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Perspective

Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: Update and areas of immediate need

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Abstract Alzheimer's disease and related dementias (ADRDs) are a global crisis facing the aging population and society as a whole. With the numbers of people with ADRDs predicted to rise dramatically across the world, the scientific community can no longer neglect the need for research focusing on ADRDs among underrepresented ethnoracial diverse groups. The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART; alz.org/ISTAART) comprises a number of professional interest areas (PIAs), each focusing on a major scientific area associated with ADRDs. We leverage the expertise of the existing international cadre of ISTAART scientists and experts to synthesize a cross-PIA white paper that provides both a concise "state-of-the-science" report of ethnoracial factors across PIA foci and updated recommendations to address immediate needs to advance ADRD science across ethnoracial populations.
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Keywords: Alzheimer's disease; Alzheimer's related dementias; Diversity; Ethnoracial; Underserved; Translational; Ethnicity

1. Introduction

Alzheimer's disease and related dementias (ADRDs) are a global crisis facing the aging population and society as a whole. The number of people aged 65 years and older is more than 35 million in Japan (the world's fastest growing aging population) [1,2], approximately 48 million in the United States (U.S.) [3], nearly 120 million in China [4], and 104 million in India (≥60) [5], and these numbers are expected to grow rapidly over the next several decades [2–5]. With this growth, ADRDs are predicted to become the single greatest challenge facing health care and medical systems across the world [6]. This includes low- and middle-income countries [7]. It is anticipated that the nearly 47 million ADRD cases globally will increase by 10 million new cases each year [8]. Despite the fact that the global population is already ethnically and racially diverse [9–11], there remain substantial gaps in the scientific literature regarding the impact of ethnic and racial factors (herein referred to as ethnoracial) on ADRDs.

The extant literature supports the need for additional research into the impact of ethnoracial factors on ADRDs. Ethnoracial factors have been found to be important when considering biological (e.g., genetic, cerebrospinal fluid [CSF], and blood proteomics) [12–17] and medical risk factors for AD (e.g., hypertension, diabetes, obesity, depression) [14,18]. These factors may be related to previously demonstrated differences in incidence, timing of diagnosis, clinical presentation, and course of AD between different ethnoracial groups [14,19,20]. Ethnoracial factors, with regard to perceptions of the normality of cognitive changes [21,22], insurance coverage and access to health care [17,19], and agreement to participate in clinical trials [17,19,23], are also previously documented factors for consideration. Additional factors such as differing emphasis on family and respect for elders are important considerations when seeking to enroll diverse ethnoracial groups into research studies on ADRDs [17,21,24]. Oftentimes, scientists are not trained to effectively partner with diverse communities to build trust to facilitate recruiting, communicate strategies about health research to study potential participants, and develop culturally informed retention strategies. For example, there are oftentimes few, if any, researchers or staff from underrepresented groups on the research teams [25]. Study design resources and expertise barriers include insufficient budgets for recruitment costs, limited resources to translate documents or adapt literacy levels, inability to develop relationships with minority physicians [26], and limited expertise to culturally tailor and translate study documents. Participant-level barriers, more often cited than those regarding scientists and study design, reflect a myriad of concerns such as mistrust, and limited knowledge about clinical research that affect both recruitment and retention [27]. These factors are relevant to each topic area covered below. In the U.S., the 2012 National Alzheimer's Project Act specifically calls for increased enrollment of diverse ethnoracial populations into ADRD research studies.

The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART; alz.org/ISTAART) comprises a number of Professional Interest Areas (PIAs), each focusing on a major scientific topic associated with ADRDs. These PIAs include leading scientists from across the globe with substantial expertise covering crucial topics for ADRDs. Previous reviews have documented factors contributing to or associated with ethnoracial disparities in ADRD research [17,28,29]. To expand on prior work on the topic, we leveraged the expertise of an international group of ISTAART scientists to synthesize a cross-PIA white paper to accomplish the following goals:

1. Provide a concise "state-of-the-science" report of ethnoracial factors across PIA foci.
2. Provide recommendations regarding most immediate needs to advance ADRD science across ethnoracial populations.
3. Provide a working model that provides specific key foci for advancing the field of health disparities in ADRDs.

This white paper is organized into the following sections with specific contributions from each ISTAART PIA.

- Factors related to disease detection and biomarkers
  - Reserve, resilience, and protective factors PIA
  - Diversity and disparities PIA
  - Neuroimaging PIA
  - Electrophysiology PIA
  - Biofluid-based biomarkers PIA
  - Immunity and neurodegeneration PIA
- Factors related to interventions and methods
  - Clinical trials advancement and methods PIA
  - Nonpharmacological interventions PIA
- Ethnoracial factors related to subjective concerns and affect in ADRDs
  - Subjective cognitive decline PIA
  - Neuropsychiatric syndromes PIA
- Ethnoracial factors related to atypical AD and other ADRDs
  - Atypical Alzheimer's disease and associated syndromes PIA
  - Down syndrome and Alzheimer's disease PIA
  - Vascular cognitive disorders PIA
- Other factors related to cognitive impairment and dementia
  - Perioperative cognition and delirium PIA
  - Nutrition, metabolism, and dementia PIA
  - Technology PIA
- List of recommendations to collectively and collaboratively advance the gaps identified by the respective PIAs

- All PIAs, including specific methodological considerations from the design and data analytics PIA
- Advancing the Science of Health disparities in ADRDs
  - All PIAs

1.1. Factors related to disease detection and biomarkers in ADRDs

1.1.1. The influence of ethnoracial factors on reserve, resilience, and protective factors

Cognitive reserve is a heuristic to help explain individual differences in brain health and cognition relative to aging and brain disease [30–32]. These individual differences could reflect higher capital (higher to start with), better maintenance (lower decline), or greater resilience/tolerance and compensation capacities [30–32].

Very little research has assessed whether cognitive reserve differs across ethnoracial groups. Because ethnoracial groups are characterized by distinct social and behavioral practices and may have different genetic background, differences in reserve can be expected as a function of ethnoracial factors. Differences in cognitive reserve might in turn explain differences in the prevalence or incidence of AD or in the age at disease onset between ethnoracial groups [5,6,29,33]. For instance, some ethnoracial populations are characterized by a lack of formal education, which is strongly associated with lower cognitive reserve [34]. However, years of education has been shown to be a poor reflection of the value of educational experience and native ability among ethnoracial groups, whereas literacy levels may be more strongly associated with reserve in diverse cohorts [35,36].

Differences in reserve across ethnoracial groups may be reflected in differences in (1) the baseline capital (of brain health and cognition), (2) the maintenance of this capital over time, and (3) the resistance/resilience of cognitive performance to pathological brain changes. Empirical evidence for the two first cases (higher capital or better maintenance) may manifest both by differences in brain health markers and in cognitive performance in diverse ethnoracial populations. Difference in maintenance may be more accurately assessed longitudinally by measuring the rate of brain or cognitive changes over time in different groups. For instance, African Americans have been found to have a lower level of global cognition at baseline but a slower rate of cognitive decline over time, compared with non–African Americans [37]. An important goal that emerges is to understand the relative contributions of different genetic and sociobehavioral/lifestyle factors on the observed differences among ethnoracial groups in markers of brain health or cognition.

Finally, differences in resilience/resistance to pathology among ethnoracial groups may reflect different relationships between brain health and cognitive performance, for example, higher levels of brain pathology for a given degree of cognitive impairment. This was found in one previous study showing lower CSF phosphorylated-tau (p-tau$_{181}$) and total tau (t-tau) levels in African Americans compared with Caucasians, independent of cognition [15].

1.1.2. The influence of ethnoracial factors on diversity and disparities

Mungas (2006) presented a model illustrating how ethnoracial factors, aging, and disease may influence cognitive ability through the interplay of environment, genes, and brain structure [38]. Based on this model, the influence that ethnicity exerts on cognitive functioning would be modulated by the relationships of multiple factors. In this section, we address these factors from the perspectives related to the examinees (i.e., individuals with ADRDs and caregivers), the examiners, and the specific assessments used.

Cognitive testing is important for detecting, monitoring, and distinguishing differences among ADRDs. Most cognitive measures are influenced by linguistic, educational, or cultural factors, which affect the ability to accurately identify cognitive impairment and decline in diverse individuals. One of the challenges in assessing ethnoracial groups is limited formal education and/or high illiteracy rates and/or cultural nuances to learning and ways of thinking and solving problems. Lower education has consistently been associated with worse health status on a number of outcomes, including dementia. Reading measures created in one language do not necessarily translate well into other languages due to a variety of factors [39]. Translating tests across cultural boundaries may not capture the diverse impact that cultures have on cognition [40,41]; however, it has been reported that appropriate adjustment for ethnicity can improve validity of test findings [42,43]. Neuropsychologists need training to work with minority groups [17,44]; however, the number of neuropsychologists with competency to work with ethnoracial groups and/or possess proficiency in non-English languages is limited [44,45].

Finally, there are factors related to the cultural validity, cost-effectiveness, representativeness, and availability of reliable norms of neuropsychological testing itself. It remains unclear whether translated tests measure constructs retain a similar meaning within and across cultural groups. As Luria [46] noted, tests developed and validated for use in one culture frequently result in experimental failures and are invalid for use with other cultural groups. For instance, one study showed that relative difficulty of subitems on the widely used Mini–Mental State Examination could differ due to cultural factors between the U.S. and Japan, which could affect sensitivity and specificity of identifying those with cognitive impairment [47]. Although many groups have attempted to generate appropriate normative data across ethnic groups [48–50], the numbers of such norms remain small and the availability of norms for individuals with little education remains limited [48,50]. Cost-effective screening tools that have little reliance on

background education would be of tremendous utility to large-scale longitudinal epidemiological studies of diverse ethnoracial groups [45], which is preferable to different sites using different tests or different versions of the same tests.

1.1.3. The influence of ethnoracial factors on neuroimaging biomarkers

The utilization of neuroimaging biomarkers in ADRDs has become increasingly important as structural, functional, and molecular imaging have led to earlier diagnosis [51–53]; disease staging, including prodromal and preclinical stages [54,55]; and identification of individuals for clinical trial participation [56]. However, although great strides have been made in the field of AD neuroimaging, relationships between biomarkers and ethnoracial factors remain understudied. For example, the 2012 demographic report from the Alzheimer's Disease Neuroimaging Initiative (ADNI) describes the sample as comprising fewer than 5% African American or Hispanic participants [57]. As with ADNI, the Australian Imaging, Biomarkers, and Lifestyle (AIBL) study of aging [58] does not contain broad representation from ethnoracial populations. However, the recently initiated Study of Latinos Investigation of Neurocognitive Aging (SOL/INCA) and Health & Aging Brain among Latino Elders (HABLE) studies will soon offer unique opportunities to study imaging markers related to cognitive aging among U.S. Latino adults and seniors.

Only a few studies have explored the link between ethnoracial factors and brain structure along the AD continuum, and their findings have not been consistent. DeCarli et al. examined ethnoracial differences in brain volume and cerebrovascular disease (CVD) and found greater total brain volume in Hispanics compared with non–Hispanic whites (nHWs) regardless of diagnosis and found no ethnoracial differences in CVD measures [59]. Similarly, the Chicago Health and Aging Project did not find significant interactions between race and CVD [60]. Although the Washington Heights-Inwood Columbia Aging Project (WHICAP) demonstrated greater brain volume in Hispanics and African Americans than nHWs, they also demonstrated significantly higher CVD in these groups than nHWs [61]. The Atherosclerosis Risk in Communities (ARIC) study has similarly demonstrated that African American race was a predictor of an increased number of silent infarcts [62]. In addition, ARIC demonstrated higher rates of atrophy in African Americans at baseline and a greater worsening of atrophy over time [62]. Many of the ethnoracial differences in CVD are linked to differences in clinical risk factors, but it is worth noting that some of these risk factors, such as smoking, conferred a more than 4-fold greater risk of CVD in African Americans compared to nHWs [63]. There are also inconsistencies in the research literature with some work failing to identify ethnoracial differences in the relationships between brain function and cognition [59,64], whereas others have shown a significant relationship between cognitive dysfunction and structure [65,66]. WHICAP demonstrated that magnetic resonance imaging predictors of cognition differed across ethnoracial groups. For example, CVD was associated with worse language and executive performance in African Americans than nHWs [65].

Over the last decade, positron emission tomography imaging has played a seminal role in the field of AD neuroimaging, allowing for accurate *in vivo* detection of β-amyloid pathology in the brain [67], advancing the field significantly. However, few published studies have systematically explored ethnoracial differences in amyloid positron emission tomography, and no studies have been published to date in ethnoracial diverse populations that assess the more recently developed tau imaging agents. The ARIC study demonstrated significantly increased odds of elevated brain amyloid in African Americans, after adjusting for other risk factors such as apolipoprotein E (*APOE*) ε4, age, and CVD [68]. Interestingly, the effect size was similar to the well-established increased risk of amyloid positivity in *APOE* ε4 carriers [69]. In addition, when examining a multiethnic group of nondemented older adults (n = 116), baseline cognitive scores were not associated with amyloid burden. However, higher amyloid levels were associated with faster longitudinal cognitive decline among African Americans and *APOE* ε4 carriers [66]. These data highlight the need for not only neuroimaging studies with more diverse samples but also a better understanding of the interaction between ethnoracial factors, risk factors, genetics, and neuroimaging biomarkers in these populations.

1.1.4. The influence of ethnoracial factors on EEG/event-related potentials-based biomarkers

Compared with structural, molecular, and functional neuroimaging techniques, measurements of brain electroencephalographic activity (EEG) during sleep, resting state (rsEEG), and sensory and cognitive-motor events (event-related potentials [ERPs]) are less invasive, more readily accessible, and cost-effective. EEG also has the unique temporal resolution (i.e., milliseconds) to explore abnormal oscillatory or dynamical neurophysiological mechanisms of brain neural synchronization and functional connectivity in individuals with neurological disease and animal models of diseases [70].

EEG biomarkers are promising candidates for an instrumental assessment of neurophysiological brain functions across disease progression and intervention in AD populations [71]. Previous EEG biomarker research with ethnoracial groups is inconclusive. A study carried out in 236 patients with AD reported a higher risk of unprovoked seizures and epileptiform EEG activity in African Americans than nHWs [72]; however, this ethnoracial effect was not replicated in a larger number of individuals diagnosed with AD (N = 453) [73].

Motivation for future EEG investigations testing possible ethnoracial differences in AD rests on previous evidence. An EEG study on sleep spindles in healthy individuals

(N = 11,630) reported differences between nHWs and African Americans in several EEG features characteristic of sleep architecture, though these differences decrease with advanced age [74]. Recent reports have unveiled abnormal sleep and circadian rhythms with cognitive change and AD [75], suggesting race/ethnic factors may translate to differences in AD phenotypes. These studies suggest that ethnoracial and genetic factors impact EEG activity.

1.1.5. The influence of ethnoracial factors on biofluid-based biomarkers

The impact of ethnoracial factors on biofluid-based biomarkers is well documented across numerous disease processes [76–88]. Despite the extensive literature on biofluid-based biomarkers in other areas, the study of the link between ethnoracial factors and biofluid-based biomarkers in ADRDs is nearly nonexistent [89,90]. A meta-analysis of genome-wide allelic association study data from several cohorts that included over 500 Hispanics AD cases to cross-validate four of the top previously identified AD genes found that the *APOE* ε4 genotype was significantly associated with AD status among all ethnic groups. However, CLU, CR1, and PICALM were only associated with AD status among nHWs [89]. In addition, *APOE* ε4 has been found to be *less frequent* among Mexican Americans diagnosed with mild cognitive impairment (MCI) and AD [14,91]. The ARIC study reported overlapping and race-specific genetic markers linked to plasma β-amyloid levels when comparing African Americans and European Americans [92]. Ting et al. presented data on a novel PSEN1 mutation associated with early-onset AD in African American women [93], whereas a different mutation for early-onset AD among Caribbean Hispanics has been identified [94]. Regarding nongenetic blood-based biomarkers, plasma biomarkers of $A\beta_{40}$, $A\beta_{42}$, and tau were recently examined among an ethnically diverse sample of females clinically diagnosed with amnestic mild cognitive impairment (aMCI) [95]. Although increased $A\beta_{42}$ levels were associated with incidence of aMCI among Hispanics, this association did not hold for nHWs or African Americans. Plasma $A\beta_{40}$ levels were significantly higher among Hispanic aMCI cases than Hispanic controls; this difference was not found among African Americans. However, plasma total tau levels were significantly decreased among African American aMCI cases but was not found among nHWs or Hispanics [95]. C-reactive protein (CRP) levels have been found to be significantly elevated among Mexican Americans diagnosed with AD and MCI as compared with non-Hispanics [96]. Furthermore, the overall proteomic profile indicative of AD has been found to be different between Mexican Americans and nHWs [16,97].

Despite the extensive literature on diagnostic biomarkers of AD in CSF, there has been only one study specifically examining the impact of ethnoracial factors on these diagnostic markers. Howell et al. [15] recently recruited 135 older adults (n = 65 African Americans and n = 70 nHWs) spanning normal cognition, MCI, and AD, all of whom underwent lumbar puncture for an assay of CSF-based AD pathological markers. The ethnoracial groups were not significantly different with regard to age, gender, or education. African Americans had lower levels of CSF p-tau_{181}, t-tau, and $A\beta_{40}$ levels when compared with nHWs, whereas $A\beta_{42}$ levels did not vary by the ethnoracial groups [15]. These results suggest that absolute cut-scores on these markers may be impacted by ethnoracial factors and highlight the need for additional work examining the impact of such factors on CSF biomarkers of ADRDs.

1.1.6. The influence of ethnoracial factors on immunity and neurodegeneration

Although ethnoracial factors have not been explored with specific reference to the immune system in AD, there is a significant body of data that have explored immune differences across ethnoracial groups in other disorders and suggest further investigation. In vascular disease, for instance, ethnoracial factors impact expression of adhesion molecules, known to attract lymphocytes to the endothelium contributing to the formation of atherosclerotic plaques. Elevated soluble levels of many factors including ICAM-1 and VCAM-1 are associated with increased risk of coronary artery disease and, more generally, atherosclerosis. Surprisingly, lower levels of soluble ICAM-1 and soluble VCAM-1 were found in individuals of African origin than nHW or South Asian populations [98,99]. Importantly, these results remained significant when controlled for homocysteine and socioeconomic status. These findings were replicated [100] where soluble ICAM-1 and soluble VCAM-1 were decreased in African Americans as opposed to nHW Americans. The results are counter-intuitive given the increased risk of heart disease in the African American population.

CRP has long been used as a determinant of systemic inflammation and is frequently measured in the study of many diseases including CVD, AD, and vascular dementia [101]. CRP has been shown to be significantly elevated in the non–Hispanic African American population as opposed to nHWs [102]. In another study, the CRP elevations in African Americans were attenuated significantly when controlling for sociodemographic and health variables [103].

Inflammatory cytokines have been explored with respect to ethnoracial differences. Circulating levels of IL-6 have been shown to be elevated in African Americans compared with nHWs in a cross-sectional study of 508 men and women with 38% African American participants. The IL-6 elevation remained when controlling for sociodemographic and health variables. In the same study, IL-10 and TNFα were found to be unchanged when comparing African Americans and nHWs [102]. Other studies examining cytokines present disparate findings, most likely attributable to the extremely small sample sizes; some as low as n = 10 per group. A good example is IL-1β, where a study concluded IL-1β levels were elevated in African Americans, but there were 83 African Americans and 24 nHWs in this study [104].

Another study found a *nonsignificant* increase in IL-1β in African Americans as opposed to nHWs, which was in a sample size of only 10 per group [105]. Finally, a study with 48 nHWs and 47 African Americans found that there was no difference in IL-1β levels [106]. These disparate findings speak to the need to have sufficiently powered and controlled studies to achieve reliable data and strong conclusions.

A recent study explored the impact of income and educational attainment in ethnoracial disparities in inflammatory risk as it relates to cardiovascular disease [103]. The results showed that higher CRP levels in non–Hispanic African Americans and Mexican Americans, compared with nHWs, were explained entirely by educational attainment. The authors concluded that studies should move beyond examining income to include other socioeconomic factors, with education level being a key part of this. There are no studies examining neuroinflammation in the brain, and therefore, we understand very little regarding ethnoracial microglial differences. The systemic inflammatory differences, and the immune changes related to cardiovascular disease, highlight the potential for significant differences that could have implications for disease progression and treatment in ADRDs.

1.2. Factors related to interventions and methods

1.2.1. Ethnoracial factors related to clinical trials

There is a well-established widespread failure to successfully enroll diverse ethnoracial populations into clinical trials for such ADRD trials. One review found that fewer than 1% of volunteers recruited into AD trials (over 11,000 patients) were of Hispanic ethnicity and 2% were African Americans [107]. In general, enrollment of diverse ethnoracial groups remains less than 5% of the trial subjects [108]; however, in the U.S., NIH-funded trials appear to have higher representation of diverse populations when compared with industry-sponsored trials [107]. Despite this, novel approaches for recruitment are urgently needed [109]. In addition to lack of representation in clinical trials, underrepresented individuals diagnosed with AD are less likely than nHWs to be prescribed regulatory-approved (e.g., U.S. Food & Drug Administration, European Medicines Agency) therapeutics [110].

Ethnoracial factors are frequently covaried in statistical analyses rather than outcomes being reported by subgroups [111,112]. These factors alone make understanding the impact of ethnoracial factors on therapeutic response difficult. ADNI and AIBL studies are frequently used for estimating sample size for clinical trials, but as noted earlier, they lack ethnoracial diversity and the estimates might not be valid if trials were conducted among non-HWs. Lack of diversity could also mask potential ethnoracial differences in efficacy due to different biological mechanisms as discussed earlier, in addition to different rates of attrition/dropout and medication adherence across groups. One study, which investigated the structural magnetic resonance imaging regions of interest associated with MCI, showed that once the attrition bias is controlled using propensity score models, fewer regions were found significant [113]. This study underlines the potentially large bias in study results if attrition bias is neglected and suggests that documenting rate of attrition for ethnoracial groups in trials is important.

Utilizing technologies to monitor disease progression (potential trial outcomes) or identify those who develop cognitive impairment (study enrichment) has generated great interest in ADRDs. It is not well known whether ethnoracial differences may explain willingness in volunteering for trials that involve modern technologies and naturalistic methodologies for data collection (e.g., in-home and in-vehicle monitoring, wearable devices, Internet/webcam). One study found a volunteer bias for the randomized clinical trial, where Internet, webcam, and personal computers are being used intensively [114]. Identifying potential volunteer bias before the study recruitment begins by closely assessing past studies or distributing questionnaires, which allows for assessment of the characteristics of potential participants, could aid diversification of study participants, especially when specific types of technologies are involved.

Significant barriers to enrollment of diverse groups into trials must be addressed. For example, recent work has found that African Americans are less likely to agree to participate in preclinical or asymptomatic AD trials [23] and have higher dropout rates in AD trials when compared with nHWs [115]. Regardless of these barriers, it is important that the research community continues to improve recruitment of diverse populations into clinical trials of ADRDs. This will increase the generalizability of study results as well as investigate potential biological differences across ethnoracial groups and their effects on drug efficacy, adverse events, and drop out/adherence. Recent efforts by the National Institute on Aging, with support of the Alzheimer's Association, are developing a national strategy for clinical study recruitment and retention, with a direct emphasis on local and diverse recruitment and retention strategies [116].

1.2.2. The influence of ethnoracial factors on nonpharmacological interventions

Nonpharmacological intervention research examines the effect of therapeutic interventions such as cognitive training, exercise, functional retraining, and psychological supports (e.g., counseling or meditation), to delay and/or prevent the onset of ADRD symptoms or remediate their impact [117,118]. Relative to pharmacological treatments, nonpharmacological interventions are more likely to target not only primary symptoms (e.g., cognitive and functional decline) but also secondary symptoms that may not be caused directly by disease but that lead to excess disability (e.g., stigma, anxiety, reduced self-esteem). In this vein, nonpharmacological interventions also seek to maintain the individual's autonomy and the highest quality of life

possible during dementia-related cognitive and functional decline. Researchers working with distinct ethnoracial population groups have developed successful nonpharmacological interventions for these groups such as the "Six Arts" framework developed from a Confucian philosophy that emphasizes art, music, and math to improve everyday function [119]. However, less understood is the generalization of nonpharmacological intervention studies from one subgroup to others, especially those with different access, experiences, and beliefs about medical care.

Sociocultural factors may have an impact on differential outcomes in nonpharmacological intervention research at different methodological levels. These factors might hinder the ability of nonpharmacological intervention researchers to *recruit* participants and caregivers from diverse ethnoracial groups. Sociocultural factors might influence the *retention* of participants in activities, in particular when activities are less suitable for diverse groups, and in consequence might influence the *outcome* of the effectiveness of such interventions. In an analysis of the Resources for Enhancing Alzheimer's Caregiver Health (REACH II) trials, researchers concluded that the negative effects of ethnoracial factors on primary outcomes were diminished after controlling for demographic variables such as level of education and relationship of the caregiver to the person with dementia [120]. Furthermore, evidence suggests that beliefs, expectations, quality of life, and even intent-to-participate in nonpharmacological interventions are impacted by ethnoracial factors in some chronic conditions [118,121,122], thereby providing support for the need to study the impact of ethnoracial factors in nonpharmacological interventions in ADRDs.

1.3. Ethnoracial factors related to subjective concerns and neuropsychiatric symptoms in ADRDs

1.3.1. Subjective cognitive decline across ethnoracial groups

One of the primary challenges ahead of prevention and treatment interventions in ADRDs is the ability to screen those at higher risk of developing dementia. The concept of subjective cognitive decline (SCD; sometimes restricted to memory only and referred to as subjective memory complaints [SMCs]) has been proposed to unify the research conceptualization of the earliest nonclinical stage, with potential significance for prevention trials in those with higher risk of AD [123]. In fact, SCD has been associated with AD-related neuropathological processes in nonclinical cohorts [124] and has been identified in individuals aged 30 years and above [125], which provides a 20- to 30-year window for potential prevention approaches.

SCD prevalence, incidence, and final outcomes in ethnoracial groups are areas that have received little attention. One of the very first yet largest studies of older African Americans (n = 1250) showed that 48.3% of these individuals reported memory problems [126]. The authors concluded that memory complaints in this group could be explained by health problems, stressful life events, hearing loss, or depressive signs and symptoms [126]. A more recent publication on a smaller cohort of African Americans (n = 150) reported that a third of participants complained about their memory and cognitive abilities, and their reported cognitive difficulties were mostly associated with increased health problems, depression, and social problems [127]. Interestingly, a previous publication reported a discrepancy between objective cognitive abilities and SMCs reported by African Americans, where they seemed to report lower numbers of SMCs in the presence of objectively more impaired abilities [128]. This finding was reported by a more recent study reporting "unique patterns of variability" in SMCs of African Americans and the relationship between SMCs and psychological wellbeing [129]. However, it seems that in nondepressed African Americans, SMCs are more related to cerebrovascular risk factors [130].

The prevalence and incidence, as well as the outcomes of SCD in other ethnoracial groups, have also been less investigated. For example, in a memory clinic cohort, Hispanic individuals reported more cognitive complaints than their nHW peers [131]. In a recent study of cognitively normal, community-dwelling Mexican Americans (n = 319), it was found that those with SCD exhibited poorer cognition and were more likely to endorse affective dysfunction [132]. A qualitative study of SCD in six different ethnic groups including African Americans, American Indians, Chinese Americans, Latinos, Vietnamese Americans, and nHWs indicated that most of the participants were concerned about their cognitive functioning as they age [133]. However, this study did not provide detailed information on the prevalence, incidence, and follow-up outcomes for the different ethnoracial groups.

1.3.2. Neuropsychiatric symptoms of AD in ethnoracial groups

Neuropsychiatric symptoms (NPSs), which include symptoms such as depression, agitation, and psychosis, are common in dementia and are associated with faster disease progression, diminished quality of life, and early institutionalization [134]. Racial and ethnic disparities in prevalence and knowledge of NPSs exist in the U.S.; however, few studies of these disparities of NPSs in AD exist, and they primarily focus on NPS prevalence [135,136]. Because NPSs create much distress for caregivers and care recipients, it is critical to determine their impact on different ethnoracial groups.

The Neuropsychiatric Inventory Questionnaire (NPI-Q) is the most common measure of NPSs used in AD studies [137–140]. Existing literature suggests incidence disparities of NPSs in AD among different ethnoracial groups. African Americans may experience hallucinations more frequently [135,136], and noninstitutionalized African Americans and Latino Americans with dementia have more frequent behavioral symptoms than nHWs

[137]. Another study found that being from a member of some ethnoracial minority groups was associated with psychosis as well [138]. A higher presence and severity of NPS have been found among Latinos diagnosed with MCI and AD [14,20,139], which suggests that they may seek treatment at more advanced stages of AD [137,140]. However, nHWs have been found to exhibit higher levels of apathy [135,138]. Asian Americans diagnosed with AD showed frequent emotional disinhibition in one study [135], but more literature on NPSs in that demographic is needed. No studies on the prevalence of NPSs in American Indians with AD currently exist.

Regarding knowledge of AD-related NPSs, Korean Americans knew less about AD behavioral changes than about cognitive changes, and Latino caregivers (not specified by ethnicity) could not attribute NPSs to AD specifically [141,142]. No literature exists on African Americans' knowledge of NPSs in AD, but this group appears to view NPSs as a source of stress in caregiving [143]. African Americans may cope with NPSs through their faith and assistance from loved ones and may find behavioral interventions centered on emotional distress to be less useful [144,145]. No studies were found on access to AD care for NPS specifically, but minority elders have lower access to mental health care relative to nHWs and are institutionalized for AD less frequently [146,147]. Nevertheless, a cultural emphasis on family, respect for elders, and perceptions of AD symptoms as "natural" parts of aging may cause members of those minority groups to take more time before seeking external care for NPSs [21,24]. African Americans are less frequently prescribed medications overall for AD and discontinue AD medication more frequently [148–150]. The only study to look specifically at medication use for NPSs in AD (antipsychotics) among different racial groups found that the usage was higher among Hispanic Americans, likely due to the higher prevalence of NPSs in that population [151].

Bridging gaps in NPS prevalence, knowledge, and care should involve creating tailored interventions for a group delivered by interventionists who understand (and ideally come from) cultural dynamics [145,152,153], as well as through bettering educational outreach to populations with a lower understanding of NPSs. In addition, much more research is needed to understand the ethnoracial, systematic, and possible genetic influences on NPSs occurrence, neuropathology, and treatment.

1.4. Ethnoracial factors related to atypical ADRDs

1.4.1. The impact of ethnoracial factors in atypical AD and associated syndromes

Atypical AD was acknowledged in the revised diagnostic guidelines for AD in 2011 [53] and has since become an umbrella term encompassing nonamnestic clinical presentations, early-onset (young) AD, and neuropathologically defined subtypes of AD (i.e., hippocampal sparing or limbic predominant) [154–158]. Clinical and neuropathologic studies suggest that younger age and absence of an *APOE* ε4 allele are associated with greater likelihood of atypical AD [156,159–161]. Regardless of etiology, approximately 5%–10% of individuals present with nonamnestic mild cognitive impairment (naMCI) [162–164] and 20%–33% of individuals present with atypical AD [158,165,166]. Compared with typical AD, clinical diagnosis of atypical AD is often delayed and very little is known about its pathogenesis, risk factors, natural history, and response to treatments [167,168] overall, and more so across ethnoracial groups.

The estimated prevalence and incidence of naMCI in non–Hispanic African Americans are approximately 16%–18% [162,169] and 3-4 per 100 person-years [162,170], respectively, with up to a two-fold increased risk compared with nHWs even after controlling for sex and education [162,171]. The two-fold increased risk is suspected to be driven by higher rates of cardiovascular risk factors among African Americans [172–174], suggesting a primary or superimposed vascular etiology. A large cross-sectional study of community-dwelling Colombian adults showed that naMCI was more common in young-onset dementias and in individuals with lower education [175]. Another study investigating the dysexecutive variant of AD identified that after controlling for covariates (vascular risk, *APOE* ε4, and global cognition), the MCI dysexecutive subgroup was older, less educated, and more likely identified as African Americans than the aMCI subgroup. In contrast, the AD dysexecutive subgroup was younger than the amnestic AD subgroup and did not differ in education or ethnicity [176]. These results suggest there may be an even more nuanced aspect related to clinical progression that may need to be accounted for in ethnoracial studies.

With respect to associated syndromes that may or may not be related to AD pathology, the prevalence of dementia among 2011-2013 Medicare beneficiaries ages ≥68 years showed that frontotemporal dementia (FTD) was clinically diagnosed in 0.6% of African Americans, 0.7% of Hispanics, 0.8% of Asian/Pacific Islanders, 0.6% of American Indians or Alaska Natives, and 1.1% in other/unknown nonwhite groups [177]. A study examining a community sample of Hispanics ages ≥55 years found that approximately 9% had clinical diagnosis of FTD and 3% had a diagnosis of dementia with parkinsonian features [178]. A study investigating African Americans clinically diagnosed with FTD revealed AD pathology along with *PSEN1* (M139V) and *MAPT* polymorphism in exon 7 (A178T) mutations, suggesting that *M139V* may present differently among different ethnoracial groups [179]. Studies also show that *PSEN2* is closely involved in FTD [180,181] and is also found in Asian [182–184] and African populations [184–187]. Low-frequency coding variants for genetic susceptibility to AD and FTD have also been reported in African Americans, Asians, and Hispanics [188,189].

Overall, studying clinicopathologic differences in atypical AD poses great challenges due to their low disease prevalence, as well as to the interrelated biopsychosocial and cultural factors affecting participation in clinical studies and health outcomes in ethnoracial groups. A paradigm incorporating those factors is necessary to better understand and improve dementia treatments in these historically underserved, ethnoracial populations [190].

1.4.2. The influence of race and ethnicity in Down syndrome

Individuals with Down syndrome (DS) are at high risk for developing AD compared with the general population [191]. All individuals with trisomy 21 show AD neuropathology by the age of 40 years, and over 90% show dementia in the seventh decade [192]. The International Workgroup suggests DS may be a genetically determined atypical AD [154].

There are numerous barriers to early diagnosis of dementia in DS that reflect an interaction between ethnoracial and health disparities. For example, symptoms of dementia may be missed or not identified [193]. Often, there are differing symptom presentations in people with DS relative to sporadic AD, and there are concerns about the appropriateness of the diagnostic tools [194]. Challenges of dementia diagnosis in DS within the context of intellectual disability require specialized expertise and tools [195].

In a preliminary analysis, the incidence of MCI and of AD was 6% higher among African Americans with DS than among nHW adults with DS (data from the Aging and Dementia in Adults with Down Syndrome Study, W. Silverman). Age at onset of MCI did not differ between African American and nHW adults with DS, whereas age at onset of AD was slightly earlier among African Americans, suggesting a more rapid decline in cognitive function after onset of MCI. In the general population, the higher rates of AD among African Americans than among nHWs have been related to an increased prevalence of cardiovascular risk factors and CVD, which in turn may elevate risk for AD. These factors are less likely to influence risk among adults with DS [191]. Current cohorts under study have relatively few minority participants, and few studies have examined ethnoracial disparities in risk factors for dementia.

Mortality rates also vary across ethnic groups in DS; disproportionately more African Americans with DS die as young adults [196]. The ability to determine contributors to the age of onset of dementia in individuals with DS is confounded by differences in age at death across different ethnoracial groups. Disparities are also present in the care of individuals with DS and dementia. In the U.S., access to group homes (related to intellectual disability) rather than dementia special care units is common as group homes are reported to provide care in a home-like environment, with more economical costs [197,198]. However, gaps in services and unmet service needs are reported for adults with DS in rural/remote settings and their caregivers rely on informal support [199–201]. In the United Kingdom, aging-in-place models are encouraged if appropriate support is available. Most adults with intellectual disability in the U.S. live at home, and this is more common among diverse ethnoracial groups (e.g., African Americans, Hispanics) with DS [202–204]. These differences in care models impact the caregivers, with poorer health reported for caregivers of individuals with DS who are also minorities [203,205,206], which in turn could be a reflection of socioeconomic status and possibly cultural practices. Collaborative studies with combined and harmonized cohorts of older adults with DS are needed to determine differences in risk factor profiles and to provide accurate estimates of any differences in risk for AD and rates of progression after onset.

1.4.3. Ethnoracial factors and vascular cognitive disorders

Vascular cognitive disorders are caused and exacerbated by health disparities experienced by ethnoracial groups. Globally, these disparities can be attributed partially to burgeoning obesity, combinations of lifestyle factors associated with poor vascular health, and unknown genetic and lifestyle susceptibilities among increasing immigrant populations. Being overweight and obese are cornerstones of vascular risk, leading to hypertension, type 2 diabetes, CVD, cardiovascular disease, and stroke, as well as cognitive impairment and multiple etiologies dementias.

The prevalence of overweight and obesity is over 50% among adults in the U.S. and Europe, and within certain global urban centers such as the Brooklyn Borough of New York City, the prevalence is over 70%. Of the top 10 causes of death worldwide in 2015 [207], half are related to obesity, and account for approximately 1/3 of all deaths. These include ischemic heart disease, CVD/stroke, type 2 diabetes, and ADRDs [207]. Vascular risk is a costly burden. In Brooklyn, hospitalizations and deaths from heart disease, diabetes, and disabilities are higher than the New York City average. Part of the reason is that ethnoracial minority adults typically present late, at more advanced stages of disease, and in nontraditional settings, such as the emergency department. Given adults from diverse ethnoracial groups also present with high vascular risk, they are even more compromised.

Stress is a major facilitator of vascular risk in ethnoracial minority groups. Stress is a cause, correlate, and consequence of obesity. Not only do stress and obesity lead to downstream adverse vascular events, they are often accompanied by discrimination and unfair treatment, leading to additional stress responses [208]. Health disparities–related stress is also associated with ethnoracial differences, older age, family, employers, stigma due to ethnorace, sexual orientation, infectious disease status, employment status and/or sex/gender, poor access to health care services, built environment, lack of social support, depression, and anxiety [209]. Cumulatively, these stressors challenge social interactions and may manifest as inability to work, difficulties with personal relationships [210], and challenges to social inclusion [211]. Over the life course, the cost of chronic exposure

to fluctuating or heightened neuroendocrine responses resulting from repeated or chronic environmental challenges and social burden that an individual react to as being particularly stressful [211,212] directly affects neural mechanisms contributing to cognitive function [213,214].

Potentially modifiable vascular risk factors contribute to cognitive aging and risk and progression of ADRDs through their effects on cerebral vasculature. The accumulation of small vessel cerebral vascular disease that results from years of exposure to vascular risk is best visualized on T2-weighted magnetic resonance imaging as white matter hyperintensities. Increased white matter hyperintensity burden is associated with risk for development of ADRDs [215–217] and progression of symptoms in ADRDs [218] and is even evident in individuals with autosomal dominant AD up to 20 years before expected symptom onset [219]. The severity of white matter hyperintensities differs across racial and ethnic groups [61] and relates differentially to specific cognitive outcomes as a function of race/ethnicity [220,221]. Given the well-documented disparities in vascular risk factors, differences in CVD, and differential relationships with cognition between racial and ethnic groups, vascular disease is a major topic of focus with respect to racial and ethnic disparities in ADRDs.

1.5. Other factors related to cognitive impairment and dementia

1.5.1. Ethnoracial factors related to perioperative cognition and delirium

Delirium is a focus for both research investigation and clinical care around the world. For example, one of the delirium screening tools, the Confusion Assessment Method (CAM), has been translated into 19 languages and used in over 4000 original publications, demonstrating an active clinical and research interest in delirium [222]. Perioperative cognitive disorders may contribute to further cognitive decline and are known to be associated with poor outcomes. Despite this, there are few studies examining ethnoracial factors in either delirium or perioperative cognitive disorders, with studies being predominantly restricted to those who are fluent in English.

Campbell et al. [223] evaluated 1275 older adults aged ≥65 years who were admitted to general medical hospital services. The goal of the study was to determine if race is a factor in the agreement between clinical documentation and screening results for delirium and cognitive impairment. The authors compared clinical documentation with scores on a screening measure (the Short Portable Mental Status Questionnaire) and found that there were no differences in delirium documentation rates between African Americans and non–African Americans. However, African Americans had a higher adjusted odds ratio than non–African Americans for clinical documentation of cognitive impairment among those who screened positive for impairment on the Short Portable Mental Status Questionnaire, as well as among those who screened negative on the Short Portable Mental Status Questionnaire.

One study examining the recorded diagnosis of delirium in acute inpatient units found that African Americans were more likely to receive a confusional diagnosis or an organic psychoses diagnosis as opposed to a diagnosis of delirium [224]. Individuals who received the diagnosis of organic psychoses had longer lengths of stay and higher rate of discharge to nursing homes. One of the potential explanations for these differences was that elderly African American individuals are significantly more likely to receive diagnosis of psychotic disorders than nHWs [225]. Another study examining the prevalence of delirium among older adults presenting with psychiatric complaints to an emergency department, it was found that although minority individuals (African American and Hispanic) comprised 55.8% of the study cohort, 74.1% of delirium visits were comprised of minority individuals [226].

The most frequent etiology of delirium in sub-Saharan Africa (SSA) reported in the literature is infection including HIV, typhoid fever, and malaria. However, the number of older adults is expected to increase by 64% in Africa in the next 15 years [227], and it is unknown whether the available expertise of diagnosing and treating delirium by health care providers in Sub-Saharan Africa can meet the increasing demand. In addition, with increasing access to higher levels of care in Sub-Saharan Africa, clinical entities such as ICU delirium, which is a new concept to many physicians in these regions, are also emerging.

Cognitive decline associated with anesthesia and surgery is known to occur in more than 10% of individuals 3 months postoperatively [228] and has been termed postoperative cognitive dysfunction (POCD). POCD has been limited to predominantly English speakers due to limitations of existing neuropsychological tests, with some limited European languages included as part of the International Study of POCD [229]. POCD studies have been undertaken in some Asian populations, but most of these are limited to very short follow-up of days rather than weeks, months, or years [230]. It is unclear if POCD precipitates long-term cognitive decline, but it is known that POCD is associated with poor outcomes including increased risk of mortality as far as 7.5 years after surgery [231]. Thus, it is important for future research to focus on ethnoracial factors that may contribute to perioperative cognitive disorders. The recent recommendations for new nomenclature should assist in facilitating this research agenda.

1.5.2. Ethnoracial factors related to diet and nutrition

Diet is complex and varies considerably by ethnicity and socioeconomic status [232–234]. It is well established that some ethnoracial groups experience diet-related disparities and consequently have poorer nutrient profiles relative to nHWs [235,236]. According to the U.S. Behavioral Risk Factor Surveillance Survey (BRFSS) [237], only 21.3% of African Americans consume fruits and vegetables ≥5 times

per day, the lowest of any U.S. ethnoracial group. Similarly, in the third National Health and Nutrition Examination Survey, NHANES (1999–2002), non–Hispanic African Americans were 43% less likely than nHWs to meet fruit and vegetable guidelines [238]. These racial disparities differ by geographic region. For example, Hispanic groups consumed lower-quality diets than nHWs, including more refined carbohydrates and fewer vegetables and fruits [232,233,239], whereas in other studies, Hispanics had higher-quality diets than either nHWs or African Americans [234].

Poor diets and malnutrition are important contributors to cognitive impairment [240–242]. Nutritional deficiencies in older people, particularly in minority groups, are common, but studies across diverse ethnoracial populations are limited [242–245]. Randomized trials of nutritional supplements are needed to examine their impact on ethnoracial groups (e.g., African Americans) that have known nutritional deficiencies. Unfortunately, most randomized clinical trials of dietary supplements have not targeted populations with low nutrient status, and trial results have been null overall [246]. Conducting dietary supplement trials in diverse ethnoracial populations with nutrient insufficiencies has the potential to close some of the ethnoracial disparities in ADRDs.

The few studies that have examined dietary associations with AD and other brain neurodegenerative outcomes in multiethnic participants in most cases do not present their findings by race or ethnic group [241,247–257]. Rather, these studies have reported *P* values (usually null) for tests of effect modification by race/ethnicity [247,248,250,251,253,257,258]. This is inadequate as there are clear examples of nutrition having different cognitive effects by ethnoracial groups as shown in the Healthy Aging in Neighborhoods of Diversity Across the Lifespan Study (vitamin E with various cognitive domains) and the Health, Aging, and Body Composition study (the Mediterranean diet with cognitive decline) [259,260].

Cultural differences in dietary practices pose methodological challenges in dietary assessment. Many food frequency questionnaires have not been designed and tested to accurately capture the foods, serving sizes, and meal preparations of different cultural groups [261]. Consequently, the dietary assessments from these studies likely produce biased estimates of nutrient relations with dementia, particularly for ethnoracial minority populations. To adequately address ethnoracial disparities in diet, nutrition, and ADRDs, it is imperative that greater attention is devoted to cultural validation of the dietary assessment methods.

1.5.3. Ethnoracial factors related to the development of technologies

Technology for dementia has developed in several main areas: assessment of cognitive functions [262] and daily activities [263]; direct cognitive [264] or behavioral support [265]; monitoring [266]; and direct caregiving [267] and supporting caregivers [268]. Different ethnoracial groups have been involved in the creation and testing of technologies, but the potential impact of these differences has not been explored. The focus of most research has been on the effectiveness or impact of the technology, with a lack of consideration of the role ethnoracial factors may play in utilization or impact potential.

Two key issues in development of technology for dementia relate to cognitive function and accessibility of technology. Understanding cognitive function is central to developing technology for individuals with dementia and this is where the lack of ethnoracial consideration is most apparent. Much technology development has focused on improving cognitive assessment [269] to enhance or improve dementia diagnosis. However, these studies have not reported on possible inclusion or on differences in cognitive performance and profiles [270] and rate of decline [271] in ethnoracial minority groups.

There is also limited information available on access to technology in ADRDs. The "digital divide" is an issue that reflects socioeconomic factors, whereby lower-income groups have less access to technologies. There are no existing survey data on access and use of technologies by people with dementia that consider ethnoracial factors. However, we can gain some insight from two large U.S. surveys that looked at the use of assistive technologies (ATs) by different racial groups. Reed et al. [272] conducted the Community Research for Assistive Technology Survey in California. They divided ATs into three categories: high-tech (e.g., computers), medium-tech (e.g., scooters), and low-tech (e.g., magnifiers). The proportion of white respondents (23%) using high-tech devices was higher than Asian Americans (16%), African Americans (13%), and double the number of Latinos (11%) suggesting unequal access to the same technology [272]. This lack of access and awareness was echoed in a 2009 U.S. National Health Survey, which looked at ATs usage across groups with mobility, visual, auditory, and emotional disabilities [273]. Their findings suggested that income status, particularly receiving Medicaid or veteran's benefits, and mental impairment reduced the likelihood of people using ATs [273]. To address these challenges, they proposed a list of changes including more cultural competency training, ensuring the attitudes and values are included in evaluating AT needs among underrepresented groups and designing effective outreach and health marketing appropriately tailored to different ethnoracial populations. In relation to dementia technology specifically, a survey of American and German family caregivers found low awareness of what technology is available for themselves or the people they care for [274]. In addition, lack of access to broadband Internet and limited availability of specialized technologies have been identified as key barriers to technology for dementia [275]. However, there are signs that the growing need to address these problems is starting to take hold through recent efforts to meet the needs of ethnic minority dementia

caregivers through apps [276], online education [277], YouTube [278], and a survey of their preferences for technology [279].

Overall, there remains a significant dearth in research specifically designed to understand and address heath disparities in ADRDs. Diverse ethnoracial populations remain underrepresented in studies across all areas covered by the PIAs. However, given the substantial amount of work that has been accomplished across these respective areas, there remain tremendous opportunities to rapidly advance the state of the science. Broad areas of immediate need, based on the information provided above, are provided below.

1.6. Recommendations for advancing the field of health disparities in ADRDs

As highlighted across each of the major topic areas and expert groups listed, there remain substantial knowledge gaps regarding the ADRDs among diverse ethnoracial groups globally. The science of ADRDs has advanced considerably over the last few decades, and the same can be accomplished regarding an understanding of ADRDs among diverse populations. First and foremost, the expertise of the various PIAs and global experts across fields needs to be leveraged to design and implement research programs to address the gaps identified in a rapid fashion.

Primary recommendations proposed by the working group are as follows:

- Develop specific health disparities models/frameworks and implement data-driven strategies for targeted recruitment and retention of diverse ethnoracial populations into ADRD observational studies and clinical trials.
- Identify differing perspectives and views held by ethnoracial groups regarding ADRD research and interventions, to tailor appropriate methodologies for addressing gaps identified here as well as widely disseminating findings.
- Uniformly, examine the prevalence of specific life experiences/status (e.g., poverty, war/conflict, stigma, disability, sex, gender) and whether they play a role in ADRD disparities among diverse ethnoracial groups across countries.
- Create training modules, webinars, and related educational opportunities for researchers, payors, funders, community members, and even research participants to learn how to effectively develop diverse and inclusive study designs and recruitment and retention strategies in ADRD studies.
- Train practitioners and researchers (e.g., neuropsychologists, neurologists, geriatricians), including those from diverse ethnoracial groups, to implement culturally appropriate research methodologies (e.g., assessments, interviews, interventions) across different ethnoracial groups.
- Develop and validate appropriate research tools along with appropriate use and interpretative guidelines (e.g., normative references). This can include generation of instruments that can be used across groups, development of novel tools that are group-specific, and the development of appropriate analytic methods for working across tools when needed.
- Establish collaborative infrastructure across existing longitudinal registries and cohorts that include diverse ethnoracial populations to address gaps identified here. Also, leverage existing infrastructures and knowledgebase for the establishment of additional targeted research cohorts to advance the field of health disparities in ADRDs.
- Implement methodological strategies that enable post hoc analyses across diverse groups, comparisons across longitudinal cohorts; consistently report ethnoracial subgroup data even when not analyzed; and include refreshment samples in cohort studies to maintain statistical power—including addition of replacement for attrition in ongoing studies that are not representative of ethnoracial groups with diverse populations.
- Implement analytic methods to weigh observations from underrepresented groups to attenuate the impact of small sample size; investigate the impact of ethnoracial disparities on retention, attrition, and mortality; and consistently report ethnoracial subgroup data, even if such differences are not analyzed due to low group sample sizes.
- Develop and validate statistical models of risk and protective factors germane to ethnoracial groups, including complex interaction terms to better refine prevalence and incidence of ADRDs between different groups.
- Employ structured "precision medicine" and "precision public health" approaches to combine, translate, and share findings from ADRDs research including ethnoracial groups across the world to target and continually refine diagnostics, disease monitoring, treatment, and development of new therapeutics.
- Include diverse ethnoracial groups in studies examining sociocultural, biomarker, biological mechanism, and all other aspects of ADRD science.
- Develop and disseminate educational materials regarding ADRDs specifically focused on caregivers from diverse groups; include caregivers from diverse ethnoracial groups in scientific inquiries addressing caregiver and family needs.

1.7. Advancing the Science of Health disparities in ADRDs

As previously discussed, there are several gaps in the extant literature in many of the key areas of science currently being examined in ADRDs. Aside from the large gap in

literature examining ethnoracial factors in ADRDs documented by this working group, there is also no comprehensive framework to address the gaps. Specifically, the vast majority of the science conducted in the articles reviewed addressed one question at a time without the end in mind (i.e., a comprehensive understanding of the full complexity of ADRDs, including ethnoracial factors). To advance the understanding of ethnoracial factors in ADRDs, the field needs to not only directly test importance of ethnoracial factors but also test these constructs within the context of the "big picture" including, but not limited to, factors such as gender, neuropathology (e.g., the 2018 NIA-AA research criteria for AD explicitly for testing of these new concepts in diverse populations), molecular biology, environmental factors, and more.

If the comprehensive framework is to explicitly test and understand the complexity of ADRDs, then more advanced analytic modeling approached are needed as is longitudinal data. Studies that iteratively propose a unique hypothesis, test the hypothesis, refine the question, and start-over using large-scale longitudinal data are needed. Multiscale modeling, advanced artificial intelligence learning tools, and structural equation modeling are some of the tools that are explicitly designed to manage such large-scale and complex questions. The statistical/bioinformatics models can grow and expand iteratively as the hypotheses are tested, refined, and reanalyzed. Many of these tools were refined in the human genome project but have been applied to life sciences at large scale. The translational work in ADRDs has begun to break down silos; however, the questions posed do not directly test the complexity of the problem faced. If these more complex tools are utilized, the complexity of ethnoracial factors, within the context of ADRDs more broadly will become more in focus. This approach can lead to a precision medicine approach to treating and preventing AD.

To continue the momentum of this working group and other ongoing efforts, we propose that a formal meeting occur in conjunction with the National Alzheimer's Project Act meeting (or other meeting), specifically to address the advancement of health disparities in ADRDs. This meeting would serve as a "think tank" on how to move the field forward rather than a venue for individuals to present their recent (or remote) findings. Experts from diverse backgrounds (epidemiology, health disparities, neuropathology, sociology, etc.) would be invited to discuss and provide strategies for next steps to advance the field.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional sources (e.g., PubMed) and meeting abstracts and presentations. Several recent publications have described the role of ethnoracial factors on the incidence, diagnosis, and clinical presentation of Alzheimer's disease and related dementias (ADRD). These relevant citations are appropriately cited.
2. Interpretation: The manuscript clearly identifies the study of ethnoracial factors in key topic areas of ADRD science as substantially lacking. Despite the global search for improved diagnostic and therapeutic understandings of ADRD, research is needed on these topics across ethnoracial populations.
3. Future directions: Experts from Professional Interest Areas of ISTAART provide specific immediate needs on ethnoracial research across a wide range of topic areas that, when dealt with, will greatly advance the field of ADRD. Addressing these needs will be key to implementing culturally-appropriate interventions, as well as improving access to care for ethnoracial groups.

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