

REVIEW ARTICLE

Using the Alzheimer's Disease Neuroimaging Initiative to improve early detection, diagnosis, and treatment of Alzheimer's disease

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Abstract

Introduction: The Alzheimer's Disease Neuroimaging Initiative (ADNI) has accumulated 15 years of clinical, neuroimaging, cognitive, biofluid biomarker and genetic data, and biofluid samples available to researchers, resulting in more than 3500 publications. This review covers studies from 2018 to 2020.

Methods: We identified 1442 publications using ADNI data by conventional search methods and selected impactful studies for inclusion.

Results: Disease progression studies supported pivotal roles for regional amyloid beta ($A\beta$) and tau deposition, and identified underlying genetic contributions to Alzheimer's disease (AD). Vascular disease, immune response, inflammation, resilience, and sex modulated disease course. Biologically coherent subgroups were identified at all clinical stages. Practical algorithms and methodological changes improved determination of $A\beta$ status. Plasma $A\beta$, phosphorylated tau181, and neurofilament light were promising noninvasive biomarkers. Prognostic and diagnostic models were externally validated in ADNI but studies are limited by lack of ethnocultural cohort diversity.

Discussion: ADNI has had a profound impact in improving clinical trials for AD.

KEYWORDS

Alzheimer's disease, amyloid, AV1541 tau positron emission tomography, disease progression, mild cognitive impairment, plasma biomarker, tau

1 | INTRODUCTION

Currently in its 17th year and fourth phase, Alzheimer's Disease Neuroimaging Initiative (ADNI)^{1,2} continues in its quest to increase understanding of Alzheimer's disease (AD) pathology and improve clinical trials for AD-modifying or -preventive treatments by leveraging its now expansive set of data and samples, which are made available to researchers worldwide. This review updates previous works³⁻⁶ detailing all the publications arising from ADNI data and samples until the end of 2017. Here, we provide a full listing of all publications and discuss key studies published from 2018 to 2020 with the goal of exploring how ADNI has contributed to our understanding of disease progression in AD and how this knowledge can be translated into successful clinical trials, leading to approved treatments which slow the progression of, and ultimately prevent the development of, AD.

The well-documented struggles of clinical trials to demonstrate significant cognitive benefits of disease-modifying therapies targeting amyloid beta ($A\beta$)^{7,8} despite the substantial body of evidence supporting its toxic role emphasize several major problems. Which species of $A\beta$ (e.g., fibrils, oligomers) is the appropriate target? Is tau responsible for symptom progression? Which species of tau is the appropriate target for treatment? What other pathologies contribute to symptom progression? Which population (dementia, mild cognitive impairment [MCI], cognitively unimpaired [CU]) is most likely benefit to from treatment? Which biomarkers best detect AD pathology and monitor progression?⁹ ADNI is uniquely positioned as a resource to examine these issues given the depth and breadth of its data and the availability of its samples.

Since its inception in 2004, ADNI participants have been followed for up to 15 years, providing crucial longitudinal data to aid in understanding progression for a disease in which pathology is now thought to arise decades before the onset of clinical symptoms.¹⁰ The most recent 5-year phase of ADNI, ADNI3,² is nearing its completion. In addition to the continuity of established biomarkers, ADNI has collected longitudinal positron emission tomography (PET) using the AV1451 (Flortaucipir) tau radiotracer (tau PET) that has allowed examination of disease progression from different perspectives. A lipidomics¹¹ data set and a bile acid targeted data set¹² have been generated from ADNI samples in collaboration with the Alzheimer's Disease Metabolomics Consortium, led by collaborator Rima Kaddurah-Daouk of Duke University, in an effort to monitor molecular alterations that occur throughout disease progression and to better understand the complex and multifactorial etiology of AD.

ADNI is unique in several respects. First, ADNI participants are followed longitudinally with blood sampling and plasma banking, clinical evaluation, neuropsychological evaluation, genetics, lumbar puncture for cerebrospinal fluid (CSF; $A\beta$ and tau), magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) PET, $A\beta$ PET, tau PET, and at-home digital cognitive testing, and participants are followed for autopsy (further details at: <http://adni.loni.usc.edu/study-design/>). Second, all ADNI data are available on <http://adni.loni.usc.edu/data-samples/access-data/> without embargo. Third, ADNI biospecimens including samples of CSF, blood, urine, and brain tissue are available to researchers.

The impact of ADNI's data- and sample-sharing policies cannot be overstated. Unrestricted sharing of research data has been

unequivocally demonstrated to drive science progress,¹³ and as an early adopter of this strategy, ADNI has had a particularly outside influence. There have been more than 140 million downloads of ADNI data by researchers worldwide, and > 30,000 samples have been shared. These have resulted in more than 3500 publications in which ADNI is used as a primary data set, as a cohort in the external validation of developed models, as a control cohort, or in genetic studies requiring large sample sizes. The cumulative impact of this body of work is reflected in a calculated *h*-index of 123 with ADNI publications garnering an average of almost 30 citations for a total of more than 75,000. In comparison to National Institutes of Health (NIH)-funded studies in the same field, ADNI publications from the breadth of PubMed have a mean relative citation ratio (RCR)¹⁴ of 2.22, a median RCR of 1.20, and a weighted RCR of 6065 (calculated May 16, 2021). The RCR metric is indexed against the expected influence of an NIH-funded study (RCR of 1) and has been demonstrated to identify works of differential influence and to correlate with opinions of subject experts.¹⁴ These numbers therefore suggest a scientific impact of \approx twice that of the average NIH-funded study and are comparable to those of other large, longitudinal studies on aging such as the Health and Retirement Study.¹⁵ The median RCR score of ADNI publications is also comparable to that of the \approx 3500 publications arising from the long-running Framingham Heart Study (FHS),¹⁶ started in 1948 (1.36 vs. 1.20 for ADNI). The highest impact ADNI publication¹⁷ has an RCR of 91.13, and 39 ADNI publications are in the 99th or above percentile of influence with RCRs of > 13.4. It should be noted that ADNI has also provided convenient data sets to test primarily image processing methodologies in computer science and engineering studies that are not captured by the PubMed system. In this way, ADNI has become an integral part of AD research across the globe.

This review initially examines how recent ADNI publications have contributed to our understanding of disease progression. We consider the extent to which $A\beta$, tau, and neurodegeneration can predict disease course, and conversely, we also consider the limitations of these canonical AD neuropathologic features before examining the influence of factors beyond established AD pathology. Subsequent sections describe approaches to determining $A\beta$ status; the exciting and rapidly developing field of blood biomarkers for AD; and finally, improvements to clinical trials. We have taken an integrated approach to topics, including evidence from a variety of fields that reflects their growing interdependence. A reader's guide to the review structure summarizing its main points is presented in Table 1. This review focuses exclusively on ADNI publications and does not attempt a comprehensive review of the field. A full list of the 1442 ADNI publications from 2018 to 2020 can be found in the supporting information. All ADNI publications are searchable at <http://adni.loni.usc.edu>.

2 | STUDIES OF DISEASE PROGRESSION

2.1 | Data-driven models of disease progression

Understanding the sequence of biomarker changes in the continuum of AD progression is of increasing importance. Since 2017, ADNI data

RESEARCH IN CONTEXT

- 1. Systematic Review:** The authors identified 1442 journal publications using Alzheimer's Disease Neuroimaging Initiative (ADNI) data from 2018 to July 2020 using standard search methods (PubMed, Google Scholar, Web of Science).
- 2. Interpretation:** ADNI studies have contributed to a greater understanding of the factors influencing Alzheimer's disease (AD) progression, including the role of amyloid and tau (from tau positron emission tomography [PET]), and the contributions of resilience, cerebrovascular disease, sex, and immune response. ADNI studies have applied this knowledge to improving diagnosis and prognosis, developing blood biomarkers, and making other improvements to clinical trials for AD. However, results may not be generalizable due to limited cohort diversity.
- 3. Future Directions:** The next 5-year phase of ADNI (ADNI4) will enroll more minorities and less-educated individuals to ensure generalizability of prognostic and diagnostic methods and disease progression studies. High sensitivity assays of plasma phosphorylated tau (ptau)₂₁₇ and ptau₁₈₁ will allow further investigation of AD blood biomarkers. ADNI will continue to impact improvements to AD clinical trials.

have been used to validate previously published models in different cohorts, and to develop new models based on the expanded set of biomarkers, or which consider continuous instead of dichotomous biomarkers. These widely support the Jack et al. model for the ordering of biomarkers¹⁸ but also highlight heterogeneity in disease course, which at times challenges assumptions underlying the $A\beta$ cascade hypothesis.^{19,20} A model that jointly considered longitudinal changes in $A\beta$ PET and tau PET in $A\beta$ + ADNI individuals estimated the temporal and spatial ordering of $A\beta$ and tau lesions. The earliest sites of $A\beta$ deposition were identified as the posterior cingulate cortex and precuneus in which $A\beta$ PET uptake increased first, becoming abnormal between 10 and 5 years before symptom onset. These regions of $A\beta$ PET uptake were followed by frontal lobe and several parietal lobe regions of interest (ROIs; Figure S1 in supporting information). Examination of CU participants who had not yet passed the threshold for $A\beta$ positivity identified the banks of the superior temporal sulcus as an even earlier site of $A\beta$ accumulation, occurring prior to accumulation in the posterior cingulate cortex and precuneus.²¹ Regional tau deposition was observed initially in the amygdala, inferior temporal lobe, and banks of the superior temporal sulcus, with deposition in the entorhinal cortex accelerating to become prominent 5 years before dementia diagnosis (Figure S1). A probabilistic Markov model¹⁰ estimated the expected time to reach different diagnostic states using 27 cognitive tests, and fluid (CSF and plasma) and imaging (FDG, PET, and MRI) biomarkers in

TABLE 1 Reader's guide

1. INTRODUCTION		From 2018 to 2020, ADNI data were used in 1442 publications. We have selected key studies to examine their contribution to our understanding of disease progression and how these aid in fulfilling the overarching goal of ADNI, the validation of biomarkers for AD clinical trials.
2. STUDIES OF DISEASE PROGRESSION	2.1. Data-driven models of disease progression	Models constructed using multimodal data largely recapitulate the theorized ordering of biomarkers but also highlight temporal and spatial heterogeneity in disease course.
	2.2. A β in disease progression	Subthreshold A β accumulation is linked to subtle cognitive deficits in memory. Staging of CU individuals by sequential regional A β accumulation predicted memory decline and is associated with CSF biomarkers and the APOE ϵ 4 allele. Recent ADNI studies have identified some of the genetic architecture underlying A β accumulation.
	2.3. Tau deposition in disease progression	Tau PET studies suggest that regional tau accumulation is dependent on antecedent A β deposition and leads to regional atrophy. Genetic factors beyond those associated with A β underlie tau deposition and subsequent neurodegeneration.
	2.4. AT(N) biological classification of AD	Different sequences of AT(N) biomarker abnormality have been identified such as tau preceding A β . The use of binary cut-points for AT(N) biomarkers may be insufficient to capture progression. Biomarkers of neurodegeneration are poorly correlated. Additional biomarkers including plasma markers may improve patient staging.
3. BEYOND AT(N): OTHER INFLUENCES ON DISEASE PROGRESSION	3.1. Heterogeneity	Multiple different approaches have identified subtypes of AD. Common subgroups are "normal" or "healthy," "typical AD" and a faster declining group with executive function deficits and posterior cortical atrophy. Increasing evidence supports their biological and clinical relevance.
	3.2. Cerebrovascular disease	Vascular risk factors have a detrimental effect on neurodegeneration and cognitive decline. Recent ADNI studies support multiple mechanisms of action: directly, via A β or tau or both, mediated by APOE ϵ 4, or by a combination of these.
	3.3. Immune response	Involvement of microglial associated innate immune response in modulating AD risk has been implicated by genetics, fluid biomarker, and other approaches using ADNI data. Levels of soluble TREM2, a microglial transmembrane receptor (gene product of AD risk allele <i>TREM2</i>), may attenuate the detrimental effect of the APOE ϵ 4 allele, and act only after A β and tau pathology appear.
	3.4. The role of resilience	AD pathology-dependent cognitive resilience acts to preserve cognitive abilities. Rapid decline may occur once pathology "outpaces" resilience. Resilience may be biologically based on components of the vascular, lipid-metabolic, and immune system. Mechanisms may be sex dependent.
	3.5. Sex effects in AD	Biological sex influences AD progression and may be attributed to differences in genetics, hormones, environment, or resilience. Greater susceptibility to AD in women may be due to the greater vulnerability to tau deposition in temporal regions resulting in differences in tau network structure. Female specific reserve may counteract the increased vulnerability.
4. TESTS FOR AD	4.1. Improvements to the measurement of A β	The Centiloid method may overcome inconsistencies between CSF A β 42 and A β PET measures. Optimization of the Roche ElecSys platform improved reliability of CSF measures. Other low cost and/or noninvasive methods for determining A β status masks circumvent the need for CSF or PET and lower clinical trial costs.
	4.2. Low cost and/or noninvasive approaches for the determination of A β status	ADNI studies have validated low cost and/or noninvasive A β screening approaches which include practical algorithms based on clinical information or using MRI scans collected in routine screening. These may lower screening and clinical trial enrollment costs.
	4.3. Blood tests for AD	ADNI has contributed to the acceleration of research into plasma assays for AD. While plasma A β shows promise for replacing costlier/more invasive PET or CSF tests, plasma ptau predicts A β deposition, tau accumulation, atrophy, and diagnostic progression. Blood tests for other markers of neurodegeneration such as NFL show promise as markers of neuronal injury. Other blood factors have been investigated for their predictive ability.

(Continues)

TABLE 1 (Continued)

5. IMPROVING CLINICAL TRIALS AND CLINICAL PRACTICE	5.1. Clinical trials of prodromal AD	Improvements to clinical trials of prodromal AD participants include broadening selection criteria in accordance with AT(N) staging, better predicting the time frame of progression to AD, and accounting for treatment effects.
	5.2. Clinical trials of preclinical AD	A stochastic model of a clinical trial of CU participants provided guidance for clinical trial design. Subject selection based on subthreshold regional cortical A β accumulation may improve trial power. Alternatively, subtle subjective and objective cognitive changes may be used for subject selection. Tau PET may be an effective surrogate outcome measure with appropriate subject selection using A β Centiloid measures.
	5.3. Assessing an individual's risk of progression	The ability to predict an individual's risk of decline in the clinic is fundamental to implementing personalized medicine. Models using multimodal data have been operationalized into practical tools to aid the clinician.
	5.4. Automated diagnosis and prognosis	Machine learning approaches to diagnosis and prognosis have continued to develop rapidly. Some algorithms have undergone extensive validation in ADNI and other cohorts to ensure generalizability. These may aid clinicians in diagnosis, and can rely on readily available, non-imaging data, or MRI data if available. Several multimodal classifiers predict progression with high accuracy.
6. ADDRESSING ETHNOCULTURAL DIFFERENCES IN AD		Results of ADNI studies may not be generalizable due to the lack of ethnocultural diversity in its cohort. Several ADNI studies have highlighted differences in APOE regulation and effects based on ancestral background. ADNI plans to enroll a more diverse cohort in the future.
7. CONCLUSIONS		Recent ADNI studies have supported the central role of A β and tau in disease progression and highlighted a number of contributing factors that affect disease trajectory. Methodological improvements such as blood tests may revolutionize screening. Improved participant selection may increase clinical trial power. However, as the ADNI cohort lacks ethnocultural and other diversity, results are not necessarily generalizable to other populations. Future enrollment aims to address this shortcoming.

Abbreviations: AD, Alzheimer's Disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; CSF, cerebrospinal fluid; CU, cognitively unimpaired; MRI, magnetic resonance imaging; NfL, neurofilament light; PET, positron emission tomography.

individuals across the depth and breadth of ADNI. Although individual measures were highly variable and insufficient for clinical diagnosis, average trajectories suggested that early changes in memory and levels of CSF A β 42 could occur > 25 years before dementia onset. This and other recent models of disease progression based on ADNI data (Table S1 in supporting information) widely support the ordering of biomarkers proposed by Jack et al.^{18,22}

The use of a wider range of longitudinal multimodal data incorporated as continuous rather than dichotomous variables based on binary definition of abnormality identified heterogeneous paths of disease progression.²³ The study, which used hidden Markov models to align participants' trajectories and estimate disease progression, identified 12 disease stages in which CU individuals were largely positioned in stages 1 to 4, AD individuals in stages 10 to 12, and individuals with MCI spread between. Individuals frequently skipped stages in their progression to AD. Two prominent and distinct paths with little interchange were identified in MCI and AD: path A, going through stages 8 \rightarrow 10 \rightarrow 12 and characterized by greater neurodegeneration with lower levels of AD pathology, or path B, going through stages 9 \rightarrow 11 \rightarrow 12 and characterized by relatively greater A β burden for the degree of cognitive impairment (Figure S2 in supporting information). Compared to individuals on path A, individuals on path B were younger, had a higher

frequency of the apolipoprotein E (APOE) ϵ 4 allele, and had a faster transition to AD. A novel approach to uncovering underlying molecular mechanisms of neuropathology used unsupervised machine learning to infer longitudinal gene expression trajectories from cross-sectional gene expression data sets.²⁴ The molecular disease score generated from the Religious Orders Study-Rush Memory and Aging Project (ROS-MAP) autopsy cohort and from ADNI blood samples was therefore independent of phenotypic variables yet still predicted pathological evolution and was associated with diagnosis, clinical progression, executive function, and memory performance. Molecular pathways important for pathological progression largely overlapped between blood and brain, and included common pathways associated with neurodegeneration such as axon guidance and apoptosis. Additionally, this analysis highlighted the key contributions of immune system response and vascular structure and functioning. The use of gene expression data in this manner may aid in understanding molecular mechanisms underlying neurodegenerative heterogeneity.

The accumulation of neurofibrillary tangles in the sequential spatiotemporal pattern described by the Braak stages has led to the development of hypotheses positing the prion-like misfolding, aggregation, and propagation of pathological tau species cell to cell through anatomical connections.^{25,26} ADNI longitudinal tau PET data were

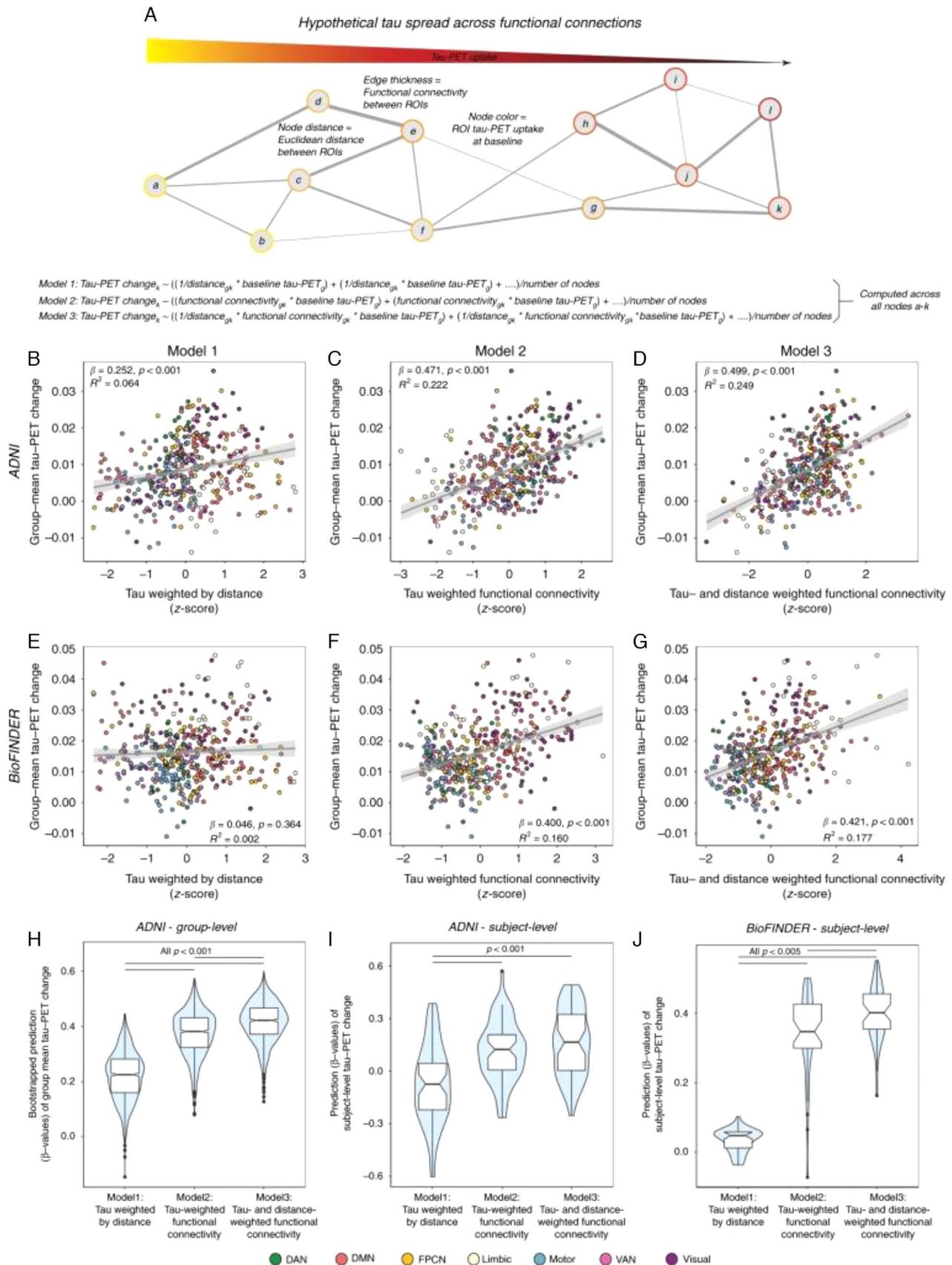


FIGURE 1 Prediction of longitudinal tau-PET change. A, Hypothetical network spreading model of tau pathology. Each node within the network represents a brain region, where color indicates local tau pathology, distance between regions indicates connection length (i.e., Euclidean distance), and edge thickness indicates functional connectivity strength. Example formulae for models 1 to 3 illustrate how tau-weighted distance (Model 1), tau-weighted functional connectivity (Model 2) or tau- & distance-weighted functional connectivity (Model 3) that were used to model

instrumental in two studies investigating these hypotheses. The first²⁷ tested the hypothesis that the pathological tau propagated preferentially along functionally strong and spatially short connections using resting state functional MRI (rs-fMRI) to assess interregional connectivity. A β + CU individuals had increased baseline and longitudinal tau PET uptake in temporoparietal and frontal regions, corresponding to regions with higher functional connectivity, compared to CU A β - participants. Seed ROIs with higher tau accumulation rates were associated with tau PET changes in regions with higher functional connectivity (Figure 1a). A model based on baseline tau, functional connectivity, and the spatial remoteness of connections predicted longitudinal tau spread at both group and individual levels better than models based on baseline tau and functional connectivity or distance alone (Figure 1b-j). This demonstration that such stronger and closer functional connections predicted greater change in tau binding is consistent with transneuronal tau propagation. A second study²⁸ investigated propagation of pathological tau from different seed regions based on an epidemic spreading model.²⁹ The seeding of this model in the entorhinal cortex explained the greatest proportion of tau spread (70% of group and 51% of average individual tau spread) and was consistent with autopsy findings. The use of a structural connectome assessed by diffusion tensor imaging (DTI) tractography predicted the observed pattern of tau spreading better than a functional network assessed by rs-fMRI (Figure S3 in supporting information), even in normal aging (CU A β - individuals with low overall tau burden). Regions with greater than predicted tau accumulation had greater A β burden, but antecedent A β deposition could not fully explain the observed pattern of tau PET, suggesting that although regional A β may accelerate the spread of tau tangles, tau spread may be influenced by other factors or be self-perpetuating.^{25,26}

A disease progression score based on the differences in trajectories of cortical A β burden and hippocampal volume of an individual, compared to population curves derived from data-driven models, tracked longitudinal disease progression and predicted worsening clinical diagnosis.³⁰ The disease progression score was used as a quantitative phenotype in a genome-wide association study (GWAS) and identified a novel locus in *LCORL* that was expressed in the hippocampus and associated with better prognosis. Disease progression models may therefore be of use in discovering regional and temporal genetic variation in AD.

These data-driven models illustrate the power of considering different modalities in elucidating the intricacies of disease progression. These extend beyond the biomarkers considered by Jack et al. to include tau PET, measures of early cognitive changes such as Rey

Auditory Verbal Learning Test, plasma biomarkers, gene expression, and structural and functional brain networks. While the timing and ordering of biomarkers included in the Jack et al. model was recapitulated in recent data-driven models,^{21,31} newer modalities suggested that the first cognitive dysfunction³¹ and in vivo tau deposition²¹ may occur around the same time as the first A β abnormalities arise. These discrepancies may be due to not only the use of different modalities or cognitive tests, but also to the existence of heterogeneous pathways of progression.²³

2.2 | A β in disease progression

The extracellular deposition of A β into plaques is part of the definition of AD pathology and represents an early step in all models of disease progression discussed above. Increased cortical A β accumulation below the threshold for A β positivity in CU elders was associated with worse memory decline, but not with decline in executive function.³² The fastest-changing tertile of subthreshold CSF A β 42 was associated with greater CSF biomarker abnormality, greater cortical A β burden, glucose hypometabolism, decline in the Mini-Mental State Examination (MMSE), and an increased risk of clinical progression to MCI.³³ Faster-changing subthreshold CSF A β 42 was in turn predicted by higher baseline CSF levels of β -secretase 1, A β 40, and A β 38, markers of amyloid precursor protein (APP) processing, suggesting that these proteins signal early pathophysiological events on the road to biomarker abnormality. The region of greatest early A β PET uptake, the banks of the superior temporal sulcus, was operationalized as a staging method to investigate this association further.³⁴ The rate of memory decline in CU elders in stage I (positive for A β accumulation in this region but negative for uptake in a composite cortical region)³⁵ had a rate of memory decline 2.5 times faster than CU elders in stage 0 (no evidence of A β accumulation). Those individuals in stage 2 (positive for A β binding in both the superior temporal sulcus and in the composite cortical region) had memory decline 4.8 times faster than those in stage I, faster rates of decline in executive function, and worse CSF biomarkers. A similar five-stage multitracer model of cortical A β ³⁶ added successive areas of A β abnormality detected in A β PET scans in a CU cohort, beginning with no tracer uptake in stage 0, followed by initial uptake in cingulate regions in stage 1, and eventually spreading to widespread temporal and occipital regions in stage 4. When this staging was applied to six additional cohorts of CU, MCI, AD, and non-AD dementia individuals scanned using four different radiotracers, baseline stage predicted MMSE decline, and was associated with the

group-mean annual tau-PET change in the 53 A β + ADNI (B-D) and 41 A β + BioFINDER subjects (E-G) were computed. For ADNI, the computed association is illustrated in (B-D) for 1000 bootstrapped samples. H-J, Resulting β -value distributions (y-axis) were compared between Models 1-3 using an ANOVA with post-hoc Tukey-test (x-axis). F, Prediction Models 1-3 were assessed on the subject-level for 53 ADNI A β + and 41 BioFINDER A β + subjects using subject-level annual tau-PET change and subject-level connectivity (ADNI) or HCP-derived group-level functional connectivity (BioFINDER). Subject-derived β -value distributions were compared across Models 1-3 using an ANOVA. Linear model fits are indicated together with 95% confidence intervals. A β , amyloid beta; ADNI, Alzheimer's Disease Neuroimaging Initiative; ANOVA, analysis of variance; DAN, dorsal attention network; DMN, default mode network; FPCN, frontoparietal control network; HCP, host cell protein; PET, positron emission tomography; ROIs, regions of interest; VAN, ventral attention network. Reproduced with permission from Franzmeier et al.²⁷

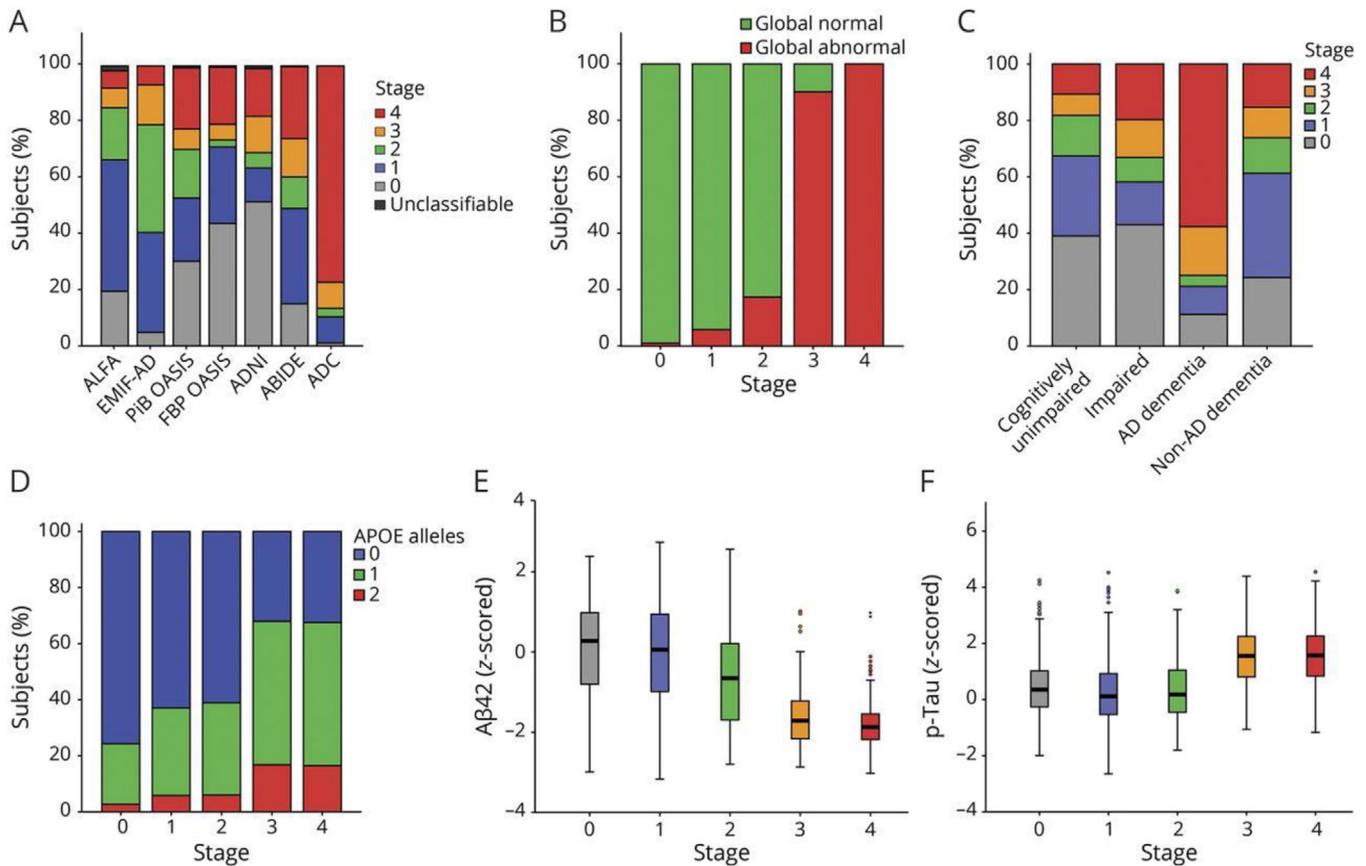


FIGURE 2 (A) Baseline distribution of staging classification per cohort. Stages refer to a model developed in CU individuals based on the sequential addition of four clusters of regional A β : Stage 0: no tracer uptake; Stage 1: cingulate regions; Stage 2: precuneus, paracentral gyrus, lateral orbital cortex, and insula; Stage 3: basal temporal, frontal, and additional associative cortices; Stage 4: other temporal and occipital regions. Classification based on A β staging model vs (B) global A β PET classification. (C) syndromic diagnosis, (D) genetic risk, (E) z-scored CSF A β 42 levels, and (F) log-transformed z-scored phosphorylated tau (p-tau) values. A β , amyloid beta; ABIDE, Alzheimer's Biomarkers in Daily Practice; ADC, Amsterdam Dementia Cohort; ALFA, Alzheimer's and Family cohort; EMIF-AD, European Medical Information Framework for AD; FBP, florbetapir; PIB, Pittsburgh compound B. Reproduced with permission from Collij et al.³⁶

number of APOE ϵ 4 alleles, CSF A β 42, and CSF phosphorylated tau (p-tau181). The staging system outperformed global standardized uptake volume ratio (SUVR) in identifying progressors and detected early A β deposition in all diagnostic categories (Figure 2) indicating its validity and generalizability. Differing gene expression profiles were associated with different regions reported in a similar four-stage system,³⁷ including those associated with voltage gated ion channel activity, lipid transport, axon guidance, and blood circulation.

These subtle changes in memory performance in CU individuals linked to subthreshold cortical A β are consistent with some of the first pathological changes predicted by data-driven models discussed in Section 2.1 (e.g., Hadjichrysanthou et al.¹⁰). A β -associated domain-specific cognitive changes may be mediated by functional brain changes within the subsystems of the default mode network (DMN) and visual network, with the strongest effect in the precuneus and lateral inferior parietal lobe.³⁸ An A β - and FDG-PET study³⁹ sheds further light on the involvement of the DMN. In CU and MCI individuals, regional patterns of hypometabolism were associated with A β deposition in distant regions connected by the DMN. Furthermore, clinical

progression was associated with an interaction between this regional hypometabolism and overlapping local A β . The authors suggest a model in which distant A β induces, via the DMN, regional metabolic vulnerability, and in which this vulnerability synergistically interacts with local A β to drive progression to dementia. It should be noted that the association of A β with cognitive changes does not necessarily mean that A β accumulation directly impairs cognition. Considerable data from ADNI^{2,3} and other publications show that accumulation of tau is much more closely linked with cognitive impairment than is A β .

The genetic architecture underlying brain amyloidosis appears to be complex, involving multiple loci, and differing across disease stages. Studies of summary scores of polygenic risk (polygenic risk scores and/or polygenic hazard scores) indicated that their association with CSF A β 42 or cortical A β was driven primarily by the APOE ϵ 4 allele.⁴⁰⁻⁴² Of the top 20 AD risk variants beyond APOE ϵ 4, ABCA7 was the most strongly associated with amyloidosis in both asymptomatic and early symptomatic disease⁴³ (Figure S4 in supporting information). Loss of function of the ABCA7 protein, involved in membrane transport particularly in microglia, increased β -secretase cleavage of APP

leading to higher levels of cortical A β . Risk variants in this gene may therefore play a greater role earlier in disease progression during rapid accumulation of A β before its levels plateau. In contrast, the association of *FERMT2* with amyloidosis was stage-dependent, peaking in MCI (Figure S4). Weaker associations with A β deposition were also identified for *CLU*, *DSG2*, *EPHA1*, *SORL1*, *PICALM*, and *ZCWPW1*, of which *CLU*, *EPHA1*, and *SORL1* are associated with innate immune signaling. A novel locus associated with brain amyloidosis in CU individuals, *RBFOX1*, was identified from a multicenter GWAS that included ADNI participants and validated using pathologic samples from ROS-MAP.⁴⁴ This locus encodes a neuronal RNA binding protein that was found to be localized in A β plaques. Reduced expression of *RBFOX1* was associated with poor global cognition and with higher A β burden, although its mechanism of action is not yet understood. *FAM222A*, recently identified as a putative brain atrophy susceptibility gene, encodes the protein aggregatin which accumulates in A β deposits and facilitates A β aggregation by physically interacting with A β .⁴⁵ Beyond specific loci, epistatic interactions may influence amyloidosis through gene regulation. Single nucleotide polymorphism (SNP)–SNP candidate interactions identified in a genome-wide epistasis analysis of A β in *post mortem* brains in ROS-MAP and subsequently validated in ADNI using CSF biomarkers, were primarily involved in the regulation of cell development, nervous system development, and cell fate commitment.⁴⁶

2.3 | Tau deposition in disease progression

ADNI tau PET data have allowed researchers to move beyond neuropathological studies to investigate neurofibrillary tau pathology in vivo. A feature of normative aging is the accumulation of tau tangles within the medial temporal lobe (MTL), termed primary age-related tauopathy (PART), which is associated with subtle cognitive effects.⁴⁷ In A β - participants, regional MTL tau PET SUVR was not associated with longitudinal cortical atrophy,⁴⁸ suggesting that PART does not drive neurodegeneration. However, in the same individuals, regional MTL tau PET SUVR was associated with MTL subregional atrophy that recapitulated Braak staging, suggesting that 18F-flortaucipir detects tau pathology from PART in the MTL.⁴⁹ The sequence of events leading to tau-dependent neurodegeneration beyond normative aging in individuals with suprathreshold A β deposition was investigated by several ADNI studies. First, temporal region tau PET accumulation was observed only in CU participants with high (>68 Centiloids [CL]) antecedent A β deposition in the Mayo Clinic Study of Aging,⁵⁰ suggesting that a critical level of A β deposition must be reached to trigger the subsequent chain of events. However, these findings were not totally supported by ADNI data. Second, tau PET binding in the entorhinal cortex, an early site of neurofibrillary tangle accumulation, was positively associated with longitudinal atrophy within the MTL in CU and impaired A β + but not A β - individuals.⁵¹ Broader MTL tau PET binding in A β + individuals was positively associated with longitudinal atrophy in temporal and orbitofrontal regions⁴⁸ (Figure 3). Taken together, these results support an active process of neurodegeneration specific to tau pathology that is dependent on antecedent A β deposi-

tion and that spreads from the entorhinal cortex to laterotemporal and orbitofrontal regions. However, the A β plaque deposition measured by A β PET may not be the species of A β that drives tau deposition, neurodegeneration, and cognitive decline. Some have suggested that A β oligomers (not detected by A β PET), which are associated with A β plaques, may be toxic A β species.

Tau accumulation may be influenced by genetic factors independently of APOE ϵ 4-influenced A β accumulation. Beyond APOE, polygenic risk scores and/or polygenic hazard scores were associated with CSF total tau (t-tau) and p-tau181,^{40,41} clinical diagnosis,⁴⁰ and CSF proteomic markers of neurodegeneration such as neurofilament light (NfL), YLK-40, and neurogranin.⁴¹ The established risk locus, rs74473 in *BIN1*, was associated with higher global tau PET uptake independently of A β status, and with elevated tau in regions corresponding to Braak stages II–VI (Figure S5 in supporting information) in nondemented elders.⁴¹ These results are consistent with the hypothesis that the protein encoded by *BIN1* risk variants aggravates tau but not A β pathology. A genome-wide interaction analysis of epistatic interactions⁴⁶ identified SNP–SNP pairs related to tau pathology, predominantly involved in axon development, axonogenesis, and forebrain development. The pair with the most significantly altered expression was MAPK9, associated with t-tau, p-tau181, and neurofibrillary tangles, and CAMKK1, involved in tau phosphorylation.

Although it is well known that the APOE ϵ 4 allele is associated with levels of A β , it may also independently modulate tau. In two independent cohorts of participants across the AD spectrum, APOE ϵ 4 carriers had increased tau PET SUVR in the bilateral entorhinal cortex and hippocampus independently of A β PET global SUVR, implicating greater tau pathology as a cause of increased regional neurodegeneration observed in these individuals.⁵² Therefore, it is likely that the deleterious consequences of APOE ϵ 4 in AD extend beyond its link with A β .

It has been known for many years that the regional pattern of A β plaque spread in AD differs from that of closely associated patterns of tau spread and neurodegeneration (Figure S6 in supporting information).⁵³ The molecular underpinnings of this differential regional vulnerability to A β deposition and subsequent neurodegeneration were investigated by examining the brain transcriptional architecture underlying these patterns.⁵³ Regional expression of the genes coding for the APP (*APP*) and for tau (*MAPT*) was correlated with regional A β deposition and regional neurodegeneration, respectively, but not vice versa. Gene set enrichment analysis identified differential gene sets underlying regional vulnerability to A β deposition and neurodegeneration. A β -vulnerable regions were characterized by low expression of genes implicated in protein folding and degradation, suggesting that these may contribute to A β aggregation, and also by the low expression of mitochondrial respiration genes. Regions vulnerable to neurodegeneration were characterized by the high expression of genes involved in neural plasticity, and by the tau kinases CDK5 and MAPK1/ERK2, along with components of the Ras-ERK signaling pathway. This study provides intriguing insight into the differential molecular properties underlying vulnerability of the affected neural systems in A β accumulation compared to neurodegeneration.

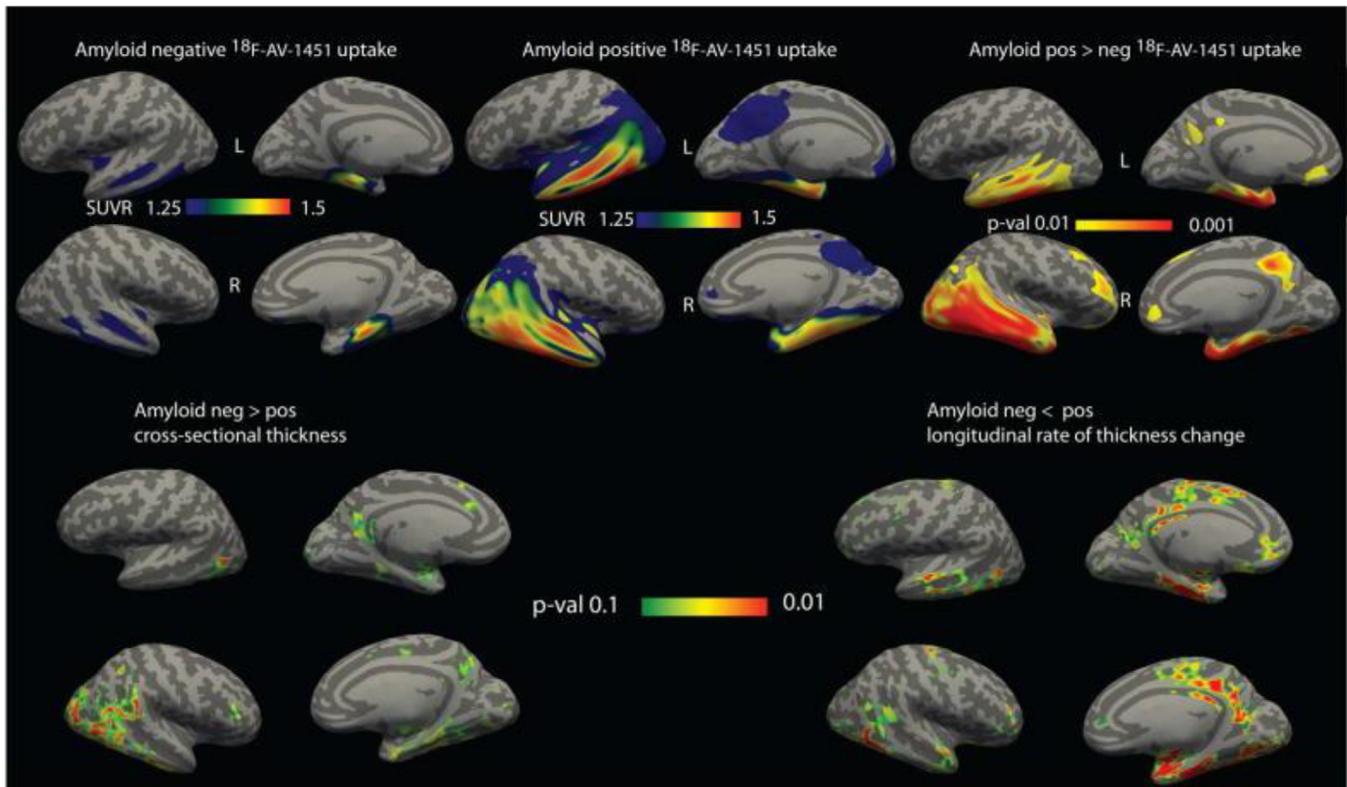


FIGURE 3 Association of tau positron emission tomography uptake with cortical thickness and atrophy. Top, Mean standardized uptake value ratio of ^{18}F -AV-1451 uptake in amyloid beta ($\text{A}\beta$) $^-$ (left) and $\text{A}\beta$ $^+$ (middle) individuals. Right panel shows areas of significantly greater tracer uptake in amyloid-positive group ($P < .01$ family-wise error rate). Bottom, Areas of significantly greater thickness (left) and lower rate of thickness change (right) in $\text{A}\beta$ $^-$ individuals. Maps are shown at an uncorrected threshold of $P < .1$ for visualizing trends in the data. Effects were not statistically significant after correction for multiple comparisons. Reproduced with permission from Das et al.⁴⁸

2.4 | AT(N) biological classification of AD

The National Institute on Aging-Alzheimer's Association AT(N) research framework for the biological definition of AD⁵⁴ is based on biomarkers for $\text{A}\beta$ deposition (A), pathologic tau (T), and neurodegeneration (N) that are defined as abnormal above predetermined thresholds. The ADNI data set has been a rich source of material for those investigating the value of the AT(N) approach. Despite data-driven models of disease progression^{10,21,23,55–59} largely recapitulating the classic temporal sequence of events (i.e., amyloidosis preceding pathologic tau aggregation leading to neurodegeneration), other sequences of biomarker abnormality are possible, such as that found in primary tauopathies in which tau aggregation precedes amyloidosis. A study of ADNI CU and MCI participants that followed trajectories of AT(N) biomarkers found that the biomarker for amyloidosis most commonly became pathological first, and subsequently diverged into a faster-progressing $\text{A}\rightarrow\text{T}\rightarrow\text{N}$ evolution and the much slower-progressing $\text{A}\rightarrow\text{N}\rightarrow\text{T}$ evolution (Figure S7 in supporting information).⁶⁰ In some elders, tau deposition preceded amyloidosis by an average of more than 40 months in a $\text{T}\rightarrow\text{A}\rightarrow\text{N}$ sequence of biomarker abnormality, suggesting that tau and $\text{A}\beta$ may independently arise from separate pathophysiological processes. Individuals with an $\text{N}\rightarrow\text{A}\rightarrow\text{T}$ sequence had the fastest rate of pathological progression,

suggesting that different etiologies, such as vascular brain injury or TDP43, underlie initial neurodegeneration in this instance (Figure S7).

A recent mediation study suggested that the degree to which the effect of baseline $\text{A}\beta$ on cognition is explained by tau or neurodegeneration differs depending on disease stage and region. In CU elders, $\text{A}\beta$ deposition affected change in memory via predominantly MTL atrophy in the absence of changes in tau, suggesting that $\text{A}\beta$ may interact with tau already present in the MTL due to PART or other pathological processes early in disease progression. This effect continued into early and late MCI, but in early MCI, the effect of $\text{A}\beta$ on memory was also mediated by tau and lateral temporal lobe atrophy. In late MCI wider tau-dependent atrophy affected both memory and executive function.

The application of binary cut points to define “normality” versus “abnormality” is an issue with any biomarker for any disease process that occurs over decades. There may exist a biologically relevant “gray zone” around the biomarker threshold that reflects the difficulty in defining the exact point at which changes in biomarkers result in a significantly worse cognitive trajectory that may be indicative of other etiologies or mixed pathologies contributing to cognitive decline. The NIA-AA framework document discussed this at length and pointed out that while binarizing the AT(N) groups into \pm is one option, all AT(N) measures are continuous and other options for cut points might be more useful in certain situations.⁵⁴ The trajectory of impairment in the

preclinical Alzheimer's cognitive composite (PACC)⁶¹ in CU individuals was indistinguishable within 0.1 from the florbetapir PET SUVR threshold of 1.11, a spread which included $\approx 40\%$ of individuals (Figure S8 in supporting information).⁶² Subthreshold changes in A β and tau that are not detected in the dichotomous AT(N) classification may represent a state of worsening yet not abnormal biomarkers with implications for disease trajectory. In CU elders, subthreshold A β accumulation, but not baseline A β load, was associated with decline in a composite memory score, but not in a composite executive function score,³² indicating that very early A β accumulation can be associated with subtle effects on cognition.

The ADNI data set has been especially useful in studying how the choice of biomarker within each AT(N) category may affect patient staging. CSF and PET measures of A β pathology provide different information as evidenced by the finding that decreases in CSF A β 42 precede A β PET positivity.⁶³ The transition to CSF A β abnormality was predicted at a cutoff of 12 CL of A β PET, whereas the transition to A β PET positivity occurred at ≈ 30 CL.⁶⁴ In a similar manner, CSF p-tau181 abnormality may precede tau PET positivity.⁶⁵ Regardless of tau PET status, individuals with suprathreshold CSF p-tau181 were more likely to be A β +, have elevated tau PET binding in Braak stage ROIs, and have accelerated rates of antecedent p-tau181 accrual than those with subthreshold CSF p-tau181.⁶⁵ The CSF+/PET- discordance in tau may therefore represent an intermediate stage in AD pathogenesis that may or may not be recognized by AT(N) staging depending on the biomarker used.⁶⁶ A systematic study of AT(N) classification highlighted staging discrepancies resulting from the use of different biomarker classes at different disease stages.⁶⁶ Compared to staging using CSF core AD biomarkers, substitution of A β PET resulted in increasing misclassification from CU to MCI to AD (Figure 4A-D). Different markers of neurodegeneration (hippocampal volume, cortical AD signature, FDG PET SUVR, and CSF t-tau) were poorly correlated at all disease stages, resulting in substantial misclassification (Figure 4A-D) but performed best in individuals with AD, presumably due to more advanced neurodegeneration in this group. Tau PET was not included in this study but another study⁶⁵ suggested that this measure would likewise result in misclassification as CSF p-tau181 abnormality appeared to precede tau PET positivity. As AT(N) groups are associated with different trajectories of decline,⁶⁰ misclassification may result in incorrectly ascribed progression risks with implications in clinical trials and clinical practice.⁶⁷

The use of additional biomarkers of different aspects of neurodegeneration has been an active area of study and may increase staging precision and the prediction of decline. CSF neuronal pentraxin, a marker reflecting the loss of synaptic regulation, was decreased in AD compared to CU elders, strongly predicted both memory and global cognition, and in a ratio with tau accurately discriminated between AD and CU individuals independently of A β .⁶⁸ Additional synaptic markers, neurogranin, and synaptosomal nerve-associated protein 25 (SNAP-25), also predicted cognitive decline.⁶⁸ Levels of CSF neurogranin, SNAP-25, and visinin-like protein 1 were highly correlated and elevated at baseline as a function of A β positivity.⁶⁹ NfL, a marker of neuronal damage, can now be accurately measured in plasma in addi-

tion to CSF,⁷⁰ opening the possibility of the use of low cost and minimally invasive blood biomarkers (Section 4) in AT(N) staging. Longitudinal changes in plasma NfL were associated with both AD neuropathology and neurodegeneration across diagnostic groups.⁷⁰

3 | BEYOND AT(N): OTHER INFLUENCES ON DISEASE PROGRESSION

The multifactorial nature of AD is well recognized and there has been increasing acknowledgment that the cascade of A β deposition leading to tau deposition and neurodegeneration is insufficient to fully explain the diversity of disease trajectories. What other factors, then, influence disease progression and how do they affect the selection of participants for clinical trials and subsequent interpretation of findings? Several studies described in Section 2 identified heterogeneous pathways of disease progression^{23,57,60} or implicated other factors that may affect progression such as immune function^{24,43} or vascular structure and function.²⁴ In addition, neuropathological examination frequently identifies co-pathologies such as cerebral amyloid angiopathy, limbic-predominant age-related TDP-43 encephalopathy neuropathological change, and Lewy bodies.⁷¹ Although we do not comprehensively review these pathologies, several studies highlight their contribution to AD. CSF α -synuclein, the major component of Lewy bodies, predicted cognitive measures and progression to AD dementia,⁷² a frontotemporal neurodegenerative pattern observed in A β - MCI and AD dementia participants may have been underlain by limbic predominant age-related TDP43 encephalopathy,⁷³ which in turn modulated A β PET signal.⁷⁴

Although the AT(N) research framework is currently most commonly implemented using the biomarkers in Section 2.4, it was constructed to be flexible in the incorporation of new biomarkers and to the addition of new biomarker categories reflecting the multifactorial etiology of AD such as genetic risk, cerebrovascular disease, cognitive reserve, and inflammation.^{54,62} The use of these additional categories of biomarkers may help to better define cognitive trajectories in elders with "gray zone" A or T biomarkers.⁶²

This section will discuss evidence for subtypes of AD that have different disease trajectories, the effect of cerebrovascular disease on both A β and tau pathways, the growing recognition of the importance of the immune system in AD, mechanisms of cognitive resilience, and how sex influences disease progression. It is important to note that these are not discrete categories of factors; there is ample evidence for their interplay. Recent ADNI genetic studies that have identified novel loci or investigated established AD risk alleles have predominantly identified the factors described above. While a discussion of these findings is beyond the scope of this review, these studies are summarized in Tables S2 and S3 in supporting information, respectively.

3.1 | Heterogeneity

AD is an inherently heterogeneous disorder with wide variance in biomarkers or cognitive tests that confound understanding disease

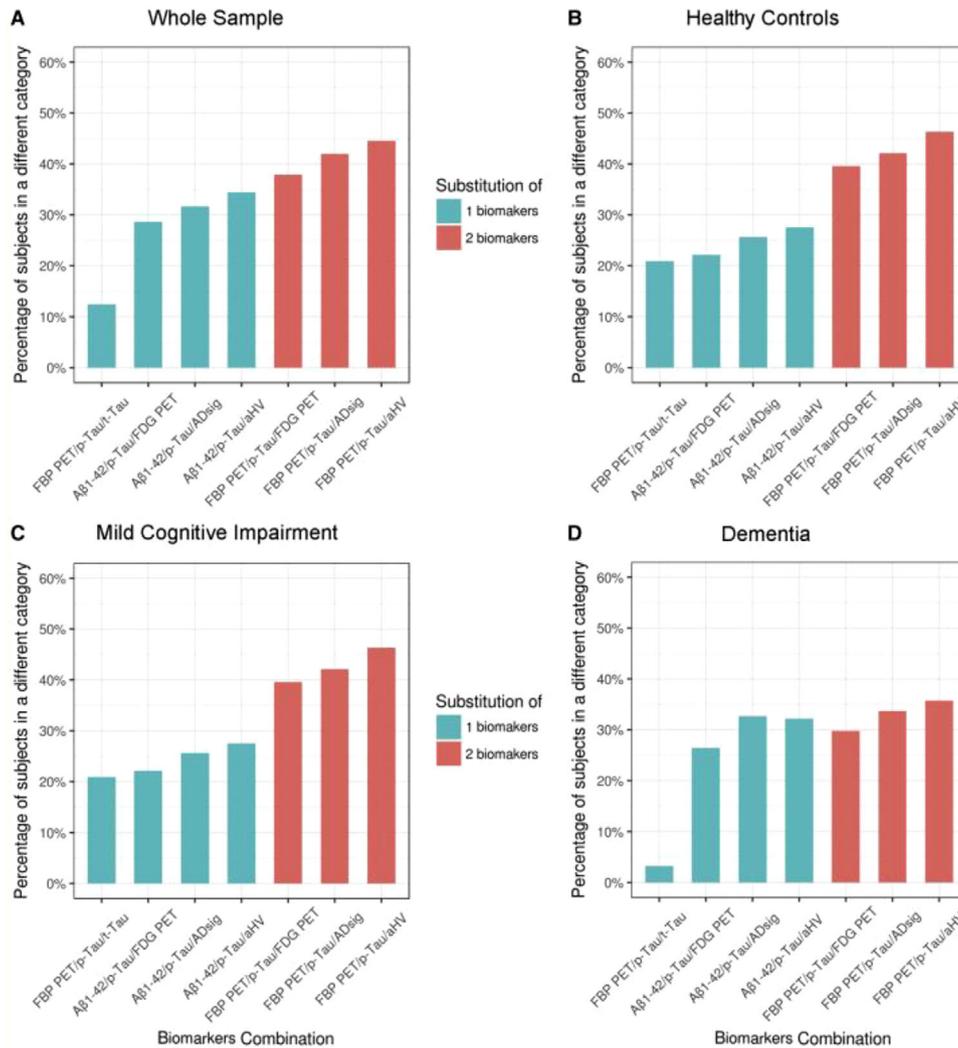


FIGURE 4 Discrepancies in AT(N) classification using different biomarker combinations. Percent of AT(N) misclassifications for the different biomarker combinations in (A) the whole sample, (B) cognitively unimpaired, (C) mild cognitive impairment, and (D) dementia subjects. The percent of participants classified in different categories are shown for each biomarker combination compared to classification with CSF Aβ42, p-tau181, and t-tau. Percent of misclassifications are shown in green when one biomarker was changed, and in orange when two biomarkers were changed. Aβ, amyloid beta; ADsig, Alzheimer's disease cortical signature; aHV, adjusted hippocampal volume; FBP PET, [18F] florbetapir positron emission tomography; FDG PET, [18F] fluorodeoxyglucose positron emission tomography; p-tau181, phosphorylated tau; t-tau, total tau. Reproduced with permission from Illán-Gala et al.²⁰²

progression and treatment. ADNI has continued to be instrumental in identifying sources of heterogeneity and characterizing subtypes of AD. A data-driven approach using a wide range of neuropsychological tests identified six clusters across the spectrum of ADNI participants and identified their characteristic biomarkers.⁷⁵ In addition to a “healthy” subgroup with normal cognition and biomarkers, a second “worried well” subgroup with no diagnosis of cognitive impairment was characterized by higher subjective cognitive decline and may represent preclinical AD. Two MCI groups were identified, a lesser-impaired, younger, and more highly educated “affective MCI” subgroup comprised mostly of early MCI participants and a more highly impaired “uncompensated MCI” group split between ADNI early and late MCI groups that had an increasing severity of other biomarkers (MRI, FDG PET, CSF). Two distinguishable subtypes of AD were identified.

“Anosognosia dementia” was characterized by maximum severity of cognitive impairment with low self-awareness of impairment and widespread atrophy and comprised almost entirely ADNI AD participants. In addition, “insightful dementia” had better cognitive scores and self-awareness, regional rather than whole brain atrophy, and included some late MCI and early MCI participants. It is unclear whether these clusters represent different stages or different trajectories of progression, but the novel identification of distinct AD subgroups, distinguished in part by levels of self-awareness, has implications for diagnosis and treatment assignments.

Neuropsychologically derived MCI subtypes may represent different trajectories of progression underlain by differences in biomarkers. A “neuropsychological early MCI” subtype was characterized by impairment in memory and naming domains, a “neuropsychological

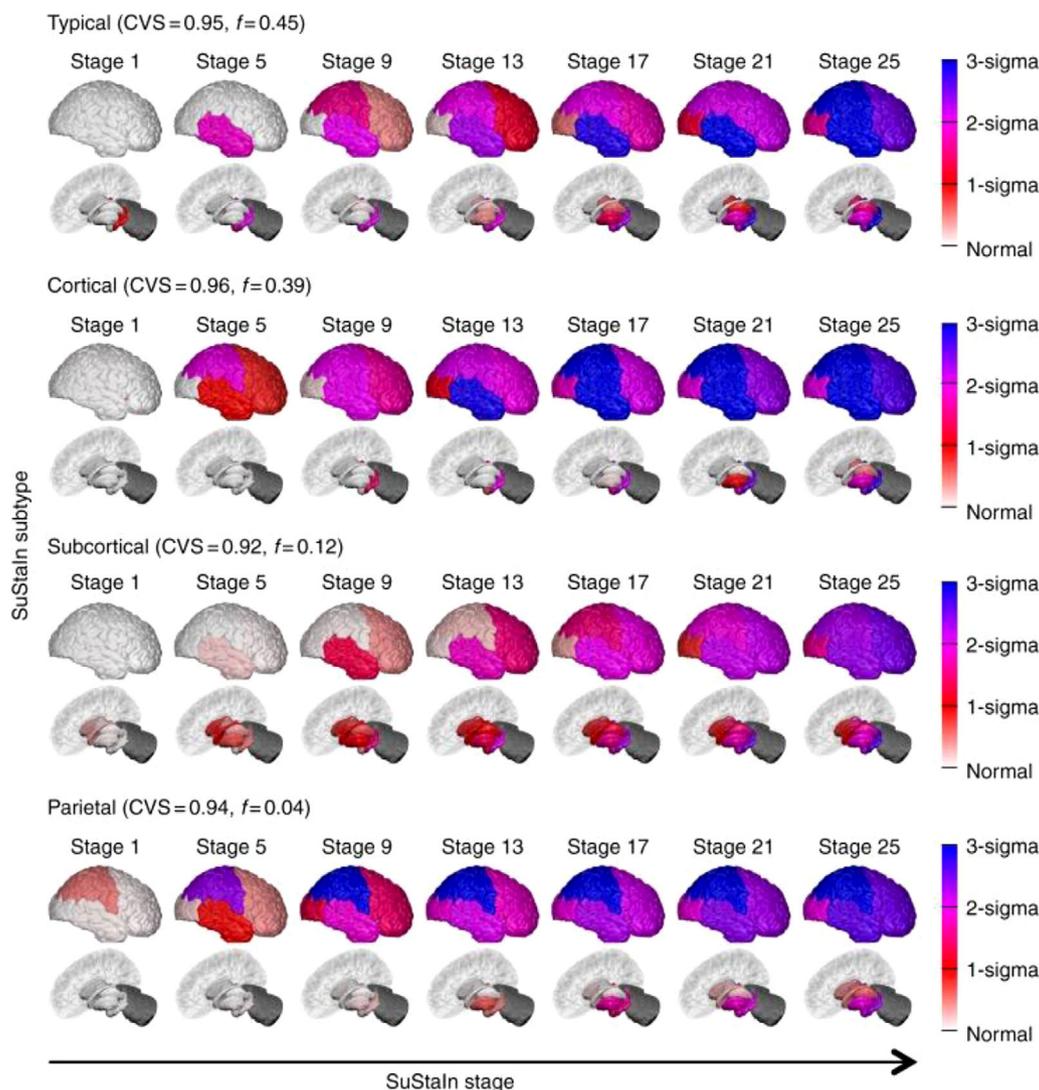


FIGURE 5 Progression of regional atrophy of subgroups of temporal and phenotypic heterogeneity. Rows show the progression pattern of three major subtypes: a typical, a cortical and a subcortical subtype, as well as an additional very small outlier parietal group (only 4%) that may represent outliers with a posterior cortical atrophy phenotype. CVS, cross-validations. Reproduced with permission from Young et al.⁷⁹

late MCI” subtype by widespread cognitive deficits, and a third “false positive” subtype lay within normal limits.⁷⁶ These groups had non-overlapping survival curves (Figure S9 in supporting information), and were differentiated by CSF biomarker levels with the “false positive” group indistinguishable from CU. In contrast, ADNI early and late MCI groups were less well defined in their survival curves (Figure S9) and levels of CSF biomarkers, and there was little difference between the ADNI early MCI and clustered-derived “false positive” groups. Widespread cortical thinning was only observed in the clustered-derived late MCI group. The use of multiple neuropsychological measures may therefore stage MCI into biologically relevant subgroups with distinct trajectories, both a faster progressing group and potentially misclassified CU elders. Similarly, amnesic, dysnomic/mixed, and mixed MCI subtypes were characterized by MTL, lateral temporal, and widespread longitudinal cortical atrophy, respectively, supporting the validity of the subtypes as separate entities rather than differ-

ent points in disease progression.⁷⁷ Further studies of neuropsychologically derived MCI subtypes are described in Table S1. Similar cognitive subtypes were identified in AD,⁷⁸ implying that differing trajectories of disease progression extend across diagnostic stages. One subtype had predominantly memory impairments characterized by an older age of onset, lower frequency of APOE $\epsilon 4$, less MTL atrophy, and slower progression, and a second had mostly non-memory impairment characterized by younger age of onset, higher frequency of APOE $\epsilon 4$, more posterior cortical atrophy, and faster progression. Future studies are required to fully validate these cluster-derived subgroups and to determine their clinical utility.

Consideration of temporal in addition to phenotypic heterogeneity⁷⁹ identified subgroups that evolved different atrophy patterns in multiple distinct stages that were reproducible across cohorts (Figure 5). The Typical subgroup, Cortical, and Subcortical subtypes were characterized by atrophy beginning in the

hippocampus and amygdala; insula and cingulate; and pallidum, putamen, and caudate, respectively. A parietal subtype was also identified in one data set that was characterized by posterior cortical atrophy, younger age, and worse performance on special subtests. Although mixtures of the subtypes were expressed within individuals, more AD than MCI individuals were strongly assigned to a subtype, raising the possibility that these phenotypes may be more strongly expressed later in disease progression. A similar approach that jointly considered both cognitive deficits and atrophy patterns identified three latent factors in MCI and AD participants that were stable across time.⁸⁰ The first was associated with MTL atrophy, episodic memory deficits, and tau binding in MTL regions, and appears consistent with the "Typical" pattern described above.⁷⁹ The second latent factor was characterized by lateral temporal atrophy and language deficits and had no associations with tau deposition. The third latent factor was characterized by posterior cortical atrophy, deficits in visuospatial abilities and executive function deficits, tau binding in lateral temporal and posterior cortical regions, and younger age. Individuals differed in their expression of each of the latent factors, reflecting the possibility of multiple coexisting pathologies.⁸⁰

Genetic differences may underlie identified subgroups.⁸¹ Reproducible genetic differences were found in subgroups of AD individuals defined by impairments in memory, executive function, language, visuospatial, or multiple domains.⁸¹ Relative memory impairment was associated with higher levels of APOE ϵ 4 than other subgroups, and 33 novel suggestive loci outside APOE approached genome-wide significance for at least one subgroup, suggesting that these subgroups are biologically coherent (Figure S10 in supporting information). In a novel approach, subgroups of participants across the AD spectrum were identified from differences in blood proteins and metabolites, primarily levels of β 2-microglobulin, cystatin-C, thrombospondin, and seven other plasma proteins (Figure S11 in supporting information).⁸² Subgroups were characterized by distinct patterns of cortical and subcortical atrophy, suggesting that biochemical differences may underlie the subtypes identified using atrophy patterns.

Biological subtypes of AD were identified based on differences in CSF proteomes between AD and CU participants across two cohorts.⁸³ Three distinct subtypes were identified, characterized by hyperplasticity, activation of the innate immune system, and blood brain barrier dysfunction, respectively, and each subtype was associated with distinct cognitive, cortical thickness, and CSF biomarker profiles. All subtypes had an excess of genetic risk for AD and did not differ in disease severity or presence of co-pathologies.

Converging evidence from multiple angles—neuropsychological, imaging, blood biomarkers, genetics, and proteomics—points to substantial heterogeneity underlying disease progression. A "classic" AD subgroup was identified by multiple approaches,^{76,79–82,84} typified by initial atrophy in hippocampus and amygdala followed by MTL atrophy, and primarily memory deficits, and underlain by APOE ϵ 4. Other subgroups feature primarily non-memory cognitive deficits, commensurate atrophy patterns, and associations with distinct genetic loci. Of note, a subgroup was characterized by younger age of onset, faster progression, posterior cortical atrophy, cognitive deficits in visuospa-

tial tasks, and a higher frequency of APOE ϵ 4 carriers by multiple studies^{78–80} and bears a striking similarity to the "pathway B" of disease progression²³ described in Section 2.1. A very recent study described and replicated four similar subgroups with distinct trajectories from tau PET scans.⁸⁵ These characteristics may aid in the identification of patients likely to progress faster in a clinical setting. Further investigation of disease subgroups is required to establish biological coherence and the relationship between subgroups defined by cognitive measures, atrophy, and plasma biomarkers. These studies will play an important role in both identifying participants for clinical trials and guiding clinical care with the development of personalized medicine approaches.

3.2 | Cerebrovascular disease

Cerebrovascular disease, consisting of microvascular changes that cause impaired cerebral perfusion such as white matter (WM) lesions, microinfarcts, and hemorrhages is increasingly recognized as a major contributor to AD, vascular dementia, Lewy body disease, and other conditions. It is observed in 60% to 90% of AD patients and may act to exacerbate clinical dementia risk although the underlying mechanisms are complex.⁸⁶ Cerebrovascular disease may act directly, as an additive contribution to cognitive decline, independently of A β and tau pathology, or may interact with A β deposition or tau burden. Recent ADNI studies have made important contributions of cerebrovascular disease to an emerging framework of these mechanisms.

Cerebrovascular events can be directly caused by a lack of blood flow to the brain due cardiovascular disease.⁸⁶ Smoking,⁸⁷ hypertension,⁸⁸ body mass index (BMI),⁸⁹ and overall cardiovascular risk⁹⁰ were associated with impaired glucose metabolism, neurodegeneration or cognitive decline (Table S1). Cognitive decline in ADNI participants with Type 2 diabetes mellitus was mediated by baseline cortical thickness.⁹¹ These participants also had decreased regional cerebral cortical A β compared to participants without Type 2 diabetes mellitus,⁹² although they were reported to have higher levels of CSF A β 42 that may be attributable to diabetes-related pathological changes such as hyperglycemia. These studies are consistent with a mechanism by which Type 2 diabetes mellitus exerts its effect on cognition via "classic" AD pathology and neurodegeneration.

A major manifestation of cerebrovascular disease is WM hyperintensities (WMHs) on T2-weighted MRI. These have been associated with decline of global cognition rather than the specific cognitive domains typical of AT(N) pathology.⁸⁶ Greater WMH volume was associated with worse baseline and longitudinal performances over a range of cognitive and functional tests across ADNI participants (Figure S12 in supporting information), and with an elevated risk of MCI to AD progression.⁹³ Increased WMHs were also associated with higher levels of plasma NfL, a marker of axonal degeneration, in MCI and AD participants.⁹⁴ The relationship was significantly attenuated by age, suggesting that WMHs are linked to neuronal damage in an age-dependent manner. It is important to note that these associations have been identified in the relative absence

of cerebrovascular disease due to ADNI's cerebrovascular exclusion criteria (<https://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf>), suggesting that they may be stronger in the wider population.

How does cerebrovascular disease worsen cognition? Its effect may be direct, or mediated by "classic" AD pathologies, or both. Individuals with neurodegeneration in the absence of A β deposition (i.e., having suspected non-AD pathology) had high WMH burden, suggesting that cerebrovascular disease may directly drive hippocampal atrophy and cognitive decline.⁹⁵ Increased WMH burden was to a lesser degree associated with lower CSF A β 42 across diagnostic groups, independently of CSF p-tau181 and CSF t-tau, and APOE status,⁹⁶ supporting a less prominent link with A β pathology. In A β - CU elders, regional increases in WMHs spanning superior regions of the frontal and parietal lobes were associated with faster rates of regional sub-threshold A β accumulation in cortical regions characterized by early A β accumulation.⁹⁷ This study is consistent with models in which cerebrovascular alterations are one of the earliest AD pathological changes.⁹⁸ Across CU, MCI, and AD participants, increased cortical A β load and WMH volume were associated with lower cortical thickness.⁹⁹ However, the association between WMH volume and cortical thickness in AD-associated regions held even in the absence of A β , suggesting an additive effect of A β and cerebrovascular disease on neurodegeneration.⁹⁹ Together, these results support independent and additive mechanisms for the effect of cerebrovascular disease on cognitive decline: one age-related and independent of "classic" AD pathology, and a second, related to AD pathology, that may occur very early in disease progression.

An additional A β -independent pathway for the effect of cerebrovascular disease on cognitive decline in AD may involve tau pathology.¹⁰⁰ Increased WMH volume was associated with higher plasma t-tau concentration independently of CSF A β 42, with an increasing strength of the interaction across diagnostic stages (Figure S13 in supporting information). The interaction of WMH and plasma t-tau, independently of CSF A β 42, was associated with increased likelihood of MCI and AD, indicating their combined impact on cognitive decline. Although the plasma measurement of t-tau reflects neurodegeneration rather than phosphorylated tau, neuropathological studies of ADNI participants in which arteriosclerosis was positively associated with Braak neurofibrillary tau staging support the association of cerebrovascular damage with neurofibrillary tangles. Future confirmatory studies using plasma measures of phosphorylated tau may clarify these associations.

The effect of cerebrovascular disease on cognition may be modulated by carriage of the APOE ϵ 4 allele, which has far-reaching effects via numerous A β -dependent and independent pathways. Some studies reported APOE ϵ 4-independent associations between vascular disease and AD biomarkers^{90,96} and/or cognitive decline.^{90,101} However, in a study conducted in the Sunnybrook Dementia Cohort and replicated in ADNI,¹⁰² greater WMH volume was associated with worse attention/executive functions and language in APOE ϵ 4 carriers but not non-carriers across the spectrum of AD and dementia with Lewy bodies. Neuropathological assessment revealed that 100% of APOE ϵ 4 homozygotes but only 64% of heterozygotes had cerebral amyloid

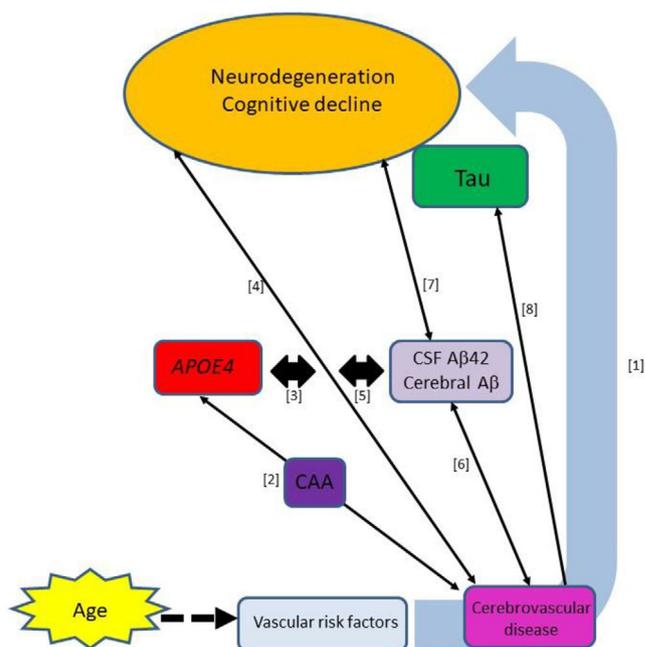


FIGURE 6 Cerebrovascular impacts in AD supported by recent ADNI studies. (1) Cardiovascular risk factors are associated with markers of neurodegeneration and cognitive decline.^{87,88,90,203} (2) The apolipoprotein E (APOE) ϵ 4 allele may increase WMHs via induction of CAA.¹⁰² (3) APOE ϵ 4 exacerbates effect of vascular risk factors on cognition.⁸⁸ (4) CVD has an age-related effect on general cognition which increases MCI to AD transition.^{93,94} (5) A β -mediated and direct effects of CVD are additive.²⁰⁴ Other studies have found both direct and additive interactions.⁸⁶ (6) A β is associated with WMHs independently of tau.^{96,97} (7) A β mediates association between WMH and cognition.²⁰⁴ This could occur directly or via tau. (8) Tau was associated with WMHs independent of A β .¹⁰⁰ CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; CVD, cerebrovascular disease; MCI, mild cognitive impairment; WMHs, white matter hyperintensities

angiopathy, suggesting that accumulation of A β in the cerebral vasculature may be the etiology for WMH in APOE ϵ 4 carriers.¹⁰² The APOE ϵ 4 allele may interact synergistically with vascular disease. In CU elders, hypertensive APOE ϵ 4 carriers had a steeper decrease in glucose metabolism than hypertensive non-carriers, carriers with normal blood pressure, or non-carriers with normal blood pressure suggesting that the APOE ϵ 4 allele acts to exacerbate the effect of hypertension on glucose metabolism.⁸⁸

Overall, these studies provide further evidence for the detrimental effect of vascular risk factors on neurodegeneration and decline. Cerebrovascular disease may exert its effect directly, via A β or tau deposition, or by a combination of pathways, and its effect may be exacerbated by the APOE ϵ 4 allele (Figure 6).

3.3 | Immune response

Multiple strands of evidence from recent studies using ADNI genetics data, blood and CSF samples, and other approaches, support a crucial

role of microglial-associated innate immune response in modulating AD risk. Microglia, the primary innate immune cells of the central nervous system, facilitate A β and tau clearance, and contribute to neuroinflammation that damages neurons.¹⁰³ Therefore, the immune response and inflammation can both slow and accelerate AD pathology. Many AD risk alleles (e.g., *APOE*, *TREM2*, *CD33*, *CLU*, *ABCA7*, *BIN1*, *SORL1*, *IL-34*, *MS4A* gene cluster, *TREML2*, *SHARPIN*) affect innate immune signaling pathways. A study examining associations between a polygenic risk score and CSF proteomic profiles in ADNI participants identified three clusters of associations.⁴¹ The first cluster, enriched for a “complement and coagulation cascades” pathway involved in immune response, was dominated by the association between the *APOE* ϵ 4 allele and A β . A second cluster, enriched for cytokines and cell adhesion molecules involved in inflammatory responses, was largely independent of associations with *APOE* ϵ 4. The third cluster was enriched in proteins that reflect neuronal injury, synaptic degeneration, and dyslipidemia (such as neurogranin, YLK-40, and fatty acid binding protein), and was partially *APOE* ϵ 4-independent. The association of a similar polygenic risk score with AD risk was primarily driven by *APOE* ϵ 4 in participants younger than 80 years, but by other variants outside “classic” AD pathology in older participants.¹⁰⁴ Moreover, a pathway-specific polygenic risk score based on the activation of immune response was significantly associated with AD risk in older, but not younger, AD participants, suggesting that age may influence the degree to which immune response affects AD risk.

In two independent cohorts, nine inflammation-associated blood proteins explained \approx 10% of the variance in a δ -homolog, dT2A,^{105,106} constructed from several cognitive measures as a correlate of functional status.¹⁰⁶ Similarly, a panel of CSF AD-associated proteins beyond “classic” CSF biomarkers explained 31% of the variance in Alzheimer's Disease Assessment Score (ADAS) 11 score compared to 26% explained by CSF A β 42 and t-tau, and was strongly associated with baseline cognition, diagnosis, and cognitive decline.¹⁰⁷ The two sets of biomarkers were largely independent, together explaining 41% of the ADAS11 variance (Figure S14 in supporting information). The most significant AD-associated proteins were primarily involved in immune response, lipid metabolism, or both (fatty acid binding protein, clusterin, apoE, angiotensin-converting enzyme, chromogranin A, CD40 antigen, vascular endothelial growth factor, human growth factor, transforming growth factor α , macrophage colony stimulating factor 1). As maintenance of central nervous system lipid metabolism is important for innate immune activation, the conjunction of CSF proteins involved in both processes is consistent with a model in which cognitive and functional deficits associated with the accrual of “classic” AD pathology are modulated by the innate immune system. Both studies suggest that a substantial portion of cognition is explained by factors beyond A β and tau.

The established AD risk allele, *TREM2*, plays an important role in the brain's major innate immune response to pathogens. It encodes triggering receptor expressed on myeloid cells 2 (*TREM2*), a transmembrane receptor expressed in microglia with multiple functions including phagocytosis of A β , cytokine release, and signaling.¹⁰⁸ Rare variants in *TREM2* increase AD risk while others in the *TREM2* gene clus-

ter have protective effects.¹⁰⁸ The level of soluble *TREM2* (s*TREM2*) in CSF increases across diagnostic groups and is considered a surrogate measure of *TREM2*-mediated microglial function.¹⁰⁸ Higher baseline CSF s*TREM2* was associated with slower A β accumulation, consistent with its role in the promotion of A β phagocytosis, and also with lower tau PET uptake in early Braak regions, which may result from its promotion of signaling pathways involved in tau hyperphosphorylation.¹⁰⁹ Across the AD spectrum, higher levels of s*TREM2* attenuated the detrimental effects of *APOE* ϵ 4 on future hippocampal atrophy and decline in memory and global cognition although there was no correlation between levels of s*TREM2* and ApoE.¹¹⁰ Taken together, these results suggest that the increased immune response associated with higher levels of s*TREM2* attenuates the negative effect of the *APOE* ϵ 4 allele and may affect both A β accumulation and tau phosphorylation.

Further insight into the association of s*TREM2* levels with A β and tau came from the stratification of ADNI participants by AT(N) categories (operationalized as A β status and a combined tau and neurodegeneration status) within clinical stage (based on Clinical Dementia Rating Sum of Boxes [CDR-SB] score) to mimic disease progression.¹¹¹ Preclinical A β deposition was associated with an initial decrease in s*TREM2*, but subsequent tau pathology or neurodegeneration was associated with increased s*TREM2*. The early decrease in levels was unexpected given previous findings of increasing levels across diagnostic stage. However, a similar AT(N) staging approach examining a wider range of CSF immune response markers found a similar biphasic pattern of an initial decrease with the appearance of early A β pathology and the subsequent increase after the appearance of tau abnormality (Figure S15 in supporting information).¹¹² This pattern was observed in both the ADNI and PREVENT-AD (Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease) cohorts, even though CSF immune markers mostly differed between the two cohorts, and despite the overall direct correlation of some of the markers with CSF tau/A β 42. The mechanisms underlying the initial decrease in immune response are yet to be determined, but these results are consistent with an effect of immune response only after the appearance of both A β and tau pathology.

Further support for this framework comes from a study of the protective effect of a rare coding variant (p.P522R) in the gene encoding phospholipase-C- γ 2 (*PLCG2*), highly expressed in microglia.¹¹³ Its protective effect on AD risk was mediated by CSF p-tau181 and was strongest in MCI participants with low CSF A β 42. Co-expression analysis identified a network enriched in innate immune system proteins connecting *PLCG2* to *APOE* and *TREM2*.¹¹³ Taken together, these results support a role for p.P522R in reducing AD risk by mitigating tau pathology through reduction of A β -induced inflammation.

Overall, these studies are coalescing around the model of a key role of innate immune response in AD in which this response exerts its effect after the establishment of both A β and tau pathology. The importance of this response is underscored by the strong deleterious or protective effects of AD risk alleles such as *TREM2* and *PLCG2*, and supports the addition of a biologically relevant “immune dysfunction” category to AT(N) staging.

3.4 | The role of resilience

ADNI data have been used to study the effects of both cognitive and brain resilience. An elder with high cognitive resilience has better cognitive abilities than would be expected for their levels of AD pathology, whereas an individual with high brain resilience has higher than expected brain structure/function for their levels of AD pathology.¹¹⁴ Cognitive resilience has been measured in several ways, primarily using years of education as a lifestyle proxy. However, even though education was associated with increased cognition in MCI and AD participants, it did not moderate the effects of CSF A β 42, CSF tau, or atrophy on cognitive function, suggesting that it may not function as a proxy for cognitive resilience.¹¹⁵ Similarly, duration of education was not associated with A β deposition or brain metabolism in any clinical group and was associated with larger total brain volume only in MCI participants.¹¹⁶ Different measures of cognitive resilience have better established its impact on AD disease progression. When cognitive resilience was represented by a residual term that captured the difference between observed cognitive performance and that predicted by demographics and brain integrity measures, it predicted decline in executive function only in participants positive for CSF t-tau/A β 42.¹¹⁷ This supports an AD pathology-dependent effect of cognitive resilience that is not operative in normal aging.

Greater brain resilience, calculated from the difference between the expected and actual amount of cerebral damage (whole brain, temporoparietal, or hippocampal volume, or global WMH volume) of an individual based on their cognition (ADAS-Cog), was associated with lower risk of progression, and slower decline in both memory and executive function in MCI and CU participants, but with more rapid decline in AD participants (Figure S16 in supporting information).¹¹⁸ This paradoxical finding may represent a masking effect of brain resilience in the face of the accrual of pathology during CU and MCI, followed by a subsequent rapid decline in AD after a point at which pathology "outpaces" resilience. Participants with high and low brain resilience may reach the endpoint in the same timeframe, explaining the accelerated rate of decline in AD patients with high brain resilience.

If the effect of resilience is specific to AD rather than normal aging, what is its biological basis? As discussed in Section 3.3, CSF proteins with vascular, lipid-metabolic, and immune system functions explained substantial variance between observed cognitive scores and those predicted by the level of AD biomarker abnormality.¹⁰⁷ These may impact resilience through mechanisms such as the maintenance of brain regions important in cognition, resilience to pathological changes, and resistance to pathological changes (Figure 7).¹¹⁹ A resilience signature comprising a pattern of higher glucose metabolism in the anterior cingulate cortices and anterior temporal poles was identified in A β + participants aged 80 and older who were cognitively stable for 5 years or more.¹¹⁹ This signature, but not glucose metabolism, A β PET, or cortical thickness in AD-typical regions, predicted global cognition. Moreover, higher FDG PET uptake in this signature was associated with lower vascular risk, suggesting a role for vascular health in maintaining resilience residing in regions beyond those associated with AD.

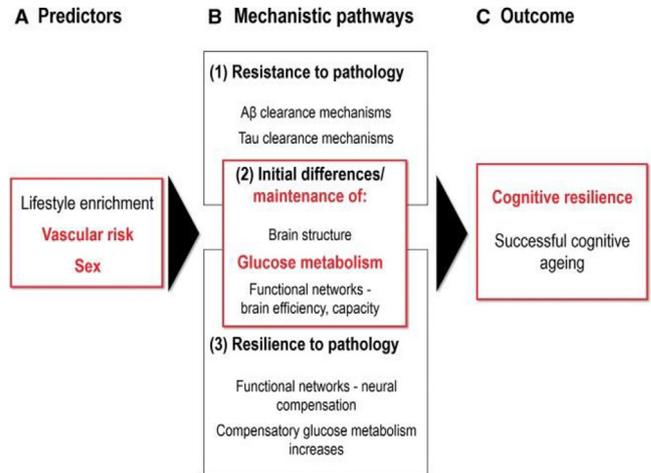


FIGURE 7 Paths to cognitive resilience or successful cognitive ageing. A β , amyloid- β . Reproduced with permission from Arenaza-Urquijo et al.¹¹⁹

Resilience may also lie in the maintenance of functional and structural connectivity. In CU participants, greater internetwork functional connectivity primarily between the default mode network and dorsal attention network attenuated the association between A β burden and memory decline.¹²⁰ The opposite relationship was observed in MCI participants, suggesting that reordering of internetwork connections may compensate for the effects of A β deposition early in disease progression but fail in the face of increasing pathology.¹²⁰ MCI non-converters and those without AD pathology had hyperconnectivity between the entorhinal cortex and hippocampus, sites of early A β and tau accumulation, whereas MCI converters and those with AD pathology, and AD participants had hypoconnectivity between these regions, supporting a compensatory role for increased regional functional connectivity.¹²¹ Greater global functional connectivity of the left frontal cortex, a major hub within the frontoparietal control network, was associated with better than expected memory in the face of neurodegeneration and so functions as a measure of reserve capacity.¹²² Higher between- and within-network connectivity in this region was unaffected by entorhinal tau or A β binding but interacted with entorhinal tau PET uptake to attenuate the negative effects of tau on memory performance.¹²² Similarly, resilience was associated with preservation of small world network organization in the brain's structural connectome.¹²³ In A β + CU participants, better-than-expected cognitive performance was associated with increased gray matter (GM) volume and WM connections of hub-like regions. Both studies implicate preservation of structural and functional brain networks as likely mechanisms for resilience.

A large genetic analysis of multiple cohorts including ADNI identified genetic variants and biological pathways associated with a combined resilience metric consisting of educational attainment and residuals of cognitive measures independent of A β status.¹²⁴ The metric was genetically correlated with educational attainment, a range of neuropsychiatric phenotypes, hormonal traits, and smoking-related factors, but not with AD or APOE. For example, genetic risk for

obsessive-compulsive disorder, old age at first birth, and at initiation of smoking were associated with high resilience whereas higher age of smoking cessation and cigarettes per day, and attention deficit hyperactivity disorder were associated with lower resilience. Top variants associated with the metric were upstream of *ATP8B1* on chromosome 18. *ATP8B1* encodes aminophospholipid transferase, an enzyme involved in the bile acid homeostasis in the liver, and additional analysis found that higher levels of two bile acids was associated with lower resilience. Finally, pathway analyses identified molecular pathways involving branched chain fatty acids and dehydrogenases, suggesting that deficits in their metabolism influence resilience. Together, these results suggest key contributors to resilience include educational attainment, vascular and metabolic risk, bile acid homeostasis, and mental health.

These results point to the contribution of vascular, metabolic, or immune-related factors acting via multiple mechanisms in maintaining cognition in the face of AD pathology until the point of failure, beyond which there is a rapid decline to cognition commensurate with AD pathology.

3.5 | Sex effects in AD

Biological sex is a critical variable for consideration in AD. More than 65% of Americans with AD are women¹²⁵ and being female is one of the strongest predictors of AD. This increased risk may be caused by genetic factors, exposure to ovarian hormones, environmental factors, differences in resilience, or some combination thereof that contributes to AD-related pathological changes,¹²⁶ although the most significant factor in greater dementia prevalence in women versus men is likely greater life expectancy. ADNI has contributed to understanding of the nature of sex-related differences in dementia risk, particularly through the availability of tau PET imaging data and serum samples for metabolomics analyses.

MCI participants stratified as being either high or low likelihood for MCI due to AD by CSF t-tau/A β 42 showed clear sex differences in cognitive decline over up to 10 years.¹²⁷ MCI females at low risk had the smallest rates of decline in cognition but those at high risk far exceeded all other groups in decline (Figure S17 in supporting information). This study also reported an additive effect of sex and the carriage of the *APOE* ϵ 4 allele on cognition such that female carriers declined faster than male carriers, consistent with previous reports of a greater adverse effect of *APOE* ϵ 4 in women than men. However, the sex-specific associations of *APOE* ϵ 4 with AD-related markers may vary across diagnostic groups. In CU men but not women, *APOE* ϵ 4 was associated with smaller hippocampal volume and hypometabolism. There were no sex differences in the associations of this allele at the MCI stage, suggesting that the effects of *APOE* ϵ 4 manifest themselves at a later stage in women than men. In AD, *APOE* ϵ 4 was associated with greater A β burden in men only. A second study reported that sex modulated the relationship between *APOE* ϵ 4 and brain tau deposition primarily in the entorhinal cortex, amygdala, and parahippocampal gyrus in MCI participants such that female carriers had a greater susceptibil-

ity to the accumulation of neurofibrillary tangles than male carriers.¹²⁸ As *APOE* ϵ 4 is commonly used for participant stratification in clinical trials, failure to account for sex differences in its effect across disease progression may complicate interpretation of results.

Vulnerability to tau deposition may underlie susceptibility to AD in women. The *APOE* ϵ 4 allele was more highly associated with CSF tau levels in women than in men, suggesting that the sex-specific effect of *APOE* on AD risk acts via tau.¹²⁹ The availability of tau PET data from ADNI has facilitated studies of the effect of sex on in vivo tau binding. In CU and MCI women but not men, significantly higher tau PET SUVR across multiple cortical regions was associated with faster cognitive decline.¹³⁰ Compared to CU men, CU women had higher A β -dependent tau accumulation in primarily temporal regions¹³⁰ and increasing A β burden was associated with higher tau binding in the entorhinal cortex but not in extratemporal regions.¹³¹ These results suggest that A β -dependent entorhinal cortical tau accumulates in a female sex-specific manner early in disease progression. It would be expected that this degree of pathology would impact early cognitive decline, but in fact a verbal memory advantage for CU women is well documented and may be related to sex-specific reserve. Despite higher florbetapir SUVR uptake, CU women had higher verbal memory scores than men, and A β + women had higher than expected verbal memory scores for their level of tau pathology. At autopsy, this sex advantage was observed at the earlier Braak stages I/II and III/IV, but no sex differences in verbal memory were observed at late stages V/VI. Interestingly, sex-specific differences in tau propagation across the brain were observed using tau-PET to construct tau connectivity networks.¹³² The most striking difference was that widespread tau PET uptake increased from CU to MCI to a much greater extent in women than men. In MCI women, the tau network was dense with a high number of direct connections between individual brain regions and may have developed from differences in network nodes at the CU stage (Figure 8). The maintenance of female verbal advantage despite the more "advanced" tau network in CU and MCI women underscores the importance of reserve in maintaining cognition at the early stages. Eventually, greater numbers of interregional tau network connections may accelerate the spread of tau and explain the faster progression of women from MCI to AD.¹³² The *APOE* ϵ 4 allele may modulate tau accumulation in different regions, although studies have been inconsistent.^{130,131,133} These results suggest that there is not only a female-specific vulnerability to tau in temporal regions such as the entorhinal cortex, but a female-specific reserve able to overcome early tau load to maintain verbal memory. Tau deposition and changes in network structure may eventually overcome mechanisms of reserve and lead to a rapid decline in memory, resulting in women "catching up" with men in tau distribution and memory impairment in AD. Hormonal differences may underlie the greater vulnerability to tau pathology in women. Lower testosterone levels were associated with higher CSF p-tau181 levels, especially in *APOE* ϵ 4 carriers, regardless of sex.¹³⁴ The lower testosterone levels typically found in women may therefore predispose them to pathological tau, and this vulnerability may be worse in female *APOE* ϵ 4 carriers.

What are the mechanisms underlying the effect of sex, alone or in combination with the *APOE* ϵ 4 allele, in disease progression? Framing

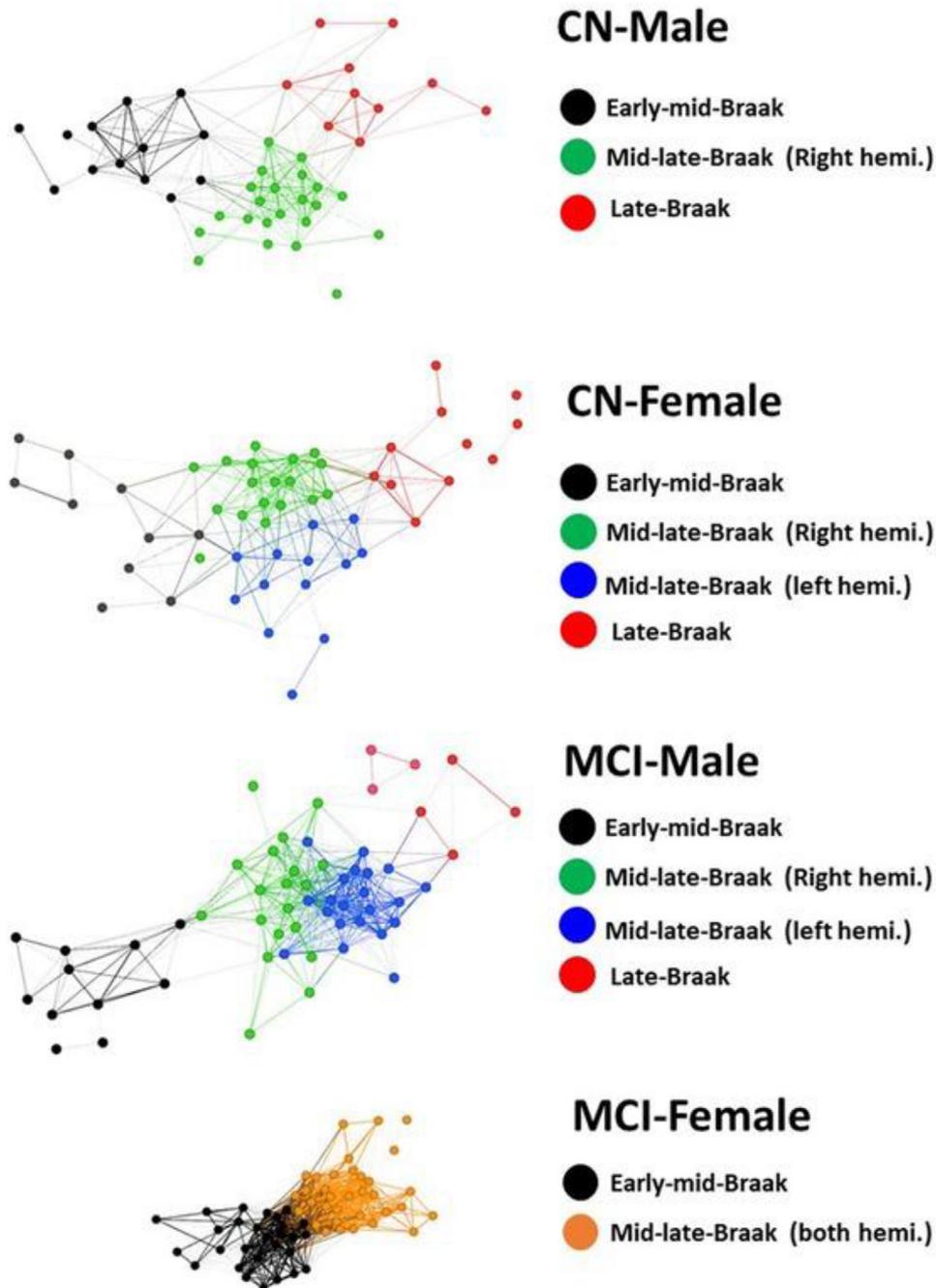


FIGURE 8 Sex differences in tau-based brain networks in four subject groups. Each node represents a brain region. The position of each node within the network is determined based on the strength of its PET SUVR correlations with other nodes. Regions that have higher PET correlations with each other than with the rest of the brain congregate to each other as communities depicted with different colors. CN, cognitively unimpaired; hemi., hemisphere; MCI, mild cognitive impairment; PET, positron emission tomography; SUVR, standardized uptake value ratio. Reproduced with permission from Shohouki et al.¹³²

AD as a metabolic disease, a recent study investigated how these factors affect associations between AT(N) biomarkers (CSF A β 42, CSF p-tau181, FDG PET) and metabolites.¹³⁵ From 139 blood metabolites tested, the study identified and replicated 8 homogeneous (the same between sexes), 15 heterogeneous (differed by sex), and 3 sex-specific interactions with AT(N) biomarkers (Figure S18 in supporting information). Metabolites adversely affected in females were predominantly involved in energy metabolism (acylcarnitines, valine, glycine, proline)

or energy homeostasis (asparagine, glycine, proline, histidine), suggesting that impaired mitochondrial energy production may play a role in the greater susceptibility of women to AD pathology. Further stratification of participants by APOE ϵ 4 status identified associations of three phosphatidylcholines with pathological CSF A β 42, acylcarnitine C10 with CSF p-tau181, and proline with FDG PET in females only, suggesting a molecular basis for the adverse effects of APOE ϵ 4 in females.

Overall, these studies suggest that differential A β -dependent tau deposition, and mechanisms of reserve may contribute to sex differences in disease progression. Failure to account for the effect of these sex differences through disease progression could complicate interpretation of trial data. An additional topic for future research is the interaction between sex differences and aging and the ADNI database provides information that could be used to address this.

4 | TESTS FOR AD

Effective testing for AD in an array of settings—clinical, research, or trial—is fundamental to progress in understanding disease progression and treatment. ADNI cohorts have been instrumental in the development, replication, and external validation of improved or new approaches. Many studies have focused on the measurement of brain A β , as the initial pathology in the biological definition of AD. This can be detected in vivo as CSF A β 42, or by A β PET. CSF A β 42 has excellent accuracy, but lumbar puncture is invasive, and MRI or PET scans are expensive and may have limited availability in remote communities. Recent publications have focused on improving traditional measures and developing low-cost and/or noninvasive alternative measures of A β , or reported improved tests for tau or for combinations of pathology. Development of ultrasensitive blood tests for AD has been a particular highlight.

4.1 | Improvements to measurement of CSF A β and A β PET

Although CSF A β 42 and A β PET are highly correlated,¹³⁶ they cannot be considered equivalent. CSF A β 42 measures a soluble form of A β , which may reach abnormality in individuals at a different point in disease progression than the cortical fibrillar forms of A β detected by A β PET.¹³⁷ Moreover, A β PET uses different radiotracers (¹¹C-PiB, ¹⁸F-florbetaben, ¹⁸F-florbetapir, or ¹⁸F-flutemetamol) and scans are commonly interpreted using cohort-specific cut points for A β status. Underscoring these differences, examination of simultaneous longitudinal trajectories of A β PET and CSF A β 42 suggested that the CSF measure becomes abnormal prior to abnormality on A β PET, but that abnormality on A β PET better predicts cognitive decline.¹³⁸

The false equivalence of A β status determined by a variety of methods can hamper the development of prediction models, and therefore the development of a set of universal and generalizable thresholds for A β positivity in both methods of measurement is crucial. The CL method enables the direct comparison of A β radiotracers by representing tracer SUVR on a 0 to 100 scale.¹³⁹ Two inflection points in A β deposition were observed in a study deriving optimal CL thresholds in CU participants.⁶⁴ The first at 12 CL predicted CSF A β 42 positivity and may represent the early transition to subtle A β pathology, and the second near the threshold established by visual raters at \approx 30 CL predicted CSF tau/A β 42 and is consistent with the transition to widespread A β pathology. Multi-tracer staging models of A β binding may also circum-

vent the use of cohort-specific global SUVR cutoffs and detect sub-threshold A β abnormality.^{36,34}

The measurement of CSF A β 42 is affected by pre-analytical and analytical variables, an issue partially overcome by the ADNI Biomarker Core's use of the Roche ElecSys platform. CSF immunoassays of A β 42, p-tau181/A β 42, and t-tau/A β 42 using this platform predicted decline in MMSE and progression to AD.¹⁴⁰ Global cutoffs were established for their concordance with A β PET SUVR-based classification.¹⁴¹ These were transferable across independent cohorts despite different PET tracers, patient populations, pre-analytical protocols, and other variables; had a high concordance with A β PET classification; and predicted 2-year clinical decline in MCI individuals. CSF biomarkers measured using the ElecSys platform and dichotomized with these cut points may therefore obviate the need for costlier and less accessible A β PET.

4.2 | Low-cost and/or non-invasive approaches for the determination of A β status

In the United States, an estimated 14.9 million patients aged 55 and over with MCI due to AD may be eligible for an anti-A β therapy, should one be approved, a number representing a huge screening challenge.¹⁴² Low-cost and/or non-invasive tests for A β status may circumvent drawbacks of CSF and PET assessments.

Several externally validated algorithms using readily available clinical information were designed to function as a primary care prescreen funneling high-risk patients toward CSF or PET confirmation of A β status.¹⁴³⁻¹⁴⁵ A practical algorithm based on age, APOE ϵ 4 status, and a cognitive test of immediate recall achieved moderate predictive ability (area under the curve [AUC] of \approx 0.7 across three cohorts) and was estimated to identify between 0.1 and 3.4 million A β + patients in the potential eligible US population, while at the same time preventing from 1.0 to 2.8 million negative A β CSF or PET confirmatory tests.¹⁴³ A similar algorithm was estimated to reduce screening PET scans for clinical trial enrichment by \approx 23%, a savings of > US\$25 million based on the enrollment of a cohort of 1000 A β + MCI individuals.¹⁴⁵ Beyond readily available clinical information, MRI scans collected in routine screening may offer an alternative noninvasive method for determining A β status. A classifier based on features selected from T1 MRI and DTI was estimated to eliminate 60% of unnecessary confirmatory PET or CSF tests in the enrollment of CU participants, reducing overall trial costs by 47%.¹⁴⁶ Other ADNI studies have developed models using demographics, APOE ϵ 4 status, cognition, 'omics data, MRI features, and other factors (Table S1). Plasma assays for A β are described in the following section.

4.3 | Blood tests for AD

Perhaps the most exciting and impactful recent ADNI studies have concerned the development of blood tests for AD. Detection of AD pathology in blood is far more challenging due to the much higher concentration of non-AD proteins, but improvements in ultrasensitive assay

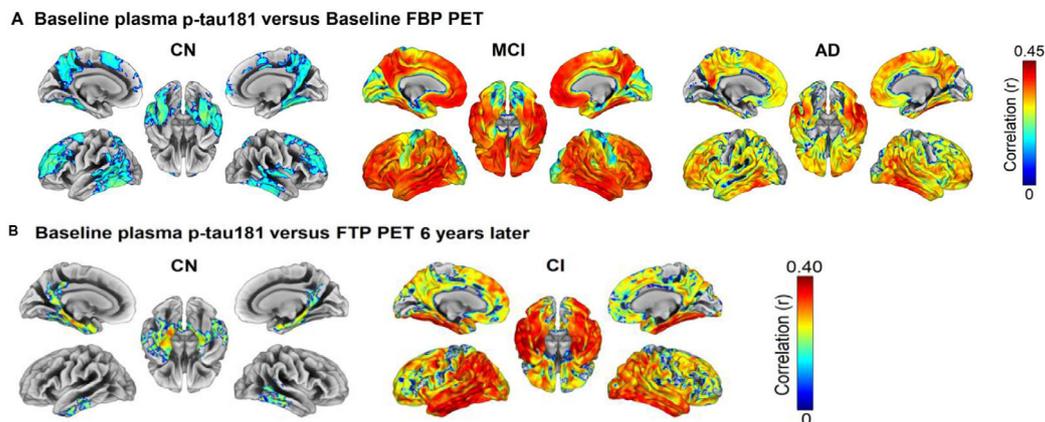


FIGURE 9 Regional associations of plasma p-tau181 with A β and tau PET. A, Regional associations between baseline plasma p-tau181 levels and baseline A β PET SUVR. B, Regional associations between baseline plasma p-tau181 levels and tau PET 6 years later. Color panels on the right display Pearson correlation coefficients r of the effects on global measures. AD, Alzheimer's disease; CN, cognitively unimpaired; CI, cognitively impaired; MCI, mild cognitive impairment; FBP, florbetapir (A β) PET; FTP, flortaucipir (tau) PET. Reproduced with permission from Moscoso et al.⁹⁷

technology now allow us to find and measure the proverbial needle in a haystack. ADNI's large, well-characterized cohort with available longitudinal plasma samples has played an outsize role in accelerating discovery and validation of plasma assays for AD. Vive la revolution!

A substantial body of work now supports the ability of ultrasensitive plasma A β immunoassays and mass spectroscopy assays to accurately and detect brain A β (reviewed in Ashford et al.¹⁴⁷). Blood samples from ADNI CU and MCI participants were used to validate a model developed in the Swedish BioFinder study that combined age, APOE groups, a cognitive test (10 word list delayed recall), and plasma A β 42/40 to predict individual brain A β (AUC of 0.83).¹⁴⁸ Although plasma A β 42/40 improved prediction only slightly, the model was calculated to reduce the number of unnecessary A β PET scans by \approx 90% in a clinical trial requiring assessment of brain A β for enrollment. Plasma A β 42/40 alone accurately predicted brain A β (AUC of 0.80 to 0.87) in a systematic assessment of blood biomarkers and clinical information, and the subsequent addition of APOE genotype or MRI features further improved prediction. A blood-based signature of CSF A β 42 developed in ADNI CU and MCI participants consisted of plasma A β 42 and three additional plasma proteins, age, and APOE genotype (AUC of 0.80).¹⁴⁹ An ongoing study funded by the Biomarkers Consortium of the Foundation for the NIH will compare a number of different immunoassays and mass spectroscopy methods for measurement of plasma A β 40 and A β 42.¹⁵⁰

As the AT(N) biological construct for AD requires not only A β , but tau abnormality, a blood biomarker that correlates with both pathological proteins and thus predicts AD is somewhat of a Holy Grail of AD research. Several ADNI studies used an ultrasensitive single molecule array (Simoa-Quanterix) assay to measure plasma p-tau181 and to investigate its associations with A β and tau pathology,^{151,152} and its ability to predict AD.¹⁵³ As a predictor of A β status, plasma p-tau181 has variable results across studies and appeared more predictive in MCI and AD than CU participants. This biomarker alone was a moderate predictor of A β status (AUC of 0.67) in MCI but not CU in one study; an accurate predictor in combination with age and sex in MCI (AUC

of 79.9) but not CU (AUC 70.4) in a second study (Figure S19 in supporting information);¹⁵³ and in a third study was associated with both A β and tau pathology measured by PET most strongly in MCI and AD, but also in CU participants.¹⁵¹ Baseline levels of plasma p-tau181 were strongly associated with widespread A β deposition in MCI and AD participants (Figure 9a).¹⁵¹ Moreover, weaker associations were detected in CU participants with subthreshold A β deposition in sites of early A β accumulation (precuneus and temporal and superior frontal regions; Figure 9a).¹⁵¹ Longitudinal and, to a lesser degree, baseline plasma p-tau181, was also associated with an AD-typical pattern of widespread cortical tau aggregation 6 years later (Figure 9b).¹⁵¹ Like CSF p-tau181, the plasma biomarker reached abnormality \approx 6 years after measures of A β .¹⁵¹ Plasma p-tau181 increased with worsening diagnostic status, and predicted MCI to AD progression, cognitive decline, and hippocampal atrophy.¹⁵³ These results validate plasma p-tau181 as a biologically relevant biomarker that accurately reflects both A β and tau pathology. It may therefore both fulfill a need for a rapid and cost-effective "first pass" test of AD in primary care that could identify patients requiring further, more expensive diagnostic tests, and enable the identification of individuals at high risk of AD for clinical trials. In addition to p-tau181, there is considerable excitement concerning other species of phosphorylated tau such as p-tau217.¹⁵⁴ As assays for p-tau181, p-tau217, and possibly others become more widely available, head-to-head comparison studies will become possible.

Neurodegeneration is the final requirement in the biological staging of AD. NFL reflects axonal injury and can be measured in blood by immunoassays. Plasma NFL levels increased linearly across diagnostic groups^{70,155} and were higher in A β + than A β - participants.⁷⁰ Longitudinal NFL changes were associated with longitudinal changes in a wide range of AD measures (CSF, FDG PET, GM and WM volumes, ADAS-Cog) increasing differentially across diagnostic groups in a manner consistent with disease progression. In CU participants, longitudinal NFL was more strongly associated with "early" pathological features such as low hippocampal volume and lower CSF A β 42, whereas an association with ADAS-Cog was predominant in AD participants.⁷⁰ Distinct

NfL trajectories were observed in participants stratified by AT(N) status, CSF A β 42 status, CSF p-tau181 status, or the status of a temporal cortical atrophy composite (Figure S20 in supporting information).⁷⁰ Plasma NfL was associated with AD-typical regions of A β PET uptake in CU but not in MCI participants, and of tau PET uptake in MCI but not CU participants.¹⁵⁵ In CU participants, plasma NfL was associated with hippocampal and frontal lobe atrophy in APOE ϵ 4 carriers only, whereas in MCI participants, was associated with widespread GM atrophy regardless of APOE ϵ 4 status.¹⁵⁵ These differential associations of plasma NfL with AD markers at distinct diagnostic stages suggest that it may be a marker of A β -related neuronal injury prior to symptom onset, but of tau-related neuronal injury when cognitive impairment becomes apparent. As such, plasma NfL may be a cost-effective marker with which to monitor effects on neurodegeneration in disease-modifying drug trials.

Could plasma markers of AT(N) replace the equivalent CSF markers or PET for the prediction of future decline? The ability of plasma A β 42/40, p-tau181, and NfL to predict progression of MCI participants to AD in 4 years or decline in MMSE in MCI participants over the same timeframe was systematically studied in the BioFINDER and ADNI cohorts. The best performing models included p-tau181 and NfL, but not A β 42/40, likely reflecting the tighter association of tau than A β with cognition. This combination of plasma biomarkers improved the 4-year prediction of MCI to AD dementia progression over a base model of age, sex, education, and baseline MMSE and was comparable to a model including CSF A β 42/40, p-tau181, and NfL (AUCs of 0.88 to 0.89 in replication, and 0.73 to 0.79 in external validation). This model was operationalized as an online tool available at predictprogression.com that provides an individualized 4-year prognosis for MCI to AD dementia progression or MMSE decline.

Other factors in blood associated with A β or tau pathways or with additional contributors to disease progression, were reported to have predictive value. Plasma-based expression of genes predominantly related to vascular structure/functioning and immune system response predicted diagnosis, clinical progression, and decline in executive function and memory, and was associated with A β , tau, and infarcts.²⁴ Similarly, the expression of AD-related genes enriched with inflammation, Wnt signaling, and mitochondrial pathways discriminated AD from CU patients (AUCs of up to 0.86).¹⁵⁶ A brain metabolite signature of AD had a similar accuracy for the same classification challenge, and a subset of four sphingomyelins were associated with increased risk of progression in CU individuals.¹⁵⁷ The selected lipids were involved in pathways that are directly related to AD pathology such as tau phosphorylation and A β metabolism, but also in apoptosis, acetylcholine biosynthesis, and calcium homeostasis. An expanded lipidomics platform allowed the characterization of a lipid signature of AD that improved both the diagnosis of AD dementia and prediction of future onset of AD dementia over a base model of age, sex, BMI, and APOE ϵ 4 genotype.¹⁵⁸ The 10 most predictive lipids included ether lipids, and sphingolipids previously associated with AD as well as phosphatidylethanolamines and triglycerides associated with cardiometabolic disease. Long chain polyunsaturated fatty acid containing triglycerides were associated with MCI and AD, hippocampal volume,

and entorhinal cortical thickness, and were more highly associated in APOE ϵ 4 carriers.¹⁵⁹ Finally, a peripheral signature of AD risk containing plasma markers of cardiovascular health, immune and inflammatory systems, hormone levels, and lipid metabolism outperformed brain features when combined with CSF biomarkers to predict diagnostic progression.¹⁶⁰ These approaches offer complementary information to plasma AT(N) biomarkers and have the potential to fine-tune the prediction of future decline. They may be particularly relevant if additional categories reflecting, for example, vascular or immune system dysfunction were added to AT(N) staging.

5 | DEVELOPMENT OF TOOLS TO IMPROVE CLINICAL TRIALS AND CLINICAL PRACTICE

The structure of ADNI as a simulated clinical trial with clearly defined inclusion and exclusion criteria and a wealth of longitudinal data and samples has made it an ideal testing ground for novel approaches to improve clinical trials and to fulfill its primary objective. As an ancillary benefit, ADNI data have also been used in studies aimed at improving patient diagnosis and management in clinical practice. In many cases, these improvements are informed by knowledge gained from the disease progression studies described in previous sections.

5.1 | Clinical trials of prodromal AD

A substantial proportion of clinical trials are targeted at nondemented but symptomatic MCI participants. The design of the ADNI study has enabled the simulation and quantification of various approaches for more targeted participant selection and outcome measure refinement and for overcoming other trial challenges.

Prodromal AD trials commonly incorporate a biomarker of A β as an inclusion criterion, in keeping with its position as the earliest AD biomarker, but the choice of CSF or PET biomarker may be crucial. Low CSF A β 42 as an eligibility criterion enrolled 15% more MCI participants than A β PET, consistent with disease progression studies positioning this CSF biomarker abnormality earlier than the cut point for cortical A β burden.⁶³ However, few clinical trials of MCI have broadened selection criteria to include additional AT(N) biomarkers, which could target an expanded pool of participants likely to benefit from intervention. An alternative selection criteria of high CSF p-tau181/A β 42 or p-tau181 was estimated to enroll an additional 15% of MCI participants over CSF A β 42 alone.¹⁶¹ Furthermore, machine learning-based selection of MCI participants using a combination of A β PET, CSF biomarkers, FDG PET, and MRI volumes in an externally validated model reduced sample sizes to detect a treatment effect by 50% to 75% over selection with A β PET alone, depending on trial power, duration, and cognitive outcome measure.¹⁶² These studies therefore suggest that AT(N) biomarkers can select a broader pool of participants further along the AD continuum with a high likelihood of decline than A β alone.

Determining the timeframe of progression to AD is important for clinical trial design. Faster neurodegeneration might be expected to

lead to earlier diagnostic progression, but a recent study suggests otherwise.¹⁶³ Using 10 years of follow-up ADNI data, both baseline global and regional volumes, and annual change rates in the same regions significantly predicted time to AD progression but atrophy rate depended on baseline volume. For example, all MCI participants with low baseline hippocampal volumes converted to AD within 3 years, but in those with high baseline volumes, the rate of hippocampal atrophy determined time to progression (Figure S21 in supporting information). Consideration of baseline volume may therefore improve detection of a treatment effect in clinical trials that use reduction in atrophy rate as an outcome measure.

Other issues may affect the ability of a clinical trial to detect a treatment effect. The ADAS test is a common outcome measure used in clinical trials of MCI and AD, but it is susceptible to practice effects which manifest as a stable or improved score instead of a declining score over time. A meta-analysis of 18 clinical trials and observational studies reported that more than half of MCI participants and more than a third of AD participants had practice effects in ADAS, resulting in an increase in the estimated sample size per arm to detect a treatment effect of up to 35%.¹⁶⁴ Failure to account for practice effects in clinical trial design may therefore result in underpowering. Another common issue is whether to include or exclude observations from the up to 10% of MCI placebo patients who initiate AD medications such as donepezil or memantine after the start of the trial. Modeling the use of medications in ADNI as a simulated trial revealed that MCI participants who began concurrent medication were at a more advanced stage and declined faster despite treatment than those who did not. Excluding these participants would result in a placebo arm that declined more slowly and was not representative of the trial population, decreasing the power to detect treatment effects.

5.2 | Clinical trials of preclinical AD

AD clinical trials aimed at targeting A β pathology in the preclinical phase have posed numerous challenges regarding the selection of asymptomatic participants and the development of outcome measures able to detect a treatment effect. ADNI studies have capitalized on knowledge gleaned from disease progression studies to detect the earliest A β deposition and subtle changes in memory, and to characterize how these changes predict progression to symptom onset. A multicohort study¹⁶⁵ of preclinical AD participants designed to update clinical trial assumptions estimated that the average time to progress to MCI was 6 years, and that to detect a 25% treatment effect with 80% power would require 2000 participants per arm. Likewise, a stochastic model developed using ADNI data that took into account the rates of CU to MCI and MCI to AD dementia progression, and the rates of withdrawal from clinical trials at each diagnostic state provided guidance for clinical trial design.¹⁶⁶ The model suggested that treatments of moderate efficacy would require trial durations of at least 5 years, and that trials in CU individuals would be more successful when treatments are effective immediately. However, this preliminary model did not examine participant selection strategies or surrogate outcome mea-

asures that can substantially increase the power trial to detect a treatment effect. Both studies suggest that clinical trials of preclinical participants would need to be lengthy and large to succeed.

Subthreshold regional cortical A β accumulation in the precuneus and posterior cingulate cortex was calculated to reduce sample sizes by \approx 60% over global A β PET SUVR in CU A β - participants enrolled in a primary prevention trial. Estimated sample sizes for a secondary prevention trial enrolling CU A β + participants were similar using both selection criteria, suggesting that the early A β composite may be valuable in trials of participants with minimal A β deposition and accumulation over the trial timeframe. A pattern of WMHs across the superior frontal and parietal regions was associated with future A β accumulation and may offer a practical alternative to identifying early A β accumulators without the need for an A β PET scan or lumbar puncture. Finally, an A β PET-based regional staging method¹⁶⁷ better predicted progression from CU to MCI than binary cortical A β (hazard ratio of 4.8 for the highest stage compared to 3.1 for binary A β ; Figure S22 in supporting information).

Predicting the time to onset of symptoms or diagnostic progression in CU individuals, rather than predicting progression within a certain timeframe, is also a challenge given the extended preclinical AD phase. Such a tool would allow the enrollment of participants who are most likely to convert to MCI within the duration of a clinical trial. Structural MRI measures in the posterior cingulate, lateral temporoparietal cortex, and prefrontal cortex combined with rs-fMRI connectivity features within the default, salience, and limbic networks predicted > 20% of the variance in estimated time to symptom onset in participants with a parental history of AD in the PREVENT-AD cohort and years to diagnostic progression in ADNI participants.¹⁶⁸

Early cognitive decline in PACC increased risk for progression to MCI and worsening function,¹⁶⁹ and was associated with faster A β accumulation and entorhinal cortical thickening¹⁷⁰ in preclinical AD individuals, demonstrating its "clinical meaningfulness." Even more subtle cognitive decline linked to subthreshold A β accumulation may offer an alternative to CSF A β 42 or A β PET in determining A β status. Poor baseline performance on either the PACC or ADNI-Mem cognitive tests was associated with increased odds of progression to A β positivity in CU A β - participants.¹⁷¹ A particularly sensitive measure of subtle cognitive decline may be "process" errors such as an increased susceptibility to interference, a greater frequency of intrusion errors in the delayed recall test, or a flattening of the learning slope.¹⁷² Process errors, particularly word list intrusion, better predicted progression to MCI than existing criteria for subtle cognitive decline,^{172,173} predicted worsening CDR scores,¹⁷³ and were associated with changes to CSF biomarkers.¹⁷² Variability in an individual's performance across multiple measures or in a single testing session may be another indicator of early cognitive changes. Increased intra-individual variability was associated with elevated odds of progression to MCI comparable to CSF biomarkers,¹⁷⁴ and with lower WM integrity in multiple brain regions,¹⁷⁵ increased hippocampal and entorhinal cortical atrophy,¹⁷⁶ and functional decline.¹⁷⁶ Intra-individual variation may therefore be a sensitive measure of future decline that is not confined by cognitive measurements against population averages.

Early neuropsychological breakdown may also be indicated by self-reported and study partner-reported subjective memory concerns (SMCs; measured by the Everyday Cognition test). In CU individuals, baseline study partner SMCs outperformed the self-report measure in predicting baseline cognition and cognitive decline across multiple domains.¹⁷⁷ In A β + CU individuals, baseline self-report and study partner Everyday Cognition test scores both predicted decline in ADAS13, but study partner reporting became increasingly predictive over time, likely reflecting decreasing self-awareness of the participant, and increasing awareness of functional difficulties by the study partner.¹⁷⁸ Similarly, baseline self-report Everyday Cognition test outperformed study partner reporting in the prediction of diagnostic progression of preclinical participants to MCI.¹⁷⁷ In this group, self-report SMCs were associated with tau binding in frontal regions involved in conscious thought, whereas study partner SMCs were associated with tau binding in parietal regions linked to memory concerns likely apparent to an observer.¹⁷⁹ Study partner and self-report SMCs may therefore provide complementary information and be practical screening tools to identify CU participants, particularly those with A β pathology, at risk of future cognitive and clinical decline.

Tau PET is a potential surrogate outcome measure for preclinical trials in which cognitive endpoints are difficult to measure as A β -dependent tau deposition is closely linked to cognitive decline. However, preclinical tau accumulation is typically a slow process occurring over many years and its measurement is difficult in a clinical trial timeframe, requiring a large sample size to achieve the necessary trial power. The enrollment of CU participants with global A β PET CL of > 68 CL, a level of A β deposition usually associated with MCI and AD participants, reduced sample sizes nearly 10-fold over CU participants with A β PET CL of between 22 and 67 for a trial with an AD meta-ROI in tau PET as an outcome measure.

5.3 | Assessing an individual's risk of progression

The ability to predict an individual's risk of clinical progression in non-demented patients is highly desirable. This differs from simply testing for AD in that it does not predict AD pathology, but rather the probability of progression within a given timeframe, a difficult challenge given the heterogeneity of disease courses and biomarker levels. Numerous studies have capitalized on ADNI's longitudinal data set, now spanning 15 years, to develop or validate a variety of prognostic approaches, some grounded in the AT(N) biological construct, and others exploring the predictive ability of additional contributing factors. ADNI has also been instrumental in the external validation of prediction models, a crucial step in the development of clinically applicable techniques that must be generalizable across diverse populations and cohort designs, and for different biomarker measurements and methods.¹⁸⁰

An 11-year follow-up study of ADNI MCI participants found that individual CSF biomarkers, imaging measures, and cognitive tests predicted clinical progression to AD.¹⁸¹ As in participant selection for clinical trials, a broader range of biomarkers reflecting AT(N) outperformed A β positivity alone, which was not highly predictive with one third of

A β + MCI remaining stable throughout the study timeframe.¹⁸¹ Participants with MTL atrophy, AVLT impairment, and an abnormal CSF t-tau/A β 42 ratio had the highest hazard ratio of 15.1 for progression, and progressed to AD within a median of 1.3 years compared to > 11.5 years for those in the normal range for these risk factors, suggesting that combinations of AT(N) biomarkers provide complementary information.¹⁸¹ A similar prognostic model comprising age, sex, MMSE, CSF A β 42, CSF p-tau181, and hippocampal volume as continuous rather than dichotomized markers was externally validated across several cohorts including ADNI.¹⁸²

A previously developed AT(N) model that stratified MCI participants by percentile into those with good, very good, poor, or very poor prognoses was externally validated across several single-center and multi-center cohorts including ADNI and outperformed models based on demographics, hippocampal volume, or CSF biomarkers alone (Figure 10).¹⁸³ This model was operationalized into a spreadsheet calculator intended to facilitate personalized medicine that takes into account the platform used for CSF analysis and method used to calculate hippocampal volume and provides an estimate of the probability of progression to AD dementia based on individual risk factor availability (more information at: <https://www.alzheimercentrum.nl/professionals/adappt-contact>).

Factors beyond AT(N) contribute to disease progression, and therefore their inclusion may improve prediction. Two studies focused on developing practical tools for clinical screening that included measurements reflecting vascular injury. The first tested the use of not only hippocampal atrophy, cortical atrophy, and ventricular enlargement but small vessel disease in MCI diagnostic progression.¹⁸⁴ Each imaging factor was quantified visually and combined in a comprehensive visual rating scale that outperformed individual subscales. This method has the advantage of requiring only brain MRI, which may be routinely acquired, and may funnel individuals toward more expensive or invasive confirmatory analyses. A second study calculated the 10-year absolute risk of developing AD based on a simple model consisting of age, subjective memory decline, the need for assistance with finances or medication, and a history of symptomatic stroke.¹⁸⁵ This model was developed in the Rotterdam study and externally validated in two cohorts including ADNI, and assigned overall risk based on scores in each component factor, making it suitable as an initial screening test in primary care (Figure S23 in supporting information). An extended model that added APOE status, cognitive scores, and imaging data improved prediction and was intended for interpretation by neurologists in specialized clinical care. Given the highly educated, predominantly European composition of the ADNI cohort, it must be noted that these results may not be generalizable to the wider population.

5.4 | Methodological improvements to automated diagnosis and prognosis

Automated diagnostic approaches that use machine learning algorithms, in particular deep learning strategies,¹⁸⁶ to extract and combine information from multiple modalities have the potential to aid

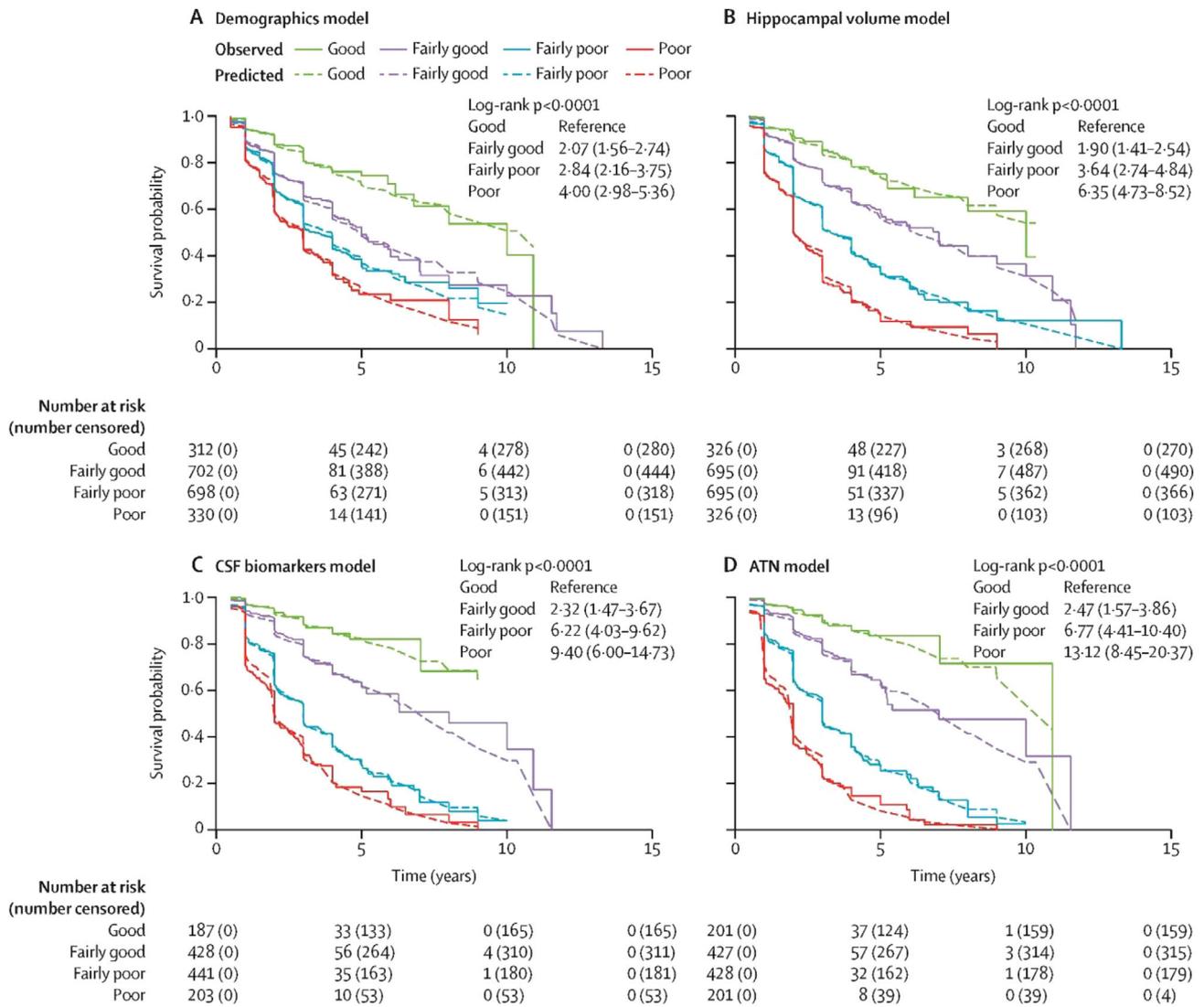


FIGURE 10 Survival curves for biomarker-based models of decline. Observed progression is analyzed by Kaplan-Meier whereas predicted progression is analyzed with Cox models. Findings are based on data from four cohorts. ATN, amyloid, tauopathy, and neurodegeneration; CSF, cerebrospinal fluid. Reproduced with permission from van Maurik et al.¹⁸³

clinicians in making an accurate and timely diagnosis of AD. However, barriers remain to their incorporation into clinical practice including a lack of objective comparison of methods and a lack of reporting of classifier generalizability in external cohorts. Although many studies have used the ADNI data set to test or validate their machine learning approaches (reviewed in Veitch et al.⁶), it has been difficult to objectively compare results because of differences in patient subsets, imaging preprocessing pipelines, feature selection and machine learning methods, statistical methods for cross-validation, and reported metrics. Two recent works have sought to overcome some of these barriers. Longitudinal atrophy rates measured using MRI are powerful predictors of future decline. A multi-atlas automated segmentation method applied to baseline and follow-up MR images was used to develop a morphometry database that removes some of the variability in image preprocessing.¹⁸⁷ This database is available to the research community to allow direct comparison of MRI-based machine

learning frameworks. Another issue with publicly available data sets is their continual incorporation of new participants whose images may be processed using updated methods. A framework that accounts for new participants, and additionally uses a modular set of preprocessing pipelines and feature extraction methods was developed to allow the reproducible evaluation of machine learning algorithms for AD prediction.¹⁸⁸ MRI and FDG PET data were automatically converted into a standard format using this framework, which enabled comparison of the influence of methodological differences and the two imaging modalities across multiple cohorts. Classifiers developed using this framework were generalizable to external cohorts and the framework is publicly available at: <https://gitlab.icm-institute.org/aramislab/AD-ML>.

A lack of transparency of automated methods that produce a prediction without providing information on underlying diagnostic decisions to the clinician can also hinder its clinical use. A deep-learning strategy

that predicted AD status from non-imaging data such as demographics and MMSE score, or MRI data, or a combination of both, generated interpretable visualizations of the probability of AD in a cerebral morphology map¹⁸⁹ (Figure S24A in supporting information). Models were developed in ADNI and validated across three independent cohorts, consistently outperforming diagnoses by clinical neurologists (Figure S24B). The generalizability of the framework and its presentation for neurologists as an intuitive graphic interface address key issues with automated clinical diagnosis.

Several MRI-based automated diagnostic approaches have been validated in ADNI. Morphological metrics such as gyrification index and cortical thickness selected from surface-based morphometry distinguished MCI from CU participants with $\approx 80\%$ accuracy, improving classification over volumetric measures alone.¹⁹⁰ The addition of DTI features from diffusion MRI representing the structural connectome selected using a novel feature ranking method improved the same classification challenge over T1-weighted MRI (AUC of ≈ 0.67).¹⁹¹ The selection of top diffusion MRI features varied considerably between cohorts, and models based on the overlap between cohorts were more generalizable, emphasizing the need for external validation of diagnosis models. Last, spatial patterns of functional connectivity selected using multivariate pattern analysis from rs-fMRI data were used to construct an extreme learning machine classifier for the automated discrimination of AD and MCI versus CU across two cohorts.¹²¹

Combining multiple modalities is a popular approach for predicting MCI to AD dementia progression because of the complementary information that each modality provides. However, it suffers from a lack of applicability to clinical settings in which the assembly of different fluid and imaging biomarkers is challenging. Therefore, constructing multimodal classifiers based on a minimum number of inputs that are generalizable across populations may help make automated classification a viable alternative to neurologist-based diagnosis. The Characterizing Alzheimer's disease Risk Events (CARE) index is an individual score based on sMRI, rs-fMRI, and cognitive tests that staged participants across disease progression without the need for CSF biomarkers. A classifier based on this index was developed in ADNI and validated in a clinical single-center study, predicting MCI to AD progression in 3 years with high accuracy.¹⁹² Finally, an MRI-based deep learning time-to-event model that was developed and validated in ADNI and Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing, accurately predicted MCI progression to AD, and was improved with the addition of APOE status, and demographic and cognitive variables.¹⁹³ Recent internally validated diagnostic and prognostic models developed using ADNI data are briefly described in Table S2.

6 | ADDRESSING ETHNOCULTURAL DIFFERENCES IN AD

Although AD disproportionately affects ethnoculturally diverse populations (e.g., Latina/o, Black/African American), these populations have

been underrepresented in AD research. A meta-analysis of nine data sets from major clinical cohort studies including ADNI¹⁹⁴ reported that their participants were 79.3% White, 11.5% Black, 5.6% Latina/o, 2.7% Asian, and 0.8% Native American. This poses a major challenge as results may not be generalizable to wider populations. This issue particularly applies to ADNI as its cohort (e.g., primarily non-Latina/o White, highly educated, few comorbidities) is highly selected as the study is designed to resemble an AD clinical trial with strict inclusion and exclusion criteria. Therefore, ADNI results alone must be interpreted with the caveat that they may have limited external validity for more diverse populations.

Of the limited available research on ethnocultural differences in AD, ADNI participants have been included for non-Latino/a White comparison groups. For instance, a study that compared a Caribbean Latina/o cohort to a cohort of non-Latina/o, including ADNI participants, found that although the APOE $\epsilon 2$ allele was protective and the APOE $\epsilon 4$ allele increased AD risk in both cohorts these effects were substantially smaller in the Caribbean Latina/o compared to the non-Latina/o White cohort.¹⁹⁵ Local European ancestry (vs. African ancestry) at APOE was associated with increased AD risk, after adjusting for the $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles, supporting the contribution of additional genetic variation at this locus.¹⁹⁵ Similarly, haplotypes linked to the APOE $\epsilon 4$ allele differed between Asian, African, and European populations and conferred differing susceptibility to AD,¹⁹⁶ and combinations of race (Korean vs. European) and APOE status affected regional and whole brain atrophy.¹⁹⁷ Carriage of the APOE $\epsilon 4$ allele affected A β SUVR cut points for positivity in non-Hispanics more than Hispanics.¹⁹⁸ Cardiovascular risk factors differentially affected cognition in Latina/o versus non-Latina/o White adults, such that hypertension and obesity were not associated with poor memory in either cohort but were associated with poorer executive function only in the Latina/o group.¹⁹⁹ Further studies are required to uncover the biological and sociocultural mechanisms underlying these effects and to determine how ethnocultural factors may impact clinical trials.

With regard to international research, the Japanese ADNI study has enabled comparison of regional variation in Asian and North American populations and to examine the feasibility of international trials.^{200,201} Despite the possible impact of cultural differences on functional end measurements²⁰⁰ and differences in APOE $\epsilon 4$ allele frequency, MCI participants in both J-ADNI and North American ADNI had similar levels of A β positivity, and decline in cognitive or functional measures. The finding that ADNI biomarkers are generalizable to this Asian population is an important step toward the international harmonization of clinical trials in AD.

7 | CONCLUSIONS

Since its inception, the overall goal of ADNI has been to validate biomarkers for AD clinical trials. This goal has been met by validating MRI, FDG PET, A β PET, tau PET, and CSF measures of A β and tau. ADNI data have been widely used by academic groups and pharmaceutical companies to design and statistically power clinical AD

trials. As this review shows, the publicly available ADNI data set has been used as a sample of convenience to investigate the use of biomarkers to predict and monitor cognitive decline across the AD continuum from CU to MCI to dementia. Data-driven models of disease progression constructed from imaging, cognitive, and gene expression data largely recapitulated the ordering of biomarkers proposed by Jack et al.,¹⁸ highlighted the very early transition to abnormality of certain biomarkers, and elucidated underlying molecular pathways. Sub-threshold, declining A β may be an early marker of future decline linked to subtle memory dysfunction. Tau PET data helped elucidate patterns of tau accumulation tied to antecedent A β deposition. Genetic analyses identified distinct gene sets underlying amyloidosis, and tau deposition and neurodegeneration. Stratification of ADNI participants using the AT(N) biological construct of AD identified multiple possible trajectories of biomarker abnormalities, but issues with the non-equivalence of biomarkers within each category remain to be resolved. Subgroups of all diagnostic classes were identified based on cognition, MRI, and blood proteins and metabolites and differed in associations with cognitive domains, AD biomarkers, and underlying genetics and biochemistry, supporting their biological coherence. Additional factors modulating disease trajectory included cerebrovascular disease acting to exacerbate AD by multiple mechanisms, microglial associated innate immune response and inflammation, cognitive and brain reserve, and sex differences. Additional common co-pathologies may modulate disease progression but further neuropathological studies are required to understand their influence.

Taking into account these often interacting factors in the selection of participants may improve clinical trials. The determination of A β status will certainly be improved by methodological changes to PET and CSF and plasma assays as well as the development of practical algorithms based on clinical information. Other improvements to clinical trials hinge on the more nuanced understanding of disease progression and included fine-tuning of selection tools, determining the time frame of progression, and modifications to outcome measures. An explosion of interest in plasma biomarkers led to ADNI studies of plasma A β , p-tau181, NFL, and others, suggesting that future studies will use the ADNI biofluid repository to investigate and compare additional biomarkers such as p-tau217 and various analytical methods. ADNI data were widely used to validate various image processing and analysis methods.

A major limitation of ADNI is its strict inclusion and exclusion criteria that have resulted in a highly educated largely European cohort with few comorbidities. ADNI participants are not representative of the wider general population and therefore the studies using ADNI data described in this review may not necessarily ensure generalizability. A smattering of studies using ADNI as a control cohort highlighted ethnocultural differences that must be investigated further. One goal of a renewal application to the NIA, called ADNI4, to be submitted in October 2021, will be to increase generalizability by reducing the exclusion criteria (e.g., allowing more cerebrovascular disease), increasing the ethnocultural diversity of newly enrolled participants, and recruiting individuals with lower levels of education. Finally, ADNI samples including genetics, CSF, and plasma

can be requested here: <http://adni.loni.usc.edu/data-samples/access-data/>.

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SUPPORTING INFORMATION

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

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