National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

Understanding the Biological Mechanisms Underlying the Health Consequences of Racism, Marginalization, and Discrimination

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and Via Zoom Virtual Platform

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SUMMARY

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Welcome and Opening Remarks

Griffin P. Rodgers, M.D., MACP, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Raquel Greer, M.D., M.H.S., Division of Kidney, Urologic, and Hematologic Diseases (KUH), NIDDK

NIDDK Director Griffin P. Rodgers, M.D., MACP, welcomed the participants. He explained that the primary objectives of the meeting were to identify opportunities to understand the biological pathways through which racism, marginalization, and discrimination (RMD) contribute to disease and to foster the cross-pollination of ideas and collaborations that are needed to advance this science. The marginalization of groups based on socially constructed categories of race, ethnicity, sexual orientation, gender, and other identities produces biological consequences that contribute to health disparities in a variety of diseases and conditions, including many under the purview of NIDDK. For example, substantial racial and ethnic disparities exist in obesity, diabetes, and end-stage kidney disease. RMD is embedded into the structure of American society, and this increases exposure to adverse social determinants of health (SDOH)—or social risks—for marginalized populations. Social risks are known to affect health outcomes by constraining or modifying health-related behaviors (e.g., diet, physical activity, smoking). However, experiences with RMD—as well as exposure to social risk—may also directly alter biology by triggering stress pathways and modifying biological homeostasis.

Dr. Rodgers explained that the meeting aligns with key research recommendations from *Pathways to Health for All*, a 2023 report from the Health Disparities and Health Equity Research Working Group of the NIDDK Advisory Council. The meeting demonstrates NIDDK's commitment to strengthening community engagement through partnership, power sharing, and capacity building to improve research; advancing research on the mechanisms by which biological, behavioral, environmental, and structural factors interact to affect health, disease, and resilience; and enhancing NIDDK collaboration, structures, and programs to support robust research in health disparities and health equity. Dr. Rodgers noted that the meeting would open with a patient and community panel; he encouraged researchers in attendance to seek out community partnerships. Dr. Rodgers thanked the external planning committee—including the co-chairs, Dr. Tracy Bale, University of Colorado, and Dr. Shakira Suglia, Emory University, and other National Institutes of Health (NIH) Institutes, Centers, and Offices—for coordinating the workshop.

Dr. Raquel Greer, Program Director, NIDDK, provided an overview of research questions to be addressed during the workshop, which included the following:

- What are the direct biological mechanisms and pathways underlying the relationships among RMD, social risks, and NIDDK diseases and conditions? How do these biological mechanisms interact with social and behavioral drivers of disease? Specific biological mechanisms, pathways, and systems of potential interest for this workshop include, but are not limited to, weathering, stress, allostatic load, the hypothalamic–pituitary–adrenal axis, developmental programming, epigenetics, the microbiome, immune function, inflammation, neuroendocrine status, endocrine disruption, and telomere shortening.
- How do these biological mechanisms and pathways differ or overlap across the various population groups that experience RMD? How do these mechanisms combine for populations crossing multiple intersecting, marginalized identities?
- How do these biological mechanisms and pathways differ or overlap in the context of structural versus interpersonal forms of RMD, as well as between RMD and associated social risks?
- What biopsychosocial factors prevent or mitigate disease—resulting in differential health outcomes within subpopulations—despite exposure to structural and interpersonal RMD? What are the biological mechanisms through which this resilience occurs?
- How do we identify biological markers to describe the experience of RMD?
- Does RMD contribute to the population-level differences in markers of key biological functions (e.g., differences in serum creatinine observed between Black and non-Black people in the United States)?
- What tools (e.g., measures, assessments, assays, wearables, apps) do we need to employ or develop to assess the impact that RMD may have on biology and health outcomes?

Dr. Greer reviewed the meeting agenda and thanked the attendees for their participation.

Synthesizing the Findings, Projecting the Future for Biomechanistic Research on Discrimination, Racism, and Health-related Outcomes
Keith Norris, M.D., Ph.D., University of California, Los Angeles (UCLA)

Dr. Keith Norris opened his presentation with a video of a flock of starlings—called a murmuration—twisting, turning, and swooping together in unison across the sky. This phenomenon is a metaphor for the creativity, awareness, and coordination needed to make progress in addressing the complex and interacting factors contributing to the health consequences of RMD. Dr. Norris discussed the clinical implications of RMD. For example, structural racism and racial discrimination alter kidney health by creating disproportionate exposure among marginalized populations to social risks, such as reduced access to appropriate housing and health care, food insecurity, barriers to education and employment, and exposure to pollutants. The lifestyle implications of these social risks include increased ingestion of cooked meat, hyperglycemia, and high blood pressure. RMD also has direct effects on biology, including increased allostatic load, altered gene expression, increased activity of the sympathetic nervous system, and altered hormone metabolism. These social and biological factors combine and lead to pathophysiological kidney changes (e.g., hyperfiltration, decline in estimated glomerular filtration rate [eGFR], activation of the renin-angiotensin-aldosterone system and inflammation) that lead to the development and progression of kidney disease. Dr. Norris noted that parallel changes occur in other biological systems, including other NIDDK diseases and conditions. The psycho-bio-social distress caused by RMD can impede cognitive processing and executive function and result in maladaptive biological processing, leading to the reduced ability to process and respond to stress. For patients who are from marginalized, under-resourced communities, the impact of adverse social risks and chronically altered biology due to RMD, as well as impaired cognition (i.e., ability to remember and implement tasks) due to distress caused by RMD, makes suboptimal clinical outcomes inevitable.

Dr. Norris described two common terms in this research area: (1) "weathering," defined as the cumulative damage caused by exposure to stress, and (2) "allostatic load," defined as the clinical and biomarker indicators of cumulative stress. Both weathering and allostatic load have been shown to be strongly associated with various forms of discrimination, including lifetime discrimination, everyday discrimination, and childhood racial discrimination. Dr. Norris presented the findings of a key study that showed that higher baseline allostatic load scores were associated with an approximately sixfold increase in 7-year mortality risk. Other studies exploring the impact of RMD on biologic processing have revealed associations between famine and intergenerational health, racial discrimination and increased leukocyte telomere shortening, and racial discrimination and differences in leukocyte gene expression. The latter study showed that experiences of racial discrimination accounted for more than half of race-related differences in proinflammatory transcription factor activity and that race was no longer significant when controlled for racial discrimination.

In summary, RMD affects structural factors, such as residential segregation, low and underemployment, poverty, and limited health care access. These factors contribute to stress and maladaptive coping and behaviors, which can lead to the biological consequences of chronic inflammation and stress, such as neuro-hormonal activation, oxidative stress, immune dysregulation, and epigenetic changes. This ultimately leads to increased weathering and allostatic load; impaired cognitive process; reduced telomere length; increased chronic disease; and premature morbidity and mortality. Key factors that can attenuate these downstream biological consequences include positive racial identity, greater supportive family environments (e.g., connectedness), and greater perceived control (i.e., the belief that one has control over oneself and one's surroundings. Dr. Norris emphasized that these positive mitigating factors should be incorporated into research exploring the biological consequences of RMD.

Dr. Norris shared considerations for future studies investigating the biological effects of RMD. Potential interventions to mitigate the impact of RMD include precision nutrition, lifestyle changes, and contemplative practices, as well as novel therapeutics that may impact biological pathways that are affected by RMD (e.g., NRF2 inducers, glutathione analogs, antiproliferative agents, cytokine inhibitors). Other areas for future studies include noninvasive, wearable physicochemical-sensing for stress response monitoring; impact of RMD on the microbiome; and cell studies to understand how RMD is operating at the cellular level. RMD studies should consider studying people who appear healthy despite exposure to lifelong insults. New methods to measure RMD and its effect on stress biomarkers and tools to capture intersectional discrimination across the life course must be developed. Dr. Norris advised that careful attention should be paid to the methodological use of race in precision medicine and artificial intelligence–based algorithms. He also emphasized that improving NIDDK-related health outcomes will require collaborative and creative interdisciplinary teams to employ an integrated socio-bio-cognitive and equity-minded framework to develop and evaluate community-engaged, multilevel interventions. These studies will target social determinants of health and stress-reduction elements—such as physical activity and sleep—and will work to understand how these interventions are linked to biological factors (e.g., immune cell characteristics, cytokines and stress-related biomarkers, proteomics, transcriptomics).

Questions and Answers

- When asked how to best measure structural racism, how to quantify the stress response that is unique to RMD (as opposed to other chronic stressors), and whether stress caused by RMD is additive or multiplicative, Dr. Norris responded that these questions are extremely complex. Structural racism is the result of multiple structures that exist in any given community, and it affects each person differently. People also possess different protective factors that mediate against negative health outcomes that result from adverse events. Such issues are the precise questions that future research must address.

Patient and Community Panel
Moderators: Sheena Martenies, Ph.D., University of Illinois
Glenda Roberts, University of Washington
Speakers: Claudia Camacho, University of Colorado, Anschutz Medical Campus
Phyllis Harris, The LGBT Community Center of Greater Cleveland
Bobby Howard, LifeLink of Georgia

Dr. Sheena Martenies introduced the panelists and noted that the goals for the panel were to set the stage for the workshop and emphasize the importance of incorporating the patient and community perspectives into research on RMD and health outcomes. She reminded the meeting participants that all discussions should be tailored to be inclusive of patients with and those at risk for NIDDK-related diseases who are in attendance at the workshop. She invited the panelists to tell the stories of their personal experiences with RMD and health outcomes.

Ms. Phyllis Harris stated that she is a Black feminist lesbian and is the executive director of a community center for lesbian, gay, bisexual, and transgender (LGBT) and other sexual and gender minority (SGM) youth. She described being raised by a working-class single mother who worked in a factory for many years and, as a direct result, is now facing many health challenges. Ms. Harris noted that the opening remarks of the meeting made her emotional because they echoed her understanding that mitigating a loved one's stress can delay the progression of disease. She described her efforts to assist her mother with finances, housing, and other sources of stress. Ms. Harris expressed hope for younger generations to change the narratives surrounding RMD.

Ms. Claudia Camacho works as a patient navigator for Latino patients on dialysis. She relayed her own experience with illness—her father was diagnosed with end-stage kidney disease (ESKD) in the early 2000s. Ms. Camacho shared her difficulties navigating the health system with her father, despite being employed as a Spanish interpreter in health care at that time. She expressed sadness that her father might still be alive if she had been equipped to help him with her current knowledge. Ms. Camacho described health challenges that are specific to Hispanic and Latino communities. Many people in these communities experience legal and other difficulties associated with their immigration status. They are afraid to visit hospitals for fear of deportation and separation from their families, and when they seek help despite the risk, health care organizations often refuse care to people who are not citizens. Ms. Camacho expressed hope for more awareness of the situation. Hispanic and Latino communities contribute so much and deserve more from the system.

Mr. Bobby Howard, a former National Football League (NFL) player and 30-year kidney transplant recipient, shared how he received a diagnosis of ESKD shortly after retiring from the NFL. He recounted an early experience with kidney disease, when his mother received a kidney transplant in 1976 and died shortly thereafter. He saw a need to raise awareness about kidney disease and became dedicated to using his fame to bring attention to the cause. He emphasized that community and patient partners are needed for decision-making and better health outcomes for all.

Panel Discussion

Dr. Martenies asked the panelists to share how RMD negatively affected their health or the health of their communities.

- Ms. Camacho emphasized how her family had to navigate the health care system, which was difficult, even with her background in health care and the benefits of citizenship. She described seeing the condition of Hispanic and Latino patients decline faster because they did not have access to medical insurance, transportation, healthy food, or a family support system.

- Ms. Harris talked about the challenges that the lesbian community faces trying to access medical care. Few organizations respect lesbians and their unique needs. Ms. Harris described how myomectomy—surgery to remove uterine fibroids that leaves the uterus intact—was offered to her as a treatment for fibroids only in the presence of her white partner. After the premature birth of her child and when she fell ill later in life (because of calcified fibroids that were missed during the myomectomy), Ms. Harris experienced anti-Black and other biases in the medical system, including such microaggressions as being asked about drug use, having her literacy questioned, and having her pain and perspective dismissed. She discussed having to counteract the same internalized oppression, politics of respectability, and deference to white and male authorities that she had witnessed with her mother as they tried to navigate health care.
- Mr. Howard described the lack of health care available to Black people in his home state of Georgia. He has not had many personal experiences with RMD, but he has seen how it affects others in his community. He tries to help people who are being treated unfairly, recommending that they bring a friend or family member with them to medical appointments to help with personal advocacy and communication with health care professionals.

Dr. Martenies asked the panelists to share advice for researchers as they work to understand how RMD affects health.

- Mr. Howard recommended that more patients and community members be involved in RMD studies that will directly affect their lives. He also would like more information about community resources that have the strongest effects on overall health.
- Ms. Harris acknowledged that understanding racism and other biases is a challenging, uncomfortable, and ongoing process. She requested that health care providers stop struggling against their marginalized patients and instead focus on fighting unfair health insurance practices and efforts to roll back training for diversity, equity, and inclusion.
- Ms. Camacho echoed Mr. Harris' call for more marginalized people in the research space because they have a deeper understanding of the challenges associated with RMD and the cultural awareness needed to communicate with the broader community. She added that researchers must improve recruitment for RMD studies, clearly communicate their results, and address the issue of mistrust that marginalized communities feel toward biomedical researchers.

Ms. Glenda Roberts thanked the panelists for their moving comments about their experiences with RMD. She suggested that the meeting participants consider their own identities and how their identities affect their relationship with RMD. Ms. Roberts encouraged researchers to initiate difficult conversations about marginalization and social risks with patients who experience RMD; include more marginalized people on their research teams; solicit research input and feedback from patient partners via advisory boards; and build trust and engage patients by providing updates on their studies.

Epidemiology of Racism, Marginalization, and Discrimination in NIDDK Diseases
Moderator: Nicole VanKim, Ph.D., University of Massachusetts

Discriminatory Stressors in African American Women: Implications for Cardiometabolic Disease and Systemic Lupus Erythematosus
Tené Lewis, Ph.D., M.A., Emory University

Dr. Tené Lewis discussed the effects of discrimination on cardiometabolic disease in African American women. Dr. Lewis described her early work, which demonstrated that chronic exposure to discrimination was significantly associated with the prevalence of coronary artery calcification in Black (and not white)

populations of middle-aged women. She noted that at the time, she was discouraged from pursuing such research by an NIH program officer because "it makes people uncomfortable." Ultimately, similar dose–response associations were observed between discrimination and C-reactive protein (CRP) levels, visceral fat, sleep quality, incident cardiovascular disease (CVD), and incident diabetes. In recent years, Dr. Lewis has focused on women with systemic lupus erythematosus (SLE), a chronic autoimmune disease that involves multiple organs and systems. Women comprise 90 percent of SLE patients, and 75 percent of these women are African American and/or Latina. CVD and chronic kidney disease (CKD) are major complications in people with lupus, and studies have shown that African American women experience these complications more rapidly and at higher rates than African American women without SLE.

The Vascular Aging, Inflammation Stress, and Atherosclerosis in African American Women (or VISTA) study cohort was recruited to further investigate how aspects of the lived experience of female African Americans contribute to CVD in people with SLE compared with those without. In a study limited to parents within this cohort (70 percent of the total cohort of 402 African American women, half of whom had been diagnosed with SLE), participants were interviewed about concern for their children's exposure to racism. Concern about children's exposure to racism was associated with lower eGFR in women with (but not without) SLE; the effect was slightly stronger in the context of medical racism (i.e., when the calculation used to determine eGFR incorporated race). Dr. Lewis hypothesized that SLE might contribute to weathering in African American women via inflammation or other biological mechanisms. She noted that the negative effects associated with concern for children might be particularly strong in women with low life expectancy; seven participants with SLE have died since the study's inception in 2017.

Kidney Disease in Sexual and Gender Minority Populations
Mitchell R. Lunn, M.D., M.A.S., FACP, FASN, Stanford University

Dr. Mitchell R. Lunn began by emphasizing the unique inequities that SGM communities experience regarding their health and health care. According to a recently published Gallup poll, approximately 8 percent of Americans identify as LGBT or queer. However, limited federal collection of data about sexual orientation and gender identity prevents the basic epidemiology of many diseases in SGM populations. SGM communities are underserved and understudied. They commonly have negative experiences with health care providers (e.g., being blamed for their health status, receiving verbal or physical abuse, having their concerns dismissed) and barriers to care (e.g., cost and fear of mistreatment) that limit their engagement with health care and clinical research.

Limited data on kidney disease in SGM populations have been collected. A 2022 study found that a cohort of transgender patients experienced high prevalence of both acute kidney injury (AKI) and CKD. A 2023 analysis determined that gay men had higher odds of reporting kidney disease than heterosexual men. Surprisingly, an analysis of SGM participants in the *All of Us* Research Program showed that SGM populations had lower odds of many diseases, including diabetes, heart disease, hypertension, and CKD. However, these results likely were due to sampling bias associated with the populations that participated in the *All of Us* study.

Accurate eGFR measurement is a critical component of the assessment and treatment of CKD. The equation currently used to calculate eGFR (from serum creatinine levels) has eliminated the race-based coefficient but still incorporates a sex-based coefficient that might result in inaccurate measurements for gender-minority patients. Additionally, how gender-affirming hormone therapy affects eGFR based on creatinine—a muscle-dependent biomarker—remains unclear. Accurate methods for measuring eGFR in gender-minority patients might rely on non-creatinine-based measures (e.g., cystatin C–based eGFR). Dr. Lunn concluded that improved collection of sexual orientation and gender identity data is needed at the local and federal levels before the health care challenges of SGM populations can be addressed. More

research is needed to determine the kidney burden in SGM populations and to develop accurate measurements of kidney function in gender minority patients.

Structural Racism and Diabetes Outcomes
Leonard E. Egede, M.D., M.S., Medical College of Wisconsin

Dr. Leonard E. Egede discussed the connections between structural racism and diabetes outcomes. He noted that the prevalence of diabetes in U.S. adults varies among different racial and ethnic groups. He provided two definitions of structural racism: (1) the totality of ways in which societies foster racial discrimination through mutually reinforcing inequitable systems that, in turn, reinforce discriminatory beliefs, values, and distribution of resources, and (2) organized systems within societies that cause avoidable and unfair inequalities in power, resources, capacities, and opportunities across racial or ethnic groups. Both definitions emphasize the inequitable distribution of power. Dr. Egede provided examples of structural racism, including housing segregation due to historical redlining, unequal distribution of wealth and educational resources, state-sanctioned police violence, inequalities in the judicial system, and mass incarceration of African American men.

Dr. Egede described his recent study that focused on the association between historic redlining and health outcomes related to diabetes. The study sample combined mortality data from King County in the state of Washington, redlining data for the city of Seattle, and 2010 census tract information from the U.S. Census Bureau into a data set of 109 census tracts accompanied by outcomes data from 1990 to 2014. The study found that an area's redlining score explains approximately half of the variation in the census tract–level diabetes mortality rate. A systematic review of structural racism and diabetes outcomes found significant associations between structural racism and poorer clinical outcomes, worse diets and levels of physical activity, lower standards of care, higher mortality, and more years of life lost. To investigate the mechanisms underlying these relationships, structural equation modeling was used to apply a validated conceptual model to geographical and health data from 11,375 census tracts and interrogate relationships among the model components. Redlining had significant direct and indirect relationships with diabetes prevalence; incarceration, poverty, discrimination, substance use, housing, education, unemployment, and food access. Dr. Egede explained that his future work will concentrate on direct and indirect relationships between structural racism and disparities in social risk, human capital, health care resources, and other health outcomes. His goal is to work with diverse partners to identify effective strategies and interventions to mitigate the damaging effects of structural racism.

Panel Discussion

- In response to a question about associations between discrimination and autoimmune diseases other than SLE, Dr. Lewis noted that rheumatoid arthritis and other inflammatory diseases are associated with exposure to discrimination. Inflammation is a known contributor to cardiovascular and kidney disease, as well as other adverse health outcomes. She added that SLE is unique in that it is a complex multisystem disease. SLE particularly affects Black women for reasons that are not yet understood.
- Dr. Norris commented on eGFR measures and the methodological challenge of applying group-level modifiers to individuals within a group. For example, the inclusion of a sex-based coefficient in eGFR calculations to account for sex-based differences in body mass might not be accurate for individuals who fall outside the average mass of their group.
- Dr. Jenna Norton, NIDDK, asked about common mechanisms that might be shared by the different associations found in various marginalized populations. Dr. Egede explained that rather than varying by disease or population, the underlying mechanisms likely are a shared result of societal RMD. Dr. Lunn agreed and noted that multiple stress and inflammation pathways likely

are involved. He pointed out that the future standard of care for patients might involve in-depth assessments of the biological changes associated with exposure to RMD. Dr. Lewis highlighted research showing that the stress associated with social rejection is particularly damaging to human beings. For example, Black Americans with higher socioeconomic status (SES) report the highest levels of individual exposure to racism because they live in less segregated communities than Black Americans with lower SES. Dr. Egede emphasized that downstream effects likely are caused by multiple pathways.

- In response to a question about potential connections between interpersonal or community violence and SLE outcomes in African American women, Dr. Lewis answered that she has collected information about interpersonal violence, as well as other measures that are connected to gender. She plans to analyze these data in the future.
- Dr. Norris asked about experimentally distinguishing between the effects of social isolation and discrimination. For example, could health outcomes in more segregated Black communities with lower SES (i.e., high connectedness and high systemic discrimination) be compared with those in Black individuals with high SES who live in more mixed communities (i.e., with low connectedness and low systemic discrimination). Dr. Egede explained that his group plans to tease apart the varying effects of social isolation and discrimination at the census tract level across all U.S. states. Dr. Lewis commented that experiences reported by Black study participants vary widely, but their concerns remain constant. Not all Black Americans report direct exposure to racism, but they often describe worrying about it.

Telomeres and Epigenetic-Related Mechanisms
Moderator: Ludmila Pawlikowska, Ph.D., NIDDK

Social Stressors and Epigenetic Aging among Hispanic and Latino Adults
Shakira Suglia, Sc.D., Emory University

Dr. Suglia explained that cardiovascular risk factors and diseases are highly prevalent among Hispanic and Latino communities. She reviewed various correlates of acculturative stress (i.e., the mental and emotional challenges of adapting to a new culture), which include language skills and SES at the individual level, social and family support at the interpersonal level, discrimination and neighborhood stress at the community level, and legal status and immigration policies at the institutional level. Dr. Suglia described the focus of her research, which is to investigate the effects of stressors on cardiometabolic health and the roles that accelerated epigenetic aging and sociocultural modifying factors play within this association. She noted that aging biomarkers have been developed to predict chronological age in the absence of disease, and that DNA methylation age is a way to measure stress effects on the epigenome. Deviations between chronological and estimated epigenetic age are predictive of morbidity and mortality.

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a multicenter epidemiologic study, was designed to assess the connection between acculturation and the prevalence and development of disease in Hispanic and Latino populations. Participants from several Hispanic and Latino backgrounds (e.g., Cubans, Central Americans, Mexicans, Puerto Ricans, South Americans) were recruited and underwent baseline and follow-up clinical visits comprising anthropometric measurements, blood draws, and survey completions. Dr. Suglia described results from the Stress, Epigenetics, and Cardiometabolic Health Study, an ancillary HCHS/SOL study in which she was involved. Analysis of the cohort showed that foreign-born study participants experienced accelerated epigenetic aging compared with those born in the United States. Participants who immigrated to the United States as adults showed a protective effect on their epigenetic aging compared with those who arrived in the United States as children, likely because immigrants arrive in a healthy state that wanes with time spent in the United States. This accelerated

aging effect was stronger when foreign-born participants were compared with people born on the U.S. mainland.

Dr. Suglia reviewed measures of economic and social stress and potential modifiers of interest that her group has investigated using self-organizing maps. Populations of interest were found to cluster into different aging categories based on their experiences with different stressors; three of the four categories exhibited accelerated epigenetic aging. Dr. Suglia's group also is investigating positive associations between adverse childhood experiences (ACEs) and epigenetic age acceleration and the role of nativity status as a modifier of this connection. Future steps will involve examining associations between epigenetic aging and cardiovascular health measures.

The Role of DNA Methylation in the Connections between Early Life Stress, Protective Factors, and Health Disparities in Early Markers of Chronic Disease
Sylvie Mrug, Ph.D., M.S., M.A., The University of Alabama at Birmingham

Dr. Sylvie Mrug discussed her studies of early life stress (ELS), epigenetics, and health disparities in the United States. Huge health disparities exist between Black and white Americans, and these differences emerge early in childhood and young adulthood and have profound consequences throughout the life span. The biological effects of chronic psychosocial stress include alterations in DNA methylation, stress reactivity, metabolism, and inflammation. Dr. Mrug is interested in delineating the developmental timing of and racial differences in the connections between ELS and DNA methylation, as well as identifying protective factors that might mitigate the epigenetic effects and poor health outcomes associated with ELS.

Dr. Mrug presented results from the Healthy Passages study, a multisite prospective study of children that is focused on multilevel risk and protective factors for multiple health outcomes. After adjusting for age, sex, and body mass index (BMI), Black race predicted accelerated rates of several measures of epigenetic aging. This effect was partly explained by increased exposure to violence, neighborhood disadvantage, and lower family income. Recent instances of witnessing violence were predictive of epigenetic aging in younger participants (i.e., youth between the ages of 11 and 16 years) but not in 19-year-old participants. Notably, recent episodes of direct victimization with violence did not correlate with epigenetic aging at any age.

The Birmingham Youth Violence Study followed youth from early adolescence to young adulthood, with a main focus on risk and protective factors for youth violence and substance use. Results from this study showed that neighborhood disorder and neighborhood poverty in childhood were associated with a proinflammatory DNA methylation profile and lower cortisol levels, respectively, in adulthood. Importantly, the relationships between childhood neighborhood characteristics and adult health varied by parental discipline and nurturance in childhood. These results support the hypothesis that supportive and consistent parenting mitigates the biological embedding of neighborhood disadvantage in the epigenome during childhood, with implications for health across the life span. Additional studies have not found any protective factors that mitigate the epigenetic aging effects associated with early exposure to community violence. Future efforts will assess the differential effects of specific types of ELS and protective factors; intersectional effects, such as sex and racial differences in links between adversity and epigenetic markers; the developmental timing of ELS exposure and changes in DNA methylation; the transgenerational effects of ELS; and protective factors that interrupt the intergenerational transmission of health disparities.

Biological Mechanisms Linking Social Adversity and Health: Insights from Studies in Nonhuman Primates
Noah Snyder-Mackler, Ph.D., Arizona State University

Dr. Noah Snyder-Mackler shared insights from studies in nonhuman primates on how environmental and social adversity alters health and aging. He noted that Americans with higher SES live at least a decade longer than those with lower SES, and this mortality gap is increasing with time. Increased SES correlates with improved outcomes across a variety of physical and mental health conditions.

The effects of social and environmental influences on health can be modeled in nonhuman primates, which exhibit similar associations between health, life span, and status. Rhesus macaques form structured, hierarchical societies that can be manipulated by researchers to directly assess the effects of social status on health and biological functions. When female macaques are introduced into new social groups, the animals' order of introduction strongly and stably predicts their subsequent dominance rank. Animals with lower social status exhibited robust alterations in immune and inflammatory gene expression at baseline and in response to infection. Chromatin accessibility and gene expression analysis of peripheral blood mononuclear cells collected from these animals demonstrated epigenomic changes that corresponded to social rank. Glucocorticoid-activated genes were more accessible and more highly expressed in high-ranking females, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)–activated genes were more accessible and more highly expressed in lower-ranking females. Notably, the effects of social status on immune cell function could be reversed by changing an animal's social rank, demonstrating that primate immune systems can respond rapidly to changes in the social environment. Further studies have shown that higher social status is associated with younger relative transcriptional ages in female macaque brain tissue. Dr. Snyder-Mackler's current studies are focused on investigating the acute effects of natural disasters on biological aging and the mechanisms of resilience and vulnerability to the long-term consequences of such exposures.

The Potential Role of Racism, Marginalization, and Discrimination in Systemic Dysfunction and Biological Aging
Idan Shalev, Ph.D., The Pennsylvania State University

Dr. Idan Shalev described his research related to the effects of ELS on health and aging. Moment-by-moment changes at the cellular level compound over time and result in variable systemic dysfunction, aging, and disease decades later. Adverse exposures *in utero* and across childhood and adolescence must be studied to develop a comprehensive understanding of the early origins of health and disease risk. In 2023, Dr. Shalev and his colleagues hypothesized that aging and development are two sides of the same coin. Compared with adults, children age at an accelerated biological rate, and earlier interventions likely will delay the onset of negative outcomes related to ELS later in life. A systematic review and meta-analysis of samples from approximately 750,000 people revealed that the rate of telomere shortening was not linear across the life span. Telomere length was closely correlated with chronological age only during the early years of life, and this early period represents a window for ELS to profoundly alter the aging trajectory.

Biological aging clocks reflect biological and lifestyle influences on aging and can be based on telomere length, gene expression levels, protein levels, DNA methylation levels, and composite measures. These influences can be unidirectional (e.g., prenatal stress and childhood trauma contribute to biological aging) or bidirectional (e.g., mental disorders and age-related diseases both contribute to and are influenced by biological aging) and can be mitigated by healthy lifestyle factors. The mechanisms through which stressors increase aging (e.g., reduced telomere length) are not defined but likely involve inflammation and oxidative stress. Dr. Shalev noted that the potential health effects of RMD during early life are understudied. He highlighted one study showing that Black teenagers who attended segregated and highly

disadvantaged primary schools exhibited increased rates of epigenetic aging compared with those who attended segregated schools with moderate disadvantage. School contexts were not associated with epigenetic aging in white youth.

Panel Discussion

- Dr. Norris asked whether the concepts of neighborhood violence and poverty are subjective. The same neighborhood might feel safe and affluent or dangerous and poor depending on the perspective of different populations. Drs. Mrug and Suglia shared that they both have observed effects that are associated with objective measures of neighborhood disadvantage, as well as effects that are associated with self-reported indicators of neighborhood disadvantage.

- In response to a question about the contributions of genes and the environment to intergenerational trauma (e.g., post-traumatic slavery syndrome), Dr. Snyder-Mackler shared his perspective that the environment plays a major role—whether through inherited epigenetic changes or developmental exposures—in the transmission of traumas between generations.

- Dr. Gregory G. Germino, NIDDK, commented that type 2 diabetes is more severe and associated with worse complications in young patients than in adults. He asked whether the intersection between the effects of RMD and biological aging had been investigated in the setting of type 2 diabetes in youth. Dr. Mrug highlighted her involvement in a multisite study to identify the predictors of type 2 diabetes in youth. ELS is a factor that will be addressed by the study.

- The meeting participants discussed the relative contributions of genes and the environment to biological stress response. People will exhibit variable responses to identical environments because of their genetic makeup; however, differences observed at the population level are due to social and environmental factors.

- In response to a question about the health consequences of accelerated epigenetic aging, Dr. Suglia noted that her studies have demonstrated an association between accelerated aging and increased incidence of metabolic syndrome. Dr. Mrug added that biological clocks are robust predictors of morbidity, mortality, cognitive ability, and many chronic health conditions.

- In response to a question about the role that social behaviors play in the macaque experiments, Dr. Snyder-Mackler emphasized that social connection is essential for survival and reproduction in primates. He noted that differences in immunity and inflammation observed in the low-ranking macaques primarily were driven by social isolation.

Prenatal and Fetal Mechanisms
Moderator: Tracy Bale, Ph.D., University of Colorado, Anschutz Medical Campus

Epigenetic Mechanisms of Prenatal Social Environmental Stressors and Offspring Health
Chantel Martin, Ph.D., M.S.P.H., The University of North Carolina at Chapel Hill

Dr. Chantel Martin presented research focused on understanding how the prenatal social environment contributes to early offspring health disparities via epigenetic mechanisms. Residential segregation is a manifestation of structural racism that is a fundamental cause of persistent racial health disparities. Even decades later, areas that were once redlined continue to suffer from disinvestment, poverty, limited resources and opportunities, and higher levels of air pollution, policing, and violence. Epigenetic changes, which alter gene expression, are one mechanism through which patterns of health and disease can be "embodied" as stress responses to RMD, structural racism, and related adverse exposures. Preliminary

studies have shown that neighborhood poverty and deprivation are associated with epigenetic changes in the offspring of affected people.

Gestational exposure to neighborhood crime differs by race and ethnicity, with Black and Latina pregnant people having higher exposure to local crime than white pregnant people. Dr. Martin shared results from the Newborn Epigenetic Study (or NEST), a prospective birth cohort study of mother–child pairs in and around Durham, North Carolina, with follow-up of the children into adolescence. Within the NEST cohort, gestational exposure to neighborhood crime was associated with increased blood pressure in the children of Black (but not white or Latina) mothers. Additionally, gestational exposure to neighborhood crime was associated with methylation changes in 16 CpG sites in genes related to aging and cardiometabolic outcomes. A pilot project is underway to examine DNA methylation trajectories in childhood in response to social and chemical environmental exposures.

Exposure to neighborhood deprivation is defined by nine indicators (i.e., median household income; median home value; percent of households below the federal poverty level; percent of female-headed households; percent homeownership; percent of households receiving interest, dividends, or rental income; percent of adults 25 or older with at least a high school diploma; percent of adults with at least a bachelor's degree; percent of households with a telephone) at the census block level. Neighborhood deprivation is patterned across race and ethnicity. Increasing neighborhood deprivation scores are associated with 12 differentially methylated regions in genes related to cardiomyopathy, arteriosclerosis, lipid metabolism, and immune function. The associations varied by race and ethnicity, with positive associations in Black participants and negative effects in white participants. Differential methylation at CpG sites that correlated with neighborhood deprivation scores was also associated with offspring weight at 6 and 12 months of age.

Fetal Origins of Health Disparities: Transgenerational Consequences of Structural Racism
Nana Matoba, M.D., M.P.H., University of California, San Diego

Dr. Nana Matoba shared her research on the transgenerational consequences of structural racism. She noted that birthweights vary by maternal nativity. Foreign-born Black women who immigrate to the United States have birth outcomes similar to white women; the favorable birth outcomes disappear within a generation. Transgenerational factors that contribute to pregnancy outcomes in the next generation include the timing of the mother's birth, lifetime neighborhood economics, and shifts in economic mobility. Other social determinants of disparities in birth outcomes include neighborhood poverty, the role of fatherhood, exposure to gun violence, redlining, teen birth across generations, and social and racial polarization.

Dr. Matoba presented results from a study of neighborhood gun violence and birth outcomes in Chicago, Illinois. Geographic distributions of gun-related crime and percent low birthweight follow similar distributions in the area. Race and ethnicity were associated with birth outcomes; exposure to gun violence had no effect on these disparities, which likely were due to socioenvironmental systems, processes, and interactions for which race serves as a proxy. Another study showed that preterm birth rates were higher among African American women in redlined areas than in non-redlined areas.
Dr. Matoba introduced the concept of the placenta as a valuable source of biomarkers of differences in prenatal exposures. To investigate mechanisms by which maternal exposures are transmitted to offspring, associations between race and four types of placental pathologies were evaluated among preterm births. Race was associated with acute and chronic inflammation and fetal vascular pathology; African American race remained significantly associated with increased chronic inflammation after adjusting for maternal age, steroids, preterm labor, gestational age, and infant sex. Future studies will investigate the mechanisms through which RMD-related stress modifies pregnancy.

Panel Discussion

- Dr. Bale asked whether effects of the prenatal social environment differed by the sex of the fetus. Dr. Martin noted that gestational exposure to neighborhood crime was only associated with significant methylation changes in female offspring.

- Dr. Norris remarked that birth outcome disparities in Black populations are only partly explained by differences in SES. He asked whether epigenetic changes varied by SES. Dr. Martin explained that her studies adjusted for, but did not stratify by, SES. Several studies, however, have identified SES-related epigenetic marks in genes related to inflammation.

- A meeting participant asked about additional factors that could explain the racial differences observed in the associations between neighborhood deprivation scores and epigenetic changes. Dr. Martin answered that her group is careful not to adjust for factors that might be causally downstream from neighborhood characteristics. Factors that might predict why someone lives in a particular area (e.g., maternal age, employment status, or marital status) and maternal behavioral factors were accounted for. Dr. Martin added that she has funding to interrogate upstream policy factors that also might be responsible for sorting people into different neighborhoods. When asked about adjusting for maternal metabolic status, Dr. Martin answered that she has considered stratifying the data to determine whether the associations differ based on this parameter.

- In response to a question about whether examined predictors were causal factors or colinear with other factors that affected DNA methylation and placental function, Dr. Matoba emphasized that no predictors likely are causal; they likely exist as one of many measures of RMD.

Stress, Allostatic Load, and Inflammation-Related Mechanisms
Moderator: Debra MacKenzie, Ph.D., The University of New Mexico

Discrimination as a Stressor Influencing Brain–Gut Microbiome Alterations: Evidence from Obesity
Arpana Gupta, Ph.D., UCLA

Dr. Arpana Gupta discussed RMD as a stressor that influences the brain–gut microbiome (BGM). Discrimination is associated with a higher risk of obesity. Some research has shown that people who report higher levels of discrimination have odds ratios of obesity that are three to six times higher than those who do not report perceived discrimination. A growing body of research has implicated each component of the BGM axis in obesity. Discrimination is a chronic stressor, and stress can influence the brain and gut microbiome, as well as eating behaviors, which can lead to obesity.

To understand how discrimination affects the BGM system, Dr. Gupta's group investigated how discrimination affects the reward centers of the brain in response to different types of food. Participants in the study underwent assessments of their perceived discrimination, brain functional magnetic imaging (fMRI), and fecal collection to measure metabolites. The participants were divided into groups based on whether they experienced high or low levels of discrimination. People who reported higher levels of discrimination also reported higher cravings for unhealthy foods; experiences of discrimination did not influence cravings for healthy foods. When participants viewed images of unhealthy sweet foods, a significant increase in fMRI activity was seen in the insula. When participants viewed images of unhealthy savory foods, a significant increase in activity was seen in the putamen and orbitofrontal cortex. All these regions are also associated with reward processing and motivation. When participants looked at images of healthy foods, a significant increase in activity was seen in the middle superior frontal gyrus, a region associated with executive control. These findings suggest that discrimination might be

associated with altered food-cue responses in the brain. Whether these responses are related to reward processing or executive control is dependent on the type of food. Dr. Gupta's group also assessed how discrimination alters gut metabolites. Levels of N-acetylglutamate and N-acetylglutamine were significantly higher in the group that experienced high levels of discrimination than in the group that experienced low levels of discrimination. These metabolites are associated with inflammation and oxidative stress, hinting at a possible link between discrimination and negative health outcomes. Associations between discrimination-related brain and gut signatures were skewed toward unhealthy sweet foods after adjusting for age, diet, BMI, race, and SES. RMD stress likely contributes to enhanced food-cue reactivity and BGM disruptions that can promote unhealthy eating behaviors, leading to an increased risk for obesity.

Further studies have shown that discrimination is associated with BGM changes, which vary by race and ethnicity. Discrimination was correlated with alterations of brain networks related to emotion, cognition, and self-perception, as well as structural and functional changes in the gut microbiome. Among Black and Hispanic individuals, high levels of discrimination led to negative outcomes, like anxiety and neuroticism, as well as increased systemic inflammation. High discrimination in white individuals was associated with anxiety but not inflammation. Among Asian individuals, positive associations existed between metabolites related to cholesterol and to several clinical measures (e.g., anxiety, depression, physical symptoms)—a pattern suggesting possible behavioral responses (e.g., eating foods that are high in fat and cholesterol) to discrimination. Another study demonstrated that a history of discrimination is related to alterations of brain networks related to emotional regulation, executive cognition, and self-perception, as well as structural and functional changes in the gut microbiome suggestive of systemic inflammation.

Discrimination Exposure and Inflammation
Adolfo G. Cuevas, Ph.D., New York University

Dr. Adolfo G. Cuevas emphasized that discrimination itself is a social determinant of health. SES alone cannot fully account for health disparities observed between Black and white Americans, and evidence is emerging that experiences with RMD drive racial health inequality. Discrimination challenges a person's sense of belonging in society and leads to feelings of isolation, worthlessness, and inadequacy. Experiences with discrimination are common in the United States and can alter behavioral and biological responses and change physical and mental health outcomes.

Research has demonstrated that inflammatory pathways are activated in response to perceived and actual threats. Conversely, the presence of inflammation predisposes people to perceive ambiguous situations as dangerous or threatening. Inflammation levels are elevated in Black Americans (compared with white or Asian Americans), an effect that can be observed as early as adolescence. A systematic review of the literature on inflammation and discrimination yielded further evidence: Everyday discrimination is associated with increased levels of CRP; lifetime discrimination in Black men is associated with higher levels of serum e-selectin (a surface molecule involved in the adhesion of immune cells to inflamed tissues); and adults reporting high levels of discrimination early in life had increased levels of inflammatory cytokines. Limited but supportive evidence indicates a sustained association between discrimination and inflammation over time. This association does not vary by race and is not stronger in minoritized populations. Most studies of discrimination and inflammation focus on older adults. Future work should focus on earlier life stages, increase generalizability to multiple populations, apply an intersectional approach, assess inflammation markers beyond CRP and interleukin-6, and develop improved measures of discrimination.

Inflammatory Mechanisms Linking Discrimination and Health

Carrington Merritt, The University of North Carolina at Chapel Hill

Ms. Carrington Merritt presented on behalf of her mentor, Dr. Keely Muscatell. The Muscatell group is interested in brain–body pathways linking racism and health. Higher discrimination is significantly associated with higher levels of inflammation, but little empirical evidence exists to show that inflammation mediates the relationship between discrimination and chronic health conditions. Additionally, few studies have addressed protective factors involved in this relationship.

The term "perceived control" describes a person's perception that they can influence events in their life. Increased perceived control is positively associated with reduced cortisol levels in response to discrimination, weakens the effect of chronic stress on inflammation levels, and is beneficial for overall health. Ms. Merritt explained that her study was designed to examine inflammation as a mechanism linking discrimination and cardiovascular health in Black Americans, assess perceived control as a protective factor in the relationship between discrimination and inflammation, and determine whether higher perceived control can mitigate the effects of discrimination on inflammation and cardiovascular health. Data for her study were taken from the Midlife in the United States (MIDUS) study. Her analysis revealed that CRP was a significant mediator between discrimination and the presence of cardiovascular conditions. She also found that perceived control moderated the link between discrimination and CRP levels—CRP was a significant mediator only among people with low or average levels of perceived control.

Because the findings from this study are only correlational, future studies are needed to establish the causal link between experiences of discrimination and increased inflammation. Simulating "real-world" experiences of discrimination under experimental conditions in a way that is ethical and preserves the well-being of research participants is a major issue associated with examining the direct effects of discrimination on immune activity. The Muscatell group is using physiological monitoring of participants before and after the Trier Social Stress Test to address this challenge. The protocol is being updated in response to feedback from study participants.

Panel Discussion

- In response to a question about subgroup differences in inflammatory markers, Dr. Cuevas commented that subtle differences due to experimental design might be observed. Ms. Merritt added that certain markers respond more strongly to acute versus chronic discrimination stress.
- When asked what can be done to increase perceived control (especially in the context of a marginalized person with low actual control), Ms. Merritt noted that levels of perceived control vary even among people with low SES, suggesting that it can be a target for intervention. Resources should be devoted to developing psychological and other methods for increasing perceived control and to making these methods available to those who need them. Dr. Gupta added that even small lifestyle changes or increased social connectedness have been shown to improve health outcomes and are likely to increase perceived control. Dr. Debra MacKenzie mentioned patient advocates as another possible way of increasing perceived control.
- A participant asked Dr. Gupta whether discrimination perceived as being based on race led to worse health outcomes. Dr. Gupta noted that she has not directly evaluated this but added that members of every racial and ethnic group perceive discrimination. Different groups, however, experience varying health effects because of discrimination, and these differences might be the result of brain signatures, metabolites, or microbiomes that vary among different groups.
- Dr. Norris asked whether data sets evaluating the connection between discrimination and inflammation had included measures of sleep quality. Dr. Cuevas listed several studies (including

MIDUS) that evaluated the quality of participants' sleep. These data sets present important opportunities to identify mechanisms whereby discrimination alters systemic inflammation.

Day 1 Closing Comments and Adjournment
Gregory G. Germino, M.D., NIDDK

Dr. Gregory G. Germino, Deputy Director, NIDDK, reviewed the agenda for Day 2 and encouraged meeting attendees to participate in the breakout session discussions. He thanked the day's speakers for delivering fascinating talks that highlighted a range of potential biological mechanisms that may contribute to the biological consequences of RMD. Dr. Germino thanked the external and internal planning committees for their hard work in organizing the workshop and expressed special gratitude to the patient and community panelists for grounding the day's discussions in the ultimate aim of this research—to improve health outcomes for people experiencing racism, marginalization, or discrimination. Dr. Germino thanked participants for attending and adjourned Day 1 of the meeting.

THURSDAY, APRIL 18, 2024

Day 2 Opening
Jenna Norton, M.P.H., Ph.D., NIDDK

Dr. Norton welcomed everyone to the second day of the workshop and touched on the previous day's presentations, noting the productive first day and insightful sessions.

Plenary Panel
Moderator: Karen Parker, Ph.D., M.S.W., Sexual & Gender Minority Research Office, NIH

Contextualizing Race, Racism, and Social-Psycho-Biological Pathways to Health: A Historical Lens
Amani Nuru-Jeter, Ph.D., M.P.H., University of California, Berkeley

Dr. Amani Nuru-Jeter shared a historical and conceptual overview of race and the process of racialization and marginalization in the United States to contextualize the socio-psycho-biological mechanisms underlying the relationship between racism and health. In the biomedical sciences, race often has been defined as genetic similarity. However, the authors of studies on race have themselves noted substantial substructure and admixture among African American populations and stated that genetic similarity (i.e., shared ancestry) likely correlates with social, cultural, and environmental variables that directly influence health. Definitions of race in the social sciences refute claims about the biological basis of race and instead describe the social, cultural, and political foundations of racial categorization. The definition of race in the most recent *Dictionary of Epidemiology* still focuses on a biological basis of race but notes that SES and cultural and behavioral differences often are more important than racial differences in influencing health status. This definition still ignores how SES, cultural differences, and behaviors are determined by racism.

Dr. Nuru-Jeter provided a historical overview of racial categorization in the United States. The three-fifths compromise of 1787 increased the political power of Southern states by including enslaved populations in their official population counts without allowing these people to vote. Indigenous peoples were not counted at all. In 1820, "Black" and "mulatto" were the only racial categories listed on the census. The federal process of racialization evolved to include racial purity schemes, which were motivated by socioeconomic and political interests and particularly focused on subjugating people with African and Indigenous ancestry. After the Civil War, Black Codes were adopted by Southern states, which continued to operate under *de facto* racial discrimination. Jim Crow laws adopted in the North and South after Reconstruction rendered services and facilities "separate but equal." Although the Civil Rights

Act of 1964 outlawed racial discrimination, contemporary phenomena—such as white flight, predatory lending, and gentrification—continue to uphold historical patterns of race-based segregation and discrimination. Native Americans were not granted U.S. citizenship until long after African Americans and women. Before they were officially considered U.S. citizens, Indigenous peoples were subject to forced removal and confinement to reservations. Alaska Natives and Native Hawaiians suffered many of the same abuses as Native Americans, including the loss of land and forced assimilation. Current guidelines for racial categorization—established in 1977 by the Office of Management and Budget—are a direct result of sociopolitical actions and efforts to monitor compliance with civil rights laws. This shared history defines race in the United States. Racial health disparities are not programmed in the body; rather, health inequities are encoded in the bodies of marginalized and racialized people by racism itself.

Dr. Nuru-Jeter reviewed early efforts in the field, which focused on personally mediated racism. Later research sought to address multiple levels of racism and, in recent years, increasing attention has been paid to structural racism (commonly defined as the totality of ways in which societies foster racial discrimination through mutually reinforcing systems that, in turn, reinforce discriminatory beliefs, values, and distribution of resources) and cultural racism. Dr. Nuru-Jeter noted that epidemiology studies have historically overlooked social science literature that might shed light on the emergence and maintenance of social inequalities. She concluded with several recommendations for future studies of mechanisms underlying the relationship between racism and health: (1) Conceptualize the problem within the context of racism as a multidimensional construct, (2) identify measures that are appropriate for the type of racism being studied, (3) consider heterogeneous treatment effects, and (4) consider structural and cultural racism and how racism operates across systems.

Racism as a Social–Environmental Toxin That Shapes the Inequitable Population-level Distribution of Disease

David Chae, Sc.D., M.A., Tulane School of Public Health and Tropical Medicine

Dr. David Chae explained that his research program is focused on the resilience of Black people in the face of structural impediments. He shared epidemiologic data on life expectancy disparities in the United States and noted that residents of states in the Deep South have shorter life expectancies than people in other states. For example, Alabama residents have an average life expectancy of 73.7 years, which is lower than the U.S. average of 77.6 years. Even within a state, life expectancies will vary depending on the racial composition of the subpopulations. Within Alabama, the average life expectancy in majority-white Lee County is 77.2 years; the average life expectancy in majority-Black Macon County is 72.0 years. Dr. Chae pointed out that the city of Tuskegee—the location of the infamous Tuskegee Syphilis Study—is located in Macon County.

Dr. Chae noted that populations in such areas are often labeled as “vulnerable” or “resilient” without specifying the level at which these terms apply (e.g., population vs. individual) or the source of the vulnerability (e.g., susceptibility vs. exposure). Dr. Chae added that vulnerability and resilience are more appropriate for describing social structures than communities. Furthermore, instead of expecting communities to be resilient, more resilient societal structures and systems should be built.

One characteristic that determines the vulnerability or resilience of social systems is the presence of racism. Using Google searches for racial slurs within a given region as a proxy measure of racism, Dr. Chae’s group has shown that Black mortality and poor birth outcomes correlate with regional racism. Dr. Chae shared the results of a study showing that multiple levels of racism operate jointly to increase biological aging (as measured by leukocyte telomere length) in African American men. Results from the Black Women’s Experiences Living with Lupus (BEWELL) study demonstrated that racial discrimination stress is associated with increased organ damage and disease progression in African American women with SLE. Stress from vicarious racism (seeing racism enacted on others) and

anticipatory racism (efforts to brace oneself for being a target of racism) also correlated with increased disease severity in BEWELL study participants.

Racism, in addition to being a social and moral crisis, is a fundamental cause of racial inequities in health outcomes. The next generation of research in this field must develop methods for capturing racism at the population level; address how laws and policies impact disease risk; and identify interventions addressing SDOH that are feasible to implement, result in sustained improvements in health, and eliminate racial inequities in diseases like SLE.

A Social Safety Perspective on Intersectional Health Disparities
Lisa Diamond, Ph.D., The University of Utah

Dr. Lisa Diamond presented a social safety perspective on the health effects of stigma in sexually and gender-diverse people. Minority stress theory posits that stigma-related stressors contribute to allostatic load and "wear and tear" on stress response systems. The theory correctly identifies the need to consider different stress exposures and contexts and accurately describes the psychobiological response to stigma-related stressors. However, it does not address variation in these associations at the individual level (e.g., cortisol levels do not always correlate with reported stress) that represent vulnerability or resistance to the effects of stigma-related stress.

The Generalized Unsafety Theory of Stress states that, rather than being caused by the stressors themselves, chronic stress responses result from the nervous system's inability to shut off the stress response because of a generalized (and largely unconscious) perception of unsafety. Humans evolved to live in the constant presence of threats. Rather than being a result of stressors, prolonged physiological stress responses are a result of decreased safety and increased vigilance between stressor events—in other words, the inability to return to baseline between bouts of stress. In people, chronic hypervigilance manifests as emotional dysregulation, reduced attention span and cognitive abilities, increased rumination, sleep dysregulation, isolation, self-soothing, and chronic inflammation. Notably, hypervigilance can be reduced by social safety—that is, unconditional social connection, protection, and belonging.

The Social Safety Theory hypothesizes that maximizing social safety and minimizing social threat is an organizing principle of human behavior. Humans evolved to regard social abandonment as a primal threat and are programmed to be extremely sensitive to social information. Social safety reduces the need for monitoring and vigilance and frees resources for productive work. Safety increases feelings of calm and connection and results in positive behavioral adaptations and improved health. Conversely, when people are marginalized or stigmatized, they are forced to exist in an unsafe world where positive social signals are withdrawn, and hypervigilance is needed to monitor constant social uncertainty and threat. Fewer cognitive and energetic resources are available for work, play, and rest; negative feelings and behavioral responses are induced; and health becomes compromised.

Dr. Diamond emphasized that studies of associations between RMD and health outcomes must measure social safety in addition to stress. She noted that preliminary studies have shown that the level of social safety required to reduce chronic hypervigilance in adulthood is dependent on ELS. ACEs, abuse, and trauma increase proinflammatory phenotypes and likely magnify responses to stigma. People who experience chronic exposure to unsafe conditions in childhood exhibit psychobiological adaptations that have been named complex post-traumatic stress disorder.

Dr. Diamond reviewed interventions to increase social safety and connection, including reducing overt rejection and discrimination; implementing affirmative laws and policies; and importantly, enabling regular, affirmative, protective, and in-person social contact. Research should prioritize developing better

measurements of childhood adversity at different developmental stages and deepening our understanding of hypervigilance and social safety across different domains.

Panel Discussion

- In response to a question about how best to avoid using SDOH as proxies for racism—much like SES has been used for race in the past—Dr. Nuru-Jeter emphasized the need to be clear about the variables that are being measured and the input that is being captured. Errors are introduced and the validity of research is compromised when measures are not precise. If appropriate measures are not available, they must be developed.
- A participant asked about ways to address resilience without adding to the burden of marginalized people. Dr. Diamond noted that the resilience associated with social support is effortless. Social support is the knowledge that support will be there for you without your needing to ask for it, and this form of collective resilience emerges naturally from safe environments and positive social contexts. Dr. Chae noted that marginalized communities are considered vulnerable when they actually display high levels of resilience and resourcefulness. Dr. Nuru-Jeter agreed that resilient structures can relieve the need for individual forms of resilience, which is a unique burden carried by marginalized groups.
- When asked about ways to close the gaps between scientific knowledge and implementation within communities, Dr. Diamond answered that she is looking for ways to capitalize on existing support structures—for example, ways to help connect people with safe peers and mentors, as well as ways to support that safety structure. Dr. Nuru-Jeter emphasized that communities know what works and what does not. Investigators should move beyond the gatekeeping of knowledge and rote efforts like community advisory boards to engage deeply with communities and their ways of knowing.
- In response to a question about the role of ACEs, Dr. Chae commented that his studies have demonstrated that the effects of ACEs are mediated by adult exposures. ACEs increase the risk of adverse health effects, but space for management and mitigation exists within that trajectory.

Biobehavioral Mechanisms
Moderator: William (Bill) Elwood, Ph.D., National Institute of Dental and Craniofacial Research (NIDCR), NIH

Neural Mechanisms Linking Social Inequality to Health
Gabriella Alvarez, Ph.D., University of Pittsburgh

Dr. Gabriella Alvarez presented her studies on brain–body pathways linking racism and health. She explained that the brain engages in predictions based on prior experiences and internal and internal physiological signals to manage allostasis, the adaptation to current and future environmental challenges. When a person's brain responds to a potentially threatening stimulus, recent work suggests that vigilance can be activated by relevant cues. To assess the importance of these cues, participants completed an fMRI task in which they experienced the differing conditions. The negative condition involved participants' viewing negative images followed by brief presentations of neutral faces; the neutral and positive conditions involved participants' viewing neutral or positive images followed by brief presentations of neutral faces. Functional connectivity of the allostatic-interoceptive network was investigated by analyzing activity in its two smaller intrinsic networks—the default mode network and the salience network. Her group tested whether racial discrimination (as opposed to other forms of discrimination) affected functional connectivity during presentations of faces after priming. In Black participants, only lifetime discrimination was significantly associated with increased connectivity to negatively (versus neutrally) primed faces. In summary, existing in a state of negativity or threat potentially can lower the

sensitivity or threshold for detecting negative treatment due to race. These findings are consistent with other work revealing the coordination between regions using prior memories and information from the environment to prepare the body for a context-appropriate response.

Dr. Alvarez shared results from another study assessing how the brain's communication network balances efficiency and costs. High-efficiency networks communicate faster across longer ranges but cost more in the form of energy and resources. Low-efficiency networks require fewer resources but consist of more short-range connections that do not communicate effectively. In the study, lower SES was associated with increased global efficiency that likely was metabolically costly. Future work will explore whether higher global efficiency is detrimental in the long term and could be deleterious to overall health and mental functioning.

Using a Health Equity Approach to Investigate the Role of Diet and Sex Differences in Cardiometabolic Risk Factors
Ana F. Diallo, Ph.D., M.P.H., RN, Virginia Commonwealth University

Dr. Ana F. Diallo described her investigations of how inputs from biology (e.g., age, sex, genetic makeup, chronic diseases, physical activities), health behaviors (e.g., values/priorities, emotions, memories, fears/motivations), and social context (e.g., race/ethnicity, social support system, employment, education, physical environment, culture/community) influence cardiometabolic risk. She described her involvement with the Mobile Health and Wellness Program in Richmond, Virginia. The program serves mostly older women, the majority of whom are Black women with low incomes. Food insecurity was a great challenge for one-third of the clients, and a healthy meal program was developed to connect these people to Supplemental Nutrition Assistance Program benefits and other resources. These efforts were extended into surrounding communities where food insecurity also was prevalent. A prescription produce program was established to make fresh produce more readily accessible. Measured outcomes included reduced food insecurity, increased produce intake, and reduced blood glucose levels only 6 weeks after the program was initiated. Dr. Diallo emphasized that being active and involved with the community helped her team design better interventions. An event was organized to share the research findings with the community, and trust was built by offering services over time.

Program organizers noticed that community members struggled to parse the relationship between healthy diet, cholesterol, and cardiovascular health. Dr. Diallo's group used data from the Jackson Heart Study to examine whether sex differences and genetic susceptibility intersect with SDOH in the association between diet quality and cholesterol levels. Sex-based differences were observed in all lipid measures; healthier dietary quality scores were inversely associated with dyslipidemia in male participants. Further studies showed that the presence of small and large low-density lipoproteins mediated the effects of cholesterol on gene expression.

Panel Discussion

- In response to a question from Dr. Alvarez about implementation, Dr. Diallo answered that the main challenge she experienced was funding. Building strong relationships with the community requires resources and a timeline that tenure-track researchers cannot afford. Dr. Diallo added that the research methods needed to establish the validity of the studies were challenging. Randomized trials were nearly impossible to implement when community members talked to one another and shared information related to their study participation.
- Dr. Norton asked how social safety systems for young researchers could be improved. Dr. Diallo noted that facilitating connections with experts in the field would be beneficial to young investigators. Dr. Alvarez commented that national-level policy that supports the family and

friends of young researchers from more vulnerable backgrounds would ensure that their social safety network can support them.

Breakout Groups

Workshop participants were invited to choose a breakout session on one of several topics. Guiding questions were provided to frame the discussions, and representatives from the virtual and in-person breakout groups were invited to report the results of their discussions.

Group 1: Modeling Fundamental Aspects of RMD through Experimental Science

What aspects of RMD can we model using animals, human studies, and other approaches? What are the limitations of these models and what aspects can we not model via these approaches? Can such models be used to better understand the differential impacts of RMD exposures within population groups? What are the most promising experimental models through which to better understand the biological consequences of RMD? What are their strengths and limitations? Are the appropriate techniques and methodologies available? What needs to be developed?

Modeling RMD with animals is a challenge because only humans have the cognitive ability to perceive RMD and interpret external stressors. Pervasive and chronic stress can be studied in animal and cell models over specific periods of the life course. Certain animal and cell models might be uniquely suited for answering particular questions or investigating biological mechanisms at the cellular level (e.g., aspects of the immune system, metabolic changes, hormonal effects, social rejection stress, reversibility of RMD consequences). Human research can be performed under controlled conditions to assess physiological responses to RMD. Some aspects of social support might be captured in animal models, but not the complexity of human social interactions, support, and safety. Telomere biology is different in some animal models, and not all sex differences can be modeled in rodents. Animal models to better understand the differential impacts of RMD exposures within population groups are challenging because animals can rarely be housed in large-group settings. Human controlled studies might be useful for assessing the differential impacts of RMD exposures within population groups, but stress manipulations are limited in human studies. The most promising experimental models through which to better understand the biological consequences of RMD will enable dynamic data collection rather than assess static time points. Animals can be used to investigate effects in specific organs. Methods to perform deep phenotyping in human study participants should be developed and standardized, and repeated assessments can be performed in home settings or by using wearable technology or cell phone apps. Results from animal studies should be verified and explored in human studies (and vice versa). Community advisory boards should be appointed and consulted about experimental science related to RMD. All RMD research should be guided by potential outcomes for people.

Group 2: Addressing Measurement and Analytical Challenges

How do we understand the potential additive or multiplicative effects of RMD in people with multiple intersecting and marginalized social identities? How do we account for the tension between the societal-level nature of RMD versus the individual-level nature of biological processes? How do we understand the differential impacts of RMD exposures within population groups? To what extent do reported measures capture potential changes in the way experiences of RMD vary over time? Do past measures adequately apply to today's experiences? How do we measure structural RMD versus the ways in which people experience the exposure to structural RMD? How do we address challenges in study design and analysis?

More comprehensive, nuanced, and creative analytic approaches—including combined groups, planned missingness with multiple imputation, clusters of natural groups, and more exact methods for small sample sizes—are needed to assess the effects of RMD in people with intersecting identities. These effects are unlikely to be additive because additive models show independent effects rather than intersectional effects. Statistical analyses must move beyond linear interaction terms. Qualitative and quantitative measures are both necessary. Using the same measure of racism in different contexts might not be appropriate. Machine learning models can be used to integrate the effects of RMD at the individual, community, state, and ecological levels. The work on structural racism and its drivers should be connected to individual-level structural determinants. Uniform measures of structural racism are needed. NIH can play a role in addressing the lack of consensus and clarity regarding definitions of structural racism. Measures that account for compounding and syndemic effects are needed.

Group 3: Pathways to Interventions

How can we leverage findings from this research to improve the lives of people who experience RMD? What might we learn from those who are exposed to RMD but do not experience as-severe consequences, in order to identify opportunities to mitigate the impacts of racism, marginalization and discrimination? What risks might this line of research pose to people who experience RMD, and how can we mitigate these risks? How can we ensure research in this space drives toward solutions rather than simply "admiring the problem"?

The definition of terms and their measurement should be standardized. Different communities' understanding of terms like "racism" and "marginalization" should be investigated. Supportive and protective environments are critical to mitigating the effects of RMD. The importance of creating safe spaces for children and young people should be emphasized. Researchers should learn from the community about their experiences of RMD and engage with policymakers to make change at the population level. Tools and programs should be developed to prepare young people to move from protective environments to new places where the effects of marginalization might be experienced differently. Opportunities for patients and providers to learn about bias should be developed. Research teams should include patients as equitable partners. Registries for community-based organizations and research institutions that are interested in partnering around health disparities or health equity issues would be helpful.

Group 4: Intergenerational, Transgenerational, and Life Course Implications

How might the biological consequences of RMD accumulate over the life course? How can we best measure or assess potential accumulation through research? What specific time periods across the life course may be particularly important for understanding the biological consequences of RMD? How might the biological consequences of RMD pass from parents to children? How can we best measure or assess this transmission through research?

Longitudinal studies of birth cohorts are needed. Accelerated study designs should be considered. Measures of social safety are needed. Specific adversities at specific times might be associated with specific epigenetic markers; this association could be evaluated with cross-sectional studies. Different types of adverse experiences should be assessed. Hidden trauma might occur when older generations teach hypervigilance or other behaviors that can create stress responses in the next generation. Specific life span periods that should be studied include times of rapid brain or hormonal development, prenatal and pregnancy exposures, DNA methylation at birth, and early childhood and adolescence. Biological consequences of RMD might pass from parents to children through parenting styles or manifest as epigenetic changes that persist across generations. More research is needed to identify the ideal window for assessing potential accumulation in a diverse sample. The time before pregnancy should be captured,

and investigators should follow the mother's health after childbirth. The placenta might mediate the transmission of biological consequences of RMD from parents to children. Placenta tissue can be accessed through placenta banks and compared across generations.

Group 5: Building and Nurturing a Future Workforce to Address the Biological Consequences of RMD

Who needs to be at the table to effectively conduct this research? How do we attract those groups to this space? What skills need to be developed or enhanced to advance research in this area? What existing models might we learn from to optimize the conduct of the transdisciplinary work required for research in this area? How do we address burnout in this field, particularly for those from communities that experience RMD?

Research teams should include community members with relevant lived experiences, researchers with diverse backgrounds and relevant lived experiences, interdisciplinary perspectives, policymakers, government and industry representatives, and funding organizations. NIH should continue prioritizing these issues and funding relevant programs. The ways that universities evaluate this research for tenure purposes can be changed. Workspaces should be inclusive, and work–life balance should be respected. Skills that should be developed to enhance this research include measurement-related research, interdisciplinary collaboration, team science, effective communication, and ethical considerations of research. Lessons can be learned from critical race theory, SDOH frameworks, the NIH Common Fund Program, the Cancer Moonshot℠ program, community-based participatory research, and the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, as well as from biopsychosocial and intersectionality models. Burnout in this field (particularly for those from communities that experience RMD) can be addressed by increasing awareness and promoting respect for other types of knowing, avoiding tokenism, communicating about the positive changes that are happening in an institution, and leveraging the power of mentors.

Conclusion—Closing Remarks and Adjournment

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Dr. Norton thanked the speakers, moderators, and participants for their contributions to the workshop. She encouraged researchers to continue the important conversations spurred by the meeting and to continue advancing the science of health disparities and RMD. Dr. Norton adjourned the meeting.