HHS Public Access

Author manuscript

Int Psychogeriatr. Author manuscript; available in PMC 2017 October 05.

Published in final edited form as:

Int Psychogeriatr. 2016 December ; 28(12): 2009–2018. doi:10.1017/S1041610216000995.

Subtle changes in daily functioning predict conversion from normal to mild cognitive impairment or dementia: an analysis of the NACC database

Milap A. Nowrangi, **Paul B. Rosenberg**, and **Jeannie-Marie S. Leoutsakos**

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Background—There are relatively small but observable changes in functional ability in those without Mild cognitive impairment (MCI) or dementia. The present study seeks to understand whether these individuals go on to develop MCI or dementia by assessing the association between baseline Functional Activities Questionnaire (FAQ) and conversion independent and after adjustment for cognitive tests.

Methods—The NACC database was used to conduct the analysis of which 7,625 participants were initially identified as having more than one visit and who were cognitively normal at their first visit. Cox proportional hazards were used to fit three models that controlled for executive and non-executive cognitive domains. A similar model was used to assess the effect of FAQ subcategories on conversion.

Results—Of these individuals, 1,328 converted to either MCI or dementia by visit 10. Converters had a total visit 1 FAQ score significantly higher than non-converters indicating more functional impairment at baseline. After adjustment for cognitive tests, the association between visit 1 FAQ and subsequent conversion was not attenuated. Doing taxes, remembering dates, and traveling were individually identified as significant predictors of conversion.

Conclusions—The FAQ can be used as an indirect measure of functional ability and is associated with conversion to MCI or dementia. There is a selective and significant association between changes in financial ability and conversion that is in accordance with other research of financial capacity.

Keywords

Alzheimer's disease; MCI; activities of daily living; functioning

Correspondence should be addressed to: Milap A. Nowrangi, M.D., Paul B. Rosenberg, M.D., and Jeannie-Marie Leoutsakos, Ph.D., Department of Psychiatry, Johns Hopkins Bayview Medical Center, 5300 Alpha Commons Drive, 4th Floor, Baltimore, MD 21224. Office: 410-550-2294; Fax: 410-550-1407.

Conflict of interest declaration: None.

Description of authors' role: M. Nowrangi designed the study, conducted the data collection, performed the analysis, and generated the manuscript. P. Rosenberg designed the study, supervised the data collection and analysis, and generated the manuscript. J.M. Leoutsakos designed the study, supervised the data collection, analysis, and generation of the manuscript.

Disclosures of competing interests: None.

Introduction

The number of Americans older than 65 is expected to more than double in the next 40 years, increasing from 40.2 million in 2010 to 88.5 million in 2050 (Alzheimer's, 2014). Of these older individuals, many will experience both cognitive decline and impairment in performing daily activities. Some of these declines may be signs of impending disease. While early cognitive changes often are recognized as the first symptoms of decline, impairment in daily functioning can also occur early and be quite distressing. This impairment may impact personal or environmental safety or ability to care and protect oneself. An important question is whether there are clinical characteristics of subtle yet observable functional changes before dementia that may anticipate future cognitive decline.

In elderly persons, subtle *cognitive* deficits occur within the normal range on standard testing protocols and predict the time to clinically relevant cognitive impairment before clinical symptoms are reported (Kawas *et al.*, 2003; Visser *et al.*, 2006). Similarly, there are subtle *functional* deficits, specifically with instrumental activities of daily living (IADLs) that can be identified and predate a diagnosis of MCI (Peres *et al.*, 2006; Di Carlo *et al.*, 2007; Reppermund *et al.*, 2013). Mild cognitive impairment (MCI) is commonly referred to, as a state in which there is cognitive decline in older adults that is not of sufficient magnitude to impact daily life and so meet criteria for dementia (Albert *et al.*, 2011). Because many persons with MCI are at increased risk of transitioning from normal aging to dementia it is of great public health importance to study this transition (Fischer *et al.*, 2007; Marchesi, 2012). Dementia due to Alzheimer's disease (AD), for example, is most commonly preceded by a long prodromal period during which cognitive symptoms insidiously emerge though without significant impact to one's life (Nowrangi *et al.*, 2011). The presence of brain amyloid (imaged by PET) in functionally “normal” older adults has been associated with subtle but significant cognitive deficits, which may reflect early neuropathological changes (Sperling *et al.*, 2013). As impairments in daily functioning increase, a diagnosis of the dementia syndrome is made. The extent of this impairment and its measurement, however, is not well-understood. As our population ages such IADLs as financial management, driving an automobile, medication management, and other complex judgment and decision-making processes will become areas to carefully monitor as deficits in these can lead to unwanted or even dangerous outcomes (Harada *et al.*, 2013). The development and course of functional changes that occur along the continuum towards dementia; however, are poorly defined and their relationship with the transition from no appreciable cognitive deficits to MCI or dementia has not been well-studied.

Because of both the clinical and scientific interest in identifying early stages of dementia, there is a growing body of research focused on better characterizing the transitions between those who appear cognitively normal and MCI or dementia (Vallotti *et al.*, 2001; Kryscio *et al.*, 2006; Artero *et al.*, 2008; Oulhaj *et al.*, 2009). Moreover, characterizing the earliest changes in daily functioning that might predict the onset of disease states might help identify individuals who could participate in secondary prevention trials that may halt, delay, or reverse disease progression.

Though cognition and functioning are related to each other, the overall objective of the present study is to understand the transition from apparently normal cognition to MCI or dementia from the perspective of daily functioning. Because there are relatively small but observable and measurable deficits in daily functioning in a subset of those who cognitively test as normal, we intend to investigate whether these individuals go on to develop MCI or dementia when examined independent of cognitive measures. In order to accomplish this goal, we will measure the independent utility of the Functional Activity Questionnaire (FAQ) in predicting conversion to MCI or dementia, with and without adjustment for cognitive performance. We first hypothesize that relatively small changes in the FAQ are associated with an increase in the risk of conversion to MCI or dementia. We underscore here that we are not asserting causation. Secondarily, we hypothesize that those primarily with deficits in IADLs specific to financial activities will go on to convert from normal aging to MCI or dementia compared with other IADLs. We will do this by individually examining the FAQ's component parts.

Methods

Participants and study design

National Alzheimer Coordinating Center (NACC): Volunteers were recruited from 34 past and present NIA-funded Alzheimer's Disease Centers (ADC) across the USA. NACC has developed and maintains a large database of standardized clinical and neuropathological research data (Beekly *et al.*, 2004). Data included in this study occurred between September 2005 and January 20015. All ADCs were overseen by local IRBs, and after complete description of the study to the subjects, written informed consent was obtained. Volunteers were evaluated annually by trained clinicians either in the clinic or at home. At each annual visit, a Uniformed Data Set (UDS) (Beekly *et al.*, 2007) was collected, which included demographics, medical history, family history, behavioral, and functional assessments, as well as a neuropsychological battery. Race and ethnicity were based on the participant's report. Diagnoses were made by a clinician or consensus conference using all available data (Morris *et al.*, 2006; Morris, 2008; Weintraub *et al.*, 2009). MCI diagnoses were made using modified Petersen criteria (Petersen *et al.*, 2001; Petersen *et al.*, 2009) and AD diagnoses were made using NINCDS/ADRDA criteria (McKhann, 2011). Normal participants were not diagnosed with either MCI or any type of dementia.

Measures

The Functional Activities Questionnaire (FAQ) was administered to the informant at each visit by a trained and certified NACC staff member (Morris *et al.*, 2006; Morris, 2008; Weintraub *et al.*, 2009). The FAQ (Pfeffer *et al.*, 1982), is a 10-item clinical measure of independence for completing daily tasks necessary for independent living that can be administered to either patient or caregiver. The FAQ is a consistently accurate instrument with good sensitivity (85%) and also has good reliability (exceeding 0.80) (Pfeffer *et al.*, 1982). Tests of validity have been performed on the FAQ and have established it as both a bedside as well as a research instrument. The abilities assessed in the FAQ are: (1) writing checks, paying bills, or balancing a checkbook; (2) assembling tax records, business affairs, or papers; (3) shopping alone for clothes, household necessities, or groceries; (4) playing a

game of skill or working on a hobby; (5) heating water, making a cup of coffee, or turning off the stove after use; (6) preparing a balanced meal; (7) keeping track of current events; (8) paying attention to or understanding and discussing a TV, book, or magazine; (9) remembering appointments, family occasions, holidays, medications; (10) traveling out of the neighborhood, driving, arranging to take a bus. For each activity, four levels ranging from dependence (scored 0) to independence (scored 3) are specified. Sum scores range from 0 to 30 with higher scores reflecting greater dependency. A cut-point score of 9 (dependent in 3 or more activities) is recommended to indicate impaired function and possible cognitive impairment. If the subject had never done one of these activities, a coding of "not applicable" was given and was excluded from this analysis.

Several tests of memory and executive function were selected for inclusion in the analysis because performance of daily functional tasks requires effective recruitment and execution of cognition specifically in these domains (Royall *et al.*, 2007; Hughes *et al.*, 2012; Monsell *et al.*, 2014). While other cognitive domains such as language and visuospatial ability are also necessary, most evidence suggests episodic memory and executive control are essential (Royall *et al.*, 2002; Royall *et al.*, 2007; Reinvang *et al.*, 2012). Therefore, we included the following cognitive tests to assess executive function: (1) Trail Making Test (TMT) A and B jointly assess attention, visual scanning and search skills, and psychomotor speed and coordination (Reitan, 1955). Independently, TMT A assesses processing speed whereas TMT B assesses set switching therefore, both were included in the analysis and the difference between TMT B and A as a measure of executive function. (2) Category (animals and vegetables) fluency evaluated semantic and phonemic verbal fluency (Lezak, 2004c). (3) Digit span forwards and backwards (Jensen and Figueroa, 1975) are also measures of working memory and often fall under the auspices of executive function. Memory function was primarily evaluated by use of: (3) Mini-Mental State Exam (MMSE) (Folstein *et al.*, 1975) which includes screening estimates of episodic recall but also of orientation, attention, language, and visual construction. (4) Current Logical Memory 1A Story Units Recalled is an age-, sex-, education-adjusted z-score for the total number of items recalled (Abikoff *et al.*, 1987). This test examines the ability to recall a short story and is used as an approximation of episodic memory. The Boston naming test (Kaplan *et al.*, 1983; LaBarge *et al.*, 1986) was also included in the analysis to assess effect of language function. It assesses confrontational word retrieval commonly in patients with aphasia due to a variety of neurological conditions. The Wechsler Adult Intelligence Scale (WAIS-R) digit symbol test was added to provide an estimate of processing speed (Wechsler, 1939). Finally, we included the Geriatric Depression Scale (GDS), which is a 15-item screening measure for depression in older adults. Scores range from 0 to 15, with scores greater than 5 indicating a positive screen (Yesavage, 1988).

Statistical analysis

Conversion was defined as change in diagnostic class from normal to MCI or dementia. We compared demographics, baseline cognitive measures (as described above), FAQ total (0–30) and individually (0–3) between converters and non-converters using *t*-tests or χ^2 tests ($p < 0.05$). All tests were two-sided; *t*-tests assumed unequal variances and used Satterthwaite's approximation for degrees of freedom (Satterthwaite, 1946).

In order to test our hypothesis, we fit three statistical models that systematically adjusted for cognitive variables. In the base model, (1) we fit Cox proportional hazards models and included for baseline age, sex, years of education, GDS, and total FAQ. To further investigate the effect of cognition, we fit two other models additionally controlling for, (2) non-executive (memory and naming): MMSE, logical memory, Boston naming, and (3) combined executive function and nonexecutive: TMT B–A, animal and vegetable category fluencies, and digit span forward and backward, WAIS-R (executive measures) with nonexecutive as in (2). Time to conversion or censor was measured in years.

Secondarily, we fit Cox proportional hazards models to FAQ subcategories, as referenced earlier, to investigate which abilities, if any, predicted conversion. To control for cognitive variables as well as age, sex, years of education, we applied the same three-model procedure as described above in the primary analysis. All computations were done using STATA version 11.0 (StataCorp, College Station, TX).

Results

Participant characteristics

Our data request included all visits for all 7,625 participants with more than one visit and who were cognitively normal at their first visit. Of these individuals, 1,328 converted to either MCI or dementia by visit 10. Table 1 summarizes demographic, cognitive, and functional data by conversion status. Converters were more likely to be older, female, and have slightly less education over all. On a scale of independence with 1 indicating complete independence and 4 complete dependence, converters, at baseline, were somewhat more dependent. Not surprisingly, converters tended to live less independently than their non-converter counterparts and a greater percentage lived in a retirement community or other assisted living environment. Cognitively, converters had lower MMSE, and episodic memory scores (logical memory) and tests of executive function were lower than those of non-converters.

In terms of daily living activities, converters had a total FAQ score significantly higher than non-converters though mean scores did not meet FAQ cut point of 9, which recommends loss of independence. Within each subscale, converters also scored slightly higher than their counterparts.

Functional activity hazard models

We fit Cox proportional hazard models with conversion to MCI or dementia as the outcome. Table 2 reports Hazard Ratios with standard errors for all three models (as described above). Most notably, the hazard ratio estimate for total FAQ did not change between model 1 (1.02, (0.003), $p < 0.01$), model 2 (1.01, (0.003), $p < 0.01$) and model 3 (1.01, (0.004), $p = 0.01$). Though the association between total FAQ at baseline and conversion-free survival is small, these models suggest that there is no attenuation of the association after adjusting for the cognitive tests. A separate analysis (not shown) was conducted to include various covariates into the statistical model. These included history of heart attack, stroke, seizure, traumatic brain injury, use of anxiolytics including benzodiazepines, prior diagnosis of major

psychiatric disorder, and alcohol use. The association between FAQ and hazard of conversion was not altered across all three models when including these covariates.

Subanalysis: Hazard estimation of each FAQ subscales

Table 3 reports sub analyses in which we examine the association between each FAQ subtest and conversion-free survival. The subtests associated with the greatest hazard of conversion were ability to do taxes, remember dates, and travel.

Discussion

In this analysis, we sought to examine the association between baseline functioning and conversion to MCI or dementia. We tested the hypothesis that changes in functional ability as measured by the FAQ-predicted conversion from normal to either MCI or dementia, even after adjustment for cognitive tests. We first found that indeed there was variability among total FAQ scores in older adults who tested cognitively within normal range. While FAQ scores were understandably low (since these participants were in the normal NACC cohort) and did not meet the cut point to indicate functional impairment, we did find that those who converted to MCI or dementia had higher baseline total FAQ (Table 1). We found a statistically significant association between baseline FAQ total score and risk of conversion to MCI or dementia. To our knowledge, this association has not been previously identified in a large sample. Additionally, the association between baseline FAQ and risk of conversion was not attenuated after adjustment for cognitive test scores (Table 2). Finally, we showed that the ability to do taxes, remember dates, and to travel were associated with increased risk of conversion (Table 3).

As individuals advance in age, the ability to maintain an independent and good quality of life is dependent not only on their health status but also on their cognitive and functional abilities. To date there is a consistent body of literature supporting a general pattern of age-related changes in cognitive function in which crystallized abilities (general knowledge and acquired skills) are relatively preserved with increasing age, while fluid abilities (reasoning, pattern recognition, and novel problem solving) gradually decline after they peak, typically in one's 20's–30's (Salthouse *et al.*, 2010; Harada *et al.*, 2013). Specific cognitive domains that are typically investigated in regards to normal age-related changes; namely cognitive (psychomotor) speed, attention, executive functions, and memory have also been attributed to MCI and dementia. It is often inferred, then, that declines in cognitive performance as measured by neuropsychological tests closely mirrors or even causes loss of functional abilities that ultimately define the dementia syndrome (Reppermund *et al.*, 2011; Shankle *et al.*, 2013; Caselli *et al.*, 2014).

To our knowledge, this is the first study of the FAQ as an indirect measure of functional ability to predict conversion to MCI or dementia. Other studies have examined conversion from normal to MCI or dementia in relation to functioning but have not explored association directly (Wadley *et al.*, 2007; Artero *et al.*, 2008; Jefferson *et al.*, 2008). Because the neurodegenerative process leading to dementia begins early in adulthood and progresses over decades (Braak and Braak, 1995; Bookheimer *et al.*, 2000), more research is seeking to examine earlier pre-morbid stages to identify individuals that may be more amenable to

intervention. A number of studies have now shown that daily functioning becomes impaired in the early stages of cognitive decline before a diagnosis of dementia is warranted and that these individuals go on to develop MCI or dementia (Barberger-Gateau *et al.*, 1993; Tabert *et al.*, 2002; Burton *et al.*, 2006; Peres *et al.*, 2006; Mariani *et al.*, 2008). This is set in the context that those with MCI are at increased risk of progressing to dementia (DeCarli, 2003; Bruscoli and Lovestone, 2004; Panza *et al.*, 2005; Pinto and Subramanyam, 2009). As a result, the revised criteria for MCI as put forward by Albert *et al.* (2011), suggests that while those with MCI may have mild problems performing complex functional tasks, they are able to live independently. Similarly, a number of studies have shown that early impairment in activities of daily living increased risk of conversion from normal to MCI to dementia (Perneczky *et al.*, 2006; Bangen *et al.*, 2010; Marshall *et al.*, 2014). In the Sydney Memory and Ageing Study (Reppermund *et al.*, 2013), the investigators showed that participation in highly cognitively demanding activities specifically predicted amnestic MCI but not non-amnestic MCI whereas those with low cognitive demand did not predict MCI or dementia (Reppermund *et al.*, 2013). Similarly, Peres *et al.* (2006), Di Carlo *et al.* (2007), and DeCarli (2003) found that in those with normal cognition, self-reported IADL restrictions predicted progression to dementia after 2 and 4 years, respectively.

While clinicians frequently use neuropsycho-logical measures to account for differences in functional status among older adults these tests are designed to evaluate specific cognitive abilities rather than functional abilities, and there is little evidence to support such test use in this manner (Chaytor and Schmitter-Edgecombe, 2003; Farias *et al.*, 2003). Research does suggest, however, that global cognition assessed by such measures as the MMSE as well as measures of executive functioning such as the Delis–Kaplan Executive Function System (Delis *et al.*, 2004; Homack *et al.*, 2005), account for the greatest proportion of variance of functional ability (Duda *et al.*, 2014). Several studies have shown specific associations between executive functions (Mariani *et al.*, 2008; Pereira *et al.*, 2010), memory and psychomotor speed (Barberger-Gateau *et al.*, 1993; Tuokko *et al.*, 2005). In a study by Reppermund *et al.* (2011), significant associations were observed between an instrument of functional ability, the Bayer-Activities of Daily Living (B-ADL) and five cognitive domains (Memory, Attention/processing speed, visuospatial, language, and executive functions) in tasks that designated to be “high cognitive demand” by factor analysis. Other studies including a review of 68 papers by Royall *et al.* (2005), however, showed only modest association between cognitive measures and functional outcomes. Results from this analysis show the independent association of the FAQ and hazard of conversion to MCI or dementia. This is of potential importance given that neuropsychological batteries take a long time and may be expensive to administer while the FAQ is relatively simple and take a shorter time to administer. Taken together, these results with those from other studies point to a complex interaction between cognition and daily functioning that more likely to be reciprocating rather than linear or simple causation.

The results of this analysis demonstrate a striking association between changes in financial management (taxes) with conversion to MCI or dementia. Financial ability has been the focus of insightful research in normal and pathological cognitive aging. Financial capacity comprises a broad range of conceptual, pragmatic, and judgment and decision-making abilities ranging from basic to more complex skills such as bill payment, balancing a bank

account, and exercising complex financial judgment (Marson *et al.*, 2000; Farias *et al.*, 2006). It has been systematically shown that impairment in financial capacity is one of the earliest IADL changes seen in MCI. Studies by Marson *et al.*, have shown impaired performance on a measure of financial capacity called the financial capacity instrument (FCI) (Marson *et al.*, 2000; Marson *et al.*, 2009). The neurocognitive predictors of financial ability in people with MCI and AD include measures of attention and working memory (executive function), short-term episodic memory, visuomotor tracking, and written arithmetic ability (Royall *et al.*, 2007; Okonkwo *et al.*, 2008). These cognitive abilities as they pertain to financial capacity have been associated with brain changes including the medial frontal cortex and decreases in posterior cortical volumes (Stoeckel *et al.*, 2013). Results of this analysis support the assertion that financial capacity is a significant and early indicator of future functional decline and potentially conversion to MCI or dementia. Additionally, this analysis also shows an association between conversion and remembering dates and traveling. A study by Marshall *et al.* (2014) showed that the remembering shopping items as well as appointments and events discriminated between cognitively normal individuals and MCI here suggesting agreement with other research related to memory-based functional abilities. Traveling as a specific instrumental activity to our knowledge does not appear to have been studied and so represents a potential area of focus for future investigation.

This study over-all has several strengths including large sample, which enabled analysis of the FAQ by subcategories rather than by total score as is most commonly done. Moreover, the choice of the FAQ reflects an informant-based rather than self-reported instrument, which is a common weakness in other studies. Finally, the statistical approach of the study sought to examine functioning in relation to cognition rather than in addition to it provides a useful perspective in disentangling the two. While it is desirable to develop predictive models in a participant-by-participant fashion, there are challenges to doing this, which includes needing to develop it in a training sample and test it in a separate one. The strength of this these present data is that an association has been shown between functioning and conversion independent of cognition and this may be the basis of developing separate predictive models in the future. Weaknesses included potential selection biases since the sample included typically highly educated volunteers who were mostly female. Additionally, sex differences in functioning as well as relative sensitivity and specificity of the FAQ in determining conversion was not investigated but we identify them as potential topics for future research. As our population ages, it will become important to understand both cognitive and functional transitions because of the potential for delaying the development of pathological states such as AD but also for identifying candidates for disease modifying therapies or identifying and developing effective compensatory measures and employing assistive technologies.

Acknowledgments

The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIAfunded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30

AG008051 (PI Steven Ferris, PhD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG016570 (PI Marie-Francoise Chesselet, MD, PhD), P50 AG005131 (PI Douglas Galasko, MD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P50 AG005136 (PI Thomas Montine, MD, PhD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), and P50 AG047270 (PI Stephen Strittmatter, MD, PhD).”

References

Abikoff H, et al. Logical memory subtest of the wechsler memory scale: age and education norms and alternate-form reliability of two scoring systems. Journal of Clinical and Experimental Neuropsychology. 1987; 9:435–448. [PubMed: 3597734]

Albert MS, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2011; 7:270–279.

Alzheimer's A. 2014 Alzheimer's disease facts and figures. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2014; 10:e47–e92.

Artero S, et al. Risk profiles for mild cognitive impairment and progression to dementia are gender specific. Journal of Neurology, Neurosurgery, and Psychiatry. 2008; 79:979–984.

Bangen KJ, et al. Complex activities of daily living vary by mild cognitive impairment subtype. Journal of the International Neuropsychological Society: JINS. 2010; 16:630–639. [PubMed: 20374675]

Barberger-Gateau P, Dartigues JF, Letenneur L. Four instrumental activities of daily living score as a predictor of one-year incident dementia. Age and Ageing. 1993; 22:457–463. [PubMed: 8310892]

Beekly DL, et al. The national Alzheimer's coordinating center (NACC) database: an Alzheimer disease database. Alzheimer Disease and Associated Disorders. 2004; 18:270–277. [PubMed: 15592144]

Beekly DL, et al. The national Alzheimer's coordinating center (NACC) database: the uniform data set. Alzheimer Disease and Associated Disorders. 2007; 21:249–258. [PubMed: 17804958]

Bookheimer SY, et al. Patterns of brain activation in people at risk for Alzheimer's disease. The New England Journal of Medicine. 2000; 343:450–456. [PubMed: 10944562]

Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiology of Aging. 1995; 16:271–278. discussion 278–284. [PubMed: 7566337]

Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. International Psychogeriatrics/IPA. 2004; 16:129–140.

Burton CL, Strauss E, Hultsch DF, Hunter MA. Cognitive functioning and everyday problem solving in older adults. The Clinical Neuropsychologist. 2006; 20:432–452. [PubMed: 16895857]

Caselli RJ, et al. The neuropsychology of normal aging and preclinical Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2014; 10:84–92.

Chaytor N, Schmitter-Edgecombe M. The ecological validity of neuropsychological tests: a review of the literature on everyday cognitive skills. Neuropsychology Review. 2003; 13:181–197. [PubMed: 15000225]

DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. The Lancet Neurology. 2003; 2:15–21. [PubMed: 12849297]

Delis DC, Kramer JH, Kaplan E, Holdnack J. Reliability and validity of the delis-kaplan executive function system: an update. Journal of the International Neuropsychological Society. 2004; 10:301–303. [PubMed: 15012851]

Di Carlo A, et al. CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. Neurology. 2007; 68:1909–1916. [PubMed: 17536047]

Duda B, Puente AN, Miller LS. Cognitive reserve moderates relation between global cognition and functional status in older adults. Journal of Clinical and Experimental Neuropsychology. 2014; 36:368–378. [PubMed: 24611794]

Farias ST, Harrell E, Neumann C, Houtz A. The relationship between neuropsychological performance and daily functioning in individuals with Alzheimer's disease: ecological validity of neuropsychological tests. Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists. 2003; 18:655–672. [PubMed: 14591439]

Farias ST, Mungas D, Reed BR, Harvey D, Cahn-Weiner D, Decarli C. MCI is associated with deficits in everyday functioning. Alzheimer Disease and Associated Disorders. 2006; 20:217–223. [PubMed: 17132965]

Fischer P, et al. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. Neurology. 2007; 68:288–291. [PubMed: 17242334]

Folstein MF, Folstein SE, McHugh PR. “Mini-mental state.” A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975; 12:189–198. [PubMed: 1202204]

Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. Clinics in Geriatric Medicine. 2013; 29:737–752. [PubMed: 24094294]

Homack S, Lee D, Riccio CA. Test review: Delis-Kaplan executive function system. Journal of Clinical and Experimental Neuropsychology. 2005; 27:599–609. [PubMed: 16019636]

Hughes TF, Chang CC, Bilt JV, Snitz BE, Ganguli M. Mild cognitive deficits and everyday functioning among older adults in the community: the monongahela-youghiogheny healthy aging team study. The American Journal of Geriatric Psychiatry. 2012; 20:836–844. [PubMed: 22337146]

Jefferson AL, et al. Characterization of activities of daily living in individuals with mild cognitive impairment. The American Journal of Geriatric Psychiatry. 2008; 16:375–383. [PubMed: 18332397]

Jensen AR, Figueroa RA. Forward and backward digit span interaction with race and IQ: predictions from Jensen's theory. Journal of Educational Psychology. 1975; 67:882–893. [PubMed: 1194502]

Kaplan, E., Goodglass, H., Weintraub, S. The Boston Naming Test. Philadelphia, PA: Lea & Febiger; 1983.

Kawas CH, et al. Visual memory predicts Alzheimer's disease more than a decade before diagnosis. Neurology. 2003; 60:1089–1093. [PubMed: 12682311]

Kryscio RJ, Schmitt FA, Salazar JC, Mendiondo MS, Markesbery WR. Risk factors for transitions from normal to mild cognitive impairment and dementia. Neurology. 2006; 66:828–832. [PubMed: 16567698]

LaBarge E, Edwards D, Knesevich JW. Performance of normal elderly on the Boston naming test. Brain and Language. 1986; 27:380–384. [PubMed: 3955345]

Lezak, MD. Verbal functions and language skills. In: Lezak, MD., editor. Neuropsychological Assessment. Oxford: Oxford University Press; 2004c. p. 647-693.

Marchesi VT. Alzheimer's disease 2012: the great amyloid gamble. The American Journal of Pathology. 2012; 180:1762–1767. [PubMed: 22472273]

Mariani E, et al. Influence of comorbidity and cognitive status on instrumental activities of daily living in amnestic mild cognitive impairment: results from the ReGAl project. International Journal of Geriatric Psychiatry. 2008; 23:523–530. [PubMed: 18058828]

Marshall GA, et al. For The Alzheimer's Disease Neuroimaging, I. Everyday cognition scale items that best discriminate between and predict progression from clinically normal to mild cognitive impairment. Current Alzheimer Research. 2014; 11:853–861. [PubMed: 25274110]

Marson DC, et al. Assessing financial capacity in patients with Alzheimer disease: a conceptual model and prototype instrument. Archives of Neurology. 2000; 57:877–884. [PubMed: 10867786]

Marson DC, et al. Clinical interview assessment of financial capacity in older adults with mild cognitive impairment and Alzheimer's disease. Journal of the American Geriatrics Society. 2009; 57:806–814. [PubMed: 19453308]

McKhann GM. Changing concepts of Alzheimer disease. JAMA. 2011; 305:2458–2459. [PubMed: 21673298]

Monsell SE, et al. Neuropsychological changes in asymptomatic persons with Alzheimer disease neuropathology. Neurology. 2014; 83:434–440. [PubMed: 24951474]

Morris, JC., editor. National Alzheimer's Coordinating Center: NACC Uniform Data Set (UDS) Coding Guidebook for Initial Visit Packet. Washington University: ADC Clinical Task Force; 2008.

Morris JC, et al. The uniform data set (UDS): clinical and cognitive variables and descriptive data from Alzheimer disease centers. Alzheimer Disease and Associated Disorders. 2006; 20:210–216. [PubMed: 17132964]

Nowrangi MA, Rao V, Lyketsos CG. Epidemiology, assessment, and treatment of dementia. The Psychiatric Clinics of North America. 2011; 34:275–294. vii. [PubMed: 21536159]

Okonkwo OC, et al. Cognitive models of medical decision-making capacity in patients with mild cognitive impairment. Journal of the International Neuropsychological Society. 2008; 14:297–308. [PubMed: 18282327]

Oulhaj A, Wilcock GK, Smith AD, de Jager CA. Predicting the time of conversion to MCI in the elderly: role of verbal expression and learning. Neurology. 2009; 73:1436–1442. [PubMed: 19794124]

Panza F, et al. Current epidemiology of mild cognitive impairment and other predementia syndromes. The American Journal of Geriatric Psychiatry. 2005; 13:633–644. [PubMed: 16085779]

Pereira FS, et al. Profiles of functional deficits in mild cognitive impairment and dementia: benefits from objective measurement. Journal of the International Neuropsychological Society. 2010; 16:297–305. [PubMed: 20175938]

Peres K, Chrysostome V, Fabrigoule C, Orgogozo JM, Dartigues JF, Barberger-Gateau P. Restriction in complex activities of daily living in MCI: impact on outcome. Neurology. 2006; 67:461–466. [PubMed: 16894108]

Perneczky R, et al. Complex activities of daily living in mild cognitive impairment: conceptual and diagnostic issues. Age and Ageing. 2006; 35:240–245. [PubMed: 16513677]

Petersen RC, et al. Current concepts in mild cognitive impairment. Archives of Neurology. 2001; 58:1985–1992. [PubMed: 11735772]

Petersen RC, et al. Mild cognitive impairment: ten years later. Archives of Neurology. 2009; 66:1447–1455. [PubMed: 20008648]

Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. Journal of Gerontology. 1982; 37:323–329. [PubMed: 7069156]

Pinto C, Subramanyam AA. Mild cognitive impairment: the dilemma. Indian Journal of Psychiatry. 2009; 51(Suppl. 1):S44–S51. [PubMed: 21416016]

Reinvang I, Grambaite R, Espeseth T. Executive dysfunction in MCI: subtype or early symptom. International Journal of Alzheimer's Disease. 2012; 2012:936272.

Reitan RM. The relation of the trail making test to organic brain damage. Journal of Consulting Psychology. 1955; 19:393–394. [PubMed: 13263471]

Reppermund S, et al. The relationship of neuropsychological function to instrumental activities of daily living in mild cognitive impairment. International Journal of Geriatric Psychiatry. 2011; 26:843–852. [PubMed: 20845500]

Reppermund S, et al. Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney memory and ageing study. Psychological Medicine. 2013; 43:2437–2445. [PubMed: 23308393]

Royall DR, Lauterbach EC, Kaufer D, Malloy P, Coburn KL, Black KJ. The cognitive correlates of functional status: a review from the committee on research of the American neuropsychiatric association. Journal of Neuropsychiatry Clinical Neurosciences. 2007; 19:249–265. [PubMed: 17827410]

Royall DR, Palmer R, Chiodo LK, Polk MJ. Normal rates of cognitive change in successful aging: the freedom house study. Journal of the International Neuropsychological Society. 2005; 11:899–909. [PubMed: 16519269]

Royall DR, et al. Executive control function: a review of its promise and challenges for clinical research. A report from the committee on research of the American neuropsychiatric association. Journal of Neuropsychiatry Clinical Neurosciences. 2002; 14:377–405. [PubMed: 12426407]

Salthouse CD, Reynolds F, Tam JM, Josephson L, Mahmood U. When does age-related cognitive decline begin? Neurobiology of Aging. 2010; 30:507–514.

Satterthwaite FE. An approximate distribution of estimates of variance components. Biometrics. 1946; 2:110–114. [PubMed: 20287815]

Shankle WR, et al. Relating memory to functional performance in normal aging to dementia using hierarchical Bayesian cognitive processing models. Alzheimer Disease and Associated Disorders. 2013; 27:16–22. [PubMed: 22407225]

Sperling RA, et al. Amyloid deposition detected with florbetapir F 18 ((18)F-AV-45) is related to lower episodic memory performance in clinically normal older individuals. Neurobiology of Aging. 2013; 34:822–831. [PubMed: 22878163]

Stoeckel LE, et al. MRI volume of the medial frontal cortex predicts financial capacity in patients with mild Alzheimer's disease. Brain Imaging and Behavior. 2013; 7:282–292. [PubMed: 23504597]

Tabert MH, et al. Functional deficits in patients with mild cognitive impairment: prediction of AD. Neurology. 2002; 58:758–764. [PubMed: 11889240]

Tuokko H, Morris C, Ebert P. Mild cognitive impairment and everyday functioning in older adults. Neurocase. 2005; 11:40–47. [PubMed: 15804923]

Vallotti B, et al. Determinants of functional status in Alzheimer's disease and vascular dementia. Archives of Gerontology and Geriatrics supplement. 2001; 7:419–428. [PubMed: 11431094]

Visser PJ, Kester A, Jolles J, Verhey F. Ten-year risk of dementia in subjects with mild cognitive impairment. Neurology. 2006; 67:1201–1207. [PubMed: 17030753]

Wadley VG, et al. Changes in everyday function in individuals with psychometrically defined mild cognitive impairment in the advanced cognitive training for independent and vital elderly study. Journal of the American Geriatrics Society. 2007; 55:1192–1198. [PubMed: 17661957]

Wechsler, D. The Measurement of Adult Intelligence. Baltimore, MD: Williams & Witkins; 1939.

Weintraub S, et al. The Alzheimer's disease centers' uniform data set (UDS): the neuropsychologic test battery. Alzheimer Disease and Associated Disorders. 2009; 23:91–101. [PubMed: 19474567]

Yesavage JA. Geriatric depression scale. Psychopharmacology Bulletin. 1988; 24:709–711. [PubMed: 3249773]

Table 1
Mean participant characteristics at baseline (SD)

		non-converters (*N* = 6,297)	converters (*N* = 1,328)	*p* value
Age (SD)		70.53 (9.91)	76.85 (8.75)	$p < 0.001$
Female		4,257 (67.6%)	810 (61.0%)	$p < 0.001$
Years of education (SD)		15.77 (2.90)	15.18 (3.17)	$p < 0.001$
Level of Independence *	1	6,188 (98.3%)	1,261 (95.0%)	$p < 0.001$
	2	90 (1.4%)	47 (3.5%)	
	3	19 (0.3%)	17 (1.3%)	
	4	0 (0.0%)	3 (0.2%)	
Type of residence				$p < 0.001$
Single family residence		5,694 (90.7%)	1,116 (84.2%)	
Retirement community		436 (6.9%)	169 (12.7%)	
ALF/boarding home/adult family home		17 (0.3%)	10 (0.8%)	
SNF/NH		1 (<1%)	0 (0.0%)	
Other		133 (2.1%)	31 (2.3%)	
MMSE		29.01 (1.32)	28.48 (1.63)	$p < 0.001$
Logical memory		13.81 (3.79)	11.02 (4.01)	$p < 0.001$
Boston naming		27.32 (3.09)	25.91 (3.94)	$p < 0.001$
Category fluency (animals)		20.68 (5.65)	17.86 (5.18)	$p < 0.001$
Category fluency (vegetables)		15.15 (4.26)	12.76 (4.03)	$p < 0.001$
Trails B–A		52.96 (39.71)	74.76 (51.86)	$p < 0.001$
Digit span forward		8.66 (2.03)	8.28 (2.06)	$p < 0.001$
Digit span backward		6.94 (2.25)	6.37 (2.10)	$p < 0.001$
WAIS		48.87 (12.33)	40.92 (11.56)	$p < 0.001$
FAQ total (0–30)		1.92 (6.11)	3.15 (6.74)	$p < 0.001$

* Level of Independence: 1: able to live independently; 2: requires some assistance with complex activities; 3: requires some assistance with basic activities; 4: completely dependent.

Table 2
Cox proportional hazard models for conversion to MCI or dementia

		hazard ratio (SE) *p*		
		model 1[†]	**model 2**[‡]	**model 3**[§]
Age		1.06 (0.003) < 0.01	1.05 (0.003) < 0.01	1.04 (0.003) < 0.01
Male		1.29 (0.07) < 0.01	1.17 (0.07) 0.004	1.01 (0.07) 0.92
Education		0.96 (0.01) < 0.01	1.02 (0.01) 0.107	1.03 (0.01) < 0.01
Level of independence	2	2.13 (0.32) < 0.01	1.83 (0.28) < 0.01	1.62 (0.25) < 0.002
	3	1.89 (0.48) 0.01	2.07 (0.53) < 0.01	1.78 (0.46) 0.02
	4	2.10 (1.25) 0.21	2.40 (1.43) 0.14	1.65 (0.99) 0.40
FAQ total		1.02 (0.003) < 0.01	1.01 (0.003) < 0.01	1.01 (0.004) 0.01
GDS		1.11 (0.003) < 0.01	1.10 (0.004) < 0.01	1.10 (0.13) < 0.01
MMSE			0.94 (0.02) 0.001	0.97 (0.02) 0.17
Logical memory			0.93 (0.01) < 0.01	0.94 (0.01) < 0.01
Boston			0.97 (0.01) < 0.01	1.09 (0.01) 0.44
Category fluency (animals)				0.98 (0.01) 0.01
Category fluency (vegetables)				0.95 (0.01) < 0.01
Trails B–A				1.00 (0.001) 0.115
Digit span forward				1.02 (0.02) 0.286
Digit span backward				0.99 (0.02) 0.709
WAIS				0.98 (0.003) < 0.01

[†]Model 1: adjusted for baseline age, sex, years of education, and total FAQ.

[‡]Model 2: model 1 + MMSE, logical memory, Boston naming.

[§]Model 3: model 1 + model 2 + TMT B–A, animal and vegetable category fluencies, and digit span forward and backward.

Table 3

Cox proportional hazard models for conversion to MCI or dementia using FAQ components

	hazard ratio (SE) *p*		
	model 1[**]	**model 2**[††]	**model 3**[‡‡]
FAQ total			
Bills	0.993 (0.020) 0.75	0.987 (0.019) 0.54	0.973 (0.020) 0.18
Shopping	0.974 (0.034) 0.46	0.970 (0.034) 0.40	0.961 (0.034) 0.26
Taxes	1.05 (0.016) < 0.01	1.04 (0.016) 0.019	1.042 (0.016) 0.006
Games	1.02 (0.014) 0.14	1.016 (0.015) 0.26	1.008 (0.014) 0.58
Stove	0.972 (0.044) 0.53	0.959 (0.042) 0.35	0.972 (0.042) 0.51
Meal prep	1.01 (0.015) 0.97	1.00 (0.015) 0.817	0.991 (0.016) 0.57
Events	0.991 (0.056) 0.88	0.982 (0.055) 0.75	1.001 (0.056) 0.978
Pay attention	0.860 (0.072) 0.07	0.906 (0.071) 0.21	0.944 (0.071) 0.443
Remember dates	1.178 (0.040) < 0.01	1.183 (0.040) <0.01	1.176 (0.040) <0.01
Travel	1.125 (0.038) 0.001	1.121 (0.038) 0.001	1.093 (0.037) 0.008

[**] Model 1: adjusted for baseline age, sex, years of education, and total FAQ.

[††] Model 2: model 1 + MMSE, logical memory, Boston naming.

[‡‡] Model 3: model 1 + model 2 + TMT B–A, animal and vegetable category fluencies, and digit span forward and backward.