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*Article*

# Marital Status with Rey Auditory Verbal Learning Test Cognition Performance Is Associated with Mild Cognitive Impairment

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‡ Secondary data used in preparation of this article were obtained from the Alzheimer's Disease Prediction of Longitudinal Evolution(TADPOLE) database ( https://tadpole.grand-challenge.org/Data/). As, such, the researchers within the TADPOLE contributed to the design and implementation of TADPOLE and/or provided data but did not participate in analysis or writing of this prediction challenge. A complete listing of TADPOLE key contributors can be found at: https://tadpole.grand-challenge.org/Contact/.

**Abstract:** Introduction:Few robust studies have analyzed association between cognitive tests and the marital status of Mild Cognitive Impairment (MCI) group with ADNI dataset. To test the hypothesis that Rey Auditory Verbal Learning test (RAVLT) cognition performance with marital status is associated with greater odds of MCI group than either RAVLT independently, we used TADPOLE data to evaluate cross-sectional associations between RAVLT performance in immediate response, learning, forgetting, and perception of forgetting with marital status and MCI. Methods: Subjects with MCI and Normal Cognition were included. Logistic regression models indicate associations between four RAVLT subgroups (low and high performance of immediate response, immediate response with learning, performance of immediate response with learning and forgetting, performance of immediate response with learning, forgetting and perception of forgetting) and MCI group. Models adjust for age, sex, race, marital status, ethnicity, education, APOE4 genotype, hippocampus, whole-brain, ventricles and ICV. Results: The sample (n=6560) had a mean age of 77 / 67 years, 44% were female, 58% in MCI group. Only all RAVLT subgroups test with age 61 to 70(OR 0.26, 95% CI 0.15-0.45), age 71 or older(OR 0.07, 95% CI,0.04-0.12), race:black/african american(OR 0.13, 95% CI 0.03-0.52)race:more than one(OR 0.05, 95% CI 0.01-0.24), marital status:never married(OR 0.2, 95% CI 0.12-0.34). Conclusion: Studies are needed to evaluate other cognitive test with missing data within TADPOLE dataset as modifiable risk factor for MCI.

**Keywords:** Cognitive Test; Education; Cognitive Impairment; Dementia

## 1. Introduction

Alzheimer disease (AD) is a progressive and irreversible disease that severely impairs memory and cognition [1] and leads to dementia in millions of people across the world [2]. Neuropathological confirmation is a typical avenue for AD diagnosis, in particular for people manifesting criteria for dementia [3]. Early and mild cognitive deficits can be identified during mild cognitive impairment (MCI), the preclinical transitional period between ordinary aging and the diagnosis of early AD [4–7]. Indeed, almost 50% of patients with MCI will ultimately develop AD within a few years[8].

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Learning and memory are essential functions since they allow adaptive behavior and enhance survival [1]. There is strong evidence that neurobehavioral test results, long-term cognitive decline, and dementia risk significantly vary among different race/ethnic populations, with lower scores found in African Americans compared to white [8–12].

The Rey Auditory Verbal Learning Test (RAVLT) is a standard periodic verbal memory test used in clinical practice to evaluate memory dysfunction in the elderly [13]. RAVLT assesses a participant's ability to encode, consolidate, store, and retrieve verbal information [1,14,15]. RAVLT learning score (V-I) is a crucial tool in predicting the progression from MCI to AD dementia [16–20].

In African Americans, the relationship between acculturation and neuropsychological test performance following traumatic brain injury was previously investigated. Hierarchical regression analyses suggested the close association between a low level of acculturation and significant poor performance in various neuropsychological tests, including the RAVLT test [21].

In Northern Manhattan, the neuropsychological test performance was also measured in non-Hispanic African American and white non-demented elders. Measuring different parameters such as verbal/nonverbal learning, memory, and abstract reasoning revealed a significantly lower score in African American participants compared with its counterpart white elders [22]

Meanwhile, several factors may decrease the onset of cognitive decline, and education stands as one of the potential influencing factors. Indeed, highly educated people accomplish advanced levels of cognitive performance in almost all domains of cognition. In contrast, low level of education is suggested as a risk factor for the onset of Alzheimer's disease [3–6,23].

The level of education is commonly employed as an indicator of the cognitive reserve [5,7,9]. The cohesive relationship between a higher level of education and a lower risk of dementia validates this notion. Prospective studies, on the other hand, imply that this link is primarily due to the link between education and cognitive function rather than the level' of cognitive change [10–14].

The concept that education contributes to cognitive reserve is controversial. Indeed, data analysis of various studies, including the Religious Orders Study/Memory and Aging Project (ROSMAP)[24] and Bronx Aging Study, have emphasized the significant role of a higher level of education in managing the onset of cognitive decline. In contrast, other studies contradicted this correlation [25–27]. Also, data analysis generated by the Religious Orders Study revealed the role of higher levels of education in reducing the negative association of AD pathology with the level of cognition-leading death [28].

The community-based longitudinal study, Kungsholmen Project, is one of the studies that highlighted the influence of education on dementia incidence using data of demographic variables such as sex, age, and educational level [29,30]. Participants of this study were assigned to three categories of schooling 8 years of school, 8-10 years, and the university for those with 11 years of education. Data analysis for this study suggests that participants with a low level of education are at high risk of developing dementia or AD, especially women.

Married people have more frequent social communication which decrease the risk of dementia. Those individuals have potential to cope with neuropathological impairment, maintain cognitive skill and daily activity[31,32]. In contrast, divorced people always facing stress that led to increased risk of dementia [33,34]. Furthermore, age, race, and sex of married people are also driving cognitive impairment [35–37]

## 2. Materials and Methods

### *2.1. The TADPOLE Data Study Participants*

Data used to test the hypothesis was used from the Alzheimer's Disease Prediction of Longitudinal Evolution (TADPOLE) which brings data in collaboration with the Alzheimer's Disease Neuroimaging Initiative (ADNI) [38]. TADPOLE provide a list of indi-

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viduals previously recruited to the Alzheimer's Disease Neuroimaging Initiative (ADNI). These individuals have all provided data within earlier ADNI studies and have agreed to provide follow-up data. Each feature in TADPOLE is a likely outcome measure for clinical trials: CN - Cognitively normal; MCI - mild cognitive impairment; or AD - probable Alzheimer's Disease. TADPOLE contains many types of biological markers, some with missing data but very informative.

Crucial biomarkers with ADNI-TADPOLE are:

- Target outcomes: DX, ADAS13, Ventricles;
- Cognitive tests: CDRSB, ADAS11, MMSE, RAVLT-immediate;
- MRI measures: Hippocampus, WholeBrain, Entorhinal, MidTemp;
- PET measures: FDG, AV45;
- CSF measures: (amyloid-beta level in CSF), TAU (tau level),(phosphorylated tau level);
- Risk factors: APOE4, AGE.

### *2.2. Outcome: Normal Cognitive vs. MCI*

The main outcome is the presence of normal cognition or MCI [38]. Mild cognitive impairment (MCI) is a critical phase between normal cognitive aging and advanced decline cognitive abilities[39]. However, we have a particular group in the dataset that reverse the disease from MCI to Normal cognitive[38]. Transitional cognitive decline is pervasive in Alzheimer's disease (AD) participants. Therefore, cognitive decline can be based on subjective report by the individual or participant in MCI group[40].

TADPOLE dataset is the result of several ADNI phases. The first phase, ADNI-1, collected in 2004. In total, 821 participants, which MCI was prevalent. The second and third phase, ADNI-GO and ADNI-2, with additional 200 early MCI participants. Since 2016 we have ADNI-3 that is actively enrolling up to 1200 additional participants in normal cognitive (NC), mild cognitive impairment (MCI) and Alzheimer's Disease group (AD) [41]

### *2.3. Rey Auditory Verbal Learning Test (RAVLT)*

Rey Auditory Verbal Learning Test (RAVLT) is a snap-episodic of measurements on memory. RAVLT can detect changes associated with cognitive decline in abnormal aging [40]. Previous work with ADNI data, we found RAVLT was one of most important measure in the prediction model (Ensemble Learning Model with Feature Selection), which in part, explains our interest towards RAVLT.

### *2.4. Performance for RAVLT*

Rey's auditory verbal learning test (RAVLT) show in previous studies a significant role in early diagnosis of AD [17] as well as it has been demonstrated to be significant in differentiating AD from psychiatric disorders [42–44]. In our study, we focused in MCI participants. Previous research found no corresponding association between "early" or "late" MCI. Also, a large proportion of false-positives diagnostic errors [45].

RAVLT evaluates a wide diversity of functions: short-term auditory-verbal memory, rate of learning, learning strategies, retroactive, and proactive interference, presence of confabulation of confusion in memory processes, retention of information, and differences between learning and retrieval.

We hypothesized that RAVLT performance with education level is associated with greater oddss of MCI than either RAVLT performance independently. RAVLT had shown in testing intelligent or gifted students higher scores than typical students [46] Although, intelligent is studied in more robust and holistic view than just memorizing. ADNI participants are elderly people who needs this evaluation short-term memory, working memory and long-term memory to deal with basic life.

ADNI Participants are given a list of 15 unrelated words repeated over five different trials and are asked to repeat. Another list of 15 unrelated words are given and the participant must again repeat the original list of 15 words and then again after 30 minutes.

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Approximately 10 to 15 minutes is required for the procedure (not including 30 min. interval) [18].

Our study with logistic regression assess four RAVLT subgroups:low and high performance in test for immediate response, and we start adding other three subgroups; learning, forgetting and perception of forgetting to the final model.

A modified model adjust for age, sex race, engagement, ethnicity, education, APOE4 genotype, hippocampus, whole-brain, ventricles and ICV was constructed with low and high performance RAVLT test.

### *2.5. Main Confounders*

Statistical analyses adjusted for the following sociodemographic covariates: age, sex(male or female), race(White, Black or African American, Asian, American Indian or Alaska Native, or Native Hawaiian or Other Pacific Islander), APOE4 genotype(0, 1 or 2 alleles), ethnicity(not Hispanic or Latino, Hispanic or Latino, or unknown), Engagement(Married, Never Married, Unknown, Widowed), Education(Elementary, High School, Occupational Program, College, Post-College), Hippocampus(Volumetric measurements), Wholebrain( Volumetric measurements), Ventricles(Volumetric measurements), ICV(Volumetric measurements)

### *2.6. Analytical Sample*

Our analytical sample from Tadpole longitudinal analysis used baseline follow up visit data from three "standard" data sets, derived from ADNI-1, ADNI-GO, and ADNI-2.

Standard data sets are:

- D1 - a comprehensive longitudinal data set for training;
- D2 - a comprehensive longitudinal data set on rollover subjects for forecasting;
- D3 - a limited forecasting data set on the same rollover subjects as D2;

The initial analytical sample considered all participants with baseline cognitive and educational data, we have 12741 participants from standard datasets. Participants with dementia and reverse MCI to Normal were excluded (6141), leaving 6600 participants in total. The final analytical sample consisted of 6560 participants (figure 1).

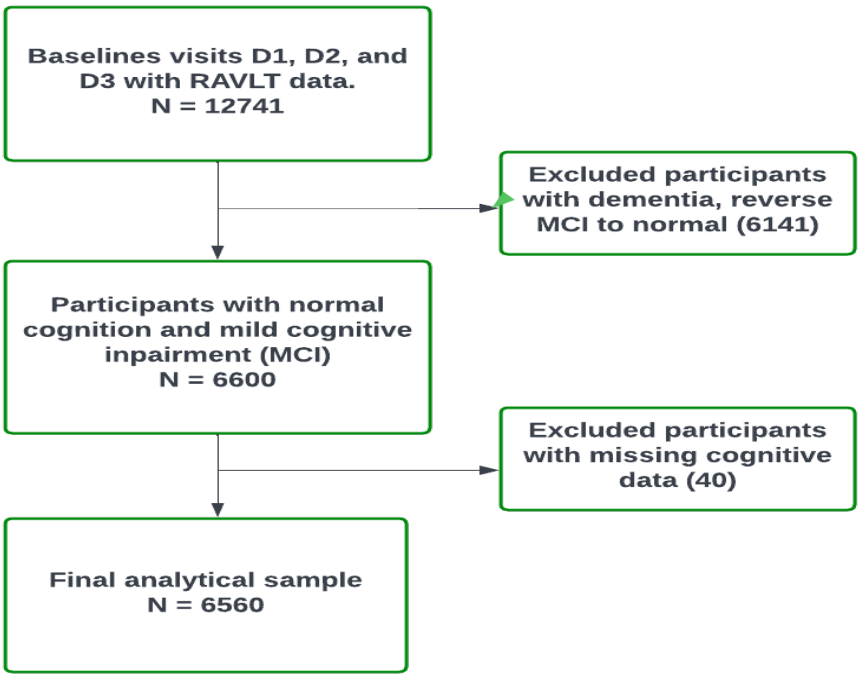


**Figure 1.** Diagram of analytical sample

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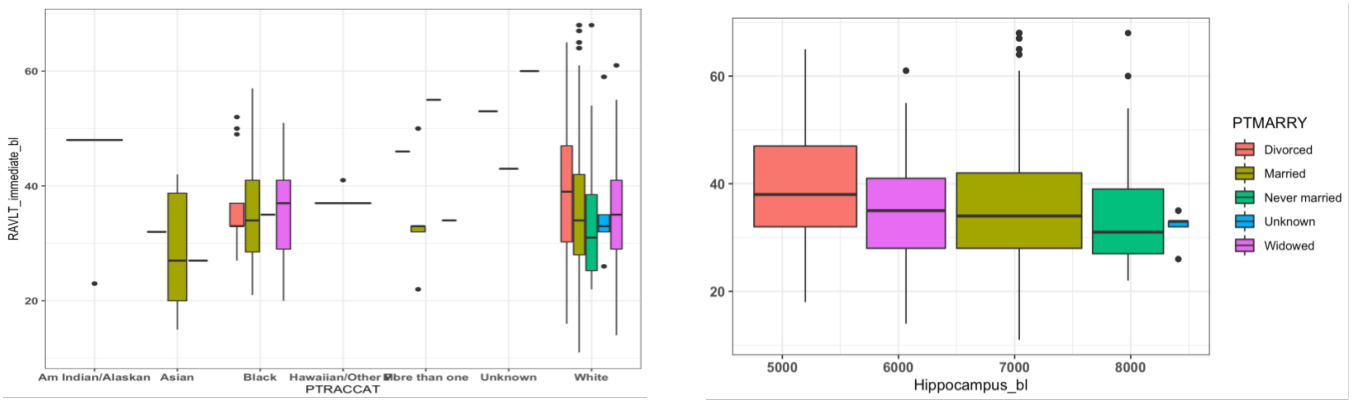


**(a)** Race **(b)** Hippocampus

**Figure 2.** Relatively concentrate distributions of race:black, marital status:never married and hippocampus measure vs RAVLT test

### *2.7. Descriptive Analysis of Significant Exposure Variables*

The RAVLT is comprised of 5 repeated learning trials of the same 15 word list, with immediate and delayed recall trials after 3 and 30 minutes, respectively, as well as recognition testing. Much of the work examining memory deficits in AD has focused on either summing words recalled across all learning trials for a measure of total encoding [47] or delayed recall measures or has sometimes regarded list learning performance as a single composite measure representing episodic memory.

Figure 2 shows RAVLT immediate response test as a sum of five trails. Participants that never married in black race shows a relatively concentrated distributions. However, significant relationship between both with respect RAVLT as we show in table 2.

## 3. Results

Descriptive statistics of the sample among MCI and NL group are presented in Table 1. The sample had a greater concentration of participants 71+, with 58% in MCI group. Study group have a 62% lacked APOE4 alleles, 93% were white, 97% were non-Hispanic, and 62% had MCI.

Some significant differences existed between the four stratified RAVLT test (Table 1). Regardless of cognitive test status, participants at risk of MCI were more often male.

In logistic regression models of RAVLT subgroups and MCI, for RAVLT alone as a model 1 unadjusted, only immediate response(OR 0.96, 95% CI 0.95-0.97), forgetting(OR 0.65, 95% CI 0.60-0.69) and perception of forgetting(OR 1.05, 95% CI 1.04-1.05) test was significantly associated with greater odds of MCI (Table 2). Learning subgroup test was not significantly associated with greater odds of MCI relative to RAVLT alone. Furthermore, in logistic regression models with model 2 adjusted for age and sex as the reference, immediate response(OR 0.95, 95% CI 0.94-0.96), forgetting(OR 0.59, 95% CI 0.55-0.65) and perception of forgetting(OR 1.06, 95% CI 1.05-1.07), and age 61 to 70(OR 0.34, 95% CI 0.22-0.53), age 71 or older(OR 0.09, 95% CI 0.06-0.15) were each significantly associated with greater odds of MCI (Table 2).

Final model 3 adjusted for sex, race, ethnicity, marital status, education, APOE4, hippocampus, wholebrain, ventricles and ICV as the reference, only immediate response(OR 0.96, 95% CI 0.95-0.97), learning(OR 0.65, 95% CI 0.60-0.69) forgetting(OR 0.65, 95% CI 0.60-0.69), perception of forgetting(OR 1.06, 95% CI 1.05-1.07), age 61 to 70(OR 0.26, 95% CI 0.15-0.45), age 71 or older(OR 0.07, 95% CI 0.04-0.12), Race-Black/African American(OR 0.13, 95% CI 0.03-0.52), more than one(OR 0.05, 95% CI 0.01-0.24), and marital status-never married(OR 0.2, 95% CI 0.12-0.34) were each significantly associated with greater odds of MCI (Table 2).

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| Category | MCI Group | | NL Group | | |
|---|---|---|---|---|---|
| | Level | Totaln, % | MCI Groupn, % | NL Groupn, % | Chi-squared P-value |
| Auditory Verbal Learning Test Performance (RAVLT) | Immediate response | 39(31,48 ) | 34(28,42) | 45(38,52) | 2.00E-16 |
| | Learning | 5(3,7) | 4(2,6) | 6(4,8) | 2.35E-06 |
| | Forgetting | 4(2,6) | 5(3,6) | 4(2,5) | 2.00E-06 |
| | Perception of forgetting | 44(23,72) | 57(31,86) | 31(15,50) | 2.00E-06 |
| Sex | Male | 3690(56) | 2373(60) | 1317(49) | 0.11226 |
| | Female | 2910(44) | 1559(40) | 1351(51) | |
| Age | Age 0 to 60 | 195(3.6) | 167(5.3) | 28(1.2) | |
| | Age 61 to 70 | 1652(31) | 1144(36) | 508(23) | 7.04E-07 |
| | Age 71 or older | 3542(66) | 1827(58) | 1715(76) | 2.00E-16 |
| Race | White | 6128(93) | 3685(94) | 2443(92) | 0.01202 |
| | Black/ African American | 271(4.1) | 116(3.0) | 155(5.8) | 0.003855 |
| | Hawaiian | 5(<0.1) | 5(0.1) | 0 | 0.976919 |
| | Asian | 114(1.7) | 73(1.9) | 41(1.5) | 0.126461 |
| | Unknown | 12(0.2) | 12(0.3) | 0 | 0.944922 |
| | More than one | 56(0.8) | 32(0.8) | 24(0.9) | 0.000166 |
| Ethnicity | Hispanic/Latino | 199(3.0) | 124(3.2) | 75(2.8) | 0.756096 |
| | Not Hispanic/Latino | 6370(97) | 3794(96) | 2576(97) | |
| | Unknown | 31(0.5) | 14(0.4) | 17(0.6) | 0.023799 |
| Engagement | Married | 4914(74) | 3016(77) | 1898(71) | 0.887499 |
| | Never Married | 222(3.4) | 81(2.1) | 141(5.3) | 3.10E-10 |
| | Unknown | 36(0.5) | 31(0.8) | 5(0.2) | 0.007498 |
| | Widowed | 824(12) | 446(11) | 378(14) | 0.816086 |
| Education | Elementary | 0 | 0 | 0 | |
| | High School | 2(<0.1) | 2(<0.1) | 0 | |
| | Occupational Program | 11(0.2) | 1(<0.1) | 10(0.4) | 0.981215 |
| | College | 1240(19) | 859(22) | 381(14) | 0.983097 |
| | Post-Collage | 5347(81) | 3070(78) | 2277(85) | 0.983097 |
| APOE4 alleles | 0 | 4077(62) | 2130(54) | 1947(73) | |
| | 1 | 2102(32) | 1429(36) | 673(25) | |
| | 2 | 417(6.3) | 370(9.4) | 47(1.8) | |
| Hipocampus | Hipocampus | 7177(6383,7817) | 6958(6129,7687) | 7431(6787,7918) | 2.00E-16 |
| Wholebrain | Wholebrain | 1033900(961397,1104800) | 1034980(962600,1113680) | 1033180(959755,1096880) | 3.35E-09 |
| Ventricles | Ventricles | 32311(21694,46110) | 33924(23127,49959) | 29415(20203,40820) | 0.054315 |
| ICV | ICV | 1524520(1422670,1640600) | 1534150(1436660,1647330) | 1505460(1401292,1630490) | 0.045143 |

**Table 1.** Demographic characteristics of the study population per RAVLT test subgroup

After controlling for confounding negative association variables. Participants with low RAVLT test of immediate response, forgetting, being black, significant hippocampus measurements and never married had 0.94 times the odds of being MCI as compared to RAVLT test alone like Model 1. At the same time, positive association compared to those who have RAVLT test alone, those with RAVLT learning test, being black significant hippocampus measurements and never married had an average 1% higher odds of being MCI, although this relationship was not statistically significant (Table 2).

## 4. Discussion

The current study employed Alzheimer's Disease Prediction Of Longitudinal Evolution (TADPOLE) data to evaluate cross-sectional associations between RAVLT performance in immediate response, learning, forgetting, and perception of forgetting with marital status and MCI. Knowingly, TADPOLE underlines various approaches that are crucial prognostic of future progression of people at risk of AD. To achieve this goal, TADPOLE utilizes a substantial set of multimodal assessments from Alzheimer's Disease Neuroimaging Initiative (ADNI), which endorse the prediction of the disease progression [48].

Unfortunately, meager robust studies have analyzed the association between RAVLT cognitive tests and the marital status of MCI group with ADNI dataset. Therefore, our current study is an attempt to address the association between the RAVLT performance and MCI using ADNI dataset. RAVLT, a well-known assessment of episodic memory, has been shown to be a helpful neuropsychological tool in distinguishing AD from psychiatric diseases and had a substantial role in identifying AD in its early stages [17,42]. In a clinical setting, RAVLT can differentiate patients with normal aging from persons with MCI and AD [49].

Our logistic regression model for RAVLT fully adjusted revealed a significant association between three subgroups of RAVLT (immediate response, forgetting, and perception of forgetting) and marital status with MCI. Meanwhile, learning subgroup test revealed

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| Category | MCI Group | Model 1: Unadjusted | | Model 2: Adjusted for Age and Sex | | Model 3: Fully Adjusted | |
|---|---|---|---|---|---|---|---|
| | Level | Odds Ratio | 95% confident Interval | Odds Ratio | 95% confident Interval | Odds Ratio | 95% confident Interval |
| Auditory Verbal Learning Test Performance (RAVLT) | No Association | Reference | Reference | Reference | Reference | Reference | Reference |
| | Immediate response | 0.96 | 0.95-0.97 | 0.95 | 0.94-0.96 | 0.94 | *0.93-0.95 |
| | Learning | Reference | Reference | Reference | Reference | 1.1 | **1.05-1.14 |
| | Forgetting | 0.65 | 0.60-0.69 | 0.59 | 0.55-0.65 | 0.57 | *0.51-0.60 |
| | Perception of forgetting | 1.05 | 1.04-1.05 | 1.06 | 1.05-1.07 | 1.06 | **1.05-1.07 |
| Sex | Male | NA | NA | Reference | Reference | Reference | Reference |
| | Female | NA | NA | Reference | Reference | Reference | Reference |
| Age | Age 0 to 60 | NA | NA | Reference | Reference | Reference | Reference |
| | Age 61 to 70 | NA | NA | 0.34 | 0.22-0.53 | 0.26 | *0.15-0.45 |
| | Age 71 or older | NA | NA | 0.09 | 0.06-0.15 | 0.07 | **0.04-0.12 |
| Race | White | NA | NA | NA | Reference | Reference | Reference |
| | Black/ African American | NA | NA | NA | NA | 0.13 | **0.03-0.52 |
| | Asian | NA | NA | NA | NA | Reference | Reference |
| | More than one | NA | NA | NA | NA | 0.05 | **0.01-0.24 |
| Ethnicity | Hispanic/Latino | NA | NA | NA | NA | Reference | Reference |
| | Not Hispanic/Latino | NA | NA | NA | NA | Reference | Reference |
| | Unknown | NA | NA | NA | NA | Reference | Reference |
| Marital Status | Married | NA | NA | NA | NA | Reference | Reference |
| | Never Married | NA | NA | NA | NA | 0.2 | **0.12-0.34 |
| | Unknown | NA | NA | NA | NA | 5.01 | 1.53-0.16 |
| | Widowed | NA | NA | NA | NA | Reference | Reference |
| Education | Elementary | NA | NA | NA | NA | Reference | Reference |
| | High School | NA | NA | NA | NA | Reference | Reference |
| | Occupational Program | NA | NA | NA | NA | Reference | Reference |
| | College | NA | NA | NA | NA | Reference | Reference |
| | Post-Collage | NA | NA | NA | NA | Reference | Reference |
| APOE4 alleles | 0 | NA | NA | NA | NA | 1.81 | 1.58-2.08 |
| | 1 | NA | NA | NA | NA | Reference | Reference |
| | 2 | NA | NA | NA | NA | Reference | Reference |
| Hipocampus | Hipocampus | NA | NA | NA | NA | 0.99 | 0.99-0.99 |
| Wholebrain | Wholebrain | NA | NA | NA | NA | 1 | 1.00-1.00 |
| Ventricles | Ventricles | NA | NA | NA | NA | Reference | Reference |
| ICV | ICV | NA | NA | NA | NA | Reference | Reference |

**Table 2.** Associations between RAVLT test for learning, forgetting, immediate response, and perception of forgetting and MCI with low and high risk for RAVLT test alone or fully adjusted

a non-significant association. Memory processes is coordinated by a highly complicated network of brain regions [50]. At the same time, aging is substantially implicated in changing brain structure, concomitant with MCI and AD [51–56]. Elderly non-demented people with less vs. high risk of developing MCI or AD can be distinguished by the organized pattern of brain alterations in the early stage of AD [57–59]. Compared with normal aging, age-related dementia usually has a slow and gradual onset; however, atrophy manifests years before the clinical symptoms [60–62].

A previous study indicated a substantial correlation between information provided by RAVLT scores and AD-linked structural atrophy. Indeed, participants from similar groups such as "AD and MCI" or "Normal control and MCI" produced lower predictive performance compared to other groups of subjects with significant structural changes in the brain, such as "AD and Normal Control" [50]. Furthermore, another study on people with prodromal AD (amyloid- and tau-positive amnestic mild cognitive impairment) realized that episodic memory impairment is also triggered by neurodegeneration in numerous cortical networks outside of the standard memory systems [63].

In AD, the pattern of atrophy is not random; instead, it usually develops slowly and follows a well-controlled pathway that starts with the entorhinal cortex and the hippocampus, eventually affecting all cortex regions. Annual atrophy in individuals with MCI was significantly higher than in others with normal aging. A continuous increase in atrophy rate was observed, along with progression to AD [64]. Furthermore, the association between p-tau level and temporal atrophy can be detected in MCI patients but not in healthy old individuals [64].

Knowingly, RAVLT score is a crucial tool in predicting the progression from MCI to AD [10–14]. In consistent, our model 2 adjusted for age and sex as the reference, immediate response, forgetting, and perception of forgetting, and age 61 to 70, 71 were significantly associated with MCI. Studying the typical memory process in cognitively normal people indicated the considerable impact of demographic parameters, particularly age, on RAVLT cognitive assessment [65]. Paradoxically, a minor improvement in the measured RAVLT scores was found when normal aging influence was excluded. This observation was linked

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to the impact of AD pathology on MRI and RAVLT, dominating the effects of normal aging [50].

Our analyses also agree with those previously highlighted the role of education level and socio-economic status in maintaining cognitive function and protecting of AD diagnosis. The community-based longitudinal study, Kungsholmen Project, highlighted the influence of education on dementia incidence using data of demographic variables such as sex, age, and educational level [30]. Participants of this study were assigned to three categories of schooling 8 years of school, 8-10 years, and the university for those with 11 years of education. Data analysis for this study suggests that participants with a low level of education are at high risk of developing dementia or AD, especially women.

In parallel with our analyses, many studies have demonstrated that longitudinal brain changes (as measured by MRI) are linked to changes in cognitive capacities, particularly episodic memory tasks [10–14]. Amyloid deposition is considered major biomarker of the histopathological classification of AD [66]. In neurodegenerative disease, amyloid is projected as the lead of detrimental events that progress to dementia and AD [61]. Neuroplasticity is a well-known cognitive decline that evolves when the brain fails to compensate for accumulating insults. Healthy normal aging and the earliest stages of AD may be related to neuroplasticity [33,47]. In the current study, we also revealed the impact of apolipoprotein 4 (APOE), the most important genetic risk factor for AD that could be implicated in neural plasticity.

Various studies outside and inside the united states highlighted the marital status difference as a crucial lead in cognitive impairment and dementia. Studied conducted outside the united states declared that Alzeheimer was substantially more likely to affect single men and women than married people , never-married, and widowed[67–70]. In consistent, a widowhood is considered a risk factor for being diagnosed with Alzehiemer among American old residents [71], however, men were more vulnerable than women [35–37]. Furthermore, a recent study involved old population of 65 or more years old confirmed these previous studies and found marital status as a protective aspect for cognitive impairment but those who were previously married (widowed and divorced) were at high risk of cognitive impairment [72].

Meanwhile we agree with those previously cited, but as anticipated in many studies, there is some limitations that urge more analysis. Therefore, more variables should be considered in future studies to validate our current models.

## 5. Limitations

This study has limitations inherent to cross-sectional studies like not able to address temporality. We measure for two exposure variables: RAVLT and marital status, but in cross-sectional studies exposures variables do not precede certain outcomes. Our use of RAVLT test do not avoid the complexity of having false positives subjects, who having the presence of brain dysfunction, errors occur when intact individuals are labeled as having brain dysfunction. The TADPOLE dataset is not a population-based-sample. We can have by design, people with MCI and dementia over-sampled. We may infer results may not generalize to community-dwelling population.

## 6. Conclusions

These design research may suggest that older individuals that never married, being race-black, changes in hippocampus measurements with RAVLT test may be a group at high risk for cognitive impairment. There are significant data on social engagement that point to a protective effect of higher levels of middle and late-life social engagement, reducing the risk of Alzheimer's disease and related dementias(ADRDs)[]. Our hypothesis is that RAVLT cognition performance with marital status is associated with greater odds of MCI group than RAVLT independently. To this end, we used TADPOLE data to evaluate cross-sectional associations between RAVLT performance in immediate response, learning, forgetting, and perception of forgetting with marital status and MCI.

Our methods involved subjects with MCI and normal cognition. Logistic regression models indicate strong associations among four RAVLT subgroups (1. low and high performance of immediate response, 2. immediate response with learning, 3. performance of immediate response with learning and forgetting, 4. performance of immediate response with learning, forgetting, and perception of forgetting) and MCI group. Models were adjusted for age, sex, race, marital status, ethnicity, education, APOE4 genotype, Hippocampus, whole brain, ventricles, and ICV. TADPOLE underlines various approaches that are crucial prognostic of the future progression of people at risk of AD. TADPOLES utilizes a substantial set of multimodal assessments from ADNI, which endorses the prediction of the disease progression.

Studies are needed to evaluate other cognitive test with missing data within TADPOLE dataset as modifiable risk factor for MCI.

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the declaration of Helsinki and approved by the local institutions review boards of each participant ADNI site. A complete list of participating ADNI sites and IRB details can be optained at adni.loni.usc.edu.

**Informed Consent Statement:** Informed consent was obtained from all subjects or authorized representative involved in the study. Details of informed consent procedures can be obtained at adni.loni.usc.edu.

**Data Availability Statement:** the data used in this study is available from the Alzheimer's Disease Neuroimaging Initiative Study Database (adni.Lni.usc.edu).

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## Abbreviations

The following abbreviations are used in this manuscript:

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| | |
|---|---|
| RAVLT | Rey Auditorial Verbal Learning Test |
| MCI | Mild Cognitive Impairment |
| ADNI | Alzheimer's Disease Neuroimaging Initiative |
| TADPOLE | Alzheimer's Disease Prediction of Longitudinal Evolution |

## Appendix A

*Appendix A.1*

The analysis was done using R language. The code and dataset are available on Kaggle.

You may follow the following steps to see and/or reproduce the results:

1. Click on the Kaggle link (https://www.kaggle.com/code/victorwealth/covariates-association-tadpole)

2. Click on Register and complete the signup process to create a Kaggle account or Login if you already possess an account.

3. Once logged in, click on Copy  Edit to make a copy of the code for your personal use.

4. In the copied version, you can either run per cell or run all cells to see the results

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