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Impact of functional deficits in instrumental activities of daily living in mild cognitive impairment: a clinical algorithm to predict progression to dementia

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Abstract

Background—The utility of functional deficits in patients with mild cognitive impairment is not established.

Method—In 3,886 individuals with mild cognitive impairment evaluated and followed at 34 National Alzheimer's Coordinating Center sites, informant-reported Pfeffer Functional Activities Questionnaire (FAQ) items associated with progression to dementia were derived in a training set ($n=1943$) and tested in the validation set ($n=1943$).

Results—In the training set, the optimal combination comprised six FAQ items (FAQ6): difficulties with finances (2 items), remembering events/appointments, playing games of skill, current events, and travel. In the validation set, hazard ratio for dementia increased from 2.00 for one FAQ6 deficit to 5.56 for six FAQ6 deficits. In patients 50–67 years old with high Mini Mental State Exam (MMSE) scores, dementia risk rose from 12.06% for no FAQ6 deficits to 56.75% for six functional deficits. Likelihood of progression to dementia reached 80–89% in older age groups with low MMSE and severe FAQ6 deficits.

Conclusion—Specific functional deficits increased dementia risk and, with age and global cognition, constituted a validated clinical algorithm to estimate dementia risk. Clinicians can use this clinically important algorithm to personalize decision-making about further investigation and identify high-risk patients for early treatment or inclusion in clinical trials.

Keywords

Function; mild cognitive impairment; algorithm; dementia

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Disclosure of Financial Conflicts of Interest

Dr. D.P. Devanand has received consulting fees from AbbVie, Lundbeck, Astellas and Intracellular Therapeutics. Drs. Brown and Liu report no conflicts of interest.

Author Contributions

Dr. Devanand conceptualized the study, Drs. Liu and Brown conducted the analyses, Dr. Devanand drafted the paper and all authors edited the paper and approved the final version for submission.

Dr. D.P. Devanand had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Introduction

Memory deficits with or without deficits in other cognitive domains occur in mild cognitive impairment (MCI), a high-risk group for Alzheimer's disease (AD), which is the most common type of dementia.¹ In MCI, the original diagnostic criterion of no functional deficits has evolved into the recognition that deficits can occur in complex instrumental, social and cognitive activities of daily living.^{1, 2} The informant's, but not the patient's, report of functional deficits is associated with an increased risk of progressing from MCI to a clinical diagnosis of AD.³⁻⁵

Few algorithms have been developed to predict the progression from MCI to clinical dementia or AD, and most have examined neuropsychological tests and neurobiological biomarkers that are not routinely or easily assessed in general medical practice.⁵⁻⁷ Even though functional decline is a required criterion for the diagnosis of dementia, it has rarely been included in prediction algorithms for the progression to dementia or AD.^{5, 6} Further, although functional deficits observed by family members and other informants are often prominent in the clinical presentation, clinicians typically do not systematically assess functional deficits. Brief cognitive screening techniques have been studied, but when used alone have not shown strong predictive accuracy for the progression from MCI to AD.⁸

Identifying the specific types of functional deficits associated with the progression from MCI to dementia can improve early diagnosis and can be valuable in determining the need for further diagnostic investigation, initiating early treatment, and planning for the patient's future. In data obtained from the National Alzheimer's Coordinating Center (NACC) multicenter project, we identified the specific informant-reported functional deficits in a sample of patients with MCI (training set) that optimally predicted the progression to dementia, and AD, and validated the findings in an independent sample of patients with MCI (validation set). This subset of functional deficits was then examined with age and Mini Mental State Exam (MMSE)⁹, which assesses global cognition, to develop a simple clinical algorithm to predict the progression from MCI to dementia, and AD, by 3-year follow-up because most transitions from the clinical presentation of MCI to the clinical diagnosis of dementia or AD are known to occur within 3 years.^{1, 5}

Methods

Participants

The National Alzheimer's Coordinating Center (NACC) compiles data from a consortium of 34 past and present Alzheimer's Disease Centers in the U.S. Study participants with MCI, mild AD, and cognitively normal controls are followed annually using standardized methods.¹⁰ For this study, the data from the Uniform Data Set (UDS) comprised participants 50 years and older who were diagnosed with MCI (amnesic and non-amnesic) at initial evaluation from 2005 to 2009 and had the Pfeffer Functional Activities Questionnaire (FAQ) completed by an informant.^{11, 12} Systematic annual follow-up with diagnostic assessment was conducted, and UDS visits through August 2013 were included in the analyses.

Functional Assessment

The FAQ comprises 10 items, each of which is scored 0 (no difficulty or independent) to 3 (dependent) with another choice of “not applicable” for the patient. FAQ item scores were trichotomized (presence/absence/not applicable) for descriptive analyses (Tables 1, 2); the total number of deficits was used in the analyses of prediction of outcome. Patients with 5 or more items rated as “not applicable” were excluded.

Other Assessments

Deficits in measures of global cognition, episodic verbal memory, and executive function are associated with the progression from MCI to AD.^{13, 14} Therefore, we chose the following cognitive measures from the NACC-Uniform Data Set (UDS) test battery: 30-item Folstein Mini Mental State Exam (MMSE) for global cognition, WMS-R Logical Memory delayed recall for episodic verbal memory, and Trailmaking Tests A and B for attention/processing speed and task switching/executive function, respectively. The Clinical Dementia Rating (CDR) Scale Sum of Boxes was rated by interview and encompassed six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.¹⁵ The Geriatric Depression Scale was used to assess depression.

Outcomes: diagnosis

The diagnosis of dementia at the last available time-point was the primary outcome. For participants whose diagnosis fluctuated from MCI to dementia to MCI, the diagnosis of dementia needed to be made at two of three consecutive time-points. The diagnosis of AD (possible or probable) was a secondary outcome.

Standard Protocol Approvals, Registrations, and Patient Consents

The NACC protocol and consent forms were approved by the Institutional Review Board at each site.

Statistical Analyses

Descriptive statistics were calculated for baseline demographic and clinical variables. Age and sex-stratified randomization was used to divide the study sample into a training set and validation set with equal number of participants (Table 1). Group differences between the two datasets were examined by χ^2 test for categorical variables and Wilcoxon rank sum test for quantitative variables. Spearman correlation coefficient was used to examine the bivariate associations between quantitative variables and Kruskal-Wallis test to examine the differences between quantitative and categorical variables.

In survival analysis, to calculate the time variable we utilized the first time-point at which dementia was diagnosed. Since both functional impairment and the likelihood of dementia or AD increased with age, we used age-stratified Cox regression models with four baseline age quartile groups: 50–67 ($n=895$), 68–74 ($n=1051$), 75–80 ($n=1032$), and 81 years and older ($n=908$). Each FAQ item had three categories (absence, presence of deficit, not applicable). Hazard ratios used the category of absence of deficit as reference.

In the training set, the C-index for discrimination accuracy was defined as the concordance probability that a subject with shorter time to dementia had more baseline FAQ deficits. The value 0.5 indicates chance probability and the value 1 indicates perfect concordance. Using the procedure that takes into account random censoring,¹⁶ we calculated the C-index (averaged over age strata) for the FAQ 10-item full scale (FAQ10). The bootstrap method was used to estimate standard error (SE) of the C-index and to construct the 95% confidence interval (CI). We then deleted one item at a time to derive a reduced scale comprising the smallest number of items that accounted for a minimum of 95% of the discriminative ability of the FAQ10 and fell within the 95% confidence interval of the FAQ10. The C-index for the FAQ10 and the FAQ reduced scale was recalculated with the validation set. Subsequent analyses were conducted in the validation set.

In the Cox regression analyses, only those baseline variables that showed associations with both baseline FAQ score and time to dementia in the age-stratified models in the training set were used as covariates in similar models in the validation set that included the main predictor of FAQ10 or FAQ reduced scale. ROC analysis was used to examine the classification accuracy of age, MMSE and FAQ (full and reduced scale) in predicting progression to clinical dementia by 3 years because most progressions from MCI to AD occur within 3 years.^{1, 5, 11} Based on logistic regression models with these three baseline predictor variables, we calculated the ROC curve and area under the curve (AUC), and then developed a clinically applicable algorithm to predict progression to dementia. Analyses were conducted in SAS 9.4 and R (v.3.13) package.

Results

Demographic and Clinical Measures

In the sample of 3886 patients with MCI, average follow-up duration was 2.60 (*SD* 1.67) years and 1455 participants (37.4%) were diagnosed with dementia at the final available time-point. The proportion of patients with MCI progressing to dementia increased by age quartile: 50–67 (244/895 = 27.26%), 68–74 (366/1051 = 34.82%), 75–80 (421/1032 = 40.79%), and 81 years (424/908 = 46.70%). Compared to patients who did not progress to dementia, at baseline patients with a final diagnosis of dementia were more likely to be white ($p < 0.0001$), older ($p < 0.0001$), and depressed ($p = 0.0084$), performed worse on all the cognitive measures examined and had more FAQ deficits (p 's < 0.0001). The training ($n=1943$) and validation ($n=1943$) sets did not differ significantly on any baseline demographic or clinical measure (Table 1).

FAQ items

In the training set, each FAQ item significantly predicted the progression from MCI to dementia (Table 2). The hazard for dementia comparing presence to absence of FAQ item deficit was highest for the two financial items (assembling tax records/business affairs/other papers, writing checks/paying bills/balancing check book) and for remembering appointments/family occasions/holidays/medications, and lowest for the item for heating water/making a cup of coffee/turning off stove. In the training set, for FAQ10 the C-index was 0.609 ($SE = 0.012$; 95% $CI = 0.586–0.631$). Six items (FAQ6, C-index 0.591) accounted

for 97.11% of the discriminative ability of the full scale and was within the 95% *CI* of the C-index for FAQ10: writing checks/paying bills, assembling taxes/financial records, playing games of skill, keeping track of current events, remembering appointments/family occasions/holidays/medications, and traveling difficulties. In the validation set, the C-index was 0.574 (*SE* = 0.012) for FAQ6 with the selected items, accounting for 95.83% of the C-index value for FAQ10 (*C* = 0.599, *SE* = 0.013).

Based on the pattern in the hazard ratios, FAQ deficits were classified as none, one, mild, moderate or severe. For FAQ6, mild = score of 2 or 3, moderate = 4 or 5, and severe = 6. For FAQ10, mild = 2 or 3, moderate = 4–6, and severe = 7–10.

In the validation set, in age-stratified Cox regression models the hazard ratio increased progressively with greater number of FAQ deficits for both FAQ10 and FAQ6, which were each significantly related to time to dementia with and without inclusion of the covariates of episodic verbal memory, attention, executive function test scores, and depression severity (Table 3; similar to the training set results displayed in Supplement Etable1). In the model without covariates, compared to patients with no FAQ deficits, for FAQ6 the hazard ratio for dementia increased incrementally with the number of deficits from 2.00 (95% *CI* = 1.52–2.62) for one deficit to 5.56 (95% *CI* = 4.10–7.54) for six deficits (severe deficits, Table 3).

In the total sample of 3886 patients, 1216 of 1455 patients (83.6%) who progressed to dementia were diagnosed with AD. In the validation set of 1943 patients, 593 of 710 patients (83.5%) who progressed to dementia were diagnosed with AD. The pattern for the number of FAQ6 deficits predicting progression to AD (Supplement Etable2 and Etable 3) was similar to the pattern for these deficits predicting progression to dementia.

FAQ with age and MMSE

In ROC analyses to examine classification accuracy for progression to dementia within three years, in the validation set (539 of 1174 patients or 45.91% progressed to dementia by 3-year follow-up) the area under the curve (AUC) for age alone was 0.553. The AUC for the combination of age and MMSE (0.705) increased to 0.761 with the addition of FAQ6 ($p < .001$). These results were similar to those obtained initially in the training set ($AUC_{age,MMSE} = 0.701$; $AUC_{age,MMSE,FAQ6} = 0.767$). The FAQ6 and FAQ10 showed similar results when combined with age and MMSE (Figure 1).

In the validation set, in the clinical algorithm increasing number of functional deficits was associated with a greater likelihood of dementia across age groups and in patients with both low (26 out of 30) and high (27–30) MMSE scores (Table 4). For example, in patients 50–67 years old with high MMSE scores, dementia risk was low (12.06%) for no FAQ6 deficits and increased progressively with number of functional deficits from 20.24% for one functional deficit to 56.75% for six functional deficits. The likelihood of progression to dementia reached 80–89% for patients in the older age groups with low MMSE and severe functional deficits (Table 4).

Discussion

Each item in the 10-item FAQ, and the total scale score, significantly predicted the progression from MCI to AD.^{4, 5, 17} The 6-item subset was similar to the full 10-item scale in predicting progression to clinical dementia in patients with MCI, and ROC analyses indicated that FAQ deficits added materially to the prediction obtained by age and MMSE. The clinical algorithm was highly informative, including in the younger age group (50–67) with high MMSE scores, where concern about cognitive and functional decline is high and the impact on the patient, family and society can be large. In a patient who is 50–67 years old with MMSE 27–30 and without deficits on FAQ6, the risk of progression to dementia over 3 years is low (12%). Therefore, the clinical decision may be to wait and reassess the patient a year later. In this group, as in the older age groups, the proportion that progressed to dementia increased moderately with one FAQ deficit and markedly with increasing number of functional deficits. Therefore, in patients with one FAQ deficit, further investigation with neuropsychological testing and possible evaluation of biomarkers is advisable, and in patients with multiple FAQ deficits such a workup is clearly indicated. The clinically applicable algorithm clearly demonstrates that information about global cognition or function alone is insufficient for accurate prediction of dementia, but evaluating age together with a global cognitive test like the MMSE and six items of complex instrumental, social and cognitive functions with the FAQ6 (12–15 minutes in total for assessment of MMSE and FAQ6) and then utilizing this algorithm can improve personalized medical decision-making to decide about the need for further investigation and to improve early diagnosis in clinical practice.

Neuropsychological test performance is associated strongly with the progression from MCI to dementia and AD.^{13, 14} In this study, after adjusting for standard tests of episodic verbal memory, attention/processing speed and task switching/executive test performance, informant-reported functional deficits still strongly predicted the progression to dementia. Biomarkers such as olfactory identification deficits,⁵ MRI medial temporal and posterior cortical atrophy,¹⁸ PET indices of metabolism and amyloid load,¹⁹ and cerebrospinal fluid Abeta, tau and phospho tau²⁰ levels show predictive utility for the progression from MCI to AD,²¹ but their added predictive value over and above clinical, functional and cognitive assessment is not fully established. Assessment of neuroimaging and cerebrospinal fluid biomarkers can be expensive and time-consuming. One theoretical model postulates that specific biomarkers become abnormal initially with subsequent decline in cognition followed by functional decline when clinical AD is diagnosed,²¹ but the findings in this study and earlier studies^{4, 22, 23} suggest that functional decline often occurs earlier, commonly at the stage of MCI before AD is diagnosed clinically. The National Institute of Aging diagnostic criteria for MCI support this view, and include the statement that these patients “commonly have mild problems performing complex functional tasks”.²

The mechanisms by which regional brain pathology leads to specific functional deficits are not clear. When difficulties with financial tasks develop, they may be related to impaired memory, abstract reasoning, slow processing speed, and executive abilities as a consequence of damage to the hippocampus and dorsolateral frontal cortex.^{22, 24, 25} The added value of the informant’s report of functional abilities to cognitive assessment may be explained partly

by the fact that compared to cognitive measures the ability to perform instrumental and social/cognitive daily tasks may be influenced less by education and ethnicity.

There were several strengths to this study. The sample was large enough to validate the findings that were very similar in the training and validation datasets. Further, the two items for difficulty with finances and the item for remembering appointments/family occasions/medications that showed the strongest associations with progression to dementia were identical to the items that best differentiated a combined sample of patients with MCI and AD from cognitively intact control participants in our earlier cross-sectional report from another study, the Alzheimer's Disease Neuroimaging Initiative.²³ Also, five of the six FAQ6 items from the current study were present in the optimal combination of 6 items that best separated MCI and AD from controls in that report.²³ Clinicians can easily complete the brief assessment needed to apply the algorithm, in contrast to more in-depth models that require extensive clinical evaluation and which have not yet been validated, including a model that examined future cognitive decline in cognitively intact community-dwelling individuals.²⁶

There were some limitations to this study. The FAQ items cover common complex functional deficits that can occur in MCI and mild AD but some deficits are not assessed, e.g., trouble understanding visual images and spatial relationships, and new problems with words in speaking or writing. The Alzheimer's Association has identified these and other deficits as early indicators of AD (http://www.alz.org/alzheimers_disease_know_the_10_signs.asp), but they have not been tested in large samples for predictive accuracy.²⁷ The quality of informant reports of functional impairment can vary and the FAQ lacks the objectivity of a performance-based functional assessment,²⁸ but the latter is difficult to implement in busy clinical practices. The NACC-UDS includes data from participants who presented for evaluation mainly at academic medical centers with memory disorders programs, and is not representative of the broader general population. The diagnosis of MCI was reached at each site by consensus in approximately 85% of patients and by a single clinician in approximately 15% of patients, but both approaches followed explicit NACC diagnostic guidelines.

Published algorithms that have examined prediction of progression from MCI to dementia have used several variables,^{5, 6} often requiring extensive interviewing or testing that is not typically done in clinical practice. Further, in most studies that derived an algorithm, cross-validation has either been limited⁶ or not been done systematically.^{7, 26} Our simple, well-validated algorithm is a clinically important strategy for physicians to use in their regular practice. The algorithm helps to estimate the likely risk of dementia and AD based on age, MMSE and FAQ6, and this risk can be discussed with the patient, family and significant others. It will be cost-effective in informing the decision about the need for further diagnostic evaluation with expensive procedures that may range from detailed neuropsychological testing to structural and/or functional brain imaging to evaluation of spinal fluid for A Beta and tau/phospho tau levels, each of which may improve accuracy in predicting diagnostic outcome and potentially identifying appropriate patients for clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. ROC curves for age, MMSE, and FAQ measures for progression to dementia (validation set, $n=1174$).

Table 1

Demographics and clinical characteristics of patients with mild cognitive impairment (MCI) at initial evaluation.

Variable	Training set N = 1943	Validation set N = 1943	p-value
	%	%	
Female	50.33 (978/1943)	50.33 (978/1943)	
Race/ethnicity			
White	76.94 (1495/1943)	76.74 (1491/1943)	0.87
African-American	13.59 (264/1943)	13.18 (256/1943)	
Hispanic	6.48 (126/1943)	6.69 (130/1943)	
Other	2.99 (58/1943)	3.40 (66/1943)	
Progression to dementia	38.34 (745/1943)	36.54 (710/1943)	0.25
	Mean $\pm$ SD (n)	Mean $\pm$ SD (n)	
Follow up time (years)	2.60 $\pm$ 1.67 (1943)	2.61 $\pm$ 1.67 (1943)	0.86
Age (years)	73.96 $\pm$ 8.78 (1943)	73.95 $\pm$ 8.78 (1943)	0.99
Education (years)	15.03 $\pm$ 3.42 (1938)	15.13 $\pm$ 3.35 (1939)	0.38
Hachinski Ischemic Index	0.97 $\pm$ 1.34 (1931)	1.02 $\pm$ 1.40 (1932)	0.30
Geriatric Depression Scale	2.18 $\pm$ 2.14 (1857)	2.13 $\pm$ 2.12 (1853)	0.47
CDR ¹ Sum of Boxes	1.36 $\pm$ 1.15 (1943)	1.31 $\pm$ 1.09 (1943)	0.37
MMSE ²	27.11 $\pm$ 2.45 (1849)	27.17 $\pm$ 2.42 (1859)	0.44
WMS-R ³ Logical Memory immediate recall	9.14 $\pm$ 4.21 (1812)	9.31 $\pm$ 4.28 (1819)	0.20
WMS-R Logical Memory delayed recall	6.84 $\pm$ 4.70 (1815)	7.00 $\pm$ 4.72 (1821)	0.27
Trailmaking A time	45.34 $\pm$ 23.70 (1830)	45.13 $\pm$ 23.04 (1845)	0.82
Trailmaking B time	139.41 $\pm$ 75.24 (1781)	140.65 $\pm$ 77.94 (1782)	0.90
FAQ ⁴ (10-items)	2.98 $\pm$ 2.83 (1943)	2.82 $\pm$ 2.67 (1943)	0.24

P-value for group difference is from Chi-square test for categorical variables and Wilcoxon rank sum test for quantitative variables.

¹CDR: Clinical Dementia Rating (higher score indicates greater evidence of dementia),

²MMSE: Mini Mental State Exam range 0–30 (higher score indicates better cognition),

³WMS-R: Wechsler Memory Scale-Revised (higher score indicates better episodic verbal memory),

⁴FAQ: Functional Activities Questionnaire (range 0–10 based on presence or absence of each item deficit, higher score indicates greater impairment).

Table 2Effect of FAQ items on progression to dementia in the training set ($n = 1943$).

FAQ ^I 10 individual items	Deficit	%	Hazard Ratio (95% CI)
1. Writing checks, paying bills, balancing check book.	No	59.44 (1155/1943)	1
	Yes	30.47 (592/1943)	2.55 (2.19, 2.98)
	N/A	10.09 (196/1943)	1.93 (1.52, 2.44)
2. Assembling tax records, business affairs, or papers.	No	53.89 (1047/1943)	1
	Yes	30.47 (592/1943)	2.77 (2.36, 3.26)
	N/A	15.65 (304/1943)	2.30 (1.88, 2.83)
3. Shopping alone for clothes, household necessities, and groceries.	No	76.79 (1492/1943)	1
	Yes	20.54 (399/1942)	2.07 (1.77, 2.43)
	N/A	2.68 (52/1943)	1.27 (0.84, 1.94)
4. Playing a game of skill, working on a hobby.	No	73.60 (1430/1943)	1
	Yes	16.31 (317/1943)	2.36 (1.99, 2.80)
	N/A	10.09 (196/1943)	1.35 (1.06, 1.20)
5. Heating water, making a cup of coffee, turning off stove.	No	87.96 (1709/1943)	1
	Yes	10.34 (201/1943)	1.66 (1.35, 2.05)
	N/A	1.70 (33/1943)	0.94 (0.53, 1.67)
6. Preparing a balanced meal.	No	70.89 (1377/1943)	1
	Yes	16.16 (314/1943)	2.11 (1.77, 2.51)
	N/A	12.97 (252/1943)	1.42 (1.15, 17.5)
7. Keeping track of current events.	No	74.68 (1451/1943)	1
	Yes	24.60 (478/1943)	2.37 (2.04, 2.76)
	N/A	0.72 (14/1943)	2.97 (1.47, 6.01)
8. Paying attention to, understanding, discussing television program, book, or magazine.	No	78.85 (1532/1943)	1
	Yes	20.84 (405/1943)	2.01 (1.72, 2.36)
	N/A	0.31 (6/1943)	1.18 (0.44, 3.17)
9. Remembering appointments, family occasions, holidays, medications.	No	54.19 (1053/1943)	1
	Yes	45.39 (882/1943)	2.38 (2.06, 2.77)
	N/A	0.41 (8/1943)	1.13 (0.36, 3.51)
10. Travelling outside neighbourhood, driving, arranging to take public transportation.	No	67.06 (1303/1943)	1
	Yes	31.96 (621/1943)	2.31 (1.99, 2.67)
	N/A	0.98 (19/1943)	1.73 (0.85, 3.51)

95% CI = 95% confidence interval;

^IFAQ = Pfeffer Functional Activities Questionnaire. Age-adjusted analyses were based on age stratification by quartiles: 50–67 years ($n=447$), 68–74 years ($n=526$), 75–80 years ($n=516$), and 81 years ($n=454$). N/A: not applicable or never did the task for the item. For each FAQ item, the comparison group was “no deficit” in survival analyses evaluating the time to the event of dementia.

Table 3

Hazard ratios (95% CI) in age-stratified Cox models for time to dementia (Validation set, n=1943).

Models	FAQ10 (Full 10-item FAQ)		FAQ6 (FAQ with 6 items)	
	HR ¹ (95% CI ²)	p-value	HR (95% CI)	p-value
FAQ³ without covariates:				
One vs. no deficit	1.71 (1.26, 2.31)	.0005	2.00 (1.52, 2.62)	<.0001
Mild vs. no deficit	2.36 (1.84, 3.04)	<.0001	2.55 (2.02, 3.21)	<.0001
Moderate vs. no deficit	3.90 (3.06, 4.97)	<.0001	4.33 (3.43, 5.46)	<.0001
Severe vs. no deficit	5.98 (4.60, 7.78)	<.0001	5.56 (4.10, 7.54)	<.0001
BIC	7378.86		7405.47	
FAQ with covariates:				
One vs. no deficit	1.50 (1.11, 2.03)	.0091	1.73 (1.31, 2.27)	<.0001
Mild ⁸ vs. no deficit	2.03 (1.58, 2.62)	<.0001	2.14 (1.69, 2.70)	<.0001
Moderate ⁹ vs. no deficit	3.06 (2.39, 3.91)	<.0001	3.22 (2.53, 4.09)	<.0001
Severe ¹⁰ vs. no deficit	4.02 (3.06, 5.27)	<.0001	3.78 (2.77, 5.16)	<.0001
White vs. non-white	1.97 (1.60, 2.42)	<.0001	2.00 (1.62, 2.46)	<.0001
GDS⁴				
High 5–9 vs. low 0–4	1.04 (0.83, 1.31)	.72	1.06 (0.75, 1.34)	.60
Missing vs. 0–4	1.26 (0.89, 1.78)	.20	1.25 (0.88, 1.78)	.21
Trailmaking A				
>45 vs. 45 seconds	0.96 (0.81, 1.14)	.64	0.98 (0.82, 1.16)	.79
Missing vs. 45	0.62 (0.32, 1.19)	.15	0.64 (0.34, 1.23)	.18
Trailmaking B				
>140 vs. 140 seconds	1.57 (1.31, 1.87)	<.0001	1.56 (1.31, 1.86)	<.0001
Missing vs. 140	1.59 (1.09, 2.32)	.02	1.59 (1.09, 2.32)	.02
MMSE⁵				
<26 vs. 27–30	1.60 (1.36, 1.89)	<.0001	1.61 (1.37, 1.90)	<.0001
Missing vs. 27–30	0.70 (0.38, 1.29)	.25	0.70 (0.38, 1.28)	.25
Logical Memory delayed recall⁶				
<7 vs. 7	2.43 (2.05, 2.88)	<.0001	2.45 (2.07, 2.91)	<.0001
Missing vs. 7	3.83 (2.51, 5.85)	<.0001	3.81 (2.49, 5.85)	<.0001
BIC ⁷	7208.44		7226.46	

Age-stratification was by quartiles: 50–67 years (*n*=448), 68–74 years (*n*=525), 75–80 years (*n*=516), and 81 years (*n*=454).

¹HR = Hazard ratio;

²95% CI = 95% confidence interval;

³FAQ = Pfeffer Functional Activities Questionnaire used as a categorical variable.

⁴GDS = Geriatric Depression Scale.

⁵MMSE Mini Mental State Exam (Folstein, range 0–30).

⁶Logical Memory test was from the Wechsler Memory Scale-Revised.

⁷BIC = Bayesian Information Criterion.

⁸Mild deficit: FAQ6 total score of 2 or 3, FAQ10 total score of 2 or 3;

⁹Moderate deficit: FAQ6 total score of 4 or 5, FAQ10 total score of 4 to 6;

¹⁰Severe deficit: FAQ6 total score of 6, FAQ10 total score of 7 to 10.

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Table 4

Estimated risk of progression to dementia (n=539) by 3 years in the validation set (n=1174).

		FAQ 6 items (FAQ6)			FAQ 10 items (FAQ10)		
		MMSE ²	26	MMSE 27-30	MMSE	26	MMSE 27-30
Age group	FAQ ¹ deficits	%	%	%	%	%	%
50-67	None	32.77		12.06	31.17		11.41
	One deficit	47.43		20.24	44.16		18.35
	Mild ³	65.70		35.01	57.96		28.16
	Moderate ⁴	70.65		40.37	70.79		40.78
	Severe ⁵	82.35		56.75	77.99		50.18
68-74	None	40.37		16.00	38.63		15.18
	One deficit	55.62		26.06	52.36		23.80
	Mild	72.68		42.80	65.71		35.26
	Moderate	76.98		48.46	77.10		48.91
	Severe	86.63		64.57	83.12		58.33
75-80	None	43.60		17.86	42.48		17.35
	One deficit	58.86		28.69	56.33		26.82
	Mild	75.23		46.06	69.22		38.99
	Moderate	79.24		51.77	79.80		52.90
	Severe	88.09		67.54	85.25		62.16
81	None	44.80		18.59	43.63		18.03
	One deficit	60.04		29.70	57.43		27.75
	Mild	76.13		47.28	70.21		40.11
	Moderate	80.03		52.99	80.55		54.06
	Severe	88.60		68.61	85.83		63.25

¹FAQ: Pfeffer Functional Activities Questionnaire.

²MMSE: Folstein Mini Mental Status Exam (range 0-30).

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- ³ Mild deficit: FAQ6 total score of 2 or 3, FAQ10 total score of 2 or 3;
- ⁴ Moderate deficit: FAQ6 total score of 4 or 5, FAQ10 total score of 4 to 6;
- ⁵ Severe deficit: FAQ6 total score of 6, FAQ10 total score of 7 to 10.