


The Alzheimer's Disease Neuroimaging Initiative in the era of Alzheimer's disease treatment: A review of ADNI studies from 2021 to 2022

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Abstract

The Alzheimer's Disease Neuroimaging Initiative (ADNI) aims to improve Alzheimer's disease (AD) clinical trials. Since 2006, ADNI has shared clinical, neuroimaging, and cognitive data, and biofluid samples. We used conventional search methods to identify 1459 publications from 2021 to 2022 using ADNI data/samples and reviewed 291 impactful studies. This review details how ADNI studies improved disease progression understanding and clinical trial efficiency. Advances in subject selection, detection of treatment effects, harmonization, and modeling improved clinical trials and plasma biomarkers like phosphorylated tau showed promise for clinical use. Biomarkers of amyloid beta, tau, neurodegeneration, inflammation, and others were prognostic with individualized prediction algorithms available online. Studies supported the amyloid cascade, emphasized the importance of neuroinflammation, and detailed widespread heterogeneity in disease, linked to genetic and vascular risk, co-pathologies, sex, and resilience. Biological subtypes were consistently observed. Generalizability of ADNI results is limited by lack of cohort diversity, an issue ADNI-4 aims to address by enrolling a diverse cohort.

KEYWORDS

Alzheimer's disease clinical trials, Alzheimer's Disease Neuroimaging Initiative, Alzheimer's disease subtypes, amyloid, cerebrovascular disease, co-pathologies, diagnosis, disease progression, generalizability, neurodegeneration, neuroinflammation, plasma biomarkers, prediction, resilience, tau

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1 | INTRODUCTION

As the Alzheimer's Disease Neuroimaging Initiative (ADNI) enters its fifth phase and 19th year, the field of Alzheimer's disease (AD), for the first time, stands on the cusp of a treatment era, finally offering hope to millions of individuals and families suffering from AD. The contribution of ADNI to reaching this point cannot be overstated. ADNI is an observational study designed like a longitudinal clinical trial, and since its founding in 2004¹ has enrolled and followed 868 cognitively unimpaired (CU) participants, 1090 with mild cognitive impairment (MCI), and 408 with dementia diagnosed as AD. ADNI's overall goal has been to provide data for the design of clinical AD trials and to validate biomarkers for such trials. Pharmaceutical companies that have used ADNI data to help design and statistically power their trials include Biogen (aducanumab), Eisai (lecanemab), Merck (verubecestat), Lilly (solanezumab, donanemab), Genentech (crenezumab), and Roche (gantenerumab).

Many of ADNI's contributions to the development of these therapies have resulted from studies explicitly designed to enhance clinical trials. However, the availability of ADNI data to scientists worldwide without embargo (<http://adni.loni.usc.edu/data-samples/access-data/>), together with sharing of biospecimens (cerebrospinal fluid [CSF], blood, urine, and brain tissue), has enabled many studies that have augmented our understanding of the complexities of disease progression, and identified additional potential therapeutic targets. Additionally, ADNI data have been increasingly used in fields outside of AD, contributing to studies of Parkinson's disease (PD),² primary tauopathies,³ coronary artery disease,⁴ traumatic brain injury,⁵ depression,⁶ and brain changes over the human lifespan,⁷ among others. One limitation of the open availability of ADNI data is that multiple statistical analyses may be performed on the same data, which raises concerns regarding multiplicity. However, there is no obvious solution to this problem.

As of the end of 2022, there have been > 4.8 million downloads of ADNI clinical data and > 300 million downloads of ADNI imaging data. More than 5000 "ADNI studies" (defined as those using ADNI data and/or samples, either as a primary cohort, part of a larger consortium, or as a replication cohort) have been published thus far and reviewed to the end of 2020.⁸⁻¹³ All ADNI studies are searchable at <https://adni.loni.usc.edu/news-publications/publications/>.

In 2021 and 2022, 1459 ADNI studies were published (see [supporting information](#) for a complete list), representing a period of unprecedented productivity and impact spanning the COVID-19 pandemic. During this time, the ADNI-3 study¹⁴ drew to a close, and ADNI transitioned to the latest study, ADNI-4,¹⁵ funded entirely by the National Institutes of Health. This review covers 291 selected impactful ADNI studies from this time frame. Studies in which ADNI data and/or samples have been used as part of a larger cohort or meta-analysis, or in which ADNI serves as a discovery or replication cohort, are noted. The review is divided into three sections that reflect ADNI's overarching goals. Section 2 examines how ADNI data have directly contributed to the development of AD therapies, describes important data harmonization efforts, outlines progress in the development of plasma biomarkers for clinical use, and reviews diagnostic and prognostic mod-

RESEARCH IN CONTEXT

1. **Systematic Review:** The authors identified 1459 journal publications using Alzheimer's Disease Neuroimaging Initiative (ADNI) data/samples from 2021 to 2022 using traditional search methods.
2. **Interpretation:** ADNI studies improved subject selection, modeling, and detection of treatment effects for clinical trials, and described harmonization methods. ADNI samples contributed to the development of plasma biomarkers such as phosphorylated tau for clinical use, and described prognostic abilities of amyloid beta, tau, neurodegeneration, and inflammation biomarkers. ADNI studies supported the amyloid cascade sequence of disease progression and detailed how genetic and vascular risk, co-pathologies, resilience, and sex contribute to heterogeneity and biological subtypes. Results may not be generalizable due to the limited cohort diversity.
3. **Future Directions:** The ADNI-4 cohort, currently enrolling, will be more diverse to ensure generalizability of results. In the age of Alzheimer's disease (AD) treatment, ADNI will continue to improve AD clinical trials and provide data for the development of personalized medicine approaches.

els. Section 3 describes how ADNI studies have contributed to an increasingly nuanced understanding of mechanisms underlying AD disease progression. While the National Institute on Aging-Alzheimer's Association (NIA-AA) AT(N) research framework for the biological definition of AD¹⁶ is based on biomarkers for amyloid beta (A β) deposition (A), pathologic tau (T), and neurodegeneration (N), these studies paint a picture of AD as a complex multifactorial disease that is not part of normal aging, and that commonly coexists with multiple pathologies, resulting in the observed heterogeneity in disease course. The deeper understanding of the biology of AD resulting from recent ADNI studies reveals more potential therapeutic targets and suggests the need for multiple simultaneous therapies. It is important to note that the generalizability of the studies may be limited by the lack of ethnocultural and educational diversity of the ADNI cohort. Section 4 addresses these limitations and describes how ADNI-4 plans to overcome them.

2 | ADNI'S CONTRIBUTIONS TO THE TREATMENT, DIAGNOSIS, AND PREDICTION OF AD

2.1 | Studies of existing and developing therapies

Even though ADNI is a non-treatment, observational study, ADNI data have been used to assess the effects of established medications for AD, the use of medications targeting risk factors for AD,

and disease-modifying therapies under development. The following reports should be interpreted with caution because they are not from randomized placebo-controlled trials. Cholinesterase inhibitors that enhance cholinergic neurotransmission (donepezil, rivastigmine, and galantamine) were for many years the only treatment option for AD symptoms. Lower longitudinal tau deposition in early Braak stages was observed in A β positive (A+) participants taking cholinesterase inhibitors. The authors suggested a neuroprotective effect of these medications.¹⁷ Non-demented users of anticholinergic medications, which are used to treat a variety of other conditions and have the opposite effect to cholinesterase inhibitors, suffered more cognitive impairment than non-users.¹⁸ This was partially mediated by an effect of gray matter (GM) density and functional connectivity in the nucleus basalis of Meynert.¹⁸ The authors suggested that the results support a hypocholinergic mechanism underlying cognitive decline. In contrast, a third study reported that long-term donepezil treatment in MCI participants was associated with greater regional A β and tau load with concomitant worse cognitive performance.¹⁹ This result could be due to the selection of more impaired patients with greater A β and tau load for treatment with donepezil long term. The greater atrophy and hypometabolism observed in acetylcholinesterase inhibitor users compared to non-users did not survive adjustment for baseline differences, likely due to a greater rate of prescription of these medications to more impaired patients rather than a drug effect.²⁰

There has been recent interest in repurposing drugs for treatment of AD risk factors such as hypertension, inflammation, and type II diabetes mellitus (T2DM) as therapies for AD. Several ADNI studies have investigated the effects of these drugs on AD disease progression. The use of angiotensin receptor blockers for the treatment of hypertension was associated with a lower risk of progression to AD dementia in MCI participants compared to other or no anti-hypertensive medications.²¹ Similarly, aspirin use was associated with slower decline in the Mini-Mental State Examination (MMSE) in participants with AD dementia²² suggesting, to the authors, a neuroprotective effect. T2DM in MCI participants was associated with worse cognition and lower brain volumes but treatment with metformin attenuated these effects, likely via a glycemia-independent mechanism.²³ Finally, selective serotonin reuptake inhibitors for the treatment of depression were not found to have any beneficial effects on cognition or A β load in ADNI participants.²⁴ Results from these observational, non-randomized studies may suggest future randomized trials to assess the benefits of these treatments.

With the lecanemab phase 3 trial results²⁵ and subsequent accelerated US Food and Drug Administration (FDA) approval, in addition to prior accelerated FDA approval of aducanumab in 2021, anti-A β therapies have been demonstrated to have a significant effect in not only clearing A β plaques, but in slowing cognitive decline. Knowledge of relationships between AD biomarkers and clinical presentation determined from ADNI data formed the basis of a model of the long-term health outcomes of lecanemab.²⁶ The model, when applied to phase 2 lecanemab trial data, estimated that long-term use of lecanemab in MCI participants would delay time to progression to AD dementia by \approx 2.5 years, and increased time in mild AD while decreasing time in mod-

erate and severe AD and in institutional care (Figure S1 in supporting information).

2.2 | Methodological improvements to clinical trials

To date, the effects on cognition of A β -modifying disease therapies have been at best modest.²⁵ ADNI studies have pointed to potential explanations for the discrepancy between these results and the body of evidence supporting a central role for A β in disease progression. Targeting of CSF A β 42 alone may miss the contribution of different A β isoforms.²⁷ Higher levels of CSF A β 38 were associated with a lower risk of conversion from MCI to AD dementia and slower cognitive decline in both the ADNI and Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably (BioFINDER) cohorts, suggesting that other A β isoforms resulting from differential processing of the amyloid precursor protein (APP) also influence disease progression.²⁷

Selection of participants for clinical trials based on A β status is increasingly common, but A β positivity does not necessarily identify those most likely to progress to biomarker-defined AD (A+T+ as per NIA-AA guidelines²⁸). A study of A+ ADNI participants identified a substantial proportion of individuals whose tau positron emission tomography (PET) scans remained normal over 5 years.²⁹ These individuals declined more slowly and were characterized by having lower frequencies of the apolipoprotein E (APOE) ϵ 4 allele, larger hippocampal volume, and lower A β PET Centiloid (CL) units,³⁰ suggesting that they can be identified from baseline characteristics. An alternative approach to identifying individuals likely to decline used a machine learning classifier developed from early post-injection 18F-florbetapir image frames. This was highly correlated with a [¹⁸F] fluorodeoxyglucose (FDG) PET AD progression biomarker and with decline in global cognitive measures, outperforming region of interest (ROI) standardized uptake value ratio (SUVR).³¹ Slow and fast decliners may also be detected using a "run-in period" without treatment to estimate rates of disease progression.³²

Subject stratification may be improved by leveraging knowledge of MCI heterogeneity. Four distinct MCI clusters were detected using neuropsychological subscores.³³ These differed in impairments in specific cognitive domains and rate of progression to AD dementia. A subtype with the most impaired memory and worst orientation had the fastest progression to AD. The addition of comorbidities to non-comorbidity data (demographics, APOE ϵ 4, magnetic resonance imaging [MRI] volumes, cognitive and functional tests, and plasma biomarkers) in cluster analysis improved the differential prognoses of identified subtypes. The comorbidities that contributed the most to defined subtypes were obesity, cardiovascular issues, hearing loss, and hypertension. In the subtype with the worst prognosis, no patients reverted to CU, and 60% converted to AD dementia over 5 years. Consideration of comorbidities may therefore enhance the probability of selecting participants who will progress to dementia within the trial time frame.

Detection of a treatment effect using cognitive decline as a primary endpoint may be made more difficult by heterogeneity in cognitive trajectories that results in unequal rates of cognitive decline between treatment and placebo groups. This may lead to underestimation or overestimation of the treatment effect.³² A simulated clinical trial in ADNI³² using inclusion criteria from recent anti-amyloid trials of MCI and mild AD confirmed heterogeneity in the rate of change of three cognitive endpoints (MMSE, Alzheimer's Disease Assessment Score–Cognitive subscale [ADAS-Cog], and Clinical Dementia Rating–Sum of Boxes [CDR-SB]) over up to 9 years. At 18 months, there was a wide range in effect sizes of simulated group differences with those from recent trials largely falling within the 95% range for all cognitive outcomes (Figure 1). Stratification based on tau positivity and APOE ϵ 4 genotype resulted in a steeper decline in cognition in high-risk groups but even greater variability in progression. These results illustrate the difficulty in detecting a statistically significant treatment effect using cognitive outcomes and may help select a trial duration at which the treatment effect overcomes variability in disease progression.

Another source of heterogeneity in disease course is the differences in MCI diagnostic criteria between cohorts. ADNI data from MCI participants form the basis of the Placebo Group Simulation Approach, which aimed to decrease the number of study participants and placebo groups in clinical trials.³⁴ However, the development of more generalizable algorithms for this approach was precluded by differing MCI criteria, which resulted in variable disease progression across cohort studies, convenience samples, and a clinical drug trial.³⁴ Likewise, ADNI MCI participants differed from those from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set in cognitive measures, most critically in prose memory tests (Wechsler Memory Scale Revised Story A in ADNI and Craft Story immediate recall in NACC).³⁵ Standardized MCI psychometric criteria would facilitate comparison of patient data from different sources by minimizing diagnostic heterogeneity, and would allow assessment of approaches such as the Placebo Group Simulation.

ADNI data have formed the basis of a modeling tool, SimulAD, designed to simulate interventions with disease-modifying drugs.³⁶ This tool uses relationships between ADNI multimodal imaging and clinical data to describe disease progression, forming the basis for simulation of a variety of anti-amyloid therapy intervention scenarios in preclinical patients. Modeling using SimulAD estimated that for an intervention that lowers A β load by 100%, > 80% power can be obtained with 1000 subjects per arm around 7 years before conversion from MCI to AD using a variety of clinical outcomes for equivalent power with fewer subjects per arm. For a goal of greater efficacy of A β removal, earlier intervention is needed (Figure S2 in supporting information). These results suggest that intervention in the preclinical phase before the pathological cascade is entrenched is critical to the success of anti-amyloid trials, and that recent anti-amyloid trials may have been consistently underpowered. However, the large sample sizes predicted to be required may not be practical. SimulAD may have utility as a multimodal enrichment tool and has recently been validated in a memory clinic sample.³⁷

2.3 | Harmonization efforts

External validation of studies in independent cohorts is complicated by lack of harmonization of methods, lack of universal cut-points for biomarkers, and issues of data set accessibility. Harmonization of methods across different data sets is crucial for enabling comparison of data obtained using different methodologies, replicating results in research and clinical trials, and pooling data for increased statistical power. Quantitative A β or tau load determined by PET requires harmonization across sites, scanners, and tracers for comparison of data from multisite studies. A study of ADNI A β PET scans³⁸ determined transformation equations for the conversion of cross-sectional and longitudinal SUVRs from 18F-florbetapir or 18F-florbetaben PET scans to CL units to promote data harmonization. Additionally, it derived CL thresholds from both a young control sample (18 CL) and from ADNI (21 CL) that were consistent with the existing 18F-florbetaben threshold for A β positivity (20 CL). Using florbetaben, cut-points around this region, 13.5 CL and 35.7 CL, were found to bracket a “gray zone” of emerging A β pathology that is predictive of faster subsequent A β accumulation in a five-cohort study.³⁹ An alternative MRI-free index of A β load, AMYQ, was developed using A β PET scans and neuropathological data from ADNI and was in high agreement with CL measures across four different PET tracers.⁴⁰ The determination of tau positivity from PET scans differs between cohorts and radiotracers and depends on both the quantity and location of tracer retention. This variability can result in differing tau positivity rates that impact inclusion into clinical trials, staging methods, and more. A systematic review of 23 cohort studies⁴¹ derived a tau PET cut-point that differentiated tau positive and negative groups on CSF phosphorylated tau (p-tau)181 and cognitive measures.

Determination of A β and tau status from CSF biomarkers is also complicated by variability in assay methods that precludes the use of universal cut-points. A method to standardize the procedure for cut-point determination in different cohorts was developed that relies on CSF p-tau181 levels to determine the cut-point values for CSF A β 42 and CSF A β 40.⁴² The method was validated against A β and tau PET and tested across 11 cohorts including ADNI and may make selection of cut-points across cohorts a more transparent process. Neuropsychological batteries also vary between cohorts, which may complicate efforts to combine data in the quest for larger sample sizes. A novel approach developed in ADNI and the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) used a machine learning algorithm to impute longitudinal neuropsychological test scores not used in one cohort to align with the other cohort, facilitating harmonization of the data sets.⁴³ A harmonized version of the widely used Preclinical Alzheimer Cognitive Composite (PACC) was developed using confirmatory factor analysis across ADNI, AIBL, and the Harvard Aging Brain Study (HABS), and outperformed the common standardized version in combined cohort analyses.⁴⁴

Another barrier to external validation in independent cohorts is accessibility of the data set and compatibility of the variables within the data sets. An interactive tool that allows exploration of features

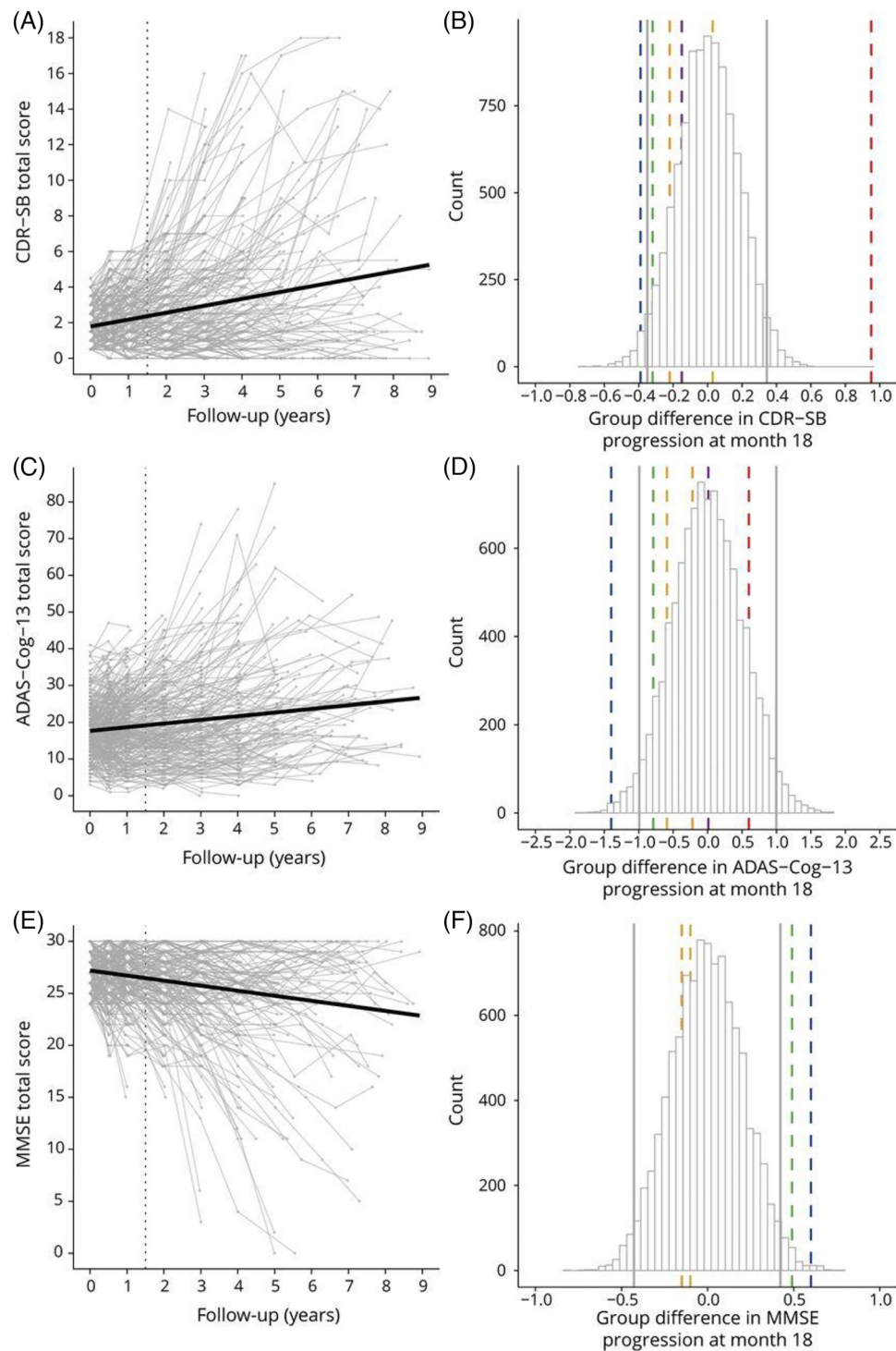


FIGURE 1 Rates of change of three cognitive outcomes in a simulated clinical trial in ADNI using inclusion criteria from anti-amyloid trials. Left column: individual trajectories on the (A) CDR-SB, (C) ADAS-Cog, and (E) MMSE. The vertical dotted lines represent scores at 18 months. Right: simulated group differences in change from baseline to month 18 based on the total sample ($n = 302$) on (B) CDR-SB, (D) ADAS-Cog, and (F) MMSE, including 95% range of effect sizes as indicated by vertical gray lines and effect sizes reported for recent clinical trials as indicated by vertical dashed colored lines (blue = EMERGE; yellow = ENGAGE; green = EXPEDITION-3; orange = DAYBREAK-ALZ; red = IDENTITY-2; magenta = BAPINEZUMAP). ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, Clinical Dementia Rating Sum of Boxes; MMSE, Mini-Mental State Examination. Reproduced under open access from Jutten et al.³²

of different data sets, AdataViewer, aims to increase the findability and interoperability of cohort data sets, saving time and effort for researchers in the field.⁴⁵ It allows researchers to access metadata from 20 cohort studies including ADNI, to select cohorts that contain their variables of interest, and to apply for data access (Figure S3 in supporting information).

2.4 | Blood biomarkers for AD

There has been a recent rapid development of blood-based biomarkers that reflect AD pathobiology for use in primary care and clinical trials. These biomarkers, assessed using ultrasensitive assay techniques, circumvent the issues of cost, invasiveness, and accessibility of PET and CSF biomarkers. Recent ADNI studies have focused on clinical assay development and validation, and retrospective longitudinal studies, two key steps toward clinical implementation.⁴⁶ These studies have primarily assessed AT(N) plasma biomarkers but also have reported novel blood-based biomarkers reflecting different aspects of disease progression. There has been extensive work in this area (recently reviewed in Balogun et al.⁴⁷). The following covers only blood biomarker studies that either used ADNI samples or analyzed existing data from the ADNI database.

2.4.1 | Plasma A β

Two head-to-head studies^{48,49} compared six candidate plasma A β assays, three immunoassays (Roche Elecsys Cobas e601, Adx NeuroSciences Simoa Neuro 4-plex E Kit, and Quanterix Simoa A β 40 and A β 42 Advantage Kit), and three mass spectrometry (MS)-based assays (Washington University immunoprecipitation [IP]-MS, Shimadzu IP-matrix-assisted laser desorption ionization time-of-flight-MS, and University of Gothenburg IP-MS assays). The first study,⁴⁸ which aimed to prioritize assays for more extensive study, identified the Roche, Washington University, and Shimadzu assays as able, in combination with age and APOE ϵ 4 status, to improve prediction of A β PET status beyond a base model (age and APOE ϵ 4 status) in participants across the AD spectrum. However, none of these assays reached the prespecified threshold for a clinical prescreening tool of an area under the receiver operating curve (AUC) of 0.90 with an increase of 0.15 in AUC over the base model. The best assay, the Washington University IP-MS, achieved an AUC of 0.842 compared to an AUC of 0.75 for the base model. The second study⁴⁹ also identified the Washington University and Roche assays as the best performing for predicting A β PET status in CU and MCI participants, and for discriminating between AD and CU participants. The Washington University IP-MS plasma A β 42/40 assay, now available commercially as Precivity AD (C₂N Diagnostics), was validated in ADNI, AIBL, and BioFINDER.⁵⁰ Combined with APOE ϵ 4 status, it predicted A β PET status with an AUC of 0.88 and CSF A β status with an AUC of 0.93 in the combined cohort. Prescreening with this assay was estimated to decrease the number of A β PET scans by up to 62% and 19% for the enrollment of CU and MCI participants,

respectively, into a clinical trial, potentially reducing screening costs 10-fold.⁵⁰

2.4.2 | Plasma phosphorylated tau

Recent ADNI studies have explored the ability of plasma p-tau to predict not only A β status but also markers of disease progression. A replication study of plasma p-tau181⁵¹ reported that a longitudinal increase in levels of this biomarker was associated with worse AD biomarkers (cortical A β accumulation, hypometabolism, atrophy, cognitive decline, and CSF A β 42, p-tau181, and total tau [t-tau]) in ADNI participants across the AD spectrum and that the association was strongest in A+ participants (Figure S4 in supporting information). In similar studies, baseline plasma p-tau181 was associated with CSF A β 42,⁵² CSF p-tau181,^{52,53} and CSF t-tau;⁵² 18F-florbetapir PET,^{53,54} 18F-flortaucipir PET,⁵⁴ regional hypometabolism;^{53,54} gray matter (GM) atrophy in CU and cognitively impaired (CI) participants;⁵⁵ white matter (WM) volume in MCI participants;^{52,55} cognitive measures;^{52,56,57} progression from CU and MCI;^{52,56} time to dementia diagnosis;⁵⁷ and Braak neurofibrillary tangle (NFT) stages at autopsy.⁵⁸ Plasma p-tau181 was additionally associated with a polygenic risk score (PRS) containing APOE in all diagnostic groups and in both A+ and A- participants, and with a non-APOE PRS in MCI and A+ participants only.⁵⁹

These studies provide strong evidence for the utility of plasma p-tau181 as a biomarker of the full panoply of AD characteristics. Levels of this biomarker increased across diagnostic categories,^{60,52,53} and differed significantly between CU and AD participants across all age ranges,⁶⁰ indicating that it may be a clinically useful diagnostic test. Plasma p-tau181 additionally distinguished between pathology-confirmed AD and A- CU^{57,58} and between pathology-confirmed AD and non-AD dementia with comparable performance to CSF p-tau181 (Figure 2).^{57,58} Combined with APOE ϵ 4 status, memory, and executive function, plasma p-tau181 predicted progression from MCI to AD dementia within 2 years in an ADNI validation cohort with an AUC of 0.90 achieving very similar results to the model developed in BioFINDER using plasma p-tau217.⁶¹ These models performed similarly to those using CSF biomarkers and outperformed clinical predictions by memory clinic physicians (AUC 0.72), illustrating the vast potential of plasma biomarkers to transform clinical diagnosis and prediction.

Investigators are beginning to focus attention on the definition and utilities of cut-point determination. For example, in one study, a cut-point based on Youdin balanced sensitivity and specificity was determined in AD dementia (autopsy diagnosis) versus CU (A- by PET) in the University of Pennsylvania (UPenn) Alzheimer's Disease Research Center (ADRC) cohort and applied to an ADNI MCI replication sample showing that values above cut-point were associated with faster rate of decline in MMSE, shorter time to functional decline, and conversion to dementia.⁵⁷ Much more work in this area is needed especially across underserved minorities and those with comorbidities.

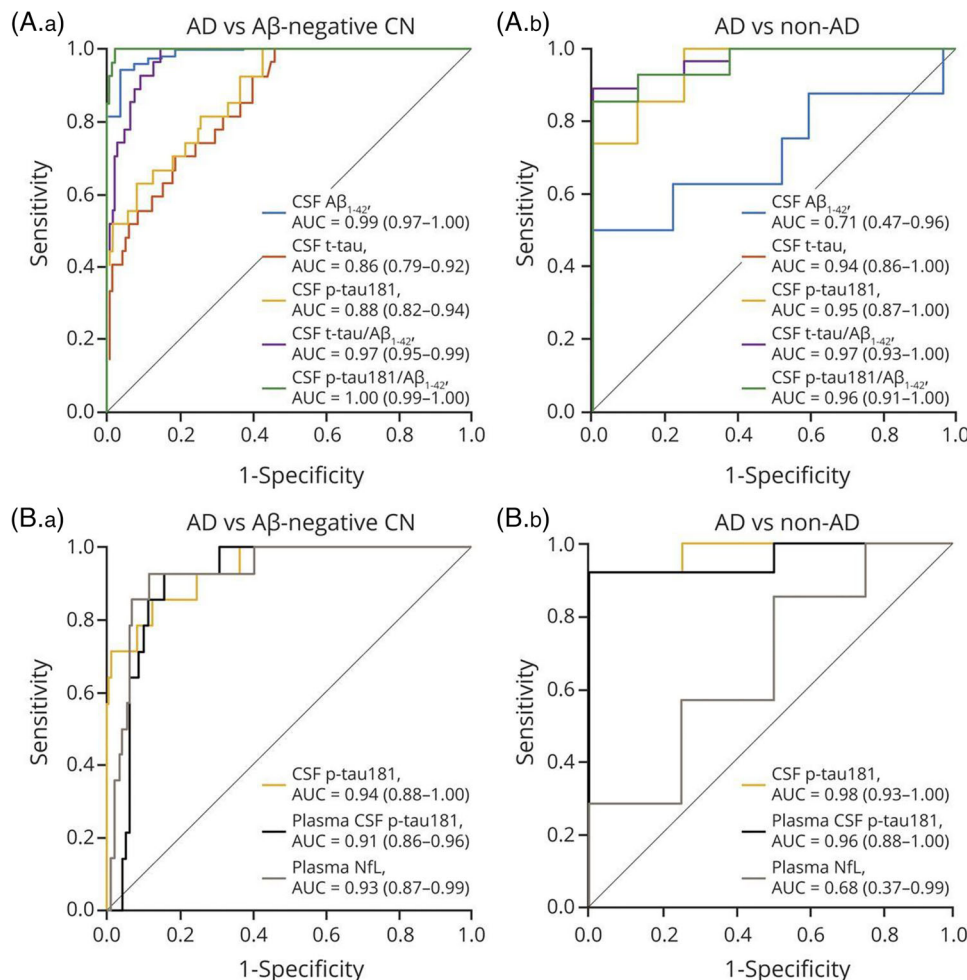


FIGURE 2 ROC curves for distinguishing pathology-confirmed AD dementia from non-AD dementia and Aβ-PET-negative healthy controls. ROC curves showing the performance of (A) Elecsys CSF biomarkers and (B) plasma biomarkers compared to CSF tau phosphorylated at threonine 181 (p-tau181) for the discrimination of pathology-confirmed AD dementia from (A.a and B.a) Aβ-PET-negative healthy controls and (A.b and B.b) non-AD dementia. AUC and 95% confidence interval are reported in the inset of each panel. Aβ, amyloid beta; AD, Alzheimer disease; AUC, areas under the curve; CN, cognitively normal; CSF, cerebrospinal fluid; NfL, neurofilament light; PET, positron emission tomography; ROC, receiver operating characteristic; T-tau, total tau. Reproduced under open access from Grothe et al.⁵⁸

Although p-tau181 provides very useful information, reports during the past 2 years suggest that p-tau217 has a greater dynamic range than p-tau181 and greater accuracy to predict Aβ positivity and cognitive decline.^{62–64} At the time of this review there have been no p-tau217 analyses of ADNI samples.

2.4.3 | Plasma neurofilament light

Plasma biomarkers of neurodegeneration may have utility in AT(N) studies, for predicting cognitive decline, and for assessing the rate of disease progression. Plasma neurofilament light (NfL), considered a non-specific marker of neuronal injury, is the most studied plasma biomarker in this category. It outperformed plasma t-tau in the prediction of atrophy and cognitive decline in a head-to-head comparison in the Mayo Clinic Study of Aging (MCSA) with replication in ADNI.⁶⁵ In

ADNI CU and MCI participants, plasma NfL was cross-sectionally associated with hippocampal volume and a range of cognitive measures, and longitudinally with hippocampal atrophy and decline in Logical Memory-Immediate Recall and ADAS-Cog13; no associations were found cross-sectionally and longitudinally for plasma tau.⁶⁵ Similarly, elevated plasma NfL at baseline predicted greater decline in function as well as cognition in ADNI MCI participants, and also predicted greater decline in the PACC scores in CU participants with subjective subtle cognitive decline⁶⁶ (Figure S5 in supporting information). In CU participants, elevated baseline plasma NfL was associated with worse measures of cerebral small vessel disease burden (lacunar infarcts, WM hyperintensities [WMH], and cerebral microbleeds), and rate of change in this measure predicted progression in cerebral small vessel disease burden.⁶⁷ A similar association was found with lacunar infarcts in the MCSA cohort but this was not replicated in ADNI,⁶⁵ so the utility of plasma NfL as a biomarker of cerebral small vessel disease has yet to be confirmed.

How does the predictive ability of plasma NFL as a non-specific marker of neurodegeneration compare to that of plasma p-tau181 as a marker of AD pathology across the AD spectrum? A head-to-head study using ADNI longitudinal data⁶⁸ reported that while both biomarkers predicted glucose hypometabolism, atrophy, and cognitive decline, plasma p-tau181 was associated with hypometabolism and atrophy in AD-typical regions in A+ participants only, whereas plasma NFL was associated with non-specific neurodegeneration in an A β -independent manner (Figure S6 in supporting information). The associations were stronger in CI than CU individuals. Similarly, elevated baseline plasma p-tau181 predicted memory decline only in A+ ADNI participants whereas plasma NFL predicted memory decline regardless of A β status.⁶⁹

2.4.4 | Other blood-based biomarkers

The current AT(N) plasma biomarkers do not reflect elements of the disease process occurring between tau deposition and neurodegeneration (described in Section 3.2). Synaptic dysfunction, reflecting the loss of communication across the synapses or actual loss of neuronal synapses, occurs before neuronal death, and represents a common point at which pathological processes in AD and other dementias converge before neurodegeneration and cognitive decline. The importance of synaptic dysfunction in the disease process is reflected in the number of therapies under development aimed at preserving synaptic function, such as those targeting glutamate receptors.⁷⁰ A marker of synaptic dysfunction is therefore desirable for assessing target engagement of these medications in addition to more finely tracking disease progression. The N-methyl D aspartate receptor 2A, the therapeutic target of memantine, is involved in synaptic function, and can be measured in blood extracellular vesicles (EVs) derived from the brain.⁷¹ Numbers of EVs carrying this receptor were lower in AD compared to CU, and also compared to PD in samples from the Pacific Northwest Udall Center of Excellence in PD Research, suggesting specificity for AD. A model containing these EVs discriminated between AD and CU with AUCs of 0.91 in the exploratory cohort and 0.81 in the ADNI external validation cohort. The N-methyl D aspartate receptor 2A measured in brain-derived EVs may therefore be a useful biomarker of neuronal synaptic loss.⁷¹

An alternative blood biomarker for AD is based on consistent differences in DNA methylation between AD and CU participants. Distinguishing epigenetic marks were identified by meta-analysis of epigenome-wide association studies from AIBL and ADNI.⁷² Five significant CpG sites of methylation were identified, including one in the *FKBP5* gene involved in the promotion of tau protein aggregation, and several biologically relevant promoter-associated CpG island regions. A model comprising age, sex, immune cell type proportions, and a methylation risk score based on significant CpG sites discriminated between AD and CU participants with an AUC of 0.696 in an external validation cohort (AddNeuroMed). As age is the greatest risk factor for AD, and DNA methylation changes with age, the study highlights the potential of methylated DNA as a source of AD biomarkers.

2.4.5 | Blood biomarkers conclusions

Ultrasensitive assay techniques have allowed development of plasma biomarkers that predict disease progression with accuracy comparable to CSF biomarkers. They therefore have the potential to revolutionize clinical diagnosis and prediction. However further hurdles remain before implementation in primary care: (1) validation in large, ethnically diverse primary care populations; (2) development of clinical grade assays; (3) standardization of protocols; (4) determination of cut-points and application in prospective studies; and (5) determination of the impact of chronic comorbid conditions. ADNI will continue to play a part in the development and validation of plasma biomarkers.

2.5 | Diagnosis and prediction approaches

ADNI data, freely available to qualified researchers worldwide, have been used for the development of many of the diagnostic and prognostic methods in AD. For instance, 56% of studies included in a review of the use of artificial neural networks to diagnose AD from brain imaging scans used ADNI data.⁷³ A number of systematic reviews of models predicting MCI progression to AD dementia reported that ADNI data were used in 67%,⁷⁴ 85%,^{75,76} and 92%⁷⁷ of included studies. The number of articles, the number of participants per article, and AUCs have all increased over time⁷⁶ (Figure S7 in supporting information). This can be considered both a resounding success of data-sharing in ADNI, but also as a huge limitation to the interpretation of these studies, given the lack of diversity of ADNI's participants and its strict inclusion and exclusion criteria thus far. Furthermore, few diagnostic and prognostic methods have been externally validated in independent cohorts to ensure generalizability, and there is considerable variability in statistical methodologies and data presentation among studies.^{74,76,77} This review will therefore highlight only studies of diagnostic and prognostic approaches notable for their thoroughness, novelty, and potential for clinical use, and otherwise present general findings from systematic reviews.

2.5.1 | Systematic reviews of prediction of progression from MCI to AD dementia

Prediction of progression from MCI to AD dementia is a much greater classification challenge than discriminating between AD and CU patients. Prediction of clinical trajectories of MCI participants is complicated by the heterogeneity in rates of progression, even within those who are A+. This hampers the ability of secondary prevention trials to detect cognitive outcomes within reasonable time frames; therefore, the development of methods to circumvent this difficulty is paramount. Many ADNI studies have used machine learning to select variables and construct predictive models. A systematic review⁷⁷ of 116 such studies from 2010 to 2021, the majority (92%) using ADNI data, reported that the most common features used were whole brain volumes (60%), glucose metabolism (27%), neuropsychological tests

(16%), APOE $\epsilon 4$ genotype (14%), and demographics (13%). Around half of studies used support vector machines (SVM) as their machine learning method, with the remainder using other methods such as random forest and neural networks. Models were most commonly cross-validated (72/116), but only three were externally validated.

A second systematic review of 111 studies from 2010 to 2018 (comprising 85% ADNI studies)⁷⁶ also reported structural MRI measures were the most common features (69%), followed by neuropsychological variables (43%), demographics (34%), and FDG PET (20%; it should be noted that few studies used A β and tau PET within the time frame of these systematic reviews, but methods using these modalities have since been developed). In a performance analysis of ADNI cohort experiments, only T1 MRI ROIs, FDG PET features, and domain targeted cognitive features significantly impacted AUC, with FDG PET features outperforming MRI features. The most common machine learning algorithm was SVM, but the use of neural networks increased from 2016 to 2018.

These reviews found little difference between the accuracies achieved using different machine learning methods, although convolutional neural networks (CNN) have a slight performance advantage and are more frequently used in recent studies.⁷⁷ Both reviews reported that the mean accuracy of predictive models converged at $\approx 75\%$ as the number of participants increased.

2.5.2 | A β -based approaches

Although baseline CSF A β 42 was not a strong predictor of cognitive decline in A+ subjects,⁷⁸ other A β measures performed better. Regional patterns of A β burden, particularly in the precuneus and parietal cortex, together with sex and APOE $\epsilon 4$ status, better predicted progression from CU to MCI, and from MCI to AD dementia over 1 and 3 years than global A β burden or CSF biomarkers.⁷⁹ Subthreshold A β deposition in similar regions also predicted conversion of amnesic MCI participants to AD dementia.⁸⁰ CL thresholds for predicting future decline in CU participants in the PACC score calculated in three independent cohorts including ADNI ranged from 15 to 18.5 CL compared to cut-points for distinguishing between A+ and A- CU individuals, which ranged from 19.0 CL to 25.7 CL.⁸¹ This suggests there is an inflection point below established thresholds for A β positivity at which cognitive decline increases significantly. Accumulating regional A β below positivity thresholds may therefore be meaningful in disease progression and should be taken into consideration in clinical trial design.

2.5.3 | Inflammation-based approaches

Microglial and T cell-mediated inflammation in response to A β deposition is an early feature of AD progression (see Section 3.2.3), and therefore biomarkers of neuroinflammation may have prognostic value. A group of CSF inflammation-related proteins comprising soluble tumor necrosis factor receptors 1 (sTNFR1) and 2 (sTNFR2), and soluble vascular adhesion molecule 1 identified using principal component

analysis, was associated with a halving of risk of progression of MCI participants to AD dementia.⁸² The addition of these inflammation markers to other AD biomarkers improved the prediction of cognitive decline over 5 years; those with worst AD biomarkers and lowest levels of sTNFR1 had the fastest decline and progression to AD dementia (Figure S8 in supporting information). In comparison, higher levels of CSF soluble TREM2 (sTREM2), a marker of microglial activation indicative of neuroinflammation, were associated with slower decline in AD dementia.⁸² Biomarkers of neuroinflammation may therefore provide complementary information to canonical AD biomarkers.

2.5.4 | Tau-based approaches

Both global and Braak stage tau PET deposition outperformed global A β PET deposition (CL) in the prediction of decline in global cognition and episodic memory in ADNI participants across the AD spectrum⁸³ (Figure S9 in supporting information). More advanced Braak stages were associated with accelerated cognitive decline, independently of global A β burden, but global A β PET did not remain a significant predictor of future cognitive decline after controlling for tau PET.⁸³ Given that tau PET scans are expensive and not readily available, several studies investigated whether fluid biomarkers of tau offer similar predictive value. While an increased tau PET temporal meta-ROI was most strongly associated with worse cognition and reduced cortical thickness in ADNI and BioFINDER-2 participants across the AD spectrum, increased CSF and plasma p-tau181 and p-tau217 were most strongly associated with old age, APOE $\epsilon 4$ status, and A β positivity⁸⁴ (Figure S10 in supporting information). Similarly, plasma and CSF p-tau181 were more closely associated with A β PET than tau PET (Figure S11 in supporting information).⁸⁵ In CU and MCI participants, these biomarkers were associated with A β PET whereas tau PET positivity was associated with worse cognition.⁸⁶ Tau PET ligands are believed to bind insoluble NFTs, whereas soluble p-tau measures the concentration of tau phosphorylated at specific amino acids that has leaked into the CSF or blood compartments from the extracellular space.⁸⁵ Fluid and PET tau biomarkers may therefore reflect different stages in disease progression with fluid tau biomarkers being more related to earlier AD pathology and tau PET to later AD pathology and cognitive symptoms. These differences may be reflected in the discordance between fluid and PET biomarkers.^{84,86} When ADNI CU and MCI participants were characterized by plasma p-tau181, CSF p-tau181, and tau PET status, discordance between measures ranged from 6.1% (plasma-/PET+) to 22.4% (plasma+/PET), with $\approx 15\%$ of participants being discordant between CSF and plasma measures.⁸⁶ Comparison of tau status determined by CSF p-tau181, tau PET SUVR, and tau PET visual read found that all three modalities were concordant in only 59% of participants across three cohorts including ADNI.⁸⁷

2.5.5 | Neurodegeneration-based approaches

Neurodegeneration, measured using MRI, FDG PET, and fluid biomarkers such as t-tau and NfL, occurs later in disease progression and so

is commonly used to predict cognitive decline or progression. MRI-based classifiers based on modulated GM maps using both a CNN and SVM were tested for generalizability to an external multicenter memory clinic cohort.⁸⁸ The classifiers achieved an AUC of 0.756 (SVM) and 0.742 (CNN) for the prediction of MCI progression to AD dementia in the ADNI development cohort, and AUCs from 0.665 to 0.702 in external validation cohorts. The performances in ADNI are consistent with the systematic reviews^{76,77} suggesting convergence of prediction methods around AUC 0.75. However, the generally lower performance in the external validation cohorts demonstrates the challenge of generalizing classifiers across diverse cohorts.

A classifier based on the specific organization (small worldness) of GM covariance networks that typify MCI progression was developed in the Amsterdam Dementia Cohort and validated in ADNI.⁸⁹ Combined with CSF p-tau181 and hippocampal volume, the classifier identified MCI participants who progressed to AD dementia within 2 years with an AUC of 0.67 in the ADNI validation cohort. Selection of participants for a 2-year randomized controlled trial using the classifier was estimated to nearly halve sample sizes required to detect a 25% slowing in the rate of decline in MMSE and CDR-SB. Consideration of APOE ϵ 4 status improved the prediction of the development of AD dementia in presymptomatic patients using structural MRI measures.⁹⁰ Disease timelines estimated using a discriminative event-based model differed between APOE ϵ 4 carriers and non-carriers in ADNI and were generalizable to the population-based Rotterdam Study cohort. This approach achieved an AUC of 0.81 and 0.88 in APOE ϵ 4 non-carriers and carriers, respectively.

Patterns of hypometabolism on FDG PET are also predictive of MCI progression to AD dementia and may outperform MRI-based methods.⁷⁶ In an ADNI validation study, an AD progression-related pattern based on hypometabolism derived from FDG PET⁹¹ predicted progression to AD dementia within 3 years with an AUC of 0.796, outperforming the neurodegeneration biomarkers, plasma NfL, and CSF t-tau.⁹² However, in a second ADNI validation study,⁹³ FDG PET and MRI regions selected using radiomics each provided comparable predictive performance. When one modality was added to the other, performance was enhanced only minimally, possibly due to the large overlap of regions selected.

These imaging-based models predict a change in clinical status, but one study suggests that these features may also reflect underlying disease processes. A model derived from structural MRI features that predicted progression from MCI to AD dementia was also associated with early metabolic changes such as insulin resistance and dyslipidemia, and with genetic variants in candidate genes involved in AD-related processes such as A β degradation, microglial activation and inflammatory response, synaptic loss, and tau phosphorylation.⁹⁴

Several data-driven approaches have used the ADNI data set to test prediction of decline in cognitive scores rather than diagnostic status. An MRI brain signature region model was associated with baseline and longitudinal episodic memory in ADNI-1, ADNI-2/GO, and the University of California Davis Aging and Diversity Cohort.⁹⁵ A data-driven MRI biomarker of dementia risk, the AD-PS score,⁹⁶ was trained in ADNI and tested in the Atherosclerosis Risk in Communities

(ARIC) data set for its ability to predict incipient cognitive decline in CU participants.⁹⁷ The ARIC cohort is more diverse than ADNI, comprised of approximately one third Black American participants, and 12% participants with < 12 years of education. In the full cohort, the AD-PS score outperformed a hypothesis-driven MRI composite ROI score, achieving an AUC of 0.692. However, significantly higher AUCs were achieved in White compared to Black participants, in females, and in APOE ϵ 4 carriers, illustrating the need for more comprehensive assessment of prognostic algorithms in diverse populations.

A complementary MRI-based approach used deviation from the norm rather than AD-typical features to detect disease progression in MCI and AD dementia participants from five data sets including ADNI.⁹⁸ Normative models were constructed from structural MRI data obtained from UK Biobank CU participants, against which the degree of deviation would indicate disease progression. This measure, most highly significant in medial temporal lobe (MTL) regions in the ventricular system, increased across diagnostic classes and was consistent over differing data sets. This approach achieved AUCs for discriminating between CU and AD dementia of between 0.74 and 0.91, and for discriminating between CU and MCI of between 0.60 and 0.64, demonstrating cross-cohort generalizability.

As MRI scans are often available in the clinic, there has been a recent emphasis on developing medical grade MRI biomarkers to assist in AD dementia diagnosis. Notably, two CNN-based models have been extensively validated for clinical applications.^{99,100} The first,¹⁰⁰ developed in a pooled MRI data set of > 85,000 scans including ADNI, and validated in three independent data sets, achieved accuracies of > 90% for diagnosis of AD dementia, and predicted 65% of MCI converters as having AD dementia compared to 20.6% of non-converters. The second⁹⁹ not only validated the classification model in multiple cohorts, but in three different MRI vendors, over different protocols, and in low-resolution MRI scans typically commonly available in the clinic. In the ADNI external validation cohort, the classifier achieved a classification accuracy of 0.88 and 0.83 for high- and low-resolution MRI, respectively.

2.5.6 | Combinations and comparisons of AT(N) biomarkers

Combinations of AT(N) biomarkers may better predict disease progression than single biomarkers. However, their predictive ability in part depends on the type of measure used and the cut-point chosen. Fluid and imaging biomarkers are often discordant,^{86,101,102} which results in considerable variability in AT(N) classification^{101,102} (Figure S12 in supporting information). Tau PET positivity predicted short-term episodic memory better than CSF p-tau181 (or any A β biomarker), likely as it becomes positive at a later stage in disease progression than CSF p-tau181.^{101,102} In CI participants, tau PET positivity combined with cortical thickness best predicted 12 year longitudinal cognition whereas in CU participants, the best predictors were MRI measures (temporal cortical thickness and hippocampal volume).¹⁰² These studies illustrate that different AT(N) biomarkers cannot be used

interchangeably, and that their ability to predict future decline differs by diagnostic stage.

Biomarkers of neurodegeneration are the least concordant.¹⁰¹ Although CSF t-tau putatively reflects axonal loss, normal CSF t-tau in the presence of neuronal loss and vice versa is not uncommon.¹⁰³ A proteomics study in participants with evidence of neurodegeneration¹⁰³ found that those with normal CSF t-tau had increased concentrations of proteins involved in blood–brain barrier (BBB) and blood–CSF barrier dysfunction whereas those with high CSF t-tau had alterations in proteins involved in neuronal plasticity. This biomarker may therefore reflect not only neurodegeneration but leakiness of the brain barriers. Alternative CSF biomarkers reflecting synaptic dysfunction (neuronal pentraxin, 14-3-3 protein ζ/δ) or synaptic plasticity (VGF) enhanced prediction of conversion of late MCI participants to AD dementia over CSF A β 42 and p-tau181 alone.¹⁰⁴ Moreover, low CSF VGF combined with normal CSF A β 42 and p-tau181 predicted conversion in early MCI participants, suggesting that it may reflect processes occurring earlier in disease progression than other markers of neurodegeneration.

The choice of cut-point of dichotomized AT(N) biomarkers influences their predictive value. Data-driven methods for the selection of cut-points for A β PET, CSF p-tau181, and FDG PET improved the prediction of MCI progression to AD dementia by 30% to 35% over 2 years and \approx 45% over 4 years over established cut-points.¹⁰⁵ Most cut-points are determined by their ability to discriminate between CU and AD dementia diagnostic groups. However, with the exception of plasma p-tau181,⁵⁷ cut-points have not been determined against the gold standard of autopsy to reflect actual neuropathological changes. Using established cut-points for CSF biomarkers, between 50% and 73% of participants across three cohorts who were designated as A+ but T– and were assessed as having an intermediate or high degree of AD neuropathologic change at autopsy¹⁰⁶ (Figure S13 in supporting information). CSF p-tau181 may therefore not accurately reflect tau neuropathology and may instead represent other disease-related processes that occur in response to A β deposition. Finally, a dichotomous system for determining biomarker positivity may classify as negative participants with subthreshold but increasing levels of biomarkers who may be on a trajectory of cognitive decline. A lower and a higher cut-point for the CSF A β 42 ElecSys assay was defined using two-graph receiver operating characteristics of CSF p-tau181/A β 42 at 90% sensitivity and 90% specificity and delineated three ranges.¹⁰⁷ These cut-points applied to the p-tau181/A β 40 ratio identified not only fast and slow CU and MCI decliners, but a group with intermediate trajectories of A β deposition and cognitive decline that would not have been identified using a dichotomous system (Figure S14 in supporting information). Identification of this intermediate group allows both its exclusion from recruitment to clinical trials, which may reduce required sample sizes, and monitoring of participants who would otherwise have been predicted not to decline under the dichotomous system.

The ability of APOE genotype, fluid biomarkers, tau PET, cortical thickness, and baseline cognition to predict decline in MMSE over 2 years in CI participants was tested systematically in BioFINDER 2 and replicated in ADNI.¹⁰⁸ Tau PET outperformed all other biomarkers,

and the most parsimonious model combined tau PET with baseline cognition (Figure 3). The prediction of functional decline by AT(N) biomarkers was enhanced by the addition of a baseline cognitive measure.¹⁰⁹ In preclinical AD and MCI participants, the previously validated Discrepancy-Based Evidence for the Loss of Thinking Abilities (DELTA) score improved the ability of A β PET SUVR, CSF p-tau181, and hippocampal volume to predict scores on the Functional Activities Questionnaire (FAQ) and CDR-SB.

2.5.7 | Cognitive tests in CU participants

A particular focus in recent ADNI studies of prediction has been identifying and operationalizing for remote use cognitive tests associated with future decline in CU participants. The first signs of subtle cognitive decline can be measured using several tests and scales such as the Everyday Cognition Scale (ECog), Cognitive Change Index (CCI), and the PACC. ECog measures subjective decline in instrumental activities of daily living that map to six cognitive domains, reported by participants themselves or their study partners. A comparison of these methods in ADNI CU participants found that different assessments predicted different measures.¹¹⁰ Only ECog was associated with future decline in the Montréal Cognitive Assessment (MoCA), whereas only CCI was associated with greater decline in ADAS-Cog. Different assessments also predicted different measures of atrophy, suggesting that measurements of decline are not interchangeable.

Implementation of these tests and assessments online holds great potential for remote screening and monitoring of participants in clinical studies. The online version of self-reported ECog was highly correlated with the in-clinic version, suggesting that remote assessments gather as much information on cognitive and functional abilities as supervised in-person assessments.¹¹¹ Another digital cognitive biomarker generated from baseline Rey Auditory Verbal Learning Test (RAVLT) word list memory was developed in the Mayo Clinic, shown to identify CU participants at risk of cognitive decline within 1 to 3 years, and validated in ADNI.¹¹² Finally, an unsupervised version of the Cogstate Brief Battery taken at home on any device had good concordance with the supervised in-clinic version in CU and MCI ADNI participants, although compliance with test completion diminished over time, suggesting the need for additional long-term support.¹¹³ These studies demonstrate the feasibility and potential of remote monitoring of CU participants and highlight some of the challenges involved in this approach.

2.5.8 | Polygenic risk approaches

ADNI studies have assessed the potential of PRS, calculated from genome-wide association study (GWAS) genotyping data, to predict progression. Ten of twelve publications included in a systematic review of machine learning models to predict lifetime AD risk based on single nucleotide polymorphisms (SNPs) used ADNI data.⁷⁵ A PRS including the APOE region was more highly associated with an increased risk of progression from MCI to AD dementia than a PRS without APOE

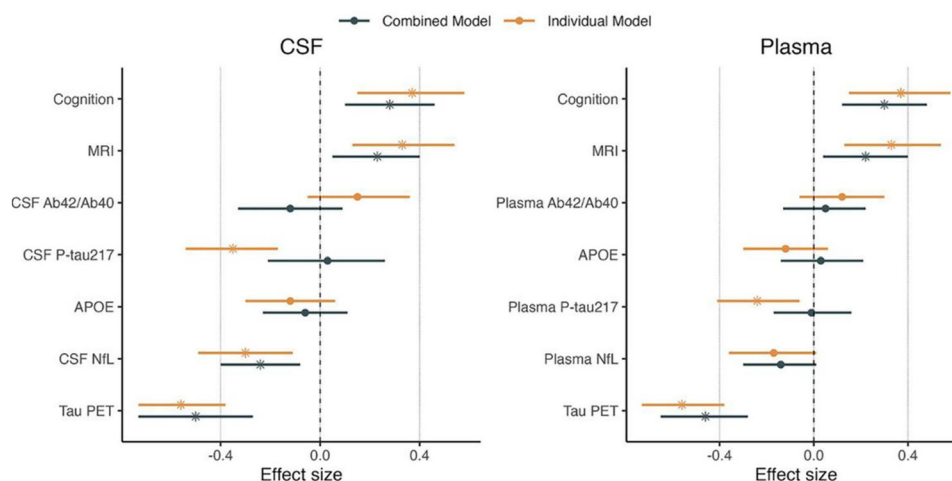


FIGURE 3 Prediction of cognitive decline using biomarkers individually or in combination. Effect sizes for each biomarker in predicting future cognitive decline either alone (orange bars, on top) or in a combined model (black bars, below). Significant biomarkers are represented with a star. The models using CSF biomarkers are shown on the left panel and the models using plasma markers on the right panel. Bars represent 95% confidence intervals. APOE, apolipoprotein E; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; NFL, neurofilament light; PET, positron emission tomography; p-tau, phosphorylated tau. Reproduced under open access from Smith et al.¹⁰⁸

(hazard ratio 1.468 with APOE and 1.293 without APOE).¹¹⁴ Both PRS were better predictors in APOE $\epsilon 4$ non-carriers than carriers. A PRS constructed from 40 independent non-APOE genome-wide significant SNPs significantly predicted MCI to AD dementia progression in ADNI, which was replicated in the NACC cohort.¹¹⁵ This PRS was also associated with increased cognitive decline, and longitudinal worsening in a range of other AD biomarkers. Genetic variants reflecting other contributors to disease progression may also be predictive. A PRS comprising genetic variants associated with T2DM explained almost 4% of the variance in MCI to AD dementia conversion, performing only slightly worse than an AD-specific PRS.¹¹⁶ These studies, together with many others, suggest that genetic loci outside of APOE $\epsilon 4$ have small but statistically significant predictive ability.

An issue with the use of PRS is a lack of standardization of PRS calculations including the optimal *P*-value threshold for SNP selection. A comparison of PRS calculations across seven data sets including ADNI reported the best predictive ability was achieved using a *P*-value threshold of ≤ 0.1 with the contribution of APOE modeled separately.¹¹⁷

2.6 | Individualized prediction of future decline

The ability to predict the cognitive trajectory of a patient in routine clinical practice would address the patient's desire to know their personal risk and plan accordingly and may motivate them to modify their lifestyle in beneficial ways. Several studies have used ADNI multimodal data to develop tools to enable this goal. NeuroPM-box, an open access software toolbox, used multifactorial models of disease progression applied to multimodal data to biologically stratify patients.¹¹⁸ This tool integrated not just imaging and cognitive data, but histopathology and molecular screening (epigenomics, tran-

scriptomics, and proteomics) by taking into account gene-level and brain-level mechanisms of disease progression as well as the potential response for patients to therapeutic intervention (Figure S15 in supporting information). Another framework based on a multifactorial cascade model of disease progression was used to simulate a personalized response to anti-amyloid therapies using either aducanumab or donanemab.¹¹⁹ The model simulated both short- (78 weeks) and long-term (10 years) individualized responses that took into account potential side effects such as amyloid-related imaging abnormalities (ARIA).

A dementia risk score, the Mild Cognitive Impairment to Dementia Risk (CIDER) score, designed to be used in primary care to predict time to all-cause dementia within 3 years of an MCI diagnosis, was developed in the NACC cohort and validated in two cohorts including ADNI.¹²⁰ CIDER was implemented as a nomogram with variables easily determined in clinic: age, sex, education, marital status, hypertension, mood disorder, and either MoCA or MMSE (Figure S16 in supporting information). It predicted dementia risk with a c-index of 0.72 (95% confidence interval: 0.69–0.75) in the ADNI external validation cohort. Knowing where a patient lies on a map of disease progression, in addition to knowing overall dementia risk, could enhance personalized medicine approaches. An AD Course Map of disease progression was developed using hippocampal shape deformations, patterns of progression of hypometabolism and cortical thinning, and neuropsychological assessments.¹²¹ When applied to an individual, the model generates a trajectory that considers an individual's age of disease onset, speed of progression, and genetics and sex.

A multimodal model to predict individual future cognitive decline based on continuous rather than dichotomous biomarker measures was developed in pre-dementia patients and validated in ADNI.¹²² The model, comprising age; education; AD signature cortical thickness; hippocampal volume; and CSF t-tau, A β 42, and A β 40, more accurately

predicted decline in cognitive scores than a base model of demographics alone. It reduced estimated clinical trial sample sizes over demographics variables alone and is available as a web-based application (https://disease-progression.shinyapps.io/disease_progression/). Similarly, a model predicting 3-year cognitive decline that was developed in BioFINDER 2 and replicated in ADNI comprised baseline tau PET, baseline cognition, CSF NfL, and cortical thickness was operationalized for individual prediction (<https://brainapps.shinyapps.io/PredictMMSE/>).¹⁰⁸ This model reduced clinical trial assessment costs by approximately half compared to no enrichment.

Dementia risk was found to be influenced by sex, APOE ϵ 4 status, and age of onset of A β positivity in a study of longitudinal biomarkers in ADNI and two additional cohorts.¹²³ The age of A β onset in APOE ϵ 4 allele carriers was earlier than in non-carriers and was dose-dependent for the ϵ 4 allele. APOE ϵ 4 allele carriers, females, and those with a later age of A β onset had a shorter time until the onset of cognitive impairment. Survival curves from the study may form the basis for individualized prediction of time to cognitive impairment based on these factors.

Clinical diagnosis based on neuropsychological tests may not accurately reflect the disease process and therefore prediction of change in diagnostic state may be inherently flawed. To overcome this limitation, a metric, termed the pathology progression rate (PPR), was developed¹²⁴ based on a network diffusion model that spatially and temporally describes the spread of AD-related neurodegeneration along brain WM fibers.¹²⁵ PPR varied across diagnostic classes and APOE ϵ 4 genotype and was associated with global atrophy rate and decline in MMSE. A model comprising a profile of baseline CSF biomarkers identified by hierarchical cluster analysis that represents an intermediate stage of AD neurodegeneration, combined with baseline MRI regional atrophy predicted PPR at the subject level with reasonable accuracy ($r^2 = 0.26$ in linear regression models). The model was less accurate in predicting a global atrophy rate. This approach may offer individualized prediction of biologically based disease progression using MRI scans commonly available in primary care, and CSF biomarkers.

The development of highly sensitive assays for plasma AT(N) biomarkers opens the possibility of their use in individualized prognosis. The ability of plasma A β 42/40, p-tau (181 or 217), and NfL, alone and in combination, to predict conversion of MCI to AD dementia and longitudinal cognitive decline in individuals over 4 years was compared in BioFINDER and models were validated in ADNI.¹²⁶ A model comprising plasma p-tau217 (in BioFINDER) or p-tau181 (in ADNI) and NfL outperformed a base model of demographics and baseline MMSE for the prediction of clinical conversion (AUC of 0.89 compared to 0.74 for the base model in the ADNI validation cohort), achieving comparable accuracies to CSF biomarkers. A β biomarkers or APOE ϵ 4 genotype did not contribute to prediction. Patient-level models for the conversion to AD dementia and change in MMSE and CDR-SB scores within 4 years were operationalized into an online tool available at predictprogression.com. Similarly, a model developed and validated in the same cohorts to predict individual conversion from MCI to AD dementia and comprising plasma p-tau, APOE, memory, and executive function was

implemented online at <http://predictAD.app>.⁶¹ As plasma biomarkers become approved for clinical use, individualized prediction algorithms have great potential, not only in primary care, but for recruitment into clinical trials, substituting for more invasive and/or expensive CSF biomarkers and PET scans. However, it must be emphasized that these studies have been performed in limited cohorts and that further validation in more diverse primary care populations is required.

2.7 | Prediction of AD pathological features

With the recent FDA accelerated approval of anti-amyloid monoclonal antibody therapies, prediction of A β status to select those likely to benefit from treatment has become an immediate challenge. As PET scans are expensive and not widely available, and lumbar puncture for CSF is invasive, recent ADNI studies have reported prediction models using modalities accessible in primary care. Such prediction models may also lower costs associated with participant selection for clinical trials.

A model for the prediction of A β status in CU participants based on data from the A4 study and optimized for both ADNI and Japanese ADNI consisted of information easily accessed in primary care: demographics, family history, CDR-SB, PACC, and APOE ϵ 4 genotype.¹²⁷ Other approaches have used additional predictors such as MRI measures and plasma biomarkers.^{128,129} Of single AT(N) plasma biomarkers, plasma A β 42/40 best predicted A β PET status in all ADNI participants while plasma p-tau181 had moderate predictive ability in MCI participants.¹²⁸ The addition of clinical information (APOE ϵ 4 status and education in CU, APOE ϵ 4 status and age in MCI participants) and an MRI score to plasma A β 42/40 improved prediction, but plasma p-tau181 and plasma NfL added little additional predictive ability over clinical information and MRI¹²⁸ (Figure S17 in supporting information). Hippocampal morphometry features also predicted A β PET burden in CU and MCI participants from ADNI and the Open Access Series of Imaging Studies (OASIS) cohort.¹²⁹

Specific regional tau accumulation is strongly linked to future neurodegeneration and cognitive decline and therefore prediction of tau accumulation may be useful for identifying CU individuals at risk of future decline. A prognostic index able to distinguish between stable CU over 5 years, and declining CU or MCI based on baseline cortical A β and MTL volume as continuous variables together with APOE ϵ 4 genotype was developed from baseline ADNI data and validated in the Berkeley Aging Cohort Study.¹³⁰ The clinically declining group defined by the index had significantly greater baseline global cortical tau and faster accumulation of cortical tau in Braak stages IV and V, and greater decline in PACC than the clinically stable group. This group also accumulated global tau faster than a sample defined by A β positivity. The index predicted individual regional variability in future tau accumulation and was estimated to reduce sample size required to detect a 25% decrease in the rate of future tau accumulation by 44%. Use of the prognostic index to define a more stringent threshold for future tau accumulation lowered sample heterogeneity in a simulated trial (Figure 4). Other methods for predicting tau accumulation have been based on the structural connectome;¹³¹ PRS based on SNPs from

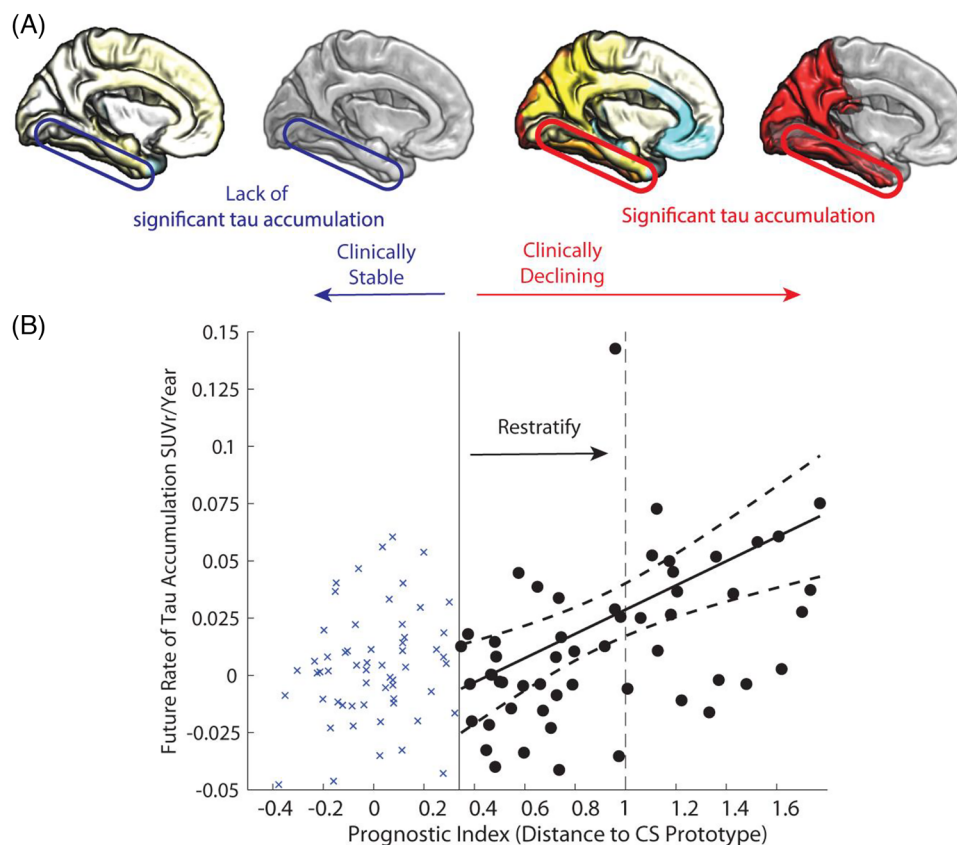


FIGURE 4 Tau prognostic index to predict future tau accumulation. (A), Cortical maps show average rate of tau accumulation for individuals classified as Clinically Stable (CS) versus Clinically Declining (CD). (B), Relationship of the scalar projection with future rate of tau accumulation within the fusiform gyrus (circled in cortical maps are shown in [A]). The solid black vertical line indicates the probabilistic boundary used to perform the binary stratification, blue crosses indicate rate of tau accumulation for the clinically stable group, black circles indicate future rate of tau accumulation for the clinically declining group. Restratiification to a more stringent threshold, indicated by the dashed black vertical line, using the prognostic index allows a new sample to be selected with higher future rates of tau accumulation and lower heterogeneity within the sample. SUVR, standardized uptake value ratio. Reproduced under open access from Giorgio et al.¹³⁰

the tau pathway,^{132,133} and a combination of demographics, regional cortical thickness, and memory tests.¹³⁴

2.8 | Conclusions

In 2021 and 2022, ADNI studies have contributed to the assessment, development, and implementation of AD therapies and blood biomarkers; described methodological improvements to clinical trials and AD research; and improved AD diagnosis and prediction methods. Of particular note were: (1) the use of ADNI data and methodologies underlying clinical trials that led to the FDA approval of lecanemab; (2) the emergence of plasma p-tau as a promising biomarker of many AD characteristics; (3) the predominance of the ADNI cohort in machine learning AD diagnosis and prediction studies, suggesting a lack of generalizability of these results; (4) the investigation of biomarkers beyond AT(N) such as those reflecting neuroinflammation as predictors of future decline; and (5) the provision of online software tools for individualized prediction of future decline.

3 | ADNI'S CONTRIBUTIONS TO UNDERSTANDING AD DISEASE PROGRESSION

Development of therapies for AD depends on a nuanced understanding of underlying biology and how this affects disease progression. It has become clear in recent years that AD is a complex, multifactorial disease with much heterogeneity in disease course and clinical manifestation. The breadth of ADNI data and availability of samples along with its longitudinal design has facilitated a wide range of approaches to untangle this complexity. In this section, we examine how AD causes cognitive decline and dementia and extensively discuss recent evidence supporting the cascade of events originally proposed in the amyloid hypothesis.¹³⁵ We then consider the influence of vascular risk factors on disease trajectory. We examine types and patterns of heterogeneity and factors that contribute to them such as co-pathologies, resilience and sex, and neuropsychiatric symptoms (NPS). By linking lines of evidence from multiple areas of research in a thematic structure, we hope to shed light on how the interaction of these complex factors may account for the observed cognitive

decline in patients and highlight possible novel therapeutic targets and strategies.

3.1 | The relationship of age to AD

In patients in a presymptomatic stage with family history of AD, author-termed “functional brain aging” measured using resting state functional MRI (rs-fMRI) accelerated near the age of parental onset but was not associated with either APOE ϵ 4 or A β positivity.¹³⁶ “Accelerated functional brain aging” was also observed in ADNI MCI and AD participants, suggesting that it was AD specific.¹³⁶ A metric predicting brain age from MRI scans was associated with cognitive deficits and was higher in amnesic MCI than CU ADNI participants, and in APOE ϵ 4 carriers and those who were A+.¹³⁷ Similarly, the brain age gap, the difference between individual brain age, assessed from a temporal pattern of hypometabolism and atrophy, and chronological age, was greater in MCI participants who progressed to AD compared to those who were stable or CU participants.¹³⁸ The brain age gap increased at a faster rate in MCI progressors and in females (Figure S18 in supporting information). These studies suggest that some features associated with brain aging such as changes in functional connectivity, glucose metabolism, and brain volume, are accelerated in AD.

Biological age, as opposed to chronological age, can also be assessed using “epigenetic clocks,” which aggregate epigenetic changes, such as changes in CpG DNA methylation patterns associated with aging. Of five first-generation epigenetic clocks tested, only the Hannum epigenetic clock was associated with hippocampal volume in ADNI and AIBL.¹³⁹ However, ADNI AD participants had extremely high ages on a more sophisticated third-generation epigenetic clock, DunedinPACE. This clock is based on methylation patterns related to the rate of physiological change that characterizes the aging process rather than deviation from chronological age, and so reflects a range of age-related physiological processes from multiple organs.¹⁴⁰ Genetic susceptibility to AD progression and epigenetic age acceleration may be shared.¹⁴¹ Systemic factors beyond AD pathology and AD genetic risk alleles may contribute to the observed accelerated pathology in AD patients. A range of neurological and systemic biological processes were implicated in a study that identified modules of coexpressed genes associated with accelerated biological aging.¹⁴²

What might these factors be? A comprehensive study of CSF proteomics in CU participants ranging in age from 46 to 89 years from three cohorts including ADNI sheds some light on this question.¹⁴³ Of 1149 proteins tested, 911 differed with age; among these 194 were altered in participants older than 60 years; 172, 22, and 352 proteins differed by A β status, APOE ϵ 4 status, and sex, respectively. Independent of these factors, 252 proteins showed age-related changes, and these were enriched for immune response, signal transduction, and cellular responses to external stimuli. At a genetic and pathway level, there was substantial overlap between healthy aging and AD in a study investigating causal relationships between RNA transcripts and neuroimaging.¹⁴⁴ A relatively small set of genes contributed sta-

bly to multimodal imaging and subsequent cognitive decline in healthy aging (Figure S19A in supporting information). In contrast, in AD, the study identified 111 genes and 65 functional pathways with stable causal alterations (Figure S19B), some of which were associated with healthy aging, but had exaggerated effects in different brain areas. Predominant pathways highlighted in AD patients were apoptosis, oxidative stress, and immune/inflammatory response. Leukocyte migration involved in systemic inflammation was associated with accelerated aging on epigenetic clocks.¹⁴² Together, the authors suggested that the changes observed in AD are a result of accelerated aging and enhanced vulnerability of brain substrate to both known risk factors for the disease (A β positivity, APOE ϵ 4 allele, and female sex), and other physiological processes.

Frailty, defined as “an age-related state of multisystem physiological decline increasing the risk of adverse outcomes,”¹⁴⁵ may modulate the relationship between neuropathology and dementia in AD. Frailty was associated with lower CSF A β 42 and hippocampal volume, worse glucose metabolism, and greater cortical A β binding, and strengthened the association between glucose hypometabolism and dementia. As frailty encompasses a variety of health deficits, these indices may conglomerate diverse mechanisms contributing to dementia such as inflammation and immunosenescence. These associations reflect the complex multifactorial nature of AD.

3.2 | Recent ADNI evidence supporting the amyloid cascade hypothesis

Until recently anti-amyloid therapies, including immunotherapy (monoclonal antibodies and vaccines) and BACE inhibitors, failed to show a significant beneficial effect in clinical trials. However, in the past 2 years, several clinical trials have associated monoclonal antibodies that greatly reduce or eliminate A β plaques with significant slowing of cognitive decline.^{25,146} These findings support the amyloid hypothesis¹³⁵ (Figure S20 in supporting information). Although ADNI is an observational study, numerous analyses of ADNI data have been performed to determine the association of brain A β , tau, neurodegeneration, and cognitive decline.

Much of the evidence to support the view that late-onset AD begins with the accumulation of A β (subsequently leading to the spread of tau and neurodegeneration) stems from studies of patients with autosomal dominant AD, resulting from a single gene mutation that causes overproduction of A β . A recent study explored the degree to which underlying pathophysiology is shared between autosomal dominant AD, in the Dominantly Inherited Alzheimer Network (DIAN) cohort and late onset AD in ADNI.¹⁴⁷ Levels of CSF A β 42, p-tau181, and t-tau were similar in preclinical and early symptomatic participants from both cohorts when the disease trajectories of both autosomal-dominant and late-onset participants were anchored at the age of symptom onset for comparison. After symptom onset, the rates of change of cognitive impairment and regional atrophy accelerated in both groups, although this acceleration was greater in autosomal-dominant AD participants. The authors conclude that the two forms

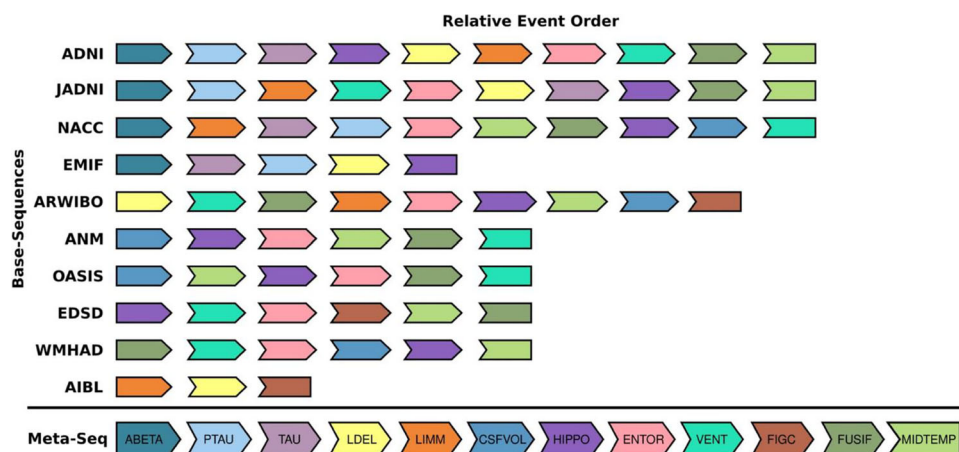


FIGURE 5 Consensus ordering of AD biomarkers from 10 cohorts. All base sequences from the 10 investigated cohorts and the resulting meta-sequence. Due to only partially overlapping lists, the determining factor for an event's position in the meta-sequence was not its absolute position in each base sequence (i.e., rank 1, 2, ..., 11), but its relative position to other biomarkers in the same sequence. ABETA, amyloid beta; AD, Alzheimer's disease; AIBL, Australian Imaging, Biomarker, & Lifestyle Flagship Study of Ageing; ANM, AddNeuroMed; ARWIBO, Alzheimer's Disease Repository without Borders; JADNI, Japanese ADNI; EDSO, European DTI Study on Dementia; EMIF, European Medical Information Framework; CSFVOL, accumulated CSF volume in the brain; ENTOR, entorhinal volume; FIGC, Figure Copy; FUSIF, fusiform volume; HIPPO, hippocampal volume; LDEL, Logical Memory-Delayed Recall; LIMM, Logical Memory-Immediate Recall; MIDTEMP, middle temporal lobe volume; NACC, National Alzheimer's Coordinating Center; OASIS, Open Access Series of Imaging Studies; PTAU, phosphorylated tau; VENT, ventricular volume; WMHAD, White Matter Hyperintensities in Alzheimer's Disease. Reproduced under open access from Salimi et al.¹⁵⁰

of AD share pathobiological underpinnings, providing support for the central role of $A\beta$ accumulation in disease progression.

A neuroimaging study of ADNI CU and MCI participants grouped by AT(N) status ($A\beta$ PET, tau PET, hippocampal volume)¹⁴⁸ provided both cross-sectional and longitudinal evidence for a unidirectional pathway beginning with $A\beta$ deposition, followed by tau deposition and neurodegeneration. Whereas A+T-N- participants had higher tau than A-T-N- controls suggesting sub-threshold tau accumulation, there was no evidence of $A\beta$ accumulation in either A-T-N+ or A-T+N+ participants. Likewise, high baseline $A\beta$ was associated with subsequent tau accumulation, but neither higher baseline tau accumulation nor lower hippocampal volume was associated with subsequent elevated $A\beta$. Faster decline in PACC was observed only in A+T+N- and A+T+N+ groups, linking tau and neurodegeneration more tightly to cognitive decline. The association of suspected non-Alzheimer's disease pathology (SNAP; T+ and/or N+ in the absence of A+) with cognitive decline likely represents a different neurodegenerative pathway. In a second PET study of ADNI CU participants,¹⁴⁹ overlapping regions of $A\beta$ and tau deposition in AD-typical regions were strongly associated with baseline and longitudinal cognition. Specifically, $A\beta$ to tau but not tau to $A\beta$, interactions in the MTL were associated with cognitive impairment, supporting $A\beta$ to tau to cognitive impairment directionality. It is important to note that these studies provide strong support for directionality, but do not establish causality of $A\beta$ in initiating AD.

Several studies have investigated the sequence of events in the amyloid cascade using biomarkers. An event-based model fitted to data from 10 cohorts including ADNI¹⁵⁰ largely recapitulated the hypothetical ordering of biomarkers in AD proposed by Jack et al.¹⁵¹ CSF $A\beta$ 42 consistently became abnormal first, followed by p-tau181 or t-

tau (Figure 5). The order of these tau biomarkers varied but they were always positioned next to each other, indicating that they are directly linked. There was some variability in the positioning of neurodegeneration biomarkers but there was a consistent sequence of clinical assessments in which memory was impaired first, followed by language and visuospatial ability, and last, executive function (Figure 5).

This ordering of biomarkers is based on established thresholds for positivity, but meaningful changes in biomarkers may occur at sub-threshold levels. When the temporal ordering of CSF and PET biomarkers as well as PACC were aligned relative to time to $A\beta$ positivity assessed by PET,¹⁵² small increases in CSF p-tau181 and MTL tau PET binding were seen 5 to 8 years before the $A\beta$ threshold was reached. Small changes in cognitive dysfunction were also observed in this time frame (Figure S21 in supporting information). CSF $A\beta$ 42 reached the positivity threshold before $A\beta$ PET and plateaued approximately two decades later. $A\beta$ accumulation assessed using serial florbetapir PET scans followed a sigmoidal curve that was consistent with hypothesized trajectories¹⁵¹ and slowed \approx 4 years after reaching the positivity threshold, \approx 10 years before MCI diagnosis.¹⁵³ In CU participants below the positivity threshold, the rate of deposition was associated with subsequent tau deposition and decline in memory.

A study that used structural equation pathway modeling to investigate the direct and indirect effects of not only global $A\beta$ PET uptake, regional tau PET uptake, and regional MRI atrophy, but demographics, APOE ϵ 4, white matter lesions, and cognition in A+ ADNI CU and CI participants also supported an $A\beta$ -tau-atrophy unidirectional pathway.¹⁵⁴ Importantly, the $A\beta$ -tau-atrophy pathway accounted for only 50% to 56% of the longitudinal variance in cognition, with $A\beta$, tau, and atrophy individually accounting for 16%, 46% to 47%, and 25% to 29% of longitudinal variance in cognition, respectively. Age,

the APOE $\epsilon 4$ allele, and WM lesions all affected cognition but were insufficient to explain the total variance in cognition combined with the A β -tau-atrophy axis. These results suggest that other factors such as α -synuclein (α -syn), TAR DNA-binding protein 43 (TDP-43), vascular risk, inflammation, and genetics also contribute to cognitive decline and may help to explain why monoclonal antibodies that remove plaques “only” slow cognitive decline by 25% to 30%. If only 50% of decline is accounted for by the AT(N) pathway, and plaque removal is slowing AT(N)-related decline by 50%, the overall effect would be a 25% slowing of decline.

Together, these studies support a unidirectional sequence of events that occurs on a timeline in which abnormal A β rises years before reaching the threshold for positivity, continues on that trajectory for years after reaching the threshold, decelerates a decade before MCI diagnosis, and subsequently plateaus. Phosphorylated tau and t-tau become abnormal followed by neurodegeneration biomarkers and cognitive assessments. The limited success of anti-amyloid therapies to see a clinical benefit in MCI and early AD dementia patients may be partially attributable to timing (at a point at which A β deposition is markedly slowing after most of the deposition has already occurred) and target, given that A β explains only a small portion of variance in cognition.

In the following sections, we outline recent ADNI studies that have provided evidence for steps in the amyloid cascade, detailing how cellular pathways link A β and tau deposition and the cascade of events that lead to neurodegeneration and cognitive decline (Figure S20).

3.2.1 | Abnormal A β processing and A β accumulation

The earliest (which is not to say causative) step in the amyloid cascade is the disruption of homeostasis of A β production. Recent ADNI studies have identified genetic variants involved in this process beyond APOE. A large GWAS of plasma A β 40, A β 42, and A β 42/40 levels in > 12,000 nondemented participants from eight studies including ADNI identified variants in amyloid pathway genes *BACE*, *APP*, and *PSEN2*, as well as in APOE.¹⁵⁵ Expression of 11 variants of the top 30 non-APOE $\epsilon 4$ AD risk alleles in ADNI blood samples, including novel variants in *ADAM10*, *IGHV1-68*, and *SLC24A4/RIN3*, were associated with brain amyloidosis.¹⁵⁶ A large case-control GWAS that included ADNI data as part of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium identified six novel genes (*ICA1L*, *DGKQ*, *ICA1*, *DOC2A*, *WDR81*, and *LIME1*), all likely involved in modulation of APP metabolism, which is central to the production of A β .¹⁵⁷ Most variants included in a non-APOE PRS of A β status were involved in biological aspects of the A β pathway: regulation of APP catabolism, A β formation, or A β clearance.¹⁵⁸ This PRS predicted A β status even in APOE $\epsilon 4$ carriers, further supporting the regulatory role of these non-APOE variants.

The micro-RNA miR20b-5p negatively regulated APP expression in human cell lines, and an SNP (rs13897515) upstream of the *MIR20B* gene was associated with CSF A β 42 and entorhinal cortical

thickness.¹⁵⁹ Cleavage of APP by β -secretase (BACE1) may be regulated by a rare variant associated with AD.¹⁶⁰ A rare variant risk association study in two cohorts including ADNI and molecular docking simulation identified rs3120654 (S742Y) in a modulator of BACE1 activity, *FLG*, which encodes an intermediate filament-associated protein.¹⁶⁰ This study provides a molecular-level explanation for the effect of a rare variant associated with AD, via influencing APP processing by BACE1.

The association of the amyloidogenic pathway with downstream events has been documented in recent ADNI studies. A PRS based on variants involved in endocytosis of APP and extracellular aggregation of A β (*BIN1*, *CD2AP*, *EPHA1*, *PICALM*, *SORL1*, and *CD33*) correlated with baseline CSF t-tau.¹⁶¹ Spatial patterns of hypometabolism measured by FDG PET were associated with patterns of expression of *BACE2* and *NDUFS4*, a mitochondrial protein that binds oligomeric A β and has been implicated in cognitive deficits.¹⁶²

Finally, the minor allele (C) of rs10751647 in *IFITM3* was associated with not only decreased brain A β deposition, but also lower CSF p-tau181, greater entorhinal cortical thickness, and slower cognitive decline and progression to AD dementia.¹⁶³ *IFITM3* encodes interferon-induced transmembrane protein 3, which upregulates γ -secretase in response to viral infection, suggesting that an innate immune response to microbial infection may increase A β deposition.

3.2.2 | Impaired clearance of extracellular A β

The removal of extracellular A β from the perivascular space into CSF via the glymphatic system has been proposed to be disrupted in AD, leading to accumulation of extracellular A β and deposition into plaques. In the glymphatic system, polarized distribution of aquaporin 4 channels in astrocytic end feet promotes the rapid movement of CSF to the brain interstitial space. There it mixes with interstitial fluid and waste solutes such as A β before being drained out of the brain via the perivascular influx pathway.¹⁶⁴ (Figure S22 in supporting information). Two SNPs in *AQP4*, the gene encoding aquaporin 4, were associated with in vivo brain A β independently of the APOE $\epsilon 4$ allele.¹⁶⁵ MRI measures reflecting the glymphatic system, such as the volume of and diffusivity into the perivascular space, were worst in participants with AD dementia, and intermediate in participants with MCI.¹⁶⁴ This indicated an enlargement of the perivascular space with disease progression and a concomitant decrease in diffusivity of CSF into that space. Changes in these measures in MCI and AD participants were significantly associated with CSF A β 42, FDG PET, and cognition.¹⁶⁴ Enlargement of the perivascular space in the centrum semiovale was associated with WMH volume,¹⁶⁶ glucose hypometabolism in A+ participants,¹⁶⁷ brain tau,¹⁶⁸ diagnostic conversion and longitudinal cognitive decline,¹⁶⁹ and sTREM2.¹⁶⁶ sTREM2, in turn, mediated the association between enlarged perivascular space in the centrum semiovale and CSF p-tau181.¹⁶⁶ There are several possible explanations for these findings. These findings may implicate dysfunction of the glymphatic system, by sleep disturbances or small vessel disease (indicated by WMH volume), as a key causal event in pathogenesis. In this scenario, disruption

of A β clearance contributes to its accumulation, which may trigger a microglial inflammatory response that results in further enlargement of the perivascular space in a feedback loop via tau. A second possibility is that these changes are secondary to the neurodegeneration that occurs in AD and so may not reflect a cause–effect relationship.

As the glymphatic system operates primarily during sleep, several ADNI studies have investigated the role of sleep, derived from self-report assessments, in the clearance of A β . An rs-fMRI study that detected CSF movements indicative of glymphatic clearance linked this signal with cortical A β binding, diagnosis, cognition, symptom severity, and the APOE ϵ 4 allele.¹⁷⁰ Disturbances to sleep appear to be associated with increased AD risk (i.e., a cause-and-effect relationship), and may offer a treatment target. A+ ADNI participants who reported insomnia had faster cognitive decline than those without insomnia.¹⁷¹ Baseline informant-reported sleep disturbances interacted with the APOE ϵ 4 allele alone, and CSF A β 42 and p-tau181/A β 42 together, to enhance regional atrophy rates.¹⁷² Self-reported obstructive sleep apnea (OSA) was associated with a shorter time of progression from CU to MCI, and from MCI to AD.¹⁷³ The risk of progression was increased by 2- to 3-fold in A+ participants with OSA, and by 3- to 5-fold in (TN)+ participants with OSA, compared to participants with no OSA.¹⁷³

These results may suggest a causal relationship in which sleep disturbances perturb the glymphatic system, resulting in a heightened risk of disease progression mediated by a synergistic interaction with A β and tau. Alternatively, it is possible that the neurodegeneration caused by AD pathology causes sleep disturbances or that both mechanisms occur.

A β metabolism in blood has been proposed to affect A β clearance from the brain.¹⁷⁴ A cis- expression quantitative trait loci (eQTL) analysis of 29 AD-associated SNPs identified elevated expression of *APH1B*, encoding a subunit of γ -secretase, in blood. This was associated with global A β burden, entorhinal cortex (EC) thickness, and MCI to AD progression, and the authors suggest that *APH1B* may represent a novel therapeutic target.¹⁷⁴

3.2.3 | Immune response and inflammation

Chronic low-grade inflammation is a hallmark feature of AD, and the importance of immune response in AD pathogenesis has been increasingly recognized. An immune pathway-specific PRS constructed from top AD risk loci was associated with increased longitudinal A β deposition, regional atrophy and hypometabolism, and worse cognition.¹⁶¹ In response to A β deposition, microglia and astrocytes are activated, causing a neuroinflammatory response that can be exacerbated by peripheral inflammation. This vital step in the cascade of disease progression links A β deposition with downstream events eventually leading to tau deposition. Recent ADNI studies have provided evidence for the importance of this step and helped identify potential normal therapeutic targets.

Several studies have investigated associations of a marker of disease-activated microglia, sTREM2 in CSF with AD biomarkers. In

ADNI participants across the AD spectrum, elevated sTREM2 was associated with old age and CSF AD biomarkers (A β 42, p-Tau181, and t-tau) as well as cytokines related to inflammation (chitinase-3-like protein 1 [YKL-40], progranulin, interleukin [IL]-10, transforming growth factor [TGF]- β 1, tumor necrosis factor alpha [TNF- α], C3, factor H) and neurodegeneration (NFL, synaptosomal-associated protein 25, neurogranin, growth-associated protein 43) but not with brain metabolism, MRI volumes, or cognition.¹⁷⁵ In contrast, in another study, elevated CSF sTREM2 predicted cognitive decline in A+ but not A- MCI and AD ADNI participants with an effect size comparable to that of CSF p-tau181 but less than MRI volumes.¹⁷⁶

The disparity between these results may reflect a stage-dependent effect of microglial activation. GWAS have identified *TREM2* as a protective gene in AD (reviewed in Veitch et al.^{8,9} and Weiner et al.¹³) that promotes anti-inflammatory cytokine expression and reduces pro-inflammatory cytokine release, activating microglia to surround and endocytose A β plaques. However, this response may eventually become detrimental later in disease progression, causing neuronal damage and facilitating disease progression. Higher levels of baseline CSF sTREM2 were associated with lower regional atrophy and WM damage in A+T+ MCI participants but with increased regional WM damage in A+T+ AD participants.¹⁷⁷ The action of CSF sTREM2 at different disease stages may be further modulated by interaction with CSF tumor necrosis receptor 2.¹⁷⁸

Microglia may also be activated by other upstream factors. Mediation analysis of CSF IL-3, a marker of astrocytic activation, sTREM2, and canonical AD biomarkers indicated that IL-3 modulated the levels of sTREM2 in response to A β deposition, and was associated with subsequent tau pathology and cognitive decline.¹⁷⁹ The authors suggest that cross-talk between astrocytes and microglia is an important link between A β and tau deposition in disease progression (Figure S23 in supporting information). Changes in iron homeostasis, critical for central nervous system function, may also affect CSF sTREM2. High levels of CSF ferritin, a biomarker of brain iron accumulation, were significantly associated with accelerated accumulation of CSF sTREM2 in participants stratified by AT(N) across the AD continuum as well as controls.¹⁸⁰ The authors suggested that this may indicate a role for iron-induced neuroinflammation. CSF ferritin levels increased across the AD continuum,¹⁸¹ and higher CSF ferritin was associated with worse cognition,^{181,182} worse CSF p-tau181,^{181,182} and with other inflammatory proteins¹⁸¹ but not A β .^{181,182} The association between CSF ferritin and p-tau181 was mediated by APOE.¹⁸² The contribution of iron metabolism to AD disease progression appears to be a complex process involving microglial activation, p-tau, and APOE.

Other markers of neuroinflammation have been associated with AD pathogenesis in recent studies. CSF IL-12p40, TNF- α , and IL-9, biomarkers involved in the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway that transcriptionally regulates many genes involved in immune response, were associated with clinical progression to MCI or AD.¹⁸³ CSF progranulin acted in a protective manner. Higher levels of progranulin were associated with lower A β burden in T+ and/or N+ participants only via interaction with neuroinflammatory markers (sTNFR1, sTNFR2, TGF- β 1, intercellular

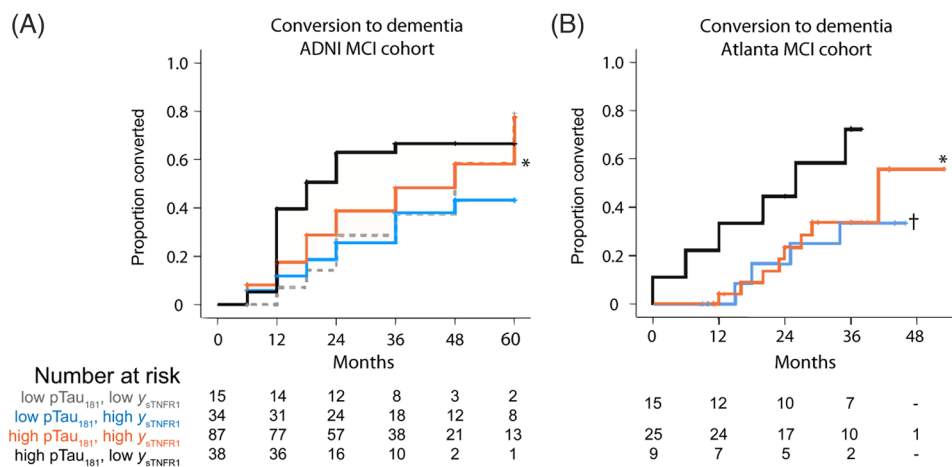


FIGURE 6 Conversion to dementia diagnosis by levels of CSF p-tau181 and sTNFR1. (A) ADNI. (B) Atlanta replication cohort. *Lower conversion compared to those with p-tau₁₈₁ \geq 24.1 pg/mL but low y_{sTNFR1} ($P = 0.049$ in ADNI and $P = 0.038$ in the Atlanta cohort). †Two subgroups with p-tau₁₈₁ < 24.1 were combined due to small numbers, $P = 0.068$ versus high p-tau₁₈₁ and low y_{sTNFR1}. ADNI, Alzheimer's Disease Neuroimaging Initiative; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; p-tau, phosphorylated tau; sTNFR1, soluble tumor necrosis factor 1. Reproduced under open access from Hu et al.⁸²

adhesion molecule 1, and vascular cell adhesion molecule 1).¹⁸⁴ This complex interplay of inflammatory proteins that are regulated by both pro- and anti-inflammatory processes makes selection of a single AD-relevant CSF biomarker of inflammation challenging. A study of 15 CSF inflammatory proteins involved in microglial- and T cell-mediated inflammation identified sTNFR1 as a prognostic biomarker in MCI that added predictive ability above and beyond CSF p-tau181.⁸² MCI patients with the lowest levels of this biomarker in addition to the highest levels of CSF p-Tau181 had the worst prognosis over 5 years (Figure 6). Higher levels of sTNFR1 therefore appeared protective, and this biomarker may provide complementary information to core AD CSF biomarkers.

The detrimental effects of neuroinflammation appear to be exacerbated by various other factors such as sex, APOE status, and cerebrovascular disease. Female APOE $\epsilon 4$ allele carriers with high levels of CSF IL-12p40, TNF- α , and IL-9 had the greatest risk of progression,¹⁸³ and higher levels of CSF sTNFR2 were associated with worse cognition, mediated by CSF p-tau181, in women but not men.¹⁸⁵ Higher levels of eight proinflammatory CSF biomarkers combined with lower levels of cerebrovascular disease, measured by pulse pressure, were associated with higher levels of CSF A β 42 in CU ADNI participants.¹⁸⁶ However, in MCI participants this combination was associated with higher levels of CSF p-tau181 and t-tau but not A β 42.¹⁸⁶ These results again support the hypothesis of an initial protective function of neuroinflammation followed by a shift to detrimental effects at later disease stages. The contributions of vascular disease to AD will be further described in Section 3.3; sex differences in Section 3.7.

Peripheral inflammation is frequently associated with cardiovascular disease and T2DM, which are risk factors for dementia. Recent ADNI papers have suggested a role for peripheral inflammation in exacerbating disease progression. Pro-inflammatory cytokines, released by neuroinflammation in response to A β deposition, can recruit peripheral immune cells which can take advantage of changes in the perme-

ability of the BBB and infiltrate the brain.¹⁸⁷ Genes associated with immune cell infiltration were identified from comparison of differentially expressed BBB- and immune-related genes in blood from ADNI participants with AD dementia and CU controls.¹⁸⁷ Five genes (*TNFRSF13C*, *CXCL3*, *CXCL12*, *CCL4L1*, and *CCL1*) overlapped between the two sets and were associated with CSF AD biomarkers.¹⁸⁷ Expression of a pro-inflammatory receptor (P2X purinoceptor 7) and two integrins (CD11b and CD11c) involved in phagocytosis on leukocytes was lower in A+ CU ADNI participants and associated with higher A β burden, more severe atrophy, and worse cognition.¹⁸⁸

In a UK Biobank study with validation in ADNI, two SNPs in two AD risk alleles involved in neuroinflammation, *CLU* and *CD33*, were associated with faster MCI to AD progression in the presence of C-reactive protein (CRP), a marker of peripheral inflammation¹⁸⁹ (Figure S24 in supporting information). Elevated CRP was found only in APOE $\epsilon 4$ homozygotes and was associated with increased CSF p-tau181 and t-tau, and worse global cognition.¹⁹⁰ These results implicate dysfunction of the peripheral immune system in AD progression, which may exacerbate genetic vulnerability for AD.

A number of studies have associated immune-related variants with AD. Gene- and pathway-level mapping of rare eQTL in ADNI blood samples and brain tissue from the Religious Orders Study/Memory and Aging Project (ROSMAP) cohort identified rare and low-frequency variants involved in inflammation mediated by cytokines and chemokine signaling.¹⁹¹ These included five genes previously linked to AD (*ALOX5AP*, *CXCR2*, *FPR2*, *GRB2*, *IFNAR1*). Rare variants in *NLR3* were associated with neuroinflammation (CSF YKL-40).¹⁹² These may act via counteracting the inhibitory action of *NLR3* on the NF- κ B and NLRP3 inflammasome signaling pathways.¹⁹² Further evidence for the central role of these signaling pathways came from a large case-control GWAS that included ADNI data as part of the CHARGE consortium.¹⁵⁷ Of the 75 risk loci identified, most were expressed in microglia. Pathway enrichment analysis identified

immune-associated gene sets involved in the regulation of the TNF- α -mediated signaling pathway. Prioritized genes included *SHARPIN*, *RBCK1*, and *OTULIN*, which implicated the involvement of the linear ubiquitin chain assembly complex, essential for the activation of the NLRP3 inflammasome and involved in TNF- α -mediated signaling. A PRS constructed from these variants and others involved in APP metabolism that excluded APOE was associated with 1.9-fold increased risk of future conversion from MCI to AD.¹⁵⁷

3.2.4 | Metabolic disturbances

Metabolic disturbances are an early feature of AD, resulting from the combined influence of AD neuropathology, genetic variations, microbiota, immune response, and lifestyle and diet.¹⁹³ Subtle changes in metabolites, predominantly amino acids and lipids, were observed in presymptomatic AD, preceding more pronounced changes later in disease progression in combined Knight ADRC and DIAN cohorts with replication in ADNI and ROSMAP.¹⁹⁴ A systems biology approach using data from the AD Metabolomics Consortium including ADNI data investigated metabolite coexpression networks and their genetic regulators in relation to AD progression.¹⁹³ Branched chain amino acids and short chain acylcarnitines decreased with disease progression with a concomitant increase in medium and long chain acylcarnitines over time correlating with NFTs in the frontal cortex. This disturbance of homeostasis was found to be regulated by *ABCA1* and *CPT1A*, and by adiponectin, a regulator of *ABCA1*. Expression of *ABCA1* and levels of adiponectin increased across diagnostic groups (Figure S25 in supporting information). A second study linked serum metabolites to global A β burden in addition to cognitive performance and MCI progression to AD dementia.¹⁹⁵ Seven phosphatidylcholines (PCs) were associated with increased cortical A β burden and an acylcarnitine (C3) and kynurenine were associated with decreased cortical A β burden. All differed in patterns of association with regional A β burden (Figure S26 in supporting information). Of these metabolites, C3, kynurenine, and several PCs were associated with worse memory and executive function, and one PC was associated with MCI conversion. A lipid metabolism PRS constructed from known AD risk loci including *CLU*, *SORL1*, and *ABCA7* was also associated with increased cortical A β burden and with neurodegeneration.¹⁶¹ These studies support the role of a wide range of A β -dependent lipid perturbations in influencing neurodegeneration, cognitive decline, and diagnostic progression.

Perturbations of PC metabolism may underlie the vulnerability of cholinergic neurons of the basal forebrain as one of the first sites of neurodegeneration in response to A β and tau deposition. Cluster analysis of serum lipids identified unsaturated PCs associated with significantly higher GM atrophy in the basal forebrain nucleus basalis of Meynert in participants with AD pathology compared to those without.¹⁹⁶ Cholinergic neurons have high metabolic demands for cell membrane maintenance. These results support the hypothesis that AD pathology contributes to their heightened vulnerability via abnormal PC metabolism.

Beyond PCs and acylcarnitines, other lipid classes have also been implicated in AD. Levels of glycerophospholipids, cholesterol esters, and complex sphingolipids, as well as PCs and acylcarnitines, were altered in MCI and AD participants compared to CU, and associated with CSF p-tau181/A β 42.¹⁹⁷ Clustering analysis identified two lipodomic endophenotypes with hazard ratios for MCI clinical progression greater than that for the APOE ϵ 4 allele (1.97 and 1.99 compared to 1.48).¹⁹⁷ Metabolism of sphingomyelin, a type of sphingolipid found in the myelin sheath and in lipid rafts in microglia, astrocytes, and neurons, is dysregulated in early AD.¹⁹⁸ An integrated multi-omics study focused on the sphingomyelin pathway, in which increased activity of sphingomyelin phosphodiesterase in response to A β deposition results in cleavage of sphingomyelin to form neurotoxic ceramides.¹⁹⁸ The study found that genes in this pathway were differentially expressed in AD patients compared to controls and used multimodal neuroimaging to identify variants (*SPTLC3* and *SGMS1*) associated with AD pathogenesis. A modulator of sphingosine-1-phosphate, an inhibitor of sphingomyelin phosphodiesterase, was identified as a potential AD drug target that may preserve synaptic function.

These metabolic changes reflect different components of the cascade of disease progression. Membrane restructuring that leads to brain A β accumulation is reflected in altered lipid metabolism¹⁹⁵ and these changes can trigger downstream responses such as apoptosis, neuroinflammation, and APP processing within lipid rafts.¹⁹⁵ Thus, changes in lipid metabolism may mediate the relationship between A β deposition and neurodegeneration. Activation of the kynurenine pathway occurs in response to neuroinflammation, and increased levels of acylcarnitines result from elevated oxidation of fatty acids and amino acids, reflecting perturbation of mitochondrial function.¹⁹⁵

3.2.5 | Mitochondrial abnormalities

Mitochondrial dysfunction, resulting in a loss of energy production (visible by FDG PET), synapses, and neuronal vitality and longevity, plays a key role in AD. The mitochondrial cascade hypothesis posits that declining mitochondrial function resulting from age and genetic and environmental factors is an upstream event that results in A β and tau pathology.¹⁹⁹ It is also possible that declining mitochondrial function is a byproduct of the amyloid cascade. Recent ADNI studies investigated the involvement of mitochondrial dysfunction in disease progression and identified novel therapeutic targets.

Several studies have investigated associations between genes involved in mitochondrial function and AD. Mitochondria have a very limited number of genes, and most genes involved in mitochondrial function are encoded in the nucleus. Mitochondrial contributions to pathogenesis are therefore likely attributable to nuclear genes. An AD PRS comprising nuclear-encoded mitochondrial genes, and three pathway PRS from genes involved in mitochondrial pathways, were significantly associated with AD with odds ratios ranging from 1.22 to 2.01.²⁰⁰ Significant mitochondrial pathways were mitochondrial transport, hallmark oxidative phosphorylation, and response to oxidative stress. A GWAS of mitochondrion-associated genes and

subsequent epistasis analysis identified six modules of nuclear genes associated with AD pathogenesis that interacted with mitochondrial genes.²⁰¹ Top hub genes identified through network analysis were involved in synaptic function, signaling pathways, and neurodegenerative pathways, demonstrating how mitochondria-related biological processes may contribute to AD pathogenesis beyond reduced energy metabolism. The only gene identified from all investigative approaches was *APP*, consistent with its central role.

Spatial patterns of tau pathology were associated with genes involved in metabolism, as well as oxidative phosphorylation, mitochondrial respiration, and electron transport, implicating mitochondrial dysfunction in addition to metabolic disturbances in tau deposition.¹⁶²

3.2.6 | Tau deposition

Tau deposition is a critical step in AD pathogenesis. Brain tauopathy was associated with 10 of the 20 top AD risk genes (*ABCA7*, *BIN1*, *CASS4*, *CLU*, *CR1*, *EPHA1*, *NME8*, *SORL1*, *DSG2*, and *ZCWPW1*)²⁰² and with expression of 7 of the 30 top non-*APOE* risk alleles.¹⁵⁶ Hyperphosphorylation of tau in microtubules occurs when signaling pathways are altered for a variety of reasons including the $A\beta$ -induced, microglia-mediated inflammatory response. This causes tau deposition into NFTs with concomitant cytoskeletal abnormalities that result in synaptic dysfunction preceding neuronal death.²⁰² AD risk genes associated with tau deposition have a variety of cellular functions involved in this process such as tau phosphorylation (*BIN1*), lipid transport (*ABCA7*), cellular adhesion signaling (*CASS4*), and immune function (*CR1*).²⁰²

Recent ADNI studies have provided further support for the critical function of tau deposition in the chain of events ultimately resulting in cognitive impairment. The *BIN1* SNP rs744373 risk allele was associated with faster tau PET accumulation in ADNI and AIBL participants.²⁰³ Carriers of the risk allele had greater global tau PET and greater cognitive decline than noncarriers. Tau accumulation was even greater in A+ risk allele carriers and mediated cognitive decline (Figure S27 in supporting information). This is in agreement with the modeling study that estimated tau to account for almost half of the variance in cognitive decline¹⁵⁴ and with a meta-analysis of 24 studies including three ADNI studies that estimated an overall weighted effect size of -0.46 (95% confidence interval [-0.73; -0.20], $P < 0.001$) for the association of tau protein biomarkers with episodic memory.²⁰⁴ Additionally, three novel variants (minor alleles in *ZBTB20*, *EYA4*, and *VNN2*) identified in a GWAS of brain tauopathy were associated with cognitive decline mediated by tau PET.²⁰⁵ *ZBTB20* is a transcription factor expressed in dendritic cells previously identified in other neurological disorders, and expression of *VNN2* is regulated by the kinase, *EYA4*, which may be involved in tau hyperphosphorylation.²⁰⁵

A haplotype of *KLOTHO* (*KL*), encoding a transmembrane protein associated with brain health, was shown to be protective in combination with the *APOE* $\epsilon 4$ allele.^{206,207} *KL***VS* heterozygosity (carrying only one copy of the functional haplotype encoding F352V and C370S) lowered risk of $A\beta$ positivity only in *APOE* $\epsilon 4$ carriers.²⁰⁶ At patho-

logical levels of global $A\beta$ PET, *KL***VS* heterozygosity was associated with lower increases in regional tau PET, especially in *APOE* $\epsilon 4$ allele carriers, which mediated better memory²⁰⁷ (Figure S28 in supporting information). These results suggest that *KL***VS* heterozygosity counteracts the detrimental effects of the *APOE* $\epsilon 4$ allele on memory by protecting against $A\beta$ -related increases in tau deposition, contributing to resilience.

3.2.7 | Axonal and synaptic dysfunction

Axonal and synaptic dysfunction prior to neuronal death is a crucial step in disease progression that has been difficult to measure, largely because well-established biomarkers to track this process are lacking.⁷¹ This step represents the first common point at which different contributing factors to AD converge, not only hyperphosphorylated tau, but inflammation, oxidative stress, genetic contributions, altered Ca^{2+} homeostasis, and more.⁷¹ A compensatory response involving microglia and astrocytes, which engulfs and clears accumulated synaptic debris, is eventually overcome resulting in a net loss of synapses.²⁰⁸ The development of CSF and, in some cases, plasma biomarkers of axonal and synaptic damage has allowed identification of additional genetic risk factors, better tracking of disease progression, and assessment of whether putative medications are engaging their target. ADNI's collection of CSF and blood samples has facilitated many of these analyses.

An exploratory analysis that linked densities of 15 neurotransmitter receptors derived from brain donors at the University of Düsseldorf with ADNI neuroimaging data (tau, $A\beta$, and FDG PET, and structural, functional, and arterial spin labeling MRI) suggested that much of the variability in cognitive decline can be attributed to receptor differences.²⁰⁹ Differences in the interactions of three neurotransmitter receptors with neuroimaging modalities explained up to 70% of population variability in cognitive decline, primarily in executive function. Glutamatergic receptor interaction changes affected neuronal activity and tau accumulation, and GABAergic receptor changes additionally affected $A\beta$ accumulation. Cholinergic receptor interaction changes affected tau accumulation. Dysfunction of these neurotransmitters may be involved in AD pathological neurodegeneration.

A marker of presynaptic dysfunction, growth associated protein 43 (*GAP43*), reflects the importance of disruption of the synapses in AD disease progression. *GAP43* was measured in ADNI CSF samples by the clinical neurochemistry lab at the Sahlgrenska University Hospital, Sweden, and subsequent data were analyzed by many groups. This biomarker increased over diagnostic classes²¹⁰ and was strongly associated with CSF p-tau181 levels,²¹⁰⁻²¹² but less so with $A\beta$ PET positivity²¹² and not at all with CSF $A\beta 42$.^{210,211} Higher baseline levels or more rapidly increasing levels of CSF *GAP43* were associated with greater hypometabolism,²¹⁰⁻²¹² atrophy,²¹⁰⁻²¹² cognitive decline,²¹⁰⁻²¹² and MCI to AD dementia progression.^{211,212} This discrepancy between the association of CSF *GAP43* with $A\beta$ may be because CSF $A\beta 42$ positivity occurs earlier than $A\beta$ PET positivity, positioning $A\beta$ PET positivity closer to synaptic dysfunction. $A\beta$

PET positivity worsened cognitive outcomes in GAP43-positive and -negative participants.²¹² These studies suggest a pathway in which synaptic dysfunction driven by increased tau pathology (and to a lesser extent, A β deposition) results in neurodegeneration and cognitive decline.

Not all synaptic dysfunction resulting in cognitive decline is attributable to AD pathology. An ADNI study of CU and MCI participants investigated associations of five putative CSF biomarkers of synaptic damage and loss (chromogranin A, fatty acid binding protein, neuronal pentraxin 2 [NPTX2], secretogranin, and neurosecretory protein VGF) with AD pathology, atrophy, and cognitive decline.²¹³ Of these proteins, NPTX2 had the greatest within-subject declines over 3 years and correlated most strongly with cognitive decline. Although CSF NPTX2 declined more in participants with a positive baseline CSF p-tau181/A β 42 ratio than in those with a negative ratio, the greatest decline was seen in participants with stable or slightly declining CSF p-tau181. Therefore, CSF NPTX2, unlike CSF GAP43, may not be associated with accelerated cognitive decline that occurs because of AD pathology. This biomarker, which modulates postsynaptic AMPA-type glutamate receptors, may therefore reflect other neurodegenerative processes and represent a novel therapeutic target for intervention.

Like all CSF biomarkers, these require invasive lumbar puncture and blood biomarkers are therefore preferable. However, peripheral levels of brain proteins often do not reflect levels in the brain due to the difficulty of diffusion through the BBB. The use of brain-derived EVs that can be easily measured using techniques such as flow cytometry circumvents this problem. A study using ADNI as a replication cohort examined levels of N-methyl D-aspartate receptor 2A (NMDAR2A) in brain-derived EVs.⁷¹ NMDAR2A is a glutamate receptor that is the therapeutic target of memantine and so acts as a marker of synaptic function. Levels of NMDAR2A were lower in AD compared to CU participants and were able to discriminate between these two groups with an AUC of 0.81 in the ADNI validation cohort.

A GWAS of the CSF biomarkers NfL (axonal damage), neurogranin (synaptic degeneration), and YLK-40 (astroglial activation) used ADNI as a validation cohort.²¹⁴ This study identified rs1548884 in *TMEM106B*, an established risk gene for frontotemporal lobe dementia (FTLD), as associated with CSF NfL. A further 124 SNPs were in strong linkage disequilibrium with this variant, 80 of which reached a genome-wide significance, pointing to the importance of this gene. In contrast, established AD risk genes including *APOE* were not associated with CSF NfL. ADNI whole genome sequencing data confirmed two novel rare variants associated with AD.²¹⁵ The first locus was in *DLG2*, encoding a synaptic scaffold protein thought to be downregulated early in AD, and the second was in *DTNB*, encoding a neuronal-associated protein possibly involved in postsynaptic function.

3.2.8 | Trans-synaptic spread of tau

In AD, tau pathology usually spreads through the brain in a set pattern reflected in Braak staging.²¹⁶ From an initial hub in the EC, tau pathology spreads from the MTL via synaptic connections to the neocortex,

where it becomes closely linked to neurodegeneration.²¹⁷ Recent ADNI studies of structural and functional connectivity based on MRI tractography, cerebral blood flow (CBF), and rs-fMRI combined with A β , tau, and FDG PET have provided insights into the trans-synaptic spread of tau across these networks.

Tau PET data suggest that tau exhibited neuron to neuron transmission along topological connections of the structural connectome of WM from hub to non-hub regions, rather than along spatially adjacent connections.²¹⁸ This pattern of spread may be associated with alterations in properties of WM. The pattern of association between WM microstructural alterations characterized by greater diffusivity and lower axonal packing density and tau PET resembled Braak stages.²¹⁹ The degree of myelination in WM tracts also correlated with tau PET spread, with lower levels of myelin sheath being associated with a greater susceptibility of WM tracts to tau accumulation.²²⁰ Demyelination increased with disease severity and correlated with worse CSF A β 42, plasma NfL, and accelerated cognitive decline.²²¹

The trans-synaptic spread of tau is also associated with brain functional networks. Tau deposition was higher within functional connectivity networks.²²² Clusters of tau deposition within functional connectivity networks correlating with Braak stages were associated not only with later Braak stages, but with earlier Braak stages, suggesting that tau spread may be bidirectional.²²² Brain functional networks become more diffuse and desegregated with aging.²²³ In A+ ADNI participants with a given level of MTL tau in the EC, higher functional network segregation was associated with slower rate of tau accumulation in cortical regions corresponding to Braak stages III and IV²²³ (Figure S29 in supporting information). This relationship was also found in participants with different initial tau epicenters that resulted in patterns of spread divergent from Braak staging.²²³ A mediation analysis study in non-demented participants from the Baltimore Longitudinal Study of Aging (BLSA) and ADNI investigated the extent to which A β versus tau deposition in the MTL drove tau propagation to the neocortex.²¹⁷ Greater MTL tau in the EC was associated with greater neocortical tau in the inferior temporal gyrus (ITG), and this association was stronger in A+ participants.²¹⁷ Greater A β in the EC was associated with greater ITG tau both directly and indirectly via EC tau (Figure 7). Neurodegeneration markers were directly affected by ITG tau, but only indirectly affected by EC A β . This synergistic interaction between MTL A β and tau to influence tau neocortical propagation and subsequent neurodegeneration suggests that removal of either pathology would be insufficient to prevent neurodegeneration.

3.2.9 | Genomic basis of neurodegeneration and cognitive decline

As AD is a complex disease, neurodegeneration results from the convergence of multiple pathways. The expression of eight variants in top AD risk alleles in blood was associated with neurodegeneration.¹⁵⁶ Three of these were also associated with brain amyloidosis and one was also associated with tauopathy, implying that a range of common and distinct mechanisms underlie neurodegeneration. ADNI genomics and

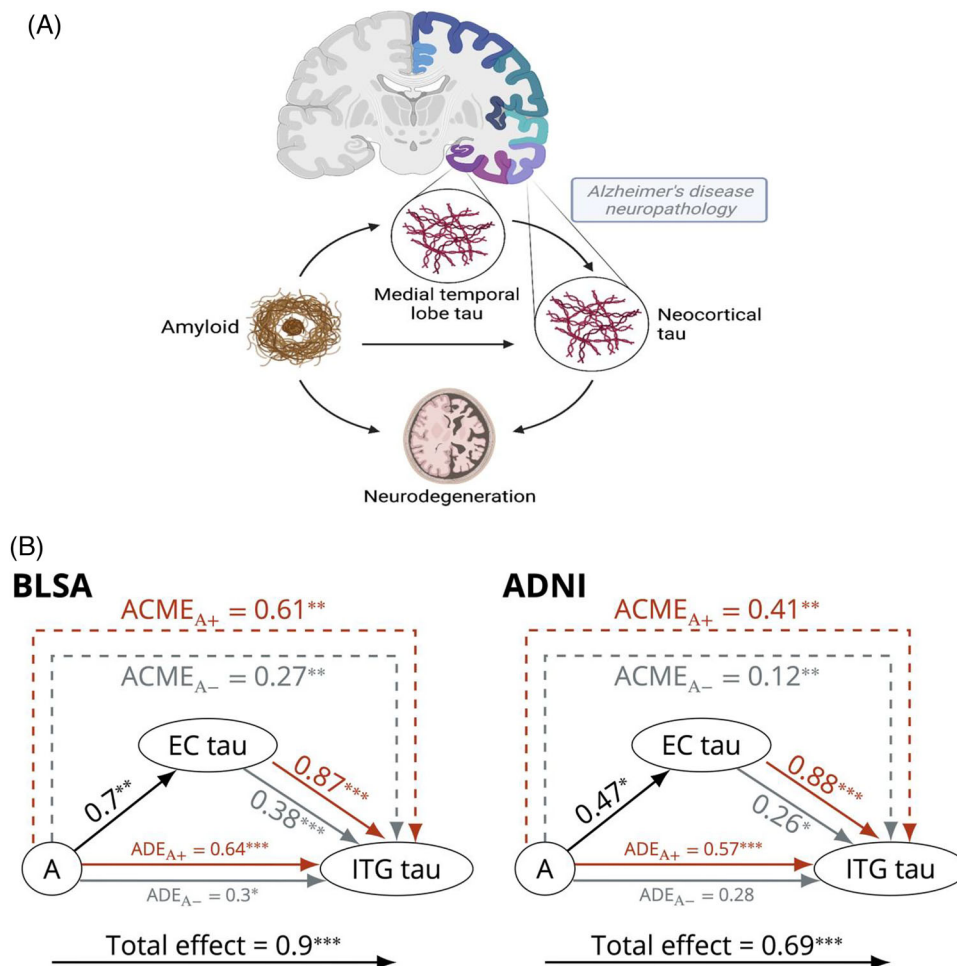


FIGURE 7 Tau neocortical progression is influenced by synergistic interaction of medial temporal lobe amyloid and tau. (A), Schematic of relationship among amyloid, medial temporal lobe tau, neocortical tau, and neurodegeneration. (B), Causal mediation analysis results for the model investigating the relationships among amyloid groups (+/-) and tau in the EC and the ITG in the BLSA and ADNI. The effect of amyloid on ITG tau is mediated by EC tau. Arrow from A to EC tau indicates the linear regression coefficient, and the gray and red arrows from EC tau to ITG tau indicate the linear regression coefficients for the amyloid negative and positive groups, respectively. Both the mediator and the outcome models were adjusted for age, sex, APOE $\epsilon 4$ positivity, years of education, and 10-year cardiovascular disease risk. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$. A, amyloid; ACME, average causal mediation effect; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; BLSA, Baltimore Longitudinal Study of Aging; EC, entorhinal cortex; ITG, inferior temporal gyrus. Reproduced from Bilgel et al.²¹⁷

proteomics data combined with imaging modalities used in recent studies, often as part of larger consortia such as CHARGE, have revealed contributors to neurodegeneration and cognition, and determined underlying mechanisms.

In most cases of AD, the amygdala and hippocampus are sites of very early atrophy in disease progression. When machine learning was used to reprioritize hits from a GWAS of hippocampal and amygdala atrophy in AD, genes from several A β -related pathways predominated:²²⁴ (1) alteration of synaptic structure and function through effects on the cytoskeleton, (2) changes in intracellular calcium levels resulting in excitotoxicity, (3) apoptotic signaling via protein misfolding in the endoplasmic reticulum, and (4) transcriptional regulation (Figure S30 in supporting information). A possible causal association mechanism underlying hippocampal volume was identified using ADNI multiomics data from blood and hippocampal tissues combined with causal association tests.²²⁵ A non-coding SNP, rs1053218, was proposed to induce

a specific DNA methylation change that hyperactivated ANKRD37, a gene involved in cell response to hypoxia, resulting in low hippocampal volume. The exact mechanism by which ANKRD37 may exert its effect on hippocampal volume is unknown, but hypoxia can impair BBB function, accelerate A β accumulation, and increase tau hyperphosphorylation. These studies underscore the complexity of mechanisms underlying neurodegeneration.

As described in Section 2.5.5, biomarkers of neurodegeneration are not highly concordant as they reflect different, partially overlapping processes. An established neurodegeneration marker is temporoparietal hypometabolism on FDG PET. A cross-sectional study of symptomatic participants from ADNI and the University of California San Francisco found that hypometabolism in this region was associated with both local cortical thickness and tau PET SUVR but not A β PET.²²⁶ Remote brain regions with strong structural connections, such as the MTL, did not strongly influence temporoparietal hypometabolism,

suggesting that hypometabolism in this region primarily reflects local tau deposition and atrophy.²²⁶ Networks of hypometabolism became progressively disrupted during disease progression in a longitudinal study of CU participants,²²⁷ with the decreasing network modularity and strength of connections particularly pronounced in women. Eight major AD risk alleles (*APOE*, *SORL1*, *CD33*, *FERMT2*, *TREM2*, *MEF2C*, *CLU*, and *BIN1*) significantly correlated with these metabolic networks, most strongly in the MTL. Four of these genes are involved in immune response, suggesting that inappropriate immune activation may underlie hypometabolism.

A GWAS of regional cortical thickness combined with gene expression analysis identified two novel susceptibility loci underlying brain atrophy.²²⁸ *ST18* encodes a zinc finger transcription factor that is highly expressed in the neocortex and, in fibroblasts, pierced influenced the expression of *TNF- α* , *IL-1 α* , and *IL-6*. *NF1A* is highly expressed in astrocytes, implying a role in neuroinflammation.

A genome-wide association meta-analysis conducted in > 53,000 non-demented adults in the CHARGE consortium aimed to identify genetic variants underlying verbal short-term memory and learning.²²⁹ The study identified four novel loci: (1) an intronic SNP in *CDH18*, expressed in the brain and involved in maintenance of neuronal and synaptic structure and neuronal cell adhesion; (2) 14 SNPs in high linkage disequilibrium in 3p21.1, a transcriptionally active region expressed in brain tissues and containing *NT5DC2* and *STAB1*; (3) 37 SNPs in an intergenic region in 13q21; and (4) an SNP in the *APOE-TOMM40-APOC1* locus at 19q13.3. Many of these common SNPs have been linked to other neurocognitive conditions such as schizophrenia, learning difficulties, and anorexia nervosa. ADNI data were also included in gene-based GWAS of longitudinal episodic memory in seven consortia that notably included an ethnically diverse population.²³⁰ The study identified *DCDC2* as associated with the maintenance of episodic memory in *APOE* ϵ 4 non-carriers. Finally, a GWAS of the Trail Making Test Part A conducted in ADNI identified a novel locus in *INSC*, a gene involved in cytoskeleton organization, which was also associated with other cognitive measures. The loci identified by the studies may represent new avenues of investigation for facilitating precision medicine interventions.

3.2.10 | Insights into cognitive decline

Subjective cognitive decline (SCD), that is, self-reported worse cognitive performance, is measured in ADNI using self-report and informant report ECog. While SCD has been associated with an increased risk of AD, studies of its association with underlying AD pathology have been mixed. This may be due to differences in definitions and assessments of SCD between cohorts as rates of A β positivity varied widely (10% to 76% at age 70) in SCD participants from cohorts in the 20 Amyloid Biomarker Study, which included ADNI.²³¹ Specific characteristics of SCD (memory complaints, attention/concentration complaints, and informant confirmed complaints) were associated with A β positivity only in research settings including ADNI and not in memory clinics.²³¹

In the ADNI cohort alone, self-reported word finding complaints such as “forgetting the names of objects” measured in the ECog-Language subscale predicted lower CSF A β 42 levels and correlated with regional atrophy.²³²

Memory awareness, defined as the difference between subjective and objective cognitive decline, decreases with increasing cognitive impairment.^{233,234} In the IMAP cohort with replication in ADNI, subjective memory decline remained similar across increasingly impaired diagnostic groups whereas objective memory decline increased.²³³ In CU participants, greater subjective memory decline was associated with greater neurodegeneration but the opposite was true in later diagnostic stages (Figure S31 in supporting information).²³³ Informant reports of complaints across the four domains of ECog were lower than self-reported complaints in CU participants, in good agreement in MCI participants, and higher in AD participants.²³⁴ Anosognosia (lack of awareness of impairment) was associated with greater tau but not A β deposition in impaired subjects.²³⁵ These reports suggest that anosognosia increases over time with increasing tau deposition and neurodegeneration and that subjective memory complaints should be interpreted differently in those with normal cognition compared to those with dementia.

An objective measure of subtle cognitive impairment (SCI) is included in the NIA-AA staging framework for preclinical AD. In ADNI CU participants, baseline scores of the modified PACC, which measures cognitive changes that do not manifest as conspicuous impairment, were associated with baseline and longitudinal A β deposition, suggestive of tau deposition, and associated with greater clinical progression (Figure S32 in supporting information).²³⁶ Subtle deficits in multiple cognitive domains may pose an additional risk of future decline. ADNI CU participants with deficits in both memory and executive function performance on MoCA²³⁷ were associated with greater global A β burden and entorhinal cortical and hippocampal atrophy than those with only memory deficits.²³⁸

These studies support the idea that subtle cognitive changes, both subjective and objective, occur very early in disease progression and are associated with AD pathology.

3.3 | Contribution of cerebrovascular disease to disease progression

Cerebrovascular disease is a well-known risk factor for AD and is found as a co-pathology in 70% of people diagnosed with AD dementia. Risk of cardiovascular disease is associated with cerebrovascular dysfunction, and high scores on the Framingham General Cardiovascular Disease Risk Score were associated with worse baseline and longitudinal measures of glucose metabolism, executive function and other cognitive measures, and clinical progression.²³⁹ Recent ADNI studies have continued to investigate the effects of cerebrovascular disease on disease progression using measures of CBF, an indicator of neurovascular function detected using arterial spin labeling MRI, and WMH burden, an MRI marker of small vessel cerebrovascular disease. However, these studies are limited because participants with moderate to

severe cerebrovascular disease were excluded in ADNI-1, ADNI-GO, ADNI-2, and ADNI-3.

Impaired CBF was associated with AD risk alleles.²⁴⁰ An AD genetic risk score was consistently associated with worse regional CBF over the lifespan. Moreover, regions of high expression of AD risk genes overlapped with regions of worse cerebral hypoperfusion in areas affected early in the disease progression.²⁴⁰ Lower baseline entorhinal, but not hippocampal, CBF predicted entorhinal cortical thinning, faster memory decline, and increasing WMH levels in non-demented participants.²⁴¹ CBF alterations at the site of early disease may precede downstream events including the development of WMH. Alternatively, early synapse loss may lead to reduced CBF. The cause–effect relationship of these factors remains unclear.

ADNI, like many AD cohorts, restricts the amount of vascular co-pathology in its participants. To address this limitation, one study investigated the association of WMH burden with neurodegeneration and cognition in ADNI MCI participants stratified by WMH burden, and in MCI participants from an external “real-world” cohort across the AD spectrum recruited from stroke prevention clinics.²⁴² Total WMH volume was associated with poor cognition, especially EF and semantic fluency, and this association was mediated primarily by cortical thickness in AD typical regions. To a much lesser degree, this association was mediated by A β (Figure S33 in supporting information). The authors suggested that this latter A β -mediated pathway reflects exacerbation of AD-related pathology via reduced A β clearance and/or induction of neuroinflammatory responses, as described in Sections 3.2.2 and 3.2.3. Additional support for this less prominent pathway comes from a study of CU participants²⁴³ in which lower baseline CSF A β 42 together with higher WMH were associated with worse memory but not executive function. Small vessel disease early in AD progression combined with abnormal A β may therefore promote an AD-typical disease pathway characterized by memory impairment.

In contrast, a study that followed CU, A+ MCI, and A+ AD participants for up to 13 years²⁴⁴ reported that WMH burden was not only associated with memory impairment but also EF and global cognition deficits, with a maximal effect in MCI. This may represent a mixture of A β -dependent and -independent pathways for the effect of small vessel disease. The associations of WMH burden with deficits in different cognitive domains may be explained by their differential effect on regional cortical thickness. Global WMH were associated with lower thickness of frontotemporal regions in CU participants and cingulate regions in MCI participants, independent of regional A β deposition.²⁴⁵ Regional WMH, when covaried for cortical atrophy patterns in A+ participants with AD dementia, accounted for the majority of the canonical AD pattern of cortical thinning except for parahippocampal and entorhinal regions and the precuneus.²⁴⁶ These studies support a major contribution of WMH burden on neurodegeneration in AD.

These studies suggest that vascular dysregulation and hypoperfusion early in disease progression may be an important AD pathophysiological mechanism, influenced by AD risk alleles. This contributes to A β deposition, cortical atrophy, the development of regional WMH, and memory impairment early in disease progression. At the MCI stage, WMH in different regions contribute to impairments of other cognitive

domains and global cognitive impairment, independent of A β deposition. This A β -dependent and A β -independent dichotomy of the effects of cerebrovascular disease on AD strongly supports its treatment as a therapeutic strategy.

3.4 | Biological subtypes of AD

Patients on the AD spectrum (i.e., A+), often diverge from the “typical” AD pathway described in Section 3.2. They differ in rate of decline, distribution of tau and neurodegeneration, and impairment of specific cognitive domains. What is the biological basis of these deviations? This section will discuss types of biological heterogeneity and what factors underlie these differences in disease progression. AD subtypes have been previously identified using ADNI data from a variety of modalities, primarily imaging and cognition (reviewed in Veitch et al.^{8,9}). Recent studies have refined these subtypes and identified novel subtypes using CSF proteomics, lipid profiles, mitochondrial function, and comorbidities.

3.4.1 | Amyloid-based biological subtypes

A β may not follow a universal trajectory of accumulation assumed to begin in medial cortical regions and to spread sequentially to cortical association regions followed by occipital striatal regions. A Subtype and Stage Inference (SuStain) model analysis of A β PET scans from five cohorts including ADNI²⁴⁷ recapitulated the stereotypical pattern of spread when the model was set to recover one trajectory. However, an optimized model identified three spatiotemporal subtypes based on regions of initial cortical A β accumulation (Figure S34 in supporting information). Approximately half of participants were assigned a subtype with an initial site of cortical deposition in the orbitofrontal region. This frontal subtype was characterized by having the highest proportion of APOE ϵ 4 allele carriers, and higher A β and tau burden. Approximately one quarter were assigned a parietal subtype with initial A β deposition in the precuneus. This subtype was characterized by intermediate APOE ϵ 4 allele carriage and lower age. The remainder belonged to an occipital group with the lowest APOE ϵ 4 allele frequency and highest proportion of participants with dementia. The A β deposition trajectories of all subtypes converged at late stages of disease despite the initial differences. The association of the subtypes with cognitive impairment and underlying pathophysiology remains to be determined.

3.4.2 | Tau-based biological subtypes

The SuStain model was similarly applied to tau PET scans from five cohorts including ADNI.²⁴⁸ This study identified four subtypes characterized by different spatiotemporal patterns of tau deposition (Figure S35 in supporting information). These subtypes were consistent within individuals across disease progression and different PET tracers. One

third of participants had a limbic predominant-pattern of tau progression resembling Braak staging with an estimated center of tau spreading in the EC. This limbic predominant-subtype was characterized by better global cognition than other subtypes. Slightly fewer participants were assigned a subtype with an estimated tau spreading center in the fusiform gyrus. This posterior-predominant subtype was characterized by occipital lobe binding and slower cognitive decline than other subtypes and may include the posterior cortical atrophy variant of AD. Approximately one fifth of participants had a lateral temporal subtype with an estimated center for tau spreading in the ITG and a pronounced lateralization of tau spreading from the temporal to parietal and frontal cortices. This subtype was characterized by faster cognitive decline in global cognition but not memory and may include the logopenic primary progressive aphasia AD variant. Finally, an MTL-sparing subtype with early precuneus tau binding spreading in a right-sided manner to the temporoparietal and frontal cortices was identified in 18% of participants. These individuals were younger, had worse executive function and a higher overall tau burden, and were less likely to be APOE $\epsilon 4$ allele carriers. The latter subtype may typify early-onset disease. A combined tau PET and rs-fMRI study of early versus late sporadic disease²⁴⁹ examined the association of tau PET uptake with hub regions of brain functional networks. Younger age of onset, but not disease severity, was associated with a hippocampal-sparing tau PET pattern with early deposition in frontoparietal hub regions vital for cognitive function. Greater tau deposition in these hub regions was associated with faster subsequent tau accumulation and memory decline, suggesting preferential tau spread along the many connections from a key hub region.

How do tau subtypes relate to atrophy subtypes? For comparison, data-driven clusters were derived from both tau PET and structural MRI in participants with biomarker-defined AD.²⁵⁰ Four clusters of tau deposition on a gradient of severity were identified. The largest cluster, Cluster I, represented early tau deposition and contained four subclusters largely congruent with those identified by Vogel et al.²⁴⁸ Clusters II to IV had incrementally greater cognitive impairment and progression. Cluster II was distinguished by a high frequency of the APOE $\epsilon 4$ allele. Participants in Cluster IV were substantially younger than other clusters and had the largest brain age gap and fastest progression, likely representing a young onset group with faster tau deposition. All tau clusters were more highly associated with clinical measures than the three atrophy-defined clusters, which were described as having limbic predominant, diffuse, and hippocampal-sparing patterns of atrophy. These atrophy-based clusters were modulated to a greater degree by WMH volume and to a lesser degree by APOE genotype than tau-based clusters. The authors suggest that these patterns of tau spread are closely tied to clinical progression whereas those of atrophy may more closely reflect the influence of co-pathologies. Tau and atrophy-based clusters overlapped incompletely with the greatest degree of overlap between the hippocampal-sparing tau subcluster and the hippocampal-sparing atrophy cluster. This is consistent with another study demonstrating that tau PET was associated with neurodegeneration primarily within the MTL in CU participants.²⁵¹

3.4.3 | Neurodegeneration-based biological subtypes

AD subtypes based on neurodegeneration consistently identify a “typical AD” subtype as well as a subtype that spares neurodegeneration in “typical” AD regions. The “typical” subtype derived from patterns of hypometabolism, found in approximately half of AD dementia participants, showed classic posterior temporoparietal hypometabolism with lesser MTL hypometabolism²⁵² (Figure S36 in supporting information). Variations in this “typical” AD pattern of hypometabolism were associated with specific impairments to memory, language, and visuospatial ability in a study of AD dementia participants stratified by primary cognitive domain impairment.²⁵³ A second major subtype was characterized by predominant hypometabolism in limbic regions, severe memory impairments but fewer impairments in other cognitive domains, and slower progression to AD. A third minor group had a more frontal pattern of hypometabolism, and more severe EF dysfunction.²⁵² The limbic predominant and “typical” AD subtypes were also found in MCI participants^{252,254} in whom the limbic-predominant subtype was associated with slower progression to AD and a non-AD AT(N) profile of biomarkers.²⁵⁴

Atrophy-based subtypes have been extensively studied (for previous ADNI studies, see Veitch et al.^{8,9}) and validated in clinical settings after identification in research cohorts.²⁵⁵ A systematic review²⁵⁶ proposed that atrophy exists over two orthogonal dimensions: typicality, ranging from a “typical” AD limbic-predominant subtype to a hippocampal-sparing subtype; and severity, spanning minimal atrophy to typical AD dementia. The question of how these dimensions relate to AD pathology and additional co-pathologies was investigated using *ante mortem* MRI atrophy subtyping together with *post mortem* neuropathological analysis of participants with MCI and AD dementia.²⁵⁷ Although the typicality and severity dimensions were not significantly associated, the limbic predominant subtype and typical AD subtype were more associated in a regional-specific manner with all *post mortem* pathologies considered ($A\beta$ plaques, NFTs, TDP-43, and α -syn) than the hippocampal-sparing and minimal-atrophy subtypes (Figure S37 in supporting information). The authors suggest that despite lying on different dimensions, the limbic predominant and typical AD subtypes may be biologically more susceptible to a variety of pathologies than the hippocampal-sparing subtype, which may represent a different biological pathway. The minimal atrophy subtype may represent an early stage of an undetermined biological pathway.

The consistent reporting of subtypes with predominantly cortical or limbic atrophy may reflect underlying dissociable MTL functional networks. Disruption of functional connectivity networks is a feature of AD (for previous ADNI studies, see Veitch et al.^{8,9}). The anterior temporal network may underlie limbic-predominant subtypes whereas the default mode network (DMN) may underlie cortical-predominant subtypes, with these networks having differential susceptibility to accumulation of co-pathologies.²⁵⁸ Significant nodal and global changes in functional connectivity were reported in four cluster-defined AD atrophy subtypes in ADNI and German Center for

Neurodegenerative Diseases Longitudinal Cognitive Impairment and Dementia Study.⁶⁹ Subtypes with MTL predominant or diffuse atrophy had worse CSF biomarkers and pronounced cognitive decline corresponding to reduced intranetwork connectivity in the default mode, dorsal attention, visual, and limbic networks, and also with reduced global efficiency and regional clustering. These subtypes may represent a spectrum of "typical" AD. A limbic-predominant subtype with less prominent cognitive decline despite worse CSF biomarkers was characterized by substantial nodal network failure but only slight perturbations to global networks. A mild atrophy subtype with less cognitive decline showed pronounced global network failure.

Subtypes identified from clustering analysis of rs-fMRI data from the multicenter Alzheimer's Disease Imaging Consortium and replicated in ADNI had some similarities with atrophy-defined subtypes.²⁵⁹ One subtype resembling "typical" AD was characterized by decreased functional connectivity in the DMN, widespread cortical thinning, and fastest cognitive decline. Another subtype, characterized by mild and diffuse functional connectivity disruption, slow decline, and local atrophy, resembled the mild atrophy subtype. A third subtype had decreased functional connectivity in the anterior cingulate cortex but increased connectivity in the prefrontal cortex, preserved hippocampal volume, and word learning but impaired visuospatial ability and severe atrophy in the anterior cingulate cortex. The authors suggest that this corresponds to the posterior subtype identified by tau PET.²⁴⁸ A fourth subtype had lower word learning ability and visuospatial learning together with patterns of decreased connectivity and cortical volume loss consistent with corticobasal syndrome.

3.4.4 | The influence of co-pathologies

At autopsy, the presence of co-pathologies is so common that "pure" AD is not the most prevalent form. For instance, 42% of autopsied ADNI AD dementia cases had α -syn, found in Lewy bodies; 21% had TDP-43, found in limbic-predominant age-related TDP-43 encephalopathy (LATE); 18% had agyrophilic grain disease; and 6% had hippocampal sclerosis.²⁶⁰ These pathologies may modulate the susceptibility of biological subtypes to neurodegeneration. Clustering analysis applied to tau PET and FDG PET revealed six groups that differed in degree and region of neurodegeneration, but not tau deposition.²⁵⁸ The largest group had the expected hypometabolism for the level of tau. Compared to this canonical group, three groups, deemed resilient to tau deposition, had less than expected hypometabolism (two in cortical and one in limbic regions) and lower cognitive decline. Two groups, deemed susceptible to tau deposition, had worse hypometabolism than expected (one in cortical and one in limbic regions) and greater cognitive decline. The susceptible groups had a greater number of vascular risk factors. The limbic susceptible group had a pattern of hypometabolism suggestive of TDP-43. In contrast, the cortical susceptible group also had a greater burden of α -syn and other imaging markers indicative of Lewy body disease (Figure 8). The association of a pattern of MTL-sparing longitudinal cortical neurodegeneration with

dementia with Lewy bodies (DLB) was also reported in a study of participants with autopsy-confirmed AD and AD with concomitant Lewy body disease.²⁶¹

Similar canonical, resilient, and susceptible groups were identified from the degree of mismatch between tau deposition and cortical thickness.²⁶² Susceptible groups had greater WMH burden, and the authors suggested that the pattern of high temporal/limbic atrophy in some susceptible groups is consistent with the typical sites of TDP-43 deposition and with hippocampal sclerosis. Therefore, additional co-pathologies may contribute to heterogeneity in neurodegeneration beyond that expected from tau deposition. They may predominantly modulate neurodegeneration in regions beyond the MTL. The hippocampus, amygdala, and parahippocampal gyrus were strongly associated with clinically diagnosed dementia after accounting for not only AD neuropathology but also Lewy bodies and TDP-43.²⁶³ Hippocampal sclerosis was the exception, impacting cognition via hippocampal atrophy.

The importance of co-pathologies in AD was underscored by a meta-analysis of cohorts including ADNI that examined links between known AD risk variants and non-AD pathologies.²⁶⁴ Variants in several genes were found to be significantly associated with LATE neuropathologic changes (*GRN* and *TMEM106B*) and hippocampal sclerosis (*TNIP1* and *WNT3p*), and others trended toward association (*SORL1* and *TPCN1* with LATE neuropathologic change, *USP6NL* and *BIN1* with Lewy body pathology).

3.4.5 | Atypical AT(N) biomarker-defined groups

Several recent ADNI studies have investigated two groups defined by atypical AT(N) biomarker profiles. The first is SNAP having tau deposition and/or neurodegeneration in the absence of A β deposition (A-[T/N]+).²⁶⁵ The second is characterized by neurodegeneration in the absence of tau despite being A+ (A+T-N+). SNAP participants with *ante mortem* MRI and autopsy data from ADNI and UPenn had a greater number of neuropathological diagnoses such as FTLT, Lewy body disease, progressive supranuclear palsy, and agyrophilic grain disease than those with biomarker-defined AD.²⁶⁶ A subset of SNAP with elevated tau in the absence of A β deposition is consistent with primary age-related tauopathy.²⁶⁷ These individuals had AD-characteristic neurodegeneration along with a higher WMH burden. The authors suggest that subthreshold A β may interact with cerebrovascular disease to produce an AD-like pattern of decline. In contrast, in A+T-N+ MCI participants had lower episodic memory loss and greater hippocampal volume at baseline, slower decline across all cognitive domains, and less widespread cortical thinning restricted to the MTL than A+T+(N)+ individuals. These characteristics had more in common with A-T-N+ MCI participants, suggesting that a non-AD neuropathological process is driving neurodegeneration in T- MCI subjects. The authors suggest that non-AD pathologies such as cerebrovascular disease, LATE, or Lewy body disease may drive the majority of neurodegeneration in these individuals on top of a background of preclinical AD.²³⁹

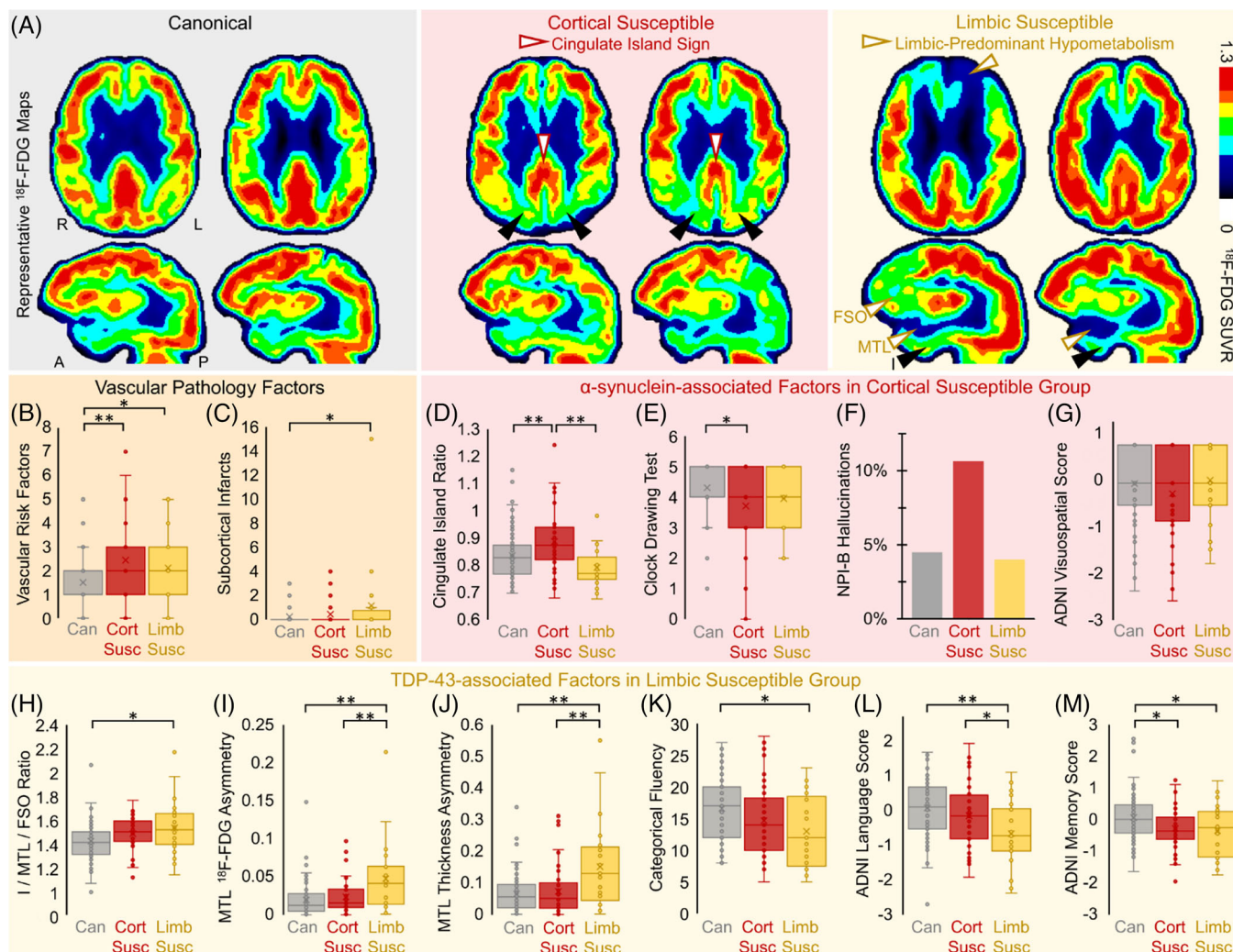


FIGURE 8 The dissociation of tau pathology and neuronal hypometabolism is related to co-pathologies. (A), Representative ¹⁸F-FDG SUVR images from six patients. Susceptible patients shown here have imaging findings consistent with co-pathology (sagittal views are slices through the right hemisphere). The cortical susceptible group (middle) had participants with cingulate island sign, the sparing of posterior cingulate cortex (white arrowheads) relative to cuneus (black arrowheads). The limbic susceptible group (right) had participants with MTL and FSO ¹⁸F-FDG hypometabolism (white arrowheads) relative to inferior temporal gyrus (I, black arrowheads). Vascular pathology features in susceptible groups included greater (B) vascular risk factors and (C) subcortical infarcts. The cortical susceptible group (D) had higher cingulate island ratio across groups, (E) had significantly worse clock drawing scores, and trended toward (F) greater proportion of participants with hallucinations on the Neuropsychiatric Inventory (NPI) item B and (G) worse ADNI visuospatial scores than the other groups. The limbic susceptible group had larger (H) I / MTL / FSO ¹⁸F-FDG ratio and worse MTL asymmetry in (I) ¹⁸F-FDG SUVR and (J) thickness, and significantly worse (K) categorical fluency, (L) language, and (M) memory z scores. Box plots show data points as dots, mean as an X symbol, median as the middle box line, first quartile (Q1) and third quartiles (Q3) as box edges (denoting the IQR), whiskers as the minimum/maximum points and outliers based on thresholds $<Q1 - 1.5(IQR)$ or $>Q3 + 1.5(IQR)$. Cognitive test comparisons included A β status, education, sex, and age as covariates. Significant differences in pairwise comparisons by two-tailed likelihood ratio tests are denoted by * $P < 0.05$, ** $P < 0.005$. A β , amyloid beta; ADNI, Alzheimer's Disease Neuroimaging Initiative; FDG, ¹⁸F-fluorodeoxyglucose; FSO, frontal supraorbital; IQR, interquartile range; MTL, medial temporal lobe; SUVR, standardized uptake value ratio. Reproduced under open access from Duong et al.²⁵⁸

3.4.6 | AD subtypes derived from early metabolic processes

Pathophysiological processes beyond the A β and tau pathways or those of co-pathologies may underlie AD heterogeneity. Early disruptions to BBB function, lipid metabolism, and mitochondrial function typify disease progression, as described in Sections 3.2.2, 3.2.4, and 3.2.5.

Subtypes based on distinct CSF proteomic profiles, previously identified in AD participants,²⁶⁸ were detected in A- CU participants.²⁶⁹ A neuronal hyperplasticity subtype with elevated levels of BACE1 had increasing CSF p-tau181 and decreasing CSF A β 42, and a BBB dysfunction subtype characterized by neuronal hypoplasticity showed only decreasing CSF A β 42. The early detection of the subtypes prior to CSF biomarker abnormality suggests that differences in early

hyperplasticity-related processes or BBB dysfunction may be a source of heterogeneity in disease progression. Subgroups defined by SNPs derived from mitochondrial haplogroup J, previously associated with AD risk, had differing rates of progression independently of CSF A β 42 and p-tau181/t-tau.²⁷⁰ Two subgroups with exacerbating SNPs had elevated risk of AD, small hippocampal volume, worse glucose metabolism, and greater clinical conversion than other subgroups, including one with protective SNPs. Lipidomic signatures were also associated with differing risk of clinical progression, reflecting underlying metabolic differences.¹⁹⁷ Five clusters of lipids were identified in CU and MCI participants, two of which were associated with a high risk of clinical progression.

3.4.7 | Summary of recent ADNI studies of AD subtypes

Recent ADNI studies have contributed considerably to our understanding of AD biological subtypes. Variability in disease progression appears to arise before AD biomarkers become abnormal, reflected in differences in lipid composition or CSF proteins. A β deposition may diverge from the stereotypical pattern of spread with some participants having different sites of initial cortical deposition that later converge. AD subtypes based on tau deposition and atrophy overlap to some degree, with tau deposition more associated with APOE ϵ 4 genotype and atrophy influenced to a greater extent by co-pathologies. Biological subtypes are summarized in Figure S38 in supporting information, along the conceptual axes of typicality and severity. Limbic-predominant and hippocampal-sparing subtypes are consistently identified and may be related to APOE ϵ 4 genotype and the effect of co-pathologies on atrophy. Other cortical predominant subtypes may represent atypical non-amnesic AD presentations.

3.5 | Resilience to cognitive decline

Just as factors such as presence of comorbidities and APOE ϵ 4 genotype can exacerbate neurodegeneration and cognitive decline beyond what would be expected for a given level of AD pathology, resilience can maintain cognition or brain structure in the face of AD pathology.²⁵⁶ This section will describe investigations of the effects and mechanisms of resilience using ADNI data.

3.5.1 | Effects of resilience

Cognitive reserve,²⁷¹ defined as the difference between actual and expected cognitive function for a level of AD pathology, had a differential effect depending on diagnostic status.²⁷² It was associated with a lower rate of progression in CU and MCI participants, but higher rate of decline in participants with AD dementia. The acceleration of decline later in disease progression may signal the point at which cognitive reserve mechanisms are “overrun” by AD pathol-

ogy after initially delaying cognitive impairment. Cognitive resilience (defined in a similar way as cognitive reserve) and brain resilience (defined by hippocampal GM measures) to A β deposition were studied in CU individuals from the Chinese Sino Longitudinal Study on Cognitive Decline cohort and ADNI.²⁷³ Both measures were associated with younger age, female sex, and better cognitive performance, and predicted longitudinal cognitive decline.

3.5.2 | Mechanisms of resilience

An understanding of mechanisms underlying cognitive resilience is important for clinical management of AD and for understanding disease trajectory in patients. Features of functional and structural networks may underlie cognitive resilience. A typical brain without disease has tightly connected functional networks with high intra-network connectivity and low inter-network connectivity.²⁷⁴ This high system segregation is correlated with higher global cognitive performance.²⁷⁴ In DIAN participants with autosomal dominant AD and in ADNI A+ participants, higher functional network segregation was associated with lower than expected episodic memory or global cognitive decline for a given temporal lobe tau burden.²⁷⁴ Moreover, higher functional network segregation was associated with slower tau accumulation relative to baseline entorhinal tau burden.²²³ The rs-fMRI metric reflecting segregation of functional networks may therefore be a biomarker of cognitive resilience. The protective effect of this functional network topology was highest in CU participants and diminished in MCI and AD participants, and was greatest in APOE ϵ 4 non-carriers.²⁷⁵ Other mechanisms of cognitive resilience to AD pathology identified in recent ADNI studies include redundancy in nodes of posterior hippocampal functional networks²⁷⁶ and higher structural network efficiency.²⁷⁷

Recent ADNI studies have pointed to a genetic component of resilience. In CU participants from a multi-cohort study including ADNI, there was a dose-response of the APOE ϵ 2 allele for larger GM volumes in areas related to cognitive resilience, and an opposite effect for the APOE ϵ 4 allele.²⁷⁸ The APOE ϵ 2 allele may contribute to resilience through the lowering of global A β burden. APOE ϵ 2 allele carriers had a lower global A β burden but no difference in tau burden or accumulation compared to APOE ϵ 3/ ϵ 3 homozygotes.²⁷⁹ Similarly, lower hippocampal volume in APOE ϵ 2 allele carriers was mediated by baseline CSF A β 42.²⁸⁰ A GWAS of cognitive resilience to A β burden in four cohorts including ADNI identified an SNP (rs62263260) related to expression of the *SEMA5B* gene, which is involved in synaptic pruning and axonal branching.²⁸⁰ Synaptic plasticity was also implicated in a second GWAS of cognitive resilience to A β burden²⁸¹ that identified *CNOT7* linked to synaptic plasticity and hippocampal-dependent learning and memory. This association was not due to cerebrovascular disease or increases in tau deposition. Many other loci may contribute to resilience. A GWAS across eight independent studies including ADNI was conducted in individuals who remained CU despite having the highest genetic risk outside of the APOE ϵ 4 allele.²⁸² Thousands of SNPs were identified and from these, a polygenic resilience score was

constructed. This polygenic resilience score was positively correlated with a PRS. In other words, individuals whose cognition remained intact despite having high genetic risk for AD also had a high polygenic resilience score. The authors suggest that multiple resilience loci interact with AD risk loci to protect against AD pathology.²⁸²

3.5.3 | Resilience in underrepresented populations

Factors such as socioeconomic status may impact resilience. Education is often used as a proxy for cognitive reserve, and high levels of education are generally recognized as being protective. However, while educational attainment was protective against memory loss in ADNI White participants, this effect was not observed in Black participants.²⁸³ This may reflect a lower quality of education experienced by Black/African-American older adults or a combination of other factors that contribute to ethnocultural health disparities. Caution should therefore be taken in interpreting ADNI studies of cognitive reserve using education as a proxy. This result underscores the need for a more diverse ADNI cohort to further study the differential contributors to resilience in underrepresented populations.

3.6 | Effects of the APOE genotype

Recent ADNI studies support a differential effect of the APOE $\epsilon 4$ and $\epsilon 3$ alleles compared to the protective $\epsilon 2$ allele in modulating disease progression. The $\epsilon 4$ risk allele affected hippocampal shape in a similar manner to age,²⁸⁴ and was associated with greater atrophy of the cholinergic basal forebrain.²⁸⁵ Both these studies suggest involvement of the $\epsilon 4$ allele in sites of early neurodegeneration. In non-demented older adults, higher cortical A β burden predicted faster hippocampal atrophy in $\epsilon 4$ carriers only but predicted faster cognitive decline in both $\epsilon 4$ carriers and non-carriers.²⁸⁶ In contrast, greater WMH predicted faster hippocampal atrophy in $\epsilon 4$ non-carriers only.²⁸⁶

APOE $\epsilon 2$ carriers may have alternative pathways of disease progression. Using a discriminative event-based model to estimate the ordering of biomarkers, $\epsilon 4$ carriers had a sequence similar to that described in Section 3.2 in which CSF A $\beta 42$ abnormality precedes that of CSF p-tau181 and hippocampal volume.²⁸⁷ A similar, but less certain, ordering of biomarkers was estimated in $\epsilon 3$ homozygotes. However, the order estimated for $\epsilon 2$ carriers differed substantially with CSF neurogranin and MMSE predicted as early biomarkers with low confidence, and CSF p-tau181 preceding CSF A $\beta 42$ abnormality.²⁸⁷ A large overlap of genes was reported between $\epsilon 3$ and $\epsilon 4$ carriers in an omics study including ADNI data.²⁸⁸ Functions of these genes were consistent with "typical" AD processes and included mitochondrial physiology, A β physiology, vesicle mediated transport, and the immune response. APOE $\epsilon 2$ carriers had a distinct set of genes with novel functions including chromatin remodeling and regulation.

3.7 | Effects of sex

Sex affects the prevalence and disease course of AD, and the impact of risk factors. Recent ADNI studies have described the influence of sex on modifying disease progression, important interactions with the APOE $\epsilon 4$ allele that enhance vulnerability to AD pathology, and the effect of sex-specific resilience on AD pathology.

A clustering study of MCI participants based on multimodal factors identified sex-specific groups of differing prognoses.²⁸⁹ In the worst prognosis group, there were almost twice as many female than male APOE $\epsilon 4$ carriers, suggesting that the $\epsilon 4$ allele has a disproportionately detrimental effect in women. Women had a greater association between whole brain atrophy and functional decline than men, and female $\epsilon 4$ carriers had the greatest functional decline for a given level of whole brain atrophy.²⁹⁰ The interaction between sex and APOE influences the accumulation of AD pathology. Female $\epsilon 4$ carriers had a faster accumulation of A β in the striatum, followed by accumulation of tau in limbic regions than male $\epsilon 4$ carriers or female $\epsilon 4$ non-carriers.²⁹¹ After correcting for A β load, female $\epsilon 4$ carriers compared to non-carriers had significantly higher tau burden in MTL sites corresponding to Braak stages I and II.²⁹² In contrast, there was no difference in regional tau burden between male $\epsilon 4$ carriers and non-carriers (Figure S39 in supporting information). APOE $\epsilon 4$ gene dosage further affects regional tau binding in a sex-specific manner. Male $\epsilon 4$ homozygotes had significantly greater regional tau binding than heterozygotes or non-carriers.²⁹³ However, in women, this increased regional tau deposition was observed for both $\epsilon 4$ heterozygotes and homozygotes compared to non-carriers.²⁹³ Female sex may therefore enhance the deleterious effect of the APOE $\epsilon 4$ on tau binding, contributing to the differential risk of AD associated with this allele in men and women. Consensus metabolic signatures differed by sex and APOE $\epsilon 4$ allele carriage and were associated with memory and ADAS-Cog,²⁹⁴ suggesting differences in underlying metabolic processes. Cardiovascular risk may further modify this sex-specific effect in a three-way interaction. In a study of CU participants, high risk of cardiovascular disease was associated with higher regional tau deposition in the EC, inferior temporal cortex, and composite temporal ROIs in female but not male APOE $\epsilon 4$ carriers²⁹⁵ (Figure S40 in supporting information). The authors suggest that treatment of cardiovascular risk factors such as hypertension may be of particular benefit in female APOE $\epsilon 4$ carriers.

Differences in resilience may also contribute to the greater vulnerability of women to AD neuropathology. A study of sex differences in genetic architecture of cognitive resilience in four cohorts including ADNI found that resilience is highly heritable.²⁹⁶ The study identified female-specific genetic architecture that overlapped with autoimmune disorders such as lupus and multiple sclerosis. These disorders also have a higher prevalence in women and this overlap may implicate a role of the immune system in resilience. The authors suggest that increased neuroinflammation in women associated with age-related metabolic shifts may underlie resilience. In men, specific loci were related to heart rate variability, a marker of good heart health

suggesting that cardiovascular-related pathways may underlie resilience in men.

3.8 | Involvement of NPS

NPS such as apathy, depression, delusions, anxiety, and hallucinations are frequently reported in MCI and are associated with greater cognitive and functional impairment. Recent ADNI studies have assessed associations among AD pathology, NPS, and cognitive and functional decline.

Late-life depression was associated with higher rates of domain-specific cognitive deficits in verbal learning and memory compared to non-depressed older adults with matched memory impairment and A β burden.²⁹⁷ These deficits partially overlapped with deficits in cognitive domains associated with AD biomarkers, and the authors suggested that a portion of the cognitive impairment associated with late-life depression could be attributed to AD.²⁹⁷ In a study including multimodal data from ADNI and two other cohorts, two dimensions of heterogeneity associated with late-life depression were identified.²⁹⁸ The first dimension had relatively preserved brain anatomy while the second had widespread atrophy and WM disruptions, greater depression and cognitive impairment, and a higher degree of progression to AD dementia.²⁹⁸ It remains to be determined whether late-life depression is a risk factor for or a prodromal feature of AD.

NPS have complex associations with A β pathology. Depressive symptoms are associated with a high risk of cognitive decline and increased progression to AD, with symptoms becoming frequent in MCI.²⁹⁹ A study of CU participants in the Age Well cohort with replication in ADNI reported that subclinical depressive symptoms were associated with lower hippocampal volume and glucose metabolism in the frontolimbic network, the site of processes related to depressive symptoms.²⁹⁹ However, these participants did not have increased brain A β , leading the authors to postulate that mechanisms such as neuroinflammation and early tau aggregation may link subclinical depressive symptoms with hippocampal degeneration. In contrast, other studies suggest that brain A β contributes to the effect of subclinical depression on cognition. In CU participants, the greater cognitive decline associated with higher rates of increase in the Geriatric Dementia Scale was mediated by worse hypometabolism and A β accumulation.³⁰⁰ When ADNI non-demented participants were stratified using AT(N) biomarkers, subclinical depressive symptoms were associated with both memory and executive function in those classified as A+ or SNAP (A-[T/N]+) but not in those with normal biomarkers.³⁰¹

Apathy was associated with faster cognitive and functional decline in non-demented participants, and this was mediated by A β deposition in prefrontal regions.³⁰² In addition, A β burden was a risk factor for apathy syndrome, suggesting a bidirectional relationship influencing early disease progression.³⁰² A β pathology also partially mediated the effects of mild behavioral impairment on decline in global cognition and increased risk of clinical conversion.³⁰³

Tau deposition may also mediate the relationship between NPS and cognitive performance. Tau deposition in frontal, occipital, and

medial temporal cortices was associated with psychosis, and accelerated cognitive and functional decline.³⁰⁴ In MCI participants stratified by A β status and the presence or absence of NPS, a greater association between tau deposition and cognition was reported in those with NPS.³⁰⁵ This association was observed in both A- and A+ participants but was stronger in the presence of A β deposition. Similarly, A β positivity enhanced the associations between tau binding in the EC and precuneus, and affective NPS such as depression, apathy, and anxiety in MCI and AD participants.³⁰⁶

All CSF AT(N) biomarkers (A β 42, p-tau181, and t-tau) were associated with a distinct class of depression and apathy identified from clustering analysis using the Neuropsychiatric Inventory in participants from ADNI and NACC.³⁰⁷ Over 5 years, the study identified classes resulting from, rather than contributing to, stable, decreasing, and increasing depression and apathy. Worse CSF biomarkers were associated with the class of increasing depression and apathy characterized by a high prevalence of AD dementia, lower MMSE, and greater use of psychotropic medications. The authors suggest that these NPS, like cognitive decline, result from the AD disease process.

4 | ARE ADNI RESULTS GENERALIZABLE?

Given the influence of ADNI studies on clinical trials of AD therapeutic interventions, the development of prognostic algorithms, and our understanding of disease progression, a critical question is: To what extent are ADNI results generalizable to the wider population, given the lack of ethnocultural and educational diversity in the ADNI cohort? Recent ADNI studies have sought to answer this question, highlighting differences between ethnocultural groups, and have plotted a course for the next iteration of ADNI that aims to address these concerns.

4.1 | Generalizability of ADNI results

The ADNI cohort is not representative of the general elderly population. Compared to US census data, the ADNI cohort underrepresents the Asian (2% vs. 4.7%), Black/African American (5% vs. 10%), and Hispanic/Latinx (4% vs. 9.2%) populations, and those with ≤ 12 years of education (16% vs. 43.7%), and overrepresents the non-Hispanic White population (87% vs. 74.6%).³⁰⁸ Ethnocultural and socioeconomic groups differ in the incidence and prevalence of AD, medical and biological risk factors, clinical and neuropathological features, and survival due to a range of genetic, behavioral, and sociocultural factors.³⁰⁸ A comparison of associations between risk factors, and neuroimaging outcomes and cognition in ADNI and in a more diverse, randomly selected sample from four communities in North Carolina, Mississippi, Minnesota, and Maryland, comprising the ARIC cohort, explored the extent to which ADNI results are generalizable.³⁰⁹ The ARIC cohort has six times the number of Black/African-American participants as ADNI (23.7% vs. 4%). One third of associations between predictors and outcomes across all modalities differed between the two cohorts (Figure S41 in supporting information). Because The ARIC

cohort is drawn from limited geographic areas, caution should be taken in extending these findings to the broader US population. However, the association between MTL structures with MMSE determined in ADNI was only partially generalizable to a Japanese cohort,³¹⁰ suggesting the issue is widespread. Further comparisons of ADNI results with diverse cohorts are required to determine its extent.

Several studies have investigated effects of ADNI's strict inclusion and exclusion criteria. Cut-points for the ADNI amnesic MCI inclusion criteria based on Story A from the Wechsler Memory Scale Logical Memory II were reported to be higher than demographically adjusted normative data.³¹¹ The authors suggest that ADNI MCI participants may have milder memory problems than the amnesic MCI participants diagnosed using memory test cut-points based on demographically adjusted normative data, limiting the generalizability of results from studies using these participants to the wider community. A critical step in establishing clinical utility of prediction models is external validation in independent and identically distributed samples. A comparison of six clinical AD cohorts including ADNI³¹² reported a wide range of probabilities of clinical progression over 10 years (Figure S42 in supporting information), which the authors attributed to differences in recruitment strategies. However, ADNI's inclusion and exclusion criteria may not fully explain issues of generalizability. Although individuals who failed the ADNI screening process were less educated and younger than those who passed, rates of screen fails did not differ between underrepresented groups and overrepresented groups.³⁰⁸

4.2 | Studies of ethnocultural differences

The issue of generalizability has also been highlighted in recent investigations of ethnocultural differences in AD risk factors, genetics, and biomarkers, both within the ADNI cohort and compared to cohorts from diverse populations. Analyses within ADNI are limited by small sample sizes of underrepresented populations, leading to variable results. No differences were reported in baseline CSF biomarkers (A β 42, p-tau181, t-tau) or plasma p-tau181 or NfL in any ethnocultural group within ADNI.³¹³ However, other studies reported differences in AD biomarkers. Latinx and Asian ADNI participants had 64% and 46%, respectively, reduced odds of A β positivity assessed by PET compared to non-Hispanic Whites.³⁰⁸ Among Black/African-American ADNI participants, levels of CSF p-tau181, t-tau, and NfL were lower compared to non-Hispanic White participants, although CSF A β 42 levels did not differ (Figure S43 in supporting information).³¹⁴ In the same study, Black/African-American participants had significantly lower levels of CSF sTREM2, a biomarker of microglial activation, and had higher frequencies of genetic variants in *TREM2* and *MS4A4A* associated with these lower levels (Figure S43). The authors suggest that these differences in biomarkers may indicate differences in the chain of events leading to neurodegeneration between ethnocultural groups.

AD biomarkers and genetic contributors have been compared between ADNI and Korean and Han Chinese cohorts. CU participants in a Korean cohort had a lower frequency of A β positivity (20%) compared to ADNI CU non-Hispanic Whites (32.8%).³¹⁵ The APOE

ϵ 4 allele impacted A β status similarly in both cohorts, but polymorphisms in *BDNF* correlated with A β status in Koreans only, suggesting genetic differences may underlie differences in A β positivity frequencies. Normative data for many cortical and subcortical structures differed between ADNI and OASIS non-Hispanic White participants and those in a second Korean cohort, affecting the performance of predictive algorithms.³¹⁶ Beyond the APOE ϵ 4 allele, additional predictive associations were reported between alleles in *ABCA7* and *SORL1* and cognitive decline in a Han Chinese population from Taiwan compared to ADNI.³¹⁷

Differences in the prevalence of risk factors for AD have been identified among ethnocultural groups. Black/African-American ADNI participants had greater total and regional WMH burden compared to non-Hispanic White participants, largely attributable to the higher rate of vascular risk factors in Black/African-American groups.³¹⁸ A Puerto Rican cohort from Boston had five times the prevalence of T2DM and nearly double that of hypertension compared to ADNI non-Hispanic White participants.³¹⁹ Those participants in the Puerto Rican cohort with comorbid T2DM and hypertension had a greater brain age gap, more hippocampal atrophy, reduced regional WM fiber integrity, and lower MMSE scores than those with no comorbidities, and were clinically comparable to the ADNI progressive MCI group. Cerebrovascular risk factors that may be elevated in different ethnocultural groups due to structural and social determinants of health are therefore important treatment targets.

Together, these studies highlight the limitations of the lack of diversity of the ADNI cohort. This prevents an understanding of ethnocultural differences and sociocultural factors involved in disease risk and progression, and of how different groups might respond to therapeutic interventions.

4.3 | The future of ADNI

In September 2022, ADNI transitioned to its next 5-year phase, termed ADNI-4, entirely funded by the National Institute on Aging.¹⁵ ADNI-4 represents a concerted effort to improve the generalizability of ADNI results by enrolling 50% to 60% of its new participants from underrepresented populations. Its enrollment approach is based on strategies tested through the ADNI-3 Diversity Task Force Project and the Brain Health Registry's Community Engaged Digital Alzheimer's Research (CEDAR) study³²⁰ and includes a culturally informed, community-engaged research (CER) for digital and in-person outreach, engagement, and retention efforts as well as several key methodological changes. For instance, ADNI-4 uses relaxed inclusion/exclusion criteria that will allow the enrollment of some middle-aged and older adults with cardiovascular disease (although people with large strokes will continue to be excluded), and lumbar punctures and study partners are now optional. Moreover, ADNI-4 participants will now be systematically paid for their time volunteering in the study and will receive feedback on their study results if they wish to receive it. Last, ADNI-4 includes measures of sociocultural determinants of health (e.g., discrimination, acculturation, socioeconomic status).

A new Engagement Core was formed to lead ADNI-4's new brain health equity aims, which are to make ADNI more ethnoculturally, socioeconomically, and geographically diverse; to examine the biological and sociocultural determinants of brain health equities; and to improve health equity training for study personnel and scientists. In close partnership with ADNI-4's Administrative and Clinical Cores, the Engagement Core aims to enroll an initial, diverse cohort of 20,000 to be screened using an online portal.¹⁵ Of these, 4000 participants including 50% to 60% from underrepresented populations will complete remote blood collection and screening for plasma biomarkers and APOE. A final in-clinic cohort of 1000 (500 new and 500 rollover participants), also comprising 50% to 60% from underrepresented populations, will complete further evaluations in a similar vein to previous ADNI phases with some technological improvements. It is hoped that ADNI-4 will improve our understanding of sociocultural contributors to heterogeneity of disease progression and provide a more diverse cohort for external validation of results, setting an example for other clinical research cohorts.

5 | CONCLUSIONS

In 2021 and 2022, ADNI has continued to profoundly impact the development of therapeutic interventions for AD and contribute to our understanding of disease progression. ADNI studies have reported improvements to clinical trial design through more focused participant selection and the detection of treatment effects in early disease. ADNI data have provided the basis for modeling tools for clinical trials, and the development of harmonization methods for PET scans and fluid biomarker cut-points. ADNI plasma samples have been instrumental in the development of plasma p-tau as a blood biomarker for AD. Machine learning-based algorithms have used ADNI AT(N) biomarker data to predict future decline, and studies have investigated whether inflammation biomarkers may add additional prognostic value, acknowledging the critical role of microglial-mediated inflammation in response to A β deposition. Several studies demonstrated that different modalities of AT(N) biomarkers are discordant, particularly those of neurodegeneration and to a lesser extent, tau. The development of online sensitive cognitive tests in CU participants for remote screening represents an innovative approach to substantially lower the cost of enrollment into research and clinical cohorts. The development of algorithms for individualized predictions of cognitive decline, and operationalization as online tools represents important steps toward personalized medicine.

Recent ADNI studies have improved our understanding of the multifactorial contributions to disease progression. Considerable evidence from these studies supports a cascade of events central to the amyloid hypothesis, from the disruption of A β homeostasis to microglial-induced neuroinflammation to perturbation of signaling pathways and metabolism to tau phosphorylation to disruption of synapses and the transneuronal spread of tau to glucose hypometabolism and neuronal cell death to neurodegeneration and cognitive impairment.

Beyond the A β cascade, ADNI studies have detailed myriad additional factors that may account for the observed heterogeneity in clinical manifestation and in underlying distributions of AD pathology. Vascular factors may affect disease progression via multiple mechanisms including perturbation of CBF early in disease, and the exacerbation of regional neurodegeneration and decline in specific cognitive domains by regional WMH burden via distinct A β -dependent and -independent pathways. Biological AD subtypes have been identified based on A β status, influenced by the APOE ϵ 4 allele. A large body of work described subtypes based on regional tau deposition, associated primarily with clinical characteristics and APOE ϵ 4 status, and on neurodegeneration, influenced by co-pathologies. A "typical AD" atrophy subtype and one with minimal atrophy may exist along the dimension of severity, while subtypes with predominantly MTL involvement or cortical involvement may exist along the orthogonal dimension of typicality. Subtypes may reflect the combined influence of genetics and co-pathologies such as vascular disease, Lewy body disease, and TDP-43 proteinopathies. Cognitive resilience appears to buffer the effect of co-pathologies and genetic risk in accelerating cognitive decline. ADNI studies have probed mechanisms underlying cognitive resilience including genetic contributions and topologies of structural and functional networks. Distinct pathways of neurodegeneration were described for carriers of the APOE ϵ 2 allele and in female APOE ϵ 4 carriers who had the fastest overall decline.

Comparisons of associations reported in the ADNI cohort with those in other cohorts revealed that the generalizability of these results is limited. Genetic, biomarker, and risk factor differences in underrepresented populations compared to the non-Hispanic White majority in ADNI emphasized the need for a more diverse cohort. A cohort more representative of the general population is critical for the external validation results, to understand differences in disease progression and response to therapeutic interventions, and to better understand the implications of health inequities that result from a high prevalence of modifiable risk factors in underrepresented populations. ADNI-4, the current 5-year study, aims to address the lack of diversity in the ADNI cohort to increase the generalizability and veracity of results.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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