Hum Biol*. 2009;22(4):463-472. doi:10.1002/ajhb.21018.

327. Merkin SS, Basurto-Dávila R, Karlamangla A, et al. Neighborhoods and cumulative biological risk profiles by race/ethnicity in a national sample of U.S. adults: NHANES III. *Ann Epidemiol*. 2009;19(3):194-201. doi:10.1016/j.annepidem.2008.12.006.

328. Carroll JE, Irwin MR, Merkin SS, Seeman TE. Sleep and Multisystem Biological Risk: A Population-Based Study. Gamble KL, ed. *PLoS One*. 2015;10(2):e0118467. doi:10.1371/journal.pone.0118467.

329. Glei DA, Goldman N, Chuang Y-L, Weinstein M. Do Chronic Stressors Lead to Physiological Dysregulation? Testing the Theory of Allostatic Load. doi:10.1097/PSY.0b013e318157cba6.

330. Goldman N, Turra CM, Glei DA, Lin Y-H, Weinstein M. Physiological dysregulation and changes in health in an older population. *Exp Gerontol*. 2006;41(9):862-870. doi:10.1016/j.exger.2006.06.050.

331. Galen Buckwalter J, Castellani B, Mcewen B, et al. Allostatic load as a complex clinical construct: A case-based computational modeling approach. *Complexity*. 2016;21(S1):291-306. doi:10.1002/cplx.21743.

332. Goldman N, Glei DA, Seplaki C, Liu I-W, Weinstein M. Perceived stress and physiological dysregulation in older adults. *Stress*. 2005;8(2):95-105. doi:10.1080/10253890500141905.

333. Song M, Giovannucci E, T A-C, et al. Preventable Incidence and Mortality of

Carcinoma Associated With Lifestyle Factors Among White Adults in the United States. *JAMA Oncol*. 2016;2(9):1154. doi:10.1001/jamaoncol.2016.0843.

334. Statistics NC for H. Plan and Operation of the Third National Health and Nutritional Examination Survey, 1988-94. Series 1: programs and collection procedures. *Vital Heal Stat 1*. 1994;32:1-407. http://ci.nii.ac.jp/naid/10026597534/. Accessed November 8, 2017.

335. Seeman T, Merkin SS, Crimmins E, Koretz B, Charette S, Karlamangla A. Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988–1994). *Soc Sci Med*. 2008;66(1):72-87. doi:10.1016/j.socscimed.2007.08.027.

336. Crimmins EM, Kim JK, Seeman TE. Poverty and biological risk: the earlier "aging" of the poor. *J Gerontol A Biol Sci Med Sci*. 2009;64(2):286-292. doi:10.1093/gerona/gln010.

337. National Center for Health Statistics. *NHANES III Laboratory Data File and Documentation, Ages One Year and Older*. Hyattsville, MD; 1996.

338. Masharani U, German MS. Pancreatic Hormones and Diabetes Mellitus. In: Gardner DG, Shoback D, eds. *Greenspan's Basic & Clinical Endocrinology*. 10e ed. New York, NY: McGraw-Hill.

339. Centers for Disease Control and Prevention. *CDC - NBP - Biomonitoring Summaries - Cotinine*.

340. Division of Nutrition, Physical Activity and ONC for CDP and HPC for DC and P. Healthy Weight. doi:10.1016/S0140-6736(14)60892-8.

341. Economic Research Service. United States Department of Agriculture. Rural-

Urban Continuum Codes Documentation. https://www.ers.usda.gov/data-products/rural-urban-continuum-codes/documentation.aspx#Methodology. Published 2017. Accessed February 8, 2018.

342. Yang Q, Cogswell ME, Flanders WD, et al. Trends in Cardiovascular Health Metrics and Associations With All-Cause and CVD Mortality Among US Adults. *JAMA*. 2012;307(12):1273. doi:10.1001/jama.2012.339.

343. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32(9 Suppl):S498-504. http://www.ncbi.nlm.nih.gov/pubmed/10993420. Accessed January 27, 2018.

344. U.S. Department of Health and Human Services (DHHS). National Center for Health Statistics. *Third National Health and Nutrition Examination Survey, 1988-1994, NHANES III Healthy Eating Index Data File (Series 11, No. 6A).* Hyattsville, MD https://wwwn.cdc.gov/nchs/data/nhanes3/6a/hei-acc.pdf.

345. National Center for Health Statistics. *NCHS 2011 Linked Mortality Files Matching Methodology*. Hyattsville, MD; 2013. http://www.cdc.gov/nchs/data_access/data_linkage/mortality/linkage_methods_analytical_support/2011_linked_mor%0Atality_file_matching_methodology.pdf.

346. Banga S, Chalfoun N. Arrhythmias and Antiarrhythmic Drugs. In: A E, ed. *Cardiology: An Integrated Approach*. New York NY.

347. RF L, DD B, M S, JF. S. Vital Signs, Anthropometric Data, and Pain. In: RF L, DD B, M S, JF. S, eds. *DeGowin's Diagnostic Examination*. 10e ed. New York, NY: McGraw-Hill.

348. Chobanian A V., Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure<SUBTITLE>The JNC 7 Report</SUBTITLE> *JAMA*. 2003;289(19):2560. doi:10.1001/jama.289.19.2560.

349. James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults. *JAMA*. 2014;311(5):507. doi:10.1001/jama.2013.284427.

350. Stern SE, Williams K, Ferrannini E, DeFronzo RA, Bogardus C, Stern MP. Identification of individuals with insulin resistance using routine clinical measurements. *Diabetes*. 2005;54(2):333-339. doi:10.2337/DIABETES.54.2.333.

351. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. *Diabetes Care*. 2003;26(12):3320-3325. doi:10.2337/DIACARE.26.12.3320.

352. Singh B, Saxena A. Surrogate markers of insulin resistance: A review. *World J Diabetes*. 2010;1(2):36-47. doi:10.4239/wjd.v1.i2.36.

353. Burtis CA, Bruns DE. Reference Information. In: *Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics*. Elsevier Health Sciences; 2014.

354. World Health Organization. Waist Circumference and Waist-Hip Ratio Report of a WHO Expert Consultation. *WHO Heal Hum Rights*. 2011.

355. D N, L.C. M, S.J M. Lab Tests. In: D N, L.C. M, S.J M, eds. *Guide to Diagnostic Tests*. 7e ed. New York: McGraw-Hill.

356. Abramson N, Melton B. Leukocytosis: basics of clinical assessment. *Am Fam Physician*. 2000;62(9):2053-2060. http://www.ncbi.nlm.nih.gov/pubmed/11087187. Accessed April 4, 2017.

357. Pagana KD, Pagana TJ. *Mosby's Manual of Diagnostic and Laboratory Tests-E-Book*. Elsevier Health Sciences; 2017.

358. Greenland P, Smith SC, Grundy SM, Meisinger C. Improving Coronary Heart Disease Risk Assessment in Asymptomatic People: Role of Traditional Risk Factors and Noninvasive Cardiovascular Tests. *Circulation*. 2001;104(15):1863-1867. doi:10.1161/hc4201.097189.

359. Schafer JL. Multiple Imputation Models and Procedures for NHANES III. 2001. https://ftp.cdc.gov/pub/health_statistics/nchs/nhanes/nhanes3/7a/doc/mimodels.pdf. Accessed February 8, 2018.

360. Enders CK. *Applied Missing Data Analysis*. Guilford Press; 2010.

361. Barnard J, Meng X-L. Applications of multiple imputation in medical studies: from AIDS to NHANES. *Stat Methods Med Res*. 1999;8(1):17-36. doi:10.1177/096228029900800103.

362. Flier JS, Underhill LH, McEwen BS. Protective and Damaging Effects of Stress Mediators. *N Engl J Med*. 1998;338(3):171-179. doi:10.1056/NEJM199801153380307.

363. Antoni MH, Lutgendorf SK, Cole SW, et al. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. *Nat Rev Cancer*. 2006;6(3). doi:10.1038/nrc1820.

364. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-Analysis of Perceived Stress and Its Association With Incident Coronary Heart Disease. *Am J Cardiol*. 2012;110(12):1711-1716. doi:10.1016/J.AMJCARD.2012.08.004.

365. Steptoe A, Hackett RA, Lazzarino AI, et al. Disruption of multisystem responses to stress in type 2 diabetes: Investigating the dynamics of allostatic load. *Proc Natl Acad Sci*. 2014;111(44):15693-15698. doi:10.1073/pnas.1410401111.

366. Borrell LN, Kiefe CI, Diez-Roux A V., Williams DR, Gordon-Larsen P. Racial discrimination, racial/ethnic segregation, and health behaviors in the CARDIA study. *Ethn Health*. 2013;18(3):227-243. doi:10.1080/13557858.2012.713092.

367. Singh GK, Siahpush M. Widening Rural–Urban Disparities in All-Cause Mortality and Mortality from Major Causes of Death in the USA, 1969–2009. *J Urban Heal*. 2014;91(2):272-292. doi:10.1007/s11524-013-9847-2.

368. Singh GK, Siahpush M, Williams SD. Changing Urbanization Patterns in US Lung Cancer Mortality, 1950–2007. *J Community Health*. 2012;37(2):412-420. doi:10.1007/s10900-011-9458-3.

369. Yang E V, Kim S, Donovan EL, et al. Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. *Brain Behav Immun*. 2009;23(2):267-275. doi:10.1016/j.bbi.2008.10.005.

370. Kubzansky LD, Kawachi I. Affective states and health. In: Berkman LF,

Kawachi I, Glymour MM, eds. *Social Epidemiology*. Oxford University Press; 2000:213-241.

371. Reiche EMV, Nunes SOV, Morimoto HK. Stress, depression, the immune system, and cancer. *Lancet Oncol*. 2004;5(10):617-625. doi:10.1016/S1470-2045(04)01597-9.

372. Chyu L, Upchurch DM. A Longitudinal Analysis of Allostatic Load among a Multi-Ethnic Sample of Midlife Women: Findings from the Study of Women's Health Across the Nation. *Women's Heal Issues*. December 2017. doi:10.1016/J.WHI.2017.11.002.

373. Upchurch DM, Rainisch BW, Chyu L. Greater Leisure Time Physical Activity Is Associated with Lower Allostatic Load in White, Black, and Mexican American Midlife Women: Findings from the National Health and Nutrition Examination Survey, 1999 through 2004. *Womens Health Issues*. 2015;25(6):680-687. doi:10.1016/j.whi.2015.07.002.

374. Karlamangla AS, Singer BH, McEwen BS, Rowe JW, Seeman TE. Allostatic load as a predictor of functional decline: MacArthur studies of successful aging. *J Clin Epidemiol*. 2002;55(7):696-710. doi:10.1016/S0895-4356(02)00399-2.

375. Borrell LN, Dallo FJ, Nguyen N. Racial/Ethnic Disparities in All-Cause Mortality in U.S. Adults: The Effect of Allostatic Load. *Public Health Rep*. 2010;125(6):810-816. doi:10.1177/003335491012500608.

376. Ong AD, Williams DR, Nwizu U, Gruenewald TL. Everyday unfair treatment and multisystem biological dysregulation in African American adults. *Cult Divers Ethn Minor Psychol*. 2017;23(1):27-35. doi:10.1037/cdp0000087.

377. Sims M, Diez-Roux A V, Dudley A, et al. Perceived discrimination and hypertension among African Americans in the Jackson Heart Study. *Am J Public Health*. 2012;102 Suppl:S258--65. doi:10.2105/AJPH.2011.300523.

378. Sims M, Diez-Roux A V, Gebreab SY, et al. Perceived discrimination is associated with health behaviours among African-Americans in the Jackson Heart Study. *J Epidemiol Community Health*. 2016;70(2):187-194. doi:10.1136/jech-2015-206390.

379. Heikkilä K, Nyberg ST, Fransson EI, et al. Job Strain and Alcohol Intake: A Collaborative Meta-Analysis of Individual-Participant Data from 140 000 Men and Women. Mazza M, ed. *PLoS One*. 2012;7(7):e40101. doi:10.1371/journal.pone.0040101.

380. Lutgendorf SK. Social Support, Psychological Distress, and Natural Killer Cell Activity in Ovarian Cancer. *J Clin Oncol*. 2005;23(28):7105-7113. doi:10.1200/JCO.2005.10.015.

381. Seeman TE, Gruenewald TL, Cohen S, Williams DR, Matthews KA. Social relationships and their biological correlates: Coronary Artery Risk Development in Young Adults (CARDIA) study. *Psychoneuroendocrinology*. 2014;43:126-138. doi:10.1016/j.psyneuen.2014.02.008.

382. Kivimäki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol*. December 2017. doi:10.1038/nrcardio.2017.189.

383. Taylor HA, Wilson JG, Jones DW, et al. Toward Resolution of Cardiovascular Health Disparities in African Americans: Design and Methods of

the Jackson Heart Study. http://www.ishib.orgwww.ishib.org/ED/journal/15-4s6/ethn-15-4s6-4.pdf. Accessed March 18, 2018.

384. Barber S, Hickson DA, Kawachi I, Subramanian S V, Earls F. Neighborhood Disadvantage and Cumulative Biological Risk Among a Socioeconomically Diverse Sample of African American Adults: An Examination in the Jackson Heart Study. *J Racial Ethn Heal Disparities*. 2015. doi:10.1007/s40615-015-0157-0.

385. Carpenter MA, Crow R, Steffes M, et al. Laboratory, Reading Center, and Coordinating Center Data Management Methods in the Jackson Heart Study. *Am J Med Sci*. 2004;328(3):131-144. doi:10.1097/00000441-200409000-00001.

386. Keku E, Rosamond W, Taylor HA, et al. Cardiovascular disease event classification in the Jackson Heart Study: methods and procedures. *Ethn Dis*. 2005;15(4 Suppl 6):S6-62-70. http://www.ncbi.nlm.nih.gov/pubmed/16317987. Accessed April 20, 2018.

387. Smitherman TA, Dubbert PM, Grothe KB, et al. Validation of the Jackson Heart Study Physical Activity Survey in African Americans. *J Phys Act Health*. 2009;6 Suppl 1:S124-32. http://www.ncbi.nlm.nih.gov/pubmed/19998858. Accessed March 18, 2018.

388. Carithers TC, Talegawkar SA, Rowser ML, et al. Validity and Calibration of Food Frequency Questionnaires Used with African-American Adults in the Jackson Heart Study. *J Am Diet Assoc*. 2009;109(7):1184--1193.e2. doi:10.1016/j.jada.2009.04.005.

389. Shallcross AJ, Butler M, Tanner RM, et al. Psychosocial correlates of

apparent treatment-resistant hypertension in the Jackson Heart Study. *J Hum Hypertens*. 2017;31(7):474-478. doi:10.1038/jhh.2016.100.

390. Sneed RS, Cohen S. Negative Social Interactions and Incident Hypertension Among Older Adults. doi:10.1037/hea0000057.

391. Sims M, Wyatt SB, Gutierrez M Lou, Taylor HA, Williams DR. Development and psychometric testing of a multidimensional instrument of perceived discrimination among African Americans in the Jackson Heart Study. *Ethn Dis*. 2009;19(1):56-64. http://www.ncbi.nlm.nih.gov/pubmed/19341164. Accessed April 20, 2018.

392. Williams DR, Yan Yu Y, Jackson JS, Anderson NB. Racial Differences in Physical and Mental Health. *J Health Psychol*. 1997;2(3):335-351. doi:10.1177/135910539700200305.

393. Krieger N, Sidney S. Racial discrimination and blood pressure: the CARDIA Study of young black and white adults. *Am J Public Health*. 1996;86(10):1370-1378. doi:10.2105/AJPH.86.10.1370.

394. Gustafsson PE, San Sebastian M, Janlert U, Theorell T, Westerlund H, Hammarström A. Life-course accumulation of neighborhood disadvantage and allostatic load: empirical integration of three social determinants of health frameworks. *Am J Public Health*. 2014;104(5):904-910. doi:10.2105/AJPH.2013.301707.

395. Tan M, Mamun A, Kitzman H, Mandapati SR, Dodgen L. Neighborhood Disadvantage and Allostatic Load in African American Women at Risk for Obesity-Related Diseases. *Prev Chronic Dis*. 2017;14:170143.

doi:10.5888/pcd14.170143.

396. Schmitt MT, Branscombe NR, Postmes T, Garcia A. The consequences of perceived discrimination for psychological well-being: A meta-analytic review. *Psychol Bull*. 2014;140(4):921-948. doi:10.1037/a0035754.

397. Lewis TT, Cogburn CD, Williams DR. Self-Reported Experiences of Discrimination and Health: Scientific Advances, Ongoing Controversies, and Emerging Issues. *Annu Rev Clin Psychol*. 2015;11(1):407-440. doi:10.1146/annurev-clinpsy-032814-112728.

398. Gravlee CC. How Race Becomes Biology: Embodiment of Social Inequality. *Am J Phys Anthropol*. 2009;139(1):47-57. doi:10.1002/ajpa.20983.

399. Kershaw KN, Lewis TT, Diez Roux A V, et al. Self-reported experiences of discrimination and inflammation among men and women: The multi-ethnic study of atherosclerosis. *Health Psychol*. 2016;35(4):343-350. doi:10.1037/hea0000331.

400. Lewis TT, Williams DR, Tamene M, Clark CR. Self-Reported Experiences of Discrimination and Cardiovascular Disease. *Curr Cardiovasc Risk Rep*. 2014;8(1):365. doi:10.1007/s12170-013-0365-2.

401. Friedman GD, Cutter GR, Donahue RP, et al. Cardia: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988;41(11):1105-1116. doi:10.1016/0895-4356(88)90080-7.

402. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988;41(11):1105-1116. http://www.ncbi.nlm.nih.gov/pubmed/3204420.

Accessed April 20, 2018.

403. Krieger N, Smith K, Naishadham D, Hartman C, Barbeau EM. Experiences of discrimination: Validity and reliability of a self-report measure for population health research on racism and health. *Soc Sci Med*. 2005;61(7):1576-1596. doi:10.1016/j.socscimed.2005.03.006.

404. Cunningham TJ, Berkman LF, Gortmaker SL, et al. Assessment of differential item functioning in the experiences of discrimination index: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Epidemiol*. 2011;174(11):1266-1274. doi:10.1093/aje/kwr253.

405. Jacobs DR, Hahn LP, Haskell WL, Pirie P, Sidney S, Sidney S. Validity and Reliability of Short Physical Activity History: Cardia and the Minnesota Heart Health Program. *J Cardiopulm Rehabil*. 1989;9(11):448-459. http://www.ncbi.nlm.nih.gov/pubmed/29657358. Accessed May 15, 2018.

406. McDonald A, Van Horn L, Slattery M, et al. The CARDIA dietary history: development, implementation, and evaluation. *J Am Diet Assoc*. 1991;91(9):1104-1112. http://www.ncbi.nlm.nih.gov/pubmed/1918764. Accessed May 7, 2018.

407. Sijtsma FPC, Meyer KA, Steffen LM, et al. Diet quality and markers of endothelial function: The CARDIA study. *Nutr Metab Cardiovasc Dis*. 2014;24(6):632-638. doi:10.1016/j.numecd.2013.12.010.

408. Cunningham TJ, Berkman LF, Kawachi I, et al. CHANGES IN WAIST CIRCUMFERENCE AND BODY MASS INDEX IN THE US CARDIA COHORT: FIXED-EFFECTS ASSOCIATIONS WITH SELF-REPORTED

EXPERIENCES OF RACIAL/ETHNIC DISCRIMINATION. *J Biosoc Sci*. 2013;45:267-278. doi:10.1017/S0021932012000429.

409. Kershaw KN, Lewis TT, Roux AVD, et al. Self-reported experiences of discrimination and inflammation among men and women: The multi-ethnic study of atherosclerosis. *Heal Psychol*. 2016;35(4):343-350. doi:10.1037/hea0000331.