Subtle Deficits in Instrumental Activities of Daily Living in Subtypes of Mild Cognitive Impairment

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Key Words

Mild cognitive impairment • Functional impairment • Activities of daily living • Memory performance • Executive function

Abstract

Background/Aims: Greater cognitive and functional deficits in mild cognitive impairment (MCI) are associated with higher rates of dementia. We explored the relationship between these factors by comparing instrumental activities of daily living (IADLs) among cognitive subtypes of MCI and examining associations between IADL and neuropsychological indices. **Methods:** We analyzed data from 1,108 MCI and 3,036 normal control subjects included in the National Alzheimer's Coordinating Center Uniform Data Set who were assessed with the Functional Activities Questionnaire (FAQ). **Results:** IADL deficits were greater in amnesic than nonamnesic MCI, but within these subgroups, did not differ between those with single or multiple domains of cognitive impairment. FAQ indices correlated significantly with memory and processing speed/executive function. **Conclusions:** IADL deficits are present in both amnesic MCI and nonamnesic MCI but are not related to the number of impaired cognitive

domains. These cross-sectional findings support previous longitudinal reports suggesting that cognitive and functional impairments in MCI may be independently associated with dementia risk.

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Introduction

Mild cognitive impairment (MCI) has been conceptualized as an intermediate stage between normal aging and dementia. General guidelines for the diagnosis of MCI include the presence of objective cognitive impairment and essentially intact activities of daily living (ADLs) [1]. These criteria are designed to distinguish MCI from both normal aging and mild dementia [although the presence of functional impairment is only a supportive feature in the NINCDS-ADRDA criteria for Alzheimer's disease (AD) [2]] and identify a population of subjects with an elevated risk of progression to dementia [3]. In an effort to improve diagnostic specificity, MCI has been further subdivided into subtypes based on the presence or absence of memory deficits and whether single or multiple cognitive domains are impaired [1]. Sev-

eral studies indicate that subjects meeting criteria for multiple-domain amnesic (mdAMN) MCI are most likely to subsequently progress to clinical AD [4–7].

Although current criteria for MCI specify ‘essentially intact’ ADLs, numerous reports suggest that subjects with MCI exhibit subtle but significant deficits in instrumental ADLs (IADLs) relative to normal controls (NC) [8–16]. Even mild IADL impairment has consistently been associated with increased rates of progression from MCI to dementia [10, 17–20]. Previous work in elderly populations has emphasized the importance of executive and/or memory function [21–27] in the performance of IADLs. However, some investigators have found that the increased risk of dementia associated with impaired IADLs appears to be independent of the degree of cognitive impairment [10, 19] and others have argued that deficits in IADLs may merely reflect duration of cognitive impairment [28].

One approach to examining the relative roles of functional and cognitive impairment for dementia risk in MCI is to explore differences in IADLs between cognitive subtypes of MCI. Conceptually, subjects with mdAMN MCI, who are at the highest risk of subsequent dementia, might also be expected to have the greatest deficits on standardized IADL assessments. However, the relatively few studies that have investigated IADLs in MCI subtypes have yielded inconsistent results. Many [16, 29–31], but not all [14] investigators have reported greater IADL deficits in multiple-domain MCI than in single-domain MCI. Similarly, IADL deficits may [14] or may not [30] be greater in amnesic MCI than in nonamnesic MCI. Studies that incorporate multiple IADL assessments report differences between MCI subgroups on some scales but not others [30, 31], suggesting that specific features of each measure (which IADLs included, self vs. informant report, questionnaire vs. performance-based) may significantly impact results. This literature is further complicated by inherent differences in sample sizes, diagnostic criteria for MCI, and population demographics across studies.

We addressed this issue by exploring the relationship between cognitive and functional impairment in MCI within the large multicenter cohort of subjects included in the standardized Uniform Data Set (UDS) compiled by the National Alzheimer’s Coordinating Center (NACC) [32]. The primary goal of the present study was to compare IADLs measured with the Functional Activities Questionnaire (FAQ) [33] between subjects diagnosed with different cognitive subtypes of MCI. A secondary aim was to clarify the association between cognitive abil-

ity (determined by subjects’ neuropsychological testing performance) and functional ability (determined by informant ratings of subjects’ IADL performance) in this MCI cohort.

Methods

Research Participants

The NACC UDS contains data from 31 Alzheimer’s Disease Centers (ADCs) with current or prior funding from the National Institute on Aging. We identified 1,108 MCI and 3,036 NC subjects who were ≥ 50 years old, had Mini-Mental State Examination (MMSE) [34] scores ≥ 24 , were assessed with the FAQ, and whose data had been entered into the UDS by May 29, 2007. MCI was a clinical diagnosis based on the Petersen criteria [1]. Subjective cognitive complaints and functional status were determined by clinician interview and judgment. Objective cognitive impairment was independently determined at each ADC through clinician judgment and/or neuropsychological testing (including additional measures beyond those incorporated in the UDS). MCI subjects were classified into single-domain amnesic (sdAMN; $n = 532$), mdAMN ($n = 340$), single-domain nonamnesic (sdNON; $n = 162$), and multiple-domain nonamnesic (mdNON; $n = 74$) groups based upon the presence or absence of memory and/or other cognitive impairment (attention, language, visuospatial, executive). To ensure a broad sampling of MCI subtypes, all subjects meeting the Petersen criteria were included, irrespective of their scores on the Hachinski Ischemic Scale [35]. Data from these subjects has previously been included in a study examining the utility of the FAQ for distinguishing MCI from very mild AD [36]. NC subjects were determined to have normal cognition by each ADC using similar methodology. Written consent, approved by the Institutional Review Board of each center, was obtained from each subject.

Functional Assessment

IADLs were quantified using the FAQ [33]. This instrument was administered to an informant, who rated each subject’s performance over the preceding 4 weeks on 10 separate categories of IADLs: (1) writing checks, paying bills, keeping financial records; (2) assembling tax or business records; (3) shopping alone; (4) playing a game of skill; (5) making coffee or tea; (6) preparing a balanced meal; (7) keeping track of current events; (8) attending to and understanding a television program, book, or magazine; (9) remembering appointments, family occasions, medications; and (10) traveling out of the neighborhood. Higher scores in each category denote increasing impairment: 0 = normal; 1 = has difficulty, but does by self; 2 = requires assistance, or 3 = dependent. Activities that could not be rated, either because the subject never performed them prior to developing cognitive difficulties, or because the informant had insufficient information to provide a valid response, were not scored. Overall FAQ performance was evaluated using two separate methods: total FAQ score, which included only subjects that had valid scores on all items (82.5% of overall subject population), and average score across FAQ items with valid responses (mean FAQ item score), which included all subjects.

Table 1. Factor analysis of the neuropsychological assessments

	Factor 1: executive/ processing speed	Factor 2: memory	Factor 3: language	Factor 4: attention
WMS-R logical memory IA	0.157	<i>0.926</i>	0.163	0.080
WMS-R forward digit span	0.016	−0.024	0.134	<i>0.869</i>
WMS-R reverse digit span	0.240	0.146	0.067	<i>0.793</i>
Animals	0.168	0.141	<i>0.815</i>	0.086
Vegetables	0.052	0.247	<i>0.714</i>	0.056
Trail-Making Test Part A	−0.789	−0.077	−0.239	−0.074
Trail-Making Test Part B	−0.731	−0.095	−0.231	−0.296
WAIS-R digit symbol	<i>0.731</i>	0.118	0.053	0.012
WMS-R logical memory IIA	0.103	<i>0.943</i>	0.137	0.041
Boston naming test, odd items	0.260	−0.036	<i>0.667</i>	0.116
Cronbach's α	0.492	0.921	0.657	0.640

Factor loadings over 0.60 are in italics.

Neuropsychological Assessment

The UDS includes selected neuropsychological data for each subject [32, 37]: MMSE [34], logical memory IA and IIA of the revised Wechsler Memory Scale (WMS-R) [38], WMS-R forward and reverse digit span [38], verbal category fluency (animals [39] and vegetables), Trail-Making Test Parts A and B [40], digit symbol of the revised Wechsler Adult Intelligence Scale (WAIS-R) [41], and the 30 odd-numbered items of the Boston Naming Test [42]. Neuropsychological testing scores from the NC group were used to generate normative data stratified by age (50–59, 60–69, 70–79, 80–89, and 90+) and years of formal education (≤ 12 , 13–16, 17+). Performance of the MCI subjects on each test was normalized by calculating z-scores derived from this sample.

Data Analysis

Statistical analyses were performed using PASW Statistics 17.0.2 for Windows (SPSS Inc., Chicago, Ill., USA). Between-group comparisons were conducted using one-way analyses of variance for age, education, number of valid FAQ item scores, and neuropsychological performance, and Kruskal-Wallis tests for gender, race, and percentage of subjects with complete FAQ data. Global FAQ indices and individual FAQ item scores were compared between groups using analyses of covariance adjusted for demographic differences between groups in age, education, gender, race, and MMSE scores. The total number of valid FAQ item scores was used as an additional covariate for the analysis of mean FAQ item scores and the presence or absence of complete FAQ data was used as an additional fixed factor for the analysis of individual FAQ item scores. Post hoc analyses were Bonferroni corrected for multiple comparisons.

In order to examine the relationship between FAQ indices and cognitive functioning, we performed an exploratory factor analysis to identify shared underlying constructs among the measures in the UDS neuropsychological battery. Principal components analysis incorporating varimax orthogonal rotation was used because it includes the common variance across all tests as well as variance that is unique to individual measures [43]. Factor extrac-

tion was based on eigenvalues >1 . Interpretation of factor components was based on highest loadings (>0.60) for each variable, and yielded a 4-factor solution (table 1). Cronbach's α was calculated to measure the internal consistency of the factors. For MCI subjects with complete data on all neuropsychological assessments, domain-specific z-scores were calculated by averaging z-scores on individual tests in each cognitive domain. Linear regression analysis incorporating age, gender, race, and years of formal education was used to ascertain any associations between neuropsychological performance in individual cognitive domains and FAQ indices.

Results

Demographics

Demographic data for the NC group and the MCI subgroups are shown in table 2. There were significant differences between groups for most variables. Bonferroni correction of post hoc comparisons resulted in critical p values of 0.005. There were fewer male participants in the sdAMN group relative to the NC ($p < 0.001$) and mdNON ($p = 0.003$) groups, and in the mdAMN group relative to the NC group ($p < 0.001$). The mdNON group consisted of a lower proportion of non-Hispanic Whites than any of the other groups ($p < 0.001$), and the mdAMN and sdNON groups had a lower proportion of non-Hispanic Whites than the NC and sdAMN groups ($p < 0.001$). The sdAMN group was older than the NC, sdNON, and mdNON groups ($p < 0.001$), and marginally older than the mdAMN group ($p = 0.008$). The NC and sdAMN groups were better educated than the mdAMN and

Fig. 1. Total FAQ scores (a) and mean FAQ item scores (b) in the NC group and MCI subgroups. Error bars represent standard error of the mean. ^a $p \leq 0.001$ versus NC; ^b $p \leq 0.001$ versus sdNON; ^c $p \leq 0.001$ versus mdNON.

Table 2. Demographic information

	NC	sdAMN	mdAMN	sdNON	mdNON	$\chi^2(4, 4,144)/$ $F(4, 4,139)$
Number	3,036	532	340	162	74	
Male, %	64.6 ^a	49.2 ^b	54.4 ^b	54.9 ^{a, b}	67.6 ^a	57.53*
Non-Hispanic White, %	82.5 ^a	86.5 ^a	72.6 ^b	69.1 ^b	47.3 ^c	99.58*
Age, years	74.8 (9.1) ^a	77.0 (9.2) ^b	75.3 (8.5) ^{a, b}	74.1 (8.6) ^a	73.0 (6.8) ^a	8.33*
Education ^d , years	15.5 (2.9) ^a	15.4 (2.9) ^a	14.4 (3.2) ^b	15.0 (3.7) ^{a, b}	14.2 (3.5) ^b	13.63*
MMSE score	29.0 (1.2) ^a	27.8 (1.8) ^b	27.4 (1.8) ^c	28.2 (1.7) ^b	27.8 (1.5) ^{b, c}	182.14*
Complete FAQ data, %	86.7 ^a	72.4 ^b	67.9 ^b	74.7 ^b	63.5 ^b	150.28*
Valid FAQ responses, n	9.8 (0.6) ^a	9.6 (0.9) ^b	9.4 (1.0) ^c	9.6 (0.7) ^{a, b}	9.4 (0.9) ^{b, c}	37.07*
Complete neuropsychological data, %	94.5	94.9	92.6	91.4	93.2	5.16

Figures in parentheses indicate SD. * $p < 0.05$. ^{a-c} Groups denoted by different letters differ by $p < 0.005$. ^d Degrees of freedom = 4, 106 due to missing data for 4 sdAMN, 1 sdNON, and 28 NC subjects.

mdNON groups ($p < 0.001$). MMSE scores were higher in the NC group than in each of the MCI subgroups ($p < 0.001$), higher in the sdNON group than in the sdAMN and mdAMN groups ($p < 0.001$), and higher in the sdAMN group than in the mdAMN group ($p < 0.001$).

FAQ Indices

Participants in the NC group were more likely to have complete FAQ data than their counterparts in the MCI subgroups ($p < 0.001$). Likewise, the average number of

valid FAQ responses for the NC group was significantly greater than for the sdAMN, mdAMN, and mdNON groups ($p < 0.001$), and marginally greater than for the sdNON group ($p = 0.006$). Both the sdAMN ($p = 0.005$) and sdNON ($p = 0.001$) groups averaged a greater number of valid FAQ responses than the mdAMN group.

Total FAQ scores are shown in figure 1a, and mean FAQ item scores are shown in figure 1b. Analyses of both global FAQ indices yielded similar results. There were significant group effects after adjustment for demo-

Fig. 2. Individual FAQ item scores for all participants. Percentages above each bar represent the proportion of subjects with valid responses for that item. Error bars represent standard error of the mean. ^a $p < 0.017$ versus NC; ^b $p < 0.017$ versus NON.

graphic factors [total FAQ scores: $F(4, 3,371) = 40.09$, $p < 0.001$; mean FAQ item scores: $F(4, 4,087) = 59.63$, $p < 0.001$]. Bonferroni-corrected post hoc analyses (critical $p = 0.005$) indicated that total FAQ and mean FAQ item scores were significantly lower (indicating less functional impairment) in the NC group than in the sdAMN, mdAMN, and sdNON groups ($p \leq 0.001$), and significantly lower in the sdNON group than in the sdAMN and mdAMN groups ($p \leq 0.001$). Mean FAQ item scores were also lower in the mdNON group than in the sdAMN and mdAMN groups ($p \leq 0.001$).

Similar scores on global FAQ indices were seen between the sdAMN and mdAMN subgroups (total FAQ scores: $p = 0.62$; mean FAQ item scores: $p = 0.43$) and between the sdNON and mdNON subgroups (total FAQ scores: $p = 0.88$; mean FAQ item scores: $p = 0.56$), despite inherent demographic differences. Therefore, these subgroups were combined into respective AMN and NON groups for further analyses of individual FAQ items (fig. 2), which included all subjects with valid responses for each item.

After adjustment for demographic factors, there was a significant group effect for each individual FAQ item ($F > 15.0$, $p < 0.001$). NC subjects had lower scores than the AMN group on all items ($p < 0.001$) and lower scores than the NON group on managing bills, preparing taxes, keeping up with current events, attending to media, remembering dates, and traveling outside the neighborhood ($p < 0.004$). The NON group had lower scores than the AMN group on managing bills, preparing taxes, shopping, playing a game of skill, cooking, keeping track

of current events, and remembering dates ($p < 0.002$). These findings survived Bonferroni correction (critical $p = 0.017$).

Correlations between FAQ Indices and Neuropsychological Performance

Neuropsychological test scores for the NC group and the MCI subgroups are shown in table 3. The MCI subgroups performed more poorly than the NC group on each test. As expected, amnesic MCI subgroups performed more poorly than nonamnesic MCI subgroups on memory measures and multiple-domain MCI subgroups generally performed more poorly than single-domain MCI subgroups on the other assessments.

Multiple linear regression analyses investigating the association between the two global FAQ indices and cognitive performance in the MCI group are detailed in table 4. Both analyses yielded similar results, indicating that only the memory and executive/processing speed z-scores were independent predictors of global FAQ indices and that memory performance was more strongly associated with functional impairment than executive/processing speed performance. However, these models produced relative modest correlations, each accounting for only about 10% of the variance in the global FAQ indices.

Multiple linear regression models incorporating individual FAQ items produced weaker correlations, with r values ranging from 0.30 (remembering dates) to 0.16 (making tea or coffee). Memory z-scores correlated most strongly with remembering dates ($\beta = -0.25$), preparing taxes ($\beta = -0.20$), and managing bills ($\beta = -0.19$). Execu-

Table 3. Neuropsychological performance (raw scores)

	NC	sdAMN	mdAMN	sdNON	mdNON	F(4, 3,871)
Number	2,843	502	315	147	69	
Logical memory IA	13.8 (3.9) ^a	9.6 (4.4) ^{c, d}	9.3 (4.1) ^d	12.6 (3.8) ^b	10.9 (4.2) ^c	191.05*
Logical memory IIA	12.5 (4.3) ^a	6.6 (5.0) ^c	6.8 (4.5) ^c	11.3 (3.9) ^b	9.9 (4.7) ^b	268.65*
Forward digit span	6.8 (1.1) ^a	6.6 (1.1) ^b	6.4 (1.1) ^c	6.3 (1.1) ^c	6.1 (1.2) ^c	19.90*
Reverse digit span	5.0 (1.2) ^a	4.7 (1.2) ^b	4.3 (1.1) ^{c, d}	4.5 (1.3) ^{b, c}	4.0 (1.0) ^d	35.32*
Animals	20.0 (5.7) ^a	16.9 (5.1) ^b	15.1 (5.1) ^c	16.2 (5.2) ^{b, c}	14.3 (4.2) ^c	102.64*
Vegetables	14.5 (4.5) ^a	11.6 (4.0) ^b	10.7 (3.6) ^c	12.1 (4.0) ^b	12.3 (3.1) ^b	101.92*
Boston naming test	27.1 (3.3) ^a	26.1 (3.5) ^b	23.6 (4.9) ^c	25.4 (3.9) ^b	22.6 (5.1) ^c	103.03*
Trail-Making Test Part A	34.8 (15.5) ^a	41.4 (19.7) ^b	45.9 (22.9) ^c	39.7 (14.1) ^b	49.1 (25.0) ^c	51.56*
Trail-Making Test Part B	91.2 (50.3) ^a	116.4 (61.4) ^b	152.2 (82.2) ^c	125.1 (67.1) ^b	168.7 (76.8) ^c	127.69*
Digit symbol	49.9 (17.4) ^a	42.0 (16.6) ^{b, c}	39.9 (19.2) ^{b, c}	44.6 (19.1) ^b	36.1 (12.5) ^c	48.66*

Figures in parentheses indicate SD. * $p < 0.05$. ^{a-d} Groups denoted by different letters differ by $p < 0.005$.

Table 4. Multiple linear regression of global FAQ indices versus neuropsychological performance adjusted for demographics

	Total FAQ (n = 733)			Mean FAQ item (n = 1,032)		
	β	t	p	β	t	p
Age	0.05	1.47	0.143	0.07	3.35	0.019
Education	-0.10	-2.81	0.005	-0.11	-3.43	0.001
Gender	0.01	0.22	0.824	-0.06	-1.93	0.053
Race	0.14	3.35	0.001	0.11	3.22	0.001
Memory z	-0.25	-6.54	<0.001	-0.23	-7.16	<0.001
Attention z	0.05	1.38	0.169	0.04	1.38	0.169
Language z	-0.03	-0.74	0.460	-0.04	-1.19	0.235
Executive/processing speed z	-0.09	-2.28	0.023	-0.13	-3.75	<0.001
Overall model		r = 0.321			r = 0.329	

tive/processing speed z-scores correlated most strongly with managing bills ($\beta = -0.17$), preparing taxes ($\beta = -0.13$), and traveling outside the neighborhood ($\beta = -0.12$).

Discussion

Our results, derived from a large multicenter database, indicate that mild IADL deficits are present in both amnesic and nonamnesic MCI, with more extensive deficits reported by informants for amnesic subjects. The degree of IADL impairment was similar between amnesic subjects with single or multiple domains of cognitive impairment. Across all MCI subtypes, global IADL mea-

sures were associated with neuropsychological assessments of memory and executive function/processing speed.

Previous studies of IADLs in cognitive subtypes of MCI have produced mixed results. Some investigators have found IADL deficits only in participants meeting criteria for mdAMN MCI [16, 29]. Others have also found deficits in single-domain (both amnesic and nonamnesic) MCI [14, 31] that are similar to those reported here. These disparate results may be attributable to differences in IADL demands across cultures, population demographics, or IADL and/or cognitive assessments across studies.

We additionally found more profound IADL limitations in amnesic relative to nonamnesic MCI, which has

not been consistently reported in prior studies. Wadley et al. [14] reported greater deficits in their amnesic MCI subgroup, while Burton et al. [30] found similar deficits in amnesic and nonamnesic MCI, but more extensive impairment amongst subjects with deficits in multiple cognitive domains. More recent work by Aretouli and Brandt [31] included two separate IADL assessments, yielding conflicting results that concur with both earlier studies. We were somewhat surprised to find similar IADL deficits in our sdAMN and mdAMN MCI groups. Our initial prediction, given earlier studies of IADLs in MCI subtypes [16, 29–31], the consistent association between IADL impairment and progression to dementia [10, 17–20], and higher rates of progression to dementia in mdAMN MCI [4–7], was that scores on global FAQ indices would be higher in our mdAMN MCI group.

There are several potential explanations for these results. The presence of memory deficits may play a larger role than the presence of additional cognitive deficits in determining IADL impairment. This interpretation is supported by our regression analyses, which indicated that memory performance was an independent predictor of global FAQ indices, and by earlier work from other groups identifying the importance of memory function in the performance of IADLs [21, 24, 27]. Nevertheless, other investigators have identified executive function as the strongest neuropsychological predictor of IADL abilities [22, 23, 25], though such discrepancies may be related to differences in the specific tests that comprise cognitive domain scores across studies. Alternatively, subjects in the UDS database with deficits in memory and other cognitive domains who exhibited greater IADL impairments may have been diagnosed with dementia and therefore been excluded from this analysis. Finally, the FAQ may be more heavily weighted towards memory-dependent IADLs than other IADLs. This last possibility seems less likely given previous work showing that total FAQ scores correlate reasonably well with other IADL indices [33] and that the sdAMN and mdAMN MCI groups in the current cohort had similar scores on each FAQ item ($p > 0.05$).

The important contribution of memory deficits to impaired IADLs suggested by differences in global FAQ indices between clinically diagnosed amnesic and nonamnesic MCI groups is further supported by regression analyses incorporating neuropsychological performance, which identified both memory and executive/processing speed as significant predictors of functional ability. However, the correlations between cognitive and IADL indices were relatively modest. The strength of these correla-

tions may have been limited by the inclusion of only MCI subjects in the regression analyses, thus restricting the range of both the cognitive and FAQ scores. Some of the prior studies demonstrating more robust correlations between cognitive and functional scores included a broader spectrum of subjects, often encompassing both normal and impaired cognition [22, 25, 44]. The relatively limited battery of neuropsychological tests included in the UDS may also have reduced the strength of these correlations. In particular, the memory factor includes only two measures from a single test of verbal memory (WMS-R logical memory), and the executive/processing speed factor includes only a single test (Trail-Making Test Part B) that is associated with executive functioning [45]. Finally, these relatively weak correlations may simply reflect the possibility that similar IADL deficits may be caused by different cognitive deficits in different subjects.

MCI subjects were less likely to have complete FAQ data than NC subjects. The underlying reason for this finding remains uncertain. One possibility is that informants for the MCI groups may have been less knowledgeable about their subjects than informants for the NC group. However, given that similar results were obtained with total FAQ scores (which included only subjects with complete FAQ data) and mean FAQ item scores (which included all subjects), it is unlikely that the differences between groups in the number of valid FAQ responses significantly affected our conclusions.

There are a few other considerations that impact the interpretation of our results. The study population was comprised of a convenience sample of highly educated subjects volunteering for research at major academic centers and therefore may not be representative of epidemiological samples or those with greater ethnic diversity. Nonamnesic MCI subjects were less likely to be non-Hispanic Whites, a finding that replicates other recent studies of nonamnesic MCI [46, 47] and is consistent with previous reports of poorer performance on nonmemory cognitive assessments in non-White populations [48, 49]. Our amnesic MCI subgroups were older and included higher proportions of women than the other diagnostic groups. Although similar age differences have been reported in previous studies of amnesic MCI, such gender differences have not [50]. Diagnostic classification in the UDS is derived from clinical diagnoses determined at each individual ADC based upon the current criteria for MCI [1]. However, the operationalization of these criteria has not been consistently standardized. Although the UDS includes a core neuropsychological battery [32, 37], the NACC does not specify which additional cognitive

tests can be used at each ADC to supplement that battery, does not establish specific performance thresholds for impairment, and does not stipulate the precise role of test scores in the diagnostic process. Since the specific neuropsychological tests and performance thresholds used to identify MCI can significantly influence subject classification [46, 51–53], it remains possible that variability in the interpretation of the diagnostic criteria for MCI across participating centers may have influenced our results. Finally, the FAQ is an informant-based assessment of IADLs, and may be susceptible to bias if informants lack or distort information regarding subjects' functional abilities. Performance-based measures of IADLs may have better ecological validity, correlate more closely with cognitive function, and allow for more subtle distinctions among diagnostic groups [54, 55].

Our cross-sectional findings, when taken together with previous longitudinal reports [10, 19], raise the possibility that cognitive and functional deficits in MCI may independently contribute to increased risk of subsequent dementia. Although mdAMN MCI subjects have been

considered the most likely to progress to dementia, their IADL deficits were similar to those seen in sdAMN MCI subjects. Conversely, although memory and executive/processing speed were independently associated with IADL performance, correlations between cognitive and functional decline were relatively modest. These results provide further support for inclusion of both cognitive and functional variables when estimating dementia risk in MCI [10, 17, 19] but require further exploration with additional longitudinal analyses.

Acknowledgements

This research was supported by grants from the National Institute on Aging (U01 AG016976 to the National Alzheimer's Coordinating Center and P50 AG16570 to the Mary S. Easton Center for Alzheimer's Disease Research at UCLA), the Alzheimer's Disease Research Centers of California, and the Sidell-Kagan Foundation. We would like to thank Nathaniel Mercaldo for his assistance with data management.

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