Neurotherapeutics (2022) 19:26–54
https://doi.org/10.1007/s13311-022-01193-z

REVIEW

Culture, Ethnicity, and Level of Education in Alzheimer's Disease

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Accepted: 22 January 2022 / Published online: 28 March 2022

Abstract

Alzheimer's disease (AD) is the most frequent cause of dementia, where the abnormal accumulation of beta-amyloid (Aβ) and tau lead to neurodegeneration as well as loss of cognitive, behavioral, and functional abilities. The present review analyzes AD from a cross-cultural neuropsychological perspective, looking at differences in culture-associated variables, neuropsychological test performance and biomarkers across ethnic and racial groups. Studies have found significant effects of culture, preferred language, country of origin, race, and ethnicity on cognitive test performance, although the definition of those grouping terms varies across studies. Together, with the substantial underrepresentation of minority groups in research, the inconsistent classification might conduce to an inaccuratte diagnosis that often results from biases in testing procedures that favor the group to which test developers belong. These biases persist even after adjusting for variables related to disadvantageous societal conditions, such as low level of education, unfavorable socioeconomic status, health care access, or psychological stressors. All too frequently, educational level is confounded with culture. Minorities often have lower educational attainment and lower quality of education, causing differences in test results that are then attributed to culture. Higher levels of education are also associated with increased cognitive reserve, a protective factor against cognitive decline in the presence of neurodegeneration. Biomarker research suggests there might be significant differences in specific biomarker profiles for each ethnicity/race in need of accurate cultural definitions to adequately predict risk and disease progression across ethnic/racial groups. Overall, this review highlights the need for diversity in all domains of AD research that lack inclusion and the collection of relevant information from these groups.

Keywords Alzheimer's disease · Biomarkers · Culture · Ethnicity · Race · Crosscultural neuropsychology

Introduction

Alzheimer's disease (AD), the most frequent cause of dementia, is a progressive degenerative brain disorder affecting approximately 5.5 million people in the United States (US) and 24 million people worldwide [1]. With brain atrophy and abnormal accumulation of proteins such as beta-amyloid and tau comes cognitive decline and weakening of behavioral abilities, resulting in the loss of independent functioning. The average post-diagnosis AD survival rate is typically 5 to 8 years [2]. However, this tends to vary among patients due to other factors such as age, gender, ethnicity, socioeconomic status, and additional health complications, including, more recently, COVID-19 [3]. In cross-cultural neuropsychology the approach to assessing neurological disorders, especially dementing diseases, is to look at the influence of cultural variables on cognition, so as to determine the manifestations of brain pathology in within various cultural contexts [4]. In this review, the topic of AD is approached from a cross-cultural neuropsychological perspective. It starts by defining culture and culture-related concepts, leading to how cultural groups are defined across the scientific literature, followed by a discussion about cross-cultural matters in psychometrics and neuropsychological testing. Then, the relevance of cultural variables is examined, including ethnicity and education, as well as the differences across ethnicities in the prevalence of AD and its cognitive profile and related biomarkers. There are three AD sections presented: (1) the influence of education in the diagnosis and progression of AD; (2) AD in diverse cultural groups (defined by ethnicity or race, native languages, and country of origin); and (3) AD biomarkers across ethnic and racial studies.

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Defining Culture

Culture is defined as the set of learned traditions and living styles shared by the members of a society [5, 6]. It includes the ways of thinking, feeling, and behaving [7], in which three components can be identified: the internal representation, the behavioral dimension, and cultural elements [8]. The internal representation of culture is subjective and includes ways of thinking and feeling, knowledge, values, attitudes, and beliefs. The behavioral dimension represents how we relate with others and how our behavior changes in different contexts and circumstances. Finally, cultures incorporate specific physical characteristics of the corresponding group, such as clothes, ornaments, houses, and instruments. Cultural elements also include symbolic objects that represent abstract concepts, in the way a wedding ring represents a bond of love and commitment between two people. Culture represents a way for an individual to adapt to and survive in specific environments. However, culture is dynamic, and cultural changes are continuously observed [4].

Grouping Cultures. Researchers in cognitive neuroscience have used different criteria to group cultures, including preferred language (e.g., Spanish speakers, English speakers). For instance, Loewenstein et al. [9] investigated the usefulness of the Fuld Object-Memory Evaluation (FOME) as a culture-fair screening for dementia, comparing the performance of Spanish and English speakers with mild dementia. Results indicated equivalent high sensitivity for both language groups, indicating that the FOME was a reliable, culturally fair test when screening patients for possible dementia, in the context of those whose native language was either Spanish or English.

Others have equated culture with the country of origin. For example, Buré-Reyes et al. [10] compared participants' performance from four different Spanish-speaking countries (Chile, Dominican Republic, Puerto Rico, and Spain) on a neuropsychological battery to highlight the importance of within-group differences between Spanish speakers. After holding education and age constant, significant differences emerged across two of the five tests administered

An additional culture-grouping criterion has been the participants' race. For example, potential differences in cross-sectional and longitudinal cognitive performance have been examined, including cardiovascular risk factors, and AD brain biomarkers in Black and White individuals, all clinically normal at baseline [11]. These racial groups did not differ in vascular or brain biomarkers. However, Blacks had a lower cognitive performance at baseline and declined faster than Whites even after adjusting for the lower levels of educational attainment and reading ability of the former.

Race is frequently described as a fixed genetic characteristic [12] despite decades of research showing that "racial groups" are defined by societies, not genetics [13]. The differences in cognitive performance noted between Black and White individuals are more likely attributable to cultural rather than racial differences. Moreover, authors who define culture as race frequently use the term Caucasian for a racial or ethnic identity equivalent to Whites or European Americans. However, the term Caucasian has no scientific basis. Historically, it has been regarded as a biological taxonomic category that usually included ancient and modern populations from all or parts of Europe, Western Asia, Central Asia, South Asia, North Africa, and the Horn of Africa. In the eighteenth century, the term meant "beautiful people (with an implication of superiority) from the Caucasus Mountains", a mountain range at the intersection of Europe and Asia [14]. Consequently, because it was developed as a concept implying inequality, the term appears to be discriminative, inappropriate, and inadequate. Not all Europeans originate from the Caucasus; the Anglo Saxons, Latins, Slavs, and others to whom the term is often applied have no historical or ethnic connection with the Caucasian peoples [15]. Regardless, this term remains ubiquitous in the medical field and will be used here only for consistency with the literature.

Lastly among the cultural grouping variables, it is common among neuroscience researchers to equate culture to ethnic origins (e.g., European, Latin, Anglo-Saxon, African, Amerindian, Asian cultures, etc.) [4]. Ethnicity, which is a broader category than race, identifies people as belonging to a group based on similarities such as common ancestry, language, history, society, culture, or nationality [4, 12]. Altogether, ethnoracial factors can be thought of as the race-ethnicity influence of both intra- and inter-personal factors, including genetics, ancestry, and self-identification [16, 17].

Several limitations have come from the classification of groups by ethnic origins. First, it is too broad and ambiguous to include continental ancestry groups such as African or African American; second, it collapses enormous diversity and erases cultural and ancestral identities. A classification that is commonly used is "non-Hispanic whites" [18], or "white non-Hispanics" [19], which represents a category of individuals which is often selected for analyses in studies, even though a decreasing number of individuals identify with this category [13].

The terms "Eastern" and "Western" refer to groupings-by-culture [20]. Eastern cultures include Asia and the Middle East, while the Western world includes South and North America, European countries, New Zealand, and Australia. A noteworthy distinction between East Asian and Western cultures is the dissimilarity in information processing biases related to their distinct cultural values and beliefs. It has been

suggested that the collectivistic and individualistic biases of East Asian and Western cultures, respectively, affect cognition as well as neural structure and function [21]. It has long been found that East Asians and peoples from European cultures attend to different aspects of the world and, therefore, reason differently. East Asians are presumed to perceive and reason holistically, attending to the field where objects are embedded and attributing causality to interactions between the object and the field [22]. In contrast, Europeans, representative of Western society, are considered analytic, attend primarily to the object, and pay little attention to the field, preferring to attribute causality to the object's properties [21]. It has been suggested that the tendency of Asians to process information holistically results in greater sensitivity and responsiveness to contextual cues in the memory domain. Masuda and Nisbett [23] observed distinctions in the attentional patterns among East Asians and Westerners, using recognition tasks in which old and new objects in diverse environments were shown. East Asians focused on contextual characteristics of objects displayed and relationships to their environments, more than Americans (Westerns). The change in the object's environment negatively affected East Asians' accuracy in their responses, while this modification had no significant effect on the ability of Americans to identify old and new objects. This finding supports the idea that Westerners think more independently, while Easterners think more interdependently.

Culture and Cognition

Cognitive abilities are culturally bound. One of the earliest analyses of the interaction between biological and cultural factors in the development of human cognition came from the Soviet neuropsychologist Luria [24, 25], who with Vygotsky [26] investigated the influence of culture and, notably, education on the development of higher-mental functions [8]. According to Luria [27], mental functions have a social origin and are hierarchically structured within complex functional systems. An intrinsic factor in Luria's proposed systematic organization of higher mental functions was the engagement of external artifacts (e.g., objects, symbols, signs), which have an independent history of development within cultures [8]. This principle of construction of functional systems of the human brain is represented in what Vygotsky [26] called the principle of *extracortical organization of complex mental functions*, implying that all aspects of human cognitive processes are formed with the support of cultural elements [8].

Central to the association between culture and cognition is the distinction between cognitive processes [22]. Primary cognition (i.e., cognitive mechanics) refers to biologically based, hardwired cognitive functions while secondary cognition (i.e., cognitive pragmatics) refers to culturally-based processes [28, 29]. However, Park et al. [22] argue, that processes that might initially be thought to be hardwired (what Baltes refers to as cognitive mechanics [29], and Geary and Lin refer to as primary processes [30]) are affected by culture [22]. These processes are operations performed on information in the environment or information built or retrieved from the individual's cognitive system and could vary across cultures [22]. For example, there are variations in perceptual attention and reasoning between individuals from East Asian and European cultures. There are well-documented differences in cognitive processes between these groups resulting from fundamental differences between their cultural environments. Furthermore, African American males have been shown to have significantly higher scores in the Seashore Rhythm test than European Americans and Hispanics [31, 32]; this has been attributed to the important role that music plays in African American culture [33].

The relevance of culture in neurocognitive processes has gained increasing interest regarding the potential of culturally related effects impacting cognitive performance [34]. A recent special issue of *Cognitive Neuroscience* examines the interaction between interoceptive and exteroceptive bodily self-awareness in Western and East Asian adults [35]. Cultural differences in levels of attention towards context, were found, using the neural event-related potential (ERP) component, N400 [36], and considerating the culture of participants while studying mathematical skills [20]. Anatomical differences in brain activation have been reported when Western and Eastern cultural groups performed the same mathematical task [37, 38] and when readers with dissimilar culture-specific orthographic demands (i.e., consistent/Italian and inconsistent/English) are compared [39].

Influence of Culture in Cognitive Assessment

Neuropsychological assessments determine the presence and characterization of cognitive impairment in AD and other dementias. However, these tests of cognitive abilities are particularly susceptible to the influence of culture [33, 40–43]. It has been proposed that performance in cognitive assessments is culture-specific because of cultural social differences in: (1) values and meanings, (2) modes of knowing, and (3) conventions of communication [44]. Differences in *values and meanings* refer to an absence of general agreement on the value of specific responses to particular questions. For example, an artistic response in the Raven's progressive matrices test may be considered superior, by some, when compared to a response that follows a conceptual principle (i.e., the figure that continues the sequence) [45]. Furthermore, identical items do not necessarily have the same meaning in different cultures,

regardless of how appropriate and accurate the translation is. For example, an item referring to the protection of animals may have a different significance in Europe than in a hunting-based society [5, 46].

In some cultures, *modes of knowing* might be a collective rather than an individual endeavor. Many members of collectivistic societies are distressed by testing situations that require individual responses without the participation of the social group. These members perform most activities collectively (e.g., many Amerindian groups), where the community or family often feels a responsibility to contribute, help, and participate in the individual's test.

Conventions of communication are highly culture-dependent. The way questions are asked can be appropriately interpreted in one culture while inappropriately interpreted in another culture. In many societies, it can be inappropriate to answer questions asked by a stranger. Therefore, interpersonal interaction is expected before testing [47]; talking and exchanging ideas before beginning an assessment can be a prerequisite for successful test performance in some Latin cultures; otherwise, testing can be impersonal and culturally disconcerting [5]. On the other hand, too much talking, proximity, and physical touch may be counterproductive for individuals from Anglo Saxon cultures.

Ardila [46] identified the following cultural variables as highly relevant to successful neuropsychological testing:

1. *Patterns of abilities.* Neuropsychological tests measure cognitive abilities that are, in most cases, learned abilities that correlate with the subject's learning opportunities and contextual experiences. Different cultural environments lead to the development of different patterns of abilities.

2. *Cultural values.* Attitudes toward testing vary across cultures and can affect test performance and engagement. Normative performance for a particular assessment tool is obtained by sampling the developer's cultural group members. Moreover, most neuropsychological testing follows psychometric principles shared by a particular psychometric-oriented society or culture but are not necessarily shared by all cultural groups in contemporary testing [8, 44]. For example, (a) One-to-one relationship during testing: There is an examiner and an examinee, and nobody else is expected to help with the test answers, emphasizing individuality. (b) Background authority: The very setup of neuropsychological testing indicates a subordinate relationship (dominance dimension) in which the examiner has and authority based on his/her educational background. In a standard testing situation, the examinee must follow the instructions given by the examiner, and hence, the examiner has the authority. (c) Best performance: The examinee is expected to perform at an optimal level. To do "one's best" may be most significant in a culture highly valuing competition, but not in a less competitive society. (d) Speed in responding: Many neuropsychological tests are timed, and speed with responding is expected. Time is understood differently across different cultures. For many cultural groups, speed tests are improper. The patient may ask, "Do you want me to perform at my best or as fast as I can?" Speed and performance quality may be contradictory as good products result from a slow and careful process.

3. *Familiarity.* Neuropsychological tests include items and stimuli that are not necessarily relevant across cultures. Some items may be unfamiliar for cultural groups other than the sample for which the test was created.

4. Language. Languages differ in phonology, lexicon (semantic field of the words), grammar, pragmatic, and reading systems. These differences may affect cognitive test performance. Therefore, tests created in a particular language must be adapted, to another language based on each culture's idiosyncrasies, not just simply translated word-for-word. This issue might be complicated by the corresponding group's representation (or lack of) among the scientists involved in the instruments' adaptation. Language usage differs according to the cultural (and subcultural) background and strongly correlates with the subject's educational level. Sometimes, test instructions are given in a formal language which may be difficult for individuals with limited education to understand due to limited exposure to this type of language. Another language-related variable that may influence neuropsychological test performance is dual language use (e.g., bilingualism). There are two competing hypotheses related to the association between bilingualism and cognitive assessment: (1) subtractive effect of bilingualism (e.g., when compared to monolinguals, bilinguals show deficiencies in neuropsychological test performance), and (2) additive effect of bilingualism (i.e., bilingualism has a beneficial effect on specific cognitive functions, particularly on those functions in which executive control is involved) [48].

5. *Acculturation.* Changes in culture can result from repeated contact among various societies over time. The modification of an individual's culture because of contact with a different culture is known as acculturation [3, 6]. Four processes have been identified in the acculturation process: *assimilation*—adoption of the dominant culture with corresponding abandonment of one's own cultural identity; *marginalization*—abandonment of one's own cultural identity, without adoption or rejection of the dominant culture; *separation*—maintenance of one's own cultural identity without adopting the dominant culture; *integration*—maintenance of one's own cultural identity and adoption of the dominant culture. Several studies have shown that lower levels of acculturation are significantly associated with lower cognitive test performance in different cultural groups [49–53], explicitly on tests relying on verbal abilities [53, 54]. Test performance is frequently confounded by the individual's gender, level of education, migration status, and language proficiency [53, 55–57].

Influence of Education Level on Cognitive Tests

Formal education, and schooling in general, play a significant role in acquiring general knowledge and training of cognitive abilities, some of which are evaluated in neuropsychological assessments. Further, schooling trains individuals in different learning strategies that may develop positive attitudes toward cognitive testing. However, well-educated individuals do not necessarily possess greater testing-taking abilities than less-educated individuals. Rather, highly educated individuals have the same test-taking abilities as less educated individuals, with the additional advantage of strategy training [58]. Furthermore, individuals with no formal education may develop abilities that educated people do not [59]. Nonetheless, cognitive testing frequently evaluates abilities that well-educated people are trained in, and it is not surprising that they outperform their lower-educated counterparts.

As expected, there is a strong association between educational level and performance on various neuropsychological tests [43, 60–65]. However, this effect is not equivalent across all tests. While some tests are more sensitive to educational variables (e.g., language tests) [65], others are not (e.g., the Wisconsin Card Sorting Test). It is also noteworthy that although the educational level has a substantial relationship with performance on some cognitive tests, it might not necessarily provide an advantage for solving everyday problems.

Additionally, years of education do not have a linear relationship with cognitive test performance; instead, the correlation weakens and then reaches a plateau. Cognitive test scores are significantly lower among individuals with 0 years, as compared to 3 years of education, while the disparity is less prominent among those with 3 years as compared to 6 years of education, and even less so among those with 6 years, as compared to those with 9 years of education, and so forth. Among those with 12 versus 15 years of education, there are virtually no differences in test performance [64]. However, recent work shows that among older adults, further university-based education may improve language processing abilities and working memory [66].

Literacy is suggested to be a better predictor of late-life cognitive status than years of education, especially for minority groups. Educational experiences can be defined by the duration (years of schooling), the degrees attained, or the quality of schooling. The extent of the cognitive benefits of education may better correspond with educational quality indices than with educational accomplishment measures [67]. Early-life educational quality and literacy in late-life explain a substantial portion of race-related disparities in late-life cognitive function [68].

Too often, educational experience and educational level are confounded with cultural factors. In the US, many Hispanic immigrants or African Americans have lower levels of educational attainment, and any differences with mainstream American individuals may be due to lack of schooling rather than to the effect of culture [69]. Differences in test performance between "Anglos" and "Hispanics" (or other cultural or subcultural groups) in the US are easily attributed to cultural variables [8]. However, and most often, differences are simply the result of differences in educational levels.

Level of Education, Cognitive Reserve, and Alzheimer's Disease

Higher education is thought to delay the onset of AD by enhancing cognitive reserve. The cognitive reserve model has been suggested as an explanation for the association between higher education and the lower frequency of AD. Cognitive reserve refers to the ability of the brain to remain functionally resilient in the presence of AD neuropathology. This theory suggests that the brain uses existing "cognitive reserve/reservoirs" to compensate for pathology [70], implying that people with higher levels of education show AD symptoms later than those with less education. Prior research has shown that years of education were associated with a lower risk of AD diagnosis. Larsson et al. [71] examined 24 potential AD risk factors, including smoking, alcohol consumption, and education level, and found that higher educational attainment was significantly associated with decreased risk of developing AD. While higher education levels may delay the onset of cognitive impairment, once cognitive decline occurs, the severity of underlying neuropathology would be expected to be greater in these individuals, and their survival post-AD diagnosis would be expected to be shorter. However, in a systematic review, it was found that only in one study, post-diagnosis survival was shorter among those with higher education levels [2]. Similarly, increase in years of education was associated with slightly earlier reports of symptom onset, but a slower decline in Mini-Mental State Examination (MMSE) scores longitudinally [72]. Another systematic review found those with higher cognitive reserve were more likely to have attended university-level classes [73]. Brain imaging studies have demonstrated an association between brain structure and education, supporting the idea that higher education increases brain reserve. The concept of brain reserve is based on the theory that larger brain volumes, as compared to smaller brain volumes, can better withstand the consequences of brain damage as manifested in clinical symptoms [74]. Liu et al. [74] conducted a longitudinal study to determine whether cortical thickness and brain volume matched with the supposed protective effect against

AD provided by higher education. They found that a greater number of years of education was associated with greater regional cortical thickness. Additionally, specific cortical regions were significantly thinner in AD patients with higher education than those with less education. These findings suggested that AD patients with higher education could cope better with degenerative brain disease than those with less education, as would be predicted in the cognitive reserve model [70, 71]. Similarly, Stern et al. [75] conducted a longitudinal study to determine whether individuals with limited cognitive reserve, measured through educational and occupational attainment, were at higher risk for developing AD than their highly educated counterparts. They found that the lower educational group (i.e., those with fewer than eight years of education) had a two fold increased risk of developing dementia than the more highly educated group. Similarly, those with lower occupational attainment were at 2.25 times higher risk of developing dementia than those with higher occupational attainment. However, they also found that once AD symptoms were observed, patients with high cognitive reserve showed a more rapid rate of cognitive decline than those with lower cognitive reserve [76].

AD pathology progresses before symptoms of cognitive decline appear, more specifically before they can be detected. Individuals with a lower cognitive reserve cannot endure AD pathology without developing overt symptoms as long as individuals with a higher cognitive reserve [70]. Kim et al. [77] explored the potential effects of education on AD pathology, diagnosis, and progression longitudinally. Participants were followed up more than three times to record their Clinical Dementia Rating (CDR) scores and were placed in one of three groups, namely, subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and advanced AD. They found that those with higher educational levels (12 years of education or higher) had slower progression from SCI to MCI than those with lower education levels (fewer than 12 years of education). Table 1 presents details of the studies aimed at analyzing the relevance of the level of education in the diagnosis and progression of Alzheimer's disease.

Anderson et al. [78] assessed whether educational attainment (i.e., years of education) and intelligence have a causal relationship with AD risk using a Mendelian randomization approach. Using existing data from the International Genomics of Alzheimer's Project database, researchers found that intelligence was highly correlated with lowered AD risk and may have mediated the association between education and AD risk. However, when associations between cognitive reserve, measured by performance on tests of verbal learning, non-verbal reasoning, mental agility, and verbal fluency, along with data from studies of functional magnetic resonance imaging (fMRI) and cerebral structure, were examined, educational attainment positively contributed to cognitive function at an older age, even after accounting for overall IQ [79]. In a longitudinal study examining whether cortical thickness and volumes obtained from MRI scans suggested a protective effect of education against AD, participants with higher educational levels were found to have greater regional cortical thickness than those with fewer years of education. Additionally, after participants' cognitive performance (measured using the MMSE and the CDR was matched, cortical areas were significantly thinner in AD patients with higher years of education [74]. These cortical regions included the temporal gyri, inferior and superior parietal gyri, and lateral occipital cortex. These findings suggest that AD patients with higher education were able to compensate cognitively for greater regional brain atrophy, supporting the cognitive reserve model [70, 71].

Nicolas et al. [80] aimed to use education (mesured in years) as a proxy for cognitive reserve related to AD clinical symptoms, cerebral structural, and metabolic changes. Brain metabolism and volume were evaluated using positron emission tomography (PET) and MRI scans and analyzed in two diagnostic (AD and MCI patients) and two education groups (i.e., those with 16 years or more of education and fewer than 16 years of education). AD patients had decreased basal forebrain and hippocampal volume and metabolism compared to cognitively normal controls. Among participants with a high level of education, those with MCI showed higher basal forebrain and hippocampal metabolism than AD participants, suggesting that the compensatory effect of education is seen at the MCI level but might be lost in later pathological stages [80].

More recently, bilingualism has been identified as a potential contributor to the cognitive/brain reserve in elderly individuals. Seemingly, bilingualism delays the onset of symptoms associated with neurodegeneration by up to 5 years [81–84]. Interestingly, bilingual/multilingual individuals who actively used two or more languages could tolerate more significant amounts of neurodegeneration than monolinguals without obvious cognitive impairments [85]. The idea is that the habitual use of two languages requires extensive and continual cognitive control mechanisms (i.e., repeated activation of neural network connections). Engaging in constant cognitive control increases the bilingual's inhibitory and switching mechanisms, resulting in advantages in other specific cognitive domains [48, 86].

Brain Reserve. Brain imaging studies have demonstrated an association between brain structure and education, supporting the idea that education increases brain adaptations, leading to differential behavioral expression in brain injury cases. Brain reserve theory suggests that larger brains can better withstand brain damage without presenting clinical symptoms than smaller ones [74]. Negash et al. [87] provided support to the brain reserve model by comparing AD

Table 1 Studies aimed at analyzing the relevance of level of education in the diagnosis and progression of Alzheimer's disease

Reference	Sample size	Ethnic/racial groups if included	Definition of each ethnic/racial group if included	Age (Mean and SD)	Education (Mean and SD)	Gender	Country where the study was performed	Cognitive test(s) used to diagnose AD, include language in which participants were tested	Finding in reference to influence of level of education and AD
Paradise et al. (2008) [2]	22 articles reviewed	NA	NA	NA	NA	NA	NA	17 studies used NINCDS-ADRDA; 1 study used DSM-IV; 1 study used DSM-III and Hachinski Index; 2 studies used DSM-IIIR; 1 study used pathological conformation on autopsy	Only 3 of the 22 reviewed studies showed a significant association between higher education and decreased survival of AD
Thow et al. (2018) [66]	344	NR	NR	59.59 ± 6.77	14.28 ± 2.69	Male = 30.8% Female = 69.2%	NR	DRS-2; HADS; LSNS; Medical health Status Questionnaire; LMII, LMII; RAVLT; PAL; Digit Span and Letter-Number Sequencing; SSP; SWM; TMT B; Stroop C 34; RVP A'; verbal fluency; BNT; tested in English	Results suggest significant language processing capacity longitudinally but no changes in episodic memory, working memory, and cognitive functioning
Larsson et al. (2017) [71]	54,162	NR; Individuals of European ancestry	NR	NR	NR	NR	International data from International Genomics Alzheimer's Project (IGAP)	NINCDS-ADRDA (criteria for possible or probable AD): NINCDS-ADRDA with DSM-IV criteria: (n =) CDR (greater than or equal to 1) CERAD (criteria for definite AD); language of examination unreported	Bonferroni method: Odds ratio of .89 per year of education completed. .74 per unit increase in log odds of completed college/university. Higher educational attainment is associated with a reduced risk of AD
Fritsch et al. (2001) [72]	258	NR	NR	73.4 ± 7.8	12.8 ± 3.1	Male = 38.4% Female = 61.6%	USA	Neuropsychological, laboratory, neurological exams; NINCDS-ADRDA criteria; CDR; MMSE	More years of education was associated with slightly earlier reports of symptom onset and slower rate of cognitive decline on MMSE

Table 1 (continued)

Reference	Sample size	Ethnic/racial groups if included	Definition of each ethnic/racial group if included	Age (Mean and SD)	Education (Mean and SD)	Gender	Country where the study was performed	Cognitive test(s) used to diagnose AD, include language in which participants were tested	Finding in reference to influence of level of education and AD
Liu et al. (2012) [74]	355	NR; individuals living in European countries	NR	AD patients (50% female; 74 ± 6 years) MCI patients (65% female; 75 ± 6 years) Healthy controls (55% female; 73 ± 6 years)	AD patients: (8 ±4) MCI patients: (9 ± 4) Healthy controls: (11 ± 5)	AD patients: (50% female) MCI patients: (65% female) Healthy controls: (55% female)	Six medical centers across Europe: Finland, Italy, Greece, UK, Poland, France	CDR scale MMSE NINCDS-ADRDA criteria	Healthy controls with more education have increased cortical thickness, leading to increased brain reserve. increasing patients coping to AD pathology AD patients with more education had thinner regional cortices than AD patients with less education
Stern et al. (1994) [75]	595	NR	NR	74.0 ± 7.6	9.6 ± 4.7	Male = 28% Female = 72%	NR	Neuropsychological battery (including memory, orientation, language, and construction tests); NINCDS-ADRDA criteria	Suggests that increased years of education may reduce the risk of AD
Stern et al. (1995) [76]	246	NR	NR	83.9 ± 7.5	6.9 ± 4.4	Male = 24.8% Female = 75.2%	USA	Neuropsychological test battery; standardized medical/neurological evaluation, assessments of functional capacity and mood; NINCAS-ADCRA rating criteria; Conducted in English or Spanish	Patients with more education has increased mortality; AD pathology is more advanced at diagnosis, providing support to the idea that education provides a reserve against clinical symptoms of AD
Kim et al. (2020) [77]	565	Asian	NR	Mean and SD NR(SCI; median = 69 (64–65) (AMCI; median = 73 (65–77)) (AD; median = 74 (68–80))	Mean and SD NR; (SCI; median = 12 (6–16 range)) (AMCI; median = 12 (6.5–16)) (AD; median = 9 (6–12))	Male = 33.1% Female = 66.9%	Korea	CDR-SB; tested in Korean	CDR-SB progression from SCI to AMCI was faster in the lower education group; this trend became insignificant from AMCI to AD

Table 1 (continued)

Reference	Sample size	Ethnic/racial groups if included	Definition of each ethnic/racial group if included	Age (Mean and SD)	Education (Mean and SD)	Gender	Country where the study was performed	Cognitive test(s) used to diagnose AD, include language in which participants were tested	Finding in reference to influence of level of education and AD
Anderson et al. (2020) [78]	54,162	Individuals of European ancestry	NR	NR	Mean NR SD = 3.6 years	NR	International data from International Genomics Alzheimer's Project (IGAP)	NINCDS-ADRDA (criteria for possible or probable AD): NINCDS-ADRDA with DSM-IV criteria: (*n* =) CDR (greater than or equal to 1) CERAD (criteria for definite AD); language of examination unreported	Increase in years of education may aid in decreasing AD risk; causal effect of years of education is likely mediated by intelligence scores
Nicolas et al. (2020) [80]	84	NR	NR	HC = 73.9 ±7.1 SMC = 70.8 ±6.6 MCI = 73.3 ±7.4 AD = 75.6 ±8.0	HC = 16.7 ± 2.8 SMC = 14.9 ±3.2 MCI = 15.5 ±2.3 AD = 16.2 ±2.1	Male = 61.9% Female = 38.1%	NR	Weschler Scale Logical Memory II CDR NINCDS-ADRDA rating criteria	Demonstrated education modulates the relationship between clinical symptoms and cerebral structures (basal forebrain; hippocampus) affected by AD
Cho et al. (2015) [89]	36	Asian	NR	70.2 ± 8.0	11.0 ± 4.6	Male = 38.9% Female = 61.1%;	South Korea	DSM-IV NINCDS-ADRDA criteria CDR scale Seoul Neuropsychological Screening Battery (SNSB) MMSE	AD patients with more years of education accelerates cortical atrophy in AD patients longitudinally, compared to AD patients with less years of education

AD Alzheimer's Disease, *NINCDS-ADRDA* National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders 5, *DSM-III* Diagnostic and Statistical Manual of Mental Disorders 3, *DRS-2* Dementia Rating Scale 2, *HADS* Hospital Anxiety and Depression Scale, *LSNS* Lubben Social Network Scale, *RAVLT* Rey Auditory Verbal Learning Test, *PAL* Physical Activity Level, *SSP* Swedish Scales of Personality, *SWM* Spatial Working Memory tests, *TMT B* Trail Making Task Version B, *RVP A* Rapid Visual Information Processing, *COWAT* Controlled Word Association test, *BNT* Boston Naming Task, *CDR* Clinical Dementia Rating Scale, *CERAD* Consortium to Establish a Registry for Alzheimer's Disease, *MMSE* Mini-Mental State Examination, *CDR-SB* Clinical Dementia Rating Scale Sum of Boxes, *IGAP* International Genomics of Alzheimer's Project, *WSLM II* Weschler Scale Logical Memory II, *SNSB* Seoul Neuropsychological Screening Battery, *SCI* Subtle Cognitive Impairment, *AMCI* Amnestic Mild Cognitive Impairment

participants with evidence of AD pathology (i.e., cerebrospinal fluid beta-amyloid and temporal lobe atrophy), who were categorized by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) score as either AD dementia (CDR-SB > 1) or AD resilient (CDR-SB ≤ 0.5). Results identified education and intracranial volume (ICV) as significant factors associated with resilience; the resilient group had more years of education and a larger brain size than the dementia group. However, in the final regression model, ICV was maintained as the highly significant factor associated with resilience, suggesting that larger cranial size is associated with resilience even with lower education. Higher levels of education and larger hippocampi were significant predictors of confrontation naming abilities and executive function skills, mainly in cognitively normal participants [88]. In AD, participants with more years of education experienced quicker cortical atrophy (in 5 years) than those with fewer years of education [89].

Alzheimer's Disease and Cultural Group Disparities

Ethnoracial Disparities in AD Research

Despite the fact that AD has become one of the most prevalent diseases, ethnoracial disparities in the prevalence, genetics, age of onset, and disease progression have not been thoroughly incorporated into current research and assessments tools. For example, US Latino/Hispanic and Black populations are disproportionately affected by AD, but tend to be the most underrepresented groups in empirical and clinical research [12, 90, 91], and in some cases, even after controlling for sociodemographic, physical, and mental health characteristics [92]. However, the mortality rate associated with AD for Whites, Asians, and American Indians seems to be substantially higher than for African American and Latino patients [93]. These minority groups do not have the same access to healthcare and early screening assessments, nor is educational attainment as high in these groups compared to non-Hispanic Whites [91]. Refer to Table 2 for summarized description of studies discussed in this section that analyze ethnic/racial disparities in AD.

While AD research aims for diversity in research samples, systemic barriers remain, leading to the underrepresentation of certain ethnoracial minority groups. Ethnoracial factors are reported to influence cognitive reserve, neuropsychological performance, biological markers (both neuroimaging and biofluid), immunity, and overall neurodegeneration in AD [16]. For example, various ethnoracial factors (e.g., language, education, culture) modulated performance on cognitive functioning tests, contributing to the lack of normative data across these ethnoracial groups [16]. If more is known about the interplay between identified social determinants of health, co-morbidities, and genetic factors in AD and ethnoracial disparities, the sensitivity of assessments can be improved for minority ethnoracial groups.

Ethnoracial Disparities Across Alzheimer's Disease Presentation

In 2019, it was reported in a population-based study of individuals 65 years of age or older 3.2 million Medicare Fee-for-Service (FFS) beneficiaries (11.2% of the sample of 28 million) and 5 million people from the US Census (10.9%) carried an AD diagnosis in 2014 [90]. AD diagnoses were more prevalent in women than men for both sample populations, and the frequency of AD diagnoses increased with standard age groups: 3.6% for those between 65 and 74 years of age, 13.6% for 75 and 84 years, and 34.6% for individuals 85 years of age and older. Matthews et al. [90] outlined the prevalence of AD by ethnoracial subgroup for both the beneficiary and the Census populations listed here: (a) Medicare Beneficiaries: Blacks (14.7%), Hispanics (12.9%), non-Hispanic Whites (11.3%), American Indian or Native Alaskan (10.5%), and Asian or Pacific Islanders (10.1%); (b) Census: Blacks (13.8%), Hispanics (12.2%), those belonging to two or more ethnoracial groups (11.5%), non-Hispanic Whites (10.3%), American Indian or Native Alaskan (9.1%), and Asian or Pacific Islanders (8.4%). Overall, for individuals 85 years or older, more than 43% of Blacks and 40% of Hispanics bear the most burden of AD and related disorders [90]. With the prevalence of AD and related disorders being substantially higher for some ethnoracial groups, these groups with higher prevalence also tend to be the most underrepresented in research [12, 90, 91]. The reasons behind the disparities in the outcomes of AD research (e.g., prevalence, incidence, onset, progression) remains largely unanswered.

Hispanics/Latinos seem to have an earlier age of onset and faster progression when compared to other ethnoracial groups [91]. Vega et al. [91] posit that the disparity in income and socioeconomic status, being lower for Hispanics/Latinos compared to non-Hispanic Whites, is a major contributor to the differences in AD presentation, alongside education and English proficiency. Acculturation also adds to the complexity of factors influencing cognitive decline in Hispanic/Latino older adults. Although the likelihood of cognitive impairment [56, 94] and risk for dementia [95] increase in older adults with lower levels of acculturation, these associations have not always been found [96]. Lamar et al. [97] used a more comprehensive acculturation approach by considering contextual social factors and found higher acculturation was positively associated with the level, but not the rate of change in global cognition, semantic memory, and perceptual speed

Table 2 Studies aimed to analyze ethnic/racial disparities in AD

Reference	Sample size	Ethnic/racial groups	Definition of each ethnic/racial group	Age per ethnic group (mean and SD)	Education per ethnic group (mean and SD)	Gender per ethnic group	Country where the study was performed	Cognitive test(s) used to diagnose AD, include language in which participants were tested	Finding in reference to ethnicity or race
Novak et al. (2020) [92]	31,516	W, AA, L	Self-identified	ADRD+: W 81.02 AA 80.31 L 79.77 ADRD-: W 74.21 AA 73.26 L 73.19	[Less than high school] ADRD+*: W .291 AA .572 L .843 ADRD-: W .174 AA .402 L .631 [High school] ADRD+: W .708 AA .427 L .156 ADRD-: W .825 AA .597 L .358	ADRD+*: W .627 female AA .685 L .616 ADRD-: W .553 AA .611 L .581	USA	Medical Expenditure Panel Survey (English)	Serious psychological distress was significantly greatest for AA and L with ADRD. Education was used as a covariate in regression analysis
Mehta et al. (2008) [93]	30,916	W, AA, L, As, AI	Self-identified	W 77.6(6.4) AA 78.1(6.7) L 77.0(6.6) As 79.3(6.2) AI 78.2(7.0)	W 13.0(3.5) AA 10.7(3.9) L 7.4(4.8) As 11.3(5.6) AI 11.1(3.5)	W 63% women AA 74% L 72% As 67% AI 68%	US (NACC–ADCs)	NINCDS-ADRDA	Even with education included as a control, AA and L patients had lower mortality from AD than W patients; W faired similarly to As and AI

Table 2 (continued)

Reference	Sample size	Ethnic/racial groups	Definition of each ethnic/racial group	Age per ethnic group (mean and SD)	Education per ethnic group (mean and SD)	Gender per ethnic group	Country where the study was performed	Cognitive test(s) used to diagnose AD, include language in which participants were tested	Finding in reference to ethnicity or race
Camacho-Mercado et al. (2016) [98]	485	San Juan, Metro Manati, North-west/central)	Regional	Metro 79.3 (6.9) North-west/central 75.8 (7.16)	Metro 13.0 (3.4) North-west/central 12.0 (2.8)	Metro 66% female North-west/central 63%	Puerto Rico	MMSE	There were significant regional differences between age-of-diagnosis and years of education, however, both regions had comparable MMSE scores and rate of cognitive decline. Caribbean Hispanics showed the worst presentation and progression even when education was controlled for
Tang et al. (2001) [99]	1788	AA, CaH, W	Self-identified	AA 75.8 (6.2) CaH 74.9 (5.8) W 76.9 (7.2)	AA 9.7 (3.5) CaH 6.0 (4.1) W 11.6 (4.1)	AA 71% women CaH 68% W 65%	US (Medicare beneficiaries)	MMSE, BNT, COWAT, Category Naming, Complex Ideational Material and Phrase Repetition subtests of the BDAE, Abstract Reasoning and Similarities (WAIS-R), MDRS, Rosen Drawing Test, BVRT and SRT (English or Spanish)	Incidence was two-folds higher for AA and CaH compared to W. Adjusting for education and other potential covariates did not impact the results
Bailey et al. (2020) [101]	9239	NHC, AA, H	Informant report	TBI + : NHC 68.53 (9.5) AA 69.11 (8.0) HL 67.63 (9.8) TBI-: NHC 70.83 (10.3) AA 72.48 (8.6) HL 70.11 (9.4)	TBI + : NHC 15.25 (3.1) AA 13.1 (3.76) HL 11.25 (5.18) TBI-: NHC 14.97 (3.04) AA 12.7 (3.53) HL 9.58 (4.93)	TBI + : NHC 455 males AA 28 HL 32 TBI-: NHC (3245) AA (353) HL (253)	USA (NACC UDS)	NINCDS-ADRDA (English)	History of TBI with LOC resulted in 2.3 years earlier onset for NHC and 3.4 years earlier for AA. HL females with history of TBI with LOC had 5.8 years earlier onset. Education was not included as a factor

Table 2 (continued)

Reference	Sample size	Ethnic/racial groups	Definition of each ethnic/racial group	Age per ethnic group (mean and SD)	Education per ethnic group (mean and SD)	Gender per ethnic group	Country where the study was performed	Cognitive test(s) used to diagnose AD, include language in which participants were tested	Finding in reference to ethnicity or race
Rajan et al. (2019) [102]	2794	EA, AA	Self-identified	EA 77.0 (.32) AA 75.6 (.25)	EA 14.4 (.15) AA 11.6 (.15)	EA 740 females AA 970	USA (Census and Chicago Health and Aging Population)	NINCDS-ADRDA (English)	Prevalence and incidence in AA were twice that of EA. Education was added into regression model slightly increased prevalence (nonsig.) and resulted in no changes to incidence
Barnes et al. (2005) [104]	452	AA, nAA	Self-identified	AA 79.0 (7.06) nAA 78.91 (8.67)	AA 10.16 (3.92) nAA 12.41 (3.22)	AA 73.60% female nAA 66.79%	USA	MMSE, BNT, Body Part Identification, Figural Recognition, Digit Span Backwards, Category Fluency, Standard Progressive Matrices, Logical Memory I-A and II-a	AA have lower global cognition at baseline, but a slower decline associated with AD compared to nAA. Even when age, gender, and education were held constant
Schwartz et al. (2004) [106]	1140	W, AA	Self-identified	50–70-year-olds	(Sample) 13.5% less than high school, 38.5% high school equivalent, 48% some college and above	(Sample) 391 men 749 women	USA (Baltimore Memory Study)	BNT, Raven's Colored Progressive Matrices, Rey Complex Figure copy, RAVLT, Stroop test, TMT A & B, Symbol Digit Paired Associate Learning, Rey Complex Figure delayed recall, finger tapping, Rey complex figure copy and delayed recall, Simple RT, and Letter and category fluency	Model 1: AA performed worse on cognitive tests compared to W (controlled for age, sex, and technician). Model 2: Adjusted for household income, household assets, educational attainment, and occupation status and AA performance declined significantly by 25.8% compared to W. Lowest educational attainment was associated with the worst performance

Table 2 (continued)

Reference	Sample size	Ethnic/racial groups	Definition of each ethnic/racial group	Age per ethnic group (mean and SD)	Education per ethnic group (mean and SD)	Gender per ethnic group	Country where the study was performed	Cognitive test(s) used to diagnose AD, include language in which participants were tested	Finding in reference to ethnicity or race
Chow et al. (2002) [108]	430	CH, CA	Informant report	Chinese: Kaohsiung 73.1 (8.7) Taipei 74.8 (6.9) Hong Kong 78.0 (8.0) Caucasian: Los Angeles 77.4 (7.5)	Chinese: Kaohsiung 6 (5) Taipei 10 (5) Hong Kong 2 (3) Caucasian: Los Angeles 13 (3)	Chinese: Kaohsiung 55% women Taipei 55% Hong Kong 87% Caucasian: Los Angeles 72%	Kaohsiung, Taiwan; Taipei, Taiwan; Hong Kong, China; and Los Angeles, California	NPI NINCDS-ADRDA (Chinese and English)	Chinese samples had higher prevalence of AD compared to the Caucasian sample
Bowirrat et al. (2002) [113]	441	Arab	Self-identified	ADRC into DAT 76.3 (2) ADRC not into DAT 72.4 (8.3)	ADRC into DAT 66.7%** ADRC not into DAT 44%**	ADRC into DAT 37.5% male ADRC not into DAT 41.7%	Northern Israel	DSM-IV criteria	The Wadi Ara population has a high prevalence of AD and lowest Apo E-e4 allele frequency compared to Europe and North America

W White, *AA* African American, *L* Latino, *ADRD/DAT* age-related cognitive decline/dementia of Alzheimer's type, *US* United States, *As* Asian, *AI* American Indian, *NACC USD* National Alzheimer's Coordinating Center uniform dataset, *NINCDS-ADRDA* National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, *ADRD* Alzheimer's Disease and Related Dementias/Disorders, *MMSE* Mini-Mental State Examination, *CaH* Caribbean Hispanic, *BNT* Boston Naming Task, *COWAT* Controlled Word Association test, *BDAE* Boston Diagnostic Aphasia Evaluation, *WAIS-R* Wechsler Adult Intelligence Scale–Revised, *MDRS* Mattis Dementia Rating Scale, *BVRT* Benton Visual Retention Test, *SRT* Selective Reminding Test, *NHC* non-Hispanic Caucasian, *H* Hispanic, *TBI* Traumatic Brain Injury (+/− with or without loss of consciousness = LOC), *EA* European Americans, *nAA* non-African American, *RAVLT* Rey Auditory Verbal Learning Test, *TMT* Trail Making Task, *CH* Chinese, *CA* Caucasian, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders 5

*Responses were coded dichotomously (0 or 1). Scoring values nor SDs were provided

**Values represent the percentage of males that lack education. Authors did not elaborate on how this was computed

among non-demented older Latinos. In contrast, higher levels of self-reported experiences of discrimination and social isolation and smaller social networks were significant predictors of lower baseline levels of global cognition, episodic and working memory, slower perceptual speed, and faster rates of decline in visuospatial abilities [97]. Further complications arise in the validity of predictive models of cognitive decline in Hispanic/Latino older adults when regional differences are examined within the same ethnic group [98, 99]. Significant regional differences emerged between Metro vs. Northwest/Central Puerto Ricans for the age at diagnosis and years of education, although MMSE scores and rate of decline remained comparable between the two regions [87]. Additionally, the incidence is nearly two-fold for Caribbean Hispanics and African Americans compared to Whites, even when education and other demographics are controlled [99]. Similarly, Gonzalez et al. [100] found variations in the prevalence of MCI between Hispanic/Latinos living in the United States of America (USA), depending on the individual background (Central American, Cuban, Dominican, Mexican, Puerto Rican, and South American). Results demonstrated the highest MCI prevalence among Puerto Rican participants and lowest in Cubans.

The prevalence and incidence of AD among African Americans were evaluated in a more focused population study conducted between 1994 and 2012. It was found that the overall prevalence and incidence (14.2% and 2.3%, respectively) were twofold greater among African Americans than European Americans with relatively little variation over the period of the study within each ethnoracial group [101]. When education was entered into their regression model, the prevalence of AD increased from 14.6 to 14.7%, while the incidence was unimpacted [102]. Furthermore, African Americans tended to have lower baseline global cognition [103], perform more poorly on cognitive tests used in the assessment of AD, have a higher prevalence of apolipoprotein E (APOE) e4 allele [103], and have a slower rate of decline associated with AD [104] compared to non-Hispanic Whites.

A large population-based study followed individuals 65 years and older for up to 18 years (64% black, 36% white) and assessed cognitive performance, cognitive decline, and AD incidence (age- and sex-adjusted) [105]. Results indicate that black participants performed worse on neuropsychological testing at baseline and had higher prevalence and incidence risk for AD than white participants, suggesting differences at the cognitive level. Furthermore, when household income, household assets, educational attainment, and occupational status were considered in a predictive prevalence model for AD, African American cognitive performance declined by 25.8% compared to Whites [106]. Nevertheless, similar to Hispanic populations, African Americans remain disproportionately affected by AD, yet they remain vastly underrepresented in studies examining ethnoracial influence on AD and related disorders.

Coverage of the ethnoracial influence on AD among Asian American, Native Hawaiian, and Pacific Islander populations is also limited. One review covers multiple domains, such as prevalence, risk factors (e.g., sociodemographic, physiological, and genetic variables), and clinical functioning in AD among Asian Americans, Native Hawaiians, and Pacific Islanders [107]. Generally, authors report that knowledge of the disease among the public in these ethnoracial groups is deficient, and seeking treatment for cognitive decline is considered stigmatizing [107].

Cross-cultural studies that transcend geographical barriers, while still needed, are even scanter. An influential report [108] compared three Chinese samples (residing in Taiwan and China) to a Caucasian sample (Los Angeles, California) and found that the Chinese samples had a significantly higher prevalence of AD, even when educational attainment was factored in. However, lower AD rates have been reported in Eastern populations compared to Western regions [109]. In a 3-year longitudinal study, Xu et al. [110] found that Chinese MCI participants were 1.7 times less likely to progress to AD than American MCI participants. Chinese participants with MCI were 2.3 times more likely to be diagnosed with vascular dementia than their American counterparts. Furthermore, cross-cultural differences in categorical memory errors have been reported in normal individuals from Eastern and Western societies [111]. For example, Gutchess and Boduroglu [112] reported that Americans make more categorical memory intrusions than Turks, even after correcting for age. Although older Turks were found to have an increased categorical error rate as compared to younger Turks, older Turks still had fewer errors compared to older Americans.

Israeli and Arab populations also remain understudied in AD research. Bowirrat et al. [113] reported the Wadi Arab population in Israel has an unusually high prevalence of AD compared to Europe and North America, yet a relatively low APOE e4 allele frequency has been found in this population. A high level of inbreeding in this population highlights the likelihood of other genetic factors which may have influenced the high prevalence of AD. Additional reports show a high association between education and prevalence of mild cognitive impairment and dementia among Israeli Arabs [114]. While illiteracy rates among Israeli Arabs are high, the relationship to cognitive performance on AD screenings in this group is highly complex and understudied. They attribute some of these complexities to potential cultural and socioeconomic influences, including low AD-related knowledge and limited access to resources among this population.

AD is understudied across multiple minority ethnoracial groups, but effects indicate that subpopulations are differentially affected in terms of disease prevalence, incidence,

onset, and progression. The next step is to examine how these groups are practically differentially affected by the AD research disparities.

Alzheimer's Disease Presentation Between Different Native Languages

Participants' spoken languages have characterized AD samples (e.g., Spanish speakers vs. English speakers), which contextualizes findings regarding the role that culture and language play in AD risk, incidence, prevalence, and influencing performance on neuropsychological tests. A study [115] comparing Spanish- and English-speaking AD patients on a neuropsychological battery and a functional assessment found group differences in functional assessment based on various aspects of the neuropsychological battery. For the whole sample, ethnicity predicted performance for only writing a check (higher for English-speakers than Spanish-speakers). The same authors [116] later examined digit span neuropsychological performance on amnestic MCI patients and clinically normal individuals in Spanish- and English-speakers. They reported that both cognitively normal and AD English-speakers performed better on all digit span aspects (i.e., forward, backward, raw score) compared to Spanish speakers with no differences in two-digit chunking. These authors [116] suggest the difference lies behind the strategy employed by the Spanish-speaking group, stemming from a potentially sizeable cultural bias. However, culture/language significantly predicted digit span scores even after controlling for age, education, fluid memory score, and language syllable-length differences indicating that chunking is less impacted by cultural bias [116]. Furthermore, some commonly used AD assessments are even less susceptible to cultural bias, like the Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L) [117]. While culture/language differences do not always impact the metrics used to assess functional decline associated with AD, but that is not to say that differences due to language are negligible. For instance, more literature is emerging that examines the prevalence and incidence of AD in more ethnically diverse populations of Arabic-speakers [118], and there is an increased urgency for understanding how healthy Arabic populations fair in different cognitive assessments, for example, verbal fluency, to provide a better understanding of atypical aging in this population [119].

Studies comparing different languages and AD incidence and prevalence are scarce outside of alphabetic languages. In a study comparing English- to Chinese-speaking AD patients on a number transcoding task [120], Chinese-speakers had more intrusions in transcoding numbers than the English-speakers with no meaningful differences in syntactic errors, indicating that the difference is not due to differences in executive function among Chinese- and English-speaking AD patients [120]. Overall, while comparisons in the incidence and prevalence of AD between speakers of different languages indicate important socio-ethnic influences across cultures, more research is needed to fully understand how AD presentation differs between speakers of different languages.

Alzheimer's Disease as a Function of Country of Origin

The prevalence of dementia, particularly AD, is increasing rapidly in both developing and developed countries, but its prevalence varies considerably worldwide. This may be attributed to the lack of methodological consistency among studies, comprising diagnostic criteria and different mean population ages [121]. However, even after considering these potential sources of bias, differences in age-adjusted dementia prevalence still exist among regions of the world [122]. In Latin America, the prevalence of dementia is 7.3%, higher than anticipated due to the combination of low average educational attainment and high vascular risk profile [123] The prevalence of dementia in Europe is 6.4% (all causes), 4.4% for AD, and 1.6% for VaD [14]. [124]. However, the average incidence rates per 1000 person-years reported in Italy were 12.47 for overall dementia, 6.55 for AD, and 3.30 for vascular dementia [124]. They found that women hold a high probability of developing AD, whereas men carry a high risk of developing VaD [125, 126]. Additionally, the predominance of specific genetic variants in different countries underscores the importance of studying diverse populations [127, 128]. The predominance of genetic variants in certain countries and not in others emphasize the importance of analyzing these factors across the world to understand AD risk better and improve patient outcomes. While it is evident that economic discrepancies between countries affect all levels of care, from risk assessment and prevention to diagnosis and treatment, there are also significant differences between Latin American countries regarding the availability of trained practitioners, access to and timely diagnosis, and possibilities of treatment. Overall, low educational background and other socioeconomic factors have been associated with a high risk of obesity, sedentarism, diabetes, hypertension, dyslipidemia, and metabolic syndrome, all of which also raise the risk of vascular dementia and AD in different countries [121]. There are considerable challenges to overcome before developing countries can advance and collaborate with the international research community [121, 129].

Biomarkers and Ethnicity in Alzheimer's Disease

AD biomarkers interact with ethnicity and race, therefore this section focuses mainly on studies that compare two or more races/ethnicities. The literature often distinguishes race as a

biological factor and ethnicity as a social factor, more related to culture than genotype. There are two possible scenarios regarding differences in clinical onset and progression of AD between races. First, if differences are not reflected in biomarkers between ethnoracial groups, any differences in cognitive diagnoses can be attributed to biased results from diagnostic tests and procedures. Lack of biologically based differences between ethnicities/races would signal flaws in tests that might have been designed for English-speaking populations of European descent, thereby yielding biased results when the same norms are applied to participants of different races/ethnicities [130]. Second, in the case in which racial/ethnic differences in diagnosis are also reflected in biomarkers, explanations involving socioeconomic status, educational attainment, diet, and other environmental factors may be used. In either situation, we are far from understanding ethnic/race variation in AD in the current state of aging science. Science is just not advancing fast enough to compensate for the increase in aging populations across all races and ethnicities, but there is an underrepresentation of minorities in research [131, 132].

A substantial limitation arises when discussing biomarkers and their interaction with ethnic and racial factors: most studies comparing multiethnic samples are conducted in well-developed countries with populations predominantly of European origins (i.e., US, Canada, and European countries), including minorities and immigrants or their descendants who live in drastically different socioeconomic situations from the majority groups. While being consistently underrepresented in research, African Americans, Hispanics, Asian Americans, and Native Americans in the USA have a higher prevalence and disease burden than White Americans [3]. When considering immigration as a factor, other issues related to language, bilingualism, acculturation, and immigration contribute to cognitive [133] and brain [134] reserves. Some of these variables may promote cognitive resilience in the presence of neurodegeneration. In contrast, other health outcomes, such as high blood pressure and diabetes, are more prevalent in the African American and Hispanic populations, heightening the risk of developing AD in those groups [135]. Table 3 lists studies in which AD biomarkers have been studied across cultural and ethnic/racial groups.

Genetic Biomarkers

The most salient genetic factor associated with AD is the Apolipoprotein epsilon 4 gene (APOE-ε4), which has been associated with increased susceptibility to developing AD in approximately 50% of patients [136] and increases the risk across ethnicities (Caucasian, African American, Hispanic, and Japanese) [137]. There are three forms (alleles) of the APOE gene (ε2, ε3, or ε4) and consequently, six possible combinations (ε2/ε2, ε2/ 3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4). Carriers of the ε4 allele have an increased risk of developing AD. While carriers of having the ε2 allele have a decreased risk [138]. The prevalence of the higher-risk ε4 allele seems to differ across ethnicities, with a higher frequency African Americans, as compared to Caucasians, who in turn have higher ε4 frequencies than in Asian populations, in Hispanics [3, 103, 140], Choctaw Native Americans [141], and Native Americans from South America (Amerindians) [142]. Low frequencies of the ε4 allele have also been found in Southern European populations [143]. A high frequency of the ApoE-ε4 allele has also been found among Dominicans, Puerto Ricans, and Cubans, as compared to Central Americans, Mexicans, and South Americans, who had relatively low frequencies [127], while dominantly inherited AD (DIAD) was found to have the highest prevalence in Colombia, Puerto Rico, and Mexico [128].

This allele is more strongly associated with AD risk in Japanese populations [137, 139] while Farrer et al. [137] found a weak association between the ε4 allele and AD risk in African Americans, though sample sizes and unequal group sizes were widespread across studies between different ethnic groups. This heterogeneity remains today and indicates the need for further research with larger, more diverse samples [3]. Choctaw Native Americans also have a lower frequency of the tau H2 haplotype than Whites [141]. These findings suggest that specific ancestries might lower the probabilities of developing AD.

Another allele has been found to correlate with the age of onset of AD and performance in neuropsychological tests, the deoxythymidine-homopolymer (poly-T, rs10524523) in intron 6 of the TOMM40 gene is adjacent to APOE on chromosome 19. In Caucasians, the three predominant alleles at this locus are short (S), long (L), or very long (VL). On an APOE ε3/3 background, the S/VL and VL/VL genotypes are more protective than S/S [144]. The co-occurrence of the different APOE and TOMM40 alleles seems to differ across ethnicities, highlighting the importance of investigating worldwide populations. For instance, Whites presented a higher co-occurrence of the L with the ε4 [145, 146], and VL and S with the ε3 alleles, with Hispanics presenting a similar distribution [145]. On the other hand, African Americans presented the S and the ε4 linkage more often [145, 146]. In addition, compared to Whites, African-Americans with the VL genotype presented a higher frequency of the ε4 allele. These findings suggest the relationship between genotype and phenotype as expressed under the influence of sociocultural and other environmental factors is complex and requires extensive research, including more diverse samples and controlling for said factors.

Table 3 Studies aimed to analyze biomarkers and ethnicity in Alzheimer's disease

Reference	Country where the study was performed	Testing language	Total sample size	Ethnic/racial groups	Ethnic/racial group size	Mean age (SD)	Mean years of education (SD)	Gender distribution	Biomarkers	Cognitive test(s) used in diagnosis	Main findings
Burke et al. (2018) [19]	USA	En or Sp	165	NHW and H	NHW = 90	76.86 (6.35)	14.2 (3.01)	F = 54.67%	HV and atrophy	CDR and FOME	Higher atrophy in NHW in than in H. Smaller HV in NHW than in H
					H = 75	74.06 (5.88)	12.94 (3.93)	F = 63.33%			
Duara et al. (2019) [132]	USA	En and Sp	159	H or NH regardless of race	H (n = 94)	71.1 (7.4)	14.6 (3.3)	F = 63; M = 31	SUVR; Aß + or Aß-, and APOE ε4 + or APOE ε4 -	Hopkins Verbal Learning Test-Revised (HVLT-R), Logical Memory delay recall, Category Fluency, Block Design subtest of the WAIS-IV, Trail Making Test parts A and B and MMSE	No significant differences between ethnic groups Higher SUVRs among NH than H who were APOE ε4 positive, but lower among NH than H who were not
					NH (n = 65)	73 (7.3)	16.4 (3.2)	F = 30; M = 35			
Howell et al. (2017) [140]	USA	En	135	AA and C	AA (n = 65)	9.1 (7.4)	16.1 (2.8)	F = 36; M = 29	Aβ, p-tau181, t-tau and APOE ε4, NfL, and HV	Consensus criteria and CDR	ε4 allele more common in AA than EA AA had lower CSF levels of p-tau181, t-tau and Aβ40 than EA, No differences in Aβ42 levels Lower HV in AA with cognitive impairment and family history of dementia AA had higher levels of NfL when CN but not when CI
					C (n = 70)	70.8 (7.7)	16.4 (2.7)	F = 41; M = 29			
Henderson et al. (2002) [141]	USA	NR	626	Choctaw NA (CNA) and C	APOE ε4: CNA = 172 C = 690 TAU: CNA = 131 C = 495	NR	NR	NR	APOE ε4 and Tau H2 haplotype	MMSE and GDS	Lower frequency of APOE ε4 and Tau H2 haplotype in CNA
Benedet et al. (2012) [142]	Brazil	Por	532	EA, AA, NA (Amerindian)	NR	NR	NR	NR	APOE ε4	MMSE and CDR	Lower proportion of APOE ε4 for NA than for AA and EA

Table 3 (continued)

Reference	Country where the study was performed	Testing language	Total sample size	Ethnic/racial groups	Ethnic/racial group size	Mean age (SD)	Mean years of education (SD)	Gender distribution	Biomarkers	Cognitive test(s) used in diagnosis	Main findings
Linnertz et al. (2012) [145]	USA	En	726	WH, AA and H	WH = 177	80.4 (6.1)	NR	70% F	APOE ε4 and TOMM40 gene (523 alleles [S, L, VL]	N/A	WH presented a higher co-occurrence of the L with the ε 4, H presenting a similar distribution
					AA = 370	71.9 (9.06)	NR	78% F			No differences in L allele S and VL were similarly distributed in EA and H, but the S allele was more frequent and the VL least frequent in AA
					HA = 179	54 (NR)	NR	75% F			
Yu et al. (2017) [146]	USA	En	2388	C and AA	C = 1,848	78.4 (7.4)	16.3 (3.5)	72.1% F	APOE ε4 and TOMM40 gene (523 alleles [S, L, VL]	History of cognitive decline and evidence of impairment in multiple cognitive domains including memory	Higher co-occurrence of the L with the ε 4 and VL and S with the ε3 alleles in EA and HA. Higher occurrence of S and the ε4 linkage and the VL genotype presented a higher frequency of the ε4 allele in AA
					AA = 540	73.4 (6.6)	14.8 (3.4)	77.6% F			
Barker et al. (2021) [148]	USA	En or Sp	309	NH and H	> 50% H		NR for whole sample	NR for whole sample	pNfL	NACC D1 classification protocol	No relation between pNfL and ethnicity
Gonzalez et al. (2021) [149]	USA	NR	1843	NH and H	H = 1193	67 (9)	10 (5)	F = 840 (70%)	pNfL	CDR	No significant differences across ethnicities
					NH = 650	94 (8)	15 (3)	F = 358 (55%)			

Table 3 (continued)

Reference	Country where the study was performed	Testing language	Total sample size	Ethnic/racial groups	Ethnic/racial group size	Mean age (SD)	Mean years of education (SD)	Gender distribution	Biomarkers	Cognitive test(s) used in diagnosis	Main findings
O'Bryant et al. (2021) [150]	USA	En or Sp	1703	MA and NHW	MA = 890	63.87 (8.02)	9.48 (4.61)	F = 66%	NfL	MMSE, WMS-III Digit Span and Logical Memory Digit Symbol Substitution, TMTA and B, Spanish–English Verbal Learning Test (SEVLT), Animal Naming (semantic fluency), FAS (phonemic fluency), American National Adult Reading Test (English-speakers), and Word Accentuation Test (Spanish-speakers), and CDR	Lower levels of NfL in MA than NHW. When entered into a model including age, education, sex and ethnicity, only age was significant
					NHW = 813	69.34 (8.65)	15.49 (2.55)	F = 54%			
Metti et al. (2013) [152]	USA	NR	997	BL and WH	BL = 538	74 (2.9)	NR	F = 550	Aβ40, Aβ42, and the ratio Aβ42/ Aβ40	MMSE	BL had significantly lower plasma Aβ40 and Aβ42
					WH = 459						
Morris et al. (2019) [153]	USA	NR	1255	AA and NHW	AA = 173	70.8 (9.8)	14.7 (2.9)	F = 707 M = 548	Aβ42, Tau, p-tau181, APOE ε4, HV	UDS battery and CDR	No differences in Aβ42 levels between AA and NHW. AA had lower HV only when they had a family history of dementia Tau and p-tau181 levels were lower in AA only when they were APOE ε4 +
					NHW = 1082	70.8 (9.9)	15.4 (2.9)				
Brickman et al. (2021) [154]	USA	En	113 postmortem and 300 antemortem	NHW, H, and BL	Autopsied NHW = 52 H = 29 BL = 31	83.36 (6.8)	NR	NR	Aβ40, Aβ42,(t-tau, p-tau181, and p-tau217, NfL	CDR and clinical consensus	No significant differences in biomarker concentrations across race/ethnicity groups
					Clinical: NHW = 99 H = 100 BL = 98	NR	NR	NR			

Table 3 (continued)

Reference	Country where the study was performed	Testing language	Total sample size	Ethnic/racial groups	Ethnic/racial group size	Mean age (SD)	Mean years of education (SD)	Gender distribution	Biomarkers	Cognitive test(s) used in diagnosis	Main findings
Meeker et al. (2021) [155]	USA	En	816	NHW and AA	NHW = 685	71.64 (9.0)	16.12 (2.5)	F = 403 M = 282	Amyloid and tau PET, MRI	N/A	Aβ,tau PET, was similar between races. AA had smaller AD signature than EA
					AA = 131	70.64 (8.3)	15.36 (2.8)	F = 86 M = 45			
Garrett et al. (2019) [156]	USA	En	362	AA and W	AA = 152	63.2 (6.9)	15 (2.5)	F = 230 M = 132	Aβ1-42, tau, and pTau181, and hippocampal volume	Peterson's Criteria (MoCA, CDR, Logical Memory Delay, and FAQ) and clinical consensus	After adjustment for covariates AA with MCI had higher Aβ42 and lower t-tau and pTau181
					W = 210	67.4 (8.2)	16.3 (2.8)				No differences in HV
Zahodne et al. (2015) [159]	USA	En or Sp	638	WH, AA and H	WH = 184	80.16 (5.75)	13.68 (3.24)	F = 59.78%	HV	Clinical consensus according to DSM III-R criteria based on neuropsychological scores for the memory, language, speed/executive functioning, and visuospatial functioning domains	Larger HV positively associated with memory scores in NHW
					AA = 229	79.76 (5.74)	12.34 (3.44)	F = 69%			
					H = 225	80.18 (5.22)	6.88 (4.39)	F = 74.22%			
Graff-Radford et al. (2016) [160]	USA	En	2610	AA and C	AA = 110	13 (3.7)	13 (3.7)	F = 71 M = 39	APOE genotype, and neuropathology	CDR and MMSE	Higher Braak stage, CERAD scores for neuritic and diffuse plaques in AA than C AA also had AD neuropathology, and met the NIA/Reagan and CERAD neuropathologic criteria for AD
					C = 2500	15.3 (3.0)	15.3 (3.0)	F = 1062 M = 1438			
Wilkins et al. (2006) [162]	United States	En	20	AA and WH Descendants	AA = 10	84.8 (6.4)	16.7 (2.7)	F = 5 M = 5	Neuropathology	CDR	No significant differences in AD neuropathology between groups

Table 3 (continued)

Reference	Country where the study was performed	Testing language	Total sample size	Ethnic/racial groups	Ethnic/racial group size	Mean age (SD)	Mean years of education (SD)	Gender distribution	Biomarkers	Cognitive test(s) used in diagnosis	Main findings
					WH = 10	85.9 (8.4)	12.0 (4.5)	F = 5 M = 5			
Santos et al. (2019) [163]	United States	NR	1625	WH/EA, BL/AA and H/LA	EA = 1539	82	14	F = 830 (54%)	Neuropathology (brain weight, Braak tangle stage, and coexisting hippocampal sclerosis)	MMSE	H had lower brain weight, than EA but AA and EA did not differ AA were more likely to have hippocampal sclerosis than EA, but H were similar to EA
					AA = 19	78	14	F = 9 (47%)			
					HA = 67	82	13	F = 32 (52%)			
Ferguson et al. (2017) [164]	United States	N/A	24	C and AA	C = 12	NR	NR	F = 50%	S100B, sRAGE, GDNF, Aβ 40, and Aβ 42) and the Aβ 42/ Aβ 40 ratio measured postmortem on the middle temporal gyrus (BA21)	N/A	In an adjusted model, no significant differences between race groups
					AA = 12						

En English, *Sp* Spanish, *NHW* non-Hispanic Whites, *H* Hispanic, *F* females, *HV* Hippocampal Volume, *FOME* Fuld Object Memory Evaluation, *NH* non-Hispanic, *M* males, *AA* African American, *N/A* not applicable, *C* Caucasian, *CN* cognitively normal, *CI* cognitively impaired, *NR* Not Reported, *EA* European Americans, *Por* Portuguese, *NA* Native American, *WH* White, *UDS* National Alzheimer's Coordinating Center uniform data set, *MA* Mexican American, *NACC* National Alzheimer's Coordinating Center, *BL* Black, *LA* Latino

Blood Biomarkers

Neurofilament Light (NfL), which can be detected in CSF (cNfL) and blood (pNfL), is a cytoskeleton protein that is released into the extracellular fluid after axonal damage [147], and can therefore be used as a biomarker of neurodegeneration. Levels of pNFL increase with hippocampal atrophy, amyloid positivity [148], and cognitive diagnosis, from cognitively normal to dementia [147, 148]. However, no significant differences in pNfL level have been found between Hispanic and non-Hispanic participants [148, 149] or between Mexican Americans and non-Hispanic Whites [150]. In another study, Howell et al. [140] found that African Americans had higher levels of pNfL than Whites when cognitively normal but similar levels when cognitively impaired. O'Bryant et al. [151] identified 30 out of 100 protein blood biomarkers, which were optimal in classifying participants in the AD group. However, among Mexican Americans, from the 100 original proteins, a different set of biomarkers were found to classify AD participants from that ethnicity. However, these findings need to be replicated with a larger sample while comparing biomarker profiles across different ethnicities.

Beta-amyloid and Tau

Beta-amyloid (Aβ) depositions in the extracellular space form neuritic plaques, which interfere with neural communication and result in cell death and the neurodegeneration seen in AD. In addition, Tau pathology also contributes by disrupting intracellular transport mechanisms, resulting in cell death [3]. Antemortem, Aβ can be measured in plasma and CSF, recently through amyloid PET imaging. Declines in Aβ40 and Aβ42 in CSF and plasma have been associated with a heightened risk of AD [152]. While few studies have looked at differences across ethnicities, African Americans have been found to have lower levels of Aβ40 and Aβ42 than Whites without dementia, suggesting a link with the heightened AD risk for Blacks [152]. However, Morris et al. [153] did not find any differences in Aβ42 levels between African Americans and non-Hispanic Whites. Even though phosphorylated tau (p-tau181 and p-tau217), as well as the Aβ42/Aβ40 ratio, have been found to be good predictors of the clinical diagnosis of AD, but their concentrations have not been found to be significantly different across ethnicities [153, 154]. In another study, even after accounting for genetic markers (APOE ε4 and ABCA7) and Aβ42, African Americans were found to have lower CSF p-tau, t-tau, and Aβ40 [140]. No differences between races were observed in the results of PiB PET [153, 155] or Tau PET [155]. In patients with MCI, African Americans have been found to have significantly lower levels of total Tau in CSF than non-Hispanic Whites [156]. Using amyloid positron emission tomography (Aß-PET) [157], no differences in amyloid load were identified between Hispanics and non-Hispanics whites in three diagnostic groups (normal cognition, MCI, and dementia) [132]. However, an interesting interaction of SUVR values with APOE ε4 status was found between ethnic groups, such that among those who were APOE ε4 positive, Non-Hispanics had greater amyloid load as compared to Hispanics [132].

A recent meta-analysis [158] explored the influence of race on biomarker levels across five studies and found in four of the publications that CSF ptau181 and t-tau were significantly higher in Whites compared with African Americans participants with normal cognition [140, 143, 153, 159]. However, the levels of Aβ were similar between ethnic/racial groups. In the fifth study [156], African Americans with normal cognition had higher p-tau and t-tau than Whites but lower levels of Aβ1-42. Among patients with cognitive impairment, the results were similar to those among participants with normal cognition, except for the levels of CSF ptau181 and t-tau, which were higher in Whites than in African Americans [140, 153, 156]. In one study [140], lower Aβ1-42, t-tau, and p-tau in African Americans than White participants with MCI was reported. The authors concluded that the discrepancies in these results might be related to differences in clinical evaluation and diagnosis between races, but it remains unclear if the differences can be attributed to biological interracial differences [158].

Brain Volumetric Biomarkers

Structural MRI provides volumetric biomarkers that can detect the presence of neurodegeneration in AD and track disease progression. For instance, Zahodne et al. [159] used hippocampal volume as predictors of performance on a cognitive composite (including scores in four domains: memory, language, speed/executive functioning, and visuospatial processing) in an ethnically diverse sample (non-Hispanic Whites, African Americans, and Hispanics) without dementia. They also derived an AD signature measure by calculating four cortical thickness composites: (1) rostral medial temporal lobe (entorhinal cortex and parahippocampus), (2) angular gyrus (inferior parietal lobe), (3) inferior frontal lobe (pars opercularis, pars orbitalis, and pars triangularis), and (4) inferior temporal lobe, temporal pole (temporal pole), precuneus (precuneus), supramarginal gyrus (supramarginal gyrus), superior parietal lobe (superior parietal lobe), and superior frontal lobe (superior frontal lobe). These measures were used as predictors of cognitive measures across African Americans, Hispanics, and Whites without dementia. They found that greater hippocampal volume was a significant predictor of cognitive performance among African Americans and Whites, but for Hispanics, it only trended towards significance; this indicates that hippocampal atrophy affects

ethnic groups differentially and that additional factors that also differ across the groups play a role in cognitive performance. For this particular sample, immigrant status in the Hispanic sample may have acted as a modifying factor [159].

However, in another study, among both Hispanics and Whites, there was a progressive decrease in volume of the hippocampus and entorhinal cortex and an increase in the volume of the inferior lateral ventricle (indicating increasing atrophy in the regions surrounding the ventricle) from cognitively normal to MCI and mild dementia. They also found for equivalent levels of performance on cognitive and functional measures, whites had greater levels of neurodegeneration than did Hispanic subjects across diagnostic groups suggesting the possibility of over-diagnosis of cognitive impairment among Hispanics due to performance bias on cognitive testing among this group [19]. However, when comparing hippocampal volume between African Americans and Whites, Howell et al. [140] did not find significant differences in cognitively normal or impaired groups (MCI and dementia). Decreased hippocampal volumes have also been observed in African Americans compared to White Americans with a pathological diagnosis, but only when they had a family history of dementia [153].

Neuropathology

Postmortem studies analyzing Braak staging of Tau pathology have not found consistent differences between African American and White descendants. Some studies indicated that African Americans had higher Braak stage pathology than Whites [160], and others found no differences [93, 161, 162]. In the Florida Autopsied Multi-Ethnic cohort (of 1625 pathologically verified Alzheimer's disease cases), Hispanic subjects were found to have a higher frequency of family history of dementia (58%), earlier age at onset, longer disease duration (median of 12 years), and lower MMSE score proximal to death compared with White and African American subjects. Blacks were found to have a non-significantly lower Braak tangle stage but a higher frequency of coexisting hippocampal sclerosis than the other groups [163]. Ferguson et al. [164] performed a postmortem analysis of Aβ40 and Aβ42 levels as well as the Aβ42/Aβ40 ratio in the middle temporal gyrus (Brodmann's area 21) of AD patients. The Aβ42/Aβ40 ratio was increased by nearly 493%, and Aβ42 was elevated by 121% in African Americans when compared to Whites, while no significant differences were found in Aβ40. In addition, levels of S100B, a calcium-binding protein involved in different cellular processes and produced mainly by astrocytes, also implicated in AD, were elevated in African Americans compared with Caucasians [164].

Functional Connectivity

The default mode network (DMN) is a group of brain regions that are in a functionally correlated state of activation during resting wakefulness [165]. The DMN corresponds to areas that are also vulnerable to amyloid pathology and neurodegeneration early in AD, including the precuneus, posterior cingulate cortex (PCC), the inferior parietal lobule (IPL), and the ventromedial prefrontal cortex (vmPFC) [166]. Among cognitively normal participants, African Americans have been found to have reduced connectivity between the following pairs of brain regions: (1) precuneus—ventrolateral PFC, (2) IPL—parahippocampal gyrus, (3) temporal pole—the hippocampus, whereas the remaining 52 connectivity values were not significantly different. Among Whites, greater cognitive impairment was associated with decreased connectivity, whereas among African Americans, more significant cognitive impairment was associated with increased connectivity between the following areas: (1) precuneus-lateral temporal cortex, (2) precuneus-temporal pole [166]. These findings suggest that neurodegeneration may progress at different rates in the involved brain areas [167] across races/ethnicities.

Conclusions

It is now clear ethnoracial disparities can result in differential presentations and long-term effects of AD. We reviewed some of the problems these underrepresented groups face: for one, the Hispanic/Latino population is the fastest-growing in the USA but lags in educational attainment, a known factor in AD resiliency [91]. These authors emphasize low educational attainment among the Hispanic/Latino population is linked to a lack of access to healthcare and screening tools due to language or cultural barriers, thereby suggesting many undiagnosed AD cases among this ethnoracial group.

Among various ethnoracial groups, severe psychological distress contributes disproportionately to the burden of AD and related disorders, more so for African Americans than non-Hispanic Whites [92]. Furthermore, Novak et al. [92] found that higher rates of severe psychological distress in African Americans explained 15% of the white-black difference and 40% of the white-Hispanic difference. These authors ventured that the higher occurrence of severe psychological distress in these minority groups, particularly for African Americans and Hispanics/Latinos, could be influenced by diagnostic barriers, racial bias in the healthcare field, or potentially even cultural norms around seeking and obtaining mental health assistance. Given that depression, anxiety, and related mental health disorders are

impactful risk factors for AD progression, a greater emphasis on understanding ethnoracial disparities in mental health among AD and normal populations should no longer be a recommendation but a requirement.

Outside of subjective-psychological distress, ethnoracial disparities have been examined in the pharmacological treatment of AD. For example, in clinical trials of AD the reporting of demographic information regarding race/ethnicity has been deficient so that nearly half of the studies screened in a review did not report information about race [168], and only in three studies was information provided regarding how this was assessed (e.g., by the investigator or by self-report). The issue of underrepresented reporting about race information has implications regarding the efficacy and safety of the drugs used in the treatment of AD and the external validity of some of these clinical trials across ethnoracial groups. Research in AD needs much greater emphasis on assessment methods to resolve these drastic ethnoracial disparities.

Overall, the reviewed results highlight the need for diversity in all domains of AD research. Even though most of the studies included in this revision compared non-Hispanic White participants with African American participants, the scientific literature is still far from inclusive, lacking not only in the inclusion of other groups, including Native Americans, Hispanic/Latinos, Asian Americans from different backgrounds, and much more detailed information regarding African Americans. For instance, biomarker research findings that have been described so far suggest that there may be significant differences in how various biomarkers may be informative about the onset and progression of AD across ethnic/racial groups. In addition, specific biomarker profiles might need to be defined for each ethnic/racial group to predict risk and disease progression adequately in each group. There is much room for improvement in our methods of researching the field of AD, which would allow great representativeness of various ethnoracial groups.

Researchers and clinicians should consider some steps when examining ethnoracial factors in AD that have been suggested by Weiner [12] and include the following: (1) a focus on sample groups in whom the disease is highly prevalent. Such groups may provide a better understanding of how genetic and environmental factors influence the prevalence and progression of AD (e.g., NIA-funded Alzheimer's Disease Genetics Initiative) [12]; ethnoracial groups tend to cluster together geographically and these communities can become hypersensitive to the burdens of AD and related disorders [90], thereby also yielding more culturally competent health care professionals, and more educated caregivers [12]; (2) Considering the complexity involved in defining ethnoracial and cultural groups and clustering participants within those groups, another step in more effectively mapping the course of AD is to consider the diversity and heterogeneity within ethnoracial groups, rather than a strictly conventional, broad categorizations of race [169, 170]; (3) Another necessary direction is to better identify the variables that define the different groups, including sociocultural characteristics, attitudes toward other ethnic groups, and ethnic identity conceptualized as self-identification and a sense of belonging toward one's group [170]. Additionally, better assessments of ethnoracial groups would include exploring the influence of educational and cultural background and immigration-related factors (i.e., acculturation and contextual factors, length of residence in a new country, and bilingualism) [111, 166, 171]. Attempts have been made to develop cross-cultural neuropsychological assessment batteries adequately validated for use with ethnic minorities [172, 173]. By utilizing ethnoracial screening measures that accurately reflect the diversity of all minority groups, paired with increasing advertisement and incentivization for these groups to participate, it may soon be possible to better explain the complexities in ethnoracial disparities in the biology of AD, as defined by the NIA-AA research framework [167].

Finally, socioeconomic disparities exist worldwide between countries, influencing the validity of results in cross-cultural research. These socio-economic disparities are reflected in the variability in educational levels and the quality of education. A universal socio-economic and educational assessment approach would improve reliability in comparing AD risk and progression in diverse groups, between and within countries.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13311-022-01193-z.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Funding This research was supported by the National Institute of Aging Grant number 1P30AG066506-01 Florida Alzheimer's Disease Research Center (T Golde, PI) and the Florida Department of Health grants 9AZ01 and 21A01 (M Rosselli, PI).

Declarations

Conflict of Interest The authors declare no competing interests.

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