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Tracking early decline in cognitive function in older individuals at risk for Alzheimer's disease dementia: the Alzheimer's Disease Cooperative Study Cognitive Function Instrument

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Abstract

Importance—Several large-scale Alzheimer's disease (AD) secondary prevention trials have begun to target individuals at the preclinical stage. The success of these trials depends on validated outcome measures that are sensitive to early clinical progression in individuals who are initially asymptomatic.

Objective—To investigate the utility of the Cognitive Function Instrument (CFI) to track early changes in cognitive function in older individuals without clinical impairment at baseline.

Design, Setting, and Participants—Longitudinal study over the course of 48 months at participating Alzheimer's Disease Cooperative Study (ADCS) sites. The study included 468 healthy older individuals (Clinical Dementia Rating Scale [CDR] Global = 0, above cut-off on modified Mini-Mental State Exam and Free and Cued Selective Reminding Test) (mean age = 79.4 years ± 3.6). All subjects and their study partners completed the Self and Partner CFI annually. Subjects also underwent concurrent annual neuropsychological assessment and apolipoprotein E (APOE) genotyping.

Main outcomes and measures—Comparison of CFI scores between clinical progressors (Clinical Dementia Rating Scale [CDR] 0.5) and non-progressors (CDR remained = 0), as well

as between APOE ϵ 4 carriers and non-carriers were performed. Correlations of change between the CFI and neuropsychological performance were assessed longitudinally.

Results—At 48 months, group differences between clinical progressors and non-progressors were significant for CFI Self, CFI Partner, and CFI Self+Partner total scores. At month 48, APOE ϵ 4 carriers showed greater progression than non-carriers on CFI Partner and CFI Self+Partner scores. Both CFI Self and CFI Partner scores were associated with longitudinal cognitive decline, although findings suggest self report may be more accurate early in the process, whereas accuracy of partner report improves when there is progression to cognitive impairment.

Conclusions and Relevance—Demonstrating long-term clinical benefit will be critical for the success of recently launched secondary prevention trials. The CFI appears to be a brief, yet informative potential outcome measure that provides insight into functional abilities at the earliest stages of disease.

INTRODUCTION

Recently published guidelines have outlined a “preclinical phase” of AD in which individuals are still clinically normal, but may have subtle evidence of early cognitive change in the context of amyloidosis and neuronal injury¹. This provides the opportunity to intervene at earlier stages of disease than was previously possible². Recent guidance from the Food and Drug Administration (FDA) states that a primary cognitive outcome measure may suffice for provisional approval of a preclinical treatment, but eventually would need to be supported by evidence of long-term functional benefit³. Currently, sensitive cognitive measures are available for secondary prevention trials^{4,5}, but a companion functional measure has yet to be fully realized⁶.

Increasingly, subjective report of cognitive functioning in everyday life is thought to be a sensitive indicator of decline, even at the preclinical stages of AD^{7–13}. Accordingly, over the last decade, the Alzheimer's Disease Cooperative Study (ADCS) has developed the Cognitive Function Instrument (CFI) intended to detect early changes in cognitive and functional abilities in individuals without clinical impairment¹⁴. The CFI includes 14 questions that are asked of the participant and a study partner separately that efficiently probe the full realm of subjective cognitive concerns found in older adults¹⁵. Unlike functional outcomes typically used in clinical trials at the stage of Mild Cognitive Impairment (MCI) or dementia, the CFI does not require an in-person interview or clinician judgment and measures both participant and study partner report, the combination of which has been shown to be sensitive at the earliest stages of disease¹⁶.

In the current study, the goal was to determine if the CFI is a sensitive measure in tracking longitudinal change in cognitive function in older individuals without cognitive impairment at baseline. Over the course of four years, we assessed the CFI's (self and partner) relationship with clinical progression (on Clinical Dementia Rating Scale), apolipoprotein E (APOE) ϵ 4 carrier status, and performance on a cognitive composite. Ultimately, we sought to establish the CFI as a useful functional measure appropriate for prevention trials.

METHODS

A total of 468 older individuals (60% female) with an average age of 79.4 (± 3.6) years participated in the study. Participants met inclusion criteria if they were in good physical and mental health, had no significant medical illnesses that would interfere with participation (e.g., active malignancy, stroke), and no exclusionary medications (e.g., antipsychotic agents). Participants were required to have a qualified study partner who was willing to provide information about their daily function and who had contact with the participant at least 2 times per week. The participants were enrolled at multiple ADCS sites. The local Institutional Review Board at each site approved the study protocol and informed consent form before the initiation of participant recruitment. All participants provided informed consent after the procedures of the study had been fully explained. In the current sample, participants had a global Clinical Dementia Rating Scale (CDR-G)¹⁷ score = 0 at baseline, a modified Mini-Mental State Exam (3MSE)¹⁸ of at least 88 for participants with greater than 8 years of education and at least 80 for participants with less education (taken from the Women's Health Initiative Memory Study (WHIMS)), and a score greater than 44 on the Free and Cued Selective Reminding Test total score, which includes both free and cued recall (FCSRT)¹⁹. The CFI was not used to determine participant eligibility in this study. Individuals were followed annually for 48 months following the baseline visit.

Participants and study partners were mailed the CFI 4 weeks prior to each annual assessment and were asked to return the questionnaire by mail. Participants and study partners were asked to complete the CFI independently. The study partner was not allowed to consult the subject, but could consult anyone else. The CFI contains 14 questions (see Tables 1&2); one version for the participant and one version for the study partner with the same questions. Questions were originally derived from common probes across clinical assessments of aging and dementia¹⁴ and include items regarding memory decline (e.g., compared to a year ago, memory has declined), appraisal of cognitive difficulties (e.g., misplacing belongings more often), and functional abilities (e.g., need more help remembering appointments). Responses were coded as Yes = 1, No = 0, and Maybe = 0.5, and were summed together to create a total score.

Objective cognitive performance was assessed annually with a cognitive battery called the modified Alzheimer's Disease Cooperative Study Preclinical Alzheimer Cognitive Composite (mADCS-PACC), a modified version of the ADCS-PACC⁴, described in a separate study, which has demonstrated sensitivity in detecting cognitive decline at the preclinical stage of AD. Briefly, the mADCS-PACC consisted of 1) total recall from the Free and Cued Selective Reminding Test (FCSRT) (0 to 48 words)¹⁹, 2) NYU Paragraph recall²⁰, 3) Digit-Symbol Substitution Test score from the Wechsler Adult Intelligence Scale-Revised (0 to 93 symbols)²¹ and 4) Modified Mini Mental State Exam (3MSE)¹⁸ score. NYU Paragraph recall and the Digit Symbol Substitution Test were not given at baseline, but at all subsequent visits. At each annual follow-up visit, participants were screened for the development of MCI or dementia based the same cut-offs used as inclusion criteria (3MSE and FCSRT). If an individual fell below either 2 cut-offs on the cognitive evaluation, then the site clinician initiated a clinical consensus to determine if the participant

met Petersen criteria²² for MCI or DSM IV for dementia and if so, whether or not the probable etiology was AD.

Among those with at least one follow-up CFI observation, we summarized means, standard deviations, counts, and percentages of characteristics at baseline by groups of interest. One group of interest included individuals who progressed from 0 to 0.5 or higher on CDR-G at any time point after baseline. None of the subjects who progressed on CDR regressed on CDR at a later time point. We also compared individuals who had at least one APOE ϵ 4 allele (APOE ϵ 4+) against non-carriers (APOE ϵ 4-). Groups were compared using Pearson's Chi-square test for categorical data; and the two-sample t-test for continuous data. We assessed internal consistency, using Cronbach's alpha, on the items of the CFI in our sample for both self and study partner versions. In individuals who were CDR-G stable and APOE ϵ 4-, we estimated intraclass correlation coefficients to assess test-retest reliability from baseline to 12 months later²³. To assess group differences in longitudinal change, we applied a Mixed Model of Repeated Measures²⁴ with baseline CFI, baseline Geriatric Depression Scale (GDS)²⁵, age, education, and race considered as covariates. Time was treated as a categorical variable. We assumed a compound symmetric correlation structure and heterogeneous variance over time. No adjustments were made for multiple comparisons. Secondary analyses compared CFI items that represented appraisal of cognitive abilities in everyday life (e.g., repeating questions) to those that were more related to functional abilities (e.g., change in ability to use appliances) in predicting outcomes. We also regressed CDR-G progression status on CFI and PACC baseline scores to assess the predictive value of each predictor separately and together. The predictive value of these logistic regression models were compared using the Akaike Information Criterion (AIC)²⁶. This analysis was repeated with CFI and PACC change scores, estimated by the slope estimates from subject-level ordinary least squares regression.

To assess the correlation between the CFI versions (Self, Partner, Self+Partner) and the mADCS-PACC, we estimated cross-sectional Pearson's correlation coefficients at each visit. We used the nonparametric bootstrap, resampling subjects with replacement 10,000 times, to obtain confidence intervals for the pairwise differences between these correlations at each time point (Self vs Partner, Self vs Self+Partner, and Partner vs Self+Partner). We also applied a multivariate outcome linear mixed-effect model approach to estimate the correlation of change in CFI and mADCS-PACC²⁷. Confidence intervals were again derived by nonparametric bootstrap in which we resampled subjects, with replacement, 1,000 times and refit the mixed-effect model for each resample.

RESULTS

Tables 3 and 4 provide the baseline characteristics by the groups of interest. The CDR-G Stable group demonstrated better performance than the CDR-G Progressor group on the FCSRT Free Recall, 3MSE, and all three versions of CFI (Self, Partner, and Self+Partner). The APOE ϵ 4-group was older and had higher GDS scores at baseline than the APOE ϵ 4+ group. Individuals who dropped from the study were more likely to be older, of minority status, and with lower education. Performance on the 3MSE and PACC were lower at the time of the last visit, but no differences were found on the CDR.

Cronbach's alpha of CFI Self items at baseline was 0.78 and CFI Partner was 0.85. In individuals who were CDR-G Stable and APOE ϵ 4 non-carriers, intraclass correlations for CFI Self was 0.73 and for CFI Partner was 0.54 (5% of the study partners changed from baseline to month 12).

Figure 1 demonstrates the estimated group differences in CFI change from baseline by APOE and CDR-G Progressor groups. When compared to the APOE ϵ 4- subjects, APOE ϵ 4+ subjects were found to have worse functioning on the CFI over time: The APOE group differences were significant ($p < 0.05$) for CFI Partner at months 36 ($\beta = 1.04$, $SE = 0.38$, $p = 0.007$) and 48 ($\beta = 1.10$, $SE = 0.44$, $p = 0.012$); and for CFI Self+Partner at months 24 ($\beta = 0.94$, $SE = 0.40$, $p = 0.020$), 36 ($\beta = 1.42$, $SE = 0.53$, $p = 0.007$), and 48 ($\beta = 1.56$, $SE = 0.63$, $p = 0.014$). When compared to the CDR-G stable subjects, CDR-G progressors were found to have worse functioning on the CFI over time: The CDR-G Progression group differences were significant for CFI Self, Partner, Self+Partner at every visit except at months 3 and 12 for CFI Self. At month 48 the group differences were $\beta = 2.13$ ($SE = 0.45$, $p < 0.001$) for CFI Self, $\beta = 5.08$ ($SE = 0.59$, $p < 0.001$) for CFI Partner, and $\beta = 7.04$ ($SE = 0.83$, $p < 0.001$) for CFI Self+Partner. A composite of items grouped by functional abilities (e.g., remembering appointments) versus a composite of metacognitive items (e.g., repeating conversations), performed similarly at separating CDR and APOE groups longitudinally.

Figure 2 demonstrates the cross-sectional correlation between CFI and mADCS-PACC. Worse functioning on the CFI was associated with worse cognition on the mADCS-PACC: The correlation between CFI Self and mADCS-PACC increased from $\rho = 0.20$ (95% CI 0.12 to 0.29) at baseline to $\rho = 0.39$ (95% CI 0.30 to 0.48) at month 48, while the correlation between CFI Partner and mADCS-PACC increased from $\rho = 0.09$ (95% CI 0.002 to 0.18) at baseline to $\rho = 0.44$ (95% CI 0.35 to 0.52) at month 48. The correlation between CFI Self + Partner and mADCS-PACC increased from $\rho = 0.18$ (95% CI 0.10 to 0.27) at baseline to $\rho = 0.49$ (95% CI 0.40 to 0.57) at month 48. The bootstrap 95% confidence intervals for the pairwise differences between correlations with the mADCS-PACC excluded 0 for all differences except between CFI Self and CFI Self+Partner at baseline and month 24; and CFI Self and CFI Partner at months 12, 36, and 48. The multivariate mixed-effect model analysis found the correlation of change between CFI Self and mADCS-PACC was $\rho = 0.32$ (95% CI 0.13 to 0.46), between CFI Partner and mADCS-PACC was $\rho = 0.56$ (95% CI 0.42 to 0.68), and between CFI Self + Partner and mADCS-PACC was $\rho = 0.58$ (95% CI 0.44 to 0.70). The correlation of change between mADCS-PACC and CFI-Self + Partner was significantly stronger than with CFI-Self (0.27, 95% CI 0.09 to 0.46). The correlation of change between mADCS-PACC and CFI- Self + Partner was stronger than with CFI-Partner (0.02, 95% CI -0.10 to 0.13), and stronger with CFI-Partner than with CFI-Self (0.25, 95% CI -0.02 to 0.53), but these differences were not significant at the 0.05 level.

The logistic regression models of CDR-G progression found that both baseline mADCS-PACC and CFI were independently predictive. Each point increase on the PACC was associated with a decreased risk of progression (OR=0.965, 95% CI 0.95 to 0.98, $p < 0.001$), and each point increase on the CFI was associated with increased risk of progression (OR = 1.013, 95% CI 1.01 to 1.02, $p < 0.001$). The model that included both measures had the best

predictive value (AIC = -100.2), followed by the models with mADCS-PACC alone (AIC = -89.3) and CFI alone (AIC = -78.1).

DISCUSSION

Overall, we found that both self and partner report of change in cognitive function on the CFI was associated with traditional measures of clinical progression over the course of four years. When comparing individuals who demonstrated clinical progression (CDR-G>0) to those who remained stable (CDR-G=0), there was a significant separation between groups, such that CDR-G progressors exhibited higher CFI scores, as well as a greater increase in CFI scores over time than did CDR-G stable. These findings held for both partner and self report. The combination of self+partner CFI demonstrated a slight advantage over individual report, suggesting that both perspectives on decline might be valuable over a 4 year observational period.

The CFI remained a predictor of CDR progression when objective cognitive performance was also added as a predictor, suggesting that it independently contributes to longitudinal outcomes, but that the combination of both measures may be particularly predictive. Findings are in support of a previous work that finds both subjective and objective measures improve predictive ability in individuals without clinical impairment²⁸ and with MCI²⁹.

When comparing APOE ϵ 4 carriers and non-carriers, there was a significant separation between carrier groups by month 36 for partner CFI, whereas self CFI was not different between carrier groups at any time point. However, the combination of self+partner CFI differentiated between groups at month 24 and demonstrated the greatest separation between groups, although not statistically different from self and study partner alone.

Additional analyses did not reveal significant differences between CFI items that represented appraisal of cognitive abilities in everyday life (e.g., repeating questions) compared to report of functional abilities (e.g., change in ability to use appliances). Questions regarding cognitive difficulties or functional abilities performed equally as well at differentiating between progressors and non-progressors, or APOE ϵ 4 carriers and non-carriers, suggesting that both are valuable in assessing subjective report of everyday functioning.

When assessing the correlation between longitudinal change in CFI compared to longitudinal change on an objective cognitive composite, we found that both increased partner CFI and self CFI were associated with greater objective cognitive decline. When we examined the correlation between CFI and objective cognitive performance on the mADCS-PACC at each time point, we saw, at baseline and month 24, that self CFI demonstrated significantly stronger correlations with cognitive performance than partner CFI. Both self and partner report were significantly inferior to the combined report at months 12, 36 and 48, suggesting that the combination is particularly powerful in detecting subtle cognitive decline. Self-report was significantly superior to partner-report at baseline and month 24; while partner report was numerically superior (but did not reach statistical significance) at months 36 and 48. One interpretation is that while self-report is more reliably correlated

with cognition earlier in the process of decline, partner-report might become more useful later with development of anosognosia^{16,30}.

Reliability analyses revealed that internal consistency of items was at acceptable levels for both self and study partner report. Intraclass correlations revealed that in individuals who were CDR-G stable and APOE ϵ 4 non-carriers, self-report was more reliable after 12 months than for the study partner despite only a 5% turn over rate in study partners. This finding may be due to the fact that study partners are not in a caregiving role as participants were all independent in their everyday activities at baseline, and suggests that the combination of self and partner report may be more reliable in tracking change in individuals who begin at an asymptomatic stage.

Results suggest that the CFI can serve as a sensitive functional outcome measure in secondary prevention trials. Brief and easily administered on an annual basis in the current study, it contains questions that cover the full realm of early functional change. Importantly, the CFI can be self-administered at home, with forms mailed¹⁴, and with the potential to administer over the phone or transmit electronically; thus the CFI could be used in large, lengthy prevention trials with minimal in-person contact between participants and investigators. Historically, clinical trials involving patients at the stage of MCI or AD dementia have included more detailed functional measures such as the CDR¹⁷, which requires a clinician's judgment, or the Disability Assessment for Dementia (DAD)³¹, which is weighted heavily toward a study partner's report. In addition to the CFI, the ADCS has developed a more extensive functional measure, called the Activities of Daily Living-Prevention Instrument (ADL-PI)³². This questionnaire has also demonstrated sensitivity in detecting early functional change, however it takes longer to administer than the CFI and does not include questions about self-appraisal of memory function, a feature that may be important to capture early progression along the preclinical stages of AD.

Several potential limitations of this study deserve mention. Biomarker data was not available to confirm the etiology of cognitive decline in our sample. While items of the CFI were originally selected to target changes commonly experienced in functional impairment due to AD, it is possible that this instrument is sensitive to changes associated with other etiologies. Follow-up studies that explore relationships with putative AD biomarkers will be informative.

Additionally, there is some overlap in the types of questions asked in the CFI and the CDR, which may lead to enhancement of findings when looking at clinical progression outcomes. However, differences on CFI were found at baseline when all participants had a CDR = 0, suggesting that the CFI could be more sensitive than the CDR in a sample without clinical impairment. Furthermore, we found that the CFI tracked with objective cognitive decline providing support for its utility.

As the Alzheimer's field moves toward prevention at the preclinical stages of disease, many new hurdles emerge. In addition to identifying the appropriate target for disease modification, finding the right tools to detect the earliest evidence of clinical progression is challenging. Demonstrating long-term clinical benefit will be critical, since maintaining

independence in everyday functioning is what matters most to patients and their families. Subjective assessment of an individual's level of functioning over time, using the CFI, may prove to be a sensitive and efficient outcome for secondary prevention trials in preclinical AD.

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R. Amariglio: design of the study; interpretation of the data; preparation of the manuscript

M. Donohue: design of the study; analysis and interpretation of the data; preparation of the manuscript; review and approval of the manuscript

G. Marshall: design of the study; interpretation of the data; review and approval of the manuscript

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P. Aisen: design of the study; collection and interpretation of the data; review and approval of the manuscript

R. Sperling: design of the study; interpretation of the data; review and approval of the manuscript

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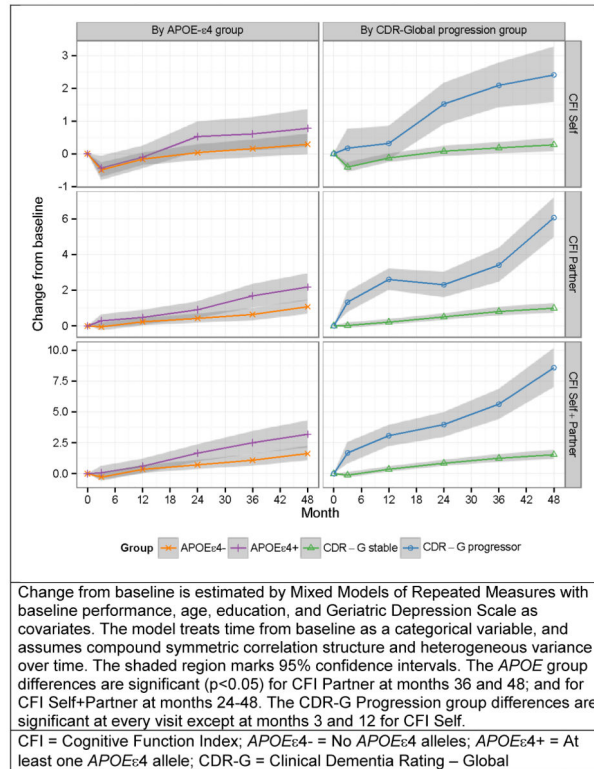


Figure 1. Comparison of CFI Self, Partner, and Self+Partner change from baseline by APOE ϵ 4 carrier status and by global Clinical Dementia Rating Scale (CDR) progression status
 Change from baseline is estimated by Mixed Models of Repeated Measures with baseline performance, age, education, and Geriatric Depression Scale as covariates. The model treats time from baseline as a categorical variable, and assumes compound symmetric correlation structure and heterogeneous variance over time. The shaded region marks 95% confidence intervals. The *APOE* group differences are significant ($p < 0.05$) for CFI Partner at months 36 and 48; and for CFI Self+Partner at months 24–48. The CDR-Global Progression group differences are significant at every visit except at months 3 and 12 for CFI Self.

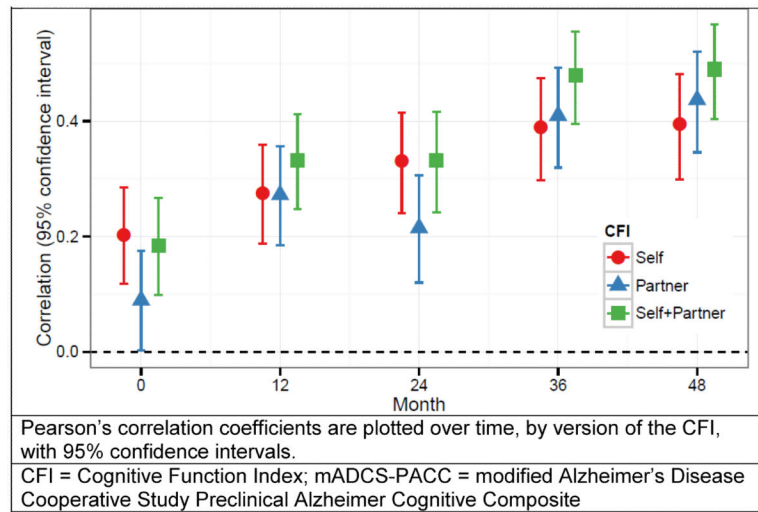


Figure 2. Correlation between CFI (Self, Partner, and Self+Partner) and mADCS-PACC over time

Pearson's correlation coefficients are plotted over time, by version of the CFI, with 95% confidence intervals. Signs for the correlations are inverted.

Table 1

Cognitive Function Instrument: Self report

Answer all questions with reference to one year ago.

1.	Compared to one year ago, do you feel that your memory has declined substantially?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
2.	Do others tell you that you tend to repeat questions over and over?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
3.	Have you been misplacing things more often?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
4.	Do you find that lately you are relying more on written reminders (e.g., shopping lists, calendars)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
5.	Do you need more help from others to remember appointments, family occasions or holidays?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
6.	Do you have more trouble recalling names, finding the right word, or completing sentences?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
7.	Do you have more trouble driving (e.g., do you drive more slowly, have more trouble at night, tend to get lost, have accidents)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
8.	Compared to one year ago, do you have more difficulty managing money (e.g., paying bills, calculating change, completing tax forms)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
9.	Are you less involved in social activities?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
10.	Has your work performance (paid or volunteer) declined significantly compared to one year ago?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
11.	Do you have more trouble following the news, or the plots of books, movies or TV shows, compared to one year ago?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
12.	Are there any activities (e.g., hobbies, such as card games, crafts) that are substantially more difficult for you now compared to one year ago?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
13.	Are you more likely to become disoriented, or get lost, for example when traveling to another city?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
14.	Do you have more difficulty using household appliances (such as the washing machine, VCR or computer)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe

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Table 2**Cognitive Function Instrument: Study partner report****Answer all questions with reference to one year ago.**

1.	Do you feel the subject has had a significant decline in memory compared to one year ago?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
2.	Does the subject tend to ask the same question over and over?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
3.	Has the subject been misplacing things more often?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
4.	Does it seem to you that lately the subject is relying more on written reminders (e.g., shopping lists, calendars)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
5.	Does the subject need more help from others to remember appointments, family occasions or holidays?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
6.	Does the subject have more trouble recalling names, finding the right word, or completing sentences?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
7.	Is the subject having more trouble driving (e.g., do you drive more slowly, have more trouble at night, tend to get lost, have accidents)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
8.	Compared to one year ago, is the subject having more difficulty managing money (e.g., paying bills, calculating change, completing tax forms)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
9.	Is the subject less interested in social activities?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
10.	Do you believe, based on your own observations or comments from the subject's co-workers, that the subject's work performance (paid or volunteer) has declined significantly, compared to one year ago?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
11.	Does the subject have more trouble following the news, or the plots of books, movies or TV shows, compared to one year ago?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
12.	Are there any activities (e.g., hobbies, such as card games, crafts) that are substantially more difficult for the subject now compared to one year ago?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
13.	Is the subject more likely to become disoriented, or get lost, for example when traveling to another city?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe
14.	Does the subject have more difficulty using household appliances (such as the washing machine, VCR or computer)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Maybe

Table 3

Descriptive statistics by CDR-G Progression group.

	N	CDR-G Stable (N=441)	CDR-G Progressors (N=27)	Combined (N=468)	P-value
<i>APOE</i> ε4+	286	60 (22%)	4 (24%)	64 (22%)	0.906
Female	468	260 (59%)	19 (70%)	279 (60%)	0.241
Age (years)	468	79.4 (3.6)	80.5 (3.8)	79.4 (3.6)	0.131
Education (years)	468	15.1 (2.9)	14.1 (3.5)	15.1 (3.0)	0.152
Ethnicity					0.125
American Indian or Alaskan Native		2 (0%)	0 (0%)	2 (0%)	
Asian or Pacific Islander		8 (2%)	2 (7%)	10 (2%)	
Black, not of Hispanic Origin		54 (12%)	5 (19%)	59 (13%)	
Hispanic		28 (6%)	4 (15%)	32 (7%)	
White, not Hispanic Origin		348 (79%)	16 (59%)	364 (78%)	
Other or unknown		1 (0%)	0 (0%)	0 (0%)	
FCSRT Free	467	29.1 (5.5)	25.4 (6.0)	28.8 (5.6)	0.004
FCSRT Total	467	47.9 (0.4)	47.6 (0.8)	47.8 (0.5)	0.074
CDR-SB : 0.5	468	77 (17%)	8 (30%)	85 (18%)	0.111
3MSE	468	95.9 (3.3)	92.0 (4.1)	95.7 (3.5)	<0.001
GDS	468	1.2 (1.8)	1.8 (1.6)	1.2 (1.8)	0.066
CFI Self	468	1.9 (1.9)	3.4 (2.4)	2.0 (1.9)	0.003
CFI Partner	468	0.9 (1.4)	2.1 (2.5)	1.0 (1.5)	0.027
CFI Self+Partner	468	2.8 (2.7)	5.5 (4.0)	3.0 (2.8)	0.002

Data include all subjects with at least one follow-up CFI observation. For categorical data, we provide counts, percentages, and Pearson's Chi-square Test. For continuous data, we provide means, standard deviations, and two-sample t-test. P-values less than 0.05 are in bold.

*APOE*ε4+ = At least one *APOE*ε4 allele; FCSRT = Free and Cued Selective Reminding Test; CDR-SB = Clinical Dementia Rating – Sum of Boxes; 3MSE = Modified Mini-Mental State Exam; GDS = Geriatric Depression Scale; CFI = Cognitive Function Instrument

Table 4Descriptive statistics by *APOE*ε4 group.

	N	<i>APOE</i> ε4- (N=222)	<i>APOE</i> ε4+ (N=64)	Combined (N=286)	P-value
CDR-G					
Progressors	286	13 (6%)	4 (6%)	17 (6%)	0.906
Female	286	127 (57%)	39 (61%)	166 (58%)	0.594
Age (years)	286	79.6 (3.6)	78.3 (3.0)	79.3 (3.5)	0.004
Education (years)	286	15.1 (3.2)	15.2 (2.9)	15.1 (3.1)	0.715
Ethnicity	286				0.324
American Indian or Alaskan Native		1 (0%)	0 (0%)	1 (0%)	
Asian or Pacific Islander		6 (3%)	1 (2%)	7 (2%)	
Black, not of Hispanic Origin		21 (9%)	12 (19%)	33 (12%)	
Hispanic		17 (8%)	5 (8%)	22 (8%)	
White, not Hispanic Origin		177 (80%)	46 (72%)	223 (78%)	
Other or unknown		0 (0%)	0 (0%)	0 (0%)	
FCSRT Free	285	28.7 (5.9)	29.9 (5.1)	29.0 (5.8)	0.118
FCSRT Total	285	47.8 (0.5)	47.9 (0.4)	47.9 (0.5)	0.103
CDR-SB : 0.5	286	47 (21%)	11 (17%)	58 (20%)	0.485
3MSE	286	95.7 (3.8)	96.1 (3.0)	95.8 (3.6)	0.411
GDS	286	1.6 (2.1)	0.8 (1.5)	1.4 (2.0)	0.003
CFI Self	286	2.0 (2.1)	2.2 (1.7)	2.1 (2.0)	0.402
CFI Partner	286	1.0 (1.5)	1.1 (1.5)	1.0 (1.5)	0.707
CFI Self+Partner	286	3.0 (3.0)	3.3 (2.6)	3.1 (3.0)	0.450

Data include all subjects with known *APOE*ε4 status and at least one follow-up CFI observation. For categorical data, we provide counts, percentages, and Pearson's Chi-square Test. For continuous data, we provide means, standard deviations, and two-sample t-test. P-values less than 0.05 are in bold.

*APOE*ε4- = No *APOE*ε4 alleles; *APOE*ε4+ = At least one *APOE*ε4 allele; FCSRT = Free and Cued Selective Reminding Test; CDR-SB = Clinical Dementia Rating – Sum of Boxes; 3MSE = Modified Mini-Mental State Exam; GDS = Geriatric Depression Scale; CFI = Cognitive Function Instrument