

BACKGROUND

Little is known about cognitive decline and the development of mild cognitive impairment (MCI) in midlife. Published norms are not sensitive to pre-clinical cognitive decline, making it difficult to study factors that contribute to midlife decline. Increased sensitivity to preclinical change is needed in order to improve interventions to slow or prevent the development of AD.

In this study, we developed and applied robust norms^{1,2} in WRAP, a cohort of middle-aged adults enriched for parental family history of AD, to identify those who met MCI criteria;³ we then estimated the prevalence of MCI subtypes, modeled 5-year change in memory performance in WRAP, and examined baseline predictors of amnesic MCI (aMCI) risk at wave 3.

METHODS

Participants: 532 WRAP volunteers with no neurological conditions and 3 completed assessment waves.

Assessment Protocol: Volunteers return for waves 2 and 3 after 4- and 2-year intervals, respectively. Each wave includes cognitive assessment, blood tests, and a health and lifestyle questionnaire packet. Cognitive performance is summarized in terms of 6 factors. IADL informant report is summarized as the mean across 8 items (range = 0 to 2, with higher scores indicating better IADL's); IQ-Code is summarized as the mean across 16 items (range = 1 to 5, scores at or below 3 suggest no change or improvement in functioning).

Statistical Analysis:

Identified participants with MCI. First, we calculated robust lower prediction limits (rLPLs) for 4 factors using baseline data, adjusting for age, gender, and literacy.⁴ Second, we applied these rLPLs to flag low performance for each wave of data. Last, we combined flags across waves to determine MCI status after 3 waves (categories defined in **Table 1**).

Compared cognitively healthy (CH, row 1 of Table 1) and aMCI (i.e., combined rows 4 and 5 of Table 1).

1) We used **ANCOVA** to test whether there is a baseline age by aMCI interaction in predicting 5-year change in AVLT total and to obtain adjusted means of baseline predictors for descriptive purposes.

2) Using **logistic regression**, we identified baseline variables associated with increased risk of aMCI at Wave 3 after adjusting for age, education, and gender. Candidate baseline predictors include: Family history of AD, CES-D score, BMI, systolic and diastolic blood pressure, subjective rating of health status (1-5 range, 5 is best), sum of health conditions, number of prescription medications, number of OTC medications, weekly exercise self-report (1=never to 8=daily), APOE4 status, and dispersion in factor scores⁵ (=SD of factors, converted to a z-score). Variables with $p < .15$ are shown in **Table 2**.

1. Sliwinski, Lipton, Buschke, & Stewart (1996).
2. De Santi, Pirraglia, Barr, Babb, Williams, Rogers, Glodzik, Brys, Mosconi, Reisberg, Ferris, & de Leon (2008).
3. NIA and Alzheimer's Association Workgroup (MCI due to AD Recommendations, 2011).
4. Manly, Touradjji, Tang, & Stern (2003).
5. Hilborn, Strauss, Hultsch, & Hunter (2009).

TABLES & FIGURES

TABLE 1. MCI CATEGORIES AFTER 3 WAVES

MCI Category, n (%)	Criteria
Cognitively healthy 318 (59.8)	All factor z-scores greater than robust lower prediction limits (rLPLs) at all 3 waves
Unclear 133 (25.0)	At least 1 factor less or equal rLPLs at 1 of 3 waves
Non-amnesic MCI* only (naMCI) 20 (3.8)	Speed and flexibility (SF) or working memory (WM) less or equal rLPLs at 2 or more waves
Amnesic MCI* only (aMCI) 50 (9.4)	Immediate memory (IM) or verbal learning and memory (VL) less or equal rLPLs at 2 or more waves
Multi-domain amnesic MCI (m-aMCI) 11 (2.1)	IM or VL \leq rLPLs and SF or WM \leq rLPLs at ≥ 2 waves

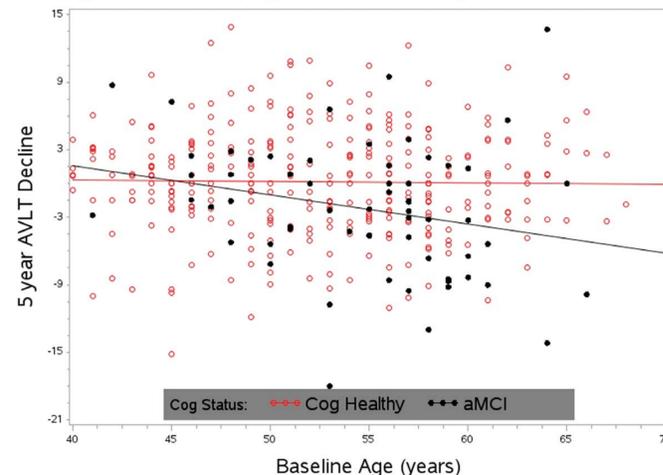
Also required informant report of normal everyday function; and no dementia.

TABLE 2. SAMPLE CHARACTERISTICS AND BASELINE PREDICTORS OF aMCI AT WAVE 3

Sample Characteristics	Cognitively Healthy n=318	aMCI n=61	p-value*
Age at baseline, mean (sd)	52.5 (6.5)	54.7 (5.6)	.01
Age at wave 3, mean (sd)	59.0 (6.4)	61.3 (5.5)	.01
Female, n (%)	226 (71.1)	38 (62.3)	.17
College degree, n (%)	197 (62.0)	40 (65.6)	.59
FSIQ, mean (sd)	114.8 (9.1)	113.3(9.7)	.23
Family history of AD (FH+), n (%)	257 (80.8)	47 (77.1)	.50
IADL mean at wave 3, median (range)	2 (1.2-2)	2 (1.4-2)	.80
IQ Code mean at wave 3, median (range)	3 (1-3.4)	3 (2.9-3.7)	.47
Self-report of memory problem at wave 3, n (%)	53 (16.8)	14 (23.0)	.25
AVLT total at baseline, Ismean (se)**	52.9 (.42)	40.7 (.81)	<.0001
AVLT delay at baseline, Ismean (se)	11.1 (.17)	7.2 (.32)	<.0001
Baseline Predictors of aMCI at Wave 3	Cognitively Healthy	aMCI	OR (95% CI)***
CES-D, Ismean (se)	5.7 (0.44)	9.0 (0.85)	1.08 (1.03, 1.12)
BMI, Ismean (se)	28.2 (0.44)	29.5 (0.84)	1.04 (.99, 1.08)
Sum of OTC meds, Ismean (se)	3.0 (0.19)	3.6 (0.37)	1.08 (.98, 1.19)
Z-Cognitive dispersion, Ismean (se)	-.09 (.07)	.75 (.13)	2.33 (1.7, 3.2)

*p-values from t-test for variables with mean (sd), 2-sample Wilcoxon for variables with median (range), and chi-square for categorical variables.
**Ismeans are adjusted for baseline age, gender, and education.
***OR=Odds ratio estimates from logistic model with baseline age, gender, and education as covariates for that predictor. Only those predictors with $p < .15$ from the larger set of candidate variables are included in this table.

FIGURE 1. BASELINE AGE BY aMCI INTERACTION IN 5-YEAR AVLT DECLINE



RESULTS

Whole Group:

81 (15.2%) met criteria for MCI of any type. (95% CI: 12.4 to 18.5%)
61 (11.5%) met criteria for amnesic MCI (aMCI, with and without m-a MCI). (95% CI: 9.0 to 14.5%)

Cognitively Healthy (CH) vs. aMCI:

Sample characteristics for the CH and aMCI groups are shown in **Table 2**.

Figure 1 displays the significant interaction between aMCI status and baseline age in predicting 5-year change in total AVLT score.

Several baseline predictors were associated with increased risk of aMCI at wave 3, after adjusting for baseline age, education, and gender (**Table 2**).

CONCLUSIONS

Robust norms identified a subgroup of WRAP with cognitive decline consistent with MCI cognitive criteria, 75.3% of whom had signs of memory impairment.

The subgroup with low memory performance may be at particular risk for progressing to AD due to their steeper longitudinal decline in memory performance.

CES-D score, BMI, sum of OTC meds and cognitive dispersion were significant baseline predictors of aMCI status at wave 3 after adjusting for age, education, and gender.

As the wave 3 sample grows, increased statistical power will facilitate identification of additional variables or clusters of variables associated with cognitive decline in midlife. Such information is necessary in order to maximize interventions designed to delay or prevent development of MCI and AD.

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