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The accelerated aging phenotype: The role of race and social determinants of health on aging

Nicole Noren Hooten,

Natasha L. Pacheco¹,

Jessica T. Smith¹,

Michele K. Evans*

Laboratory of Epidemiology and Population Science, National Institute on Aging, National Institutes of Health, 251 Bayview Boulevard, Baltimore, MD 21224, USA

Abstract

The pursuit to discover the fundamental biology and mechanisms of aging within the context of the physical and social environment is critical to designing interventions to prevent and treat its complex phenotypes. Aging research is critically linked to understanding health disparities because these inequities shape minority aging, which may proceed on a different trajectory than the overall population. Health disparities are characteristically seen in commonly occurring age-associated diseases such as cardiovascular and cerebrovascular disease as well as diabetes mellitus and cancer. The early appearance and increased severity of age-associated disease among African American and low socioeconomic status (SES) individuals suggests that the factors contributing to the emergence of health disparities may also induce a phenotype of ‘premature aging’ or ‘accelerated aging’ or ‘weathering’. In marginalized and low SES populations with high rates of early onset age-associated disease the interaction of biologic, psychosocial, socioeconomic and environmental factors may result in a phenotype of accelerated aging biologically similar to premature aging syndromes with increased susceptibility to oxidative stress, premature accumulation of oxidative DNA damage, defects in DNA repair and higher levels of biomarkers of oxidative stress and inflammation. Health disparities, therefore, may be the end product of this complex interaction in populations at high risk. This review will examine the factors that drive both health disparities and the accelerated aging phenotype that ultimately contributes to premature mortality.

Keywords

Minority aging; Health disparities; African Americans; Hispanics; Inflammation; Age; Genetics; Epigenetics

*Correspondence to: National Institute on Aging, National Institutes of Health, NIH Biomedical Research Center, 251 Bayview Boulevard, Suite 100, Room 4C-222, Baltimore, MD 21224, USA. me42v@nih.gov (M.K. Evans).

¹Equal contribution.

Declaration of Competing Interest

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1. Introduction

The purpose of this review is to discuss and review aging research in the context of minority health and health disparities. This issue is of increasing importance as we approach intersecting demographic shifts in the United States. There has been considerable attention paid to the aging of the U.S. population as 1 in 5 Americans will be 65 and older by 2030 (Vespa et al., 2020). The other demographic challenge super-imposed on the aging of the U.S. population is the majority-minority shift which demographers predict will occur by 2060 when non-Hispanic White individuals will no longer be the majority population (Colby and Ortman, 2014). The U.S. population overall will become more racially and ethnically diverse as the non-Hispanic White population contracts due to low birth rates and rising death rates among this group. Those who identify as themselves as ‘Two or More Races’ will be the fastest growing racial/ethnic group over the coming decades followed by the Asian population (Colby and Ortman, 2014). In 2060, 56.4% of the U.S. population will be members of a minority group (Hispanic Americans 28.6%, African Americans 13.0%, Asian Americans 9.1%, and those who identify themselves as Two or More Races 4.9%) (Colby and Ortman, 2014).

As the overall U.S. population ages and becomes more diverse, the segment of the population over age 65 years will also become more racially and ethnically diverse. By 2040, it is estimated that 34% of older adults will be members of a racial or ethnic minority group (2020b). While African American individuals comprised 9% of the older population in 2017, in 2060 this group is projected to be 13% of U.S. older adults (2019b). American Indian and Alaska Native individuals made up 0.5% of the over 65 years of age U.S. population in 2017; in 2060 the percentage will increase slightly to 0.7% (2019a). The Asian American population percentages are expected to double between 2017 and 2060 going from 4% of the older population to 8% (2019c). The largest percentage increase is predicted for older Hispanic Americans. In 2017 Hispanic American individuals comprised 8% of the U.S. older population; however, in 2060 they are predicted to comprise 21% of older U.S. adults (2019d).

These shifting demographics among the population overall and particularly among older Americans requires that the field indemnify efforts to understand aging in minority populations and the environmental and social factors that influence differential aging trajectories. Therefore, it is critical for researchers to consider their human aging research pursuits in the context of the social construct of race as well as ethnicity along with the social determinants of health (SDOH) which influence the course of aging, life expectancy and age-related chronic disease (Fig. 1). The SDOH are important root causes of health disparities and contribute to the accelerated aging phenotype. The SDOH which result from the political determinants of health (Dawes, 2020) may have their effects through biologic transduction pathways that include but are not limited to genomic factors including the epigenome and genetics, DNA damage and repair pathways, immune and inflammatory response pathways, as well as alterations in gene expression (Fig. 2).

Incorporation of minority study participants, minority biological samples and minority investigators has been increasing but uneven historically. Minority scholars, particularly

African American scholars, have played a critical role in highlighting the importance of studying minority aging. Beginning in the early 20th century, clinical research in Alzheimer's disease was conducted by African American psychiatrist Solomon Carter Fuller (Brown et al., 2014). He and others recognized the need to examine and to understand the characteristics of aging that are shared but also to investigate characteristics that do not overlap and may be influenced by race as a surrogate for social and environmental circumstances. It was many years before literature reviews revealed the dearth of aging research in the African American population. Jacquelyne Johnson Jackson highlighted the need for further research on African American adults, challenging gerontologists to conduct aging research on African American adults with focus on psychosocial patterns of aging that might elucidate how race and social class factors may influence aging and the need to develop relevant methods and techniques for this research (Jackson, 1967, 1974). African American researchers have made fundamental contributions to building theoretical frameworks that are integral in understanding the multifaceted interplay of SDOH such as health care access and cultural competence in aging minority populations (Campinha-Bacote, 2002, 2009).

However, it was African American sociologist, Rose C. Gordon, who was among the first who examined both White and African American populations to examine the relationships between race, sex, and socioeconomic factors over the lifespan. She pursued and developed the concept of 'double jeopardy' leading to disparities in aging among older White and African American adults and advocated for intragroup causation studies (Gibson, 1988, 1994). Her work laid the foundation for several African American scholars whose work truly propelled the broadening of aging research to more thoroughly include minority populations and the special factors that are relevant in examining differences in the trajectory of aging. These scholars include Reginald L. Jones, who felt that life course theory should be applied to African American populations over the lifespan, had the foresight to bring together fellow African American academics in gerontology and other fields to co-author *Black Adult Development and Aging* (Jones, 1989). The coauthors, including Linda Chatters, James S. Jackson and Robert Joseph Taylor, went on to make important observations in minority aging over the life course. For example, James S. Jackson (2011) developed the Law of Small Effects in Race Related Outcomes. This predicted that no single factor produced disparities among racial and ethnic sub-populations. The disparities are due to a group of small differences accumulating over the life course that produce disparate health outcomes in adulthood and in older minority populations. To a large extent, Jackson's theory has been proven correct since we know that a multifactorial and multilevel network operates to generate health disparities at all stages of life and is only one of his groundbreaking contributions to the field of aging. Jackson's work facilitated the work of other minority aging scholars including Keith E. Whitfield and Jennifer J. Manly who began investigating cognitive aging among older African American adults (Manly and Espino, 2004; Whitfield et al., 2004).

This review highlights the important work which has addressed these issues and underscores the need for a multi-level approach because it is the accumulation of 'small effects', be they sociologic or biologic, that make the difference in promoting disparity.

2. Health disparities in the United States

Health disparities in the United States related to race, ethnicity, and socioeconomic status are widespread. The governmental definition of health disparity is “a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion” (2010).

Health disparities are evident in numerous epidemiologic health statistics. Life expectancy at birth reveals persistent and, in some cases, expanding gaps related to race. This was highlighted in 2018 where a glaring life expectancy gap was reported between Hispanic women, non-Hispanic White women, African American women, non-Hispanic White men, and African American men who had the lowest life expectancy, 71.3 years compared to 79.1 years for Hispanic men who also outpaced non-Hispanic White men. In fact, the life expectancy for Hispanic men slightly exceeds that of African American women whose life expectancy is 78.0 (Arias and Xu, 2020). The differential health impact of COVID-19 has reduced life expectancy significantly for African American and Hispanic individuals. The recent National Center for Health Statistics report reveals a disproportionate decline in US life expectancy for the first half of 2020. Overall, African American individuals lost 2.7 years of life expectancy (72 years) and Hispanic individuals lost 1.9 years (79.9 years) (Arias et al., 2021).

For the African American population, this is the lowest life expectancy estimate reported since 2001. Survivorship is also significantly influenced by race. Before and after age 65, Hispanic individuals have a distinct survival advantage known as the “Hispanic paradox” (see “The Hispanic (Immigrant) Paradox” section for more details). More than 87% of Hispanic individuals survive to age 65 compared to 83% of non-Hispanic White individuals and 76% of non-Hispanic African American individuals. More than 52% of Hispanic individuals survive to age 85 compared to 42% of non-Hispanic White individuals, and only 33% of non-Hispanic African American individuals (Arias and Xu, 2020). It is important to note that U.S. mortality data reveals an African American-White mortality crossover among adults near age 85 with African American men and women surviving longer than their age matched White counterparts (Arias, 2006; Johnson, 2000). These findings may be due to poor quality data, population heterogeneity or cohort effects (Masters, 2012).

Age-adjusted death rates for 2019 also reflect significant disparities particularly for non-Hispanic African American men whose age-adjusted death rate is 1092/100,000 compared to 869/100,000 for non-Hispanic White men and 633/100,00 for Hispanic men (Kochanek et al., 2020). Unsurprisingly, the pandemic influenced the 2020 provisional mortality rates. The age-adjusted death rate increased by 15% with 11% of those increased deaths attributed to COVID-19. The racial disparities in overall mortality and COVID-19 related mortality are prominent with non-Hispanic African American individuals having the highest age-adjusted death followed by non-Hispanic American Indian individuals or Alaska Native American

individuals (Ahmad et al., 2021). However, overall statistics reveal that American Indians/Alaska Natives and Hispanic American individuals have higher incidence, hospitalization, and mortality rates. As expected, adults ≥ 85 years had the highest mortality with the highest mortality mirroring the racial/ethnic disparities seen for the overall population.

There are also notable disparities in age-associated chronic disease incidence and prevalence. For the most commonly occurring age-associated chronic disease there are significant health disparities. American Indians/Alaska Native individuals have the highest prevalence of diabetes mellitus followed by Hispanic and African American individuals. The incidence of newly diagnosed diabetes among adults reveals the highest incidence rates for African American and Hispanic individuals (2020a). African American individuals are more likely to have hypertension while non-Hispanic White individuals were more likely to have cardiovascular disease. However African American individuals have the highest age-adjusted death rate for cardiovascular disease. Non-Hispanic African American individuals are more than twice as likely to die from cardiovascular disease when compared to Asian individuals and Pacific Islander individuals. In addition, African American and Hispanic individuals were more likely to be obese (BMI >30.0) than non-Hispanic White individuals (2021b). Racial and ethnic minority groups are also more likely to report the presence of multiple age-related disease co-morbidities including diabetes, cardiovascular disease, cerebrovascular disease, and hypertension (Ahmed and Conway, 2020).

Cancer racial/ethnic health disparities, though declining, are still stark. African American individuals bear a significantly disproportionate cancer burden with the highest death rates and shortest survival than other population groups (2021a). For example, although African American women have a lower incidence of breast cancer, their breast cancer mortality is higher than White women. African American men have both higher incidence and mortality from prostate cancer when compared to all U.S. population groups.

3. Social and political determinants of health and aging

Non-medical social, political and economic factors have both direct and indirect effects on health. The Institute on Medicine has identified 12 key SDOH risk factors from 5 domains (sociodemographic, psychological, behavioral, individual level social relationships and living conditions, and neighborhoods and communities) in the context of health outcomes including morbidity and mortality. The specific factors include: neighborhoods and communities compositional characteristics, social connections and social isolation, exposure to violence, dietary patterns, physical activity, tobacco use and exposure, alcohol abuse, health literacy stress, negative mood and affect (depression and anxiety), country of origin, education, employment and financial resources/strain (2015).

These non-medical factors influence health and can be divided into upstream and downstream factors. Downstream factors or determinants are those that are spatially or temporally close to the health outcome observed. These downstream factors include but are not limited to health literacy, attitudes, beliefs, substance use, personal health care behaviors, physical activity, stress, diet, and mood (Braveman et al., 2011) (Fig. 1). Although these downstream factors may be the most apparent and immediate, they are not the fundamental

causes of health disparities over the lifespan. Downstream determinants are molded by upstream determinants of health which though indirect are fundamental causes of disparities because these are the initiating factors of multiple intricate causal pathways to result in differential health outcomes. The upstream determinants of health include social and political factors including race, racism, economic and social opportunities, and resources, living and working conditions, educational attainment, occupational status, income, and wealth (Fig. 1).

The upstream and downstream determinants are linked through a complex and interconnected network that interdigitates with other factors such as lifespan as well (Fig. 1). Upstream factors may be particularly important in aging because they are operational at every stage of life. Adversity experienced through living and working conditions, educational attainment, limited resources, racism, or any of the other upstream factors will likely have cumulative effects over the lifespan influencing health span, quality of life in old age, and longevity itself. These factors may be rapid acting exposures with immediate effects; however, the ultimate effects may not manifest until late in the lifespan and accelerate the premature development of age-associated chronic disease and disability (Braveman and Gottlieb, 2014). Geronimus proposed the ‘weathering hypothesis’ in 1992 as she examined disparities in maternal child health surmising that these disparities may be the result of the “physical consequences of cumulative socioeconomic disadvantage” (Geronimus, 1992). Lifelong stress induced by the need to cope with or overcome the adversity and marginalization triggered by race and various forms of racism is a particularly important factor throughout the lifespan for racial and ethnic minorities that also ultimately influences their health status and outcomes.

These fundamental upstream pathways are intricately emmeshed with biological transduction pathways through which these determinants result in differential health outcomes (Seeman and Crimmins, 2001). Chronic exposure to environmental stressors viewed in the broadest context can alter physiologic function as well as biologic systems and processes. The term ‘allostatic load’ refers to the accumulative weight of persistent stress and life experiences (Gehlert et al., 2008; McEwen and Gianaros, 2010; McEwen and Seeman, 1999; Miller et al., 2009; Seeman et al., 2010). The ‘allostatic load’ construct encompasses many bio-physiologic processes and regulatory systems and is assessed through selected biomarkers and clinical criteria. Allostatic load is an important factor in age-related health disparities (Geronimus et al., 2006). It is associated with frailty as well as cognitive function, brain structure, mortality, physical function and personality characteristics [For review (Guidi et al., 2021)]. This ‘load’ resulting from aspects of the SDOH is dynamic across the lifespan. The SDOH exert their effects in a stepwise gradient through which health status is linked to incremental improvement in social position and socioeconomic status up to a point. The socioeconomic gradients are particularly potent factors in aging. For example, functional limitations and disability among those 65–74 years of age are significantly influenced by socioeconomic gradients (Minkler et al., 2006). Not only are the gradients of socioeconomic status important in aging but also the cumulative risk associated with a wide range of SDOH. A cumulative risk score using data from the National Health and Nutrition Examination Survey (NHANES) comprised of SDOH, self-rated health, and functional capacity found that not only did SDOH-related Black-White

disparities persist throughout the lifespan but also that older African American individuals have a higher mean cumulative risk score than White individuals in comparable age groups (Rhee et al., 2021). This study also demonstrated that SDOH Index scores were higher among older African American and White adults with functional limitations. In the Midlife Development in the United States (MIDUS) study, African American participants reported a higher level of exposure to stressors including childhood, work, financial stress as well as perceived discrimination compared to White participants (Chen et al., 2021). This increase in cumulative stress was associated with lower levels of executive function and episodic memory in African American participants compared to White participants. As much as 8% of the disparity in executive function and over 13% of the disparity in episodic memory was accounted for by cumulative stress exposure. This finding is in line with multiple other studies that have demonstrated higher levels of cumulative stress among African American individuals including the Health and Retirement study, the Chicago Community Adult Health Study and the Women's Health Study (Burroughs Pena et al., 2019; Sternthal et al., 2011; Williams and Mohammed, 2009). However, improvement in income and social status do not completely ameliorate disparate health outcomes among African American individuals and other minorities (Institute of Medicine, 2000).

Among the upstream determinants of health are politically driven social and economic policies and actions that directly influence longevity and survival particularly among marginalized population segments (Dawes, 2020). Since the Nation has failed to guarantee equal protection under law, it has simultaneously failed to provide for the general welfare and good health of the entire population. This failure is particularly perilous over the lifespan as the accumulated stress, deprivation, and marginalization exact a toll on health span, possibly promotes the development of the accelerated aging phenotype, and contributes to truncation of lifespan.

3.1. Race as a social determinant of health

There is much debate about the role of race and ethnicity in health. Many believe that it is not possible to define a single concept of race or ethnicity. Most studies use race as a psychosocial construct to contextualize life experience since race is a powerful social category that through history has been used by societies to shape human experience. Race conveys power and privilege as well as oppression and disenfranchisement. The social determinism of race is present at every stage of life accompanying the processes of maturation as well as aging. From the perspective of social scientists, race may be considered a "...subjective social construct based on ascribed characteristics that have acquired socially significant meaning..." (2004). Although the social consequences of race working through interdigitating biological pathways likely influences health outcomes there is no objective scientific or genetic data to support a genetic or biologic basis of race. Although early generations of biologists and naturalists generated biologic classifications of race based on observable differences including skin color, physiognomy, and physique from the genetic perspective there is no proven genetic basis of race [for review (Muller-Wille, 2014)]. What the genome does reveal to us is genetic variation or clustering based on geographic origin (Keita et al., 2004). We all have a shared genetic heritage revealed by global sequencing data that supports the hypothesis that humans likely originated in

Africa. The documented genetic variations are likely evidence of descent with variation (Cooper and Rotimi, 2020). The value of studying genetic variation in the context of biology and clinical medicine is that the genetic variation noted may provide information on human disease risk and resiliency as well as avenues for potential treatment. Race as a social construct may further contextualize the interaction between the environment and the genome. Race is a risk factor for disparate health outcomes that must be considered with SDOH including social position, income, access to necessary resources (health care, transportation, employment), education, place of residence and contextualized with ancestry and genomic variation (Morning, 2011).

3.2. The Hispanic (Immigrant) paradox

Hispanic individuals have greater lifespans and reduced mortality rates compared to White and African American individuals despite having similar socioeconomic conditions as African American individuals (Markides and Coreil, 1986; Markides and Rote, 2019). These observations were first described in 1986 as the “Hispanic paradox” (Markides and Coreil, 1986) and has been extended to include observations that Hispanic individuals have similar health profiles as White individuals (Garcia et al., 2018; Markides and Rote, 2019), though this aspect has been debated (Boen and Hummer, 2019; Crimmins et al., 2007; Espinoza et al., 2013; Tarraf et al., 2020). The Hispanic paradox is even more apparent when examining health status differences in native versus foreign-born Hispanic individuals, where Hispanic immigrants have relatively better health outcomes and lower mortality rates compared to U.S. native-born Hispanic individuals (Boen and Hummer, 2019; Markides and Rote, 2019) and White individuals (Lariscy et al., 2015). For example, foreign-born Hispanic men and women 65 years of age and older had significantly reduced mortality rates compared to White men and women, while native-born Hispanic individuals in the same age range had grossly similar mortality rates as White individuals (Lariscy et al., 2015). This same study also revealed that foreign-born Hispanic individuals have reduced cause-specific mortality rates such as heart disease, cancer, and respiratory diseases compared to White individuals, while native-born Hispanic individuals only had reduced mortality rates for lung cancer and respiratory diseases relative to White individuals (Lariscy et al., 2015).

Potential contributing factors to the Hispanic paradox include migration selection, diet and other health behaviors, sociocultural factors, differential stress exposure, genetics, and ethnicity misclassification on death certificates (Boen and Hummer, 2019; Markides and Rote, 2019). Age at migration has also been found to be correlated with the Hispanic paradox (Gubernskaya, 2015), where immigrants migrating to the U.S. after 24 years old confer an immigrant mortality advantage (Markides and Rote, 2019). However, one study found an immigrant health advantage was only present in foreign-born Hispanic individuals that migrated to the U.S. between the ages of 18 and 34 years old (Gubernskaya, 2015). Interestingly, rates of decline in self-reported health at 50 years of age were significantly different based on the age of migration, but steeply decreased self-reported health rates were observed in all Hispanic immigrants after the age of 50 regardless of their age at migration (Gubernskaya, 2015).

Since its initial description, current studies seem to support the Hispanic paradox (Fenelon et al., 2017; Garcia et al., 2018; Lariscy et al., 2015), yet other studies found conflicting results (Boen and Hummer, 2019; Crimmins et al., 2007; Espinoza et al., 2013; Tarraf et al., 2020). An early study revealed both native and foreign-born Hispanic individuals had greater biological risk scores and factors compared to White individuals, and no significant differences were observed between native and foreign-born Hispanic individuals (Crimmins et al., 2007). In this study, biological risk scores were defined as a combination of 3 different clinical measurements: 1) blood pressure (pulse rate and systolic and diastolic blood pressure), 2) metabolic function (body mass index, total and high-density lipoprotein cholesterol, and glycated hemoglobin), and 3) inflammation (fibrinogen, C-reactive protein, and albumin) (Crimmins et al., 2007). The San Antonio Longitudinal Study of Aging (SALSA) detected higher mortality rates in older Mexican American adults compared to White adults after adjusting for sex and age, but was no longer significant when adjusted for socioeconomic status (Espinoza et al., 2013). A recent study found that the Hispanic paradox does not encompass health risk markers in native and foreign-born Hispanic individuals relative to White individuals and concluded there was no apparent “healthy immigrant effect” (Boen and Hummer, 2019). For example, the authors found that both foreign-born and native Hispanic individuals had greater functional limitations than White individuals, but foreign-born Hispanic individuals had greater C-reactive protein (CRP) concentrations compared to White individuals while no significant differences were observed between native Hispanic individuals and White individuals (Boen and Hummer, 2019). Interestingly, this study also observed disparities associated with functional limitations decreased with age in foreign-born Hispanic individuals versus White individuals, while the disparities between native-born Hispanic individuals and White individuals was consistent (Boen and Hummer, 2019). Another recent study found that both native and foreign-born Hispanic individuals were just as likely to be categorized as “healthy” compared to White individuals only when health habits and adult achievements variables were adjusted (Tarraf et al., 2020). Yet this same study also discovered that both native and foreign-born Hispanic individuals also had a similar or increased likelihood of having high morbidity and cognitive decline with aging compared to White individuals, suggesting that nativity may not influence health status (Tarraf et al., 2020).

While most studies on the Hispanic paradox have focused on either combined Hispanic populations or Mexican American subpopulations, recent studies have examined additional Hispanic subpopulations such as Puerto Rican and Cuban individuals (Fenelon et al., 2017; Garcia and Ailshire, 2019; Garcia et al., 2018). One study examined mortality rates associated with foreign-born and U.S. native-born Hispanic individuals broken down by 6 countries/regions of origin (Mexican, Puerto Rican, Cuban, Dominican, Central/South American, and other Hispanic) (Fenelon et al., 2017). When adjusted for socioeconomic covariates, all foreign-born Hispanic subgroups had a mortality advantage at ages 65 years and older compared to White individuals, while the only native-born mortality advantages were observed for native Mexican, Cuban, and other Hispanic men aged 65 years and older relative to White men (Fenelon et al., 2017). Garcia and colleagues reported that foreign-born Mexican, foreign-born Cuban, and island-born Puerto Rican women had greater life expectancies compared to White women, while native-born Puerto Rican and foreign-born

Mexican men had greater life expectancies compared to White men (Garcia et al., 2018). Island-born Puerto Rican women had the most years living with morbidity compared to White women and the other Hispanic subgroups, while U.S. native-born Puerto Rican men had the greatest years living with morbidity compared to White men and the other Hispanic subgroups (Garcia et al., 2018). Foreign-born Cuban men and women spent the most years of life without morbidity compared to White individuals and the remaining Hispanic subgroups (Garcia et al., 2018). A recent study investigating biological risk profiles demonstrated that foreign-born Mexican, island-born Puerto Rican, foreign-born “other” Hispanic, and U.S. native-born Mexican individuals demonstrated greater biological risk compared to White individuals (Garcia and Ailshire, 2019). The authors also used the same parameters as the Crimmins et al. (2007) study to define biological risk factors, with the following modifications: 1) the metabolic function component also included cystatin C measurements, and 2) the inflammatory component only included C-reactive protein measurements (Garcia and Ailshire, 2019). After adjusting for socioeconomic status, health behaviors, and access to care, native-born Mexican individuals had significantly greater metabolic risk while island-born Puerto Rican individuals had significantly increased risk of inflammation relative to White individuals (Garcia and Ailshire, 2019).

Several questions surrounding the Hispanic paradox still remain. Current literature has largely focused on lifespan and mortality rather than health span (Boen and Hummer, 2019). While few studies have examined morbidity associated with life expectancies (Garcia et al., 2018), more studies are needed to confirm these results and expand to other Hispanic subpopulations residing in various geographical regions within the U.S. As socioeconomic status appears to explain part of the Hispanic paradox (Espinoza et al., 2013; Fenelon et al., 2017; Garcia and Ailshire, 2019; Lariscy et al., 2015), the behavioral, environmental, and psychosocial exposures contributing to the Hispanic paradox also require further investigation. Additionally, longitudinal studies on how the Hispanic paradox evolves over time are limited (Boen and Hummer, 2019; Tarraf et al., 2020). Furthermore, more studies need to examine the Hispanic paradox in additional Hispanic nationalities, as current studies have only examined, Mexican American, Puerto Rican, and Cuban American populations.

4. Genetics and other biomarkers of aging in minority populations

4.1. Genetics of aging in minority populations

Many studies have examined the genetic contributions to human aging and longevity, which have been reviewed elsewhere (Melzer et al., 2020; Morris et al., 2019). Most recent heritability estimates of longevity range from < 10–16% (Melzer et al., 2020; Morris et al., 2019), and previous genome-wide association studies (GWAS) found that genetic variants have small to moderate effects on longevity, parental lifespan, and health span (Melzer et al., 2020; Morris et al., 2019). However, the majority of these genetic studies have focused on predominantly aging European ancestry populations (Melzer et al., 2020; Morris et al., 2019). Given the expected rise of aging non-European populations within the next few decades, understanding the genetic components of aging in racial and ethnic minority populations will be crucial. In this section, we will summarize current genetic studies of longevity, health span, and lifespan in racial and ethnic minorities.

Lee and colleagues estimated heritability of lifespan and survival in African American, Caribbean Hispanic, and White adults aged 65 years and older from the Washington Heights-Inwood Columbia Aging Project (WHICAP) (Lee et al., 2004). When adjusted for sex and birth cohort, heritability of lifespan for deceased relatives was statistically significant in Caribbean Hispanic adults ($h^2 = 0.29$) and White adults ($h^2 = 0.26$), while heritability estimates in African American adults were low and not significant ($h^2 = 0.035$) (Lee et al., 2004). As heritability estimates cannot identify specific genetic variants or affected biological pathways, genotyping, GWAS and other large-scale genomics platforms have been utilized to identify novel genomic variants associated with aging. An early genotyping study in 2003 examined the relationship between the human homolog of the *Drosophila Indy* lifespan gene and human longevity (Lee et al., 2003). The *Indy* V80L variant had a low frequency and was only present in African American individuals (Lee et al., 2003). Another study evaluated the relationship between *CRP* genotype and the number of years and healthy years lived as well as all-cause mortality in White and African American participants in the Cardiovascular Health Study (CHS) cohort (Hindorff et al., 2008). They found that *CRP* haplotypes were not associated with years of life, years of healthy life, or all-cause mortality in African American or White participants (Hindorff et al., 2008). However, more copies of the *CRP* HapD haplotype were correlated with reduced risk of all-cause mortality in African American participants (Hindorff et al., 2008).

The first genetic association study of aging in racial and ethnic minority populations was based on the Women's Health Initiative (WHI) cohort, which took a candidate gene approach to evaluate variants associated with healthy aging and survival in postmenopausal African American, Hispanic, and White women (Shadyab et al., 2017). Fourteen single nucleotide polymorphisms (SNPs) from previous GWAS studies of longevity in primarily European populations were specifically evaluated to determine if these SNPs were also associated with longevity in postmenopausal women (Shadyab et al., 2017). None of the selected SNPs were significantly associated with longevity in African American or Hispanic women in fully adjusted models, but when models were adjusted only for population stratification and age, 7 SNPs were significantly associated with survival to 85 years of age in Hispanic women (Shadyab et al., 2017). These SNPs were in linkage disequilibrium with the rs2149954 variant, which was previously associated with longevity in a separate study of European ancestry. This SNP had the opposite direction of effect on both longevity and heart disease risk in women of European ancestry (T allele associated with increased longevity and lower cardiovascular mortality risk) and Hispanic women (T allele associated with decreased longevity and higher coronary heart disease risk) (Shadyab et al., 2017).

GWAS studies have provided unique advantages and greater power compared to earlier candidate gene approaches, such as having larger sample sizes and multi-cohort designs. GWAS examining aging and longevity have included African American and Hispanic individuals as part of a trans-ethnic meta-analysis as well as individual cohorts (Deelen et al., 2019; Joshi et al., 2017; Tanaka et al., 2017; Wright et al., 2019). In a trans-ethnic meta-analysis study examining longevity variants in European, East Asian, and African American populations from 20 cohorts, *APOE* $\epsilon 4$ rs429358 and *APOE* $\epsilon 2$ rs7412 variants were associated with reduced and increased survival odds, respectively, to the 90th and 99th age percentile in each individual study cohort including African American individuals

from CHS (Deelen et al., 2019). APOE serves an important role in cholesterol metabolism and transport in the brain (Deelen et al., 2019). The *APOE* $\epsilon 4$ rs429358 variant has been previously correlated with higher risk of Alzheimer's disease and cardiovascular disease, while the *APOE* $\epsilon 2$ rs7412 variant has the opposite effect (Deelen et al., 2019).

A GWAS examining parental lifespan in European and African ancestry populations from UK Biobank and LifeGen found 1 significant variant, rs10198124, located within the intergenic region of chromosome 2, that was associated with paternal lifespan in African American individuals (hazard ratio = 1.22) (Joshi et al., 2017). The function of the rs10198124 variant remains unknown. No significant SNPs were associated with combined parental lifespans or maternal lifespans in African American individuals (Joshi et al., 2017). Another parental lifespan GWAS study was performed in European and African ancestry participants from the Health and Retirement Study (HRS), where significant variants were only identified from the trans-ethnic meta-analysis and not ancestry-specific analyses (Tanaka et al., 2017). The authors found the rs35715456 variant within the *SMAD7* gene had the greatest significant association with having a long-lived parent but could not replicate this finding in the Framingham or InCHIANTI studies (Tanaka et al., 2017). *SMAD7* is involved in TGF β signaling inhibition, and *SMAD7* expression was previously found to be increased with chronological age in a large European cohort (Tanaka et al., 2017).

Finally, a GWAS from the *AncestryDNA* database examined the relationship between genetic ancestry, rather than race and ethnicity, and parental lifespan, but only found significant correlations in European ancestry groups (Wright et al., 2019). Of note, while not significant after correcting for multiple testing, the Native American ancestral group had a negative correlation between genetic ancestral admixture and maternal lifespan (Wright et al., 2019). No significant associations between parental lifespan and genetic variants were identified in Sub-Saharan African or Native American/ East Asian ancestry populations (Wright et al., 2019). The authors attributed these findings to the smaller sample sizes in these respective populations, and thus were underpowered (Wright et al., 2019).

In the above described GWAS studies, the African American and Hispanic populations were largely underpowered and/or had small to modest sample sizes, which could explain the lack of identified significant variants associated with longevity and lifespan. This is in line with other published GWAS results of complex traits and diseases in racial and ethnic populations (Daya et al., 2019; Kang et al., 2010; Ke et al., 2018; Salinas et al., 2016). Additionally, we cannot exclude the possibility that genetic variants associated with longevity, health span, and/or lifespan are shared across multiple populations, but the allele frequencies may differ across the populations. For example, Lee and colleagues found the *I550V* variant in the *Indy* gene was shared between non-Hispanic White, Hispanic, Asian, and African American populations at similar gene frequency levels (Lee et al., 2003). While not statistically significant, differences in *CRP* haplotype frequencies were observed between White and African American participants in the CHS cohort (Hindorf et al., 2008). To the best of our knowledge, no other genetic studies of aging have examined allelic or genotypic frequency differences between geographic populations. More genetic studies including diverse, racial and ethnic populations will be required to identify allele and/or genotype frequencies

associated with healthy aging that could be enriched in certain populations. The limited number of currently identified genetic variants also suggests environmental and psychosocial factors or gene-gene interactions may play a larger role in aging for diverse populations. Furthermore, these collective results suggest that genetic variants and predictors identified from European ancestral populations cannot be extrapolated to non-European populations (Geoffroy et al., 2020; Mogil et al., 2018; Wojcik et al., 2019).

African ancestry populations have the highest levels of genomic diversity (reviewed in (Campbell and Tishkoff, 2008)), while Hispanic populations have varying degrees of genomic admixture (Banda et al., 2015; Bryc et al., 2010b; Conomos et al., 2016; Price et al., 2007), adding another level of complexity into understanding the genetic contributions to aging in Hispanic populations. Hispanic and Latino populations have varying proportions of European, African, and Native American ancestries, which differ between and within Latin American populations (Bryc et al., 2010b; Conomos et al., 2016; Price et al., 2007). For example, Mexican individuals tend to have higher levels of Native American ancestry, Cuban individuals have higher European ancestry, and Puerto Rican and Dominican populations have higher African ancestry (Banda et al., 2015; Bryc et al., 2010b; Conomos et al., 2016; Price et al., 2007). African American individuals also have varying proportions of genetic admixture, composed primarily of African and European ancestry with low levels of Native American ancestry (Bryc et al., 2010a; Tishkoff et al., 2009), and ancestry also varies by geographical region (Baharian et al., 2016).

Interestingly, studies have also shown associations between genetic ancestry levels and phenotypic markers and diseases. For example, an early study found that African genetic ancestry, in addition to other sociodemographic variables, was correlated with years of life and fasting blood glucose levels in African American participants from the CHS cohort (Reiner et al., 2005). The WHI examined whether ancestry-specific genetic variants were correlated with the aging associated biomarker CRP levels in postmenopausal African American and Hispanic women (Reiner et al., 2012). When CRP levels were adjusted for age, the authors found a negative correlation between European ancestry and CRP in African American and Hispanic women, and a positive correlation between Native American ancestry and CRP in Hispanic women (Reiner et al., 2012). A genome-wide admixture scan in African American women identified multiple significant variants in loci such as 1q23 and 6p21 that were specific to African ancestral populations, where local African ancestry was associated with higher CRP concentrations (Reiner et al., 2012). Despite current evidence demonstrating genetic heterogeneity both within and between Hispanic and African American populations, an overwhelming number of studies group these respective populations into a single, generalized “Hispanic” or “African American” group. Thus, it is possible that key genetic variants and biological processes associated with aging are not captured due to these generalizations and population stratification confounding effects. Future studies should investigate genetic variants associated with aging in Hispanic populations by country of origin rather than as a single combined ethnic group.

While race and ethnicity have often been connected to genetic ancestry (Borrell et al., 2021), it is important to emphasize that race is a social construct, not a biological construct. In contrast, genetic ancestry relies on “the genetic origin of one’s population” and is more

precise in predicting the presence of genetic variants in specific populations compared to race and ethnicity categories (Borrell et al., 2021). However, genetic ancestry only partially explains biological variation observed in diverse populations (Borrell et al., 2021). Furthermore, while some genetic variants have been linked to racial and ethnic differences in various diseases and conditions, these variants may not necessarily be directly causal of health disparities (Borrell et al., 2021). These observations could be due to various factors such as unknown non-genetic contributors, and/or the lack of diverse populations included in genetic studies (Borrell et al., 2021). Regardless of whether genetic variants directly influence health or disease outcomes, studying genetic variation in racial and ethnic minority populations will still be crucial to understand the relationship between variant effect sizes, allelic and genotypic frequencies, and health and disease risk across diverse populations (Borrell et al., 2021). As previously stated, genetic studies have overwhelmingly focused on White or European populations, and there is still much to be learned about genetic variation in racial and ethnic minority populations. Racial and ethnic minorities have not been included in many genotyping, transcriptomic, proteomic, and epigenetic studies resulting in a nonrepresentative cohort -omic data set. Until more racial and ethnic minority populations have more genetic and other “-omic” sequencing data collected, caution should be used when interpreting GWAS and other genetic association results as they relate to causality of health and disease outcomes in non-White populations (Borrell et al., 2021).

To the best of our knowledge, no GWAS studies have been performed in aging Native American or American Indian populations. Furthermore, no genetic studies have been performed using whole exome or whole genome sequencing (WGS) technologies in any aging racial and ethnic minority population. WGS captures more genetic variation compared to traditional GWAS and could serve as a powerful tool to identify low frequency and rare variants in diverse ancestral populations. Given that knowledge on rare variants in racial and ethnic minority populations remain significantly understudied, whether rare variants could explain longevity differences in diverse minority populations requires additional investigation. Future studies should utilize WGS to investigate the interplay between genetic variants, genetic ancestry, and aging aspects such as longevity, lifespan, and health span in aging ethnic and racial minority populations. The ultimate goal would be to incorporate these genetic findings into precision medicine applications at the individual level. By gaining a more thorough understanding of genetic variation at the population level, we can begin to realize the full potential of precision medicine for aging individuals from all racial and ethnic populations.

4.2. Other molecular biomarkers in minority populations

Criteria for biomarkers of aging have been defined by the American Federation for Aging Research as follows: 1) can model the rate of aging, 2) represent a core biological process of healthy aging, 3) can be frequently tested in humans without harm, and 4) can be identified and manipulated in humans and animal models (Xia et al., 2017). Our current understanding of potential biomarkers of aging come from the traditional hallmarks of aging, which include epigenetic changes, genomic instability, telomere shortening or attrition, dysregulated nutrient sensing, cellular senescence, loss of proteostasis, mitochondrial dysfunction, stem cell exhaustion, and altered intercellular communication

(reviewed in (Lopez-Otin et al., 2013)). To our knowledge, biomarkers associated with the latter 4 hallmarks of aging have not been examined in healthy, normally aging racial and ethnic populations. As epigenetics and genomic instability concepts will be covered in later sections of this review, we highlight current knowledge of telomere shortening, nutrient sensing and other metabolic processes, cellular senescence, and other aging associated biomarkers associated with healthy aging in racial and ethnic minority populations.

A recent study explored the correlation and co-dependency between 50 clinical biomarkers with age, race and sex using the National Health and Nutrition Examination Survey (NHANES) data set (Le Goallec and Patel, 2019). Differences in biomarker correlations were identified by ethnicity, with 58 correlation differences in White vs Hispanic individuals and 113 correlation differences in White vs African American individuals (Le Goallec and Patel, 2019). The authors also found few alterations in correlations of age trajectories between the ethnic groups, with only 3 correlation differences observed between White and Hispanic individuals, and 8 correlation differences between White and African American individuals (Le Goallec and Patel, 2019). When evaluating the predictability of biomarkers with age, 3 biomarkers had greater predictability in White participants compared to Hispanic participants, while 9 biomarkers had a higher prediction value in Hispanic participants (Le Goallec and Patel, 2019). Six biomarkers had improved prediction in White participants compared to African American participants, while 10 biomarkers had improved prediction in African American participants (Le Goallec and Patel, 2019). When examining the predictability trajectories of biomarkers with age by ethnicity, only 3 differences were found between White and Hispanic individuals and 1 difference between White and African American individuals (Le Goallec and Patel, 2019). The authors have provided an interactive website for readers to further evaluate biomarker correlations and predictabilities at http://apps.chiragjggroup.org/Aging_Biomarkers_Co-Dependencies/ (Le Goallec and Patel, 2019). However, the authors noted that the biomarkers used in this study were not considered to be commonly utilized chronological age biomarkers like DNA methylation clocks, telomere length and inflammatory markers, but rather a collection of blood biomarkers (such as glucose, blood cell counts, and lipid levels) and anthropometric values (such as body mass index, height, and blood pressure) (Le Goallec and Patel, 2019).

4.3. Telomere shortening and attrition

Telomeres, especially telomere length, are considered an important biomarker of aging. Previous studies found heritability estimates of telomere length range between 34% and 82% (Melzer et al., 2020). Differences in telomere length and shortening by race and ethnicity, sex, and age have been documented with conflicting results (Brown et al., 2017; Diez Roux et al., 2009; Fitzpatrick et al., 2011; Needham et al., 2019; Song et al., 2018). In the CHS cohort, average telomere length was significantly longer in African American adults aged 65 years and older (Fitzpatrick et al., 2011). Investigators using data from the HRS study examined telomere length and interactions between age and race, and found African American women had larger decreases in telomere length as age increased compared to White women (Brown et al., 2017). No significant differences in telomere length and aging were observed in Hispanic women relative to White women (Brown et al., 2017). Interestingly, Hispanic men had a significantly steep reduction in telomere length with

increasing age, while no significant differences were observed between African American and White men (Brown et al., 2017).

The associations with telomere length and race/ethnicity and age were investigated in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (Diez Roux et al., 2009). When adjusted for the sociodemographic covariates age, sex, physical activity, body mass index, diet, smoking, income, and education, Hispanics and African American participants had marginally but significantly shorter telomeres than White participants (Diez Roux et al., 2009). Additionally, there were robust associations with age and telomere attrition for both sexes in African American and Hispanic participants compared to White participants, however the racial and ethnic differences were significantly higher in women (Diez Roux et al., 2009). A follow-up study from MESA assessed telomere length changes over a 10-year period and whether sex, age, and race and ethnicity could be used as predictors of telomere shortening (Needham et al., 2019). While White participants had longer telomeres at the initial time point visit, the average telomere length at the 10-year follow-up visit was not significantly different between the three racial and ethnic groups (Needham et al., 2019). The estimated change in 10-year telomere shortening for African American and Hispanic participants were 0.05 and 0.04 units, respectively, lower than White participants (Needham et al., 2019). No significant differences in telomere shortening were observed between African American and Hispanic participants (Needham et al., 2019).

Connecting telomere length with other potential biomarkers such as hormones, the WHI cohort evaluated the relationship between telomere length and circulating sex hormone concentrations (Song et al., 2018). No significant associations were found between telomere length and estradiol levels (Song et al., 2018). However, there was a significant opposite association between telomere length and free and total testosterone in Asian/Pacific Islander women, where higher levels of testosterone were associated with shorter telomeres (Song et al., 2018).

4.4. Nutrient sensing and other metabolic biomarkers

The most well-known nutrient sensing pathways and regulators associated with aging include the insulin and insulin-like growth factor 1 (IGF-1) signaling (IIS) pathway, mTOR, AMPK, and sirtuins (Lopez-Otin et al., 2013; Xia et al., 2017). Previous studies have shown that mutations in mTOR, IGF-1 and insulin receptors, and growth hormones were associated with longevity (Lopez-Otin et al., 2013). The IIS pathway, responsible for sensing glucose levels, decreases with normal aging, yet constitutive reduction of IIS activity prolongs longevity (Lopez-Otin et al., 2013; Xia et al., 2017). mTOR, responsible for detecting high amino acid concentrations, activity increases with aging, and inhibiting the mTOR complex increases lifespan (Lopez-Otin et al., 2013; Xia et al., 2017). AMPK and sirtuins function to detect nutrient scarcity and low-energy states based on high AMP and NAD⁺ concentrations, respectively (Lopez-Otin et al., 2013; Xia et al., 2017). Increased activity of AMPK has been linked to extending lifespan, while sirtuins have decreased expression during aging and overexpression of the sirtuin family member SIRT6 led to longer lifespan (Lopez-Otin et al., 2013; Xia et al., 2017).

Currently published studies associated with nutrient sensing processes in older racial and ethnic populations have been on circulating hormones and metabolites. It should be noted that the majority of the studies described in this section examined biomarkers in older and relatively healthy adults but did not examine biomarkers directly in the context of aging. For example, the Endogenous Hormones Nutritional Biomarkers and Prostate Cancer Collaborative Group investigated the relationship between circulating sex hormones and various sociodemographic, anthropometric, and behavioral factors in healthy men aged 25–85 years old (Watts et al., 2017). They found African American men had greater estrone, estradiol, and free estradiol concentrations compared to White men, while Hispanic men had approximately 12% higher A-diol-G concentrations as White men (Watts et al., 2017). Another study from the same cohort found that African American men had reduced levels of IGFBP-1, -2, and -3 as well as IGF-II, while Hispanic men had reduced levels of IGFBP-2 and -3 as well as IGF-I and -II compared to White men (Watts et al., 2019). This is in line with previous studies showing decreased levels of growth hormone and IGF-1 during normal aging (Lopez-Otin et al., 2013). It would be interesting to differentiate whether these hormones and proteins are constitutively reduced over time, as previous studies have demonstrated constitutive reductions of the IIS pathway increase longevity (Lopez-Otin et al., 2013). Future studies should examine longitudinal changes in IGF-1 and other IIS pathway regulators' concentrations in racial and ethnic minority groups to determine whether changes in concentrations confer beneficial or detrimental effects to longevity and health span.

Lipids and lipid metabolism have recently received attention as potential biomarkers of aging. Lipids play key roles in biological processes such as inflammation and cellular stress that change with age, and lipid profiles have been shown to alter with age (Almeida et al., 2021). The WHICAP cohort compared lipids and lipoproteins in White, African American, and Hispanic participants 65 years old and above, and found that race and ethnicity was a separate predictor of lipid and lipoprotein concentrations (Rodriguez et al., 2002). African American participants had higher levels of HDL cholesterol, and lower levels of total/HDL cholesterol ratio and triglycerides compared to White participants, while Hispanic participants had lower levels of total, HDL, and LDL cholesterol compared to White participants (Rodriguez et al., 2002). Another study from WHICAP performed a 3-year follow-up of lipid levels for the same cohort, and found Hispanic participants had significantly reduced HDL-C concentrations and African Americans participants had significantly greater triglyceride concentrations compared to White participants (Schupf et al., 2005). The WHICAP cohort also found African American and White participants in the lowest quartiles of non-HDL, LDL, and total cholesterol had a higher risk of death, while no significant differences were observed in Hispanic participants (Akerblom et al., 2008). A study from the Massachusetts Hispanic Elders Study examined how diet and ethnicity affect lipid concentrations in elderly Caribbean Hispanic and White participants (Bermudez et al., 2002). The authors found that White participants had higher HDL cholesterol, while Hispanic participants had higher LDL cholesterol (Bermudez et al., 2002), opposite to findings from the WHICAP studies (Rodriguez et al., 2002; Schupf et al., 2005). However, Hispanic women had significantly lower concentrations of apolipoproteins A-I and B, as

well as HDL, LDL, and total cholesterol compared to White women, while Hispanic men had higher levels of apolipoprotein A-I than White men (Bermudez et al., 2002).

The observed LDL reductions in Hispanic participants are in opposition to previous studies showing LDL increases with age (Morgan et al., 2016). However, increased LDL concentrations were correlated with reduced mortality risk in an elderly Chinese cohort (Morgan et al., 2016). HDL levels have been shown to decrease with age (Morgan et al., 2016), and decreased HDL concentrations were observed in Hispanic populations from WHICAP (Rodriguez et al., 2002; Schupf et al., 2005) and the Massachusetts Hispanic Elders Study (Bermudez et al., 2002). However, HDL levels were increased in African American participants from the WHICAP cohort (Rodriguez et al., 2002). A previous study has shown African American participants tend to absorb more cholesterol compared to White participants, and higher HDL levels have been proposed to extend longevity (Morgan et al., 2016). It would be tempting to speculate that reduced LDL in Hispanic participants and higher HDL in African American participants could serve as protective aging factors in these respective populations. More studies examining longitudinal changes in cholesterol and lipoproteins concentrations in aging racial and ethnic minority populations are needed.

The Baltimore Longitudinal Study of Aging (BLSA) examined plasma concentrations of sphingomyelin species in participants 55+ years old (Mielke et al., 2015). African American participants from the BLSA cohort displayed greater concentrations of circulating sphingomyelin and nearly all dihydrosphingomyelins compared to White participants (Mielke et al., 2015). This is in line with previous studies showing sphingomyelins increase with aging (Almeida et al., 2021). Interestingly, GWAS studies have linked genetic variants to various circulating lipids and metabolites. One study from the CHARGE consortium identified genetic variants associated with circulating trans fatty acids in European ancestry populations, plus African American, Hispanic, and Chinese American populations (Mozaffarian et al., 2015). One SNP (rs174548) in *FADS1/2* was correlated with cis/trans-18:2 in Hispanic populations, while the rs174579 variant in *FADS2* was correlated with the same trans fatty acid in African American populations (Mozaffarian et al., 2015). However, after adjusting for cis-20:4n-6 phospholipid concentrations, the association between rs174548 and cis/trans-18:2 was not significant (Mozaffarian et al., 2015). No other studies have examined cis/trans-18:2 in the context of aging, and thus require additional studies to understand how this fatty acid contributes to healthy aging. Another GWAS study identified genetic variants associated with homocysteine levels in African American and Yoruba cohorts from the Indianapolis-Ibadan Dementia Project (Kim et al., 2016). Homocysteine plays a key role in methionine metabolism (Kim et al., 2016), has been shown to increase with age (Ostrakhovitch and Tabibzadeh, 2019), and associated with age-related diseases and conditions such as cognitive decline and Alzheimer's disease (Kim et al., 2016; Ostrakhovitch and Tabibzadeh, 2019). They found 4 significant SNPs in and surrounding *CBS* and 1 significant SNP in the intronic region of *CD2AP* (Kim et al., 2016). The *CBS* gene codes for an enzyme that converts homocysteine to cystathionine, which represents the first step of the trans-sulfuration pathway (Kim et al., 2016). *CD2AP* has multiple biological roles including cell adhesion and cytoskeletal reorganization, which are processes also regulated by homocysteine (Kim et al., 2016). However, the mechanistic relationship between *CD2AP* and homocysteine remains unclear (Kim et al., 2016). Variants

in *CBS* and *CD2AP* were associated with decreased homocysteine levels, suggesting that these variants could confer protection against increasing homocysteine levels (Kim et al., 2016).

Overall, more studies are needed to evaluate hormone, lipid, and other circulating metabolite profiles in aging racial and ethnic minority populations. Longitudinal studies examining how these metabolic profiles change over the course of healthy aging will be crucial in determining whether metabolic biomarkers can predict longevity and/or mortality in racial and ethnic minorities. This will also require a better understanding of how environmental, socioeconomic, and psychosocial factors influence metabolic profile changes in these aging populations.

4.5. Cellular senescence biomarkers

Inflammation and cellular senescence are closely linked, where senescent cells can release proinflammatory cytokines, leading to an increased inflammatory response and premature aging (Lopez-Otin et al., 2013). No studies have directly examined cellular senescent biomarkers in racial and ethnic minority populations, but few studies have examined inflammatory biomarkers. One study has examined the relationship between immigration history of multi-generation Mexican-origin immigrants over the ages of 60 years old from the SALSA study and inflammatory biomarkers (Martin et al., 2018). This study found 3rd generation immigrants had the highest levels of CRP, leptin, IL-6, sTNF-R1, and sTNF-R2, in which CRP levels were significantly higher compared to 1st generation immigrants that have lived in the U.S. for less than 15 years (Martin et al., 2018).

Additionally, in comparison to 1st generation immigrants, leptin was significantly higher for all generational immigrants (Martin et al., 2018). Second generation immigrants had roughly 20% higher levels of IL-6, and 3rd generation immigrants had approximately 31% higher IL-6 concentrations (Martin et al., 2018). Similar trends were found for CRP, sTNF-R1, sTNF-R2 levels in 2nd and 3rd generation immigrants (Martin et al., 2018).

Interestingly, 2 complementary studies from the Health, Aging, and Body Composition (Health ABC) study have examined the relationship between genetic admixture and various inflammatory biomarkers in elderly African American participants (Reich et al., 2007; Wassel Fyr et al., 2007). One study found increased IL-6 soluble receptor concentrations were significantly associated with higher European ancestry, while increased CRP concentrations were significantly associated with higher African ancestry (Reich et al., 2007). Additionally, the authors identified a novel association between the SNP rs8192284 and higher IL-6 concentrations in African American and White participants (Reich et al., 2007). A companion study investigated the association between adipocytokines and genetic ancestry, and found adiposity, other mediators of metabolic syndrome, and higher European ancestry were significantly correlated with increased IL-2 soluble receptor, IL-6 soluble receptor, TNF- α soluble receptor II, and adiponectin as well as decreased CRP levels (Wassel Fyr et al., 2007).

Collectively, these studies suggest inflammatory biomarkers increase in older Hispanic and African American populations, consistent with the previous literature demonstrating rising inflammatory responses with aging (Lopez-Otin et al., 2013). More studies are needed

to investigate longitudinal changes of inflammatory and cellular senescent biomarkers in Native American, Hispanic, African American, and other racial and ethnic minority populations. It would also be interesting to further delineate between multi-generational Hispanic immigrant populations by studying individual Hispanic sub-populations based on country of origin. The previously identified relationship between genetic admixture and some inflammatory biomarker levels (Reich et al., 2007; Reiner et al., 2012; Wassel Fyr et al., 2007) reinforces the need to further explore the role of genetic admixture in aging racial and ethnic minorities sub-populations from distinct geographical locations. It is also likely that non-biological factors could also contribute to changes in inflammatory and cellular senescent biomarkers and require future investigation.

4.6. Extracellular vesicles as biomarkers

Emerging evidence indicates that extracellular vesicles may be promising, readily accessible biomarkers since these small nano-sized vesicles are released by cells into the circulation. EVs are membrane-bound and contain bioactive cargo such as nucleic acids, proteins, and lipids. EVs can serve as messengers by interacting with cell-surface receptors and through transferring cargo to recipient cells. Through these interactions, EVs play a role in a myriad of biological processes (Kalluri and LeBleu, 2020; Yanez-Mo et al., 2015). Currently, EVs are being pursued as diagnostic and prognostic factors for various age-related diseases including cancer, and neurodegenerative, metabolic and cardiovascular diseases (Kalluri and LeBleu, 2020; Noren Hooten and Evans, 2020; Yanez-Mo et al., 2015). For EVs to be utilized as a biomarker, they must be characterized across the lifespan and in different racial groups. However, there are limited studies that have examined EVs in minority populations.

We have characterized EVs in the context of age in a racially diverse cohort of participants from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study (Eitan et al., 2017). Plasma EV concentration decreases with advancing age in both White and African American participants. There were no racial differences in EV concentration or size. In this sub-cohort, we also reported the presence of circulating cell-free mitochondrial DNA (mtDNA) in EVs and that EV mtDNA levels decline with human age (Lazo et al., 2021). There were no significant differences in EV mtDNA levels between races (Lazo et al., 2021). We designed a specific sub-cohort to address whether there were differences in EV characteristics and protein cargo with race (Noren Hooten et al., 2019). No racial differences were observed in EV concentration or size. Examination of EV protein cargo revealed higher levels of phospho-p53, total p53, cleaved caspase 3, ERK1/2 and phospho-AKT in White individuals compared to African American individuals (Noren Hooten et al., 2019). In this study, the relationship between EV protein cargo, race and clinical markers of mortality were also analyzed. The association of EV characteristics with many mortality markers differs by race. These data highlight the importance of examining EVs and their associated cargo in racially diverse populations.

5. Epigenomics, transcriptomics and social genomics and aging in minority populations

5.1. Epigenetic age in minority populations

Minority populations are exposed to environmental and lifestyle-related factors that can impact health in part through affecting transcriptional programs. Many mechanisms regulate gene expression in cells. One of the most characterized, especially in minority populations, is DNA methylation (DNAm). This epigenetic modification alters gene expression without changing the DNA sequence. DNA methylation is heritable and also influenced by age, environmental insults and lifestyle factors (Fig. 3) (Alegria-Torres et al., 2011; Noroozi et al., 2021; Peters et al., 2021). Therefore, this points to DNA methylation as an important epigenomic process that may be modified as a consequence of the SDOH. Here we will discuss the status of epigenetic studies in minority populations.

DNAm at select CpG sites across the genome has been used in mathematical models to determine the DNAm age, also referred to as epigenetic age or epigenetic clock, which has been used to predict biological age but also highly correlates with chronological age. Using these epigenetic clocks, epigenetic age acceleration can be estimated, which generally is the difference between DNAm age and chronological age (Noroozi et al., 2021). Epigenetic age acceleration is typically calculated as the residuals from regressing epigenetic age on chronological age after controlling for various covariates (Noroozi et al., 2021). Additional epigenetic age estimators have also been developed that measure intrinsic epigenetic age acceleration (IEAA) and extrinsic epigenetic age acceleration (EEAA). IEAA captures aspects of the aging process independent of changes in white blood cell composition. EEAA estimates aging of the immune system since it considers age-dependent changes in white blood cell composition (Noroozi et al., 2021).

Studies have shown that African American and White men have faster universal age acceleration versus African American women (Tajuddin et al., 2019). Ten times more age-associated differentially methylated CpG positions (aDMPs) were reported in African American individuals (4930) versus White individuals (469), suggesting more widespread DNAm changes in African American individuals. Two studies have reported that African American individuals have slower extrinsic age acceleration than White individuals (Horvath et al., 2016; Tajuddin et al., 2019). Racial differences in differentially methylated sites have also been reported in the context of metabolic syndrome (Chitralla et al., 2020).

One outstanding question in the field is to whether the various epigenetic age measures capture aspects of biological age. There are several studies that support this idea (Fig. 3). Epigenetic age acceleration was associated with faster rates of cognitive decline in African American and White men (Beydoun et al., 2020; Bressler et al., 2020). In a recent meta-analysis containing cohorts that included White, Hispanic and African American individuals, epigenetic age acceleration measures were predictive of all-cause mortality (Chen et al., 2016). In agreement with this study, recent evidence suggests that markers of target organ damage were associated with intrinsic epigenetic age acceleration, but the majority of these relationships were attenuated after adjustment for blood pressure and anti-hypertensives

(Smith et al., 2019). Examination of education and lifestyle factors in African American participants of the Genetic Epidemiology Network of Arteriopathy found that gender, education, BMI, smoking, and alcohol consumption were all independently associated with GrimAge acceleration (Zhao et al., 2019), which is a composite biomarker that includes surrogate DNAm biomarkers of 7 different plasma proteins and a DNAm-based estimator of smoking pack-years (Lu et al., 2019). In this African American cohort with a high prevalence of hypertension, several cardiovascular risk factors were also associated with various measures of epigenetic age acceleration as well (Ammous et al., 2021). In African American mothers enrolled in the Intergenerational Impact of Genetic and Psychological Factors on Blood Pressure (InterGEN) study, obesity was associated with epigenetic age acceleration (Li et al., 2019).

Most recently a new epigenetic clock was developed that incorporates additional clinical measures of phenotypic age and DNAm termed “PhenoAge” (Levine et al., 2018). PhenoAge predicts all-cause mortality across all racial groups examined including Black, White and Hispanic individuals. It also outperformed previous epigenetic clocks (Ex: DNAmAge Hannum and DNAmAge Horvath) at predicting age-related clinical outcomes. Racial/ethnic differences were also observed in PhenoAge as non-Hispanic Black individuals had the highest DNAm PhenoAge while non-Hispanic White individuals had the lowest. These data point to PhenoAge as a promising indicator of biological age in minority populations. As studies that incorporate these “second generation epigenetic clocks” (ex: GrimAge and PhenoAge) in minority populations is limited, we are only beginning to understand which of these epigenetic measures may be better at predicting biological aging and age-related health outcomes in the setting of race/ethnicity.

Psychosocial stress has also been shown to impact epigenetic age in African American individuals (Fig. 3). Epigenetic age acceleration was associated with cumulative lifetime stress in a cohort of urban African Americans individuals (Zannas et al., 2015). Given this data, the authors examined the CpG sites in the Horvath epigenetic clock and found that one third of these sites were located in glucocorticoid response elements (Zannas et al., 2015). Furthermore, glucocorticoid activation altered DNAm and transcription of stress-response genes. These stress-response genes were enriched for association with aging-related diseases (Zannas et al., 2015). Adverse neighborhood environment has also been linked to faster epigenetic aging in African American individuals (Lei et al., 2017; Martin et al., 2021). These data point to changes in DNAm as a biological consequence of the social determinants of health (Fig. 3).

Few studies have examined epigenetic age measures in other minority populations. In a large study of race/ethnicity, it was reported that Hispanic individuals have a lower intrinsic age (“younger”) but higher (“older”) extrinsic epigenetic age rates than White individuals. Age acceleration was also higher in Hispanic men compared to Hispanic women (Horvath et al., 2016). Lower extrinsic age acceleration was also associated with higher education level in Hispanic and African American individuals (Horvath et al., 2016). In Mexican American individuals, 10 CpG sites were differentially methylated in controls versus individuals with mild cognitive impairment (Pathak et al., 2019). It is important to include multi-ethnic cohorts into epigenetic age studies as results are not always replicated in different ethnic

cohorts, but this may also be due to underpowering of these cohorts (Ma et al., 2020) or different mechanisms that drive aging and age-related disease in minority populations.

The inclusion of minority populations in more and more epigenetic studies will surely enhance our understanding about whether epigenomic processes are modified as a consequence of the SDOH. The advent of new epigenetic clocks that incorporate DNAm and clinical measures will also be beneficial.

5.2. Transcriptomics and social genomics in minority populations

Alterations in DNAm of epigenetic age CpG sites or other CpG sites may result in differences in gene expression in minority populations. Indeed, one area of research in the field of social genomics has focused on how social adversity leads to changes in gene expression (Fig. 3). Cole and colleagues have reported changes in immune cell gene expression profiles from individuals facing a variety of adverse social conditions, which has been termed the Conserved Transcriptional Response to Adversity (CTRA) (Cole, 2019). This CTRA pattern describes an upregulation of specific inflammatory-associated genes and downregulation of genes in the Type I interferon antiviral response pathway (Fig. 3) (Cole, 2019). Consistent with this data, our laboratory reported differences in long noncoding RNA (lncRNA) and gene expression in individuals living above or below poverty (Noren Hooten and Evans, 2019). Top pathways that were enriched in individuals living above poverty were those involved in response to stress, immune stimuli, and viral infection (Noren Hooten and Evans, 2019). These pathways were also reported in another independent study examining SES in African Americans (Gaye et al., 2017). This transcriptomic analysis also reported higher abundance of genes in inflammatory pathways (IL-8; Nf-kB; Colony-stimulating factor 2 (CSF2)) in low SES African Americans as part of a molecular profile of SES (Gaye et al., 2017).

The effects of various social stresses on gene expression are context-dependent and therefore it is important to examine other gene networks. For example, there was no difference in the CTRA profile between low-income Black mothers living in neighborhoods with high violence versus low violence (Lee et al., 2021). Greater neighborhood stress and racial discrimination were associated with higher glucocorticoid receptor response genes (Lee et al., 2021; Thames et al., 2019), which is consistent with the epigenetic modifications of these response genes in African American individuals with cumulative lifetime stress (Zannas et al., 2015). Comparisons of African American men and women living above and below poverty identified other pathways that may also underlie the effects of poverty. In African American women, pathways related to long chain fatty-acyl-CoA biosynthetic processes, B-cell differentiation, genetic imprinting, and interleukin-12-mediated signaling were significantly different in African American women living above or below poverty (Arnold et al., 2020). Pathways related to neutrophil degranulation, toll-like receptor signaling, antigen processing and presentation and MyD88-dependent toll-like receptor signaling were significantly different between African American men living above and below poverty (Arnold et al., 2020). Endosome organization was the one overlapping pathway comparing both African American men and women living above or below poverty (Arnold et al., 2020). These studies highlight the commonalities among pathways that are

regulated by psychosocial stress, but also highlight that these effects are contextual and may lead to different biological consequences over the lifespan.

The importance of acquiring more transcriptomic data sets of minority populations is highlighted by a recent study showing that datasets trained using individuals of European descent largely are not generalizable to African American individuals (Keys et al., 2020). In response to this, a recent study incorporated ~ 50,000 Hispanic/Latino, African American, Asian, Native Hawaiian, and Native American individuals as part of the Population Architecture using Genomics and Epidemiology (PAGE) study. The authors utilized this large GWAS dataset to perform transcriptome-wide association studies (TWAS) to predict gene expression levels and gene-trait associations (Geoffroy et al., 2020). Twenty-eight different traits in the following categories were examined: inflammatory, lipid, lifestyle, glycemic, electrocardiogram, blood pressure, anthropometric and kidney. There were gene-trait associations identified for 14 out of the 28 traits using three different models incorporating different populations: the African American and Hispanic/Latino (AFHI) model, the European (EUR) model, and the African American, Hispanic/Latino, and European (ALL) model. All together there were 206 genes and 240 unique gene-trait pairs identified. However, their AFHI model, incorporating data from African American and Hispanic/Latino individuals, discovered more gene-trait associations that replicated in larger cohorts, indicating the importance of including matched populations of similar ancestry in transcriptome prediction model studies (Geoffroy et al., 2020). Furthermore, since this study was prediction-based it highlights the need for additional transcriptomic studies in diverse, minority populations as they age.

6. DNA damage/repair and aging in minority populations

Both the free radical and the DNA damage theory of aging posit that aging is caused by accumulation of DNA damage and reduced DNA repair (Gensler and Bernstein, 1981; Harman, 1956). Increased DNA damage is correlated with age-related diseases such as cancer, inversely, premature aging disorders are associated with impaired DNA repair systems and accumulation of DNA damage (Chen et al., 2020; Niedernhofer et al., 2018). Overall, there is a correlation between age and general DNA damage, although specific studies may not reflect a significant correlation depending on the methods employed to measure DNA damage or the particular variety of DNA damage investigated (Jacob et al., 2013; Soares et al., 2014).

DNA damage can be caused by exogenous or endogenous DNA damaging agents. Exogenous DNA damage occurs after exposure to environmental sources such as pollutants or ionizing radiation. Endogenous damaging agents primarily include reactive alkylating agents or oxygen species (ROS) that are naturally produced within cells, although DNA damage may also occur during replication or spontaneously (Chatterjee and Walker, 2017). Both endogenous and exogenous damaging agents may cause strand breaks or oxidative damage to DNA. The most studied ROS include hydrogen peroxide, superoxide radicals, and the hydroxyl radical. Produced in the mitochondria, ROS can interact with nearby proteins or genes to cause damage and further increase production of ROS (Niedernhofer et al., 2018). ROS and oxidative damage increase as organisms, including humans, age (Jacob

et al., 2013). Spontaneous DNA mutations are typically stochastic, but evidence shows that mutation accumulation increases with age (Ramsey et al., 1995). DNA strand breaks are highly toxic and thus difficult to measure precisely at low levels; however, multiple studies confirm that single- and double-strand breaks increase in cells taken from the elderly compared to younger populations (Chevanne et al., 2003; Rube et al., 2011; Sedelnikova et al., 2008). Conversely, long-lived humans display similar amounts of strand breaks as young adults (Chevanne et al., 2003).

DNA repair systems normally compensate for the damage that takes place daily. However, individual repair capacity may differ from the population average, overwhelming amounts of damage will exhaust repair capacity, and DNA repair efficacy appears to decline with age (Chen et al., 2020; Nagel et al., 2014; Niedernhofer et al., 2018). Studies have shown a decline with age in the expression of DNA repair proteins involved in multiple repair pathways, although results conflict depending on the cell type investigated (Zhang et al., 2020; Li et al., 2016). Nucleotide excision repair has been shown to decline with age in several studies (Goukassian et al., 2000; Moriwaki et al., 1996; Yamada et al., 2006). Base excision repair has also been shown to decline in a variety of human cell types from aged individuals (Atamna et al., 2000; Xu et al., 2015; Zhang et al., 2020). Studies investigating strand break repair have produced conflicting results (Jacob et al., 2013). While some labs have found that single- or double-strand break repair declines with age in leukocytes or human-derived cell lines (Li et al., 2016; Sedelnikova et al., 2008; Trzeciak et al., 2008), conflicting results have also been published showing no decline (Garm et al., 2013; Zhang et al., 2020). An age-related decline in repair capacity may be tissue-specific or require more precise study design to reveal repair capacity declines in certain populations (Chen et al., 2020; Jacob et al., 2013).

Research has suggested that both levels of baseline DNA damage and DNA repair capacity are not equal among all human populations (Chatterjee and Walker, 2017; Jacob et al., 2013). Measurement of DNA damage is frequently performed on cohorts stratified by age and often sex. The interplay between race and DNA damage in the process of aging is rarely studied (Møller, 2006; Neri et al., 2015). Differences in DNA damage and repair may explain some age-related health disparities observed in minority populations. This section will summarize studies on DNA damage and repair related to aging in minority populations.

Studies on DNA damage have revealed race-dependent differences in baseline DNA damage and DNA repair capacity. Lahiri et al. demonstrated an increased resistance to oxidative stress in African individuals relative to White individuals in a pilot study (Lahiri et al., 1999). In a recruitment study for breast cancer, oxidative damage was shown to be highly variable in African American patients (SD = 224.1) compared to White patients (SD = 57.5, $p < 0.001$) (Simon et al., 2000). Another study investigating the effect of antioxidants on oxidative damage noted a difference in baseline oxidative DNA damage between African American and White individuals (Huang et al., 2000). Lowered baseline urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG, ng/mg creatinine) was associated with race (15.6 ± 0.8 in African American individuals versus 20.3 ± 1.2 in White individuals, mean \pm SE; $p = 0.001$), antioxidant supplementation, and exercise (Huang et al., 2000). A study on women launderers and dry cleaners reported a difference in oxidative damage between African

American and White groups (Toraason et al., 2003). White women displayed a significantly higher level of leukocyte 8-OHdG (17.8 ± 7.4 , mean \pm SD) that was significantly greater than the observed damage in control African American women (11.8 ± 5.9 , mean \pm SD) (Toraason et al., 2003). In a study investigating the correlation between antioxidant intake and DNA damage measured by the alkaline comet assay, African American individuals were reported to have lower levels of oxidative DNA damage compared to White individuals (1.404 versus 1.559, mean tail moment; $p = 0.005$) (Watters et al., 2007). In later follow-up studies, regression models examining demographic and behavioral correlates with oxidative DNA damage levels explained more of the damage variance in White individuals than in African American individuals (27% vs 19%) (Watters et al., 2007). Finally, the same samples were examined with alternative oxidative stress and DNA damage assays urinary F₂-isoprostanes; the comet assay with formamidopyrimidine DNA glycosylase (FPG); and 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxo-dG) (Watters et al., 2007). Results for the first two assays matched previous results: African American individuals had lower oxidative DNA damage and stress levels as measured by the comet assay ($p = 0.0003$) and F₂-isoprostanes ($p = 0.27$), however damage measured by 8-oxo-dG was higher ($p = 0.05$) than White individuals (Watters et al., 2007).

In a longitudinal study from the HANDLS cohort, our laboratory reported findings that matched previous observed differences in DNA damage and repair levels between African American and White participants (Trzeciak et al., 2008). The fast component of single-strand break repair was shown to increase with age only in White women (Trzeciak et al., 2008). When comparing DNA repair levels between African American and White women, the fast component of single-strand break repair was lowered with age in African American women compared to White women (Trzeciak et al., 2008). In a follow-up study, overall single-strand break repair was shown to be higher in women than in men ($p = 0.013$); the difference persisted in African American women versus African American men ($p = 0.029$) but not in White women versus White men ($p = 0.164$) (Trzeciak et al., 2012). Repair of toxic double-strand breaks has also been examined in a racially diverse cohort (Sharma et al., 2015). No statistical difference in baseline double-strand breaks was found for a specific racial group, however, a significant interaction between age and race was observed for Hispanic participants (Sharma et al., 2015). Double-strand break repair rates were overall positively associated with age ($p = 0.025$) and specifically for White participants ($p = 0.007$) (Sharma et al., 2015).

Current limitations in correlating measured DNA damage and repair capacity to demographic or behavioral factors illustrate the need for more racially diverse studies to improve our knowledge of DNA damage response mechanisms, aging, and health disparities in all populations (Nagel et al., 2017).

7. Discrimination and accelerated aging phenotype

In the United States, the deeply rooted system of racism has permeated our culture leading to long standing effects. Prolonged negative social experiences including psychological stresses can cause detrimental health outcomes. Discrimination is a psychological stress that is defined as the prejudice and unfair treatment given to people due to their membership

in a certain group (Williams and Mohammed, 2009). These include, but are not limited to, minority racial status, and can be characterized on multiple levels ranging from an individual perspective to society in general. Discrimination as a form of social exclusion can be felt short term (everyday) or long term (lifetime) leading to adverse physiological responses.

Discrimination has been associated with several age-related health outcomes (Fig. 4). Many studies have examined the link between discrimination and risk factors and outcomes for cardiovascular disease (CVD) (Lewis et al., 2014). For example, among women, everyday discrimination predicts higher levels of blood pressure, which is mediated by adiposity (Moody et al., 2018). In the MESA and JHS studies, lifetime discrimination was associated with higher incidence of hypertension among Black Americans (Forde et al., 2021, 2020; Sims et al., 2012). Inflammation increases with age and is associated with CVD. Specifically, the inflammatory marker interleukin-6 (IL-6) and the acute phase protein CRP are risk factors for CVD. Higher levels of IL-6, but not CRP, were associated with women experiencing greater everyday discrimination and lifetime discrimination (Kershaw et al., 2016). Discrimination and race-related stressors were shown to be associated with increases in inflammatory markers even in African American children, with early exposure to discrimination also predicting later levels of inflammation in adulthood (Simons et al., 2018). This increase in chronic inflammation has been predicted to lead to accelerated aging (Levine and Crimmins, 2014; Simons et al., 2018). Another study found that older African American adults experiencing everyday discrimination had higher levels of CRP and this was modified by obesity (Lewis et al., 2010). The effect of discrimination may be modulated by socioeconomic status (SES). Several studies investigated potential effects of SES on inflammation among diverse populations. African American individuals of higher SES have been shown to report higher discrimination than African American individuals of lower SES (Borrell et al., 2013; Vines et al., 2006). Low SES was associated with overexpression of pro-inflammatory pathways in a cohort of African American individuals (Gaye et al., 2017). SES discrimination was reported to be associated with higher levels of CRP in higher educated African American individuals (Van Dyke et al., 2017). Lower educated African American and White individuals of either education level did not display the same association (Van Dyke et al., 2017). These studies, and others, indicate that the link between discrimination and CVD risk factors is complex and may be modified by other factors (Lewis et al., 2014). Importantly, recent data has shown that lifetime discrimination increased CVD risk (Everson-Rose et al., 2015).

Discrimination may also impact metabolic diseases. In a longitudinal cohort of US women from the Study of Women's Health Across the Nation (SWAN), everyday discrimination predicted a greater incidence of metabolic syndrome in all women, but was more prominent in Black, Hispanic, and Japanese women (Beatty Moody et al., 2018). Major experiences of discrimination, but not everyday discrimination, also predicted greater risk of incident type 2 diabetes mellitus in another study (Whitaker et al., 2017). Although most studies have focused on discrimination in African American individuals, it has been reported that Hispanic individuals experiencing ethnic discrimination have higher odds of diabetes but only in those individuals with higher depressive symptoms (McCurley et al., 2019).

African American individuals bear a disparate burden of poor brain health outcomes, which may be a consequence of discrimination. Black individuals experiencing more everyday discrimination have poorer episodic memory (Barnes et al., 2012a) and faster episodic memory decline (Zahodne et al., 2017). Although we are only beginning to understand how discrimination leads to deficits in cognition, one study indicated that inflammation, as measured by CRP, mediated the effects on baseline memory but not memory decline (Zahodne et al., 2019a). Using neuroimaging, other data suggests that discrimination can affect the structure of the brain. Older African American adults experiencing greater lifetime and racial discrimination had increased White matter lesion volume (WMLV) while younger African American adults with lower racial discrimination was associated with increased WMLV (Beatty Moody et al., 2019b). WMLV is a subclinical prognostic indicator in the brain associated with future stroke, dementia and cognitive decline. In cohort studies from the Rush Alzheimer's Disease Center, experience of discrimination in older Black adults was associated with differences in functional connectivity of the insula, a region of the brain that regulates emotions and trust (Han et al., 2020). Furthermore, lifetime discrimination in African American individuals with depressive symptoms had increased carotid intimal-medial thickness, which is a subclinical marker of atherosclerosis and stroke incidence (Beatty Moody et al., 2020).

Telomere attrition is a hallmark of aging and the accelerated aging phenotype. Women with high SES that experienced greater lifetime discrimination, racial discrimination and gender discrimination had shorter telomeres (Beatty Moody et al., 2019a; Pantesco et al., 2018). Interestingly, this observation was not observed in men or women with lower SES. In another study, African American men experiencing greater racial discrimination had shorter telomere length (Chae et al., 2014). In a follow up study, it was reported that African American men with lower depressive symptoms had shorter telomere length (Chae et al., 2016). In addition to telomere attrition, oxidative stress is an important driver of the aging process. Red blood cell oxidative stress was shown to be significantly associated with racial discrimination (Szanton et al., 2012). These data indicate that African American individuals experiencing psychosocial stress due to discrimination can cause biological consequences that promote accelerated aging and point to mechanisms that may explain health disparities in aging (Fig. 4).

One important question is whether experiencing discrimination affects longevity and aging. In the Chicago Health and Aging Project, older adults exposed to greater discrimination had increased mortality (Barnes et al., 2008). Consistent with this idea, data from the HRS found that everyday discrimination was associated with increased risk for all-cause mortality (Farmer et al., 2019). In both the HRS and in the Black Women's Health study, racial discrimination was not associated with all-cause mortality (Albert et al., 2010; Farmer et al., 2019). In agreement with this data, studies from the JHS indicate that everyday discrimination was not associated with CVD outcomes and surprisingly with lower all-cause mortality, which was partially mediated by perceived stress (Dunlay et al., 2017).

Combined these studies point to discrimination as a psychosocial stress that effects biological pathways that impact aging and age-related diseases (Fig. 4). This area of research is complex and may be mediated by a variety of susceptibility factors that have

yet to be explored fully. Therefore, additional studies that include minority populations and discrimination data are needed to understand the physiological impacts of discrimination on age-related clinical health outcomes.

8. Inflamm-aging and minority populations

Acute and chronic stress in life cause physiological changes in the body, and even traumatic experiences or stress in childhood have been shown to alter the immune system and inflammation responses in adulthood (Emeny et al., 2021). The normal process of aging is also accompanied by a 2- to 4-fold increase in plasma/serum levels of proinflammatory cytokines in the elderly compared to younger individuals (Ferrucci et al., 2010; Michaud et al., 2013). Elevated circulating inflammatory markers are associated with frailty, risk of morbidity, and mortality in aged individuals (Michaud et al., 2013). Low-level, chronic inflammation in the context of aged individuals, or inflamm-aging, is implicated as a marker or cause of a wide variety of age-related diseases and premature biological aging (Beydoun et al., 2019; Ferrucci et al., 2010; Franceschi et al., 2000, 2018). Minority populations are exposed to stressful life events and experiences such as discrimination, leading to increased inflammation (Cuevas et al., 2020; Djuric et al., 2008; Schmeer and Tarrence, 2018). The strength of the inflammatory response has also been shown to differ by ethnicity (Nédélec et al., 2016; Yeyeodu et al., 2019). The contribution of inflammation to the process of aging must be clarified to understand the physiological impacts of inequality on aging and age-related health disparities. Here we will discuss recent studies examining the role of inflamm-aging in the aging of minority populations.

8.1. Inflammatory markers and aging in minority populations

Immune system function differs among populations and changes with age. Race/ethnicity likely modifies inflammatory responses, as African American individuals with neuroinflammatory disorders have been shown to display more severe clinical manifestations than White individuals with the same diagnosis (Cree et al., 2009; Wharton et al., 2019). Research is ongoing to tease apart meaningful differences in immune system marker baseline levels and function that may translate to diverse rates of aging.

Circulating levels of proinflammatory factors such as interleukins, CRP, and TNF- α generally increase with age. Higher levels of inflammatory markers have been linked with age-related diseases such as cancer and frailty, although evidence is mixed based on the populations studied and study design (Jacob et al., 2013). Conflicting results associated with IL-6 levels may be attributable to differing sources of samples (e.g., blood, serum, plasma, or cerebrospinal fluid), the age of the cohort in the study, or the methods used to measure IL-6. In a middle-aged cohort, frail White individuals displayed higher IL-6 expression in PBMCs than African American individuals (Prince et al., 2019). In a small pilot study with only older White participants, serum IL-6 levels correlated with frailty and a reduction in hemoglobin and hematocrit (Leng et al., 2002). In contrast, studies on populations of older African American and White women observed higher serum IL-6 levels in African American women (Allison et al., 2006; Walston et al., 2005). No significant differences in serum IL-6 were observed in African American versus White individuals in a mixed gender

sample aged 70–79 (Yaffe et al., 2003). A study balanced between African American and White participants who were middle-aged and older did not find an association between CRP levels and race (Waldstein et al., 2016). A large meta-analysis in 2016 found that pre-frailty and frailty were associated with IL-6 and CRP in cross-sectional studies, however, the three longitudinal studies in the meta-analysis did not display a correlation between elevated inflammatory markers and future development of frailty (Soysal et al., 2016). Data from the diverse Cardiovascular Health Study (CHS) All Stars Study showed that a subset of aged participants developed higher IL-6 and CRP levels with increasing age (IL-6: 23%, CRP: 21%) (Jenny et al., 2012). In addition, a doubling in either IL-6 or CRP levels was correlated with higher risk for physical or mental impairment (IL-6 odds ratio, 1.45; 95% confidence interval 1.20–1.76; CRP odds ratio 1.29, 95% confidence interval 1.15–1.45) (Jenny et al., 2012). However, data from the CHS All Stars Study was not broken down for potential associations between levels of inflammatory markers and race (Jenny et al., 2012). A study based on the longitudinal HRS cohort found that African American individuals displayed higher CRP levels than both White and Hispanic individuals (Mitchell and Aneshensel, 2017). CRP levels of Hispanic individuals did not differ from White individuals (Mitchell and Aneshensel, 2017). A later study also performed on data from the HRS showed both higher baseline levels of CRP and greater increases in CRP over the study's period in African American participants compared to White participants (Zahodne et al., 2019b). Hispanic participants also showed a higher baseline CRP than White participants but no difference in CRP over time was found (Zahodne et al., 2019b). Significant differences in other inflammatory markers, including receptor for advanced glycation end products, intracellular adhesion molecule-1, vascular cell adhesion protein-1, and monocyte chemo-attractant protein-1, have also been reported between African American and White women (Noren Hooten et al., 2012).

8.2. Oxidative stress, DNA damage, and inflamm-aging in minority populations

Inflammation that increases the pace of biological aging can arise from many potential pathways. Oxidative stress, and the DNA damage and damage-associated molecular patterns (DAMPs) that subsequently occur, has been linked to inflammation (Goldberg and Dixit, 2015; Kapetanovic et al., 2015). Inflammation is a response to oxidative damage, and often additional oxidative stress will occur from the inflammatory response (Venkataraman et al., 2013). Of interest is a potential difference in oxidative stress levels in varied populations, and how these differences contribute to inflamm-aging and development of age-related disease, especially given the unequal burden of age-related diseases in minority populations. African American individuals have been reported to have higher levels of oxidative stress compared to White individuals, even when differences in inflammation levels and risk factors for cardiovascular disease were controlled for (Morris et al., 2012). Chronic self-reported racial discrimination has been linked to markers of oxidative stress such as fluorescent heme degradation products in a diverse cohort from the HANDLS study (Szanton et al., 2012). Of interest is the observation that the results were only significant for African American individuals when the cohort was stratified by race (Szanton et al., 2012). Higher levels of oxidative stress in certain populations can lead to patterns of DNA damage or reduced DNA repair capacity. Fluorescent heme degradation products were found to be correlated with DNA single-strand breaks in African American men but not women

(Trzeciak et al., 2012). Other markers of oxidative stress may or may not be associated with DNA damage: CRP was found to induce DNA base lesions but not single- or double-strand breaks in vitro (Noren Hooten et al., 2012). However, in a diverse cohort of women, the base lesion and oxidative stress marker 8-oxo-dG was significantly associated with serum CRP levels (Trzeciak et al., 2012). Finally, a racially diverse cohort of retired football players was examined for inflammatory markers and their association with atherosclerosis (Virani et al., 2012), as inflammation plays a key role in the development of atherosclerosis (Hansson, 2005; Libby et al., 2011). Atherosclerosis was associated with measures of atherogenic cholesterol and lipoproteins (Virani et al., 2012). CRP levels were not associated with atherosclerosis in the study; however, CRP was higher in individuals with metabolic syndrome (Virani et al., 2012).

The process of aging is complex and multifaceted. Aging is influenced by physical as well as social determinants of health. The contribution of inflammation to the process of aging must be clarified to better understand aging in underserved and disadvantaged populations.

9. Conclusions

Here, we have discussed factors that contribute to the accelerated aging phenotype frequently manifest in minority populations. The interplay of the upstream and downstream SDOH with complex biological factors and pathways are the root causes of disparate health outcomes with aging. Aging and health disparities operate through common converging pathways that ultimately result in similar health outcomes just with different trajectories. The different trajectories may be influenced by many factors including dysfunctional gene-environment interactions, the social and political determinants of health and numerous biologic transduction pathways that may be modulated through adversity. Although there is evidence that inflammation, oxidative stress, immune function and DNA repair may all play a role in the development of the accelerated aging phenotype of health disparities phenotype, the multi-level interacting factors and pathways are incompletely understood. Equally important in future research will be examination and identification of resilience factors that are present and may explain factors that underlie the Black-White cross over and the Hispanic survival paradox. However, we have yet to completely understand this process. Observational, longitudinal, and interdisciplinary studies that include minority populations with clinical, psychosocial and health outcome data are required as important cornerstones that would propel this area of research. As a guide for aging researchers interested in minority aging, we have included a table of studies cited in this review that include minority populations (Table 1). We hope this review and the information it provides will spur additional focus on the health disparities in aging and age-related diseases in minority populations.

Future directions

Aging research must be a place of equity for groups from all segments of society, and we must also focus our research efforts to be inclusive of all; racial/ethnic minorities, low SES, as well as considerations of geographic location. We should actively pursue facilitated discussions to make aging researchers leaders in the important step on this

journey to diversify the biomedical workforce and to understand the differential influence of SDOH and political determinants of health on aging. The ultimate goal is to inform appropriate interventions to ameliorate these factors, improve health span, and lengthen lifespan. Addressing upstream SDOH especially structural racism will hopefully reduce the harmful stress exposures among all minority groups African Americans, Hispanics, Native Americans/Alaska Natives, and Asian/Native Hawaiians and Pacific islanders over the lifespan and eliminate health disparities and insure health equity for all.

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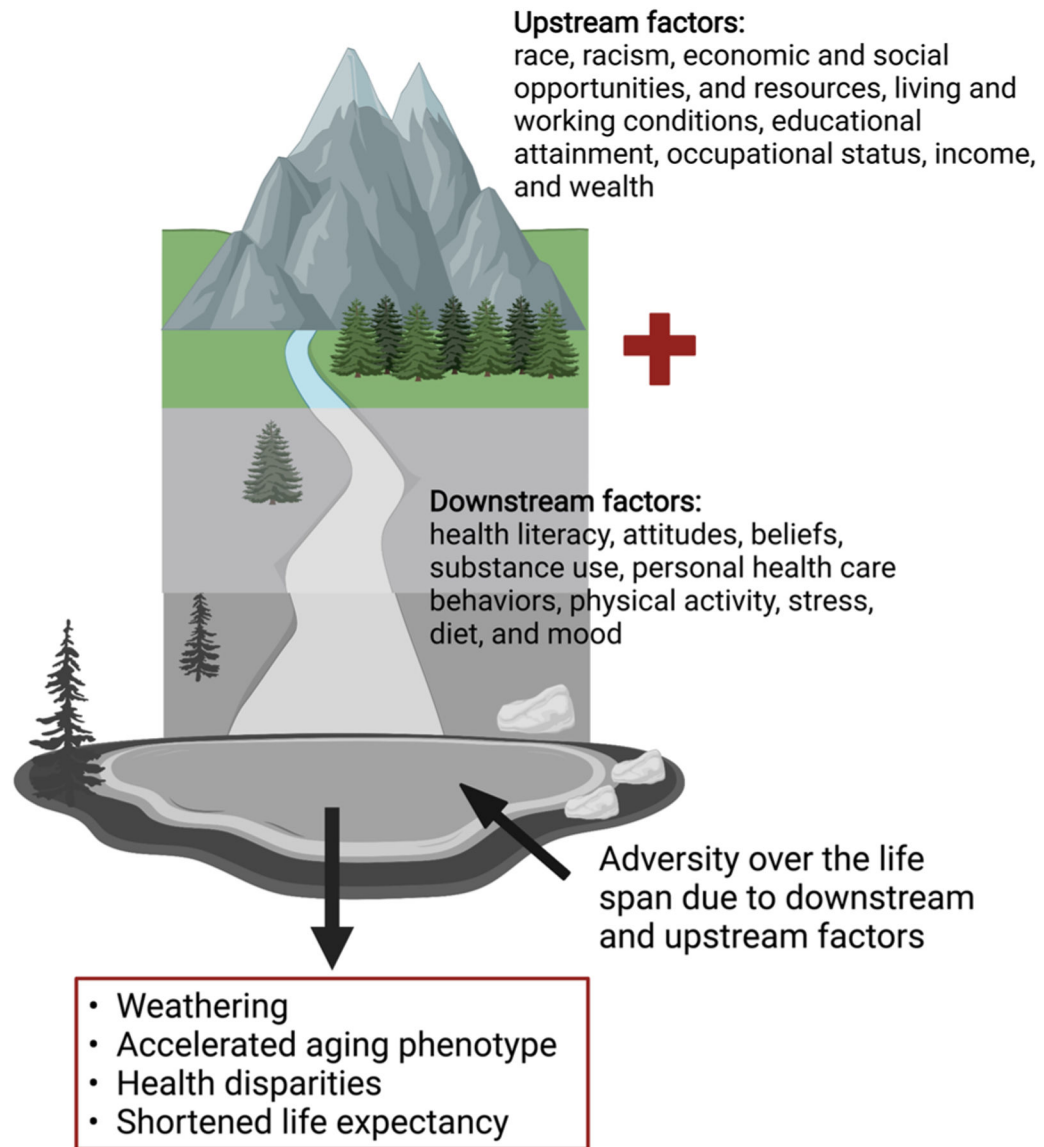


Fig. 1. Upstream and downstream determinants of health influence outcomes over the lifespan.

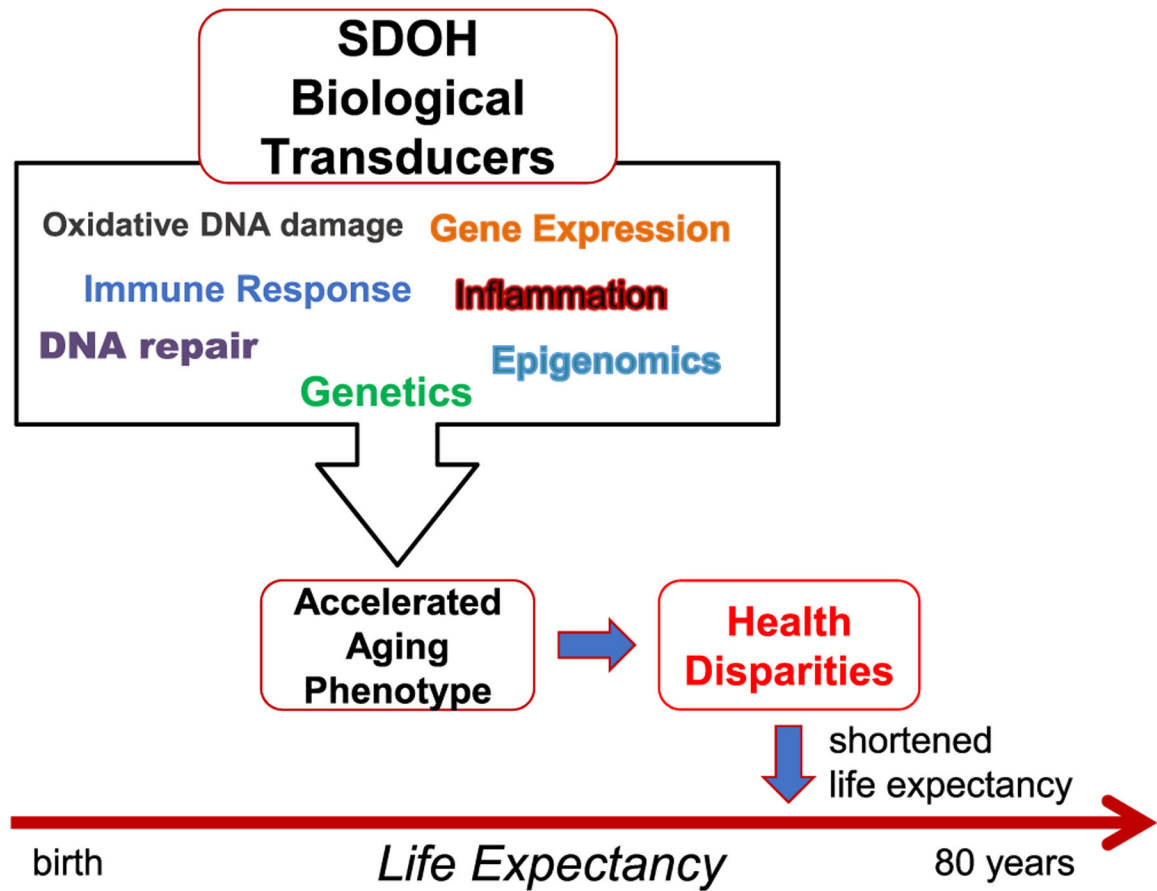


Fig. 2. Social determinants of health biologic transducers that lead to the accelerated aging phenotype and health disparities in aging and age-related disease.

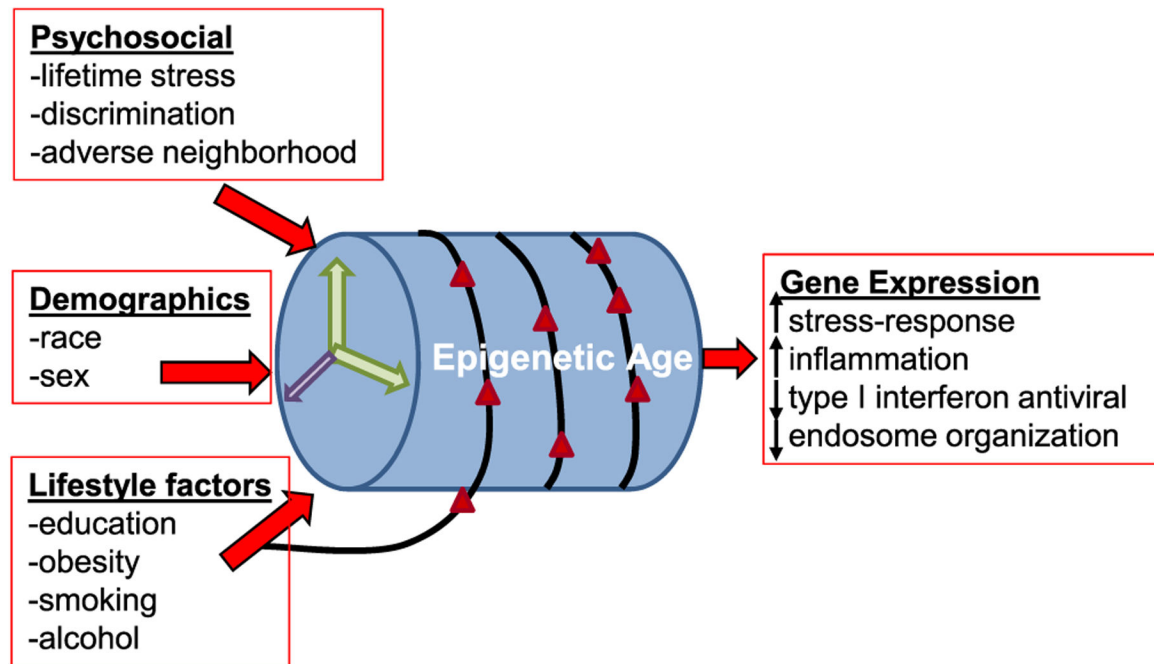


Fig. 3. Factors leading to epigenetic age acceleration in minority populations. Psychosocial, lifestyle factors as well as demographics contribute to changes in DNA methylation that have been categorized as accelerated epigenetic aging. These epigenetic alterations may result in the observed gene expression changes in minority populations in response to the social determinants of health.

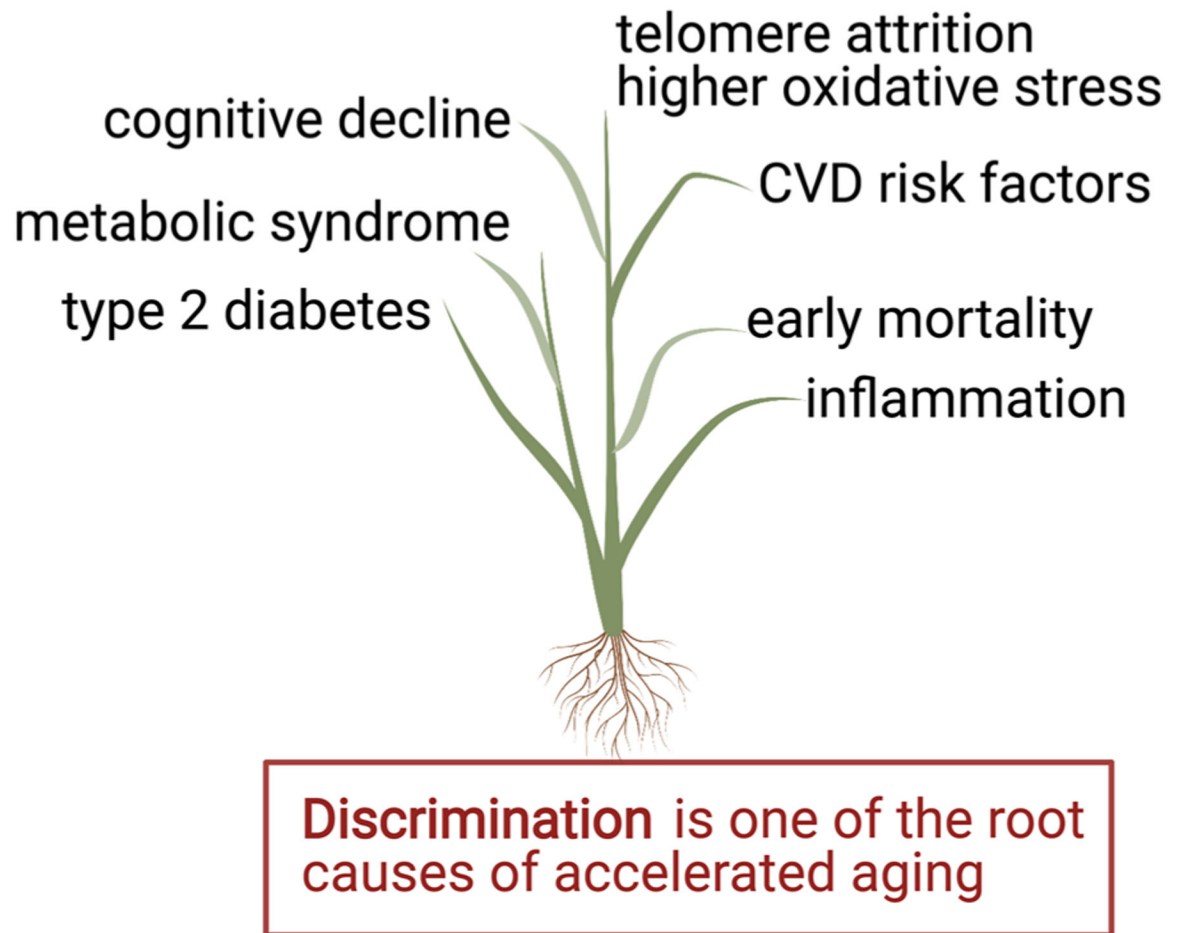


Fig. 4. Discrimination lays the roots for health disparities in health outcomes.

Table 1

Cohort studies with minority populations.

Full study name	Study website	Race/ethnicity distribution						Reference
		Total	White	African American	Hispanic	Asian	NA/ PI ^a	
Age/Aging-related								
Americans' Changing Lives study	ACL	3617	2443	1174				(House, 2018)
Advanced Cognitive Training for Independent and Vital Elderly	ACTIVE		73.3%	26%			0.7%	(Temstedt and Unverzagt, 2013)
National Longitudinal Study of Adolescent to Adult Health ^c	Add Health	15,140	8372	3312	2393		1063	(Popkin and Udry, 1998)
Baltimore Longitudinal Study of Aging	BLSA		70%	25%			5%	(Shock, 1984)
Chicago Health, Aging, and Social Relations Study	CHASRS	229	35.8%	35.4%	28.8%			(Cacioppo and Cacioppo, 2018)
Healthy Aging in Neighborhoods of Diversity across the Life Span	HANDLS	3720	1520	2200				(Evans et al., 2010)
Health and Retirement Study (total)	HRS	42,226	29,148	7877	5201			(Sonnega et al., 2014)
Long Life Family Study	LLFS	3690	99.3%				0.7%	(Newman et al., 2011)
Hispanic Community Health Study/Study of Latinos	HCHS/SOL	16,415			16,415 ^d			(Lavange et al., 2010)
Minority Aging Research Study	MARS	366		366				(Lewis et al., 2010)
Minority Health Genomics and Translational Research Bio-Repository Database	MH-GRID	1637		1637				(Zilbermint et al., 2019)
Mid-life in the United States Wave 1 + 2	MIDUS	7138	5860	962			316	(Brim et al., 2020)
National Health and Nutrition Examination Survey	NHANES III	18,825	83%	12%	5%			(Ezzati et al., 1992)
National Health and Nutrition Examination Survey	NHANES IV	11,432	75.6%	10.9%	13.4%			(Liu et al., 2018)
National Health Interview Survey ^e	NHIS	72,831	46,222	8487	12,481	4455	1186	((NCHS), 2018)
Washington Heights and Inwood Community Aging project ^f	WHICAP	-6000	19.4-29.5%	30.7-34.1%	38.5-47%			(Manly et al., 2005; Tang et al., 2001)
Women's Health and Aging Study ^g	WHAS	1002	71.2%	28.3%				(Onder et al., 2002)
Age-related diseases								
Atherosclerosis Risk in Communities	ARIC	15,792		4328				(The ARIC investigators, 1989)
Genetics of Pancreatic β -cell Failure in Mexican-Americans	BetaGene study	-2000			2000			(Watanabe et al., 2007)
Bogalusa Heart study	BHS	12,138	7786	4352				(Berenson, 2001)

Full study name	Study website	Race/ethnicity distribution						Reference
		Total	White	African American	Hispanic	Asian	NA/ Pt ^a	
Boston Puerto Rican Health Study	BPRHS	1200			1200 ^h			(Tucker, 2005)
Cardiovascular Health Study (+ All Stars)	CHS (+ All Stars)	5888		16%				(Fried et al., 1991)
Diet, Supplements, and Health Study	DISH	155	79	76				(Watters et al., 2007)
Coronary Artery Risk Development in Young Adults	CARDIA	5116	2472	2644				(Friedman et al., 1988)
Genetic Epidemiology Network of Arteriopathy	GENOA		1583	1854	1812			(Daniels et al., 2004)
Health, Aging, and Body Composition	Health ABC	3075	1794	1281				(Santanasto et al., 2017)
The Health & Aging Brain Study-Health Disparities	HABS-HD	2000	1000	1000 ⁱ	1000			(O'Bryant et al., 2013)
Indianapolis-Ibadan Dementia Project	IIDP	8537		8537 ^j				(Hendrie et al., 2001, 1995)
Jackson Heart Study	JHS	5301		5301				(Fox et al., 2016)
Massachusetts Hispanic Elders Study	MAHES	1030	154		876			(Falcon et al., 1997; Gao et al., 2004)
Rush Memory and Aging Project	MAP	1407	1298	109				(Barnes et al., 2012b)
MAP - Clinical Core of the Rush Alzheimer's Disease Core Center	MAP-RADC Clinical Core	218		218				(Barnes et al., 2012b)
Multi-Ethnic Study of Atherosclerosis	MESA	6500	2623	1891	1496	804		(Bild et al., 2002)
Morehouse and Emory Team up to Eliminate Health Disparities	META-Health	3391	1936	1455				(Morris et al., 2011, 2012)
San Antonio Longitudinal Study of Aging ^k	SALSA (v2)	749	355		394			(Espinoza et al., 2010, 2013)
Women's Health Initiative baseline	WHI	27,347	22,027	2741	1543	527	131	(The Women's Health Initiative Study Group, 1998)
Women's Health Initiative ^l	WHI	67,140	87%	7%	3%	2%	1%	(The Women's Health Initiative Study Group, 1998)
Psychosocial factors								
Detroit Neighborhood Health Study	DNHS	2081	192	1757		10	21	(Goldmann et al., 2011)
Family and Community Health Study	FCHS	889		889				(Simons et al., 2016)
Grady Trauma Project	GTP	12,000		12,000				(Gillespie et al., 2009)
Intergenerational Impact of Genetic and Psychological Factors on Blood Pressure	InterGEN	250		250				(Taylor et al., 2016)
Study of Women's Health Across the Nation	SWAN	3302	1550	935	286	531		(Sowers et al., 2000)
Sacramento Area Latino Study on Aging	SALSA (v1)	1789			1789			(Haan et al., 2003)
Veterans Aging Cohort Study	VACS	5998	23.5%	66.7%			9.5%	(Justice et al., 2006)

Study cohort information was based on publications, websites and in some cases communication from the study investigators.

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^aNative American, American Indian, Alaskan Native, or Pacific Islander

^bOther/Missing/"Non-W"/Multi-Racial

^cDNA archived Wave IV

^dHispanic or Latino

^eTaken from the NHIS 2018 Data Release. Person file variable frequencies document ("HHC.200_01.000: Race/ethnicity recode- HISCODI3"; variable); sample sizes vary by years

^fA range of percentages were based on recent cohort description papers.

^gFirst WHAS cohort (only 3 years)

^hHispanic adults of Puerto Rican origin

ⁱFuture recruitment

^jBaseline enrollment: 2212 AA, 2494 Nigerians; 2nd enrollment stage: 1892 AA, 1939 Nigerians

^kThe SALSA cohort participants were recruited from the San Antonio Heart Study (SAHS) cohort (PMID: 6507426) and numbers were estimated based on publications.

^lNumbers were taken from the "About WHI" on WHI website, and reflect Active WHI participants as of March 2019