IS CDR = .5 ASSOCIATED WITH WORSE COGNITION IN A MIDDLE-AGED SAMPLE? RESULTS FROM THE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION

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BACKGROUND

The Clinical Dementia Rating (CDR) global rating is a reliable indicator of dementia in older samples. We observed in our consensus review that people with normal CDR ratings sometimes had abnormal cognitive performances and vice versa. Our study examined whether CDR was associated with concurrent cognition and psychometric MCI status in a late-middle-aged sample.

METHODS

Participants: Participants in the Wisconsin Registry for Alzheimer's Prevention (WRAP) with a CDR at wave 4 of cognitive assessment and no neurological disorders known to affect cognition were included (n = 318; mean(sd) age = 63(6.1); 86.8% AD family history; 39.6% APOE4 carriers; 64.5% women).

Dependent Variables: Memory and executive function factor scores assessed at wave 4 (and tests contributing to each factor) included: Immediate Memory (IM; Trials 1 and 2, Rey AVLT), Verbal Learning and Memory (VLM; Trials 3-5 & Delayed Recall, Rey AVLT), Speed and Flexibility (SF; Trails A and B, Stroop Color-Word); and Working Memory (WM; Letter-Number Sequencing, Digit Span Forward and Backward).

Independent Variables: CDR rating (0 or .5); psychometric MCI status (Normal = no assessment waves with factor scores at least 1.5 SD below age, gender, and literacy-based internal robust norms; aMCI = at least two assessment waves with at least one abnormal memory score; naMCI = at least two assessment waves with at least one abnormal executive function score); and covariates: age, gender, and education. CDR ratings and MCI statuses were combined into 4 levels for secondary analyses (aMCI_CDR for memory factors and naMCI_CDR for executive function factors).

Statistics: T-tests and chi-square tests were used to compare CDR groups for a variety of sample characteristics.

Analysis of covariance (ANCOVA) was used to examine whether CDR ratings were associated with concurrent (wave 4) cognition after adjusting for covariates.

Agreement between CDR ratings and MCI statuses were assessed with Kappa statistics.

Low agreement between CDR & MCI ratings prompted follow-up exploratory analyses including spaghetti plots depicting within person patterns across four visits and overall group trends across four MCI x CDR levels.

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TABLES & FIGURES

TABLE 1. Baseline Characteristics

Baseline Characteristics	CDR = 0	CDR = .5	p-value
Age, mean (SD)	52.5 (6.0)	55.1 (6.4)	0.001
Female, n (%)	152 (63.6)	53 (67.1)	0.57
Family history of AD, n (%)	208 (87.0)	68 (86.1)	0.83
APOE ε4, n (%)	99 (41.4)	27 (34.2)	0.25
Self-report of memory concerns at baseline, n (%)	45 (23.4)	28 (45.9)	0.0007
FSIQ, mean (SD)	115.0 (8.6)	113.1 (9.8)	0.12
AVLT total, adjusted mean (SE)	51.3 (.49)	50.1 (.84)	0.22
IM, adjusted mean (SE)	.13 (.06)	-.06 (.10)	0.12
VLM, adjusted mean (SE)	.08 (.06)	-.04 (.10)	0.33
WM, adjusted mean (SE)	.20 (.07)	-.10 (.11)	0.02
SF, adjusted mean (SE)	.13 (.06)	-.09 (.12)	0.09

TABLE 2. Wave 4 Variables

Wave 4 Variables	CDR = 0 n=239	CDR = .5 n=79	p-value
Age at CDR, mean (SD)	61.8 (5.9)	64.4 (6.3)	0.001
AVLT total, adjusted mean	50.5 (.61)	48.1 (.95)	0.02
IM, adjusted mean (SE)	.04 (.08)	-.18 (.12)	0.10
VLM, adjusted mean (SE)	-.05 (.08)	-.33 (.12)	0.03
WM, adjusted mean (SE)	.12 (.07)	-.15 (.11)	0.03
SF, adjusted mean (SE)	.09 (.07)	-.26 (.11)	0.003

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TABLE 3. Intercepts and Simple Slopes

Factor Score	1. CDR = 0, no MCI		2. CDR = .5, no MCI		3. CDR = 0, MCI		4. CDR = .5, MCI	
	Int (SE)	Slope (SE)	Int (SE)	Slope (SE)	Int (SE)	Slope (SE)	Int (SE)	Slope
IM	**.84 (.09)**	**-.02 (.005)**	**.39 (.19)**	-.003 (.009)	**-.52 (.21)**	**-.02 (.01)**	-.46 (.45)	-.01 (.02)
VLM (Figure 1)	**.80 (.08)**	**-.02 (.004)**	.21 (.17)	.003 (.008)	-.34 (.26)	**-.04 (.01)**	-.71 (.49)	-.01 (.02)
SF (Figure 2)	**1.44 (.08)**	**-.06 (.004)**	**.87 (.14)**	**-.04 (.007)**	**-.51 (.24)**	**-.03 (.01)**	.07 (.82)	-.06 (.03)
WM	**.46 (.09)**	-.007 (.005)	-.035 (.15)	.004 (.007)	**-.92 (.36)**	.017 (.017)	**-1.35 (.50)**	.03 (.02)

Boldface indicates p<.05 in test of hypothesis that the intercept or slope coefficient = 0.

IM= Immediate Memory; VLM = Verbal Learning and Memory; SF = Speed and Flexibility; and WM = Working Memory

FIGURE 1. VLM by CDR Rating and aMCI Status

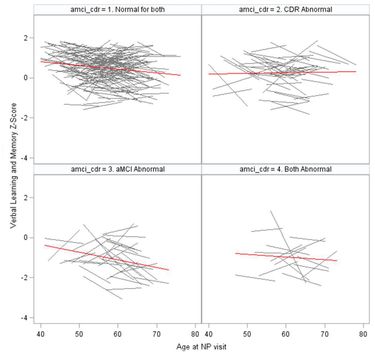
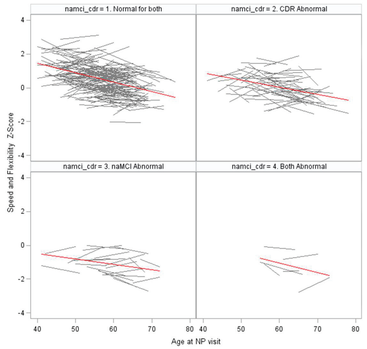


FIGURE 2. SF by CDR Rating and naMCI Status



RESULTS

CDR 0 vs .5: One-fourth of the sample (n=79) had CDR=.5 ratings. As shown in Table 1, the two CDR groups did not differ in terms of gender, family history of AD, APOE ε4 status, or most baseline cognitive variables examined. The CDR=.5 group was older, had a higher percent of participants who reported memory concerns at baseline, and had worse Working Memory. After adjusting for covariates, CDR at Wave 4 assessment was a significant predictor of concurrent VLM (β=.28, .003), SF (β=.35, .004), and WM (β=.26, p=.03); cognitive scores were higher among those with CDR=0; summary statistics are shown in Table 2.

Low Agreement between CDR and pscyhometric MCI ratings: Twenty-three percent of the participants with CDR=.5 also showed objective evidence of memory decline (i.e., met psychometric aMCI criteria); 84.4% with CDR=0 also were normal over all waves of cognitive assessment; 32.6% of those with abnormal objective memory scores had CDR=.5; and 77.4% with normal cognitive scores had CDR=0 (Kappa = .09, 95% C. I. = (-.04, .21)). Similarly, 8.6% of those with CDR=.5 also showed objective evidence of executive function decline (i.e., met psychometric naMCI criteria) while 90.1% of those with CDR=0 also had normal executive function across all waves; 22.2% of those with abnormal objective executive function performance had CDR=.5; and 74.9% of those with normal cognitive scores had CDR = 0 (Kappa = -.02, 95% C. I. = (-.11, .08)).

Factor Scores by CDR and MCI groups: Figures 1 and 2 depict spaghetti plots and group patterns by CDR and psychometric MCI status for one memory and one executive function outcome. The black lines represent patterns of individual performances over 4 waves while the red lines depict the group intercepts and slopes. Table 3 presents the simple intercepts and slopes for the four CDR x MCI categories for each cognitive factor.

CONCLUSIONS

In this relatively young sample, CDR=.5 was associated with slightly older age and modest decrements in concurrent measures of memory and executive function, aspects of cognition that are often associated with early AD.

Many participants with abnormal CDR's had normal memory and executive function performance. Similarly, many participants with normal CDR's had memory and executive function scores more than 1.5 SD's below expected levels. These two patterns of discrepancy between subjective CDR reports and objective psychometric data suggest that both types of data are important to consider when identifying participants with cognitive decline that is consistent with MCI or pre-clinical AD. These data are consistent with Bondi and Smith's insight (2014) that psychometric data will provide important early indications of disease.

Longitudinal follow-up is needed to determine whether: a) abnormal CDR scores in the early 60's are associated with increased conversion to AD, and b) whether CDR scores can be combined with objective assessment of cognitive trajectories to improve prediction of risk of conversion to AD in subsequent years.