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Original Article

Informing etiological heterogeneity of mild cognitive impairment and risk for progression to dementia with plasma p-tau217

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ABSTRACT

Background: Mild cognitive impairment (MCI) is a clinical diagnosis representing early symptom changes with preserved functional independence. There are multiple potential etiologies of MCI. While often presumed to be related to Alzheimer's disease (AD), other neurodegenerative and non-neurodegenerative causes are common. Wider availability of relatively non-invasive plasma AD biomarkers, such as p-tau217, can provide invaluable insights into MCI clinico-pathology and the associated implications for symptom etiology, prognosis (e.g., risk for progression to dementia), and treatment options.

Objectives: The main goal of this study was to evaluate differences between individuals with MCI with and without plasma p-tau217 biomarker evidence of AD (MCI_{AD+} and MCI_{AD-}) as well as a control group of clinically normal older adults with negative AD biomarkers (CN_{AD-}). We evaluated group differences in demographics, recruitment, clinical scales, fluid biomarkers, and brain imaging. We further probed these factors as independent contributors to symptoms among MCI_{AD-} participants, for whom symptom etiology is most poorly understood. Lastly, in a subset of participants followed longitudinally, we investigated how these factors related to odds of clinical progression to dementia.

Design: We conducted an observational cross-sectional and longitudinal clinical research study. Study groups were compared cross-sectionally on demographics, recruitment, clinical measures, and biomarkers (chi square analyses, analyses of covariance). Contributors to functional changes were evaluated with multiple linear regression. Factors associated with the odds of progression from MCI to dementia longitudinally were evaluated with binary logistic regression.

Setting: 1Florida Alzheimer's Disease Research Center.

Participants: Cross-sectional analyses included 378 older adults classified as CN_{AD-} (N = 76, age 66.1 ± 7.2, 63.2% female, 23.7% non-Hispanic/White), MCI_{AD-} (N = 198, age 68.9 ± 7.9, 51.5% female, 29.3% non-Hispanic/White), or MCI_{AD+} (N = 104, age 73.9 ± 7.4, 52.9% female, 49.0% non-Hispanic/White). Longitudinal analyses focused on 207 participants with MCI (68.5% of cross-sectional MCI sample) followed for an average of 3 years.

Measurements: Demographics (age, sex, years of education, self-identified race and ethnicity, primary spoken language), National Alzheimer's Coordinating Center-defined clinical phenotypes (Clinically Normal, Impaired – Not MCI, Amnestic MCI, Nonamnestic MCI, Dementia), recruitment source (clinic-based versus community-based), genetics (*APOE* genotype), functional evaluation (Clinical Dementia Rating scale), global cognition (Mini

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Mental State Exam), vascular history (Vascular Burden Score), neuropsychiatric symptoms (NPI-Q Total score), plasma biomarkers (ALZPath p-tau217, Quanterix Simoa-based GFAP and NfL), and brain imaging (grey matter volume in select AD-relevant regions of interest, global white matter hyperintensity volume).

Results: Among those with MCI, 104 (34.4%) had plasma biomarker evidence of AD. MCI_{AD+} participants were more frequently recruited from clinic-based settings than MCI_{AD-} (74.8% vs. 47.5%, $p<.001$). Over half (51.5%) of MCI_{AD+} carried at least one *APOE* e4 allele compared to 26.6% of MCI_{AD-} and 29.4% of CN_{AD-} ($p<.001$). Both MCI_{AD+} ($p<.001$, Cohen's $d = 0.93$) and MCI_{AD-} ($p<.001$, $d = 0.75$) reported more severe neuropsychiatric symptoms than CN_{AD-}. MCI_{AD+} had higher plasma GFAP and NfL than both MCI_{AD-} (GFAP: $p<.001$, $d = 0.88$, NfL: $p<.001$, $d = 0.86$) and CN_{AD-} (GFAP: $p<.001$, $d = 0.80$; NfL: $p<.001$, $d = 0.89$). For the AD signature region of interest, MCI_{AD+} had lower volume than both CN_{AD-} ($p<.001$, $d = 0.78$) and MCI_{AD-} ($p=.018$, $d = 0.39$). For the hippocampus, both MCI_{AD+} ($p<.001$, $d = 0.87$) and MCI_{AD-} ($p<.001$, $d = 0.64$) had lower volume than CN_{AD-}. Longitudinally, older age (OR=1.14 [1.06–1.22], $p<.001$), higher levels of p-tau217 (OR=10.37 [3.00–35.02], $p<.001$) and higher neuropsychiatric symptoms (OR=1.19 [1.02–1.39], $p=.023$) were associated with higher odds of progression to dementia.

Conclusions: MCI is etiologically heterogeneous. The presence of Alzheimer's pathology defined by elevated plasma p-tau217 in individuals with MCI significantly worsens prognosis. Neuropsychiatric symptoms may contribute to cognitive complaints and risk for progressive decline irrespective of AD pathology. Plasma p-tau217 can inform our understanding of base rates of different MCI phenotypes on a larger scale. As with other AD biomarkers, frequency of elevated plasma p-tau217 and odds of progression to dementia requires careful consideration of recruitment source (clinic- vs. community-based), especially across ethno-racially diverse older adults. Ongoing integration of emerging neurodegenerative disease biomarkers with detailed clinical evaluations will continue to improve treatment specificity and prognosis.

1. Introduction

Mild cognitive impairment (MCI) is a clinical diagnosis representing an early stage of cognitive decline that for the most part does not interfere with functional independence. MCI was proposed as a construct in the 1990s after recognizing the importance of identifying patients at earlier symptom phases prior to dementia [1], when cognitive changes do interfere with functional independence. Identifying MCI traditionally was focused within the context of memory loss (i.e., amnestic MCI) due to suspected Alzheimer's disease (AD) related brain changes. The MCI concept, including non-amnestic profiles, as well as earlier recognition of subtle behavioral and motor changes has more recently been applied to multiple neurodegenerative conditions [2–4]. An MCI diagnosis in clinical and research settings remains one of the most heterogeneous etiologically and one of the most uncertain prognostically. Conversion rates from MCI to dementia classically are quoted as 10–15% annually [1], but rates are much higher for certain MCI etiologies, such as when MCI is due to AD [5].

Improving sensitivity to early symptom changes with clinical constructs like MCI often comes at the expense of etiological specificity. The rapid evolution and wider implementation of AD biomarkers (e.g., amyloid positron emission tomography [PET], CSF p-tau/Aβ42, plasma p-tau217) has helped emphasize that MCI, including amnestic MCI, may be due to a wide range of AD and non-AD causes (neurodegenerative or potentially reversible) [6,7]. Roughly 50% of individuals diagnosed with MCI in memory clinics who undergo AD biomarker testing have results supporting AD as a potential primary or contributing etiology [8]. Put differently, at least half of MCI cases are due to non-AD etiologies. Disease modifying therapies for AD are thought to be most effective when initiated at earlier symptom phases like the MCI stage [9], but are not appropriate for patients with MCI due to non-AD causes [10].

Common comorbidities like vascular disease and psychiatric conditions may impact cognition with aging and lead to MCI with or without AD present [11–14]. These non-AD factors may disproportionately impact traditionally underrepresented ethno-racial populations with different risk profiles for conditions like diabetes, renal dysfunction, or stroke [15–18]. Relatedly, rates of AD-related MCI differ by recruitment sources. Research participants with MCI enrolled from clinic-based settings tend to have higher rates of AD and clinical progression compared with community-based referrals [19,20], and ethno-racial minority groups tend to more commonly be recruited from the community [21] in addition to having different likelihoods of comorbidities that negatively influence cognition [22,23].

There are also limitations of widely used assessment tools that aid in classifying cognitive and functional status (e.g., Clinical Dementia Rating scale; CDR) in traditionally underserved populations [24]. The CDR is a common measure for broadly classifying cognitive function status into categories like MCI vs. dementia [25] and is a primary clinical endpoint in many neurodegenerative disease-focused clinical trials [9]. The type and severity of cognitive symptoms that fall within CDR-defined MCI (e.g., amnestic vs. nonamnestic, single- vs. multi-domain) may also meaningfully differ in likelihood of underlying AD pathology, recruitment source, and progression risk [26].

By integrating relatively noninvasive AD biomarkers (e.g., plasma p-tau217) with thorough clinical examinations in older adults with MCI, we can gain invaluable insights into MCI clinico-pathology and the associated implications for symptom etiology, prognosis, and treatment [27,28]. Both the Alzheimer's Association [5] and International Working Group [29] recommendations for AD diagnosis require biomarker support for presence of AD pathology, while the former emphasizes the separation of syndrome (symptoms) and disease biology (etiology) and allows for AD diagnosis based on biomarker evidence alone. Plasma p-tau217 is the most promising blood-based biomarker for AD detection and currently is categorized among the Core 1 AD biomarkers, which define the initial stage of AD and considered capable of detecting AD pathology in both symptomatic and asymptomatic individuals [5].

The main goal of this study was to evaluate differences between CDR-defined MCI with and without plasma p-tau217 biomarker evidence of AD (MCI_{AD+} and MCI_{AD-}) in older adults recruited from clinic and community settings into the 1Florida Alzheimer's Disease Research Center (ADRC). Along with a control group of clinically normal older adults with negative AD biomarkers (CN_{AD-}), we set out to test the hypothesis that MCI_{AD+} and MCI_{AD-} would differ on recruitment source, global cognition, *APOE* genotype, vascular risk factors, psychiatric history, brain volume, and other plasma-based measures of neurodegenerative disease (GFAP, NfL). We further probed these factors as independent contributors to symptoms specifically among MCI_{AD-} participants, for whom symptom etiology is most poorly understood, and hypothesized that vascular and psychiatric factors would be associated with level of function. Lastly, in a subset of participants with MCI followed longitudinally, we investigated how these factors related to odds of clinical progression to dementia and hypothesized that plasma p-tau217 would most strongly relate to odds of progression.

2. Methods

2.1. Participants

All study participants were enrolled in the 1Florida ADRC, which includes older adults spanning the continuum of normal cognition, MCI, and dementia invited to undergo annual study visits. The current study focused on participants with normal cognition or MCI at baseline and all data were obtained from study visits occurring between 2016 and 2023. 1Florida ADRC recruitment involves outpatient memory disorders clinics (i.e., referred from professional/healthcare provider contact) and other sources including free memory screening programs and community outreach (i.e., non-professional contact or self/relative/friend referral). Over 50% of participants in the 1Florida ADRC self-identify as either Hispanic/Latino (referred to as "Hispanic" throughout), mostly of Cuban or South American origin, or Black/African American.

2.2. Clinical evaluation

1Florida ADRC participants completed comprehensive neurological and neuropsychological evaluations including the National Alzheimer's Coordinating Center (NACC) Uniform Data Set [30]. Overall functioning was assessed with the Clinical Dementia Rating (CDR [25]) scale and global cognition was assessed with the Mini Mental State Exam (MMSE [31]). Participants were evaluated in either Spanish or English according to participant preference by bilingual clinicians and psychometricians.

The primary group classifications for this study were based on CDR-defined level of function using the CDR Global score. CDR-Global score options are 0, 0.5, 1, 2, or 3, where CDR-Global=0 indicates clinically normal functioning (CN), CDR-Global=0.5 indicates MCI, and CDR-Global≥1 indicates at least mild dementia. We also report and analyze the CDR-Sum of Boxes score, which ranges from 0 to 18 and represents the total score from each of 6 sub-domains in the CDR that are independently scored as 0, 0.5, 1, 2, or 3.

Participants also underwent a multidisciplinary consensus review of neurological and neuropsychological data, including the CDR, and were further classified by clinical syndromes per NACC categories: Clinically Normal, Impaired – Not MCI, Amnestic MCI (single or multi-domain), Nonamnestic MCI (single or multi-domain), or Dementia. The "Impaired – Not MCI" category typically reflects participants with evidence of clinical symptoms either per subjective report or based on low cognitive test scores, but are not judged by the consensus team to fit neatly into any formal "MCI" diagnostic subgroup. Further, our center enrolls participants with suspected Parkinson or Lewy body disease (PD/LBD), and we specify multidisciplinary consensus diagnosis of MCI due to PD/LBD rather than combining within other MCI classifications for descriptive purposes. Biomarker data including brain imaging (MRI, PET) and blood-based biomarker assessment do not factor into clinical syndrome classification.

2.3. Medical history

We included medical history data related to vascular disease risk factors and neuropsychiatric factors hypothesized to contribute to cognitive changes with or without the presence of AD. For vascular risk, we calculated a modified vascular burden score (VBS) based on prior publications [32] as the sum of 7 possible vascular risk factors or diagnoses: cardiac-arrhythmias (atrial fibrillation OR defibrillator), coronary artery disease (angina OR angioplasty/endarterectomy/stent OR cardiac bypass OR heart attack), congestive heart failure, cerebrovascular disease (stroke OR transient ischemic attack), hypertension, hypercholesterolemia, diabetes (max score = 7). For psychiatric symptoms, we analyzed the total score of the Neuropsychiatric Inventory Questionnaire (NPI-Q), an informant-based survey assessing a range of mood and behavior symptoms with higher scores indicating greater severity or distress [33].

2.4. Plasma Alzheimer's disease biomarkers

Venous blood was collected using standardized NACC and National Centralized Repository for Alzheimer's Disease and Related Dementias protocols implemented at the 1Florida ADRC (see **Supplemental Methods**). Duplicate blood samples were analyzed using single molecule array (Simoa®) technology and blinded to all clinical and demographic data for p-tau217 (ALZPath), glial fibrillary acidic protein (GFAP), and neurofilament light (NfL). Plasma p-tau217 was measured at the Quanterix Accelerator Lab (Quanterix, Billerica, MA). GFAP and NfL were measured at the University of Florida using Quanterix Neurology 2-Plex B kits. All samples included in this study had coefficients of variation < 20% (p-tau217: 4.9 ± 3.8%, GFAP: 7.5 ± 5.1%, NfL: 6.9 ± 4.7%).

We previously derived cutoffs for plasma p-tau217 within a partially overlapping sample of 239 1Florida ADRC participants with concurrent plasma and amyloid PET scans [34]. The results supported a single cutoff of ≥0.56pg/mL that corresponded with an optimal balance of sensitivity (89.0%) and specificity (82.4%) to a positive amyloid PET visual read (AUC=0.91). Correspondence between plasma p-tau217 and amyloid PET did not differ as a function of ethno-racial group and applying ethnicity-specific cutoffs did not meaningfully alter sensitivity or specificity to positive amyloid PET. We therefore applied the 0.56pg/mL cutoff in the current sample to all participants to define presence or absence of Alzheimer's pathology. For simplicity, the CDR-defined MCI participants were grouped as MCI_{AD+} and MCI_{AD-} based on plasma p-tau217, though it is important to note that AD diagnosis based on plasma p-tau217 is not perfectly equivalent to a neuropathological diagnosis of AD. Only CN participants with a "negative" plasma p-tau217 test (concentration <0.56 pg/mL) were included (CN_{AD-}). Sample size availability of CN_{AD+}participants was insufficient for inclusion in the current study (see other recent studies for analyses focused on this important subgroup, e.g., [28,35–38]).

2.5. Neuroimaging

Brain MRIs were acquired on 3T Siemens scanners qualified for the AD Neuroimaging Initiative (see **Supplemental Methods**). Sequences relevant to this study included volumetric T1-weighted scans using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence and T2/FLAIR to evaluate white matter hyperintensity volume (global) as a proxy for suspected cerebrovascular disease burden. T1 image processing was performed using an automated reconstruction pipeline in FreeSurfer (version 7.1.0). Cortical volume measures were calculated using the Desikan–Killiany atlas. Volumetric regions of interest (ROI) for this study included total grey matter volume, an AD signature region reflecting a sum of ROIs susceptible to AD-related atrophy (entorhinal cortex, fusiform gyrus, inferior temporal, middle temporal) [39], and the hippocampus.

2.6. APOE genotyping

APOE genotyping for ε2, ε3, and ε4 alleles was performed at Mayo Clinic Jacksonville using predesigned TaqMan SNP Genotyping Assays for SNPs rs7412 and rs429358 (Thermo Fisher Scientific, MA, USA) on the QuantStudio 7 Flex Real-Time PCR system (Applied Biosystems, CA, USA) following the manufacturer's protocol. Genotypes were grouped based on presence or absence of at least one e4 allele.

2.7. Statistical analyses

Data were analyzed using R and SPSS v28. We report frequency and descriptive data for CN_{AD-} and MCI participants with and without evidence AD. Demographics and recruitment characteristics were

compared using analysis of variance and chi square analyses. Group comparisons either involved two (MCI_{AD+}, MCI_{AD-}) or three (plus CN_{AD-}) groups. Continuous variables were compared using analysis of covariance (ANCOVA) with Bonferroni's post hoc pairwise comparisons. Dependent variables with evidence of deviation from a normal distribution were log transformed. Covariates for analyses with CDR or MMSE as the dependent variable were age, sex, years of education, and primary language. For analyses with plasma biomarkers as the dependent variable(s), we covaried for age. For analyses with grey matter volume and white matter hyperintensity burden as dependent variables, we covaried for age and total intracranial volume. To better understand contributors to clinical symptoms in individuals with CDR-defined MCI without biomarker evidence of Alzheimer's disease (i.e., in the MCI_{AD-} group), we performed multiple linear regression with CDR-Sum of Boxes as the dependent variable. Predictors included demographic (age, sex, years of education, primary language), genetic (*APOE* e4 carrier status), plasma biomarkers (p-tau217, GFAP, NfL), NPI-Q total score, and VBS. Post hoc models focused on MCI_{AD-} participants that were diagnosed by consensus as an amnestic MCI phenotype (single- or multi-domain).

A subset of participants with longitudinal clinical data supported analyses focused on predictors of progression from CDR-defined MCI to dementia. Progression based on the CDR-Global score was defined as a baseline CDR-Global = 0.5 and CDR-Global ≥ 1 at final visit. "Reversion" was defined as baseline CDR-Global = 0.5 and CDR-Global = 0 at final visit. Progression based on CDR-Sum of Boxes was defined as an increase in ≥ 1 point between baseline and final visit irrespective of stability or progression in CDR-Global score [40]. To identify factors associated with increased odds of progression from MCI to dementia, we used binary logistic regression with progression vs. stability/reversion as the dependent variable and multiple predictors (age, sex, education, referral source, *APOE* e4 carrier status, VBS, NPI-Q total score, p-tau217, GFAP, NfL). Odds ratios with 95% confidence intervals were extracted from logistic regression models to interpret the effect of individual factors on the odds of progression.

Effect sizes are provided where appropriate and were interpreted as: Cohen's *d* (0.2 = small, 0.5 = medium, 0.8 = large), standardized β (0.1 = small, 0.3 = medium, 0.5 = large).

3. Results

Our total cohort was 378 participants, including 302 with CDR-defined MCI and a healthy reference group (N = 76) determined to be clinically normal by consensus and with negative AD biomarkers (Table 1). Overall, 53.5% of participants were recruited from clinic-based settings. There were notable differences across ethno-racial subgroups in recruitment source, with 70.4% of White/non-Hispanic, 63.4% of White/Hispanic, and 21.8% of Black participants recruited from clinic-based settings. The most common consensus clinical diagnosis among CDR-defined MCI was amnestic MCI (N = 192, 63.6%), of which 73 (38.0%) were single-domain.

3.1. Biomarker evidence for AD pathology in MCI

Of 302 participants with CDR-defined MCI, 104 (34.4%) had biomarker evidence of AD based on elevated plasma p-tau217. MCI_{AD+} participants were more frequently recruited from clinic-based settings than MCI_{AD-} (74.8% vs. 47.5%, p<.001), which intersects with the lower frequency of MCI_{AD+} among Black participants (17.1%), 78% of whom were recruited from community-based settings. Frequency of MCI_{AD+} was slightly higher in White/non-Hispanic (46.8%) than White/Hispanic (35.8%) overall, though not statistically significant (p=.10). When matching on clinic-based recruitment source, the difference in frequency of MCI_{AD+} between White/non-Hispanic (51.2%) and White/Hispanic participants (38.4%) was not significantly different (p=.11). Though a small sub-sample (N = 12), 50% of Black/African American participants recruited from clinic-based settings were MCI_{AD+}.

Table 1
Cohort Descriptive Characteristics.

	Overall	CN_{AD-}	MCI_{AD-}	MCI_{AD+}
N	378	76	198	104
Age	69.7 ± 8.1	66.1 ± 7.2	68.9 ± 7.9	73.9 ± 7.4
Sex, N(%) Female	205 (54.2)	48 (63.2)	102 (51.5)	55 (52.9)
Education	15.0 ± 3.5	15.7 ± 3.4	14.2 ± 3.6	15.8 ± 3.3
Race/Ethnicity, N(%)				
White/Non-Hispanic	127 (33.6)	18 (23.7)	58 (29.3)	51 (49.0)
White/Hispanic	131 (34.7)	22 (28.9)	70 (35.4)	39 (37.5)
Black[*]	110 (29.1)	34 (44.7)	63 (31.8)	13 (12.5)
Other/Unknown	10 (2.7)	2 (2.6)	7 (3.5)	1 (1.0)
Recruitment Source[†]				
Clinic	201 (53.5)	30 (40.0)	94 (47.5)	77 (74.8)
Community/Other	175 (46.5)	45 (60.0)	104 (52.5)	26 (25.2)
***APOE* e4**[‡]**, N(%)**	121 (34.3)	20 (29.4)	49 (26.6)	52 (51.5)
CDR-Sum of Boxes	1.2 ± 1.0	0.0 ± 0.1	1.3 ± 0.8	1.8 ± 1.1
Consensus Diagnosis				
Clinically Normal	76 (20.1)	76 (100.0)	0 (0.0)	0 (0.0)
Impaired-Not MCI	51 (13.5)	0 (0.0)	45 (22.7)	6 (5.8)
Amnestic MCI	192 (50.8)	0 (0.0)	120 (60.6)	72 (69.2)
Nonamnestic MCI	24 (6.3)	0 (0.0)	20 (10.1)	4 (3.8)
PD/LBD-MCI	22 (5.8)	0 (0.0)	13 (6.6)	9 (8.7)
Dementia	13 (3.5)	0 (0.0)	0 (0.0)	13 (12.5)
Plasma, pg/mL				
p-tau217	0.52±0.44	0.29±0.10	0.32±0.11	1.09±0.49
GFAP	174±115	137±70	146±103	255±122
NfL	15.5 ± 13.4	11.7 ± 6.9	13.2 ± 12.2	22.8 ± 16.3
NPI-Q[§]	3.0 ± 3.1	1.6 ± 2.6	3.1 ± 3.0	3.7 ± 3.2
VBS[‖]	1.5 ± 1.2	1.4 ± 1.0	1.6 ± 1.2	1.6 ± 1.3

Data shown either as N (%) within the diagnostic group or as mean ± standard deviation.

[*] Black participants self-reporting non-Hispanic (94%) and Hispanic (6%) ethnicity were combined into the "Black" race/ethnicity group.

[†] Recruitment source known for N = 376 (99.5%; CN_{AD-} N = 75, MCI_{AD-} N = 198, MCI_{AD+} N = 103).

[‡] *APOE* genotype known for N = 353 (93.4%; CN_{AD-} N = 68, MCI_{AD-} N = 184, MCI_{AD+} N = 101).

[§] NPI-Q scores known for N = 351 (92.8%; CN_{AD-} N = 72, MCI_{AD-} N = 181, MCI_{AD+} N = 98).

[‖] VBS score known for N = 366 (96.8%; CN_{AD-} N = 73, MCI_{AD-} N = 191, MCI_{AD+} N = 102).

Both nonamnestic MCI (10.1% vs. 3.8%) and Impaired-Not MCI (22.7% vs. 5.8%) were more common consensus diagnoses in MCI_{AD-} than MCI_{AD+}. While all CDR-defined MCI participants had a CDR-Global score of 0.5, MCI_{AD+} had significantly higher CDR Sum of Boxes than MCI_{AD-} (1.8 ± 1.1 vs. 1.3 ± 0.8, p<.001; Fig. 1**A**). There was also a stepwise decline in global cognitive function (MMSE) from CN_{AD-} (28.8 ± 1.4), to MCI_{AD-} (27.2 ± 3.0), to MCI_{AD+} (26.4 ± 2.9; all pairwise post hoc comparisons statistically significant, ps <0.001 - 0.002; Fig. 1**B**). Of note, among the subset of participants with presumed MCI due to PD/LBD (N = 22), 9 (41%) were in the MCI_{AD+} group.

3.2. APOE genotype, vascular risk, and neuropsychiatric symptoms

We compared MCI_{AD+}, MCI_{AD-}, and CN_{AD-} participants on frequency of having at least one *APOE* e4 allele, vascular risk (VBS), and neuropsychiatric symptoms (NPI-Q). *APOE* genotype was known for 353 (93.4%) of participants. Over half (51.5%) of MCI_{AD+} carried at least one *APOE* e4 allele compared to 26.6% of MCI_{AD-} and 29.4% of CN_{AD-} (p<.001). Both MCI_{AD+} (p<.001, d = 0.93) and MCI_{AD-} (p<.001, d = 0.75) reported more severe neuropsychiatric symptoms than CN_{AD-}, but did not differ significantly from each other (p=.36, d = 0.20; Fig. 1**C**). Groups did not differ in VBS (main effect, p=.79).

3.3. Plasma biomarkers and neuroimaging

There was a significant main effect of group for both plasma GFAP and NfL concentrations (ps <0.001; Fig. 2**A-B**). Pairwise post hoc com-

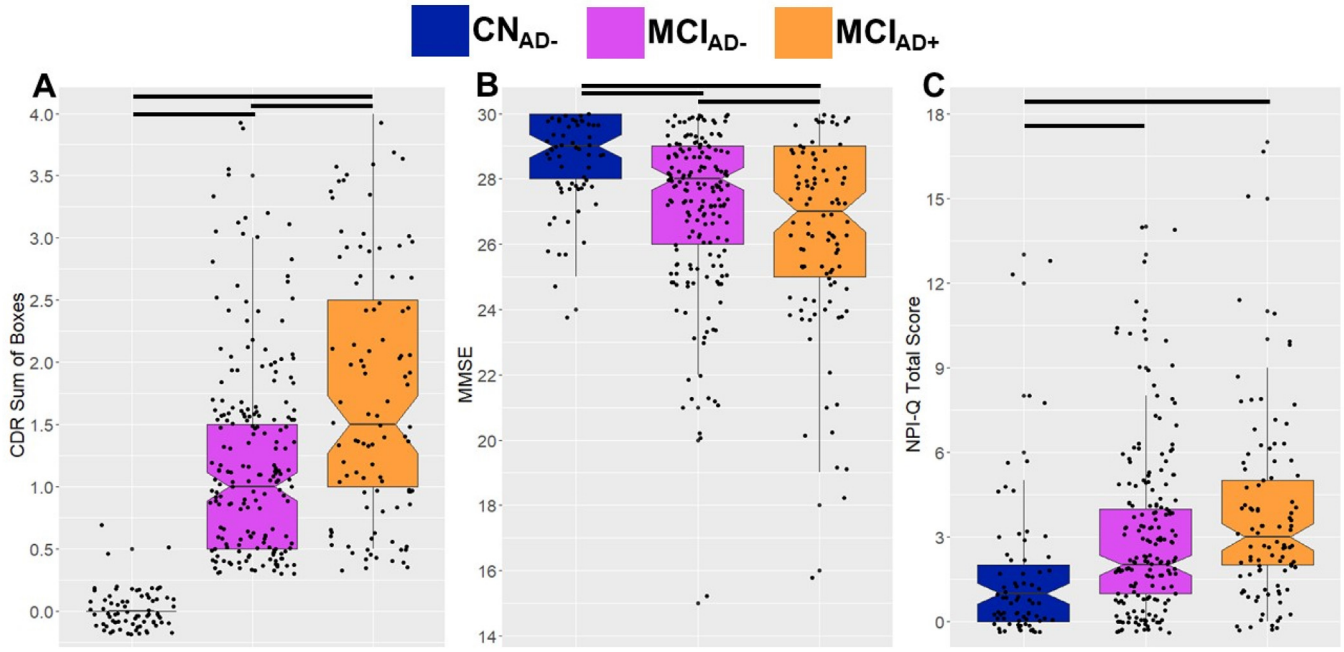

Fig. 1. Group differences in (A) CDR Sum of Boxes, (B) Mini Mental State Exam, and (C) NPI-Q Total scores. Raw values are shown. Black lines represent statistically significant pairwise comparisons controlling for age, sex, years of education, and primary spoken language.

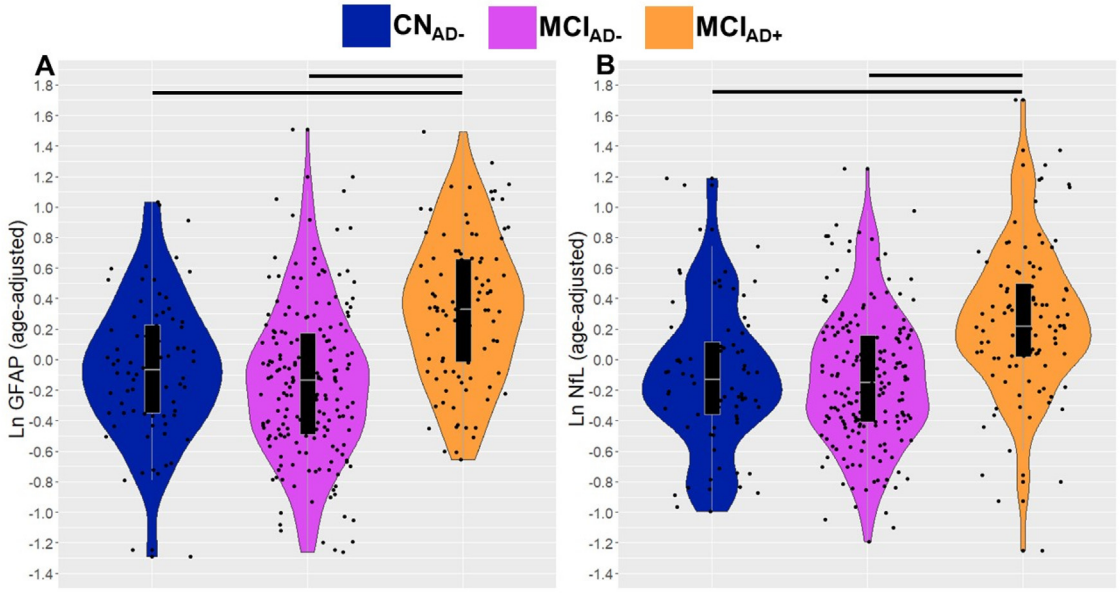

Fig. 2 (A-B). Group differences in (A) plasma glial fibrillary acidic protein (GFAP) and (B) plasma neurofilament light (NfL). Plasma biomarker concentrations are shown log transformed and adjusted for participant age. Black lines represent statistically significant pairwise comparisons.

parisons showed MCI_{AD+} had significantly higher plasma GFAP and NfL than both MCI_{AD-} (GFAP: $p<.001$, $d = 0.88$, NfL: $p<.001$, $d = 0.86$) and CN_{AD-} (GFAP: $p<.001$, $d = 0.80$; NfL: $p<.001$, $d = 0.89$), while MCI_{AD-} and CN_{AD-} did not differ (GFAP and NfL: ps>0.99, *d's* < 0.08).

Neuroimaging comparisons included total grey matter volume, an AD signature ROI, hippocampal volume, and white matter hyperintensity volume (CN_{AD-} $N = 50$, MCI_{AD-} $N = 131$, MCI_{AD+} $N = 81$; **Supplemental Figure 1 A-D**). All comparisons had a significant main effect of group (ps <0.001 - 0.02) except for white matter hyperintensity burden ($p=.76$). Bonferroni-adjusted post hoc pairwise comparisons suggested MCI_{AD+} had lower total grey matter volume than CN_{AD-} ($p=.018$, $d = 0.51$) but did not differ from MCI_{AD-} ($p>.9$, $d = 0.13$). For the AD signature ROI, MCI_{AD+} had lower volume than both CN_{AD-} ($p<.001$, $d = 0.78$) and MCI_{AD-} ($p=.018$, $d = 0.39$). For the hippocampus, both MCI_{AD+} ($p<.001$, $d = 0.87$) and MCI_{AD-} ($p<.001$, $d = 0.64$) had lower volume than CN_{AD-}, but did not differ significantly from each other ($p=.27$, $d = 0.24$).

3.4. Correlates of CDR-defined symptoms in MCI_{AD-}

Given the relative ambiguity of symptom etiology in MCI_{AD-} compared to MCI_{AD+}, we evaluated contributors to clinical symptoms specifically in MCI_{AD-} participants ($N = 160$ with complete data; 80.8% of MCI_{AD-} cohort). Fewer years of education ($\beta = -0.177$, $p=.013$), being

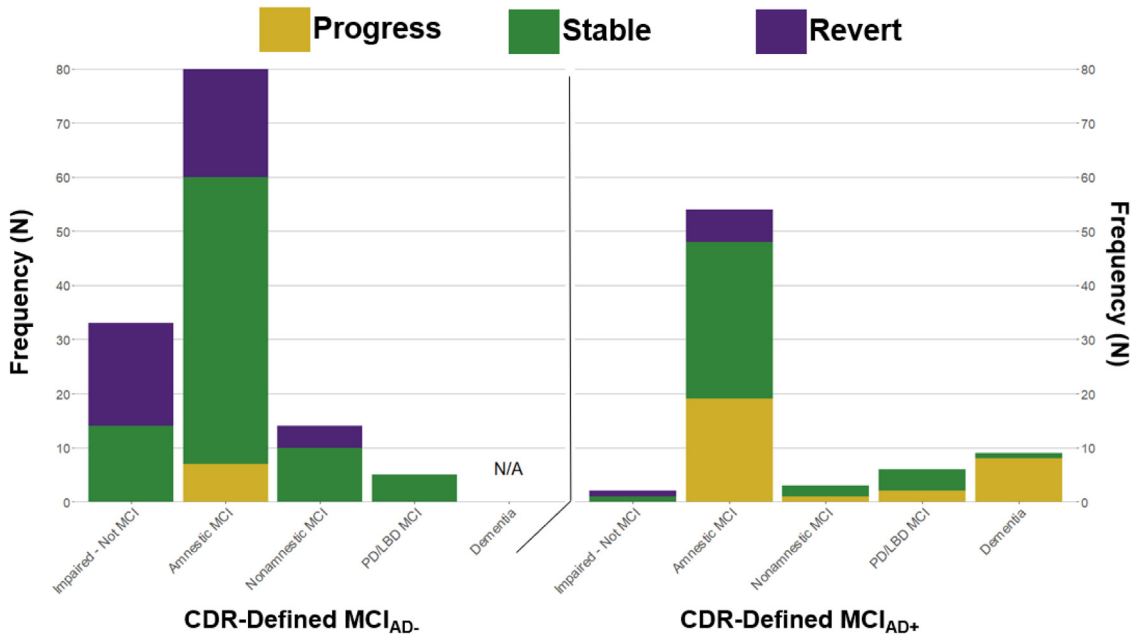

Fig. 3. Frequency data showing number of participants followed longitudinally that either progressed to dementia (gold), remained stable (green), or reverted to functionally normal (purple). Functional status was defined by CDR Global score (0 = functionally normal, 0.5 = MCI, 1+ = dementia). Data are stratified by participants with CDR-defined MCI without a positive plasma p-tau217 biomarker at baseline (left) and those with a positive plasma p-tau217 biomarker at baseline (right). Frequency information is further stratified by the multidisciplinary consensus diagnosis determined clinical phenotype within the CDR-defined MCI group, which also takes into account clinical history, medical history, and neuropsychological testing results.

primarily English-speaking ($\beta = 0.198$, p=.013), and more severe psychiatric symptoms (NPI-Q Total; $\beta = 0.301$, p<.001) were associated with higher CDR-Sum of Boxes within MCI_{AD-} (**Supplemental Table 1)**. Interestingly, despite prespecifying a "negative" p-tau217 test within the MCI_{AD-} group, higher plasma p-tau217 also related to higher CDR-Sum of Boxes ($\beta = 0.200$, p=.013). These results were similar when the analyses were restricted to MCI_{AD-} with an amnestic MCI phenotype.

3.5. Clinical progression from MCI to dementia or reversion from MCI to clinically normal

Of 302 participants with CDR-defined MCI at baseline, longitudinal clinical data were available for 207 (68.5%; MCI_{AD+} N = 75, MCI_{AD-} N = 132; **Supplementary Table 2**) with an average follow-up time of 2.8 years (range 1–7 years). Follow-up duration did not significantly differ between MCI_{AD+} (2.9 ± 1.8yrs, range 1–7yrs) and MCI_{AD-} (2.6 ± 1.9yrs, range 1–7yrs; p=.28). Among MCI_{AD+}, 30 (40%) participants progressed to at least mild dementia (CDR Global 1+) at follow-up compared to 7 (5.3%) of MCI_{AD-} (Fig. 3). Of note, among 35 participants with longitudinal clinical data who were diagnosed as "Impaired – Not MCI" by consensus, 0 (0%) progressed to dementia and over half (20/35, 57%) reverted to functionally normal (CDR-Global=0).

3.6. Predictors of clinical progression from MCI to dementia

There were 184 participants (88.9% of the longitudinal sample) with complete data to test multiple variable associations with odds of symptom progression from MCI to dementia defined by CDR-Global score change from 0.5 to 1+ by the last study visit (N = 35 progressors). Older age (OR=1.14 [1.06–1.22], p<.001), higher levels of p-tau217 (OR=10.37 [3.00–35.02], p<.001) and higher NPI-Q total score (OR=1.19 [1.02–1.39], p=.023; Fig. 4) were associated with higher odds of progression to dementia. When using our sample-derived cutoff for plasma p-tau217 positivity (≥0.56 pg/mL) rather than continuous p-tau217 concentration, a "positive" p-tau217 test was associated with 12x greater odds of progressing to dementia than those with a "negative" p-tau217 test (OR=12.00 [3.78–38.11], p<.001).

Odds ratios corresponding to Z-score transformed model predictors are provided in **Supplemental Tables 3A-3B** to aid comparison of relative magnitude of effect sizes between variables with different scales. Findings also were generally similar when defining progression based on CDR-Sum of Boxes increase > 1.0 (**Supplemental Tables 4A-4B)**.

4. Discussion

Etiological heterogeneity within MCI has key diagnostic, prognostic, and treatment implications. We characterized the etiological heterogeneity of MCI (defined by CDR Global score 0.5) in older adults recruited from clinic- and community-based settings and investigated factors predicting progression from MCI to dementia. About one third (34%) of all participants had biomarker evidence of AD pathology, and those that were MCI_{AD+} were more likely to have been recruited from a clinic-based setting than the community. Individuals classified as non-amnestic MCI and Impaired – Not MCI typically were MCI_{AD-}. Presence of an *APOE* e4 allele, elevation of other plasma biomarker (GFAP, NfL), atrophy in AD-relevant brain regions, and more severe cognitive symptoms (MMSE, CDR-Sum of Boxes) all related to being MCI_{AD+}, while elevated neuropsychiatric symptoms and hippocampal atrophy were noted in both MCI_{AD+} and MCI_{AD-}. Consistent with typical estimated conversion rates [1,5], about 20% of our sample progressed to dementia over the ~3-year follow-up period, but this comprised 40% of MCI_{AD+} compared to just 5% of MCI_{AD-}. Elevated plasma p-tau217 increased the odds of progression 12-fold. Increasingly easier access to AD biomarkers enables better understanding MCI causes as well as informing treatment options across diverse older adult populations.

Several of our study findings suggest that AD-related MCI is more severe clinically and worse prognostically than non-AD MCI, which aligns with prior work [28,41], though differences likely are highly dependent on the populations within the broad MCI_{AD-} framework (e.g., other neurodegenerative vs. non-neurodegenerative etiologies). Similarities between MCI_{AD+} and MCI_{AD-} are also compelling. For exam-

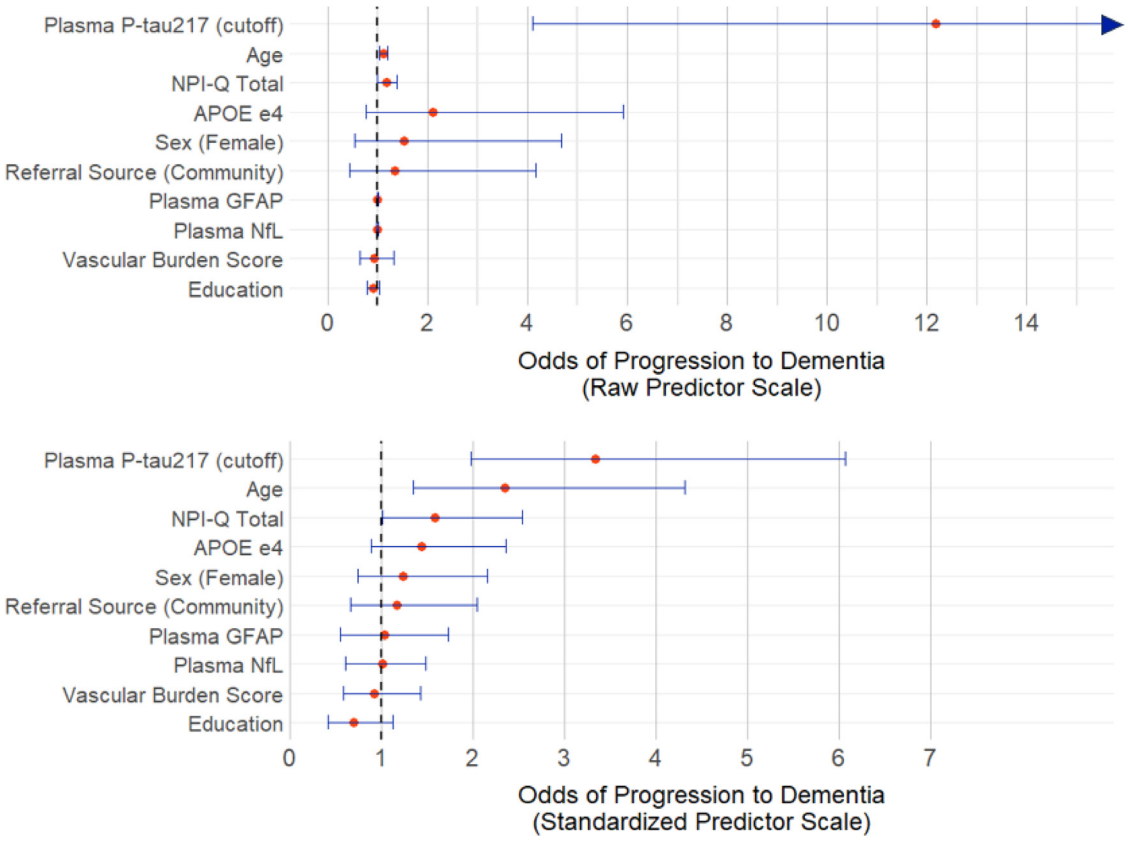

Fig. 4. Forest plots showing odds ratios associated with individual predictor variables and odds of progression from CDR-defined MCI to dementia (vs. stability/reversion at follow-up). Odds ratios (orange dot) and 95% confidence intervals (blue whiskers) are shown both with predictor variables on their raw scales (top) and with all predictor variables z-transformed (bottom) to aid direct comparison of the magnitude of effects between variables measured on different scales. The upper limit of the confidence interval for being above the plasma p-tau217 cutoff (raw scale model; top) was >38 and is shown with a right-facing blue arrow to avoid x-axis distortion.

ple, hippocampal volume did not significantly differ between MCI_{AD+} and MCI_{AD-}. While AD pathology undoubtedly is linked to hippocampal atrophy, the hippocampus is susceptible to multiple neurodegenerative proteinopathies associated with aging, such as primary age-related tauopathy, argyrophilic grain disease, aging-related tau astrogliopathy, and limbic-predominant TDP43 proteinopathy (i.e., LATE) [42–46].

At times referred to within the spectrum of suspected non-Alzheimer's pathology or SNAP, these diseases, especially LATE, are implicated in subtle and slowly progressing memory loss as well as hippocampal atrophy, and do not clearly influence other plasma biomarker concentrations like GFAP or NfL [44,47]. Hippocampal atrophy alone in the presence of MCI is not specific to AD and other etiologies should be considered, particularly in the presence of low concentrations of plasma p-tau217. Though speculative and based on a small number of participants, it is noteworthy that the few MCI_{AD-} who progressed to dementia were an average of ~80 years old compared to those that were stable (~69 years old) or reverted (~66 years old), and diseases like LATE disproportionately impact cognition for individuals in this older age range.

Both MCI_{AD+} and MCI_{AD-} also reported more severe neuropsychiatric symptoms than healthy controls, and these symptoms increased odds for progression to dementia even when controlling for AD biomarkers. Though very few MCI_{AD-} progressed to dementia in our study window, neuropsychiatric symptoms represent an important treatment target that may mitigate MCI symptoms or clinical progression. Longer follow-up of MCI_{AD-} participants with elevated neuropsychiatric symptoms is key as neuropsychiatric symptoms may be a prodrome to AD-related cognitive decline [12,48] potentially presenting before AD pathology is sufficient to be detected by existing biomarkers. Efforts to carefully study the implications of early neuropsychiatric or behavior symptoms (i.e., mild behavioral impairment or MBI) are underway [49].

Cerebrovascular disease contributes to cognitive impairment risk and commonly is proposed as a potential explanation for cognitive decline in MCI especially when AD biomarker testing is negative. Disproportionately high prevalence of vascular risk factors and disease may also be important for understanding differences in MCI etiologies across ethno-racial minority populations. We did not identify differences in vascular risk factors or white matter hyperintensity burden between MCI_{AD-} and MCI_{AD+} groups in our study, nor were these variables associated with function (CDR Sum of Boxes) or odds or progression to dementia. Indicators of vascular risk and disease vary widely across studies and may not adequately capture the spectrum of relevant cerebrovascular changes, which may contribute to inconsistent results. Continued investigation of vascular contributions to MCI with or without evidence of AD may benefit from additional neuroimaging metrics capturing vascular disease (e.g., ARTerioloSclerosis or ARTS score) [50] or emerging blood-based biomarkers associated with vascular contributions to cognitive decline (e.g., PlGF, VEGF) [51].

Clinical phenotypes related to less common non-AD neurodegenerative diseases like frontotemporal lobar degeneration (FTLD; e.g., behavioral variant frontotemporal dementia, semantic or nonfluent variant primary progressive aphasias, atypical parkinsonism) are not targeted explicitly for recruitment within 1Florida ADRC and therefore are not likely a significant portion of the MCI_{AD-} group. This is further supported by the high frequency of clinical stability or reversion and low plasma NfL among MCI_{AD-} participants. The 1Florida ADRC does however recruit participants with suspected PD/LBD-related MCI. Consistent with autopsy data showing that up to 50% of brain donors with a primary

diagnosis of AD have comorbid LBD, and vice versa [52,53], around 40% (9/22) of PD/LBD MCI participants in our study were MCI_{AD+}. Future efforts are focused on better understanding the clinical and biomarker impact of AD pathology within participants diagnosed with PD/LBD.

Further characterizing clinical phenotypes within the broader construct of MCI helps improve specificity to the underlying pathology and informs the risk for dementia progression. While we focused on NACC-defined diagnostic groups based on multidisciplinary consensus, others have proposed sophisticated methods for empirically deriving distinct cognitive subtypes within MCI that may classify participants differently and improve sensitivity to objective cognitive changes [26,41,54]. Based on cognitive data alone, amnestic multidomain MCI seems to best predict underlying AD pathology (more so than amnestic single domain or nonamnestic MCI) and is associated with greatest risk for progression to dementia [41]. Specific amnestic features such as susceptibility to semantic intrusions and failure to recover from proactive interference have also shown associations with AD biomarkers and increased risk for progression from MCI to dementia [55,56].

Amnestic MCI was the most common consensus diagnosis in our MCI cohort regardless of AD biomarker status, but other MCI phenotypes clearly differed by AD biomarker status. Clinically ambiguous cases with a CDR-Global of 0.5 that ultimately were classified as "Impaired – Not MCI" had low rates of AD biomarker positivity (6/51, 11.8%) and none with longitudinal data progressed to dementia (0/35) over an average of about three years of follow-up. On the contrary, 57% of Impaired – Not MCI reverted to clinically normal at follow-up. Most of the Impaired – Not MCI participants were community-based recruits (34/51, 67%), further highlighting the important considerations for disease base rates and clinical prognosis when study cohorts represent a combination of both clinic-based and community-based recruitment settings. Of note, traditionally underrepresented ethno-racial groups tend to be disproportionately recruited from community-based rather than clinic-based settings, which requires additional careful consideration for interpreting ethno-racial differences in clinical diagnosis, rates of positive AD biomarkers, and clinical prognosis [21,57].

CDR-defined MCI classification is common, and the CDR is a primary clinical endpoint in several AD clinical trials [9]. We found that English as a primary language in our cohort was associated with *worse* CDR-Sum of Boxes score (i.e., lower/better CDR-Sum of Boxes in primary Spanish-speakers who mostly come from our White/Hispanic cohort). The CDR heavily weights informant-based reporting of symptoms and daily difficulties and was developed in predominantly White/non-Hispanic populations [25]. While validated for detecting cognitive impairment in a few other populations (e.g., Mexican Americans [58]), individuals from traditionally underrepresented ethno-racial groups may be less likely to share concerns about their loved ones in medical and research settings or might attribute difficulties to "normal aging," risking a CDR score that underestimates potentially meaningful changes [59,60]. There remains a critical need to understand the cultural biases and limitations of existing measures currently used for establishing both subjective and objective evidence for a clinical diagnosis like MCI [61,62].

Initial attempts to better predict the individuals with MCI that progress to dementia, remain stable, or revert to clinically normal relied primarily on symptoms. Measuring AD pathology with in vivo biomarkers, historically with amyloid PET or CSF AD biomarkers and more recently with plasma, has perhaps led to the most pronounced advancement in specifying those with MCI at greatest risk for progression to dementia. Across all MCI participants in our cohort, a positive plasma p-tau217 test, defined based on correspondence with a positive Aβ-PET scan, increased the odds of progression to dementia 12-fold. Recent work suggests plasma p-tau217 demonstrates relative equivalence to CSF AD biomarkers for AD diagnosis, and collectively there is strong support for plasma p-tau217, CSF AD biomarkers, and amyloid PET all having significant prognostic utility [28,63–65].

In the absence of high suspicion for alternative progressive neurodegenerative etiologies like FTLD or LBD, a negative AD biomarker in such a patient with MCI should increase confidence that decline is not imminent and that there is a greater chance for reversion to normal, particularly if alternative treatable causes are identified. A positive AD biomarker may prompt consideration for AD-directed therapies provided that other appropriate use recommendations are met [10]. Whether related to improved prognosis or treatment decisions, our findings provide further support for a clinically meaningful impact of incorporating validated blood-based biomarkers like plasma p-tau217 into diagnostic workups in memory clinic settings.

An important study limitation is that participants did not have autopsy confirmation of all possible neuropathological findings and mixed neuropathology is the norm in individuals with progressive cognitive decline, so we cannot draw firm conclusions attributing MCI symptoms to any particular etiology. The predictive accuracy of plasma p-tau217 for Alzheimer's pathology is <100% and the "ground truth" for plasma assay validation typically is positron emission tomography, which itself does not perfectly capture Alzheimer's pathology. Plasma p-tau217 therefore does not equate to neuropathological diagnosis of AD, particularly lower levels of pathology, and accuracy differs by p-tau217 assay. There is some risk for both false positive and false negative AD classifications based on plasma p-tau217 alone. We focused on non-AD factors like vascular disease and psychiatric conditions based on existing literature support as contributors to cognitive changes with aging, but there are many medical history and social determinants of brain health variables not accounted for in our study that may relate to MCI symptoms. Multiple classification and diagnostic schemes have been proposed for "MCI," and our results may not generalize across all methodologies. Data were all from the 1Florida ADRC and replication in other cohorts is necessary. Our center's ethno-racial diversity and emphasis on early symptom phases of neurodegenerative disease provided a strong foundation for the current study on etiological heterogeneity within individuals with MCI. As is often the case, a limiting factor is the imbalanced recruitment of ethno-racial groups across clinic- versus community-based settings, which may limit generalizability. It is essential for future work to better match ethno-racial groups on recruitment sources to optimally compare rates of AD biomarker positivity and to investigate MCI clinico-pathological heterogeneity as a function of race/ethnicity. Ethno-racial groups are not monolithic and our findings may not generalize to Hispanic or Black communities that are not well represented in our cohort. The determination of MCI_{AD+} vs. MCI_{AD-} was made based on a well-studied plasma p-tau217 assay (ALZPath) using center-derived cutoffs corresponding to a positive amyloid PET scan, but binary cut-points are imperfect and might sacrifice important variability on either side of the cutoff. Future work with a larger sample may benefit from leveraging a two-cutoff approach with low, intermediate, and high p-tau217 classifications of AD pathology [27].

5. Conclusions

The clinical diagnosis of MCI is etiologically heterogeneous and often unrelated to underlying Alzheimer's disease. The presence of Alzheimer's pathology in individuals with MCI significantly worsens prognosis. Treating neuropsychiatric symptoms may help reduce cognitive complaints or lower risk for progressive decline irrespective of AD pathology. Interpreting base rates of different MCI phenotypes, frequency of positive AD biomarkers, and progression to dementia requires careful consideration of recruitment source (clinic- vs. community-based), especially for observed variability across ethno-racial groups. Ongoing integration of emerging neurodegenerative disease biomarkers with detailed clinical evaluations of ethno-racially diverse older adults will continue to improve treatment specificity and prognosis by untangling the complex clinico-pathological associations underlying MCI.

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Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2024.100011.

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