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Predicting conversion of patients with Mild Cognitive Impairment to Alzheimer's disease using bedside cognitive assessments

Abby Clarke, Calvin Ashe, Jill Jenkinson, Olivia Rowe, ADNI -, Philip Hyland and Sean Commins

Department of Psychology, Maynooth University, Maynooth, Ireland

ABSTRACT

Introduction: Patients diagnosed with Mild Cognitive Impairment (MCI) often go on to develop dementia, however many do not. Although cognitive tests are widely used in the clinic, there is limited research on their potential to help predict which patients may progress to Alzheimer's disease (AD) from those that do not.

Methods: MCI patients (n = 325) from the longitudinal Alzheimer's Disease Neuroimaging Initiative (ADNI-2) dataset were tracked across a 5 year period. Upon initial diagnosis, all patients underwent a series of cognitive tests including the Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog 13). Twenty-five percent (n = 83) of those initially diagnosed with MCI subsequently developed AD within 5 years.

Results: We showed that those individuals that progressed to AD had significantly lower scores upon baseline testing on the MMSE and MoCA, and higher scores on the ADAS-13, compared to those that did not convert. However, not all tests were equivalent. We showed that the ADAS-13 offers the best predictability of conversion (Adjusted Odds ratio (AOR) = 3.91). This predictability was higher than that offered by the two primary biomarker Amyloid-beta (Aβ, AOR = 1.99) and phospho-tau (Ptau, AOR = 1.72). Further analysis on the ADAS-13 showed that MCI patients that subsequently converted to AD performed particularly poorly on delayed-recall (AOR = 1.93), word recognition (AOR = 1.66), word finding difficulty (AOR = 1.55) and orientation (1.38) test items.

Conclusions: Cognitive testing using the ADAS-13 may offer a simpler, less invasive, more clinically relevant and a more effective method of determining those that are in danger of converting from MCI to AD.

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Mild cognitive impairment; Alzheimer's disease; Mini Mental State Examination (MMSE); Montreal Cognitive Assessment (MoCA); Alzheimer's Disease Assessment scale (ADAS-Cog 13); Alzheimer's Disease Neuroimaging Initiative (ADNI); spatial cognition

Introduction

Mild cognitive impairment (MCI) is a clinical stage between normal aging and dementia (Grundman et al., 2004; Petersen et al., 1999). Individuals with MCI experience a higher degree of memory loss then one would expect for normal aging but fall short of reaching the criteria to receive a dementia diagnosis. MCI can be subclassified further into amnestic MCI (memory impairments present) and non-amnestic MCI (no memory impairments present; Csukly et al., 2016). The prevalence of MCI is thought to be four times greater than dementia (DeCarli, 2003), with prevalence rates among 65–69 old adults at 8.4% and rising to 25.2% in the 80–84 age cohort (Petersen et al., 2018). The conversion rate of MCI to dementia is approximately 10–15% per year; however, after six years with MCI, this conversion rate increases to 80% (Eshkoor et al., 2015). Given this, and the global aging population, early detection of both MCI and those that may convert to Alzheimer's Disease (AD) is critical but challenging.

Many biomarkers including genetic analysis, cerebrospinal fluid analysis of P-tau and/or β-amyloid, neuroimaging, as well as recent blood plasma analysis of P-tau, neurofilament light and the ratio of Aβ42/ Aβ40 have all aided in the diagnosis of AD and the prediction of dementia development in those with MCI (Cullen et al., 2021). Recent models show that blood plasma P-tau can predict AD accurately within four years but that the addition of simple cognitive measures can further improve this accuracy (Palmqvist et al., 2021). However, detection of biomarkers is often invasive, expensive, may not equate to clinical outcomes, and are often not feasible in many care-settings. As such, the role of cognitive tests is critical, especially as they are more clinically relevant, patient-centered, and are often easier and cheaper to administer.

Given the large number of cognitive tests available, it is often difficult to determine the appropriate test to use. A recent review by Tavares-Júnior et al. (2019) showed that of the wide range of cognitive assessment tools used for MCI and AD diagnosis, the Mini-Mental State

CONTACT Sean Commins Sean.Commins@mu.ie Department of Psychology, Maynooth University, Co. Kildare, Ireland

Examination (MMSE, Folstein et al., 1975) and the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) were the mostly frequently used, especially when testing older adults with lower levels of education, at 86.1% and 27.7%, respectively. In addition, the Alzheimer's Disease Assessment Scale-cognition subscale (ADAS-Cog; Rosen et al., 1984) is the most widely used general cognitive measure in clinical trials of AD (Connor & Sabbagh, 2008; Ihl et al., 2012; Rozzini et al., 2007). Given this, an important topic of research is to determine how these tests can be used to help determine MCI progression to AD, and which of these tests best predicts disease progression.

Using the longitudinal Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset that followed MCI participants (and others) across a five-year period, we analyzed scores on three commonly used cognitive tests (MMSE, MOCA and ADAS-13), and two biomarker tests (amyloid-beta (Aβ) and phospho-tau P-tau)) to determine progression from MCI to AD. Hierarchical binary logistic regression analysis was used to determine if these tests significantly contributed to the prediction of transitioning from MCI to AD, and which might offer a better prediction. Further analyses were done to examine whether particular test items within a given cognitive test can help determine MCI to AD conversion.

Methods

Data used in this study

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

Participants

We examined participants from the 5-year ADNI2 longitudinal study (2011–2016, http://adni.loni.usc.edu). All participants were required to be between 55 and 90 years of age, of good health generally, and not have any health-related issues which might interfere with their ability to participate. Sufficient visual and auditory acuity were also required.

Individuals classified as Cognitively Normal must have been free from any memory complaints and have the ability to carry out daily tasks without any cognitive impairment. All individuals also must have had "normal memory" function documented by scoring above education adjusted cutoffs on the Logical Memory II subscale (e.g., ≥ 9 for 16 or more years of education) from the Wechsler Memory Scale–Revised (Wechsler, 1987). A score of 24 or above was required on the Mini Mental State Exam, as well as a Clinical Dementia Rating (Morris, 1993) of 0.

Individuals classified as Mild Cognitive Impairment must have had subjective memory concerns. In addition, individuals must have had "abnormal memory" function documented by scoring within the education adjusted ranges on the Logical Memory II subscale from the Wechsler Memory Scale–Revised. However, similar to healthy participants a score of 24 or above on the Mini Mental State. Participants also required a Clinical Dementia Rating score of 0.5.

Individuals classified as having Alzheimer's Disease must have had subjective memory concerns. Individuals must also have had "abnormal memory" function documented by scoring within the education adjusted ranges on the Logical Memory II subscale (e.g., ≤ 8 for 16 or more years of education) from the Wechsler Memory Scale–Revised. A score between 20 and 26 was required on the Mini Mental State Exam. A score of 0.5–1 on the Clinical Dementia Rating scale was necessary, as well as meeting the criteria for probable AD as defined by the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA).

The presence of any significant neurological disease (e.g., Parkinson's Disease, Huntington's disease or multi-infarct dementia) or psychiatric disorder (e.g., depression or bipolar disease, history of schizophrenia) were exclusionary. Individuals having a history of alcohol or substance abuse within the last 2 years were also excluded from the study. We also generated a number of our own exclusion criteria for the purpose of the analysis. First, multiple conversions were removed from the data set. For example, if an individual was MCI at baseline, then classified as AD, and later reverted back to MCI (MCI-AD-MCI), they were excluded. This ensured only single conversions were analyzed (i.e., MCI-CN, MCI-MCI and MCI-AD). Eleven participants were excluded using this criterion. Second, in cases where baseline scores were missing for a particular test (the MMSE, MoCA or ADAS-13), the individual was excluded. Five participants were excluded as result of missing baseline scores pertaining to the MoCA. Third, we only used new participants to ADNI2. Any

participants that were rolled over from ADNI1 or ADNI GO were excluded.

Following this, data was analyzed using 764 participants. At baseline, 290 of these participants were classified as being cognitively normal (male(m)/female(f): 132/158), 325 had been diagnosed with MCI (m/f: 175/150) and 149 with AD (m/f: 88/61). Of the 325 participants that were diagnosed with MCI at baseline, 222 (m/f: 126/96) continued with a diagnosis of MCI (MCI-MCI) for the remainder of the study, 83 (m/f: 41/42) converted to AD (MCI-AD), and the final 20 (m/f: 8/12) reverted to being cognitively normal after an initial diagnosis of MCI (MCI-CN).

Cognitive tests

Participant's MMSE (Folstein et al., 1975), MoCA (Nasreddine et al., 2005) and ADAS-13 (Rosen et al., 1984) baseline scores were used for the present analysis. The MMSE is a 30-point cognitive based assessment which takes 10–15 minutes to administer. The test is made up of 6 test items, each relating to a different cognitive domain. These test items are orientation, registration, attention and calculation, recall/memory, language and copying/visuospatial. The lower the score indicates poorer performance. The MoCA takes 10 minutes to administer and is also scored out of 30. Test items included in the MoCA assess visuospatial ability, executive functions, attention, concentration, memory, language and orientation. The ADAS-Cog is a measure of cognitive performance (Cano et al., 2010). The original ADAS-Cog, the ADAS-Cog 11, does this by assessing how people perform on 11 tasks (Cano et al., 2010). These tasks include word recall, commands, constructional praxis, naming, ideational praxis, orientation, word recognition, remembering instructions, comprehension of spoken language, word-finding difficulty in spontaneous speech, and spoken language ability. Seven of these tasks are scored based on the number of incorrect answers, and the other four tasks are scored from zero to five, with zero representing no limitations and 5 representing maximum limitations. The lower a person scores on the ADAS-Cog, the better their cognitive performance (Rosen et al., 1984). The ADAS-Cog 13, used here, includes the 11 tasks used in the original assessment, as well as tasks involving delayed word recall and number cancellation (Kueper et al., 2018). The ADAS-Cog administration time lasts approximately 30–45 min (Skinner et al., 2012).

Biomarkers

The details of the CSF analysis have been described in http://adni-info.org. Briefly, pristine aliquots were examined by the validated and highly automated Roche Elecsys electrochemiluminescence immunoassays. Cerebrospinal fluid (CSF) concentrations of amyloid beta (Aβ1-42) and 181phospho-tau (Ptau) were examined for this study.

Statistics

Data were exported to IBM SPSS (version 28) for statistical analysis. The data analytic plan for this study involved three phases. First, one-way analysis of variance (ANOVAs) tests were conducted to compare age, education, MMSE, MoCA, ADAS-13 scores between groups. Statistical significance was indicated at the $p < 0.05$ level for all analyses. Eta squared values are reported throughout the results section and are referred to as effect size. Raincloud plots were constructed using the website https://gabrifc.shinyapps.io/raincloudplots/ and described by Allen et al. (2019).

Second, hierarchical binary logistic regression analysis was used to determine how well scores on the three cognitive tests and the two biomarker tests predicted transitioning from MCI to AD. The criterion variable was MCI to AD progression and the reference category was the group of individuals who maintained their MCI status along with those that transitioned from MCI to CN status. The predictor variables were the various cognitive and biomarker tests. In the first step of the model, total scores on the MMSE, MoCA, and ADAS-13 were entered. This step determines the unique effect of each cognitive test to predict MCI to AD transition. In the second step, total scores for Aβ and Ptau were entered. This step tests if the use of biomarker tests significantly contributed to the prediction of transitioning from MCI to AD above and beyond the three cognitive tests, and if the cognitive tests predict MCI to AD transition independent of biomarker tests. In the third step, three covariates (age, gender, and years in education) were added to determine if the independent associations between test scores and transitioning from MCI to AD were influenced by these individual characteristics. Unadjusted associations are reported as odds ratios (ORs) and adjusted associations as adjusted ORs (AORs). To determine the relative predictive strength of the different cognitive and biomarker tests, all variables were standardized by creating z-score variables, and the model was re-estimated.

Third, a set of potential post-hoc analyses were planned based on the findings from phase 2. If one or more of the cognitive tests was found to be independently associated with transitioning from MCI to AD, the subcategories of that test would be entered as predictor variables in a binary logistic regression analysis to

determine which subcategory independently predicted MCI to AD transition.

At the variable level, missing data ranged from 0.0% (on the MMSE test) to 9.0% (on the Ptau and Aβ tests). The missing values were deemed to be missing completely at random (Little's MCAR test: $\chi 2$ (14) = 15.11, p = .371). Missing data were handled by the default listwise deletion option in SPSS for binary logistic regression.

Ethics

Informed written consent was obtained at each site by the ADNI from all participants before any screening procedures or data collection began, as outlined in the ADNI2 procedure manual (https://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf). The study was also approved by the institutional review board of each site.

Results

General demographics

At the start of the study, 325 participants had been diagnosed with MCI (of the amnestic type). Across the five-year study period (2011–2016), 222 of the 325 MCI participants (68%) continued with a diagnosis of MCI (i.e., MCI-MCI), 83 (26%) converted to Alzheimer's Disease (MCI-AD), and 20 (6%) reverted to being cognitively normal (MCI-CN). At baseline, the three MCI groups were not statistically different from each other in terms of age (F = 2.306, df = 2,322, p = 0.101, partial η2 = 0.014), or years spent in education (F = 2.782, df = 2,322, p = 0.063, partial η2 = 0.017). Gender was also generally well matched across the three MCI groups (See, Table 1 for details).

Phase 1: Tests of cognition and biomarkers

When we compared baseline **MMSE** scores across the three MCI groups (Figure 1(a)) an overall statistical difference was found (F = 13.639, df = 2,322, p < 0.001, partial η2 = 0.078). *Post hoc* analysis using Tukey's HSD revealed that the MCI-AD group (M = 27.20, SD = 1.74) had significantly lower MMSE scores than both the MCI-CN group (M = 29, SD = 1.12, p < 0.001) and the MCI-MCI group (M = 28.14, SD = 1.69, p < 0.001). No significant difference was found between the MCI-CN group and the MCI-MCI group (p = 0.075). The groups baseline **MoCA** scores were also found to be significantly different (Figure 1(b)), F = 24.696, df = 2,319, p < 0.001, partial η2 = 0.134). Tukey's HSD *post hoc* test showed that the MCI-CN (M = 25.60, SD =2.32) group had significantly higher mean MoCA scores compared to the MCI-MCI group (M = 23.51, SD = 3.1, p = 0.008) and the MCI-AD group (M = 21.27, SD = 2.7, p < 0.001). The MCI-AD group was also significantly lower than the MCI-MCI group (p < 0.001). Likewise, baseline **ADAS-13** scores also showed an overall a statistically significant effect (F = 65.69, df =2,318, p < 0.001, partial η2 = 0.41). *Post-hoc* comparisons using the Tukey HSD test indicated that MCI patients that progressed to AD (MCI-AD) obtained significantly higher scores (M = 22.05, SD = 6.65) compared to those whose MCI that reverted to healthy (MCI-CN, M = 10.79, SD = 4.53) and those that remained the same (MCI-MCI, M = 13.84, SD = 5.65). There were no

Table 1. Comparison of demographics of the three Mild Cognitive Impairment (MCI) cohorts (MCI-CN (Mild Cognitive Impairment to healthy control conversion), MCI-MCI (those that remained with MCI diagnosis) and MCI-AD (Mild Cognitive Impairment to Alzheimer's disease conversion)) at the start of the study.

	MCI-CN (n = 20)	MCI-MCI (n = 222)	MCI-AD (n = 83)
Age			
Mean years (SD)	68.8 (1.58)	71.6 (0.51)	72.6 (0.75)
Education status			
Mean Years (SD)	17.6 (0.50)	16.1 (0.18)	16.5 (0.28)
Gender			
Male	8 (40%)	126 (57%)	41 (49%)
Female	12 (60%)	96 (43%)	42 (51%)
Marital Status			
Never Married	1 (5%)	9 (4%)	4 (5%)
Married	14 (69%)	162 (73%)	62 (75%)
Divorced	4 (21%)	27 (12%)	7 (9%)
Widowed	1 (5%)	22 (10%)	9 (11%)
Unknown	0	2 (1%)	0

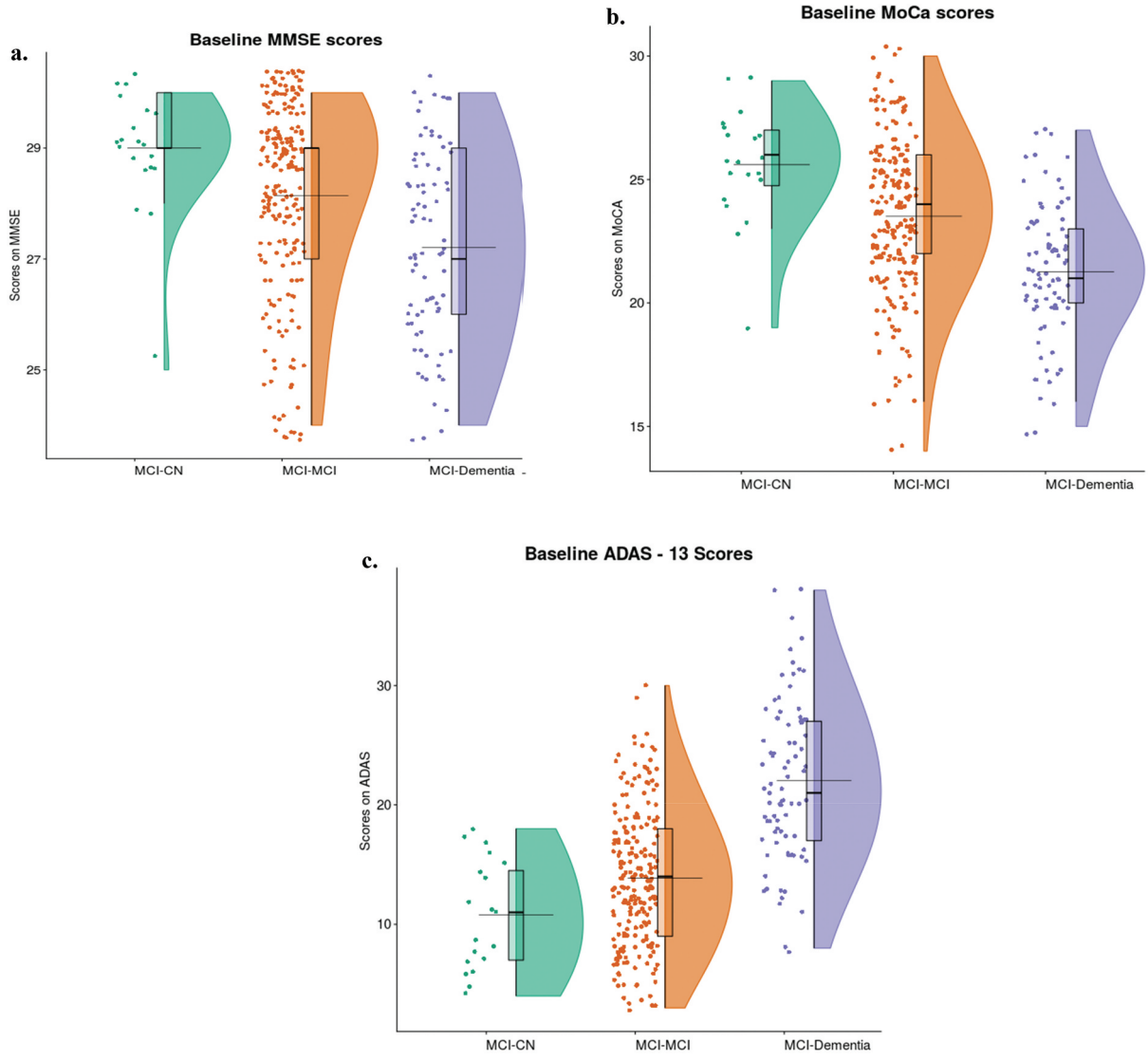

Figure 1. Boxplot, individual scores and distribution of the overall baseline Mini Mental State Examination (MMSE) (1a), Montreal Cognitive Assessment (MoCA) (1b) and Alzheimer's Disease Assessment Scale (ADAS-13) (1c) scores obtained by diagnosed MCI patients that subsequently reverted to healthy normal (MCI-CN, green), remained as MCI (MCI-MCI, brown) or converted to AD (MCI-AD, purple) over a 5 year period. Dark horizontal line in boxplot = median. Large horizontal bar = mean.

significant differences between those MCI-CN and MCI-MCI groups (see, Figure 1(c)).

Analysis of Aβ showed that those in the MCI-AD group (M = 751.29 pg/ml, SD = 273.02) had statistically different levels when compared to both the MCI-CN (M = 1144.74 pg/ml, SD = 398.71) and MCI-MCI (M = 1052.44 pg/ml, SD = 426.84) groups ($F(2,292) = 18.99$, $p < 0.001$, partial $\eta 2 = 0.13$). Similarly, analysis of Ptau showed an overall significant difference between the three groups ($F(2,292) = 30.36$, $p < 0.001$, partial $\eta 2 = 0.21$), with the MCI-AD group (M = 36.81 pg/ml, SD = 17.01) having statistically higher levels when compared to both the MCI-MCI (M = 24.02 pg/ml, SD = 12.47) and MCI-CN (M = 17.29 pg/ml, SD = 5.42) groups.

Phase 2: Predictors of MCI to AD conversion

The unadjusted and adjusted ORs for the associations between each predictor variable and transitioning from MCI to AD are reported in Table 2. When considered in isolation, each cognitive and biomarker test was significantly associated with transitioning from MCI to AD. Notably, none of the covariates (age, gender and education status) were bivariately associated with conversion from MCI to AD.

Scores on the three cognitive tests were entered into the first step of the hierarchical binary logistic regression model, and this was statistically significant ($\chi 2\ (3) = 94.90$, $p < .001$) with 79.9% of participants being correctly classified. The ADAS was the only cognitive test

Table 2. Hierarchical binary logistic regression results predicting transitioning from Mild Cognitive Impairment (MCI) to Alzheimer's Disease (AD). Odds ratios represent the unadjusted effect of each variable to predict conversion from MCI-AD. In step 1 the regression model, the three cognitive tests (Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Alzheimer's Disease Assessment Scale (ADAS-13) were added to the model. Step 2 adds the biomarkers (phospho-tau (Ptau) and Amyloid β (Aβ) to the model. Step 3 then adds the covariates (age, gender and education level).

	MCI-AD	MCI-AD	MCI-AD	MCI-AD	MCI-AD
	OR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	Standardized AOR (95% CI)
Cognitive Performance tests					
MMSE	**0.72 (0.63, 0.84)**	1.02 (0.83, 1.24)	1.15 (0.92, 1.43)	1.12 (0.89, 1.40)	1.21 (0.82, 1.80)
MOCA	**0.77 (0.71, 0.85)**	0.93 (0.82, 1.06)	0.92 (0.80, 1.06)	0.89 (0.77, 1.03)	1.43 (0.90, 2.28)
ADAS	**1.25 (1.18, 1.32)**	**1.23 (1.15, 1.31)**	**1.21 (1.13, 1.29)**	**1.22 (1.14, 1.30)**	**3.91 (2.41, 6.33)**
Biomarker tests					
Ptau	**1.06 (1.04, 1.09)**		**1.04 (1.02, 1.07)**	**1.04 (1.01, 1.06)**	**1.72 (1.23, 2.42)**
Aβ	**0.99 (0.99, 0.99)**		**0.99 (0.99, 1.00)**	**0.99 (0.99, 0.99)**	**1.99 (1.30, 3.05)**
Covariates					
Age	1.03 (0.99, 1.06)			0.98 (0.93, 1.03)	0.84 (0.59, 1.22)
Gender (0 = males, 1 = females)	1.30 (0.79, 2.15)			1.96 (0.94, 4.10)	1.40 (0.97, 2.02)
Education	1.04 (0.95, 1.14)			1.13 (0.98, 1.29)	1.38 (0.96, 1.98)

Statistically significant effects in bold; OR = odds ratio; AOR = adjusted OR; 95% CI = 95% confidence intervals.

significantly and independently associated with conversion from MCI to AD. The two biomarker tests were added to the model at step 2 and made a statistically significant contribution ($\chi 2$ (2) = 29.05, p < .001), with 81.9% of participants being correctly classified. The ADAS remained significantly and independently associated with conversion from MCI to AD, and Ptau and Aβ scores were also significantly and independently associated with transitioning from MCI to AD. The addition of the covariates at step 3 did not significantly contribute to the model ($\chi 2$ (3) = 6.79, p = .079). In the final model, 84.3% of people were correctly classified. The sensitivity (i.e., those predicted to convert from MCI to AD that did so) was 65.4%, and the specificity (i.e., those predicted not to convert from MCI to AD that did not) was 91.5%. In the final step, the ADAS (AOR = 1.22), Ptau (AOR = 1.40), and Aβ (AOR = 0.99) remained significant predictors of MCI to AD conversion. The final column of Table 2 presents the AORs when all predictor variables were standardized and unidirectional. As can be seen, the strongest predictor of MCI-AD conversion was scores on the ADAS.

Phase 3: Analysis of subcategories

Based on the findings of the hierarchical binary logistic regression analysis in phase 2, we examined how the 13 subcategories of the ADAS independently predicted MCI to AD conversion. The model was statistically significant ($\chi 2$ (13) = 113.99, p < .001), correctly classified 83.2% of participants, and had a sensitivity of 50.0% and a specificity of 94.6%. The effects for each subscale are presented in Table 3. Four subcategories significantly predicted MCI to AD progression, and when the scores on each subcategory were standardized, the strongest effect was for delayed recall (AOR = 1.93), followed by word recognition (AOR = 1.66), word finding (AOR = 1.55), and orientation (AOR = 1.38).

Table 3. Hierarchical binary logistic regression results predicting transitioning from Mild Cognitive Impairment (MCI) to Alzheimer's Disease (AD) but using multiple cognitive tests and biomarkers tests. Step 1 provides adjusted odds ratio (AOR) if using 1, 2 or 3 cognitive tests compared to none. Step 2 adds the use of 1 or 2 biomarker tests versus none, and step 3 adds the three covariates.

	MCI-AD	MCI-AD
	Unstandardized AOR (95% CI)	Standardized AOR (95% CI)
Word recall	1.31 (0.96, 1.80)	1.53 (0.94, 2.49)
Commands	2.27 (0.94, 5.49)	1.35 (0.98, 1.85)
Constructional Praxis	0.82 (0.46, 1.47)	0.89 (0.65, 1.24)
Naming	1.70 (0.82, 3.52)	1.24 (0.92, 1.66)
Ideational Praxis	1.16 (0.58, 2.33)	1.06 (0.81, 1.38)
Orientation	**1.46 (1.05, 2.02)**	**1.38 (1.04, 1.82)**
Word recognition	**1.20 (1.05, 1.38)**	**1.66 (1.15, 2.39)**
Remembering instructions	2.39 (0.61, 9.45)	1.27 (0.87, 1.84)
Comprehension of spoken language	0.34 (0.10, 1.12)	0.67 (0.43, 1.04)
Word finding difficulty	**2.22 (1.17, 4.22)**	**1.55 (1.09, 2.20)**
Spoken language	0.98 (0.37, 2.59)	0.99 (0.73, 1.35)
Delayed recall	**1.28 (1.07, 1.53)**	**1.93 (1.21, 3.07)**
Number cancellation	1.22 (0.84, 1.77)	1.19 (0.85, 1.67)

Statistically significant effects in bold; AOR = adjusted OR; 95% CI = 95% confidence intervals.

Discussion

Overall, the results suggest that the three cognitive tests (MMSE, MoCA and ADAS-13) can be used to help predict the conversion of patients with MCI to AD within a 5-year period. However, the 3 tests were not equivalent. In this respect, our findings suggest that poor scores on the ADAS-13 seem to offer a better prediction of subsequent conversion from MCI to AD. The ADAS-cog is considered the gold standard for

examining the efficacy of antidementia treatments (Kueper et al., 2018) but tends not to be used in the clinic. There are two primary reasons for this, first the ADAS requires much longer to administer compared to other tests; second, recent reports have questioned its sensitivity, especially being able to detect deficits early on (at the pre-dementia stage, see, Raghavan et al., 2013). However, our findings suggest that the ADAS-13 can be used successfully to detect dementia conversion at an early stage. This, along with recent scoring modifications of the ADAD-cog that have improved its sensitivity (see, Verma et al., 2015) may allow for the more widespread adoption of the test, particularly in a clinic setting. It may come as no surprise that the MMSE emerged as a poor predictor (see, also Tsoi et al., 2015). However, we are unable to offer a firm conclusion on this test as MCI patients were required to perform within the normal range of the MMSE (as part of the inclusion criteria). We acknowledge this as a limiting factor of our study.

Furthermore, the extra subcategories (e.g., word finding/recognition in ADAS) and extra tests in particular subcategories may help explain the additional sensitivity of the ADAS tests compared to the MMSE or indeed the MoCA. In this respect, delayed recall, word recognition, word finding and orientation are among the key cognitive processes that were found to be particularly sensitive for predictions of conversions. These findings support and extend the recent study by Choe et al. (2020) that used the MMSE only. These results would indicate that MCI patients scoring poorly on these particular categories may be at a greater risk of developing AD within 5 years, and may warrant extra attention and follow-up. Interestingly, although episodic memory is currently the most widely used cognitive marker for AD, orientation and spatial cognition deficits may offer better markers for earlier diagnosis of the disease (Coughlan et al., 2019, 2018), and particularly the risk of conversion from MCI to AD. Compared to episodic memory, orientation deficits are rarely seen in normal individuals or other forms of dementia (Coughlan et al., 2018); therefore, follow-up assessments that focus on orientation and memory may allow for an even better prediction of AD in the future.

In a recent model Palmqvist et al. (2021) showed that by adding cognitive tests to Ptau analysis offers better predictability than using Ptau alone. Here we provide evidence of the opposite, that cognitive testing (especially the ADAS-13) offer excellent predictability, and may be even better than two of the most commonly used biomarkers. Given the invasive nature of biomarker extraction (via blood tests or more commonly through CSF tests) and the time taken to analyze biological samples, using cognitive tests may prove to be a simpler, cheaper, more efficient, and, importantly, just as effective and reliable method at predicting the conversion from MCI to AD compared to biomarkers. Although in our analysis we were unable to clearly offer a distinction between the predictive nature of Aβ compared to Ptau, there is emerging evidence that Ptau is the critical biomarker of AD (Hedden et al., 2013; Huber et al., 2018). Furthermore, as tangles first appear in the entorhinal cortex and hippocampal regions of the brain, before spreading onwards causing greater neurodegeneration (Commins & Kirby, 2019; Medina & Avila, 2014), it may come as no surprise that these brain regions are critically involved in aspects of orientation (in time and place) and memory (Barry et al., 2016; Coughlan et al., 2019, 2018; Diviney et al., 2013). The next step is to determine the mechanistic link between these specific cognitive processes and biomarkers, especially Ptau (see, Choe et al., 2020).

The study has a number of limitations. First, the findings are limited to a single database. Using other databases may allow for better validation; however, other databases may use different criteria for assessing MCI and may also differ in terms of the cognitive and neuropsychological tests administered. The order of test administration may have also had in impact. Furthermore, the ADNI is a very select database, it is taken from a single country (UAS), with the majority of participants being white. As such we must be very careful with our interpretation, and be aware of the environmental settings, race and social demographics of the clinical sample. For example, the progression rate from MCI to AD differs depending on whether the sample is clinical or community-based. Tomaszewski Farias et al. (2009) showed that a clinic sample had an annual conversion rate of 13%, compared to 3% with a community sample. Similar discrepancies have been reported by others – annual progression rates to dementia in clinical samples are 10% −15% compared to 6% −10% in community samples (see, Oltra-Cucarella et al., 2018). Despite these, our results do support the recent broader findings of Palmqvist et al. (2021) and also Choe et al. (2020).

Second, while this study is one of the first to examine multiple cognitive tests, others tests of cognition such as the Mini-Cog test and Addenbrooke's Cognitive Examination-Revised (ACE-R) may offer similar predictability, particularly those that also examine orientation, visual spatial (e.g., ACE-R), as well as, memory components. Third, the low number of participants that reverted to healthy normal from MCI (MCI-CN, only 6%) prevented us from doing a deeper analysis on this particular group. Understanding potential protective

characteristics in this cohort may allow for better preventative strategies based on cognitive or other therapeutic interventions. Finally, as with many longitudinal studies patients tend to drop out across the years, which is an issue. In this study, there was an average attrition rate overall of approximately 10% per annum. The attrition increased with time, from 2% between years 1 and 2 to 23% between years 4 and 5. However, both our groups of concern (MCI-MCI and MCI-AD) had similar attrition rates at 13% and 14%/annum, respectively. These rates also compare favorably to other studies. For example, Facal et al. (2016) reported an attritional rate of 21.5% and showed no significant difference in cognitive performance between MCI respondents and non-returners.

In conclusion, this study demonstrated that the ADAS-13 is a very useful tool in helping to identify those MCI patients that are a greater risk of progressing to AD. Particular attention should be paid to those MCI patients that perform badly on memory, orientation and word recognition and finding aspects of the task.

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Disclosure statement

No potential conflict of interest was reported by the author(s)

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Ethical approval

Data analysed was from the ADNI dataset, which is freely available for secondary analysis. Written informed consent was obtained by ADNI according to the Declaration of Helsinki, and procedures were approved by site-specific Institutional Review Boards for the Protection of Human Subjects (see http://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/clinical/ADNI-2_Protocol.pdf).

Author contributions

CA, JJ, OR: Analysed data; AC, PH, SC: Analysed data, edited and wrote manuscript; ADNI: provided data.

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