Early Functional Limitations in Cognitively Normal Older Adults Predict Diagnostic Conversion to Mild Cognitive Impairment

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OBJECTIVES: To examine whether specific types of early functional limitations in cognitively normal older adults are associated with subsequent development of mild cognitive impairment (MCI), as well as the relative predictive value of self versus informant report in predicting diagnostic conversion to MCI.

DESIGN: As a part of a longitudinal study design, participants underwent baseline and annual multidisciplinary clinical evaluations, including a physical and neurological examination, imaging, laboratory work, and neuropsychological testing.

SETTING: Data used in this study were collected as part of longitudinal research at the University of California, Davis Alzheimer’s Disease Center.

PARTICIPANTS: Individuals diagnosed as having normal cognition at study baseline who had an informant who could complete informant-based ratings and at least one follow-up visit (N = 324).

MEASUREMENTS: Participants and informants each completed the Everyday Cognition Scale (ECog), an instrument designed to measure everyday function in six cognitively relevant domains.

RESULTS: Self- and informant-reported functional limitations on the ECog were associated with significantly greater risk of diagnostic conversion to MCI (informant: hazard ratio (HR) = 2.0, 95% confidence interval (CI) = 1.3–3.2, P = .002), with self-report having a slightly higher hazard (HR = 2.3, 95% CI = 1.4–3.6, P < .001). When controlling for baseline cognitive abilities, the effect remained significant for self- and informant-reported functional limitations.

CONCLUSION: Deficits in everyday memory and executive function domains were the strongest predictors of diagnostic conversion to MCI. Detection of early functional limitations may be clinically useful in assessing the future risk of developing cognitive impairment in cognitively normal older adults. J Am Geriatr Soc 65:1152–1158, 2017.

Key words: functional ability; normal cognition; mild cognitive impairment; self-report; informant report

Loss of autonomy is a top concern of older adults.1 A hallmark feature of a dementia syndrome is functional disability, or loss of independence in performing the major instrumental activities of daily living (IADLs) that are critical for autonomous living (e.g., managing finances). Although loss of independence in major IADLs represents important disease milestones, the more subtle functional limitations that precede disability develop gradually and early in the disease process.2,3 A better understanding of when functional changes start to emerge and what types of early functional limitations are associated with risk of progressive disease and loss of independence is critical to implementing early-detection strategies and informing when and how to intervene.

Mild cognitive impairment (MCI) is a transitional state between normal cognition and dementia. Subtle changes in everyday functional abilities are evident in MCI,4–10 and a greater degree of functional limitation is associated with faster cognitive decline11,12 and disease progression or conversion to dementia.13–20 Subtle functional changes may be detectable in older adults with normal cognition who eventually develop MCI or dementia. Population-based studies have shown that subtle functional changes can precede a dementia diagnosis by 10 to 12 years.2,3 Similarly, a longitudinal study of functional trajectories demonstrated that cognitively normal older adults who later developed MCI or dementia evidenced greater everyday functional limitations at baseline and...
faster functional decline over time than cognitively stable older adults.21

Little is known about which types of functional limitations develop earliest and are associated with a particularly poor prognosis. For individuals with MCI, functional tasks that depend most on higher-level cognitive abilities are affected earliest.19,22 For older adults without dementia, functional limitations related to everyday memory and executive abilities have been shown to be most strongly associated with risk of incident IADL dependency and conversion to dementia.18

Questionnaire-based measures that the older individual or a knowledgeable informant completes are used to measure the magnitude of change in functional abilities from an individual’s baseline. When assessing older adults with dementia, self-report is often inaccurate because of poor insight, but informant-reported functional changes have been shown to discriminate between individuals with or without dementia13–26 and to be related to objective neuropsychological performance16 and disease markers (e.g., brain atrophy).16,27 In individuals with MCI, evidence of the validity of self-reported functional changes is mixed.28–31 It is unclear whether self- or informant-reported declines in everyday function are most useful in individuals with MCI.10,32–35 Self-reported functional decline in cognitively normal older adults has been associated with risk of developing preclinical Alzheimer’s disease.36,37

It appears that functional changes progress over an extended period of time and are an early indicator of neurodegenerative disease. It remains unclear when the earliest changes can be detected, what types of functional changes occur first, and how best to detect such early changes. Thus, the goals of this study were to evaluate whether early functional limitations in cognitively normal older adults are associated with greater risk of developing MCI, determine whether there are particular types of functional limitations associated with risk of MCI, and evaluate the relative predictive value of self- and informant-reported functional abilities in predicting conversion to MCI. It was hypothesized that cognitively normal older adults with greater functional limitations at study baseline would have higher risk of subsequent diagnostic conversion to MCI. Based on the contribution of executive function and memory abilities on everyday function,16,29,38 it was hypothesized that functional limitations related to everyday executive and memory abilities would pose the greatest risk for a future conversion to MCI. It was hypothesized that self- and informant-report would predict development of MCI. Because subtle decrements in cognition may aid in identifying those at greater risk of developing MCI, prediction models included baseline measures of neuropsychological function.

**METHODS**

**Participants**

Data used in this study were collected as part of a longitudinal study at the University of California, Davis Alzheimer’s Disease Center (ADC). Participants were recruited through clinic referrals and community outreach. Participants spoke English or Spanish (27 participants were tested in Spanish), had an informant with whom the participant had regular contact and who could complete informant-based ratings, were diagnosed as being cognitively normal at study baseline, and had at least one follow-up visit. Exclusion criteria included unstable major medical illness or current debilitating psychiatric disorder (milder forms of depression were acceptable).

All participants underwent baseline and annual diagnostic evaluations that included a physical and neurological examination, imaging, laboratory work, and neuropsychological testing using the Alzheimer’s Disease Uniform Dataset Neuropsychological Battery.41 Diagnoses at each annual visit were categorized as normal cognition (i.e., stable normal) or MCI according to standardized criteria.42 Individuals with MCI could not have impairments in basic activities of daily living (ADLs) or be dependent in IADLs. Clinical diagnoses were made without knowledge of Everyday Cognition Scale (ECog) scores (the primary functional assessment predictor).

Three hundred twenty-four older adults who were cognitively normal at study baseline and had at least one follow-up assessment were included in the study (see Tables 1 and 2 for demographic data). On average, the sample was followed for 4 years. Average time from study baseline to development of MCI was 1 year shorter (3 years) than the average length of follow-up for those who did not convert. (Nonconverters were followed for an average of 4 years.) Converters were slightly older. MMSE scores and neuropsychological performance were slightly lower in participants who progressed to MCI, although scores were well within the average range, consistent with their initial diagnosis of cognitively normal. As measured using the informant- and self-rated ECog at study baseline, participants who progressed to MCI had slightly higher scores on the total ECog and on several of the domains (memory, some executive domains). All participants signed informed consent, and appropriate institutional review boards approved human subject involvement.

**Assessment of Everyday Functional Limitations**

The ECog is an informant- and self-rated questionnaire of cognitively based everyday abilities. It was designed to be sensitive to mild functional limitations that precede loss of independence and are relevant to functional changes associated with MCI.6,19 The ECog comprises 39 items on which the participant’s current level of everyday functioning is compared with functioning 10 years earlier. Items are rated on a 4-point scale (1 = better or no change; 4 = consistently much worse). Higher scores indicate greater limitations. A total score was calculated by summing all of the ratings and dividing by the number of items completed. Confirmatory factor analysis supports the construct of everyday function as multidimensional with six distinct cognitively based domains that correspond objectively to specific domains of neuropsychological function:19 memory, language, visuospatial abilities, planning, organization, divided attention. The ECog has good test–retest reliability (correlation coefficient \( r = 0.82, P < .001 \)).19 The ECog has been shown to discriminate between diagnostic groups20 and to be related to objective...
measures of cognition and biomarkers of neurodegenerative disease.\textsuperscript{9,43} Example ECog items are included in Table 3, and the full instrument is available at https://doi.org/10.1037/0894–4105.22.4.531.supp.

Neuropsychological Assessment

Cognitive functioning was assessed using the Spanish English Neuropsychological Assessment Scales battery (SENAS), which has undergone extensive development as a battery of cognitive tests relevant to diseases of aging.\textsuperscript{44–46} This study used two composites: episodic memory (list learning) and executive function (working memory).

Table 1. Baseline Demographic Characteristics

| Variable                        | Total, N = 324 | Stable Normal, n = 264 | Converters to Mild Cognitive Impairment, n = 60 | P-Value |
|---------------------------------|---------------|------------------------|-----------------------------------------------|---------|
| Age, mean ± SD                  | 75.5 ± 6.9   | 74.9 ± 6.8             | 78.0 ± 7.1                                    | .002    |
| Education, years, mean ± SD     | 13.9 ± 3.7   | 14.0 ± 3.7             | 13.3 ± 3.7                                    | .19     |
| Female, n (%)                   | 205 (63.3)   | 168 (63.6)             | 37 (61.7)                                     | .77     |
| Race and ethnicity, n (%)       |               |                        |                                               |         |
| African American                | 77 (23.8)    | 63 (23.9)              | 14 (23.3)                                     | .28     |
| Caucasian                       | 154 (47.5)   | 128 (48.5)             | 26 (43.3)                                     | .15     |
| Hispanic                        | 69 (21.3)    | 53 (20.1)              | 16 (26.7)                                     | .08     |
| Other or unknown                | 24 (7.4)     | 20 (7.6)               | 4 (6.7)                                       |         |

SD = standard deviation.
Stable normal refers to participants who did not convert to MCI.

Table 2. Everyday Cognition Scale (ECog) and Cognitive Function Scores

| Variable                        | Total, N = 324 | Stable Normal, n = 264 | Converters to Mild Cognitive Impairment, n = 60 | P-Value |
|---------------------------------|---------------|------------------------|-----------------------------------------------|---------|
| Mini-Mental State Examination   | 28.1 ± 1.9    | 28.2 ± 1.8             | 27.3 ± 2.3                                    | .007    |
| ECog Informant                  |               |                        |                                               |         |
| Memory                          | 1.60 ± 0.61   | 1.55 ± 0.60            | 1.83 ± 0.63                                   | <.001   |
| Language                        | 1.35 ± 0.50   | 1.33 ± 0.49            | 1.45 ± 0.52                                   | .052    |
| Visuospatial                    | 1.26 ± 0.46   | 1.26 ± 0.48            | 1.31 ± 0.38                                   | .03     |
| Organization                    | 1.36 ± 0.54   | 1.33 ± 0.50            | 1.50 ± 0.68                                   | .15     |
| Planning                        | 1.25 ± 0.44   | 1.23 ± 0.43            | 1.34 ± 0.48                                   | .08     |
| Divided attention               | 1.50 ± 0.66   | 1.45 ± 0.62            | 1.73 ± 0.79                                   | .01     |
| Total score                     | 1.40 ± 0.46   | 1.37 ± 0.46            | 1.53 ± 0.46                                   | .002    |
| ECog Self                       |               |                        |                                               |         |
| Memory                          | 1.72 ± 0.67   | 1.66 ± 0.62            | 1.99 ± 0.78                                   | .001    |
| Language                        | 1.50 ± 0.57   | 1.46 ± 0.53            | 1.67 ± 0.70                                   | .03     |
| Visuospatial                    | 1.28 ± 0.46   | 1.25 ± 0.41            | 1.41 ± 0.62                                   | .14     |
| Organization                    | 1.41 ± 0.55   | 1.38 ± 0.55            | 1.51 ± 0.56                                   | .04     |
| Planning                        | 1.26 ± 0.45   | 1.24 ± 0.45            | 1.35 ± 0.44                                   | .02     |
| Divided attention               | 1.56 ± 0.71   | 1.51 ± 0.69            | 1.73 ± 0.76                                   | .02     |
| Total score                     | 1.46 ± 0.47   | 1.42 ± 0.44            | 1.63 ± 0.55                                   | .004    |
| Spanish English Bilingual Neuropsychological Assessment Scales | | | | |
| Episodic memory\textsuperscript{a} | 0.2 ± 0.8 | 0.3 ± 0.7 | −0.2 ± 0.7 | <.001 |
| Executive function\textsuperscript{b} | 0.04 ± 0.59 | 0.1 ± 0.6 | −0.2 ± 0.6 | .008 |
| Time to incident mild cognitive impairment or last assessment, years | 3.9 ± 2.4 | 4.2 ± 2.4 | 3.0 ± 2.1 | <.001 |

\textsuperscript{a}Available for 218 participants (172 stable, 46 converters).
\textsuperscript{b}Available for 221 participants (175 stable, 46 converters).
Stable normal refers to participants who did not convert to MCI.

Statistical Analyses

Two-sample t-tests, Wilcoxon rank-sum tests (for ECog scores, follow-up time), and chi-square tests (for categorical variables) were used to compare participants who progressed to MCI with those who remained stable on demographic characteristics, functional limitations, and neuropsychological function. Cox proportional hazards models were used to assess associations between functional limitations and diagnostic conversion to MCI. Those who did not develop MCI were considered to have been censored at the last assessment. Models were adjusted for baseline age, education, and ECog domain or total score.
Table 3. Example Everyday Cognition Scale Items

| Item               | Examples                                                                 |
|--------------------|--------------------------------------------------------------------------|
| Memory             | Remembering a few shopping items without a list; remembering appointments or meetings |
| Language           | Remembering names of objects; communicating thoughts in conversation    |
| Visual perception  | Following map to a new location; finding way back to meeting spot in mall |
| Planning           | Planning the sequence of stops on a shopping trip                        |
| Organization       | Keeping living and work space organized; keeping financial records       |
| Divided attention  | Returning to a task after being interrupted; keeping track of multiple things while cooking |

Results examining the association between baseline informant-rated ECog and subsequent diagnostic conversion to MCI are presented in Table 4. Simple models adjusted for age and education showed that older adults with higher baseline ECog total scores, reflecting greater functional limitations, were at a greater risk of developing MCI at follow-up. (A one-unit increase on the ECog total was associated with twice the risk of converting to MCI.) The greatest risk of converting to MCI at follow-up was associated with greater baseline limitations in Everyday memory, planning, organization, and divided attention. (A one-unit increase was associated with approximately twice the risk of converting to MCI.) The latter three domains reflect aspects of everyday executive function. Everyday language and visuospatial were not significantly associated with conversion to MCI. Results were similar after removing participants reclassified as cognitively normal after to converting to MCI (data not shown).

A second set of models controlled for baseline objective neuropsychological performance in memory and executive function (and age and education). The magnitude of the association between baseline ECog total and risk of subsequent diagnostic conversion to MCI was slightly attenuated but remained significant. It appeared that the adjustment of neuropsychological performance affected the risk associated with converting to MCI at follow-up based on baseline scores in the domains of Everyday planning, organization, and divided attention although baseline memory and planning scores remained significantly associated with risk of converting to MCI at follow-up, even after controlling for baseline neuropsychological performance. Results were similar after removing participants reclassified as cognitively normal, except that divided attention was no longer significant as a predictor (hazard ratio (HR) = 1.62, 95% confidence interval (CI) = 0.99–2.66, P = .05).

Table 4. Associations Between Everyday Cognition Scale (ECog) Scores at Baseline and Diagnostic Conversion to Mild Cognitive Impairment at Follow-Up

| ECog Domain | Hazard Ratio (95% Confidence Interval), P-Value |
|-------------|-----------------------------------------------|
| Informant   |                                               |
| Memory      | 2.0 (1.4–2.9), < .001 1.8 (1.2–2.9), .006     |
| Language    | 1.5 (0.9–2.4), .12 1.3 (0.7–2.4), .46          |
| Visuospatial| 1.4 (0.8–2.4), 18 1.1 (0.6–2.2), .69           |
| Planning    | 1.8 (1.1–3.1), 02 2.0 (1.1–3.6), .03            |
| Organization| 1.9 (1.3–2.8), .001 1.9 (1.1–3.0), .01          |
| Divided attention | 1.7 (1.2–2.4), .001c 1.7 (1.1–2.7), .02 |
| Total score | 2.0 (1.3–3.2), .002 1.9 (1.1–3.2), .02          |
| Self        |                                               |
| Memory      | 1.9 (1.3–2.6), < .001 1.6 (1.1–2.4), .02        |
| Language    | 1.8 (1.2–2.7), .003 1.6 (0.9–2.6), .10          |
| Visuospatial| 1.8 (1.1–2.9), .03 1.6 (0.9–2.8), .10           |
| Planning    | 1.8 (1.1–3.0), .01 1.6 (0.8–3.0), .17           |
| Organization| 1.9 (1.2–2.9), .003 1.4 (0.8–2.4), .21          |
| Divided attention | 1.6 (1.1–2.3), .006 1.7 (1.1–2.5), .01 |
| Total score | 2.3 (1.4–3.6), < .001 1.9 (1.1–3.4), .03        |

aAdjusted for age, education, and baseline ECog domain or total score.

bAdjusted for age, education, baseline ECog domain or total score, and cognitive function (memory and executive function).

cThe assumption of proportional hazards is not met in this model (P = .03). When an interaction between baseline everyday divided attention and logarithm of time was included in the model, the estimated hazard ratio was higher at early time points and lower at later time points (the hazard ratio decreased over time).
reported ECog domains significantly associated with risk of MCI once the neuropsychological variables were included than with the informant-rated ECog domains. The association was slightly attenuated for memory and ECog total but remained similar for divided attention.

DISCUSSION
In cognitively normal older adults prospectively followed over time, subtle changes in everyday functional abilities substantially increase the risk of subsequently developing MCI. These results add to a growing body of literature showing that changes in real-world abilities are among the first clinical signs of an incipient neurodegenerative disease.21,47

Whether the predictive utility of early functional changes varied according to rater was examined. Mild decrements in functional abilities predicted incident MCI regardless of whether ratings were based on self- or informant report. Specifically, a one-unit increase in ECog total score (e.g., going from no change in functional ability to occasionally performing worse) based on informant ratings was associated with twice the risk of developing MCI over an average of 3 years. The self-reported ECog total score was associated with a similar, although slightly higher risk of incident MCI. This study is among the first to directly compare the value of self- and informant-rated functional limitations in predicting risk of developing MCI and suggests that self-report is a strong predictor. Results of this study are consistent with the growing body of literature that demonstrates that subjective concerns regarding functional changes can be associated with biological markers of Alzheimer’s disease and related disorders, including greater amyloid burden,48,49 greater brain atrophy,50 and greater risk of incident dementia.18

This study also examined what types of functional limitations predicted incident MCI. When examining informant-based functional ratings, as hypothesized, functional limitations in everyday memory and executive functions conferred the greatest risk of developing MCI. The ECog domain of memory was associated with the highest risk, and this domain alone performed as well as the ECog total score. Such findings are not unexpected given that memory deficits are the hallmark symptom of Alzheimer’s disease, and therefore, memory changes manifest in daily life are likely to be a harbinger of early Alzheimer’s disease. Poorer informant ratings of everyday executive domains with a similar relative risk included organization and planning. Organizational abilities include being able to structure ones’ environment to allow for maximum efficiency and manage important tasks (e.g., finances) in a timely and error-free manner. Planning refers to the ability to think ahead, anticipate possible hurdles, and sequence ones’ actions in an efficient way. The everyday executive domains have previously been identified as strong predictors of loss of independence in IADLs in cognitively normal individuals or those with MCI.18 The current findings further highlight the importance of loss of everyday executive function as an early warning of neurodegenerative disease and risk of eventual loss of autonomy.

When examining the types of self-reported functional limitations associated with incident MCI, a somewhat different pattern of results emerged. In this case, all of the ECog domains were associated with a similar level of risk. The most striking difference was that the language and visuospatial domains were predictive of incident MCI when using self- but not informant report. This discrepancy may be due to the relatively internal processes that these domains assess and are thus more difficult for others to perceive. Language assesses ones’ ability to use language to comprehend new information and formulate and communicate ones’ thoughts, which may be less apparent to outside viewers, particularly if the person has developed compensation strategies to hide his or her weaknesses. The visuospatial domain assesses geographic navigation ability (e.g., following a map to a new location). If a person is still driving independently, as would be presumed given their status as cognitively normal, it is less likely that these areas of difficulty will be apparent to an observer.

Detailed neuropsychological test results are often not available when people initially start to express concerns about changes in their ability to perform complex functional tasks, so understanding the predictive value of functional complaints while not considering cognitive performance is of value. However, there was also interest in evaluating the degree to which reports of functional changes are of utility in predicting incident MCI when cognitive performance is considered. Baseline cognitive performance scores did not, for the most part, attenuate the influence of informant-reported functional limitations on incident MCI. Additionally, the overall pattern of results between the individual ECog domains and MCI conversion was similar (e.g., similar ECog domains were associated with conversion to MCI). As such, even in the context of knowing cognitive test results, greater functional limitations as reported by a knowledgeable informant independently contributed to predicting development of MCI. There was, perhaps, a slightly greater effect of including baseline cognition on the effect of self-reported functional limitations and incident MCI. Overall, when cognitive performance was included in the model, fewer self-rated ECog domains remain predictive of MCI conversion, although the magnitude of the effect of self-reported functional limitations on incident MCI when using the ECog total was the same as when the informant-reported ECog total was used. The current results provide evidence that subtle functional limitations, assessed using self- or informant report, increase the risk of developing MCI independent of the effect of cognitive test performance.

Study Strengths and Limitations
Participants of this study were part of a well-characterized cohort, all of whom undergo a comprehensive diagnostic evaluation annually and are diverse in terms of demographic factors and background. Nonetheless, older adults who volunteer to participate in research may be different from the general population, potentially limiting generalizability. Although participants who converted to MCI over follow-up had slightly lower cognitive scores at baseline, they had all undergone extensive neuropsychological testing to confirm their normal cognitive status. Furthermore, cognitive and functional tests used for diagnostic purposes were distinct from tests used as predictors or outcomes in
the present study. Finally, functional assessment was based on self- and informant report, and both are subject to reporting bias, although the similarity in findings between raters supports the validity of the results. Previous studies have also showed that ECog ratings may be related to objective biomarkers.9

Clinical Implications and Future Directions

Results of this study suggest that it is important for clinicians to take concerns about subtle changes in everyday function seriously, whether the individual or a knowledgeable informant reports them. Such changes substantially increase an older adult’s risk that they will develop MCI within a few years. Generally speaking, clinicians should inquire about how older adults are functioning in their daily life, particularly with regard to tasks heavily dependent on memory (e.g., remembering appointments) and executive function (e.g. organization). The presence of such subtle changes should serve to trigger further examination or enhanced monitoring over time. These results suggest that the ECog, in particular, may be a useful instrument to help screen for risk of MCI. Previous work suggests that measurement of functional abilities may be particularly helpful in older adults from diverse backgrounds, with low education, or for whom English is not their primary language.20 In future work, it will be important to more specifically examine the predictive utility of the ECog in ethnically and educationally diverse older adult populations.

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