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Exploration of salient risk factors involved in mild cognitive impairment

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Abstract

Mild cognitive impairment (MCI) is a prevalent and complex condition among older adults that often progresses into Alzheimer's disease (AD). Although MCI affects individuals differently, there are specific indicators of risk commonly associated with the development of MCI. The present study explored the prevalence of seven established MCI risk categories within a large sample of older adults with and without MCI. We explored trends across the different diagnostic groups and extracted the most salient risk factors related to MCI using partial least squares. Neuropsychological risk categories showed the largest differences across groups, with the cognitively unimpaired groups outperforming the MCI groups on all measures. Apolipoprotein E4 (ApoE4) carriers were significantly more common among the more severe MCI group, whereas ApoE4 non-carriers were more common in the healthy controls. Participants with subjective and objective cognitive impairment were trending towards AD-like cerebral spinal fluid (CSF) biomarker levels. Increased age, being male and having fewer years of education were identified as important risk factors of MCI. Higher CSF tau levels were correlated with ApoE4 carrier status, age and a decrease in the ability to carry out daily activities across all diagnostic groups. Amyloid beta$_{1–42}$ CSF concentration was positively correlated with cognitive and memory performance and non-ApoE4 carrier status regardless of diagnostic status. Unlike previous research, poor cardiovascular health or being female had no relation to MCI. Altogether, the results highlighted risk factors that were specific to persons with MCI, findings that will inform future research in healthy aging, MCI and AD.

Abbreviations: AD, Alzheimer's disease; ADAS, Alzheimer's Disease Assessment Scale-Cognitive; ADNI, Alzheimer's Disease Neuroimaging Initiative; ANOVA, analysis of variance; ApoE4, apolipoprotein E4; Aβ_{42}, amyloid-beta$_{1–42}$ peptide; BMI, body mass index; B-PLS, behavioural partial least squares; CF, Category Fluency Test; CSF, cerebral spinal fluid; DBP, diastolic blood pressure; EMCI, early mild cognitive impairment; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; H/L, Hispanic/Latinx; HC, healthy controls; LMCI, late mild cognitive impairment; LV, latent variable; MCI, mild cognitive impairment; MC-PLS, mean-centred partial least squares; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; PLS, partial least squares; p-tau, phosphorylated tau at threonine 181; RAVLT, Rey Auditory Verbal Learning Test; SBP, systolic blood pressure; SMC, significant memory concern; TMA, Trail Making Test A; TMB, Trail Making Test B; t-tau, total tau; WMS-I, Wechsler Memory Scale-Logical Memory Immediate Test.

KEYWORDS
Alzheimer's disease, cognitive decline, dementia, exploratory study, pathology

1 | INTRODUCTION

Mild cognitive impairment (MCI) has been identified in a proportion of older adults and is often described as precursor to clinical dementia (Petersen et al., 2014). MCI does not interfere with daily functioning and is characterized by cognitive decline that is unexpected for a person's age or education level (Werner & Korczyn, 2008). Many cases of MCI progress to Alzheimer's disease (AD) dementia (Boyle et al., 2006; Glynn et al., 2021); in clinical settings, patients with MCI have been demonstrated to convert to AD at an annual rate of 10% to 30% (Michaud et al., 2017; Ottoy et al., 2019). However, there are some individuals with MCI that remain stable or even return to normal cognition over time (Gauthier et al., 2006). A recent meta-analysis of the Americas, Europe and Australia demonstrated 22.5 MCI diagnoses per 1000 person-years for 75- to 79-year-olds, and the incidence increased with age (Gillis et al., 2019). With the predicted global growth of the aging population (United Nations, 2020) and the likely accompanying increase in MCI diagnoses, there is a great need to further understand MCI, especially as a prodromal stage to AD.

There are many indicators of risk for the development of MCI, such as lifestyle factors (e.g., alcohol consumption; Koch et al., 2019), environmental factors (e.g., educational attainment; Meng & D'Arcy, 2012) and non-modifiable factors (e.g., age; Gillis et al., 2019). Furthermore, cerebral spinal fluid (CSF) biomarkers have been reported and emphasized as salient indicators of cognitive decline, MCI and neurodegeneration. These include amyloid-beta$_{1-42}$ peptide (Aβ_{42}), total tau (t-tau; Arai et al., 2000) and phosphorylated tau at threonine 181 (p-tau; Andreasen et al., 1999; Andreasen, Vanmechelen, et al., 2003; Hampel et al., 2004; Hansson et al., 2006; van der Vlies et al., 2009). Specifically, low Aβ_{42} CSF levels, and elevated t-tau and p-tau CSF levels are seen in people diagnosed with MCI, especially those who later develop AD (Mattsson, 2009; Park et al., 2019). The identification of these risk factors has shown how a person might be more susceptible to an MCI diagnosis. However, these CSF changes have also been demonstrated in healthy older adults who remain cognitively healthy (Stomrud et al., 2015). Thus, whether one CSF biomarker is a better predictor of MCI or whether there is a particular CSF biomarker concentration that is specific to MCI and not a result of the normal aging process is unknown.

MCI is a heterogeneous condition with a range of risk factors that can co-occur and interact with each other. Consequently, there is considerable individual variability of risk for MCI that reflects the multifactorial nature of the mechanisms that are involved in its development. To mitigate MCI and dementia, risk factors need to be recognized and understood to develop preventative plans or treatments.

Despite the mixed aetiology of MCI, previous MCI observational studies have mainly focused on single risk factors (Ganguli et al., 2013; Kivipelto, 2001; Schrader et al., 2020; Solfrizzi et al., 2004; Tervo et al., 2004). For the current study, we sought to analyse the relationships of multiple MCI risk factors within a large sample of older adults with and without MCI. The aim of this exploratory study was to investigate whether putative MCI risk factors were predominantly found within MCI participants in comparison with cognitively healthy older adults. If this result is true, then we can assume with that these risk factors are specific to MCI and are not related to healthy aging. To explore these risk factors prevalence across diagnostic group, partial least squares (PLS) analysis (Krishnan et al., 2011; McIntosh & Lobaugh, 2004) was used to identify the risk factors particular to MCI participants.

2 | METHODS

2.1 | Alzheimer's Disease Neuroimaging Initiative (ADNI)

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). 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, positron emission tomography, 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 were recruited, scanned and tested at 57 different sites across the United States. For the present work, data from ADNI-GO, ADNI-2 and ADNI-3 were used.

2.2 | Participants

The clinical description of the ADNI cohort has been previously published (Petersen et al., 2010). From 3000 screening and baseline data, all risk factor measures of interest were available for 531 participants. Participants were between the ages of 55 and 93 years and their data aggregated into four different diagnostic groups: healthy controls (HC), significant memory concern (SMC), early MCI (EMCI) and late MCI (LMCI). Outliers in each risk factor were assessed and removed from each diagnostic group separately if they were 4 standard deviations above or below the mean ($n = 25$). Once outliers were removed, there were 506 participants (53% female). HC participants ($n = 133$) included those with normal cognition and no memory complaints whereas SMC participants ($n = 118$) had normal cognition but expressed subjective memory complaints. Diagnoses of EMCI ($n = 129$) or LMCI ($n = 126$) were established at the screening visit based on subjective memory concerns and performance on the Wechsler Memory Scale-Logical Memory Delayed Test (Wechsler, 1945), Mini-Mental State Examination (Kurlowicz & Wallace, 1999) and the Clinical Dementia Rating (Morris, 1993). For more information on the breakdown of EMCI and LMCI, see Table S1 or ADNI-GO, 2 and 3 clinical protocols (http://adni.toni.usc.edu and Study Documents). The main difference between the two MCI groups was that EMCI participants had less severe cognitive, memory and functional impairments than LMCI and thus their rate of progression to AD would be slower. Both participant groups meet criteria for amnesic MCI, but EMCI participants are at an earlier point in the clinical spectrum (Aisen et al., 2010).

All participants were required to provide written informed consent, complete the screening and baseline visits, have a minimum of 6 years of education, be fluent in English and have no general health issues, other than MCI, that would interfere with the study timeline. For further inclusion and exclusion criteria and protocol measures, see the study protocol (Weiner et al., 2016).

2.3 | Demographics

A 13-item questionnaire was used to collect participant demographic data. The questionnaire was completed by the participant or a qualified study partner, that is, someone who is in frequent contact with the participant (minimum average of 10 h/week) if the participant was unable to provide the information. Demographic factors included in the current study were sex, age, marital status, years of education, ethnicity and race. The ethnicity options were Hispanic/Latinx (H/L) or non-Hispanic/Latinx (non-H/L). The race options were American Indian or Native Alaskan, Asian, Indigenous Hawaiian or other Pacific Islander, Black or African American, Caucasian or Multiracial.

2.4 | Cardiovascular health measures

To assess cardiovascular health, systolic blood pressure (SBP), diastolic blood pressure (DBP) and body mass index (BMI), measured in kilograms divided by metres squared, were used.

2.5 | Apolipoprotein E4 (ApoE4) genotyping

Participants gave a 10 ml blood sample for genome-wide genotyping. ApoE was the only gene analysed in the current study. Blood was drawn and pre-processed at each of the research centres according to ADNI protocol (Weiner et al., 2016). ApoE genotypes were determined using standard polymerase chain reaction methods. Although there were seven different ApoE gene status combinations in our sample (see Table S2), we split the participants into ApoE4 non-carriers ($n = 304$) or ApoE4 carriers ($n = 201$).

2.6 | CSF biomarker collection

A small sample of CSF was collected at the baseline visit and the samples were processed as previously described (Shaw et al., 2009). $A\beta_{42}$, t-tau and p-tau CSF concentrations were measured in picograms per millilitre using the Roche Elecsys immunoassays on the Cobas e601 automated system (http://www.adni-info.org and Supporting Information).

2.7 | Neuropsychological data

Ten neuropsychological tests were analysed in the current study; tests that were used to diagnosis MCI were not included, that is, the Wechsler Memory Scale-Logical Memory Delayed Test, the Mini-Mental State Examination and the Clinical Dementia Rating. All assessments were performed during the participants' screening or baseline visits. The assessments were split into two categories based on their main objectives: cognition and memory, or functional health measures. Cognitive assessments consisted of the Alzheimer's Disease Assessment Scale-Cognitive (ADAS; Rosen et al., 1984), Montreal

Cognitive Assessment (MoCA; Nasreddine et al., 2005) and the Trail Making Tests A and B (TMA and TMB, respectively; Reitan, 1958). The memory assessments included Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), Category Fluency Test (CF; Butters et al., 1987) and the Wechsler Memory Scale-Logical Memory Immediate Test (WSM-I; Wechsler, 1945). To measure functional health, the Functional Activities Questionnaire (FAQ; Pfeffer et al., 1982), Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986) and Neuropsychiatric Inventory (NPI; Cummings, 1997) were used; for these measures, a lower score indicated fewer functional health issues. For the cognitive and memory measures, a higher performance score indicated a better performance on all assessments expect for ADAS, TMA and TMB tests; these latter scores were flipped in the following multivariate analyses to help with the interpretation of the results. Further descriptions of each assessment are reported in Table S3.

2.8 | Statistical analysis

To explore the risk factors of interest and their relationship to the four diagnostic groups, a mean-centred PLS (MC-PLS) analysis was used. PLS was used because it operates well on large datasets, such as ADNI, as well as it has the ability to extract important features in the form of latent variables (LVs) that may not be extracted from univariate tests. MC-PLS focuses on multivariate patterns that differentiate groups, similar to discriminant function analysis (see paper by Krishnan et al., 2011, for more information on applications of MC-PLS and other PLS techniques).

In the current study, risk factors were assigned to seven categories (see Table 1). All risk categories were assessed between diagnostic groups. Race was not assessed further because of the lack of variability in the sample (see Table 2).

The first MC-PLS analysis consisted of 22 risk factors. The input matrix consisted of 28 columns (506×28) because the categorical risk factors were contrast coded depending how many categories they contained. For example, sex had two categories (i.e., male and female); therefore, male and female became their own risk factors whereby a female participant would be coded as 1 for the female risk factor but would be coded as 0 for the male risk factor and vice versa (see Table 1 for more information). After being contrast coded, all the risk factor variables were mean-centred. This matrix was centred with respect to the grand mean, so each risk factor mean was expressed as the group's mean deviation from the grand mean. The mean-centred matrix was then decomposed with singular value decomposition to identify the structure of the LVs. Three outputs were obtained from the singular value decomposition that were used to interpret

TABLE 1 Risk factor categories, their risk factor variables and variable types

Risk categories	Risk factors	Variable type
ApoE4 gene	ApoE4 carrier status	Categorical (ApoE4 carrier or ApoE4 non-carrier)
CSF concentrations	$A\beta_{42}$ levels	Continuous
	t-tau levels	
	p-tau levels	
Cognitive performance	ADAS	Continuous
	MoCA	
	TMA	
	TMB	
Memory performance	RAVLT	Continuous
	CF	
	WMS-I	
Functional health measures	FAQ	Continuous
	GDS	
	NPI	
Cardiovascular health measures	SBP	Continuous
	DBP	
	BMI	
Demographics	Sex	Categorical (male or female)
	Age	Continuous
	Education	Continuous
	Marital status	Categorical (married, widowed, divorced or never married)
	Ethnicity	Categorical (Hispanic/Latinx or non-Hispanic/Latinx)

Abbreviations: ADAS, Alzheimer's Disease Assessment Scale-Cognitive; ApoE4, apolipoprotein E4; $A\beta_{42}$, amyloid-beta$_{1-42}$; BMI, body mass index; CF, Category Fluency Test; CSF, cerebral spinal fluid; DBP, diastolic blood pressure; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; p-tau, phosphorylated tau at threonine 181; RAVLT, Rey Auditory Verbal Learning Test; SBP, systolic blood pressure; TMA, Trail Making Test A; TMB, Trail Making Test B; t-tau, total tau; WMS-I, Wechsler Memory Scale-Logical Memory Immediate Test.

TABLE 2 Demographic characteristics of the participants considered in this study

	HC	SMC	EMCI	LMCI	*p*-value
Participants	133	118	129	126	
Sex, female	73 (54.9%)	79 (66.9%)	58 (45.0%)	57 (45.2%)	.01*
Age (years)	73.8 ± 7.8	71.3 ± 6.1	74.4 ± 7.2	74.6 ± 7.7	.001*
Education (years)	17.0 ± 2.4	16.7 ± 2.0	16.2 ± 2.7	16.5 ± 2.5	.04
Marital status, married	89 (66.9%)	83 (70.3%)	101 (78.3%)	86 (68.3%)	.41
Ethnicity, Hispanic or Latinx	8 (6.0%)	5 (4.2%)	8 (6.2%)	3 (2.4%)	.44
Race					
Caucasian	112 (84.2%)	105 (89.0%)	114 (88.3%)	117 (92.8%)	.10
American Indian/Alaskan Native	2 (1.5%)	0 (0%)	1 (.8%)	0 (0%)	
Asian	4 (3.0%)	1 (.9%)	5 (3.9%)	2 (1.6%)	
Native Hawaiian/Pacific Islander	0 (0%)	0 (0%)	1 (.8%)	0 (0%)	
Black or African American	13 (9.8%)	7 (5.9%)	2 (1.5%)	5 (4.0%)	
Multiracial	2 (1.5%)	5 (4.2%)	6 (4.7%)	2 (1.6%)	
ApoE4					
+ApoE4	35 (26%)	52 (44%)	48 (37%)	67 (53%)	<.01*
−ApoE4	98 (74%)	66 (56%)	81 (63%)	59 (47%)	
CSF					
$A\beta_{42}$	1329.7 ± 621.2	1265.2 ± 611.4	1257.0 ± 656.2	956.2 ± 505.7	<.01*
p-tau	19.6 ± 7.97	21.8 ± 9.6	23.2 ± 11.0	27.0 ± 12.9	<.01*
t-tau	219.6 ± 81.0	239.0 ± 88.2	251.5 ± 100.1	281.0 ± 118.7	<.01*

Note: Data are in *n* (%) or mean ± standard deviation.

Abbreviations: +ApoE4, ApoE4 carriers; −ApoE4, ApoE4 non-carriers; ApoE4, apolipoprotein E4; $A\beta_{42}$, amyloid $beta_{1-42}$ peptide (pg/ml); CSF, cerebral spinal fluid concentrations; EMCI, early mild cognitive impairment; HC, healthy controls; LMCI, late mild cognitive impairment; p-tau, phosphorylated tau at threonine 181 (pg/ml); SMC, significant memory concern; t-tau, total tau (pg/ml).

*Indicates statistical significance at alpha .01.

the relationship between groups and risk factor scores. The first was a diagonal matrix of singular vectors that indicated the proportion of the covariance attributable to each LV. The second and third outputs represented the structure of the LVs whereby the right singular vectors defined the relationship between group saliences (singular value weights) and the left singular vectors defined the relationship between the risk factor saliences. Reliability of the singular vector weights were assessed using bootstrapping procedures (1000 replications), and to assess statistical significance of the LVs based on the singular value, 1000 permutation tests were run (McIntosh & Lobaugh, 2004).

We also investigated correlations between the three CSF biomarker levels ($A\beta_{42}$, t-tau and p-tau) and the remaining risk factors (17 risk factors) within each of the four diagnostic groups. Then these correlations were compared across groups. This further investigation was done because $A\beta_{42}$, tau and p-tau CSF concentrations have been reported as being valuable instruments in diagnosing MCI especially MCI as a symptomatic pre-dementia phase of AD (Albert et al., 2011). To assess CSF concentrations and diagnostic group relations to the other risk factors, a behavioural PLS (B-PLS) was used. This approach is used to determine group-dependent relationships between the brain CSF concentrations by diagnostic group and risk factor variables. One B-PLS was run that assessed the associations between risk factor scores and continuous CSF biomarker levels across each diagnostic group. For this analysis, correlations were run within 12 groups representing each of the CSF concentrations separated by diagnostic groups; Matrix X contained the CSF-diagnostic groups (506 × 12; e.g., Aβ42-HC, t-tau-HC and p-tau-HC), and Matrix Y contained the remaining risk factor variables (506 × 25).

As a complement to the full group PLS analyses, we also performed reduced analyses either to compare specific groups (e.g., MC-PLS) or to examine within group relations (e.g., B-PLS). This was done primarily as a qualitative assessment of which groups were driving the effects derived from the full analyses, similar to what would be done in a factorial analysis of variance

(ANOVA) where post hoc and simple main effect tests serve to guide the interpretation of interactions. In the present case, we computed the dot product of the singular vectors from the full and reduced analyses, where the dot product is the cosine of the angle between the singular vectors. An absolute value close to 1 indicates high similarity. This has been used in previous work to guide interpretation of higher order multivariate patterns from PLS (Garrett et al., 2010; Kovacevic & McIntosh, 2007; McIntosh, 2021; McIntosh et al., 1999). We emphasize that we use this here as a qualitative assessment rather than a test of statistical significance.

Univariate statistical techniques were used to complement the multivariate results. To investigate differences between diagnostic groups and risk factor scores, Pearson's chi-squared and one-way ANOVA methods were used for each risk factor separately. Categorical risk factors were assessed using chi-square tests whereas continuous or ordinal data were assessed using ANOVAs. Post hoc pairwise comparisons were performed with Bonferroni corrections.

Results were considered significant at an alpha level of .05 for multivariate tests and .01 for univariate tests. We adopted a more conservative alpha level for the latter to minimize false positives given the large number of tests done on the data.

3 | RESULTS

3.1 | Risk factors across diagnostic groups

Two significant LVs were identified by the MC-PLS analysis comparing all the risk factors across diagnostic groups (LV1: $p < .001$, 90.10% cross-block covariance explained, and LV2: $p = .004$, 7.20% cross-block covariance explained; see Figure 1). LV1 illustrated an effect of diagnostic group whereby the cognitively healthy groups (HC and SMC) were in contrast with the MCI groups (EMCI and LMCI). In terms of the risk factor scores, the first LV extracted strong positive saliences for the cognitive and memory performance measures, $A\beta_{42}$ CSF levels, ApoE4 non-carrier status, education and being female, which demonstrates that these measures were all more prominent in the HC and SMC groups compared with the MCI groups. Strong negative saliences were extracted for the functional health measures, tau CSF concentrations, ApoE4 carrier status, age and being male, demonstrating that these measures were all more prominent in the EMCI and LMCI groups. LV2 highly characterizes the SMC and EMCI groups because these groups' confidence intervals do not cross zero in comparison with the HC and LMCI groups (see Figure 1b); bootstrap ratio confidence intervals that do not include zero are considered the most reliable. The strongest positive risk factor salience was the ApoE4 non-carrier status followed by $A\beta_{42}$ CSF levels, WMS-I performance scores, age and being male, which illustrates that the EMCI group had more ApoE4 non-carriers, higher $A\beta_{42}$ CSF levels, performed better on the WMS assessment, were older and had more male participants. The strongest negative risk factor saliences were positive ApoE4 status, MoCA performance scores, blood pressure (BP) levels (both DBP and SBP) and being female, which illustrates that SMC participants were more likely to be ApoE4 carriers, to be female, to have high BP and to have higher MoCA scores.

To evaluate whether the effect of the first two LVs was driven by a particular diagnostic group, further MC-PLS analyses were run comparing all risk factor scores across different combinations of diagnostic groups: (i) HC, SMC and EMCI groups, (ii) HC and SMC groups, (iii) SMC and EMCI groups and (iv) EMCI and LMCI groups. These group combinations were chosen based on their similarities to one another. The dot product between the risk factor scores from the full MC-PLS analysis and the risk factor scores from the reduced MC-PLS analyses was calculated separately for each LV. Three of the four dot products between the full MC-PLS and reduced MC-PLS models for LV1 elicited a large cosine, including the reduced models (i), (iii) and (iv); cosines: .95, .90 and .80, respectively. The reduced model of HC and SMC groups did not show a large cosine with the original model (.12). For LV2, there was a large correlation between the full model and the (ii) reduced model (.74) and a modest correlation between the full model and the (iv) reduced model (.54). These results can be interpreted as the difference between HC and SMC groups (reduced model (ii)) did not show a large contribution to LV1 (see Figure 2). Reduced models (ii) and (iv), on the other hand, were reflected in the full model's LV2 demonstrating that the difference between HC and SMC groups and the difference between EMCI and LMCI groups both contributed to this LV.

Follow-up univariate analyses illustrated that the SMC group was significantly younger than any other group ($p = .001$), and there were significantly more females in the SMC group ($p = .01$; see Table 2). There was a significant difference in years of education across diagnostic groups; however, Tukey's post hoc test demonstrated that the greatest difference was between the HC and the EMCI groups ($p = .03$; see Table 2). There was a significant relationship between ApoE4 status and diagnostic group ($\chi^2_3 = 20.73$ [$n = 506$], $p = .0001$). Post hoc tests indicated HC participants were more likely

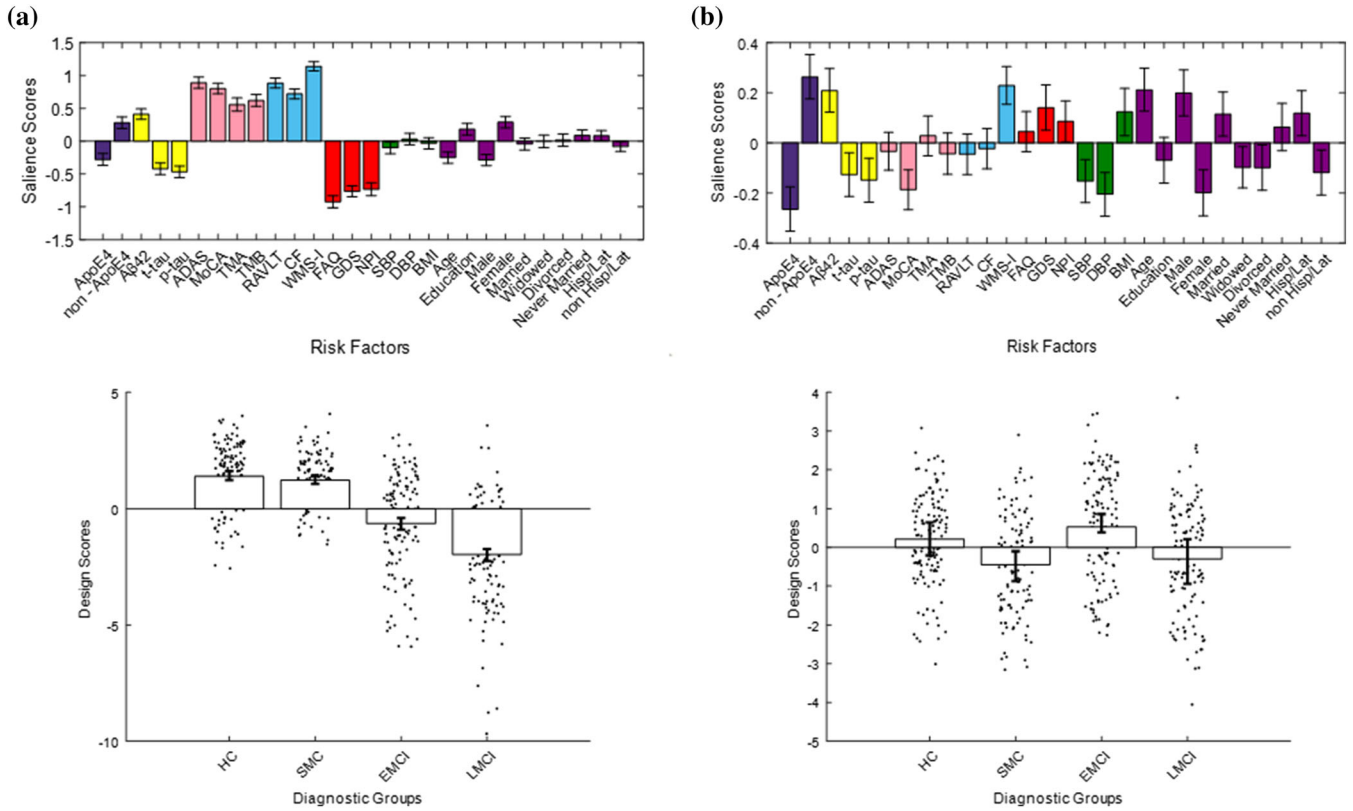

FIGURE 1 Results of mean-centred partial least squares analysis comparing risk factor scores across diagnostic groups. Two significant LVs were extracted. (a) LV1 and (b) LV2. For both graphs, the top graph represents the risk factor saliences scores (saliences multiplied by their singular values), colour coded by risk category, and the bottom graph represents the design scores for the diagnostic group contrasts; the black dots represent each participant's design score. ADAS, Alzheimer's Disease Assessment Scale-Cognitive; ApoE4, apolipoprotein E4; $A\beta_{42}$, amyloid-beta$_{1-42}$ peptide; BMI, body mass index; CF, Category Fluency Test; DBP, diastolic blood pressure; EMCI, early mild cognitive impairment; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; HC, healthy controls; LMCI, late mild cognitive impairment; LV, latent variable; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; p-tau, phosphorylated tau at threonine 181; RAVLT, Rey Auditory Verbal Learning Test; SBP, systolic blood pressure; SMC, significant memory concern; TMA, Trail Making Test A; TMB, Trail Making Test B; t-tau, total tau; WMS-I, Wechsler Memory Scale-Logical Memory Immediate Test

to be ApoE4 non-carriers, whereas LMCI participants were more likely to be ApoE4 carriers compared with any other group (see Table 2). Additionally, three one-way ANOVAs demonstrated a significant decrease in $A\beta_{42}$ across the diagnostic groups (HC > SMC > EMCI > LMCI) and a significant increase in p-tau and t-tau across the diagnostic groups (HC < SMC < EMCI < LMCI; see Table 2). A pairwise comparison test with Bonferroni corrections demonstrated that the LMCI group $A\beta_{42}$ CSF concentrations differed the most from the other groups (all $p < .001$), whereas the LMCI group p-tau and t-tau CSF levels only statistically differed between the HC and SMC groups (all $p < .001$) but not with the EMCI group (all $p > .03$). In terms of neuropsychological measures, the MCI groups showed scores that were consistent with cognitive impairment (all $p < .01$; see Table 3). Mean cardiovascular risk factor scores did not significantly differ across diagnostic groups (all $p > .13$).

3.2 | Risk factors across CSF biomarkers-diagnostic groups

A B-PLS was run to determine diagnostic group-dependent relations between the brain CSF concentrations and the remaining risk factor variables to assess whether CSF concentrations, which are strong MCI predictors, correlate with other putative MCI risk factors. The B-PLS yielded two significant LVs (see Figure 3). LV1 ($p < .001$, 73.06% cross-block covariance explained) differentiated the $A\beta_{42}$ concentrations from the tau concentrations suggesting a main effect of CSF concentrations across diagnostic groups. $A\beta_{42}$ CSF levels demonstrated strong positive correlations with ApoE4 non-carrier status, cognitive and memory scores, GDS scores and cardiovascular health scores. Meanwhile, tau CSF (t-tau and p-tau) levels had strong positive correlations with ApoE4 carrier status, worse FAQ functional health measures and older age. LV2

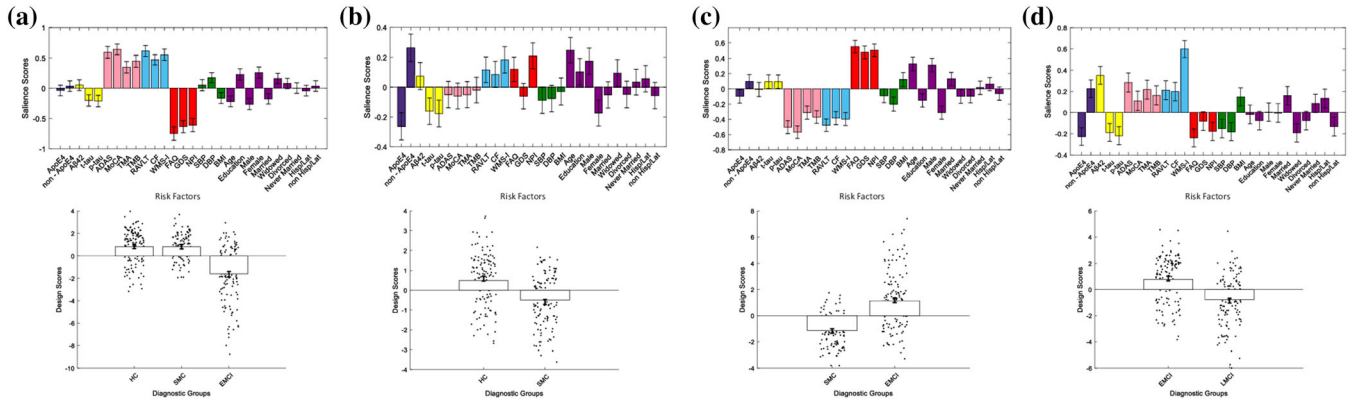

FIGURE 2 Results of the reduced mean-centred partial least squares analyses comparing risk factor scores across different combinations of diagnostic groups. (a) HC, SMC and EMCI diagnostic groups, LV1; (b) HC and SMC diagnostic groups, LV1; (c) SMC and EMCI diagnostic groups, LV1; and (d) EMCI and LMCI diagnostic groups, LV1. For all graphs, the top graph represents the risk factor saliences scores (saliences multiplied by their singular values), colour coded by risk category, and the bottom graph represents the design scores for the diagnostic group contrasts; the black dots represent each participant's design score. ADAS, Alzheimer's Disease Assessment Scale-Cognitive; ApoE4, apolipoprotein E4; $A\beta_{42}$, amyloid-beta$_{1-42}$ peptide; BMI, body mass index; CF, Category Fluency Test; DBP, diastolic blood pressure; EMCI, early mild cognitive impairment; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; HC, healthy controls; LMCI, late mild cognitive impairment; LV, latent variable; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; p-tau, phosphorylated tau at threonine 181; RAVLT, Rey Auditory Verbal Learning Test; SBP, systolic blood pressure; SMC, significant memory concern; TMA, Trail Making Test A; TMB, Trail Making Test B; t-tau, total tau; WMS-I, Wechsler Memory Scale-Logical Memory Immediate Test

TABLE 3 Neuropsychological assessment scores across diagnostic groups

	HC	SMC	EMCI	LMCI	*F*-value	*p*-value
ADAS (/85)	11.9 ± 5.0	11.6 ± 4.2	16.1 ± 7.1	19.2 ± 8.1	41.47	<.01*
MoCA (/30)	25.4 ± 2.9	25.7 ± 2.5	23.1 ± 3.3	22.6 ± 3.5	33.94	<.01*
TMA (in seconds)	31.6 ± 10.6	30.9 ± 9.2	36.2 ± 13.6	42.0 ± 22.7	14.48	<.01*
TMB (in seconds)	77.0 ± 40.2	75.9 ± 37.7	102.4 ± 57.3	117.5 ± 72.7	17.84	<.01*
RAVLT (/75)	48.1 ± 11.3	46.3 ± 10.0	37.8 ± 13.5	33.9 ± 12.1	42.08	<.01*
CF	22.3 ± 6.0	21.7 ± 5.1	18.7 ± 5.4	17.2 ± 5.1	25.55	<.01*
WMS-I (/25)	15.1 ± 3.5	14.3 ± 3.2	12.1 ± 4.3	8.1 ± 4.1	85.60	<.01*
FAQ (/30)	.2 ± .7	.1 ± .3	2.9 ± 4.6	4.7 ± 5.7	45.77	<.01*
GDS (/15)	.6 ± 1.0	.7 ± 1.0	1.8 ± 2.0	2.1 ± 1.8	30.85	<.01*
NPI (/144)	1.0 ± 2.2	.5 ± 1.1	3.4 ± 5.2	5.0 ± 7.0	26.60	<.01*

Note: Data are in mean ± standard deviation, *df* (3, 527) for all.
Abbreviations: ADAS, Alzheimer's Disease Assessment Scale-Cognitive; CF, Category Fluency Test; EMCI, early mild cognitive impairment; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; HC, healthy controls; LMCI, late mild cognitive impairment; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; RAVLT, Rey Auditory Verbal Learning Test; SMC, significant memory concern; TMA, Trail Making Test A; TMB, Trail Making Test B; WMS-I, Wechsler Memory Scale-Logical Memory Immediate Test.
*Indicates statistical significance at alpha .01.

($p = .01$, 9.85% cross-block covariance explained) by and large demonstrated reliable results for the HC CSF concentrations and SMC t-tau and p-tau concentrations. This LV depicted positive correlations between these CSF concentrations and WMS-I performance, age, being widowed or divorced and being non-H/L.

4 | DISCUSSION

The goal of this study was to explore seven previously established risk categories of MCI and their relationship to participants diagnosed with probable AD-related MCI. PLS was used and highlighted risk factors that differentiated groups. Through the use of univariate and

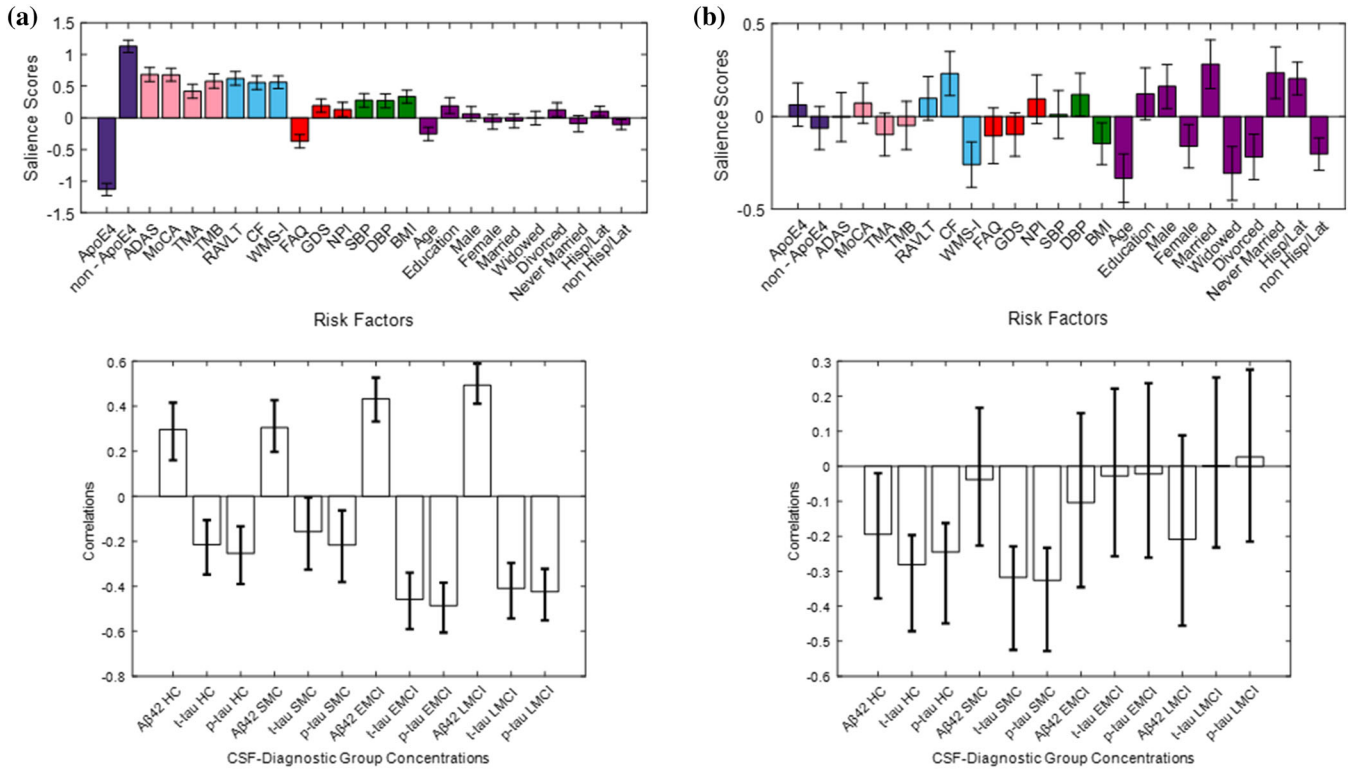

FIGURE 3 Results of behavioural partial least squares analysis when assessing correlations between risk factor scores and CSF-diagnostic groups. Two significant LVs were extracted. (a) LV1 and (b) LV2. Top graph represents the risk factor saliences scores (saliences multiplied by their singular values), colour coded by risk category, and the bottom graph represents the correlation scores for the CSF-diagnostic groups. ADAS, Alzheimer's Disease Assessment Scale-Cognitive; ApoE4, apolipoprotein E4; $A\beta_{42}$, amyloid-beta$_{1-42}$ peptide; BMI, body mass index; CF, Category Fluency Test; CSF, cerebral spinal fluid; DBP, diastolic blood pressure; EMCI, early mild cognitive impairment; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; HC, healthy controls; LMCI, late mild cognitive impairment; LV, latent variable; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; p-tau, phosphorylated tau at threonine 181; RAVLT, Rey Auditory Verbal Learning Test; SBP, systolic blood pressure; SMC, significant memory concern; TMA, Trail Making Test A; TMB, Trail Making Test B; t-tau, total tau; WMS-I, Wechsler Memory Scale-Logical Memory Immediate Test

multivariate statistical methods, six of the seven risk categories were emphasized as significantly different across the diagnostic groups including ApoE4 gene status, CSF concentration levels, cognitive performance, memory performance, functional health measures and demographic measures, suggesting that these risk factors may be specific to MCI.

At the diagnostic group level, the cognitively healthy groups (HC and SMC) demonstrated similar risk factor scores whereas the MCI groups (EMCI and LMCI) demonstrated similar risk factor scores. Nevertheless, the two healthy groups were not identical (see Figure 1a). There was a distinction between HC and SMC participants, such that SMC participants shared similar mean neuropsychological measures with HC but they also shared similar risk factor scores with the MCI groups. That is, CSF concentration levels were similar to those in the EMCI group (see Table 2) and the SMC also had a high percentage of ApoE4 gene carriers like the LMCI group (see Table 3). Subjective memory complaints, such as those seen in the SMC participants here, have continuously been demonstrated as good indicators of risk for conversion to MCI (Cook & Marsiske, 2006; Studart & Nitrini, 2016) and early AD (Choe et al., 2018). Thus, our findings support this notion that SMC participants may be in a prodromal stage of MCI. On the other hand, ADNI's decision to classify MCI participants as either EMCI or LMCI has caused some controversy because the difference between the two diagnoses is based solely on the Wechsler delayed memory performance score (Weiner et al., 2016; see Table S1). In previous work, HC and MCI participants from the ADNI dataset were re-evaluated using ADNI's conventional 'one test' diagnostic criteria compared with an actuarial neuropsychological diagnostic criteria (Bondi et al., 2008; Jak et al., 2009). Findings from these studies demonstrated that many MCI participants were falsely diagnosed using ADNI's conventional approach, thus suggesting that some MCI participants within the ADNI dataset are misclassified as MCI instead of HC (Bondi et al., 2014). This has also

been demonstrated using other methods such as cluster analysis (Edmonds et al., 2015). These results may explain why our EMCI participants appeared more similar to the HC group in the significant MC-PLS LV2 (see Figure 1b) and support the idea that MCI participants should be diagnosed based on more strict cut-points on neuropsychological scores (Taylor & Heaton, 2001). However, the results extracted for the LMCI participants in our study, and in previous studies (Jessen et al., 2014), identified a more AD-like pattern in comparison with EMCI and SMC groups. Specifically, a high percentage of LMCI participants were trending towards pathological CSF levels, commonality of the ApoE4 gene status, and on average the LMCI participants performed worse on neuropsychological assessments compared with all the other diagnostic groups.

ApoE4 carrier status differentiated between diagnostic groups (see Figure 1b) but not in the direction that would be expected; the SMC group had more ApoE4 carriers compared with the EMCI group (see Table 3). Because ApoE4 carrier status is one of the greatest genetic risk factors for AD and individuals diagnosed with MCI are often considered to have an early form of AD (Morris et al., 2001), it would be assumed that the majority of individuals diagnosed with MCI (EMCI or LMCI) would be ApoE4 carriers. However, in our study, this was only the case for the LMCI group and not the EMCI group. These results could have arisen for many different reasons. One possibility is that SMC is a more accurate prodromal stage to AD than EMCI because cognitive memory complaints, despite no frank cognitive deficits, have been demonstrated as a form of self-awareness of the internal degenerative process involved in potential AD (Barnes et al., 2006; Saykin et al., 2006). Alternatively, because ApoE4 carrier status is a greater risk factor for females than males (Altman et al., 2014; Bretsky et al., 1999; Payami et al., 1996; Subramaniapillai et al., 2021), and there were fewer female ApoE4 EMCI carriers (18%) in our sample compared with female ApoE4 SMC carriers (32%). This may explain why ApoE4 carrier status was extracted as a salient risk factor for SMC but not EMCI participants and, as mentioned earlier, some of the EMCI participants may have been incorrectly diagnosed.

Both subjective (SMC) and objective (EMCI and LMCI) cognitive impairment groups were trending towards AD-like pathological $A\beta_{42}$, p-tau and t-tau CSF concentrations (see Table 2), which provides additional support that these biomarkers are risk factors for MCI. Previous work and our results suggest that all three of these biomarkers have sufficient diagnostic accuracy for MCI (Andreasen et al., 1999; de Leon et al., 2006) and incipient AD in patients with MCI (Baldeiras et al., 2018; Hampel & Blennow, 2004; Mattsson, 2009). When aggregating the diagnostic groups into participants with pathological versus healthy CSF concentration levels according to the cut-point values presented at the 2017 ADNI Teleconference (Shaw & Trojanowski, 2017), the majority of LMCI participants had pathological levels of all three CSF biomarkers of interest (≥55.6%; >980 pg/ml for $A\beta_{42}$, <245 pg/ml for t-tau and <21.8 pg/ml for p-tau), whereas in the other diagnostic groups, the majority of participants had healthy CSF levels (≥52.7%; ≤980 pg/ml for $A\beta_{42}$, ≥245 pg/ml for t-tau and ≥21.8 pg/ml for p-tau). Nonetheless, pathological CSF concentrations were evident in participants from all diagnostic groups including the HC group. Because previous research has illustrated an age-related increase in CSF tau levels (Blomberg et al., 2001; Sjögren et al., 2001) and a decrease in CSF $A\beta_{42}$ levels (Sutphen et al., 2015) in cognitively normal individuals, having some participants with pathological CSF biomarker levels may be associated with the process of normal healthy aging rather than cognitive decline. However, these healthy individuals may also be at risk for future decline; further longitudinal research is required. All in all, it is evident from our results that higher CSF p-tau and t-tau concentrations and lower CSF $A\beta_{42}$ concentrations are related to a diagnosis of SMC and MCI, but whether these biomarker levels must change in combination (i.e., Bloom, 2014; Han & Shi, 2016) or independently (i.e., Hardy & Selkoe, 2002; Kametani & Hasegawa, 2018) to better predict risk of cognitive impairment is unclear.

The largest salience risk factor scores extracted from the full MC-PLS model were from the memory performance scores, specifically WMS immediate recall measures, which evidently makes sense as a diagnosis of MCI requires an objectively low memory score (Collie & Maruff, 2002; Feldman & Jacova, 2005; Petersen, 2004). Alternatively, the smallest saliences risk factor scores established were the TMA and TMB cognitive performance scores. As shown in Petersen et al. (2010), the neuropsychological measures differentiated the most across diagnostic groups (see Figure 1 and Table 3). Unlike previous research (Kivipelto et al., 2006; Tervo et al., 2004), cardiovascular health and some demographics (e.g., marital status and ethnicity; see Figure 1a) were not identified as salient risk factors in MCI participants. There is a possibility that the variables chosen to represent cardiovascular health in the present study (BP and BMI) were not sensitive enough to capture the effects of this risk category. Past research on cardiovascular health risk and MCI used variables such as diabetes, physical inactivity or smoking habits in addition to the variables used here (Alonso et al., 2009; Norton et al., 2014; Schrader et al., 2020). Furthermore, there is

evidence to suggest that poor cardiovascular health at midlife is a greater risk factor for the development of MCI in later life (Kivipelto, 2001) whether poor cardiovascular health metrics were present in late-life or not (Liang et al., 2020), which could explain our insignificant results within a cross-sectional older sample.

The results extracted from LV1 of the full B-PLS analysis were not surprising as the $A\beta_{42}$ concentrations and tau concentrations (t-tau and p-tau) differed from each other across all the diagnostic groups, as previous research has shown (Andreasen, Sjögren, & Blennow, 2003). It was evident that having higher $A\beta_{42}$ CSF levels was correlated with better memory and cognitive scores and non-ApoE4 gene status, whereas having higher tau levels was correlated with ApoE4 carrier status and higher FAQ functional health scores. The two most interesting positive correlations from LV1 were the ones between tau and FAQ scores, as well as between $A\beta_{42}$ and cardiovascular health measures. The former correlation has also been illustrated in previous research (Blennow et al., 2019; Okonkwo, 2010), suggesting that an increase in CSF tau concentrations may be related to a decrease in functional skills such as carrying out daily activities. The latter finding suggests that elevated $A\beta_{42}$ CSF levels, which is considered healthy, may be related to increased BP and BMI. This result is in line with the obesity paradox whereby a higher BMI in late-life has been associated with less dementia risk (Fitzpatrick et al., 2009). The second significant LV extracted strong positive correlations between all three of the CSF biomarker concentrations in the HC groups and tau CSF concentrations in the SMC group with WMS-I and different demographic variables. Specifically, there was a positive correlation between higher CSF levels with age, being widowed or divorced and being non-H/L. As mentioned earlier, an age-related increase in CSF tau in cognitively normal individuals has been observed before (Blomberg et al., 2001; Sjögren et al., 2001), but, to our knowledge, there have been no reported correlations between elevated CSF levels and being widowed or divorced. Although being divorced or widowed has been identified as a potential risk factor for cognitive impairment in older adults (Liu et al., 2019), the relation between marital status and increased $A\beta_{42}$ or tau CSF concentrations requires further investigation. Similar to marital status, there has been minimal research that has assessed the relation between ethnicity and AD CSF biomarkers. A study using the National Alzheimer's Coordinating Center dataset found that H/L and non-H/L ethnic groups may not be comparable when it comes to MCI risk as normal cognition H/L participants exhibited significant risk of conversion to MCI compared with non-H/L, whereas H/L participants with MCI at baseline were significantly associated with reduced risk of dementia or death compared with non-H/L (Salazar et al., 2020). For these reasons, differences among ethnic groups warrant future research.

Several limitations should be noted. First, the cross-sectional nature of the study did not allow us to assess changes in risk factor categories or to follow participants who may have converted to different diagnostic groups over time. Additionally, longitudinal analyses of these data would provide a more complete approach to the research question that would allow for a clearer understanding of the relationship between MCI risk factors and the likelihood of progressing to AD or other dementias. Second, ADNI is a highly selective sample that may not generalize well to the broader population (e.g., 89% Caucasian participants in the current study). For this reason, future studies should expand to more diverse populations such as ethnically diverse samples (e.g., Manly et al., 2008) and samples with lower education levels (e.g., Custodio et al., 2017) for more generalizable findings.

5 | CONCLUSION

Everything considered, our exploratory study suggests that some of the putative MCI risk factors that were investigated were specific to MCI but not all. As seen in previous research, a relationship between ApoE4 carriers and risk for MCI was present, specifically for those with an LMCI diagnosis. Further, the CSF biomarkers established themselves as strong risk factors for MCI represented by low $A\beta_{42}$ and high p-tau and t-tau concentrations, which also correlated with worse memory, cognitive and functional health measures. Cognitive, memory and daily functioning performance were significantly associated with diagnostic status, exemplifying that the assessment measures chosen for this study were strong predictors of cognitive and functioning status. Increased age, being male and having fewer years of education were demonstrated as important risk factors of MCI. However, unlike previous research, cardiovascular health, indexed by SBP, DBP and BMI, and being female were not related to the development of MCI. All in all, we can assume from our findings that ApoE4 carrier status, AD-like pathological levels of CSF biomarkers, poor cognitive and memory performance, high functional health measures, increased age, being male and lower educational attainment are risk factors specific to MCI and not healthy aging in our sample, whereas cardiovascular risk factors, marital status and ethnicity were not identified as specific to an MCI diagnosis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: ADS and ARM: conceptualization and designed research; ADS and KS: data curation; ADS and ARM: data analysis and interpretation; ADS and ARM: draft manuscript preparation; KS, CLG and ARM: critical revisions of the article. All authors reviewed the results and approved the final version of the manuscript. ADNI (http://adni.loni.usc.edu) provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The syntax and code used for this project have been made available for review on a public Github repository (https://github.com/nosmasa/MCI-Risk-Factors). The data that support the findings of this study are obtained from Alzheimer's Disease Neuroimaging Initiative (ADNI), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission from the ADNI Data and Publications Committee. Data used in preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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