Neurotherapeutics (2022) 19:8–25
https://doi.org/10.1007/s13311-022-01185-z

REVIEW

Heterogeneity in Alzheimer's Disease Diagnosis and Progression Rates: Implications for Therapeutic Trials

Ranjan Duara[1,2,3] · **Warren Barker**[1]

Accepted: 5 January 2022 / Published online: 27 January 2022

Abstract

The clinical presentation and the pathological processes underlying Alzheimer's disease (AD) can be very heterogeneous in severity, location, and composition including the amount and distribution of AB deposition and spread of neurofibrillary tangles in different brain regions resulting in atypical clinical patterns and the existence of distinct AD variants. Heterogeneity in AD may be related to demographic factors (such as age, sex, educational and socioeconomic level) and genetic factors, which influence underlying pathology, the cognitive and behavioral phenotype, rate of progression, the occurrence of neuropsychiatric features, and the presence of comorbidities (e.g., vascular disease, neuroinflammation). Heterogeneity is also manifest in the individual resilience to the development of neuropathology (brain reserve) and the ability to compensate for its cognitive and functional impact (cognitive and functional reserve). The variability in specific cognitive profiles and types of functional impairment may be associated with different progression rates, and standard measures assessing progression may not be equivalent for individual cognitive and functional profiles. Other factors, which may govern the presence, rate, and type of progression of AD, include the individuals' general medical health, the presence of specific systemic conditions, and lifestyle factors, including physical exercise, cognitive and social stimulation, amount of leisure activities, environmental stressors, such as toxins and pollution, and the effects of medications used to treat medical and behavioral conditions. These factors that affect progression are important to consider while designing a clinical trial to ensure, as far as possible, well-balanced treatment and control groups.

Keywords Alzheimer's disease · Heterogeneity · Clinical trials · Genetics · Progression

Introduction

Heterogeneity in Alzheimer's disease (AD) includes a broad spectrum of traits, from genotype to phenotype [1–3], and the complexity of these interactions with environmental factors, which result in complex and distinct cognitive, neurological, psychiatric, and functional profiles of impairment. This etiological and clinical heterogeneity is increasingly recognized as characteristic of Alzheimer's disease and related disorders (ADRDs); it can complicate the diagnosis, treatment, and the design and testing of new drugs for AD. Heterogeneity in AD begins in the very definition of the disease, the criteria for which continue to evolve. The definition of AD may refer to a purely clinical entity, one that is based entirely on histopathological criteria, or as a clinical-pathological entity, in which underlying pathology is identified with the use of biomarkers, such as Aβ and tau, assessed as fluid-based (CSF and blood) and/or image-based biomarkers. The use of biomarkers, especially the thresholds at which those biomarkers are considered indicative for establishing the presence of a particular pathological entity, may also inject an element of heterogeneity in the definition of the disease. Because Alzheimer's disease occurs most frequently in the elderly and is often accompanied by other age-related diseases, the term ADRDs may be more appropriate for most cases diagnosed as AD. These non-Alzheimer disease entities, which often accompany AD and contribute to the heterogeneity in its

✉ Warren Barker
warren.barker@msmc.com

1 Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Miami Beach, FL, USA

2 Departments of Neurology, University of Florida College of Medicine, Gainesville, FL, USA

3 Herbert Wertheim College of Medicine, Florida International University, Miami, FL, USA

clinical presentation and prognosis, include cerebrovascular disease, other neurodegenerative and non-degenerative diseases of the brain, and the effects of systemic diseases, including infections, organ failures, and toxic elements in the internal or external milieu. These in turn may result in neuroinflammation and synaptic dysconnectivity, preceding loss of volume or cortical thickness on standard neuroimaging measures, such as MRI.

Alzheimer's disease, even when defined by purely pathological criteria, is recognized to have considerable heterogeneity in the form of subtypes that have different demographic and clinical features as well as rates of progression. Genetic and environmental factors that increase the risk for late-onset Alzheimer's disease are being recognized with increasing frequency, contributing to the heterogeneity of AD. In the design of clinical trials of AD therapies, the inclusion and exclusion criteria and the choice of endpoints for a particular trial, may be significantly influenced by the heterogeneity in AD. In this review, we have divided the description of various potential sources of heterogeneity into the following sections: (1) Genetic, (2) Neuropathological, (3) Demographics, (4) Cognitive and Functional, (5) Neuropsychiatric, (6) Biomarker, and (7) Implications for Clinical Trials.

Genetic Heterogeneity

Genetic studies of autosomal dominant forms of AD strongly suggest that amyloid precursor protein (APP) processing and the large amount of Aβ deposition resulting from the effects of individual mutations are the initiating factors in the disease process. In contrast, in the common late-onset AD (LOAD), symptom onset occurs more than a decade after Aβ and tau depositions occur, with subsequent cognitive and behavioral changes [4]. The onset of the clinical syndrome in LOAD occurs in the setting of aging and appears to be driven by the presence and location of several factors, including neuro-inflammation, enhanced glucose metabolism, oxidative stress, excitotoxicity, and synaptic disconnection, which are also factors involved in normal aging and longevity [5]. These factors may influence the age of onset, the clinical phenotype, and the rates of progression of LOAD [6]. Therefore, it is not surprising that the many clinical trials on LOAD patients, employing antibodies to remove Aβ from the brain or prevent its deposition, have shown very little, if any, clinically significant benefits. As a consequence, it seems necessary to identify as targets for intervention the genetic and nongenetic factors, such as neuroinflammation, neuronal and volume loss, amyloid angiopathy, and white matter changes found on imaging and pathology, which drive the clinical syndrome after Aβ deposition among both LOAD and early-onset AD (EOAD) cases [5]. The following sections on genetic factors associated with LOAD may provide clues regarding which factors, in addition to removing Aβ from the brain, should be targeted in future clinical trials.

Genetic heterogeneity in autosomal dominant AD (ADAD) is primarily related to the specific mutations involved in the pathogenesis of individual cases, which result in relatively rapid pathological accumulation of Aβ protein in the brain at an early age. The effects of point mutations on chromosomes 14, 21, and 1 are the primary drivers of the clinical heterogeneity in ADAD. Other factors which influence age at onset, phenotype, and rates of progression of ADAD are the epistatic effects of other genes, such as apolipoprotein E (APOE), the age at onset of the parents of individual ADAD cases, and the mean ages at onset for the carriers of the same mutation [7]. The progression rates of ADAD cases appear to be primarily related to the age of onset of individual cases. Those having earlier ages of onset (e.g., before age 35 years) and those with the oldest ages of onset (e.g., after age 65 years) appear to have the fastest rates of progression [7].

The APOE ε4 allele is also associated with earlier deposition of Aβ and an earlier age at onset, but its relationship with the rate of cognitive decline is controversial and may depend on the stage of AD [8–10]. APOE has its greatest influence on the risk for AD between about 65 and 70 years of age and declines substantially by age 85 due to survival effects [11]. A genetic trait with phenotypic features characterized by the appearance of psychotic symptoms at an early stage of the disease has been identified, with apparent modification of the downstream effects of abeta deposition and resulting in a rapid rate of cognitive decline [12, 13]. Other genes, which have been found to modify the risk for LOAD, include CLU, CR1, phosphatidylinositol-binding clathrin assembly protein (PICALM), BIN1, ABCA7, and CD33, after accounting for the effects of the APOE4 allele [14]. A faster rate of cognitive decline was associated with a single-nucleotide polymorphism (SNP) (rs11136000) in CLU, which encodes the protein clusterin (expressed at elevated levels in the brains of LOAD patients), which prevents fibrillization of Aβ, and which inhibits complement activation. A SNP (rs3818361) in CR1 (a complement receptor, expressed in the cerebral cortex, involved in neurodegeneration via astrocyte-mediated processes) was associated with more rapid longitudinal decline. A SNP in PICALM was associated with an earlier age at onset but not in the rate of cognitive decline [15].

In utilizing GWAS studies, at least 30 genes have been associated with LOAD on 14 different chromosomes [16], implicating four biological pathways in AD pathogenesis. These include immune response, endocytosis, cholesterol transport, cell-to-cell adhesiveness, and proteasome-ubiquitin activity. The role of the APOE gene on chromosome 19q13.2

is well-known and has been widely confirmed in numerous studies. ApoE is associated with Aβ aggregation and deposition. It appears to interact with the Aβ oligomers and fibrils [17], thereby influencing risk for AD development by increasing Aβ accumulation in the brain and CSF [18]. APOE likely modulates Aβ transfer across the blood–brain barrier, playing an important role in regulating the clearance of soluble Aβ [19]. APOE is synthesized predominantly by astrocytes [20], and APOE e4 allele carriers show an increased density of Aβ deposition within the brain, reduced capacity to clear Aβ, and enhanced neuroinflammation [21]. However, many APOE4 noncarriers develop AD. It has been shown that among people without an APOE ε4 allele, a SNP (rs2075650) in the TOMM40 gene, which is closely associated with APOE, is associated with AD [22, 23], even after accounting for age and sex [24], thereby suggesting an APOE4-independent mechanism for TOMM40, which increases the risk for AD. The SNP rs2075650 in the TOMM40 gene is linked to AD, longevity, cholesterol levels, and macular degeneration and is involved in protein precursors imported into mitochondria [25–28].

In three major GWAS studies, including the Framingham Heart Study (FHS) [29], Cardiovascular Health Study (CHS) [30], Health and Retirement Study (HRS) [31], and Late-Onset Alzheimer's Disease Family Study (LOADFS), the same four AD-associated genes have been identified as being the most influential risk factors [32]. These genes are TOMM40, APOE, APOC1, and poliovirus receptor-related 2 (PVRL2), all of which are on chromosome 19, in or near the APOE gene. The SNP rs6859, located in PVRL2 (NECTIN2), may be most closely related to AD, via its role in maintaining an intact blood–brain barrier, including its permeability, thus preventing viral infections which could play a role in AD pathogenesis [33–36]. Therefore, mutant forms of PVRL2 may allow cell-to-cell spreading of viruses and entry of certain mutant strains of herpes and pseudorabies viruses. The role of cell adhesion and the brain's susceptibility to viral infections has also been suggested for the combination of APOE and APOC1 genes [37, 38]. Moreover, in GWAS of late-onset AD in African Americans, genome-wide significant associations with AD were found in SNPs related to APOE, PVRL2, TOMM40, and APOC1 [39]. Importantly, the association of AD with PVRL2 (SNP: rs6859) remained statistically significant after adjusting for the effect of APOE, which supports its independent role in AD. Mutations in APOC1 combined with those in the APOE e4 allele result in a major increase in risk for AD [40]. A minor allele of rs157580 in the TOMM40 intron area is significantly associated with a reduced risk of AD, whereas a minor allele of rs2075650 is significantly associated with an increased risk of AD (TOMM40 intron area) [41].

APOC1 gene is expressed primarily in the liver but also in the brain. APOC1 encodes a member of the apolipoprotein C1 family, which plays a central role in high-density lipoprotein (HDL) and very-low-density lipoprotein (VLDL) metabolism. The APOC1 gene includes six SNPs associated with type 2 diabetes mellitus (T2DM) and AD [42], which have also been detected in GWAS of human longevity [25, 26, 43–49]. The connection of this set of genes with human longevity suggests that they may play some roles in risks for other diseases or in biological processes that influence such risks, including those associated with lipid metabolism [50, 51], rate of information processing [52], cardiovascular risk [53], inflammation [54], cancer [55, 56], and T2DM [57–65]. AD and T2DM have comparable pathological features related to the abnormal behavior of Aβ in the brain in AD patients and of amyloid peptides in the islets of the pancreas in T2DM. Growing evidence supports the concept that AD is, in part, a metabolic health disorder caused by the brain's progressive inability to respond to insulin and insulin-like growth factor. The connection between T2DM and AD is also manifested in several similarities between the developments of two pathologies [66], including a direct effect of insulin on Aβ metabolism, oxidative stress, abnormal protein processing, stimulation of inflammatory pathways, dyslipidemia, and production of advanced glycation end products [67].

The existence of connections between AD and other health disorders suggests a likely contribution of systemic mechanisms of aging and the biological processes that influence such risks. Of these, mitochondrial dysfunction induced by TOMM40 mutations may be most relevant [68], as shown by a meta-analysis of polymorphisms in the TOMM40 gene [69] which convey risk for sporadic AD, with mitochondrial dysfunction being the driver of Aβ deposition, synaptic degeneration, NFT formation, neuronal dysfunction, and death through the accumulation of reactive oxygen species.

Genome-wide association study (GWAS)-derived polygenic risk scores (PRS) are constructed by combining multiple single-nucleotide polymorphisms (SNPs) that implicate one or more biological mechanisms in AD, derived from previously detected SNPs. As would be expected, PRSs are better at discriminating AD from cognitively normal subjects than single-gene analysis [70, 71]. To identify genetic risk beyond that of APOE alone [72], several studies have assessed PRS with (APOE-PRS) versus without APOE (non-APOE-PRS). APOE-PRS is associated with age at onset of Alzheimer's disease symptoms, decreased Aβ and increased tau in CSF, increased atrophy, and tau and amyloid-beta load in the brain. APOE-PRS is also associated with plasma inflammatory markers in Alzheimer's disease patients [73]. Inclusion of a rare TREM2 (triggering receptor expressed on myeloid cells 2) variant with APOE-PRS discriminated those with Alzheimer's disease dementia from those with normal cognition, such that higher PRS scores were associated with decreasing age at onset, and CSF amyloid-b42,

and improved diagnostic accuracy, as demonstrated using a pathologically confirmed Alzheimer's disease cohort [74]. However, the total contribution of APOE and non-APOE-PRS to the variability in age at onset was found to be less than 6% [23], implying that heritability in AD has a large polygenic contribution beyond the known genetic factors associated with AD risk [75–77].

Implications for Clinical Trials

Most clinical trials do not specifically exclude participants with an autosomal dominant form of AD. Instead, due to the low prevalence of such mutations and trial inclusion criteria for age, the largest source of genetic heterogeneity comes from the APOE gene, followed by a PRS. In several clinical trials, APOE ε4 + genotype has been associated with a faster rate of decline among subjects with late MCI and mild to moderate AD [8, 9] in both placebo and treatment groups. However, a recent study of biomarker-confirmed late MCI and early AD participants from ADNI showed that APOE genotype had little effect on the speed of cognitive decline over 3 years [10]. These findings suggest that the relationship between APOE and cognitive decline is complex and may depend on the stage of illness and the presence of non-amyloid pathology. The presence of an ε4 allele is also associated with greater hippocampal atrophy, increased cerebral amyloid deposition, and increased cerebral tau-PET uptake in some brain regions [78, 79]. Therefore, accounting for ε4 carrier status, either through stratification during randomization or through statistical techniques, is likely to result in improved clinical trial design and more reliable outcomes. This is illustrated in the "Vitamin E and Donepezil for the Treatment of MCI" trial, in which there was a significant treatment effect for donepezil among APOE e4 carriers, but not among APOE noncarriers [8]. APOE genotype may also affect dropout rates in immunotherapy clinical trials because the frequency of amyloid-related imaging abnormalities (ARIA) related to immunotherapy is increased twofold among ε4 heterozygotes and even more for ε4 homozygotes [80–82].

Neuropathological Heterogeneity

Among the elderly, cognitive impairment and dementia may occur as a consequence of single, or more often, multiple brain pathologies, including the accumulation of neurodegenerative changes, such as Aβ plaques, tau neurofibrillary tangles (NFTs), α-synuclein, TAR-DNA-binding protein 43 kDa (TDP-43), and a host of cerebrovascular pathologies, including lacunar and large vessel infarctions, amyloid angiopathy, and brain hemorrhages [1, 83, 84]. Pure AD neuropathology is observed in less than half of patients diagnosed with probable AD dementia in life [85–87]. Some level of AD pathology has also been observed in nearly 40% of dementia patients, who were considered to have non-AD diagnoses during life [88]. Moreover, many elderly individuals considered cognitively normal proximate to the time of death have been demonstrated to have AD pathology at autopsy [88]. It remains unclear whether such individuals would have developed Alzheimer's disease symptoms with time, should they have lived longer [89]. Boyle et al. [90] reported that among 467 individuals who had been studied longitudinally and remained non-demented till autopsy, the vast majority had beta-amyloid, all had tangles, about a quarter had macroscopic infarcts, another quarter had microinfarcts, and between 5 and 10% had neocortical Lewy bodies. In these individuals, the presence of abnormal beta-amyloid, neocortical Lewy bodies, and neurofibrillary tangles together were linked with global levels of cognitive deterioration among those in the non-demented range. They also found that episodic memory was strongly associated with tangles, working memory with Aβ alone, semantic memory with the combination of amyloid and tangles, and semantic memory, working memory, and perceptual speed combined were associated with Lewy bodies. TDP-43 is a common proteinopathy in the brain after the age of 80 years for which an acronym had been created — limbic-predominant age-related TDP-43 encephalopathy (LATE) [91]. TDP-43 frequently occurs with and exacerbates AD pathology, which may complicate or obscure treatment paradigms. Many older subjects with clinical AD, who are amyloid-negative (suspected non-Alzheimer's pathology [92]), may have LATE.

The oldest old are much more likely than younger individuals to have multiple pathologies associated with the presence of cognitive impairment, as has been found in the 90 + Study [2]. The various pathologies identified among the oldest old included AD, microinfarcts and macroinfarcts, hippocampal sclerosis, Lewy body disease, and cerebral amyloid angiopathy. In this study, the estimated odds of dementia, as well as the severity of dementia, were found to increase with higher numbers of pathologic diagnoses. Those with intermediate to high severity of AD pathology were four times more likely to have dementia if a second non-AD pathology was present and the effect of multiple pathologies may be additive or synergistic. It was also found that for those without significant AD pathology, dementia was associated with hippocampal sclerosis, age-related astrogliopathy, TDP-43, and Lewy pathology [93]. These findings emphasize the importance of preventing non-AD pathologies, especially cerebrovascular disease, to improve resilience to dementia in the oldest old.

Karanth et al. [94] studied a total of 1346 participants, enrolled in two large cohorts in which longitudinal evaluation continued until they came to autopsy. Similar trajectories of cognitive decline were identified in each cohort, predicted individually by age at death, Braak neurofibrillary tangles (NFT) stage, presence of TDP-43, α-synuclein, and brain weight. Those with multiple pathologies were most common in trajectories with moderate or accelerated decline, and of these, the Braak NFT stage was found to be the most powerful predictor of the rate of progression [94]. Braak and Del Tredici [95] studied a cohort of 648 patients with repeated follow-ups until they came to autopsy and were diagnosed with AD. They identified variable topographic distributions of brain atrophy and the frequent co-occurrence of other pathological entities and clinical phenotypes during life. The presence of alpha synucleinopathy, in particular, was associated with more pronounced executive and visuospatial dysfunction.

Although in their study Karanth et al. [94] did not find an association between the rate of progression and Aβ alone, other studies have suggested that conformational heterogeneity of $A\beta_{42}$ may be associated with the heterogeneity in the rates of progression of AD. Cohen et al. [96] investigated the relationship between diverse structural assemblies of Aβ and rates of clinical decline in 48 cases of AD with distinctly different disease durations. Their findings indicated that a wide spectrum of Aβ42 structural states exists and that prion-like conformational strains of Aβ42 are associated with rapid clinical decline. Similarly, Condello et al. [97] investigated the structural variability of Aβ deposits that were found in familial and sporadic AD, as well as cerebral amyloid angiopathy. They demonstrated that point mutations in the Aβ-coding region produced mutant forms of Aβ conformation which "kinetically dominate the spread of prions in the brain, yielding heterogeneous clinicopathological forms of AD.

The pathological heterogeneity observed in AD also consists of variation in the distribution of neurofibrillary tangles. Murray et al. [98] identified 889 AD cases from a brain bank database with a Braak neurofibrillary tangle stage of more than IV. They assessed the density and the distribution of neurofibrillary tangles in three cortical regions and two hippocampal sectors and classified AD cases into three main subtypes, of which 11% was described as a "hippocampal-sparing" (i.e., neocortical predominant) subtype, 14% was described as "limbic-predominant" (medial temporal predominant) subtype, and the remaining 75% as "typical" subtype with combinations of both subtypes. Patients with hippocampal-sparing AD were younger at death, with shorter disease duration, and were more frequently male, whereas those with limbic-predominant AD were older at death, had slower progression rates, and were more frequently female. Apolipoprotein E (APOE) ε4 allele status was more frequent in those with younger age of onset, regardless of the pathological subtype.

Implications for Clinical Trials

The inclusion of subjects with mixed pathology in clinical trials may reduce treatment efficacy, especially among older participants who are more likely to have more than one pathology. In addition, subjects with mixed pathologies may progress faster. For example, among autopsied subjects in the National Alzheimer's Coordinating Center (NACC), those with AD and co-occurring LBD pathology progressed slightly faster than those with AD pathology alone [99]. Another common pathology, cerebrovascular disease, has been studied extensively and found to have a complex relationship with cognition [100]. To reduce comorbid vascular pathology, almost all AD clinical trials have criteria to exclude participants with significant abnormalities on MRI, other than AD-related atrophy. In trials using anti-amyloid therapy, due to the concern for amyloid-related imaging abnormalities due to edema (ARIA-E) and microhemorrhages (ARIA-H), more attention is given to evidence of cerebrovascular disease during screening. In the future, radioligands for other non-AD pathologies (α-synuclein, TDP-43) may be utilized in AD clinical drug trials to reduce pathological heterogeneity. Given the importance of vascular pathology in increasing the risk of dementia among those who have AD, it may be important to combine methods to minimize the impact of incident vascular disease, by including strict methods of lowering vascular risk, such as lowering systolic blood pressure, restricting salt intake, and adding a statin drug, in the treatment group.

Demographic Heterogeneity

The frequency of Alzheimer's disease is known to vary by demographic characteristics, including the age of onset, sex, race, and ethnicity. Age is by far the strongest risk factor for sporadic AD, with 3% of people age 65–74, 17% of people age 75–84, and 32% of people age 85 and older having AD [101]. In 2011, the average annual incidence in people age 65–74 was 0.4%; age 75–84 was 3.2%; and for age 85 and older, the incidence was 7.6% [101, 102].

Sex differences in the risk for and prevalence of ADRDs have been widely reported, and about two-thirds of patients diagnosed with ADRDs are women, although these studies lack autopsy confirmation. The higher prevalence of AD and other dementias in women has been attributed to the greater longevity among women, on average, than men, with age being the greatest risk factor for AD [103–105]. Differences in the risk for developing

AD between men and women have also been attributed to social, health, and biological factors such as sex hormones [106]. However, there have been mixed findings regarding the age-specific differences in risk for developing AD or other dementias between men and women, which may depend on the prevalence of various risk factors in different age groups and geographic regions [107, 108]. Using pooled analysis among over 34,000 participants in cohort studies, conducted between 1971 and 2017, with a median follow-up of 7.9 years, females evidenced a significantly higher performance relative to men in memory, global cognition, and executive function at baseline. On longitudinal follow-up, women had more rapid declines in global cognition and executive function, compared with men, and a similar decline in memory performance by sex was found [106]. Overall, these results suggest that women may have greater initial cognitive reserve, but at some point, underlying brain pathology may override this reserve capacity, resulting in greater declines among women, thereby contributing to sex differences in late-life dementia [106]. Among 1625 participants in the Florida Autopsied Multi-Ethnic (FLAME) cohort [109, 110], men were found to be younger at the onset of cognitive symptoms, had a shorter disease duration, and more often had atypical (non-amnestic) clinical presentations. Regional neurofibrillary counts, when examined by age intervals, were greater among women, especially in the hippocampus. Men were more often classified as having hippocampal sparing AD, whereas limbic predominant AD was more common in women. Atypical clinical presentations, younger age at onset, and shorter disease duration among men may contribute to misdiagnoses of AD and lower reported frequency of AD among men.

Ethno-racial differences in the risk for developing ADRDs are well documented, with most studies showing that older Black/African Americans have twice the risk as older whites, and older Hispanics/Latinos have about 1.5 times the risk of older whites [111–114]. Hispanics/Latinos comprise a very diverse group in terms of cultural history, genetic ancestry, and health profiles, and there is evidence that prevalence may differ from one specific Hispanic/Latino ethnic group to another [115–117]. Although some differences in the influence of genetic risk factors for ADRDs may be related to race [118–120], genetic factors do not appear to account for the large differences in prevalence or incidence among racial groups [121, 122]. Instead, health conditions such as cardiovascular disease and diabetes, which are associated with an increased risk for Alzheimer's and other dementias, are believed to account for these differences, as these conditions are more prevalent in Black/African American and Hispanic/Latino people [123, 124]. Socioeconomic characteristics, including lower levels and quality of education, higher rates of poverty, and greater exposure to adversity and discrimination, may also account for the increased risk for AD among Black/African American and Hispanic/Latino communities [119, 121, 123–125].

In light of how vascular risk factors, such as hypertension, diabetes mellitus, atrial fibrillation, and alcohol consumption, can increase the risk for ADRDs and contribute to the heterogeneity of AD, lifestyle measures which can reduce the impact of these risk factors are important to emphasize. Engagement in social leisure and physical activities has been previously identified as a factor that can help older adults maintain their cognitive and psychological status [126–129], possibly accounting for modifiable heterogeneity in the rate of cognitive decline among patients with mild cognitive impairment and dementia, regardless of etiology. After taking physical activities and mental health into account, social activities appear to have "a direct impact on cognitive functioning" [130]. Among a cohort of over 1000 elderly individuals without dementia at baseline, followed for an average of 12 years, the rate of global cognitive decline in five domains of cognitive function was reduced by an average of 70% in persons who were at the 90th percentile of social activity, compared to persons who were at the 10th percentile) [131]. These results confirm that more socially active older adults experience less cognitive decline in old age.

Implications for Clinical Trials

In clinical trials, age and education criteria are usually included to reduce some of the heterogeneity of participants related to demographics. Older participants with MCI or AD are more likely to have mixed pathology contributing to cognitive decline, such as cerebrovascular disease, TDP-43, and hippocampal sclerosis [2, 83, 84, 86–88]. The majority of patients with AD are over the age of 80, but only 22% of participants in AD trials have been over the age of 80, according to a recent review [132]. Most clinical trials exclude participants over the age of 85, [133] because of the high prevalence of exclusion criteria in older subjects and the higher risk of attrition associated with greater age [134, 135]. Non-authorized diseases resulting in exclusion from AD clinical trials that occurred during screening in more than 5% of participants were cardiovascular disorders, history of cancer, and psychiatric disorders [134]. The most frequent exclusionary mediations included those affecting cognition, cardiovascular medications (e.g., warfarin), and systemic immunosuppressants. Excluding participants who are older or have medical comorbidities limits the generalizability of a clinical trial, although it increases the heterogeneity in the cohort.

Among participants with MCI or mild to moderate AD in observational studies, the rate of cognitive decline decreases with age [136, 137]. The difference in the rate of decline

between the youngest group (< 61) and the oldest group (86 + years) over 24 months exceeds the expected treatment differences of trials in mild to moderate AD patients [137]. Therefore, to account for potential differences in age between treatment and placebo groups, most clinical trials covary for age during analysis or use age during randomization. Similarly, factors such as education and sex are usually not used for stratification during randomization in clinical trials but are included as covariates in modeling treatment effects. In some studies, such as the A4 trial, in which solanezumab was used for the treatment of asymptomatic AD, stratification at randomization was used for those with high versus low education to have a balance of high (13 years of education) and low education (12 years or less of education) to account for the effect of cognitive reserve on cognitive decline [138, 139].

Ethnic minorities have been underrepresented in research studies in general, due to barriers related to factors associated with participants, scientists, and study design [140]. These barriers are even more challenging to overcome in trials involving older adults with memory disorders and their caregivers, who provide essential information and support in such studies [141]. To overcome these barriers, studies such as New IDEAS have designed strategies to increase study awareness and engagement, including the identification of regions with dementia specialists who have experience with minority patients, identifying community partners, and providing additional resources such as transportation [142]. As the elderly population in the USA becomes more ethnically diverse, it is important to understand the generalizability of research findings to racial and ethnic minorities [101].

Cognitive and Functional Heterogeneity

Episodic memory is often the earliest and most characteristic cognitive domain impaired among AD patients, although a minority of patients may present with early impairment in non-memory cognitive functions. The classification of patients with different combinations of cognitive deficits may provide prognostic information to classify subgroups with different expected rates of progression in clinical trials. A prodromal stage of dementia, commonly labeled "mild cognitive impairment (MCI)," is clinically and pathologically heterogeneous, with different risks of progression to dementia [143]. Clinical subtypes of MCI include "amnestic MCI" (aMCI) when memory loss is the predominant symptom. MCI is termed "non-amnestic MCI" (naMCI) when impairments are in domains other than memory, such as language, executive function, visuospatial function, and behavior. Individuals with naMCI are more likely to convert to dementia other than AD, including vascular dementia, dementia with Lewy bodies [144]. Furthermore, the combination of a cognitive profile with one or more biomarkers of the disease may be instrumental in stratifying patients participating in clinical trials, as well as accounting for their expected rates of progression. Variation in the clinical presentation may be related to non-amnestic presentations of ADRDs, including posterior cortical atrophy (PCA), logopenic primary progressive aphasia, the frontal variant of AD, and corticobasal syndrome (CBS) [145].

Subgroups of patients diagnosed with AD have been identified by various statistical techniques, including factor analysis and cluster analyses. Phillips et al. [146] analyzed cognitive data from 146 EOAD subjects, which was Z-normalized to data from cognitively normal individuals. They included data from MRI and FDG-PET scans. Their cluster analyses suggested a 4-cluster solution: (1) memory-predominant impairment with atrophy and hypometabolism in medial and lateral temporal, lateral parietal, and posterior cingulate regions; (2) memory and visuospatial-predominant impairment with atrophy/hypometabolism of medial temporal, temporoparietal, and frontal cortices; (3) memory, language, and executive function impairment with atrophy in all regions, except the sensorimotor cortex; and (4) global cognitive impairment with atrophy and hypometabolism throughout the brain. Longitudinally, between-cluster differences in the visuospatial and language/executive domains were significant, suggesting "phenotypic variation."

Qian et al. [147] evaluated longitudinal neuropsychological data from patients with mild to moderate Alzheimer's disease, with typical versus atypical cognitive profiles, in the US National Alzheimer's Coordinating Center (NACC) database. Among a subset of over 1000 patients with autopsy-verified AD, about 80% was found to have a typical AD cognitive profile, whereas atypicality in the cognitive profile was associated with younger age, male sex, lower probability of *APOE* ε4 genotype, less severe global dementia, higher depression scores, lower Braak stage at autopsy, and slower cognitive decline.

Lam et al. [148] have identified specific cognitive profiles associated with regional anatomical deficits in the brain, including (1) a pure amnestic syndrome, with prolonged decline, and atrophy and NFTs primarily limited to the medial temporal region, including the entorhinal cortex; (2) predominant language impairment (i.e., progressive non-fluent speech patterns with agrammatism, phonemic paraphasias, and relative memory preservation), younger age of onset, and faster rate of decline, associated with left parietal atrophy and/or hypometabolism, and with a distribution of NFTs within the left neocortex, sparing the hippocampus in some cases; (3) predominant visuospatial symptoms associated with right parietal lobe atrophy/hypometabolism; and (4) executive dysfunction, inconsistent with the degree of memory decline, with or without prominent behavioral symptoms such as disinhibition and/or apathy (i.e., frontal variant) associated with frontal lobe

atrophy and dysfunction [148]. Peter et al. [149], who distinguished cognitive profiles using principal components and cluster analysis, based on 24 cognitive scores, studied subjects longitudinally over 24 months in the ADNI database, found that those with focal semantic impairment progressed significantly faster than those in the other clusters. They investigated the composition, stability over time, and the interactions of each cluster assignment with disease severity. Longitudinally, focal deficits increased relatively rather than tending toward average disease severity [149].

Early-onset Alzheimer disease (EOAD), which presents in patients younger than 65 years, has frequently been described as having different features from that of late-onset Alzheimer disease (LOAD). Atypical symptoms on presentation are more likely in EOAD, with poorer executive and visuospatial functioning and praxis, but with less marked memory impairment than in LOAD. Neuropathological studies show that among those with EOAD, NFTs are more dense and widespread as compared to LOAD. Structural and functional neuroimaging studies show greater atrophy and metabolic impairment, especially in neocortical areas, in EOAD than in LOAD [150]. Nearly two-thirds of patients with early-onset AD (EOAD) have atypical (non-memory) presentations and faster progression rates than those with late-onset AD (LOAD) cases, the vast majority of whom tend to have typical (memory-predominant) cognitive impairments [151, 152]. Some studies suggest that after memory, the language domain is most severely affected in EOAD, but the visuospatial function is preserved, while other studies suggest that praxis and visuospatial function are most affected [153, 154]. In their study, Phillips et al. [146] found significant heterogeneity in cognitive presentation, corresponding to patterns of atrophy and hypometabolism among EOAD subjects in the ADNI cohort on cluster analysis. Genotypic differences, especially the absence of apolipoprotein E e4, were often associated with atypicality in younger-onset AD.

There is also considerable heterogeneity in the ability to perform activities of daily living independently among patients with AD [155]. This is important, in that the clinical threshold for dementia is established by the lack of abilities to successfully perform activities of daily living, which may be a function of task complexity, environmental supports and cues in the environment, and person-specific compensatory mechanisms. The concept of functional heterogeneity has not been as thoroughly studied as cognitive heterogeneity but is clearly important in diagnosis and management. Functional heterogeneity may also be apparent in variability in gait and balance, which is a clinical feature of neurodegenerative diseases and has been found to increase in severity from the MCI stage of AD to more severe stages of dementia stages [156].

Implications for Clinical Trials

AD clinical trials range from prevention trials in asymptomatic individuals positive for AD markers (preclinical AD), to treatment trials in people with MCI, to trials in people with AD. In contrast to older trials, which used McKhann criteria [157] for AD dementia, more recent trials have required a clinical diagnosis of MCI or mild dementia due to AD, consistent with the NIA-AA Working Group Criteria [158, 159]. Prodromal AD, also known as MCI due to AD, is usually operationalized in clinical trials using a variation of Petersen's MCI criteria [160]. The rate of decline within these trials is predicted by the baseline cognitive level, even when cognitive assessment is restricted to a narrow range of cognitive deficits at screening. Among ADNI participants, those with lower baseline scores on the MMSE and RAVLT progress faster within each stratum: (1) from cognitively normal stage to MCI (2) and from MCI to AD [160]. This is the rationale for the stratification of treatment and placebo groups in some clinical trials based on the severity of disease at screening (e.g., MMSE scores of: 24–26, 27–30) [161] or for the use of severity of cognitive impairment as a covariate in statistiycal analyses of the outcomes [162].

Neuropsychiatric Heterogeneity

Neuropsychiatric symptoms (NPS), frequently measured using the Neuropsychiatric Inventory (NPI) [163], appear to contribute to the phenotypic heterogeneity in AD and to its progression rate. In a large sample of patients in a Norwegian national registry of memory clinics, NPS were common in all stages of impairment and increased with severity of cognitive impairment [164]. The most frequent NPS in MCI were depression and apathy, whereas anxiety, apathy, delusions, and depression were the most frequent NPS across different stages of severity of AD [164]. Hashimoto et al. [165], who studied the prevalence of 10 behaviors in the NPI among 393 patients with AD, reported that apathy was the most common symptom in the NPI, across all stages of impairment, followed by delusions, irritability, dysphoria, and anxiety, which were present in more than half the patients, and aberrant motor behavior, agitation, disinhibition, and hallucinations were present in a quarter to half of the patients. Euphoria was the least frequent behavioral symptom, occurring in about an eighth of patients. These less frequent behaviors, especially, agitation, euphoria, and aberrant motor behavior, were related to the level of functional impairment, as measured by the CDR sum of boxes and other functional measures.

Neuropsychiatric symptoms are associated with a higher risk for rapid progression from MCI to AD. Dietlin et al. [166] studied subjects with MCI from the Mayo Clinic Study of Aging. They found that among those who were followed for 4 years, progression from a CDR score of 0.5 to 1, or greater (after adjusting for potential confounders, such as age and sex) was predicted most strongly for those presenting with psychosis and delusions and moderately so for those with aberrant motor behavior, agitation, and aggression. Similar, but less prominent findings were reported by Peters et al. [167] from the Cache County Dementia Progression Study, which included 335 patients with incident Alzheimer's dementia. They found that specific types of neuropsychiatric presentations were predictive of shorter survival time from mild AD dementia to severe dementia or death. Among 68 participants in this study who progressed to severe dementia over a 4-year follow-up period (adjusting for several variables), agitation/aggression was the NPS in the NPI that was most strongly predictive of a shorter length of survival. Roberto et al. [168] evaluated a sample of 2137 MCI patients in Barcelona and identified four clusters of NPS, in these patients, including (1) irritability, (2) apathy, (3) anxiety/depression, and (4) an asymptomatic cluster. Irritability was the least prevalent neuropsychiatric condition in this sample, but patients with this cluster of NPS had the fastest progression. Overall, those in the irritability and apathy clusters showed a faster cognitive decline in two memory domains (verbal learning and cued recall), as compared to those in the anxiety/depression or the asymptomatic cluster. Other factors may have a synergistic effect on the rate of progression when combined with individual NPS. For example, Burke et al. [169] analyzed data from the National Alzheimer's Coordinating Center that included evaluations of 11,453 cognitively intact participants. They used survival analysis to explore relationships between individual NPS from the NPI and found an increased hazard of developing AD among participants with any of the symptoms assessed by the NPI, especially among ε4 carriers. The hazard of developing AD was almost thirteen times higher for ε4 carriers with delusions and eleven times greater for ε4 carriers with apathy and disinhibition. Similar findings were obtained in the Mayo Clinic Study of Aging by Pink et al. [170], who prospectively followed 332 participants with MCI (aged 70 years and older) for a median of 3 years. They found that baseline agitation, nighttime behaviors, depression, and apathy significantly increased the risk of incident dementia, and that the risk of incident dementia was further increased among ε4 carriers with depression and apathy. Babulal et al. [171] found among 118 cognitively normal elderly individuals that Aβ positivity, assessed by CSF and/or PET biomarkers, predicted changes in mood in 1 year, even though there was no statistically significant decline in cognitive functioning. Greater mood disturbances, including negative symptoms such as anxiety, depression, and confusion, were associated with Aβ positivity in preclinical AD.

To further explore the biological basis for the synergistic impact of cognitive deficits with NPS, Tetreault et al. [172] used resting-state functional MRI to identify a memory network (i.e., for delayed recall), including medial temporal lobe regions. They found the memory network for delayed recognition was localized posteriorly in the medial temporal lobe. By comparing atrophy network mapping in patients with and without delusions (as measured by the NPI), they identified a "delusions network" that included the bilateral ventrolateral frontal, orbitofrontal frontal, and superior frontal cortices, in addition to the mesial temporal lobe.

Mild behavioral impairment (MBI) is a construct that describes the emergence of sustained and impactful NPS, as a precursor or accompanying feature to cognitive decline and dementia. MBI describes NPSs of any severity, which are not captured by traditional psychiatric nosology, persist for at least 6 months, and occur in advance of or in concert with mild cognitive impairment [173]. The syndrome of MBI has been operationalized with the MBI-C, a newly developed instrument that more precisely measures NPS [174]. MBI has been linked with faster cognitive decline over a 3-year follow-up in cognitively normal older subjects [175]. In the ADNI cohort, MBI was associated with a faster rate of amyloid accumulation on PET, and greater progression from cognitively normal to MCI, and from MCI to AD dementia [176].

Implications for Clinical Trials

The inclusion of subjects with neuropsychiatric symptoms (NPS) in an AD clinical trial can increase the heterogeneity of participants and also increase the risk for progression [177]. NPS are highly prevalent in MCI patients (35–85%), so using them as an exclusion criterion in clinical trials is not practical and would impact the generalizability of the trial psychotic symptoms, which are associated with a relatively high risk for progression. The inclusion of subjects with NPS in AD trials can also increase the etiological heterogeneity. For example, subjects with NPS are more likely to have underlying Lewy body dementia [177], thereby adding to the heterogeneity among the subjects in a clinical trial.

Structural and Fluid-Based Biomarker Heterogeneity

Neuritic plaques, containing Aβ, and NFTs containing tau protein lead to neurodegeneration and are present a decade or more before cognitive symptoms appear [178, 179]. Neurodegeneration can be quantified for the whole brain or

regionally, using volumetric MRI scans and measures of cortical thickness. Aβ and tau levels can be measured in CSF and have been well validated for identifying the pathological levels of these proteins, indicative of the presence of AD pathology. Positron emission tomography (PET) biomarkers enable in vivo detection of Aβ deposition and load, as well as the presence and distribution of tau protein in the brain in asymptomatic AD, as well as those with MCI and dementia [180]. As outlined in the research framework for AD [181], the use of these biomarkers has redefined the research diagnosis of AD as a pathophysiological continuum, independent of the clinical stage of the disease. More recently, core biomarkers measured in plasma are showing great promise as a convenient and widely available diagnostic tool in the early stages of AD pathology and potentially for tracking the course of Alzheimer's disease in the population [182]. Variability in biomarker profiles among cognitively normal subjects, as well as those with MCI and dementia, may reflect the biological heterogeneity of the disease, but may also reflect methodological variability, especially in the choice of specific thresholds used to distinguish "normal" from "abnormal levels of atrophy, amyloid load, and tau deposition."

Structural MRI

Magnetic resonance imaging (MRI) scans are widely used to evaluate elderly patients with cognitive complaints. The primary clinical purpose is often to use information derived from MRI scans to identify or exclude the presence of various lesions that could contribute to the cause of cognitive impairment and dementia, including vascular lesions, hematomas, neoplasms, and hydrocephalus in the diagnosis. Alterations in the brain's structure, such as hippocampal atrophy and neocortical atrophy, especially in the parietal/precuneus regions, are an early marker of neurodegeneration in AD that correlates with the presence and severity of cognitive impairment [183]. Neuropathological studies show that the pathological features of AD may be present for years before clinical symptoms are evident and are often present in individuals with memory impairment who are not demented. In this regard, Jack et al. [184] found that a 2-SD reduction in hippocampal volume (corrected for age and sex) was associated with a fourfold increase in the percentage of individuals with MCI converting to dementia within 5 years.

Heterogeneity in the form of distinct subtypes of brain atrophy in AD closely matches findings reported in autopsy studies. These subtypes of atrophy (typical, limbic predominant, and hippocampal sparing) have been identified by Murray et al. [98] in pathological studies. Volumetric MRI data does reflect the severity of underlying neurodegeneration [183], can be quantified easily, and is more amenable to identifying such subtypes of AD [184, 185]. Volumetric measures from MRI scans can be used to classify these neurodegenerative subtypes along a continuum between limbic predominant and hippocampal sparing [186]. It has been shown that these subtypes of AD predict which patients are likely to have earlier onset and shorter disease duration (i.e., rapid progression), as well as the likelihood of being APOE ε4 positive [187]. Using volumetric MRI, Persson et al. [188] demonstrated four different subtypes of atrophy in 123 patients with mild Alzheimer's disease dementia (AD), including a "typical subtype" in 48%, "limbic-predominant subtype" in 24%, "hippocampal-sparing subtype" in 15%, and a subtype with "minimal atrophy" (previously referred to as no-atrophy AD) in 13%. Although in this study no cognitive differences were found and progression rates were similar between the different subtypes, the minimal-atrophy subtype group was found to be less educated and had greater functional impairment (as reflected in baseline CDR sum of boxes scores), but higher levels of Aβ in the cerebrospinal fluid, possibly indicating greater vulnerability to the effects of Aβ in subjects with low cognitive reserve. Patterns of cortical atrophy, also measurable on volumetric MRI, correlate with patterns of cognitive impairment, reflecting focal cortical syndromes, such as the frontal-behavioral variant of AD, progressive aphasia, or posterior cortical syndrome [189]. Patients presenting with behavioral and dysexecutive syndromes may have underlying AD or FTD. It was reported that patients with poor memory scores who had marked atrophy in bilateral temporoparietal regions, but limited atrophy in the frontal cortex usually, have AD, whereas those with greater frontal atrophy, less temporoparietal atrophy, and only mild memory impairment usually have FTD [189].

Identification of these subtypes, especially the extent of cortical rather than hippocampal atrophy, could be used to classify participants in a clinical treatment trial to predict individual rates of cognitive and functional progression associated with each subtype [184, 186]. Young et al. [190] have developed a machine learning method that combines the assessment of phenotypic (consisting of different subtypes) and temporal (consisting of different rates of progression) heterogeneity. They successfully used data from 819 ADNI-1 participants to identify three distinct functional progression patterns, which allowed for stratifying participants into groups, combining phenotypic and temporal heterogeneity.

Patterns of Functional Connectivity

Ferreira et al. [191] evaluated functional subtypes of AD using resting-state functional MRI, consistent with the findings in a meta-analysis [192] reported among 130 subjects participating in ADNI 2. Alterations in connectivity in three networks in patients with MCI and AD dementia were found

including the default mode, salience, and limbic networks. They hypothesized that the typical, limbic-predominant, and hippocampal-sparing subtypes of AD would show regional changes in network topology mostly paralleling the regional pattern of atrophy that defined each subtype but would also extend to other brain regions reflecting the involved networks. An aberrant pattern of network disruption was found, with the salience and default mode networks showing increased within-network connectivity and negative connectivity between networks and the limbic network showing increased connectivity with frontal and occipital regions [192]. These findings were presumed to reflect the spread of neurofibrillary tangles from limbic to neocortical regions before overt brain atrophy could be detected in those regions [191].

Fluid biomarkers in AD include cerebrospinal and blood-based (plasma) biomarkers. The heterogeneity of the pathophysiology of AD is clearly reflected in these fluid biomarkers, which is described below but is likely to grow to include those reflecting inflammation, synaptic dysfunction, vascular dysregulation, and α-synuclein pathology [193].

Amyloid and Tau Biomarkers in Aging and AD

The National Institute on Aging — Alzheimer's Association Framework on AD provides biomarker profiles of individuals in the AD spectrum using three types of biomarkers — Aβ (A), tau (T), and neurodegeneration (N), known as the ATN framework. Each element of the ATN framework is rated as negative or positive and characterized as follows: A − /+ , T − /+ , and N − /+ [194]. These biomarkers may be measured in CSF, by MRI, and by PET scanning. The measures for "A" include CSF Aβ-protein 42 (Aβ42/40) and amyloid plaque load in the brain by PET; for "T," CSF and phospho-tau (p-tau) and tau positron emission tomography; and for "N," CSF total tau, atrophy on MRI measured volumetrically and by cortical thickness and by the presence of metabolic deficits on fluorodeoxyglucose (FDG) PET. More recently, plasma biomarkers of Aβ, tau, and neurodegeneration have also been developed.

Using these biomarker profiles, Jack et al. [195] assessed the prevalence of Aβ ($n=1524$) and tau pathology ($n=576$) in the Mayo Clinic Study on Aging using PET measures. They found that the prevalence of all diagnostic entities (biological and clinical) increased rapidly with age. Not surprisingly, the prevalence of biological AD was found to be greater than clinically defined probable AD. Jack et al. [196] also evaluated memory decline in relation to the ATN profile among non-demented participants in the Mayo Clinic Study on Aging, who were followed for a median of 4.8 years. As would be expected, memory declined fastest in the A + T + (N) + , A + T + (N) − , and A + T − (N) + groups compared with the other 5 AT(N) groups.

Jansen et al. [197] evaluated the prevalence of amyloid pathology among individuals 50 to 90 years of age, using CSF and PET Aβ imaging. Pathological amyloidosis was present 2–3 times more frequently among carriers of one or more APOE-ε4 alleles as compared to noncarriers. The frequency of Aβ positivity increased with age from 10 to 44% among participants with normal cognition and subjective cognitive complaints and from 27 to 71% of MCI patients. Importantly, this investigation indicated a 20- to 30-year interval between the initial development of Aβ positivity and the onset of dementia.

Plasma-Based AD and Neurodegenerative Biomarker Profiles

The recent development of plasma biomarkers has generated much interest in the possibility that molecular biomarkers for AD could be assessed conveniently and inexpensively and be used as a screening test. These plasma biomarkers have been found to predict AD pathology and clinical progression in older adults without dementia and are associated with brain Aβ burden, tau pathology, and neurodegeneration. Studies have been done on validating the methodology and evaluating new insights about AD diagnosis and progression rates. Shen et al. [198] conducted a cross-sectional and longitudinal analysis of data from 183 participants enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI), divided into those who were cognitively normal ($n=97$) and those with MCI ($n=86$). Plasma amyloid-beta (Aβ) 1–42/Aβ1-40 ratio was selected as the marker for amyloid pathology, p-tau181 for tau pathology, and neurofilament light for neurodegeneration. The participants were categorized into eight groups at baseline by plasma amyloid/tau/neurodegeneration (A/T/N) cutoffs. Those who were A + had significantly higher proportions of APOE ε4 carriers than those who were A − , and those who were A + T + N + or A + T + N − were at the highest risk of clinical progression. Compared to those who were A − T − N, MCI patients who were A + T + N + had faster cognitive worsening and faster brain atrophy.

Currently, there is a concern that the different methodologies used to measure plasma Aβ42/40, in particular, may provide very different discriminative accuracies. In a recent head-to-head comparison of 8 different Aβ assays, using data from two different cohorts (Biofinder and ADNI) [199], plasma Aβ42/40 findings were compared to those from Aβ PET imaging and CSF. As compared to findings from CSF Aβ42/40, the results from 2 independent cohorts indicated that certain mass spectrometry-based studies

performed significantly better than most of the immunoassays for plasma Aβ42/40. In addition to p-tau181, phospho-tau217 (p-tau217) has recently been introduced as a marker of tau pathology and has been found to be increased even in early preclinical AD when the tau PET signal in the entorhinal cortex is still normal [200].

Biomarker findings, including those from structural and functional MRI, FDG-PET, Aβ, and tau imaging, in combination with demographic, genetic, clinical, and neuropsychological data, have been gleaned from the cumulative data in the ADNI multimodal longitudinal database by Veitch et al. [201]. Among some insights gleaned from this analysis, it was found that β-amyloid (Aβ) deposition occurs concurrently with functional connectivity changes within the default mode network in preclinical subjects, followed by specific and progressive disconnection of functional and anatomical networks. Also, it was found that changes in functional connectivity, volumetric measures, regional hypometabolism, and cognition were detectable at subthreshold levels of Aβ deposition, and that tau PET imaging studies identified a specific temporal and spatial pattern of tau pathology based on prior Aβ deposition and related to subsequent cognitive decline. Other important insights from this analysis include the finding that vascular pathology appears to act through both Aβ dependent and independent mechanisms to exacerbate AD progression, and that the APOE ε4 allele interacts with cerebrovascular disease to impede Aβ clearance.

Implications for Clinical Trials

The foundation for many clinical trials starting in the 1990s is the amyloid cascade hypothesis [202, 203]. With the advent of disease-modifying treatments for amyloid and, more recently, tau, the emphasis has shifted to finding participants who are earlier in the course of illness and have specific genotypes or biological phenotypes. Biomarkers have been shown to identify which subjects are at the greatest risk for cognitive decline and those most appropriate for treatment trials [204]. The enrichment of trials by selecting subjects who are more likely to decline increases the power of the trial to detect treatment differences [205]. The progression rate in people at any cognitive level is greater among those who are Aβ positive compared to those who Aβ negative [92] so that the impact of the inadvertent inclusion or exclusion of Aβ-positive individuals in any arm of a clinical trial is likely to reduce power to find an effect in prevention and treatment trials. Before the advent of methods for determining cerebral amyloid levels, prevention trials included many cognitively normal participants positive for Aβ, while AD clinical trials included many individuals negative for Aβ. In the Amyloid Biomarker Study, the frequency of amyloid positivity increases with age with only 10% of cognitively normal subjects at age 50 years but 44% of those at age 90 years being amyloid positive [197]. In this study, among those with MCI, the percentages of Aβ positivity was 27% at age 50 and 71% at age 90, and APOE e4 carriers have a 2- to threefold higher prevalence of Aβ positivity compared to noncarriers.

Tau pathology measured by PET has been shown to predict cognitive decline in people with AD and older subjects with normal cognition or MCI, independent of Aβ deposition [206, 207]. The use of PET scanning with new tau radioligands using the regional pattern of tau deposition has led to in vivo Braak staging for: use as an inclusion criterion, stratification of subjects based on Braak stage [208], and the exclusion of participants considered to have a Braak stage too advanced for effective treatment. It appears that even though subjects with high Braak staging have faster rates of decline, they also have greater heterogeneity in the rate of progression than those with a lower risk for progression (e.g., those with low tau) [209].

The Challenge in Designing Clinical Trials, Accounting for the Heterogeneity in Presentation and the Rates of Progression of AD

Alzheimer's disease is heterogeneous in its clinical presentation and its rates of progression, with considerable overlap in the phenotypic and temporal heterogeneity. A major challenge in the design of clinical trials is to either disentangle this phenotypic and temporal heterogeneity or combine them to identify distinct subtypes and then characterize their individual characteristics to enable the stratification of trial populations with predictable rates of progression. Several models have emerged, using a variety of modeling techniques and using machine learning methods, cluster analyses, and neural network analyses [210, 211]. Current models use only a small subset of available risk factors and biomarkers, and more longitudinal data with richer features are needed to better determine and subtype the drivers of progression rates [77, 201]. Placebo versus treatment group differences on cognitive outcome measures may depend on variation in the sampling of slow versus fast progressors as well as cognitive reserve and resilience [139]. Equivalent severity of brain pathology often presents with different severities of clinical symptoms and rates of progression [208, 212]. Exclusion of certain factors, especially certain known medical and psychiatric conditions, medications, and environmental stressors, will also help in ensuring a successful clinical trial. Such personalized medicine approaches should provide the adaptive designs to enable tailored cognitive interventions and help characterize more homogeneous AD groups for clinical

trials. After a medication has been shown to have a greater benefit than risk in a homogenous group, subsequent trials can study the medication in a more heterogeneous population. For example, donepezil was originally approved by the FDA for use in mild to moderate AD but subsequently has been studied in people with MCI, dementia with Lewy bodies, and vascular dementia.

In summary, AD is a heterogeneous disorder with multiple phenotypes and genotypes. Currently, AD drug trials do not account sufficiently for the heterogeneity of the disease in trial design, impeding the development of effective drugs. Greater effort in accounting for this heterogeneity should yield better outcomes in AD clinical trials [213].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13311-022-01185-z.

Acknowledgements This research was supported by the National Institute of Aging grant number 1P30AG066506-01 Florida Alzheimer's Disease Research Center (Todd Golde, PI).

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

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Boyle PA, Yu L, Leurgans SE, Wilson RS, Brookmeyer R, Schneider JA, Bennett DA. Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies. Ann Neurol. 2019;85(1):114–24.
2. Kawas CH, Kim RC, Sonnen JA, Bullain SS, Trieu T, Corrada MM. Multiple pathologies are common and related to dementia in the oldest-old: the 90+ Study. Neurology. 2015;85(6):535–42.
3. Komarova NL, Thalhauser CJ. High degree of heterogeneity in Alzheimer's disease progression patterns. PLoS Comput Biol. 2011;7(11):e1002251.
4. Hanseeuw BJ, Betensky RA, Jacobs HIL, et al. Association of amyloid and tau with cognition in preclinical Alzheimer disease: a longitudinal study. JAMA Neurol. 2019;76(8):915–24.
5. Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. Nat Rev Neurosci. 2018;19(11):687–700.
6. Rabinovici GD. Late-onset Alzheimer disease. Continuum (Minneap Minn). 2019;25(1):14–33.
7. Ryman DC, Acosta-Baena N, Aisen PS, et al. Dominantly inherited Alzheimer network. Symptom onset in autosomal dominant Alzheimer disease: a systematic review and meta-analysis. Neurology. 2014;83(3):253–60.
8. Petersen RC, Thomas RG, Grundman M, Alzheimer's Disease Cooperative Study Group, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005;352(23):2379–88.
9. Stone DJ, Molony C, Suver C, Schadt EE, Potter WZ. ApoE genotyping as a progression-rate biomarker in phase II disease-modification trials for Alzheimer's disease. Pharmacogenomics J. 2010;10(3):161–4.
10. Suzuki K, Hirakawa A, Ihara R, et al. Effect of apolipoprotein E ε4 allele on the progression of cognitive decline in the early stage of Alzheimer's disease. Alzheimers Dement (N Y). 2020;6(1):e12007.
11. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer disease meta-analysis consortium. JAMA. 1997;278(16):1349–56.
12. Sweet RA, Nimgaonkar VL, Devlin B, et al. Psychotic symptoms in Alzheimer disease: evidence for a distinct phenotype. Mol Psychiatry. 2003;8:383–92.
13. Emanuel JE, Lopez OL, Houck PR, et al. Trajectory of cognitive decline as a predictor of psychosis in early Alzheimer disease in the Cardiovascular Health Study. Am J Geriatr Psychiatry. 2011;19(2):160–8.
14. Moreno DJ, Ruiz S, Ríos Á, et al. Association of GWAS top genes with late-onset Alzheimer's disease in Colombian population. Am J Alzheimers Dis Other Demen. 2017;32(1):27–35.
15. Sweet RA, Seltman H, Emanuel JE, et al. Effect of Alzheimer's disease risk genes on trajectories of cognitive function in the Cardiovascular Health Study. Am J Psychiatry. 2012;169(9):954–62.
16. Yashin AI, Fang F, Kovtun M, et al. Hidden heterogeneity in Alzheimer's disease: insights from genetic association studies and other analyses. Exp Gerontol. 2018;107:148–60.
17. Garai K, Verghese PB, Baban B, Holtzman DM, Frieden C. The binding of apolipoprotein E to oligomers and fibrils of amyloid-β alters the kinetics of amyloid aggregation. Biochemistry. 2014;53(40):6323–31.
18. Resnick SM, Bilgel M, Moghekar A, et al. Changes in Aβ biomarkers and associations with APOE genotype in 2 longitudinal cohorts. Neurobiol Aging. 2015;36(8):2333–9.
19. Huynh TV, Liao F, Francis CM, et al. Age-dependent effects of apoE reduction using antisense oligonucleotides in a model of β-amyloidosis. Neuron. 2017;96(5):1013–23.
20. Koldamova R, Fitz NF, Lefterov I. The role of ATP-binding cassette transporter A1 in Alzheimer's disease and neurodegeneration. Biochim Biophys Acta. 2010;1801(8):824–30.
21. Castellano JM, Kim J, Stewart FR, et al. Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. Sci Transl Med. 2011;3(89):89ra57.
22. Bekris LM, Galloway NM, Millard S, et al. Amyloid precursor protein (APP) processing genes and cerebrospinal fluid APP cleavage product levels in Alzheimer's disease. Neurobiol Aging. 2011;32(3):556.e513-523.
23. Naj AC, Jun G, Reitz C, et al. Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. JAMA Neurol. 2014;71(11):1394–404.
24. Ma XY, Yu JT, Wang W, et al. Association of TOMM40 polymorphisms with late-onset Alzheimer's disease in a Northern Han Chinese population. Neuromolecular Med. 2013;15(2):279–87.
25. Deelen J, Beekman M, Uh HW, et al. Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited. Aging Cell. 2011;10(4):686–98.
26. Shadyab AH, Kooperberg C, Reiner AP, et al. Replication of genome-wide association study findings of longevity in White, African American, and Hispanic women: the Women's Health Initiative. J Gerontol A Biol Sci Med Sci. 2017;72(10):1401–6.
27. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet. 2009;41(10):1088–93.
28. Holliday EG, Smith AV, Cornes BK, et al. Insights into the genetic architecture of early stage age-related macular degeneration: a genome-wide association study meta-analysis. PLoS One. 2013;8(1):e53830.

29. Weinstein G, Wolf PA, Beiser AS, Au R, Seshadri S. Risk estimations, risk factors, and genetic variants associated with Alzheimer's disease in selected publications from the Framingham Heart Study. J Alzheimers Dis. 2013;33(Suppl 1):S439–45.
30. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The cardiovascular health study: design and rationale. Ann Epidemiol. 1991;1:263–76.
31. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JW, Weir DR. Cohort profile: the Health and Retirement Study (HRS). Int J Epidemiol. 2014;43:576–85.
32. Yashin AI, Fang F, Kovtun M, Wu D, Duan M, Arbeev K, et al. Hidden heterogeneity in Alzheimer's disease: insights from genetic association studies and other analyses. Exp Gerontol. 2018;107:148–60.
33. Urosevic N, Martins RN. Infection and Alzheimer's disease: the APOE epsilon4 connection and lipid metabolism. J Alzheimers Dis. 2008;13(4):421–35.
34. Miklossy J. Emerging roles of pathogens in Alzheimer disease. Expert Rev Mol Med. 2011;13:e30.
35. Itzhaki RF. Herpes and Alzheimer's disease: subversion in the central nervous system and how it might be halted. J Alzheimers Dis. 2016;54(4):1273–81.
36. Itzhaki RF, Lathe R, Balin BJ, et al. Microbes and Alzheimer's disease. J Alzheimers Dis. 2016;51(4):979–84.
37. De Chiara G, Marcocci ME, Sgarbanti R, et al. Infectious agents and neurodegeneration. Mol Neurobiol. 2012;46(3):614–38.
38. Porcellini E, Carbone I, Ianni M, Licastro F. Alzheimer's disease gene signature says: beware of brain viral infections. Immun Ageing. 2010;7:16.
39. Logue MW, Schu M, Vardarajan BN, et al. A comprehensive genetic association study of Alzheimer disease in African Americans. Arch Neurol. 2011;68(12):1569–79.
40. Zhou Q, Zhao F, Lv ZP, et al. Association between APOC1 polymorphism and Alzheimer's disease: a case-control study and meta-analysis. PLoS One. 2014;9(1):e87017.
41. Omoumi A, Fok A, Greenwood T, Sadovnick AD, Feldman HH, Hsiung GY. Evaluation of late-onset Alzheimer disease genetic susceptibility risks in a Canadian population. Neurobiol Aging. 2014;35(4):936.e935-912.
42. Gao L, Cui Z, Shen L, Ji HF. Shared genetic etiology between type 2 diabetes and Alzheimer's disease identified by bioinformatics analysis. J Alzheimers Dis. 2016;50(1):13–7.
43. Ang LS, Cruz RP, Hendel A, Granville DJ. Apolipoprotein E, an important player in longevity and age-related diseases. Exp Gerontol. 2008;43(7):615–22.
44. Nebel A, Kleindorp R, Caliebe A, et al. A genome-wide association study confirms APOE as the major gene influencing survival in long-lived individuals. Mech Ageing Dev. 2011;132(6–7):324–30.
45. Lu F, Guan H, Gong B, et al. Genetic variants in PVRL2-TOMM40-APOE region are associated with human longevity in a Han Chinese population. PLoS One. 2014;9(6):e99580.
46. Garatachea N, Emanuele E, Calero M, et al. ApoE gene and exceptional longevity: insights from three independent cohorts. Exp Gerontol. 2014;53:16–23.
47. Garatachea N, Marin PJ, Santos-Lozano A, Sanchis-Gomar F, Emanuele E, Lucia A. The ApoE gene is related with exceptional longevity: a systematic review and meta-analysis. Rejuvenation Res. 2015;18(1):3–13.
48. Deelen J, Beekman M, Uh HW, et al. Genome-wide association meta-analysis of human longevity identifies a novel locus conferring survival beyond 90 years of age. Hum Mol Genet. 2014;23(16):4420–32.
49. Lin R, Zhang Y, Yan D, Liao X, Gong G, Hu J, Fu Y, Cai W. Association of common variants in TOMM40/APOE/APOC1 region with human longevity in a Chinese population. J Hum Genet. 2016;61(4):323–8.
50. Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2010;466(7307):707–13.
51. Chang TY, Chang C. ApoE and lipid homeostasis in Alzheimer's disease: introduction to the thematic review series. J Lipid Res. 2017;58(5):823.
52. Lyall DM, Harris SE, Bastin ME, et al. Are APOE varepsilon genotype and TOMM40 poly-T repeat length associations with cognitive ageing mediated by brain white matter tract integrity? Transl Psychiatry. 2014;4(9):e449–e449.
53. Newman AB, Walter S, Lunetta KL, et al. A meta-analysis of four genome-wide association studies of survival to age 90 years or older: the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. J Gerontol A Biol Sci Med Sci. 2010;65(5):478–87.
54. Rebeck GW. The role of APOE on lipid homeostasis and inflammation in normal brains. J Lipid Res. 2017;58(8):1493–9.
55. Slattery ML, Sweeney C, Murtaugh M, et al. Associations between apoE genotype and colon and rectal cancer. Carcinogenesis. 2005;26(8):1422–9.
56. Watson MA, Gay L, Stebbings WS, Speakman CT, Bingham SA, Loktionov A. Apolipoprotein E gene polymorphism and colorectal cancer: gender-specific modulation of risk and prognosis. Clin Sci (Lond). 2003;104(5):537–45.
57. El-Lebedy D, Raslan HM, Mohammed AM. Apolipoprotein E gene polymorphism and risk of type 2 diabetes and cardiovascular disease. Cardiovasc Diabetol. 2016;15:12.
58. Sun MK, Alkon DL. Links between Alzheimer's disease and diabetes. Drugs Today (Barc). 2006;42(7):481–9.
59. Bornstein NM, Brainin M, Guekht A, Skoog I, Korczyn AD. Diabetes and the brain: issues and unmet needs. Neurol Sci. 2014;35(7):995–1001.
60. Abbatecola AM, Olivieri F, Corsonello A, Antonicelli R, Corica F, Lattanzio F. Genome-wide association studies: is there a genotype for cognitive decline in older persons with type 2 diabetes? Curr Pharm Des. 2011;17(4):347–56.
61. Barbagallo M, Dominguez LJ. Type 2 diabetes mellitus and Alzheimer's disease. World J Diabetes. 2014;5(6):889–93.
62. Bosco D, Fava A, Plastino M, Montalcini T, Pujia A. Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. J Cell Mol Med. 2011;15(9):1807–21.
63. Correia SC, Santos RX, Carvalho C, et al. Insulin signaling, glucose metabolism and mitochondria: major players in Alzheimer's disease and diabetes interrelation. Brain Res. 2012;1441:64–78.
64. Dai Y, Kamal MA. Fighting Alzheimer's disease and type 2 diabetes: pathological links and treatment strategies. CNS Neurol Disord Drug Targets. 2014;13(2):271–82.
65. De Felice FG, Lourenco MV, Ferreira ST. How does brain insulin resistance develop in Alzheimer's disease? Alzheimers Dement. 2014;10(1 Suppl):S26-32.
66. Steen E, Terry BM, Rivera EJ, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease–is this type 3 diabetes? J Alzheimers Dis. 2005;7(1):63–80.
67. Dar TA, Sheikh IA, Ganie SA, et al. Molecular linkages between diabetes and Alzheimer's disease: current scenario and future prospects. CNS Neurol Disord Drug Targets. 2014;13(2):290–8.
68. Grimm A, Friedland K, Eckert A. Mitochondrial dysfunction: the missing link between aging and sporadic Alzheimer's disease. Biogerontology. 2016;17(2):281–96.
69. Bao J, Wang XJ, Mao ZF. Associations between genetic variants in 19p13 and 19q13 regions and susceptibility to Alzheimer disease: a meta-analysis. Med Sci Monit. 2016;22:234–43.
70. Escott-Price V, Myers AJ, Huentelman M, Hardy J. Polygenic risk score analysis of pathologically confirmed Alzheimer disease. Ann Neurol. 2017;82:311–4.

71. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nat Rev Genet. 2018;19:581–90.
72. Desikan R, Fan C, Wang Y, et al. Genetic assessment of age-associated Alzheimer disease risk: development and validation of a polygenic hazard score. PLoS Med. 2017;14(3):1–17.
73. Morgan AR, Touchard S, O'Hagan C, et al. The correlation between inflammatory biomarkers and polygenic risk score in Alzheimer's disease. J Alzheimers Dis. 2017;56:25–36.
74. Sleegers K, Bettens K, De Roeck A, et al. A 22-single nucleotide polymorphism Alzheimer's disease risk score correlates with family history, onset age, and cerebrospinal fluid Aβ42. Alzheimers Dement. 2015;11:1452–60.
75. Escott-Price V, Shoai M, Pither R, Williams J, Hardy J. Polygenic score prediction captures nearly all common genetic risk for Alzheimer's disease. Neurobiol Aging. 2017;49(214):e7-214.e11.
76. Xiao Q, Liu Z-J, Tao S, et al. Risk prediction for sporadic Alzheimer's disease using genetic risk score in the Han Chinese population. Oncotarget. 2015;6:36955–64.
77. Badhwar A, McFall GP, Sapkota S, et al. A multiomics approach to heterogeneity in Alzheimer's disease: focused review and roadmap. Brain. 2020;143(5):1315–31.
78. Liu Y, Tan L, Wang HF, et al. Multiple effect of APOE genotype on clinical and neuroimaging biomarkers across Alzheimer's disease spectrum. Mol Neurobiol. 2016;53(7):4539–47.
79. Hostage CA, Roy Choudhury K, Doraiswamy PM, Petrella JR, Alzheimer's Disease Neuroimaging Initiative. Dissecting the gene dose-effects of the APOE ε4 and ε2 alleles on hippocampal volumes in aging and Alzheimer's disease. PLoS One. 2013;8(2):e54483.
80. Penninkilampi R, Brothers HM, Eslick GD. Safety and efficacy of anti-amyloid-β immunotherapy in Alzheimer's disease: a systematic review and meta-analysis. J Neuroimmune Pharmacol. 2017;12(1):194–203.
81. Sperling R, Salloway S, Brooks DJ, et al. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. Lancet Neurol. 2012;11(3):241–9.
82. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. JAMA Neurol. 2021;e214161.
83. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology. 2007;69(24):2197–204.
84. Rahimi J, Kovacs GG. Prevalence of mixed pathologies in the aging brain. Alz Res Therapy. 2014;6:82.
85. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010. J Neuropathol Exp Neurol. 2012;71:266–73.
86. Robinson JL, Lee EB, Xie SX, Rennert L, Suh E, Bredenberg C, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. Brain. 2018;141:2181–93.
87. Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord. 2002;16(4):203–12.
88. Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006;66:1837–44.
89. Jagust W. Vulnerable neural systems and the borderland of brain aging and neurodegeneration. Neuron. 2013;77:219–34.
90. Boyle PA, Yu L, Wilson RS, Schneider JA, Bennett DA. Relation of neuropathology with cognitive decline among older persons without dementia. Front Aging Neurosci. 2013;5:50.
91. Besser LM, Teylan MA, Nelson PT. Limbic predominant age-related TDP-43 encephalopathy (LATE): clinical and neuropathological associations. J Neuropathol Exp Neurol. 2020;79(3):305–13.
92. Jack CR, Knopman DS, Chételat G, et al. Suspected non-Alzheimer disease pathophysiology-concept and controversy. Nat Rev Neurol. 2016;12(2):117–24.
93. Robinson JL, Corrada MM, Kovacs GG, et al. Non-Alzheimer's contributions to dementia and cognitive resilience in the 90+ Study. Acta Neuropathol. 2018;136(3):377–88.
94. Karanth S, Nelson PT, Katsumata Y, et al. Prevalence and clinical phenotype of quadruple misfolded proteins in older adults. JAMA Neurol. 2020;77(10):1299–307.
95. Braak H, Del Tredici K. Reply: the early pathological process in sporadic Alzheimer's disease. Acta Neuropathol. 2013;126(4):615–8.
96. Cohen ML, Kim C, Haldiman T, et al. Rapidly progressive Alzheimer's disease features distinct structures of amyloid-β. Brain. 2015;138(Pt 4):1009–22.
97. Condello C, Lemmin T, Stöhr J, et al. Structural heterogeneity and intersubject variability of Aβ in familial and sporadic Alzheimer's disease. Proc Natl Acad Sci U S A. 2018;115(4):E782–91.
98. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. The Lancet Neurology. 2011;10(9):785–96.
99. Brenowitz WD, Hubbard RA, Keene CD, Hawes SE, Longstreth WT Jr, Woltjer RL, Kukull WA. Mixed neuropathologies and estimated rates of clinical progression in a large autopsy sample. Alzheimers Dement. 2017;13(6):654–62.
100. Reed BR, Mungas DM, Kramer JH, Ellis W, Vinters HV, Zarow C, Jagust WJ, Chui HC. Profiles of neuropsychological impairment in autopsy-defined Alzheimer's disease and cerebrovascular disease. Brain. 2007;130(Pt 3):731–9.
101. 2020 Alzheimer's disease facts and figures. Alzheimer's Dement. 2020;16:391-460.
102. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology. 2013;80(19):1778–83.
103. Chêne G, Beiser A, Au R, et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. Alzheimers Dement. 2015;11(3):310–20.
104. Seshadri S, Wolf PA, Beiser A, et al. Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. Neurology. 1997;49(6):1498–504.
105. Hebert LE, Scherr PA, McCann JJ, Beckett LA, Evans DA. Is the risk of developing Alzheimer's disease greater for women than for men? Am J Epidemiol. 2001;153(2):132–6.
106. Levine DA, Gross AL, Briceño EM, et al. Sex differences in cognitive decline among US adults. JAMA Netw Open. 2021;4(2):e210169.
107. Mielke MM, Ferretti MT, Iulita MF, Hayden K, Khachaturian AS. Sex and gender in Alzheimer's disease - does it matter? Alzheimers Dement. 2018;14(9):1101–3.
108. Rocca WA. Time, sex, gender, history, and dementia. Alzheimer Dis Assoc Disord. 2017;31(1):76–9.
109. Santos OA, Pedraza O, Lucas JA, et al. Ethnoracial differences in Alzheimer's disease from the FLorida Autopsied Multi-Ethnic (FLAME) cohort. Alzheimers Dement. 2019;15(5):635–43.

110. Liesinger AM, Graff-Radford NR, Duara R, et al. Sex and age interact to determine clinicopathologic differences in Alzheimer's disease. Acta Neuropathol. 2018;136(6):873–85.
111. Gurland BJ, Wilder DE, Lantigua R, et al. Rates of dementia in three ethnoracial groups. Int J Geriatr Psychiatry. 1999;14(6):481–93.
112. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of dementia in older Latinos: the influence of type2 diabetes mellitus, stroke and genetic factors. Jam Geriatr Soc. 2003;51:169–77.
113. Potter GG, Plassman BL, Burke JR, et al. Cognitive performance and informant reports in the diagnosis of cognitive impairment and dementia in African Americans and Whites. Alzheimers Dement. 2009;5(6):445–53.
114. Samper-Ternent R, Kuo YF, Ray LA, Ottenbacher KJ, Markides KS, AlSnih S. Prevalence of health conditions and predictors of mortality in oldest old Mexican Americans and non-Hispanic Whites. J Am Med Dir Assn. 2012;13(3):254–9.
115. González HM, Tarraf W, Schneiderman N, et al. Prevalence and correlates of mild cognitive impairment among diverse Hispanics/Latinos: study of Latinos-investigation of neurocognitive aging results. Alzheimers Dement. 2019;15(12):1507–15.
116. Mehta KM, Yeo GW. Systematic review of dementia prevalence and incidence in United States race/ethnic populations. Alzheimers Dement. 2017;13(1):72–83.
117. Perkins P, Annegers JF, Doody RS, Cooke N, Aday L, Vernon SW. Incidence and prevalence of dementia in a multiethnic cohort of municipal retirees. Neurology. 1997;49(1):44–50.
118. Froehlich TE, Bogardus ST Jr, Inouye SK. Dementia and race: are there differences between African Americans and Caucasians? J Am Geriatr Soc. 2001;49(4):477–84.
119. Weuve J, Barnes LL, de Leon CFM, et al. Cognitive aging in Black and White Americans: cognition, cognitive decline, and incidence of Alzheimer disease dementia. Epidemiology. 2018;29(1):151–9.
120. Reitz C, Jun G, Naj A, Rajbhandary R, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E epsilon 4, and the risk of late-onset Alzheimer disease in African Americans. JAMA. 2013;309(14):1483–92.
121. Yaffe K, Falvey C, Harris TB, et al. Effect of socioeconomic disparities on incidence of dementia among biracial older adults: prospective study. BMJ. 2013;347:f7051.
122. Chin AL, Negash S, Hamilton R. Diversity and disparity in dementia: the impact of ethnoracial differences in Alzheimer disease. Alzheimer Dis Assoc Disord. 2011;25(3):187–95.
123. Glymour MM, Manly JJ. Lifecourse social conditions and racial and ethnic patterns of cognitive aging. Neuropsychol Rev. 2008;18(3):223–54.
124. Lines LM, Sherif NA, Wiener JM. Racial and ethnic disparities among individuals with Alzheimer's disease in the United States: a literature review. Research Triangle Park, NC: RTI Press; 2014. p. 248.
125. Zhang Z, Hayward MD, Yu YL. Life course pathways to racial disparities in cognitive impairment among older Americans. J Health Soc Behav. 2016;57(2):184–99.
126. Barnes LL, de Leon CFM, Wilson RS, Bienias JL, Evans DA. Social resources and cognitive decline in a population of older African Americans and Whites. Neurology. 2004;63(12):2322–6.
127. Bourassa KJ, Memel M, Woolverton C, Sbarra DA. Social participation predicts cognitive functioning in aging adults over time: comparisons with physical health, depression, and physical activity. Aging Ment Health. 2017;21(2):133–46.
128. Cruwys T, Haslam SA, Dingle GA, Haslam C, Jetten J. Depression and social identity: an integrative review. Pers Soc Psychol Rev. 2014;18(3):215–38.
129. Hwang J, Park S, Kim S. Effects of participation in social activities on cognitive function among middle-aged and older adults in Korea. Int J Environ Res Public Health. 2018;15(10):2315.
130. Cohn-Schwartz E. Pathways from social activities to cognitive functioning: the role of physical activity and mental health. Innov Aging. 2020;4(3):igaa015.
131. James BD, Wilson RS, Barnes LL, Bennett DA. Late-life social activity and cognitive decline in old age. J Int Neuropsychol Soc. 2011;17(6):998–1005.
132. Banzi R, Camaioni P, Tettamanti M, Bertele' V, Lucca U. Older patients are still under-represented in clinical trials of Alzheimer's disease. Alzheimers Res Ther. 2016;8:32.
133. Anderson TS, Ayanian JZ, Souza J, Landon BE. Representativeness of participants eligible to be enrolled in clinical trials of aducanumab for Alzheimer disease compared with medicare beneficiaries with Alzheimer disease and mild cognitive impairment. JAMA. 2021:e2115286.
134. Rollin-Sillaire A, Breuilh L, Salleron J, et al. Reasons that prevent the inclusion of Alzheimer's disease patients in clinical trials. Br J Clin Pharmacol. 2013;75(4):1089–97.
135. Burke SL, Hu T, Naseh M, et al. Factors influencing attrition in 35 Alzheimer's disease centers across the USA: a longitudinal examination of the National Alzheimer's Coordinating Center's uniform data set. Aging Clin Exp Res. 2019;31(9):1283–97.
136. Holland D, Desikan RS, Dale AM, McEvoy LK, for the Alzheimer's Disease Neuroimaging Initiative,. Rates of decline in Alzheimer disease decrease with age. PLoS One. 2012;7(8):e42325.
137. Schneider LS, Kennedy RE, Wang G, Cutter GR. Differences in Alzheimer disease clinical trial outcomes based on age of the participants. Neurology. 2015;84(11):1121–7.
138. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: stopping AD before symptoms begin? Sci Transl Med. 2014;6(228):228fs13.
139. Li X, Song R, Qi X, Xu H, Yang W, Kivipelto M, Bennett DA, Xu W. Influence of cognitive reserve on cognitive trajectories: role of brain pathologies. Neurology. 2021;7:10.
140. Dilworth-Anderson P. Introduction to the science of recruitment and retention among ethnically diverse populations. Gerontologist. 2011;51(Suppl 1):S1–4.
141. Dilworth-Anderson P, Thaker S, Burke JM. Recruitment strategies for studying dementia in later life among diverse cultural groups. Alzheimer Dis Assoc Disord. 2005;19(4):256–60.
142. New IDEAS: imaging dementia-evidence for amyloid scanning study, study protocol, 2020. ClinicalTrials.gov identifier: NCT04426539. Updated December 31, 2021. Accessed December 25, 2021. https://clinicaltrials.gov/ct2/show/NCT04426539
143. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256:183–94.
144. Guan H, Tao L, Jiyang J, et al. Classifying MCI subtypes in community-dwelling elderly using cross-sectional and longitudinal MRI-based biomarkers. Front Aging Neurosci. 2017;9:309–22.
145. Rohrer JD, Rossor MN, Warren JD. Alzheimer's pathology in primary progressive aphasia. Neurobiol Aging. 2012;33(4):744–52.
146. Phillips ML, Stage EC Jr, Lane KA, et al. Neurodegenerative patterns of cognitive clusters of early-onset Alzheimer's disease subjects: evidence for disease heterogeneity. Dement Geriatr Cogn Disord. 2019;48(3–4):131–42.
147. Qian J, Betensky RA, Hyman BT, Serrano-Pozo A. Association of APOE genotype with heterogeneity of cognitive decline rate in Alzheimer disease. Neurology. 2021;96(19):e2414–28.
148. Lam B, Masellis M, Freedman M, Stuss DT, Black SE. Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. Alzheimers Res Ther. 2013;5(1):1.
149. Peter J, Abdulkadir A, Kaller C, et al. Subgroups of Alzheimer's disease: stability of empirical clusters over time. J Alzheimers Dis. 2014;42(2):651–61.

150. Tellechea P, Pujol N, Esteve-Belloch P, et al. Early- and late-onset Alzheimer disease: are they the same entity?. Enfermedad de Alzheimer de inicio precoz y de inicio tardío: ¿son la misma entidad? Neurologia (Engl Ed). 2018;33(4):244–53.
151. van der Flier WM, Pijnenburg YA, Fox NC, Scheltens P. Early-onset versus late-onset Alzheimer's disease: the case of the missing APOE ε4 allele. Lancet Neurol. 2011;10(3):280–8.
152. Ye BS, Seo SW, Lee Y, et al. Neuropsychological performance and conversion to Alzheimer's disease in early- compared to late-onset amnestic mild cognitive impairment: CREDOS study. Dement Geriatr Cogn Disord. 2012;34.
153. Mendez MF, Lee AS, Joshi A, Shapira JS. Nonamnestic presentations of early-onset Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2012;27(6):413–20.
154. Fujimori M, Imamura T, Yamashita H, et al. Age at onset and visuocognitive disturbances in Alzheimer disease. Alzheimer Dis Assoc Disord. 1998;12(3):163–6.
155. Loewenstein DA, Mogosky B. Functional assessment of the older adult patient. In: Lichtenberg P, editor. Handbook of assessment in clinical gerontology. New York: John Wiley; 1999. p. 529–54.
156. Montero-Odasso M, Oteng-Amoako A, Speechley M, et al. The motor signature of mild cognitive impairment: results from the gait and brain study. J Gerontol A Biol Sci Med Sci. 2014;69(11):1415–21.
157. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology. 1984;34(7):939–44.
158. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:270–9.
159. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:263–9.
160. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med. 2014;275(3):214–28.
161. Egan MF, Kost J, Voss T, et al. Randomized trial of verubecestat for prodromal Alzheimer's disease. N Engl J Med. 2019;380(15):1408–20.
162. Soininen H, Solomon A, Visser PJ, et al. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. Lancet Neurol. 2017;16(12):965–75.
163. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308–14.
164. Siafarikas N, Selbaek G, Fladby T, Saltyte Benth J, Auning E, Aarsland D. Frequency and subgroups of neuropsychiatric symptoms in mild cognitive impairment and different stages of dementia in Alzheimer's disease. Int Psychogeriatr. 2018;30(1):103–13.
165. Hashimoto M, Yatabe Y, Ishikawa T, et al. Relationship between dementia severity and behavioral and psychological symptoms of dementia in Alzheimer's disease patients. Dement Geriatr Cogn Disord. 2015;5:244–52.
166. Dietlin S, Soto M, Kiyasova V, et al. Neuropsychiatric symptoms and risk of progression to Alzheimer's disease among mild cognitive impairment subjects. J Alzheimers Dis. 2019;70(1):25–34.
167. Peters ME, Schwartz S, Han D, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. Am J Psychiatry. 2015;172(5):460–5.
168. Roberto N, Portella MJ, Marquié M, et al. Neuropsychiatric profile as a predictor of cognitive decline in mild cognitive impairment. Front Aging Neurosci. 2021. https://doi.org/10.3389/fnagi.2021.718949.
169. Burke SL, Maramaldi P, Cadet T, Kukull W. Neuropsychiatric symptoms and apolipoprotein E: associations with eventual Alzheimer's disease development. Arch Gerontol Geriatr. 2016;65:231–8.
170. Pink A, Stokin GB, Bartley MM, et al. Neuropsychiatric symptoms, APOE ε4, and the risk of incident dementia. A population-based study. Neurology. 2015;84(9):935–43.
171. Babulal GM, Ghoshal N, Head D, et al. Mood changes in cognitively normal older adults are linked to Alzheimer disease biomarker levels. Am J Geriatr Psychiatry. 2016;24(11):1095–104.
172. Tetreault AM, Phan T, Orlando D, et al. Network localization of clinical, cognitive, and neuropsychiatric symptoms in Alzheimer's disease. Brain. 2020;143(4):1249–60.
173. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement. 2016;12(2):195–202.
174. Ismail Z, Aguera-Ortiz L, Brodaty H, Cieslak A, Cummings J, Fischer CE. The mild behavioral impairment checklist (MBI-C): a rating scale for neuropsychiatric symptoms in pre-dementia populations. J Alzheimers Dis. 2017;56:929–38.
175. Ismail Z, McGirr A, Gill S, Hu S, Forkert ND, Smith EE. Mild behavioral impairment and subjective cognitive decline predict cognitive and functional decline. J Alzheimers Dis. 2021;80(1):459–69.
176. Sun Y, Xu W, Chen KL, et al. Mild behavioral impairment correlates of cognitive impairments in older adults without dementia: mediation by amyloid pathology. Transl Psychiatry. 2021;11(1):577.
177. Roberto N, Portella MJ, Marquié M, et al. Neuropsychiatric profiles and conversion to dementia in mild cognitive impairment, a latent class analysis. Sci Rep. 2021;11:6448.
178. Gustafson DR, Skoog I, Rosengren L, Zetterberg H, Blennow K. Cerebrospinal fluid beta-amyloid 1–42 concentration may predict cognitive decline in older women. J Neurol Neurosurg Psychiatry. 2007;78(5):461–4.
179. Buchhave P, Minthon L, Zetterberg H, Wallin ÅK, Blennow K, Hansson O. Cerebrospinal fluid levels of β-amyloid 1–42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. Arch Gen Psychiatry. 2012;69(1):98–106.
180. Lim YY, Ellis KA, Ames D, AIBL Research Group, et al. Aβ amyloid, cognition, and APOE genotype in healthy older adults. Alzheimers Dement. 2013;9(5):538–45.
181. Jack CR Jr, Bennett DA, Blennow K, Contributors, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535–62.
182. Qu Y, Ma YH, Huang YY, et al. Blood biomarkers for the diagnosis of amnestic mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2021;128:479–86.
183. Harper L, Barkhof F, Scheltens P, Schott JM, Fox NC. An algorithmic approach to structural imaging in dementia. J Neurol Neurosurg Psychiatry. 2014;85(6):692–8.
184. Jack CR Jr, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rates of hippocampus atrophy correlate with change status in aging and AD. Neurology. 2000;55(4):484–9.
185. Whitwell JL, Dickson DW, Murray ME, et al. Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. Lancet Neurol. 2012;11(10):868–77.
186. Risacher SL, Anderson WH, Charil A, et al. Alzheimer disease brain atrophy subtypes are associated with cognition and rate of decline. Neurology. 2017;89(21):2176–86.

187. Al-Shaikh FSH, Duara R, Crook JE, et al. Selective vulnerability of the nucleus basalis of Meynert among neuropathologic subtypes of Alzheimer disease. JAMA Neurol. 2020;77(2):225–33.
188. Persson K, Eldholm RS, Barca ML, et al. MRI-assessed atrophy subtypes in Alzheimer's disease and the cognitive reserve hypothesis. PLoS One. 2017;12(10):e0186595.
189. Ossenkoppele R, Pijnenburg YA, Perry DC, et al. The behavioural/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features. Brain. 2015;138(Pt 9):2732–49.
190. Young AL, Marinescu RV, Oxtoby NP, et al. Uncovering the heterogeneity and temporal complexity of neurodegenerative diseases with subtype and stage inference. Nat Commun. 2018;9:1–13.
191. Ferreira D, Pereira JB, Volpe G, Westman E. Subtypes of Alzheimer's disease display distinct network abnormalities extending beyond their pattern of brain atrophy. Front Neurol. 2019;10:524.
192. Badhwar A, Tam A, Dansereau C, Orban P, Hoffstaedter F, Bellec P. Resting-state network dysfunction in Alzheimer's disease: a systematic review and meta-analysis. Alzheimers Dement (Amst). 2017;8:73–85.
193. Bjorkli C, Sandvig A, Sandvig I. Bridging the gap between fluid biomarkers for Alzheimer's disease, model systems, and patients. Front Aging Neurosci. 2020;12:272.
194. Cummings J. Special topic section: responses to the NIA-AA research framework. Alzheimers Dement. 2019;15:172–8.
195. Jack CR Jr, Wiste HJ, Weigand SD, et al. Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50–95 years: a cross-sectional study. Lancet Neurol. 2017;16(6):435–44.
196. Jack CR Jr, Wiste HJ, Therneau TM, et al. Associations of amyloid, tau, and neurodegeneration biomarker profiles with rates of memory decline among individuals without dementia. JAMA. 2019;321(23):2316–25.
197. Jansen WJ, Ossenkoppele R, Knol DL, Amyloid Biomarker Study Group, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA. 2015;313(19):1924–38.
198. Shen XN, Li JQ, Wang HF, et al. Plasma amyloid, tau, and neurodegeneration biomarker profiles predict Alzheimer's disease pathology and clinical progression in older adults without dementia. Alzheimers Dement (Amst). 2020;12(1):e12104.
199. Janelidze S, Teunissen CE, Zetterberg H, et al. Head-to-Head Comparison of 8 Plasma Amyloid-β 42/40 Assays in Alzheimer Disease. JAMA Neurol. 2021;78(11):1375-1382.
200. Janelidze S, Berron D, Smith R, et al. Associations of plasma phospho-tau217 levels with tau positron emission tomography in early Alzheimer disease. JAMA Neurol. 2021;78(2):149–56.
201. Veitch DP, Weiner MW, Aisen PS, et al. Understanding disease progression and improving Alzheimer's disease clinical trials: recent highlights from the Alzheimer's Disease Neuroimaging Initiative. Alzheimers Dement. 2019;15(1):106–52.
202. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet. 1976;2(8000):1403.
203. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353–6.
204. De Meyer G, Shapiro F, Vanderstichele H, et al. Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. Arch Neurol. 2010;67(8):949–56.
205. Holland D, McEvoy LK, Desikan RS, Dale AM, Alzheimer's Disease Neuroimaging Initiative. Enrichment and stratification for predementia Alzheimer disease clinical trials. PLoS One. 2012;7(10):e47739.
206. Malpetti M, Kievit RA, Passamonti L, et al. Microglial activation and tau burden predict cognitive decline in Alzheimer's disease. Brain. 2020;143(5):1588–602.
207. Biel D, Brendel M, Rubinski A, Buerger K, Janowitz D, Dichgans M, Franzmeier N, Alzheimer's Disease Neuroimaging Initiative (ADNI). Tau-PET and in vivo Braak-staging as prognostic markers of future cognitive decline in cognitively normal to demented individuals. Alzheimers Res Ther. 2021;13(1):137.
208. Mintun MA, Lo AC, Duggan Evans C, Wessels AM, et al. Donanemab in early Alzheimer's disease. N Engl J Med. 2021;384(18):1691–704.
209. Jutten RJ, Sikkes SA, Van der Flier W, Scheltens P, Visser PJ, Tijms PM, for the Alzheimer's Disease Neuroimaging Initiative. Finding treatment effects in Alzheimer trials in the face of disease progression heterogeneity. Neurology. 2021;96(22):e2673–84.
210. Goyal D, Tjandra D, Migrino RQ, Giordani B, Syed Z, Wiens J. Characterizing heterogeneity in the progression of Alzheimer's disease using longitudinal clinical and neuroimaging biomarkers. Alzheimers Dement (Amst). 2018;10:629–37.
211. Blanken AE, Dutt S, Li Y, Nation DA, Alzheimer's Disease Neuroimaging Initiative. Disentangling heterogeneity in Alzheimer's disease: two empirically-derived subtypes. J Alzheimers Dis. 2019;70(1):227–39.
212. Blanken AE, Jang JY, Ho JK, et al. Distilling heterogeneity of mild cognitive impairment in the National Alzheimer Coordinating Center Database using latent profile analysis. JAMA Netw Open. 2020;3(3):e200413.
213. Devi G, Scheltens P. Heterogeneity of Alzheimer's disease: consequence for drug trials? Alzheimers Res Ther. 2018;10(1):122.