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REVIEW

Intersectionality in Alzheimer's Disease: The Role of Female Sex and Black American Race in the Development and Prevalence of Alzheimer's Disease

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Abstract

It is well known that vascular factors and specific social determinants of health contribute to dementia risk and that the prevalence of these risk factors differs according to race and sex. In this review, we discuss the intersection of sex and race, particularly female sex and Black American race. Women, particularly Black women, have been underrepresented in Alzheimer's disease clinical trials and research. However, in recent years, the number of women participating in clinical research has steadily increased. A greater prevalence of vascular risk factors such as hypertension and type 2 diabetes, coupled with unique social and environmental pressures, puts Black American women particularly at risk for the development of Alzheimer's disease and related dementias. Female sex hormones and the use of hormonal birth control may offer some protective benefits, but results are mixed, and studies do not consistently report the demographics of their samples. We argue that as a research community, greater efforts should be made to not only recruit this vulnerable population, but also report the demographic makeup of samples in research to better target those at greatest risk for the disease.

Keywords Biological sex · Dementia · Vascular · Alzheimer's disease · Racial disparities · Ethnicity · Health disparities

Introduction

An estimated 6.2 million adults 65 years of age and older are living with Alzheimer's disease (AD) and related dementias in the USA, and this burden is expected to more than double by 2060 [1, 2]. Increasing age is the largest risk factor for AD, and prevalence doubles every 5 years beyond the age of 65. Many studies have thoroughly reported on the increased prevalence of dementia in both Black Americans [3, 4] and women [5, 6]. About two-thirds of persons living with AD are women, and Black American adults are thought to have the highest risk of AD, with a 64% higher risk than non-Hispanic White adults (NHW) [2, 5]. Among people ages 65 and older, the African and Black American population, hereafter referred to as Black Americans, has the highest prevalence of AD and related dementias (13.8%), while the prevalence among NHW individuals is 10.3% [7–9]. That more women than men develop AD is primarily attributed to the fact that, on average, women live longer than men [10]. However, the extent to which sex differences in AD are solely due to the larger number of women or if other contributing factors are present is yet to be resolved, and findings related to this issue are mixed.

Before we begin a discussion of these factors, it is important that we define the terms we use in this review regarding sex and race. The term we use here refers to biological sex, and this review particularly covers the overlap between

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Black American race and female sex. Recently, scientists have called into question the use of the word "race" in scientific research, as the categories themselves are ill-defined with little genetic or cultural validity [11]. However, current use of census racial categories in the USA does have some utility in determining dementia risk, as individuals who self-report as Black American have an increased risk of developing AD compared to those who self-report as NHW [9]. In medical literature, race typically describes those who share phenotypic features and/or ancestral backgrounds. Race has a loose genetic interpretation, and the self-reported term we use here is more accurately described as an ethno-racial identity. The scope of this review is to outline the overlap of sex and race and how these factors may influence and interact with one another to generate the health disparities we see in this population.

Inclusion of Women and Black Americans in Research and Clinical Trials

Women and Black Americans have historically been underrepresented in clinical trials and other research studies in the field of AD. While AD risk factors, biomarkers, and clinical factors have been reported by sex in numerous studies, sex as a biological variable and differing effects by sex in randomized clinical trials (RCTs) are not well reported. While women have been included in clinical trials and psychosocial interventions, the rates of enrollment for women are significantly lower than the proportion of women living with AD [12, 13]. A systematic review of 56 RCTs found that 59% of participants were women, and women made up 58% of participants in RCT testing experimental drugs, even though women make up approximately 75% of the diagnosed AD population [5, 7]. These findings are similar to RCTs in other conditions that disproportionately affect females, such as stroke [14]. A study examining the role of sex in 9593 individuals (69% women) diagnosed with AD or mild cognitive impairment who screened for enrollment in an AD RCT found that men had significantly higher odds of meeting eligible criteria overall (OR = 1.26) and across several factors, including age (OR = 1.22), education (OR = 2.25), and medications (OR = 1.19) [12]. Men were more likely to be excluded based on comorbidities (OR = 0.86). To our knowledge, no meta-analysis or systematic reviews have reported the participation of women in observational aging or dementia studies. These figures would allow us to identify whether it is general research participation or specifically participation in RCTs that show these recruitment disparities.

Sex-stratified results in AD clinical trials and other research are not well reported in the literature. A systematic review of RCTs using established AD treatments found that of the 48 studies comprising 20,688 participants with AD, none reported data analyzed by sex and/or gender [15]. Of these studies, two studies published post hoc secondary analyses accounting for sex. These findings are surprising considering previous animal model studies demonstrating sex differences in the response to cholinesterase inhibitors and older clinical studies reporting differences in treatment effects based on *APOE ε4*genotype and sex interactions [16–18]. A study analyzing sex differences in psychosocial intervention studies found that only 62% of the 73 studies analyzed reported gender by group and women were underrepresented in the control groups [19]. Analyses by group were reported in 19% of the studies; however, significant differences by gender were found only among the studies (8%) with adequate representation of women based on prevalence [19]. In 2016, NIH issued a call to action for increased reporting and analysis of sex as a biological variable (SABV), and since this time, the analysis of SABV has increased [20]. Our hope is that these continued efforts will increase the recruitment and participation of women. It may be prudent for journals to require a statement about the analysis of SABV, where relevant, like the required data-sharing statements for most publications.

Many RCTs and observational studies of aging use cognition as a primary outcome measure [21]. Men and women have different cognitive advantages; men are typically better at motor and visuospatial tasks, while women perform better on verbal memory tasks [22, 23]. We must ensure that the cognitive tests we use as outcome measures are either broad enough to analyze and capture sex differences or tailor measures in cognitive batteries to the sex of participants.

Black Americans are enrolled in AD RCTs and other research at a lower rate, despite having the highest risk for the development of AD. We do indeed acknowledge the role that discrimination, particularly systemic racism, plays in the development of these risk factors and the role that mistrust of the scientific community plays in lower recruitment rates of minority populations [24–26]. A meta-analysis of 18 studies consisting of 5164 participants from the Alzheimer's Disease Cooperative Study and the Alzheimer's Disease Neuroimaging Initiative found that Black Americans made up 7% of participants diagnosed with AD, 4% of participants with mild cognitive impairment, and 11% of cognitively unimpaired controls [27]. Proposed factors contributing to the lack of diversity in AD clinical research include screening criteria, barriers to accessing expert care and diagnoses, logistical barriers to participation, lower motivation and interest, and a lack of trust [24, 28]. A study of six AD RCTs found that Black Americans had higher rates of screen failure for meeting cognitive criteria as compared to NHW individuals (30.7% vs. 16.2%, respectively; OR = 0.43). Analysis of 2716 individuals screened for elevated amyloid with neuroimaging found that Black Americans were more likely to be excluded than NHW individuals (OR = 0.59) [29]. A

study of 5700 BA and 31,225 NHW participants across 39 Alzheimer's Disease Research Centers in the National Alzheimer's Coordinating Center (NACC) database found that, at baseline, Black American participants were less likely to be diagnosed with AD (27% vs. 36%, respectively) and were 35% less likely to be diagnosed with AD and related dementias than NHW participants [30]. Despite lower rates of AD diagnosis, Black American participants had more AD risk factors for the disease, greater cognitive impairment, and greater symptom severity than NHW participants. A meta-analysis found a higher prevalence of cardiovascular disorders (OR = 2.10), a significant AD risk factor, but lower rates of other disorders [27]. Analysis of pooled participants from the NACC database showed that Black Americans living with AD and other dementias have more cognitive deficits, neuropsychiatric symptoms, and functional dependence as compared to NHW participants. This study further demonstrated that there was a higher rate of dropouts among Black American participants as compared to NHW individuals (OR 1.60) [27].

Eligibility criteria in many random control trials disproportionately exclude Black Americans. Franzen et al. [31] looked at 101 drug trials targeting $A\beta_{42}$ and neurofibrillary tangles and quantified the frequency of eligibility criteria related to medical conditions. Among those that could affect Black American enrollment included cardiovascular disease (71.3%), cerebrovascular disease (68.3%), cerebrovascular evidence on MRI (47.5%), and alcohol or drug abuse (58.4%). Rising evidence shows that not only do these conditions disproportionately affect Black Americans [24, 25] but they may also play a role, or have synergistic effects, in AD pathogenesis in racially diverse groups. Franzen et al. showed a large frequency of exclusionary eligibility criteria related to study procedures. These criteria and their frequency in drug trials are caregiver attendance (80.2%), caregiver consent (27.7%), language ability (34.7%), and education requirement (18.8%) [31, 32]. Furthermore, Black Americans tend to perform better on certain cognitive tasks and worse on others compared to NHW individuals. Culture has a well-documented effect on neuropsychological test performance [33, 34], and cognitively unimpaired Black Americans tend to score worse on neuropsychological tests than their NHW counterparts [35–37]. There has been a recent push for the development of culturally specific neuropsychological norms and tests that are more culturally specific and therefore more accurate [38, 39]. The Mini-Mental State Exam and the Montreal Cognitive Assessment are the most widely used tests of cognitive function both in the clinic and in Alzheimer's research [40–42]. However, both of these tests show disparities in diagnostic accuracy across sex and race such that females typically score higher on the MoCA, and Black Americans typically score lower than what their current level of daily impairment would suggest [43–46]. New ethno-racial-specific norms for Black Americans and alternative cognitive tests such as the Fuld Object Memory test may yield less false-positive MCI and dementia diagnoses [47–49]. If we are to develop effective interventions in this critically at-risk population, it is imperative that we develop cognitive batteries and assessments that accurately capture baseline cognitive functioning and track response to potential interventions.

A study examining sources of recruitment and screen failures for an RCT in a diverse group (N = 5945) of older adults with pre-clinical AD found differences in recruitment sources, demographics, study partners, and study criteria [50]. Black American participants were more likely to be recruited internally at the primary study site as compared to NHW participants (69% vs. 43%, respectively), while external recruitment efforts, such as media and trusted organizations, were a larger recruitment source for NHW participants. The proportion of women was higher among Black American participants (70%) as compared to NHW participants (59%). Study partners, an individual with whom the participant had weekly contact and could provide information on daily life and cognitive function, differed by race. NHW participants were more likely to list spouse as study partner (58%), where friend/companion (29%) and spouse (27%) were listed at similar rates in Black American populations. Black American adults were more likely to be excluded due to screen failures than NHW individuals (46% vs. 26%, respectively). Black American participants were more frequently excluded based on cognitive criteria than NHW participants (31% vs. 16%, respectively), with failures among Black Americans more likely based on Clinical Dementia Rating scores and Logical Memory II scores. Overall, Black Americans had a lower likelihood of meeting eligibility as compared to their NHW counterparts, when controlling for sex, age, and education (OR = 0.43) [50]. We acknowledge that to fully distinguish the unique contributions of the ethno-racial group from those of sex, we must increase the recruitment and participation of Black American men. Reviewing and applying the methods outlined by those who have collected data in this population will be crucial for ongoing aging research [51–53]. A literature review examining consent rates in health research studies found that racial and ethnic minoritized populations were not less willing to participate in clinical research and that disparities in research are more likely due to characteristics of individual studies, such as enrollment criteria.

Other important factors related to research participation included study site location and accessibility, caregiving responsibilities, knowledge about research participation, and travel expenses [54]. The experiences of caregivers are diverse, especially between racial groups. Compared to NHW caregivers, Black American caregivers are 69% less likely to utilize respite, are more likely to provide more than

40 h a week of care, and are more likely to be adult children of individuals with dementia with other full-time jobs, and Black male caregivers are 3.3 times more likely to experience financial burden [55–57]. These racial disparities in caregivers may contribute to the lack of Black American participation in studies with caregiver attendance and consent as eligibility criteria. Caregivers may not be able to take time out of their weeks to participate in these studies, especially if they are longitudinal and each session lasts several hours.

In 2020, the US Food and Drug Administration released guidelines to increase diversity in clinical trial participation, with the key recommendation of broadening eligibility criteria [58]. Further work is needed focusing on increasing diversity in AD research, as diverse study populations representative of clinical populations are essential components in identifying effective treatments and decreasing disease burden. Recruitment and study participation bias likely results from an interplay between convenient sampling [59], a lack of networking with diverse populations that may be less likely to seek healthcare at early stages of AD [60], and greater mistrust toward the scientific and medical community within the Black American population [61]. Promising work under the community-based participatory research framework shows that community interaction can increase research participation and increase intervention adherence [62, 63]. Despite the lack of representative participation in RCTs, there is some research that investigates sex and ethno-racial differences in AD. The studies we review in this article are a combination of research that investigates Black Americans and women and some that specifically target or include an analysis of Black American women.

Social Determinants of Health and Their Contribution to AD Risk in Black American Women

Social disparities that contribute to AD risk include poverty, educational attainment, and healthcare discrimination. Black Americans represent 13.2% of the population in the USA but make up 23.8% of individuals living in poverty [64]. Black American women are more likely to be single mothers and come from single-parent households than other races and sex combinations in the USA [65]. Single motherhood is a predictor of greater stress and puts Black American women at risk for worse cardiovascular outcomes such as stroke and obesity [66–68]. Black American women are likely to be stuck in poverty (62%) compared to black men (50%) [69], which is related to lower educational attainment [70]. Greater education levels can preserve cognitive function by compensating for memory deficits by relying on skills from other cognitive domains, otherwise known as cognitive reserve [71]. Cognitive reserve is typically lower in Black Americans and women [72–74]. Historically, women and Black Americans have had lower educational achievements due to limited access to formal education. Fortunately, there is some evidence that as women gained progressively more access to formal education during the twentieth century, the risk of dementia among women began to decrease.

However, despite educational attainment, women and Black Americans still suffer from discrimination in the workplace and in healthcare [75, 76]. A wealth of research in reproductive care and aging healthcare suggests that Black American women face a disproportionate amount of discrimination from healthcare providers [75, 77, 78]. In addition to adding to the cumulative burden of stressful life events, discrimination in healthcare is associated with poorer health outcomes including utilization of care and lower medication adherence [77, 79]. Discrimination in daily life is associated with an increase in chronic stress and accelerated markers of aging [26, 27, 80]. In a study conducted exclusively on Black American women, racial centrality, or the importance of racial identity to an individual, and emotional suppression were associated with shorter telomere length, which is typically associated with advanced cellular aging [81]. Also worth mentioning is the recent work showing that Black American women are disproportionately affected by air pollution [82], and exposure to air pollution is associated with increased inflammation and an increased risk for AD [83, 84].

A unifying factor among all of these social determinants of health is that of allostatic load in that the stressors associated with poverty and stressful life events add to an individual's burden of chronic stressors [81, 82]. Allostatic load is typically higher in Black Americans and women and is associated with a higher risk of dementia [85–89]. The overlap of gender and racial discrimination and the lack of financial mobility out of poverty for Black American women all contribute negatively to dementia risk. Future studies investigating allostatic load and aging in this population may better identify the biological outcomes related to cumulative stress as a means of capturing the burden of intersectionality.

Vascular Risk Factors and Inflammation in Black American Women

Vascular risk factors for AD such as hypertension, coronary artery disease, type 2 diabetes, and congestive heart failure are all more prevalent in Black American women than any other race by sex category [90–93]. While others have covered these factors to a greater extent [30, 94–96], it is important to note that, given the intersection of race and sex, few of these papers consider the interaction of these factors and the impact on dementia risk. Reasons for disparities in

cardiovascular risk factors in Black American women are best explained using the biopsychosocial model: sex- and hormone-related inflammatory and cardiometabolic pathways synergistically interact with the social determinants of health discussed above and psychological factors that influence behavior.

Sex differences in vascular risk factors for AD have been covered extensively [97–99], but less work specifically investigates the overlap of Black American identity and female sex. Early large-scale studies investigating cardiovascular risk factors report that young women were less likely than men to develop and die from cardiovascular conditions such as hypertension [100, 101]. However, in post-menopausal women, the prevalence and impact of cardiovascular diseases mirror that of men. Some suggest that estrogen may be a protective factor against cardiovascular disease [102, 103], which is supported by animal models [104, 105]. Further adding to the complication of understanding hormonal interactions and their effect on vascular disease, hormone replacement therapy administered to post-menopausal women has either no impact on cardiovascular risk factors [106] or is associated with a decline in cardiovascular health [107]. Recently, the "timing hypothesis" has become more widely accepted which states that the harms of hormone replacement therapy can be reduced, and benefits increased, the closer therapy is delivered to the onset of menopausal symptoms [108]. A more thorough discussion of hormone replacement therapy with specific reference to dementia risk is included below. Relatively few studies have investigated hormone replacement therapy and cardiovascular risk factors in Black American women, and those that do are over 20 years old [109, 110]. To gauge the generalizability of the timing hypothesis, more research should be conducted specifically on Black American women using hormone replacement therapy.

Increased exposure to stress and higher allostatic load in Black American females as compared to NHW females likely contribute to the observed disparities in cardiovascular risk factors. Sex differences in immunological and inflammatory responses contribute to the development of cardiometabolic disease and AD [111–113]. Women have greater pro-inflammatory responses to stressors [114] as evidenced by the greater prevalence of auto-immune diseases and type 2 diabetes in women [115]. Sex-based differences in glucocorticoid responses to stress [105] and higher pro-inflammatory cytokines in women [116] contribute to greater acute immune responses to pathogens but can lead to chronic inflammation [114]. In studies investigating insulin resistance, a component of type 2 diabetes that is a marker of chronic inflammation, insulin resistance was higher and was related to oxidative stress in Black American women [117–119]. Negative social determinants of health more prevalent in Black Americans place women from this population uniquely susceptible to the effects of chronic stress and inflammation [120]. Sustained vascular dysfunction can lead to cerebrovascular disease such as stroke or transient ischemic attacks, both of which are risk factors for AD [121, 122]. Black American women have a higher risk of stroke than other races and sex combinations, and stroke is associated with a higher risk of developing dementia in Black Americans [123, 124]. Black Americans and women have higher levels of lipoprotein (a), a robust predictor of cerebrovascular disease higher in individuals who have experienced strokes [125, 126]. Cerebrovascular lesions in the form of white matter hyperintensities (WMH) also show sex and race differences and will be covered in greater depth in the section on neuroimaging [127, 128]. Whether this increased susceptibility to AD in Black Americans and in women is due to lifestyle or purely cardiometabolic sex differences is not understood, but it is likely a combination of both.

While sociocultural and biological factors increase allostatic load and negatively impact cardiovascular health, there is room for the introduction of positive behavioral changes that can help alleviate some of this burden. A recent analysis of US Behavioral Risk Factor Surveillance Survey data found that the largest population-attributable vascular risk factors for AD were midlife obesity and physical inactivity, and these risk factors were more prevalent in Black American women than in any other race and sex combination [91]. Black American women are less likely to adhere to medication recommendations for anti-hypertensive pharmacotherapy [129]. The role of hypertension in AD risk may be obfuscated by the lack of medication-use data and understanding of whether there is an underlying mechanistic difference according to the ethno-racial group that creates an increased vulnerability in Black Americans with hypertension to dementia, or whether it is lower medication adherence that contributes to this disparity is an important topic for future research. There are other health behaviors that contribute to increased vascular health that seem to be less prevalent in the Black American community including increased physical activity and reporting adherence to a healthy diet [130, 131]. Understanding barriers to increasing these should be a key focus of future research, so we can design and implement effective, culturally relevant interventions [132]. Fortunately, researchers have begun to work with communities to gain knowledge about the cultural and lifestyle aspects that influence cardiovascular risk and introduce interventions tailored to these communities [62, 133]. Increased efforts such as these and careful attention to the needs of the communities we wish to impact should decrease these health disparities.

Hormonal Contraception, Pregnancy, and Hormone Replacement Therapy in Black Americans

Hormonal contraceptives (HCs), particularly oral contraceptives (OCs), are one of the most extensively used drugs worldwide. Approximately 400 million women around the world use OCs, which are the most prescribed medication for women between the ages of 15 and 49 [134]. However, their effect on endogenous hormones, which are highly neuroactive, can vary widely. More extensive study is needed to investigate their modulatory effects on domains of cognition.

So far, a few studies have shown conflicting results on the effects of HCs on domains such as verbal fluency, visuospatial cognition, attention, and working memory [135, 136]. It appears that more agreement is found when accounting for the androgenic formulations of the contraceptives. To our knowledge, there are no significant studies or reviews that have analyzed the long-term effects of HCs on neurodegenerative diseases. However, one study published in the *Journal of Women's Health* by Egan and Gleason analyzed the long-term effects of prolonged duration contraceptive use on cognitive abilities such as memory, verbal ability, learning, and visuospatial ability and concluded that "hormonal contraceptive use may have a protective cognitive effect even years after use is discontinued" [137].

Use of HCs differs across ethno-cultural groups. The most recent report by the National Center for Health Statistics (NCHS) included data about the current contraceptive status among women in the USA. The report revealed that 65.3% of women in the USA are currently using contraception. However, it noted a *significant* disparity in use across racial and ethnic groups, with NHW participants driving the total value with a reported use of 69.2% and Hispanic and non-Hispanic black individuals reporting only 60.5% and 61.4% use, respectively [138]. These results are not surprising: clinical studies have reported that both awareness and use of almost all types of contraceptives are significantly higher in NHW women compared to non-White women, with an exception being injectable hormones, which are used significantly more by non-White women [139]. It has been reported that these differences can be attributed to barriers to contraceptive access, such as cost [140], health insurance status [78], pharmacy-level access [141], legislation impediment [142], and clinician bias [143]. Throughout the years, HC research has suffered from a lack of representation. Considering the discovery of how small differences can produce varying cognitive effects, grouping HC users together without considering HC formulations (androgenic vs. antiandrogenic), HC mechanisms (OCs, IUDs, implants, and vaginal rings), or even differences across individuals creates a compelling barrier for the identification of new, significant knowledge, especially since these can influence cognitive function in potentially contradictory ways. Moreover, most studies on HCs have an underrepresented subject sample or simply fail to report the demographic information of their subjects [144].

Hypertensive disorders of pregnancy (HDP) include chronic hypertension that begins before pregnancy and continues during pregnancy and pregnancy-associated hypertension that begins during or after pregnancy, such as gestational hypertension, preeclampsia, and eclampsia [145]. These disorders have an incidence rate of 16%, meaning that close to 1 in 7 pregnancies are affected, and this number has been steadily increasing since 1990 [146]. HDP impact Black American, Latino, Asian/Pacific Islander, and Native American communities at higher rates, with an incidence of almost 1 in 5 [146]. Furthermore, medications used to prevent preeclampsia may not be as effective in Black Americans compared to NHW individuals [147], and residence in the USA in particular is associated with an increased risk of preeclampsia for Black pregnant women [148].

HDP have been known to cause heart attacks, strokes, intracerebral hemorrhage, and death and are a leading cause of death in pregnant people and their fetuses [145]. HDP are far more common in Black American women than in other ethno-racial groups [78, 149, 150]. Women with preeclampsia have lower cerebrovascular resistance, reduced vasodilation when inhaling CO_2, and a higher cerebral perfusion pressure at baseline, even when hypertension is treated, when compared to women without a history of hypertensive conditions during pregnancy [151, 152]. Another study also found that the brains of women who died from eclampsia, a complication of preeclampsia caused by hypertension during pregnancy, had perivascular microhemorrhages, microinfarcts, and arteriolar vasculopathy, which the authors hypothesized was due to a lack of cerebral autoregulation [153]. Finally, a recent subset of studies proposed an association between preeclampsia and subjective cognitive failure [154]. These findings paved the way for researchers to start investigating the association between HDP and disorders of cognition, specifically dementia. Several clinical studies and retrospective reviews have investigated the association between HDP and disorders of cognition and found significant conclusions. Recent findings described the potential long-term neurological consequences that disorders of high blood pressure during pregnancy can have in later life. The extracellular vesicles (EVs) of women who have experienced severe preeclampsia have a substantially greater concentration of $A\beta_{42}$ compared to the extracellular vesicles of their counterparts with non-hypertensive pregnancies. The difference in blood circulating levels of $A\beta_{42}$ in women with

conditions of preeclampsia is also significant compared to controls [155]. Also, individuals with a history of HDP show a 38% higher white matter hyperintensity volume compared to their counterparts with non-hypertensive pregnancies. The increased presence of $A\beta_{42}$ in EVs and in circulation and the findings of white matter pathology during midlife point to dementia-related brain changes and thus a higher risk of accelerated cognitive decline [156].

The conclusions drawn from these studies are definitive: individuals who experience HDP are at a higher risk of cognitive decline in later life than individuals with normotensive pregnancies. Shedding light on these findings is critical for the well-being and cognitive maintenance of both pregnant individuals and fetuses [157]. The American College of Obstetrics and Gynecology and the American College of Cardiology recently released a collective announcement in which they advised obstetrics and primary care providers to work together to identify and treat pregnant individuals at risk of short- and long-term cerebrovascular damage [158].

The transition to menopause generates many neurological changes including changes to thermoregulation, sleep, and circadian rhythms and impairment in multiple cognitive domains [159]. Hormone replacement therapy is a common treatment for symptoms associated with menopause. Multiple reviews and studies have identified that hormone replacement therapy is also associated with an increased risk of dementia [160, 161]. However, two meta-analyses did find that the window in which hormone replacement therapy was administered did have an effect on dementia risk such that hormone replacement therapy administered during the peri-menopausal stages decreased dementia risk, lending credence to the "timing hypothesis" previously discussed [163–165]. *APOE ε4* status may also affect dementia risk as one study found that hormone replacement therapy was associated with less cognitive decline in *APOE ε4*–negative women, but not in *APOE ε4*–positive women [166]. In one study that investigated different cognitive domains, long-term administration of estrogen only improved performance on the word recall test and actually decreased performance on a finger-tapping task and a paragraph memory task [162].

Unfortunately, little research has been conducted specifically on Black American women investigating the use of hormone replacement therapy in this population, or its effect on dementia risk. Most studies control for the ethno-racial group instead of analyzing it as a variable of interest. Some studies have found that the use of and adherence to prescribed hormone replacement therapy is lower in Black Americans and that quality of life is lower in Black American women using hormone replacement therapy [110, 167]. Given the interaction between vascular health, dementia risk, female sex, and hormone replacement therapy, future studies should investigate the use of hormone replacement therapy specifically in Black American women.

Alzheimer's Disease Risk Genes in Black American Women

APOE ε4, a cholesterol transporter gene, is associated with the development of $A\beta_{42}$ plaques and is the most widely recognized genetic risk factor for AD [168]. Numerous sex differences have been identified in the relationships between *APOE ε4* and AD biomarkers. Women *APOE ε4* carriers are at a greater risk of developing AD than males [169]. Women are more likely to have increased tau with the *APOE ε4* genetic variant, with some identifying that this difference does not extend itself to the presentation of tangles upon autopsy and others identifying that heterozygous *APOE ε4* females have more widespread tau deposition in vivo [169–171]. *APOE ε4* may also diminish the effect of physical activity on cognitive reserve in women [172]. Cognitively normal elderly female *APOE ε4* carriers present with brain hypometabolism, cortical thinning, and lower DMN connectivity compared to men [173, 174]. There is less conclusive evidence according to race with some studies reporting no difference or lower AD risk according to *APOE ε4* status but greater *APOE ε4* allele frequency in Black Americans [169, 175, 176]. Factors associated with resilience to the effects of positive *APOE ε4* status may differ across ethno-racial groups [175]. In studies examining genetic race versus ethnicity, researchers frequently make comparisons between Black Americans and the Yoruba tribe, an ethnic group located in Ibadan, Nigeria [177]. Diet and lifestyle factors between Black Americans and the Yoruba tribe are very different, but these individuals share similar genetic ancestry [178]. These similarities are a means of exploring lifestyle factors and related epigenetics while somewhat controlling for ancestry. There are differential effects of *APOE ε4* on the risk for AD between the Yoruba and Black American cohorts and differential effects of sex on AD risk between the Yoruba and Black American cohorts such that in Black Americans, only one copy of the *APOE ε4* allele was necessary to increase dementia risk, but two copies of the *APOE ε4* were necessary to increase dementia risk in the Yoruba [177]. Sex differences in the *APOE ε4* variant may potentially explain the contradictions in results across studies, as the interaction of ethno-racial identity by sex is not typically analyzed or reported in demographic tables.

While genetics seem to play a smaller role in the development of AD than social and vascular factors, other risk genes and epigenetic modifications may contribute to the development of AD in Black American women. The *ABCA7* gene exhibits sex and race disparities and is related to the lipid transportation process and regulation of cholesterol in the amyloid pathway [179]. A study on older Black Americans found that *ABCA7* status can

diminish the neuroprotective effect of aerobic fitness on cognitive flexibility [180]. In women, particular *ABCA7* single-nucleotide polymorphisms were selectively associated with cognitive decline and dyslipidemia [181, 182]. Other risk genes specific to women include are related to both tau and amyloid pathology [183]. In support of the genetic inflammatory pathways as a potential explanation for the increased risk of Alzheimer's disease in women, the genetic architecture associated with resilience in women contained genes that are associated with reduced risk for auto-immune diseases, suggesting that auto-immune processes contribute to AD risk in women [184].

Lifestyle and cultural factors can influence gene expression and are the focus of the field of epigenetics. Epigenetics involved in immune responses in the presence of chronic inflammation lead to AD, and AD itself can have epigenetic effects that modulate CNS immune function [185, 186]. This may explain why there seems to be a viscous downward spiral in inflammatory responses and neurodegeneration in the presence of AD [185]. Black Americans have lower genetic variation and epigenetic modification of cholesterol pathways indicating greater genetic vulnerability to the effects of dyslipidemia, while other studies have found that Black Americans have no difference in epigenetic pathways related to aging [187, 188]. Aroke et al. provide a comprehensive review of epigenetic factors associated with Black American ethno-racial identity with regard to chronic pain and inflammation and conclude that glucocorticoid stress receptor genes are altered in this population and are associated with depression, childhood stress, and low socio-economic status [189]. In a recent meta-analysis, Kunkle et al. conclude that while the endpoints of AD may be similar across races (AD pathology), the loci by which these pathologies emerge may differ in Black Americans involving genes associated with lipid dysregulation, brain metabolism, and intracellular trafficking [190]. Regarding sex, studies have identified that X-chromosome-linked gene expression has been implicated in heightened and prolonged inflammatory responses, yet one study found that women have slower rates of epigenetic aging [188, 191, 192]. Because genetic studies require a great number of participants, we think it prudent to recommend that future students analyze the overlap of sex and ethno-racial identity. This will help better characterize risk genes and potentially identify unique markers of AD specific to Black Americans.

Alzheimer's Disease Fluid Biomarker Profile of Black American Women

The use of both plasma and cerebrospinal fluid (CSF) markers including $A\beta_{42}$, total tau (t-tau), phospho-tau (p-tau), and neurofilament light chain (NFL) as diagnostic biomarkers of AD is increasing [193–195]. When considered together, Aβ and p-tau in CSF have increased sensitivity and specificity for the detection of AD [196]. NFL is a non-specific measure but a sensitive measure of neurodegeneration and can be measured in both plasma and CSF [197]. Gleason et al. summarized the race-based differences in fluid biomarkers in AD and found that the consensus across multiple studies is that Black Americans exhibit lower CSF t-tau and p-tau levels than their NHW counterparts even at similar levels of cognitive impairment and that this relationship may be partially explained by *APOE ε4* status [198–200]. CSF and plasma $A\beta_{42}$ results are less consistent, with some identifying no difference between Black Americans and NHW individuals and others identifying lower levels of $A\beta_{42}$ [201, 202]. Diagnostic models of AD that predict dementia from levels of $A\beta_{42}$ seem to be more reliable than models that use t- or p-tau and NFL in Black Americans [203, 204]. The CSF biomarker differences that we observe are likely a complex interplay between environmental and genetic factors. For example, there are genetic differences in levels of triggering receptor expressed on myeloid cells 2 (TREM2), a microglia mediator protein that handles the inflammatory immune response to $A\beta_{42}$, that differ across ethno-racial groups [205, 206]. As the amyloid hypothesis is brought into question, as a field, we may need to shift our focus to tau, particularly in studies of racial disparities, as this protein exhibits the most consistent differences between ethno-racial groups.

Sex differences in fluid biomarkers of AD have not been as well characterized as ethno-racial differences in the literature. Mielke has comprehensively reviewed sex differences in fluid biomarkers of AD and has generally found no differences in CSF $A\beta_{42}$ between men and women [207]. However, similar levels of fluid AD biomarkers may indicate a greater risk for dementia, and women may have as much as a 20-fold increase in dementia risk compared to a threefold higher risk in men [208]. Longitudinal studies have identified that in similar concentrations of $A\beta_{42}$, women experience greater hippocampal atrophy, higher p-tau levels, and worse memory performance than men [209, 210].

As previously mentioned, women have heightened inflammatory responses as confirmed by plasma markers of pro-inflammatory cytokines, particularly TNF-alpha and IL-6 [211]. Although not as widely used as specific biomarkers of AD, cytokines allow us to examine levels of inflammation and immune activation, which we know to be crucial in the development of AD and exhibit sex differences [105, 111, 212–214]. In AD, levels of the inflammatory cytokine IL-β were related to worse memory performance in women but not in men [211]. Additionally, Black American women have higher levels of circulating pro-inflammatory cytokines, and inflammatory markers are associated with psychosocial factors such as late-life dissatisfaction and perceived discrimination [215–218]. $A\beta_{42}$

and tau can activate microglia and create an inflammatory response in the brain, specific pro-inflammatory cytokines can cross the blood–brain barrier, and chronic exposure to plasma cytokines can increase blood–brain barrier permeability [219, 220]. Social, lifestyle, vascular, and sex-based immune factors could embroil Black American women in a downward spiral starting with increased systemic inflammation, which can cause CNS inflammation and trigger a metabolic cascade leading to AD pathology [221, 222].

Fluid biomarkers studies are limited by smaller sample sizes than the large population-based vascular studies mentioned previously, and these studies have limited power to analyze factorial categories of race and sex combinations [223, 224]. If authors are interested in ethno-racial differences, they will often include sex as a nuisance covariate and vice versa. Because we know that Black American women are uniquely vulnerable to the development of AD, we recommend that authors analyze sex differences in fluid biomarker studies and, when possible, analyze race and sex interactions. Furthermore, we recommend that authors report the makeup of their sample broken down into factorial categories of race and sex to assist with future meta-analyses that will ultimately be necessary to further characterize this population and fill this gap in the literature.

Racial and Sex Differences in Neuroimaging Biomarkers of AD

Racial differences in neuroimaging biomarkers of AD have been identified, but MRI studies specifically in this population are limited, especially for studies investigating the role of both sex and ethno-racial group. Most of the differences have been primarily identified in white matter hyperintensities (WMHs), which makes sense, given the vascular disparities present in this population. WMHs increase the risk of developing AD, and WMH volumes are typically higher in individuals with MCI and AD [225, 226]. A recent review by Carmichael and Newton identifies several MRI-related differences between Black Americans and NHW individuals in early, middle, and late life [227]. One important finding particularly relevant to AD is that WMH, not hippocampal volumes, more accurately predicts cognition in Black Americans [228]. Sex differences in WMH have also been identified such that women typically have greater WMH than men and that vascular risk factors may predict higher WMH in women than men [127, 229, 230]. Black Americans and NHW individuals do not consistently exhibit differences in brain atrophy patterns, but some differences have been identified in functional and structural neuroimaging. Amyloid-positive Black Americans have smaller cortical thickness than NHWs in the precuneus, and in a separate study, measures are inversely correlated with AD biomarkers (tau, $A\beta_{42}$, and cognition) between NHW individuals and Black Americans specifically within the precuneus [47, 231]. Despite the utility of other neuroimaging modalities in the identification and tracking of AD, there has been relatively little research regarding the role of the ethno-racial group. Understanding the intersectionality of race and gender can help further elucidate the role of WMH in cognitive decline and whether its effects are additive or independent of AD pathology and whether the protective benefit of female sex against the deleterious effects of WMHs extends to the Black American population.

Alzheimer's Disease Pathology in Black American Women

We have outlined sex and ethno-racial disparities in exposure to AD risk factors. AD pathology may differ according to sex and ethno-racial identity. Women typically have greater levels of tau pathology as measured ex vivo [232–234], in vivo using tau PET [209, 235], and in mouse models [236]. Studies investigating amyloid pathology have yielded mixed results with some reporting no difference between sexes and others reporting higher levels of $A\beta_{42}$ among women [209, 237]. Despite these mixed findings in amyloid, many studies have identified a trend that similar unit increases in $A\beta_{42}$ across men, and women are associated with worse clinical outcomes [209, 238, 239]. Black Americans typically do not show differences in $A\beta_{42}$ pathology either in vivo or ex vivo when compared to other ethno-racial groups, but studies investigating ethno-racial differences in pathology are not as common as studies comparing sex differences, and Babulal et al. outlined this field as an area in immediate need of research attention [200, 240]. Importantly, Black Americans are more likely to have mixed pathology than NHW individuals with AD [241]. Considering that Black Americans have lower CSF tau levels, despite the increased prevalence of vascular and inflammatory risk factors, this suggests that the increase in systemic inflammation may synergistically interact with amyloid and tau to create similar clinical outcomes at lower levels of AD pathology. In their comprehensive review of pathology differences associated with female sex in Latinos and Black Americans, Royse et al. concluded that few studies include the interaction of race and sex, but those that analyze the interaction show that women have greater tau burden than men of the same race and that Black American women have increased rates of regional atrophy and worse cognition at the same levels of $A\beta_{42}$ pathology [242]. We cannot overstate the importance of analyzing the interaction of the ethno-racial group and sex in AD pathology studies. If Black Americans generally have lower tau, but tau levels are increased in women compared to men, differences according to sex and the ethno-racial group

will be entirely dependent on the demographic makeup of the sample. Analyzing this interaction will allow us to create generalizable diagnostic thresholds appropriate for sex and ethno-racial group (Fig. 1).

Conclusion

In this review, we outline existing research on ethno-racial and sex disparities in AD but also hope to illuminate the current gaps in the literature regarding the intersectionality of Black American identity and female sex. Social factors combined with sex-based propensities for inflammatory responses to stress that have negative cardiovascular consequences are likely the biggest contributors to AD risk in Black American women. Increased diversity in sexual and ethno-racial representation that captures this intersectionality will enable us to build models of disease and wellness that are accurate for the populations most at risk for AD. If we, as a field, hope to reduce the incidence of and develop interventions for AD, we must focus our sampling and recruitment and analysis efforts on those most impacted by the disease. Many reviews of studies on women and Black Americans call for more data collection. We wholeheartedly agree with this suggestion and are pleased that studies on minoritized populations have been made a priority by funding agencies and journals [243, 244]. While we certainly want to echo this sentiment, we also include a more nuanced list of recommendations based on the needs of this population.

1. Increased reporting and analysis of ethno-racial groups stratified by sex: studies should report demographic variables stratified by ethno-racial and sex categories. Even if a study is underpowered to analyze this interaction, this data will be incredibly useful for meta-analyses and studies that track the enrollment and participation of minorities in research.
2. Development of accurate biomarker thresholds: CSF and PET markers of amyloid and tau are now part of the standard biomarker-based definition of AD based on the NIA-AA framework, and we have discussed differences in both measures within Black Americans and women. We emphasize the need to develop both sex and ethno-racially appropriate cutoffs.
3. Increase in studies that investigate the heterogeneity of the Black diaspora: now that we have established that there are social, environmental, and behavioral factors that make women from minoritized populations uniquely at risk for AD, it will be increasingly important to move away from the concept of ethno-racial group to identify individual factors that lead to the "racialization"

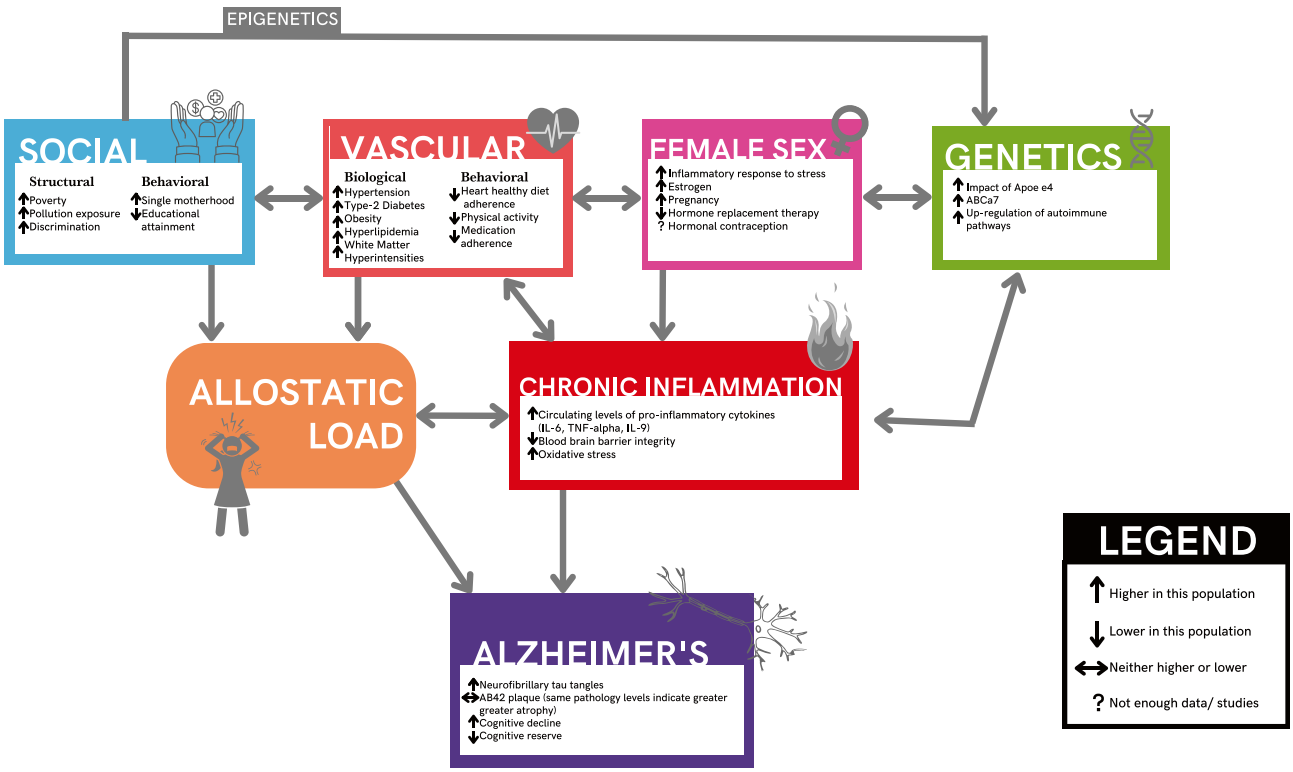

Fig. 1 Flow diagram of mechanisms of Alzheimer's disease risk and prevalence in Black American women

of certain groups upon which we can develop effective interventions. An individual growing up in urban areas of Chicago would certainly have different exposure, cultural, and lifestyle factors than someone who lives in rural Georgia, and there are well-established Black communities in both environments. Teasing apart exactly which variables contribute to ethno-cultural health disparities to develop appropriate interventions, rather than reinforce a biological-based racial divide, should be the goal of much of this research.

4. Development of culturally appropriate recruitment strategies and interventions: community-based participatory research has proven to be an effective strategy for community buy-in and adherence to interventions, particularly in Black American populations [63, 245, 246]. Culturally appropriate recruitment strategies increase participation and open a line of communication between researchers and the populations that they serve [247]. Examples include interventions and study designs that compensate for the increased caregiver burden in Black American women and limited access to transportation resources and use of less restrictive inclusion criteria so Black American women are less likely to be screened out of RCTs.

This is a short list of recommendations that we hope will increase the research representation of Black American women, who are uniquely vulnerable to the development of AD. This review brings to light significant gaps in research including the role of inflammation and exposure to negative social determinants of health on the development of dementia in Black American women, the use and role of hormone replacement therapy in peri- and post-menopausal Black American women, and the need for the validation of biomarker thresholds and cutoffs for Black American women. To reduce health disparities and develop effective interventions for AD, we must prioritize these areas of research.

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Declarations

Conflict of Interest None.

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