Functional deficits in patients with mild cognitive impairment
Prediction of AD

M.H. Tabert, PhD; S.M. Albert, PhD; L. Borukhova-Milov, BA; Y. Camacho, MS; G. Pelton, MD;
X. Liu, PhD; Y. Stern, PhD; and D.P. Devanand, MD

Abstract—*Objective:* To evaluate the predictive utility of self-reported and informant-reported functional deficits in patients with mild cognitive impairment (MCI) for the follow-up diagnosis of probable AD. *Methods:* The Pfeffer Functional Activities Questionnaire (FAQ) and Lawton Instrumental Activities of Daily Living (IADL) Scale were administered at baseline. Patients were followed at 6-month intervals, and matched normal control subjects (NC) were followed annually. *Results:* Self-reported deficits were higher for patients with MCI than for NC. At baseline, self- and informant-reported functional deficits were significantly greater for patients who converted to AD on follow-up evaluation than for patients who did not convert, even after controlling for age, education, and modified Mini-Mental State Examination scores. While converters showed significantly more informant- than self-reported deficits at baseline, nonconverters showed the reverse pattern. Survival analyses further revealed that informant-reported deficits (but not self-reported deficits) and a discrepancy score indicating greater informant- than self-reported functional deficits significantly predicted the development of AD. The discrepancy index showed high specificity and sensitivity for progression to AD within 2 years. *Conclusions:* These findings indicate that in patients with MCI, the patient's lack of awareness of functional deficits identified by informants strongly predicts a future diagnosis of AD. If replicated, these findings suggest that clinicians evaluating MCI patients should obtain both self-reports and informant reports of functional deficits to help in prediction of long-term outcome.

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In addition to progressive loss of cognitive skills, a core feature of a clinical diagnosis of AD is a decline in the ability to perform tasks required for independent living (see *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* [DSM-IV],[1] and National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association[2-4] criteria). In the early stages of AD, performance of daily household activities essential to maintaining independence (instrumental activities of daily living [IADL]) is altered.[5] In later stages, there is a progressive decline in basic activities involving self-care and mobility (ADL).[3-5] Numerous studies[6-11] have demonstrated that a large proportion of patients diagnosed with mild to moderate AD lack full awareness of this progressive decline.

Less is known about the functional status of elderly patients with mild cognitive impairment (MCI). The term "mild cognitive impairment," which has varying definitions and criteria, is used by our group to broadly define older individuals whose cognitive deficits are worse than those typical of normal aging but not severe enough to warrant a diagnosis

of dementia.[12] Many studies of MCI have been concerned with psychometric differentiation of these subjects from normal elderly and patients with AD, and the investigation of functional competence in people with MCI has been limited.

A recent study by Albert et al.[13] from our group investigated self-reported and informant-reported (e.g., spouse or child of proband) functional consequences of cognitive impairment in elderly patients who met criteria for MCI according to the Clinical Dementia Rating Scale (CDR).[14,15] These patients fell into two subcategories: those with a CDR score of 0, denoting "nondementia" but with evidence of subtle cognitive impairment with or without functional complaints, and those with a CDR score of 0.5, denoting "questionable dementia" or evidence of mild to moderate cognitive and functional impairment. Because the MCI patients in the Albert et al. study[13] were mildly impaired, functional batteries designed to assess higher levels of functioning were used, namely, the Pfeffer Functional Activities Questionnaire (FAQ)[16] and Lawton IADL Scale.[17] Analyses comparing self- and informant-reported deficits revealed that these patients with MCI, particularly

those with a CDR score of 0.5, tended to overestimate their functional abilities. While this finding is consistent with the "lack of awareness" observed in AD patients, to our knowledge, this was the first report of diminished awareness of functional deficits in MCI patients.

A related potential predictor is a discrepancy between patient and informant reports of cognitive status. While studies have shown that self-reported memory complaints are predictive of cognitive impairment and dementia,[18-21] a recent study[22] that examined the predictive utility of self- and informant-reported cognitive deficits (e.g., changes in memory for lists, events, and names of people) found that only informant-reported deficits predicted risk of AD at 2-year follow-up.

The goal of the current prospective study was to assess discrepancies between self- and informant-reported functional deficits in MCI patients as a predictor of incident AD and to determine the sensitivity and specificity of different degrees of such discrepancy. In the current study, MCI patients and normal comparison subjects (NC) were followed systematically in a clinical setting. The subjects comprised a larger sample than in the earlier cross-sectional Albert et al. report.[13] Deficits in household competencies were assessed at baseline evaluation with the Pfeffer FAQ[16] and the Lawton IADL,[17] both of which have been extensively validated and used in gerontologic research. They were separately administered to the patient and an informant (i.e., significant other) and to NC (subject only).

We hypothesized that at baseline evaluation, MCI patients, particularly those with a CDR score of 0.5, would demonstrate a lack of awareness of functional deficits, defined as having a greater number of informant-reported than self-reported functional deficits. More specifically, we hypothesized that informant-reported functional deficits would be a better predictor of a future diagnosis of AD than self-reported functional deficits and that higher scores on a discrepancy index (i.e., informant-reported minus self-reported deficits) would particularly increase the risk of incident AD. Evaluating the predictive utility of self- vs informant-reported functional deficits in MCI patients is important, given that functional scales are often administered in clinical settings to elderly patients and informants and therefore could potentially be used by primary care physicians for early detection of AD.

Methods. *Subjects.* Outpatients with MCI who presented for evaluation at a memory disorders center were recruited for a prospective study that examined putative early diagnostic markers of AD. NC (n = 46) were group matched to MCI patients (n = 107) for age, sex, and years of education. Of the 107 MCI patients evaluated at baseline, 48 met diagnostic criteria (see inclusion criteria below) for minimal cognitive impairment (CDR of 0) and 59 for "questionable dementia" (CDR of 0.5). Patients were examined at 6-month intervals, and NC were examined

annually. The institutional review boards of the New York State Psychiatric Institute and Columbia Presbyterian Medical Center approved the research protocol, and written informed consent was obtained from each patient.

Procedures. For patients with MCI, inclusion criteria were age ≥40 years, intellectual impairment for ≥6 months and ≤10 years, and the diagnosis of "nondemented with minimal cognitive impairment" (CDR of 0) or "questionably demented" (CDR of 0.5). MCI patients had a modified Mini-Mental State (mMMS)[23] score of ≥40 of 57 (equivalent to an MMS[24] score of ≥22). The following deficits on neuropsychological testing served as screening guidelines: impairment in memory, as evidenced by recall of two of three objects or fewer after 5 minutes on the MMS or a delayed recall score of >1 SD below norm in the six-trial Selective Reminding Test[25] or impaired intellectual performance as evidenced by a Wechsler Adult Intelligence Scale–Revised performance IQ ≥10 points below the verbal IQ score. Patients who did not reveal any of the neuropsychological deficits were still eligible for participation if they met the following criteria: subjective complaints of a decline in memory or cognitive functioning, objective evidence of this decline identified by an informant, and clinically significant functional impairment based on a positive score on at least one of the first eight items of the modified Blessed Functional Activity Scale.[26]

Exclusion criteria were a diagnosis of dementia, schizophrenia, schizoaffective disorder, or primary major affective disorder that clearly preceded the onset of cognitive impairment, electroconvulsive therapy within the last 6 months, current or recent (last 6 months) history of alcohol or substance dependence (DSM-IV criteria),[1] clinical or historical evidence of stroke (cortical stroke or an infarct ≥2 cm in diameter on any MRI slice; periventricular hyperintensities and small subcortical lacunae or infarcts did not lead to exclusion), cognitive impairment caused by concomitant medications, and the presence of major neurologic illness (e.g., PD or ALS). These inclusion and exclusion criteria defined a relatively broad group of patients between "normal" and "dementia" and are similar to those used in other studies of MCI.[12,27] Based on a comprehensive review of all available clinical and diagnostic information, a consensus diagnosis by expert raters determined CDR status and study entry.[28]

Functional assessment scales. The Pfeffer FAQ[16] and the Lawton IADL Scale[17] were administered by a neuropsychology technician at baseline to all MCI patients and NC. In addition, these scales were independently administered to the informants of all patients (CDR of 0 and 0.5). NC did not have informants.

The Pfeffer FAQ comprises 10 items that assess a variety of IADL and complex cognitive/social functions. These include writing checks, paying bills, and keeping financial records; assembling tax or business records; shopping alone; playing games of skill; making coffee or tea; preparing a balanced meal; keeping track of current events; paying attention and understanding while reading or watching a TV show; remembering appointments, family occasions, and to take medications; and traveling out of the neighborhood. The eight items of the Lawton IADL Scale assess housekeeping, shopping, traveling to places out of walking distance, doing laundry, handling finances, taking medications, telephoning, and meal preparation.

For the Pfeffer FAQ and Lawton IADL Scale, each item was scored dichotomously (no difficulty/any difficulty), and the sum of items rated as "any difficulty" (Pfeffer FAQ range: 0 to 10; Lawton IADL range: 0 to 8) was calculated for each subject. If a subject had never performed the task (lifetime), the item was excluded from analyses.

Statistical analyses. Two-tailed t-tests and χ^2 tests were used to compare the baseline demographic and clinical features and functional deficits of MCI patients (CDR of 0 and 0.5) and NC. Similar tests were used to compare the baseline characteristics and self- and informant-reported functional deficits of MCI patients with and without the follow-up diagnosis of dementia.

A discrepancy index was calculated by subtracting the number of self-reported deficits from the number of informant-reported deficits. The discrepancy score distribution was dichotomized to compare subjects who had greater informant- than self-reported functional deficits vs those who did not (i.e., showed no discrepancy or had greater self- than informant-reported deficits).

To test for group differences in baseline self- and informant-reported deficits in the patient groups with CDR scores of 0 and 0.5, a two-way analysis of covariance (ANCOVA) was performed, where rater (baseline self-report vs informant report) served as the within-subjects factor and diagnostic group (CDR of 0 vs 0.5) as the between-subjects factor. Age, education, and mMMS scores were covariates. ANCOVA, with the same covariates, was also used to compare baseline self- and informant-reported deficits for MCI patients who did or did not receive a diagnosis of AD on follow-up.

Survival analysis (Cox proportional hazards model) was used to examine the effect of predictors on the development of AD. Subjects were considered to have met the AD endpoint if they met criteria for AD at two consecutive assessments (6-month intervals). The time variable was the time from the initial visit to the first follow-up at which a diagnosis of AD was made. Predictor variables investigated were the total number of baseline self-reported deficits, the total number of baseline informant-reported deficits, and the discrepancy index. Age, years of education, and mMMS scores were used as covariates. To further assess the predictive utility of the discrepancy index, CDR status was entered into the regression equation as an additional covariate. In addition, a separate Cox analysis was conducted in which CDR status was the main predictor with age, years of education, and mMMS scores as covariates.

Logistic regression analyses, including the discrepancy index, age, education, and mMMS scores as predictor variables, were also conducted after restricting the group with MCI to patients who had completed the 2-year follow-up (or developed AD before that time). Sensitivity and specificity for the 2-year follow-up diagnosis of AD were calculated for the informant-reported deficit variable and the discrepancy index. Positive and negative predictive value was also calculated for a cutoff score of ≥1 on the discrepancy index.

Results. *Baseline sample.* A breakdown of the demographic and clinical feature s for the NC and MCI patient groups is presented in tables 1 and 2. Independent t-tests comparing demographic variables for the patients with

Table 1 *Baseline sample characteristics and self-reported functional deficits*

Variable	MCI, n = 107	Normal controls, n = 46	p Value*
Sex, % F	50.5	54.3	NS
Age, y, mean ± SD	67.6 ± 10.1	63.8 ± 9.7	0.032
Education, y, mean ± SD	15.2 ± 3.6	16.5 ± 2.7	0.030
mMMS score, range: 0–57, mean ± SD	51.7 ± 4.3	54.9 ± 1.5	<0.001
MMS score, range: 0–30, mean ± SD	27.5 ± 2.2	29.4 ± 0.78	<0.001
Pfeffer deficits, mean ± SD	1.79 ± 1.93	0.007 ± 0.33	<0.001
Lawton IADL deficits, mean ± SD	0.42 ± 0.96	0.00	†

* A test of significance for χ^2 (categorical variables) or two-tailed t-test (continuous variables) conducted as appropriate.

† Among normal controls, no one endorsed Lawton IADL deficits, and therefore a statistical comparison was not conducted.

MCI = mild cognitive impairment; mMMS = modified Mini-Mental State; IADL = Instrumental Activities of Daily Living Scale.

CDR of 0 and NC revealed no differences for age ($p = 0.741$), years of education ($p = 0.727$), or mMMS scores ($p = 0.118$).

Baseline self- and informant-reported deficits. On average, NC self-reported fewer baseline Pfeffer and Lawton IADL deficits than did patients (see table 1). Informant-reported deficits were not available for NC.

In the MCI sample, self- and informant-reported deficits

Table 2 *Baseline characteristics and self- and informant-reported functional deficits of patients with mild cognitive impairment (CDR of 0 and 0.5)*

Variable	CDR-0, n = 48	CDR-0.5, n = 59	p Value*
Sex, % F	41.7	57.6	NS
Age, y, mean ± SD	63.2 ± 9.9	71.2 ± 8.8	<0.001
Education, y, mean ± SD	16.7 ± 2.4	13.9 ± 4.0	<0.001
mMMS score, mean ± SD	54.2 ± 2.5	49.6 ± 4.4	<0.001
MMS score, mean ± SD	28.7 ± 1.5	26.6 ± 2.2	<0.001
Pfeffer self-reported deficits, mean ± SD	1.9 ± 2.1	1.7 ± 1.8	NS
Pfeffer informant-reported deficits, mean ± SD	1.5 ± 2.0	2.0 ± 2.1	NS
IADL self-reported deficits, mean ± SD	0.4 ± 0.9	0.5 ± 0.9	NS
IADL informant-reported deficits, mean ± SD	0.3 ± 0.7	0.8 ± 1.4	NS

* A test of significance for χ^2 (categorical variables) or two-tailed t-test conducted as appropriate.

CDR = Clinical Dementia Rating Scale; mMMS = modified Mini-Mental State; IADL = Instrumental Activities of Daily Living Scale.

did not differ between the groups with CDR of 0 and 0.5 (see table 2). On average, the group with CDR of 0 reported more deficits than their informants and the group with CDR of 0.5 showed the opposite pattern (i.e., the mean number of informant-reported deficits was greater than self-reported deficits). However, these differences did not achieve statistical significance. ANCOVA using the total number of deficits as the dependent variable and in which age, years of education, and mMMS scores were used as covariates did not reveal any significant main effects or higher-order interactions of diagnostic group (CDR of 0 vs 0.5) or rater (self vs informant).

There were, however, more self-reported and informant-reported Pfeffer FAQ deficits than Lawton IADL deficits for both groups with CDR of 0 (self-report: paired $t[47] = 5.63$, $p < 0.0001$; informant report: paired $t[47] = 5.19$, $p < 0.0001$) and CDR of 0.5 (self-report: paired $t[58] = 6.48$, $p < 0.0001$; informant report: paired $t[58] = 6.02$, $p < 0.0001$).

Follow-up sample. Of the 107 MCI patients evaluated at baseline, at least one semiannual follow-up evaluation was available in 92 patients. Fifty-three of the 92 (58%) patients had a baseline CDR of 0.5 and 39 (42%) had a baseline CDR of 0. The mean duration of follow-up was 24.5 months (SD 14.3 months). The number of subjects followed up at each time point was 85 at 6 months, 75 at 12 months, 55 at 18 months, 52 at 24 months, 30 at 30 months, 27 at 36 months, 14 at 42 months, 10 at 48 months, and 3 at 54 months. Of the 92 patients followed, all 23 who met consensus diagnostic criteria for dementia during follow-up also met criteria for probable AD. Three of the 23 incident dementia cases had a progressive clinical course consistent with AD plus other conditions (parkinsonism, depression, vascular disease) that were deemed contributing factors. All 23 patients were retained for all analyses.

Sex was not associated with a final diagnosis of AD (men: 9/46 [19.6%]; women: 14/46 [30.4%]; $\chi^2 = 1.4$, $df = 1$, $p = 0.229$), nor was it associated with the predictor variables (i.e., self-reported deficits, informant-reported deficits, and discrepancy index). Higher mean age (64.4 vs 75.6 years; $t = 5.0$, $df = 90$, $p < 0.001$), fewer mean years of education (15.8 vs 13.5 years; $t = 2.8$, $df = 90$, $p = 0.007$), and lower mean mMMS scores (52.6 vs 48.8; $t = 3.9$, $df = 90$, $p < 0.001$) at baseline were each associated with the diagnosis of AD at follow-up. Therefore, these three variables were used as covariates in subsequent analyses.

To compare group differences in baseline self- and informant-reported functional deficits for MCI patients who received a diagnosis of AD on follow-up (n = 23) vs those who did not (n = 69), a two-way rater (baseline self-report vs informant report) by diagnostic group ("converters" to AD vs "nonconverters") ANCOVA was performed using the total number of deficits as the dependent variable and in which age, education, and mMMS scores were covariates. For the Pfeffer FAQ, there was a main effect of diagnostic group (F[1,87] = 7.7, $p < 0.007$), no main effect of rater, and a rater × diagnostic group interaction (F[1,87] = 6.6, $p < 0.012$) (see figure 1). Post hoc linear contrasts revealed that (1) there were no differences in baseline self-reported deficits between converters and nonconverters ($p = 0.243$), (2) informant-reported deficits were greater for converters than nonconverters (contrast
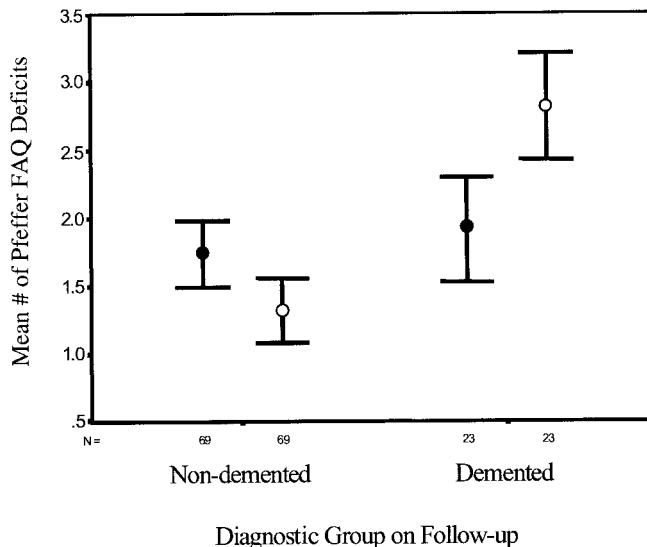

Figure 1. *Significant rater (baseline self-report vs informant report) × diagnostic group (nondemented vs demented on follow-up) interaction, revealing greater informant-reported than self-reported baseline functional deficits for patients with mild cognitive impairment (MCI) (n = 23) who met criteria for AD on follow-up and the reverse pattern for MCI patients (m = 69) who did not convert to AD (the means adjusted for age, education, and modified Mini-Mental State scores as described in text). Filled circles = self-report; open circles = informant report; error bars = SEM. FAQ = Functional Activities Questionnaire.*

estimate = 2.0, SE = 0.54, $p < 0.001$, 95% CI = 0.92 to 3.1), and (3) the difference between the mean number of informant- and self-reported deficits for the group that converted to AD was larger than that of the nonconverters (contrast estimate = 1.3, SE = 0.47, $p = 0.007$, 95% CI = 0.38 to 2.3). In similar analyses using the Lawton IADL Scale instead of the Pfeffer FAQ Scale, there were no significant main effects or higher-order interactions.

Prediction of AD at follow-up. Separate Cox proportional hazards models were used to evaluate the effect of baseline Pfeffer self-reported and informant-reported deficits on the endpoint diagnosis of AD. The total number of self-reported deficits did not predict time to develop AD (Wald $\chi^2 = 0.001$, $df = 1$, $p = 0.977$, relative risk [RR] = 1.0, 95% CI = 0.8 to 1.2), with age ($p = 0.002$), years of education ($p = 0.721$), and mMMS scores ($p = 0.079$) included in the Cox model as covariates. In contrast, the total number of informant-reported deficits did predict time to develop AD (Wald $\chi^2 = 7.6$, $df = 1$, $p = 0.006$, RR = 1.3, 95% CI = 1.1 to 1.6) when age ($p = 0.001$), years of education ($p = 0.448$), and mMMS scores ($p = 0.057$) were included as covariates.

The predictive utility of the dichotomous discrepancy index (i.e., informant- minus self-reported deficits) was also evaluated. A cutoff point of ≥1 (i.e., at least one more informant-reported deficit than self-reported deficits) on the Pfeffer FAQ was examined. The log-rank test revealed distribution differences between the two index groups (log rank statistic = 17.6, $df = 1$, $p < 0.0001$). The Cox proportional hazards model revealed a relative risk for reaching the endpoint diagnosis of AD of 4.4 (95% CI = 1.8 to 10.6,
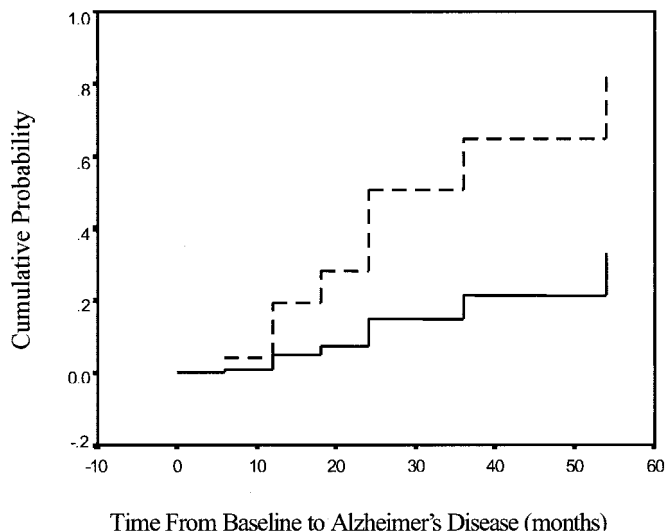
Figure 2. *Cumulative incidence curves (evaluated at the mean of the covariates in the Cox model) showing the probability of developing AD over a 4.5-year period in subjects with mild cognitive impairment at baseline, by the presence or absence of greater informant-reported than self-reported functional deficits at baseline. Solid line = self ≥ informant; broken line = informant > self.*

Wald χ^2 = 10.8, df = 1, p = 0.001), after controlling for age (p = 0.018), years of education (p = 0.825), and mMMS scores (p = 0.047). The cumulative incidence curves for the dichotomous discrepancy variable (evaluated at the mean of the covariates in the model) are presented in figure 2. The relative risk of AD remained significant even after baseline CDR status was included in the regression equation as an additional covariate (dichotomized discrepancy index: Wald χ^2 = 11.1, df = 1, p = 0.001, RR = 4.7, 95% CI = 1.9 to 11.5; CDR status, p = 0.145; mMMS, p = 0.114; age, p = 0.070; years of education, p = 0.824). Moreover, CDR status alone did not predict time to develop AD (Wald χ^2 = 2.7, df = 1, p = 0.100, RR = 3.7, 95% CI = 0.7 to 18.0), with age (p = 0.007), years of education (p = 0.616), and mMMS scores (p = 0.765) included in the Cox model as covariates. When a cutoff point of ≥1 on the Lawton IADL Scale was used as the discrepancy index predictor in the Cox proportional hazards model, it did not relate to risk of AD (Wald χ^2 = 2.6, df = 1, p = 0.078, RR = 2.6, 95% CI = 0.9 to 7.2; mMMS, p = 0.057; age, p = 0.004; years of education, p = 0.762).

To evaluate clinically relevant prediction, further analyses were conducted by restricting the clinical group with mild cognitive impairment to patients who had completed 2 years of follow-up (n = 52) or patients who had already developed AD by 2 years (n = 3). In this subsample of 55 patients with MCI (13 who had and 42 who had not developed AD), self-report (AD: mean Pfeffer FAQ score = +1.4, SD = 1.6; non-AD: mean = 2.4, SD = 2.3; t = 1.5, df = 53, p = 0.150) and informant report (AD: mean Pfeffer FAQ score = 2.5, SD = 2.0; non-AD: mean = 2.0, SD = 2.3; t = 0.8, df = 53, p = 0.426) by themselves did not predict AD on follow-up, but the baseline Pfeffer FAQ discrepancy score predicted AD on follow-up (AD: mean discrepancy score = +1.2, SD = 2.5; non-AD: mean = −0.4, SD = 1.6; t = 2.7, df = 53, p = 0.010). In a logistic regression analy-

Table 3 *Sensitivity and specificity of functional deficits (informant-reported and informant- vs self-reported discrepancy) as measured by Pfeffer Functional Activities Scale in predicting AD at 2-year follow-up in 55 patients with mild cognitive impairment**

Pfeffer, cutoff score	Total informant-reported deficits		Discrepancy index (informant-reported − self-reported deficits)	
	Sensitivity	Specificity	Sensitivity	Specificity
≥1	84.6	38.1	61.5	83.3
≥2	61.5	57.1	46.2	92.9
≥3	46.2	64.3	23.1	97.6
≥4	30.8	78.6	23.1	97.6
≥5	23.1	81.0	7.7	97.6
≥6	7.7	90.5	0	100
≥7	0	95.2	0	100

Values are percentages.

* Three patients had not yet been followed up for the full 2 years but had already developed AD.

sis that evaluated the outcome of AD at 2-year follow-up, a discrepancy score of ≥1 (i.e., dichotomized discrepancy variable) predicted AD (odds ratio [OR] = 7.9, 95% CI = 1.3 to 49.6, p = 0.028) when age (p = 0.065), years of education (p = 0.989), and mMMS scores (p = 0.138) were also included in the model.

For this subgroup followed up at 2 years, baseline informant-reported deficits of ≥1 led to 84.6% sensitivity (n = 11/16 converters) and 38.1% specificity (n = 16/42 nonconverters) for the diagnosis of AD (see table 3). A progressive decrease in sensitivity and an increase in specificity were observed with more informant-reported deficits. The optimal tradeoff between sensitivity and specificity occurred at two or more informant-reported deficits (sensitivity = 61.5% [n = 8/13] and specificity = 57.1% [n = 24/42]). For the informant- vs self-reported discrepancy index, the optimal tradeoff between sensitivity and specificity occurred at a discrepancy score of ≥1 (sensitivity = 61.5% [n = 8/13] and specificity = 83.3 [n = 35/42]) with a positive predictive value of 73% and a negative predictive value of 61% based on a 42% (23/55) prevalence in this sample followed for 2 years.

Discussion. While lack of awareness of functional deficits is characteristic of patients with mild to moderate AD, only a few studies have examined this issue in patients with MCI. In a cross-sectional study of a smaller sample from this same series of subjects, Albert et al.[13] reported that MCI patients, particularly those with a CDR of 0.5, overestimated their functional abilities compared with informant reports. The MCI patients in the current larger sample also revealed greater self- and informant-reported deficits than did NC. Moreover, at baseline, both groups of patients and their informants endorsed a greater number of Pfeffer FAQ than Lawton IADL deficits. With respect to the follow-up sample, baseline functional deficits as measured by the Pfeffer FAQ were

greater for patients who converted to AD on follow-up evaluation than for patients who did not, even after controlling for age, education, and mMMS scores. Also, the mean number of informant-reported Pfeffer FAQ deficits was greater than the mean number of self-reported deficits for patients who converted to AD. Moreover, while converters and nonconverters did not differ on self-reported deficits, informants reported more deficits for converters. These findings strongly suggest that a subset of MCI patients overestimate higher-level functional abilities and that this apparent lack of awareness predicts a future diagnosis of AD.

Survival analyses further revealed that on the Pfeffer FAQ, informant-reported deficits (but not self-reported deficits) and a discrepancy index score of ≥1 (indicating greater informant- than self-reported functional deficits) predicted time to develop AD after controlling for age, education, and mMMS scores. The discrepancy index was predictive even when controlling for CDR status. On the other hand, CDR status did not predict AD. When the sample was restricted to patients with 2 years of follow-up, only the baseline discrepancy index predicted a diagnosis of AD, with relatively high levels of diagnostic specificity and moderate sensitivity. Logistic regression analyses further revealed that a discrepancy score of ≥1 strongly predicted AD at the 2-year follow-up point with an OR of 7.9 (after covarying for age, years of education, and mMMS score). Together, these findings confirm our hypotheses that informant-reported, but not self-reported, higher-level functional deficits predict time to dementia and that among the three measures, the best predictor of time to dementia is the disparity between self-reports and informant reports, indicating lack of awareness of functional deficits.

These findings have important clinical implications. They underscore the need for primary care physicians not only to assess functional complaints of nondemented elderly individuals but also to obtain ratings from an informant, preferably a family member or close acquaintance, who can reliably report on the patient's ability to perform daily activities required for independent living. Identical standardized ratings, using the Pfeffer or another scale assessing similar functions, should be obtained from both the patient and the informant. When a disparity between these two sources is noted (showing greater informant- than patient-reported deficits), a physician's index of suspicion should be heightened, particularly if mental status deficits are also noted, and the possibility of an early diagnosis of AD and appropriate interventions should be considered.

Our findings are consistent with those of Tierney et al.,[22] which showed that informant- but not self-reported cognitive deficits (e.g., memory for lists, events, and names, finding one's way around home and neighborhood, and financial management as measured by the Cambridge Mental Disorders of the Elderly Examination [CAMDEX] scale[29]) predict a future diagnosis of AD in nondemented patients with memory impairment. In the current study, two functional scales were used to assess self- and informant-reported functional deficits in MCI patients. The difference in the frequency of reported functional deficits between these two scales is most likely due to the fact that the Pfeffer FAQ, in addition to assessing IADL, measures changes in activities representing relatively complex household competencies and occupational and social functioning (see Spector[30] for comparison of scales). These higher-level functions are most likely to be affected in MCI patients who, by definition, experience only mild levels of cognitive and functional impairment. In this regard, our findings suggest that in MCI, the predictive utility of the Pfeffer FAQ, which captures changes in complex activities representing higher levels of social and cognitive functioning, is superior to that of the Lawton IADL Scale, which measures basic household competencies. Also, while CDR status did not predict AD in our sample, a discrepancy in Pfeffer FAQ deficits was highly predictive (even after controlling for CDR status). These findings suggest that in MCI, greater informant- than self-reported deficit as measured by the Pfeffer FAQ is a more powerful predictor of AD than CDR status.

Another important issue when assessing functional competence in the elderly is the use of performance-based vs informant-based evaluations. Performance-based evaluations assess functional capacity directly by asking the patient to perform an activity, which is then evaluated in a formal way. While performance-based measures are thought to be more objective and reliable than informant reports, their use in clinical settings is limited by the fact that their administration requires significantly more time, specialized equipment, and highly trained assessors and must occur under rigorously controlled environmental conditions.[11,30-33] In contrast, physicians or nonmedical support staff can routinely administer self-/informant-based scales in a cost-effective manner. In addition, the fact that the self-/informant ratings in the current study predicted incident AD over time provides an independent source of validation for their use in making a differential diagnosis between benign cognitive impairment and possible early AD in patients with MCI.

In conclusion, our findings provide preliminary validation for the clinical utility of informant- vs self-reported functional deficits in predicting a future diagnosis of AD in patients with MCI. Self- and informant-reported ratings should also be used in follow-up visits to monitor functional changes and the effectiveness of early intervention strategies.[3]

On a precautionary note, this study sample involved elderly patients presenting for clinical services; therefore, the predictive utility of functional deficits may differ in a random sample of elderly patients. However, the careful characterization of patients and rigorous definition of MCI used in this study provide confidence that elderly patients with

MCI, who also demonstrate a discrepancy between self- and informant-reported functional deficits, are at increased risk for a future diagnosis of AD. Continued follow-up of these individuals will enable us to test the longer-range predictive utility of functional deficits in patients with MCI. Independent replication in larger clinical samples is also needed to establish clinical utility.

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