Received: 13 February 2020 | Accepted: 6 March 2020 | Published online: 17 April 2020

DOI: 10.1002/trc2.12020

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

The Cognitive-Functional Composite is sensitive to clinical progression in early dementia: Longitudinal findings from the Catch-Cog study cohort

Roos J. Jutten[1] | **John E. Harrison**[1,2,3] | **A.J. Brunner**[1] | **R. Vreeswijk**[4] | **R.A.J. van Deelen**[4] | **Frank Jan de Jong**[5] | **Esther M. Opmeer**[6,7] | **Craig W. Ritchie**[8] | **André Aleman**[6] | **Philip Scheltens**[1] | **Sietske A.M. Sikkes**[1,9]

[1]Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam, Amsterdam UMC, the Netherlands

[2]Metis Cognition Ltd, Wiltshire, UK

[3]Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[4]Department of Geriatrics, Spaarne Gasthuis, Haarlem, the Netherlands

[5]Department of Neurology, Erasmus Medical Center, Rotterdam, the Netherlands

[6]Department of Neurosciences, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

[7]Department of Health and Social Work, University of Applied Sciences Windesheim, Zwolle, the Netherlands

[8]Centre for Dementia Prevention, University of Edinburgh, Edinburgh, UK

[9]Department of Clinical, Neuro- & Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

Correspondence
Roos J. Jutten, Alzheimer Center Amsterdam & Department of Neurology, Amsterdam UMC, location VUmc, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail: r.jutten@amsterdamumc.nl

Abstract

Introduction: In an attempt to capture clinically meaningful cognitive decline in early dementia, we developed the Cognitive-Functional Composite (CFC). We investigated the CFC's sensitivity to decline in comparison to traditional clinical endpoints.

Methods: This longitudinal construct validation study included 148 participants with subjective cognitive decline, mild cognitive impairment, or mild dementia. The CFC and traditional tests were administered at baseline, 3, 6, and 12 months. Sensitivity to change was investigated using linear mixed models and r^2 effect sizes.

Results: CFC scores declined over time ($\beta = -.16$, $P < .001$), with steepest decline observed in mild Alzheimer's dementia ($\beta = -.25$, $P < .001$). The CFC showed medium-to-large effect sizes at succeeding follow-up points ($r^2 = .08$-$.42$), exhibiting greater change than the Clinical Dementia Rating scale ($r^2 = .02$-$.12$). Moreover, change on the CFC was significantly associated with informant reports of cognitive decline ($\beta = .38$, $P < .001$).

Discussion: By showing sensitivity to decline, the CFC could enhance the monitoring of disease progression in dementia research and clinical practice.

KEYWORDS

Alzheimer's disease, cognition, dementia, instrumental activities of daily living, mild cognitive impairment, outcome measures

1 | INTRODUCTION

As Alzheimer's disease (AD) clinical trials are increasingly targeting earlier disease stages,[1] it is of crucial importance that outcome measures of efficacy are adapted to these novel target populations.[2] Common guidance for the selection of acceptable endpoints for use in clinical trials, as well as observational studies in general, holds that selected measures must exhibit acceptable levels of reliability, validity, and sensitivity to change in the target population.[3] Furthermore, these tests must be free of range restrictions, and ideally be brief so as to

avoid fatigue or ennui effects, as well as appropriate for cross-cultural use.[4]

While commonly employed cognitive and functional measures selected for AD clinical trials have tended to demonstrate acceptable levels of reliability, they have fared less well with regard to their validity and sensitivity to change over time. For example, floor- and ceiling effects in scoring have been observed on parts of the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog)[5] when administered in mild cognitive impairment (MCI) and mild dementia, limiting its sensitivity to change over time.[6–8] Moreover, it has been questioned to what extent change on the ADAS-Cog, as well as other cognitive tests, reflects clinically meaningful changes.[9,10] Challenges regarding validity have also been encountered when measuring functional skills in individuals with MCI or mild dementia, as most existing measures do not feature complex instrument activities of daily living (IADL), which are most prone to early cognitive decline, or items indexing contemporary everyday activities such as electronic banking and self-organized travel arrangements.[11–13]

In the past few years the AD research community has sought to identify novel methods that yield a single, unitary, and valid measure of efficacy, including elements of both cognitive and functional performance.[14] This has also been encouraged by the Food and Drug Administration and European Medicine Agency in their guidelines for AD drug trials.[15,16] A measure that has found favor as a combined measure is the Clinical Dementia Rating (CDR) scale,[17] particularly its sum of boxes (CDR-SB) scoring.[18,19] However, a challenge when employing the CDR has been the modest rate of change over time when the scale is employed in those living with the very earliest manifestations of the disease.[20] Further challenges have been that the CDR-SB scoring requires extensive training, is subject to variability among ethnicities and languages, and showed only modest inter-rater reliability.[21]

To fulfil the need for a reliable, valid, sensitive, and clinically meaningful measure of cognitive decline in early clinical stages of AD, the Cognitive-Functional Composite (CFC) has been designed.[22] The CFC yields a brief measure (20-25 minutes) of both cognition and function, comprising seven existing cognitive tests focusing on memory and executive functioning[23] and the Amsterdam IADL Questionnaire (A-IADL-Q).[24–26] We have previously demonstrated good psychometric qualities of the CFC, such as good test-retest reliability, feasibility of use, validity, and quality for the target population.[27,28] The current study aimed to investigate the sensitivity to change of the CFC in individuals with MCI and mild AD dementia over a period of 1 year, as well as performance of the same individuals over the same period on the CDR-SB,[18] ADAS-Cog,[5] and Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale.[29] Second, we explored whether the CFC could be of use to capture change in individuals with subjective cognitive decline (SCD), and Dementia with Lewy Bodies (DLB) which is the second most common cause of dementia. We also sought to determine the clinical meaningfulness of decline detected by the CFC, by associating change on the CFC with informant reports of decline in everyday abilities.

HIGHLIGHTS

- The Cognitive-Functional Composite (CFC) is sensitive to clinical progression in mild Alzheimer's dementia
- The CFC exhibits greater sensitivity to change than traditional clinical endpoints
- Change on the CFC is related to informant-reports of cognitive decline

RESEARCH IN CONTEXT

- Systematic review: The authors reviewed PubMed for literature on existing measures to assess disease progression in Alzheimer's disease (AD). There is still an urgent need for reliable, valid, and sensitive outcome measures that could improve the monitoring of progression in early clinical stages of AD.
- Interpretation: Our findings imply that the Cognitive-Functional Composite (CFC) is sensitive to clinical meaningful cognitive decline in early AD, and provides a superior alternative approach to the use of traditional clinical endpoints. The CFC could thereby improve the monitoring of disease progression, and enhance the evaluation of disease-modifying therapies targeting early clinical stages of AD.
- Future directions: This manuscript has important implications for AD research and clinical practice, as it provides guidance for the selection of outcome measures to evaluate disease progression in early AD. It also highlights the importance of the inclusion of a sensitive functional measure to capture clinically meaningful changes.

2 | METHODS

2.1 | Study design and participants

In this longitudinal analysis, we employed data from the Capturing Change in Cognition (Catch-Cog) study: an international, observational cohort-study with baseline, 3-, 6-, and 12-month assessments.[22] Participants (N = 173) and their study partners were included at the (1) Alzheimer Center Amsterdam, Amsterdam UMC, the Netherlands (AC, n = 102); (2) Alzheimer Center of the Erasmus Medical Center, Rotterdam, the Netherlands (EMC, n = 14); (3) University Medical Center Groningen, the Netherlands (UMCG, n = 39); or (4) the Centre for Dementia Prevention, Edinburgh, Scotland (EDI, n = 18). Before inclusion, participants had undergone a standard diagnostic work-up in their memory clinic, including at least medical history, and neurological

and neuropsychological examination. A subset of participants included in the AC had AD biomarkers available as measured by a cerebrospinal fluid lumbar puncture. Amyloid positivity was based on amyloid beta (Aβ) 1-42 values (cut-off ≤813 pg./mL).[30] In all centers, clinical diagnoses were made in a multidisciplinary consensus meeting including at least a neurologist, psychiatrist, and neuropsychologist. Additionally in the UMCG, participants were recruited via advertisements in local newspapers. Individuals willing to participate were screened by a neuropsychologist and neurologist to investigate whether they were eligible for the current study.

Participants were included in the Catch-Cog study when they met the research criteria for SCD,[31] or the clinical criteria for MCI,[32] possible or probable AD dementia,[33] or possible or probable DLB dementia.[22] Other inclusion criteria were: (1) Mini-Mental State Examination (MMSE) score ≥ 18,[34] (2) age ≥50, and (3) availability of a study partner who was able to understand the study information and willing to participate. Exclusion criteria were (1) presence of another neurological disorder than AD or DLB, (2) presence of a major psychiatric disorder such as severe personality disorder or depression (Geriatric Depression Scale score ≥6),[35] (3) current abuse of alcohol or drugs, (4) simultaneously participating in a clinical trial.

Data were collected between October 2016 and December 2018. The Medical-Ethical Committee of the VU University Medical Center approved the study for all Dutch centers. The South East Scotland Research Ethic Committee approved the study for the Scottish site. All participants and their study partners provided written and oral informed consent.

2.2 | The cognitive-functional composite

Full details on the selected CFC measures have been reported elsewhere.[22,28] Briefly, the cognitive test battery of the CFC includes the three ADAS-Cog memory subscales Word Recognition (score range 0-12), Word Recall (score range 0-10), and Orientation (score range 0-8);[5] the Controlled Oral Word Association Test (COWAT; letters D-A-T in Dutch and F-A-S in English, 60 seconds);[36]; Category Fluency Test (CFT; animals, 60 seconds);[36] Digit Span Backward (DSB, score range 0-14);[37] and Digit Symbol Substitution Test (DSST, 90 seconds).[38] The functional component comprises the short version of the A-IADL-Q, a computerized, informant-based questionnaire consisting of 30 items covering a broad range of complex IADL.[26] Example items include cooking, managing finances, and modern activities such as applying everyday technology.[24,25] For each item, difficulty in performance is rated on a five-point Likert scale (ranging from "no difficulty in performing this task" to "no longer able to perform this task"). Scoring is performed using item response theory (IRT), resulting in a latent trait score (z-score) reflecting one's IADL functioning.[25]

To create CFC scores, the directionality of the three ADAS-Cog subtest scores is reversed so that higher scores reflected better performance. Subsequently, all cognitive subtest scores are z-transformed using baseline total group means and standard deviations (SD). The cognitive composite is computed as a weighted z-score of all seven cognitive subtests if at least five tests are available, with all available tests being equally weighted. This approach was chosen as it was previously shown to provide a reliable scoring method for this cognitive composite.[23] The functional component score is the A-IADL-Q latent trait z-score.[25] The overall CFC score is computed as an equally weighted z-score of the cognitive composite and A-IADL-Q scores, with higher scores indicating better performance. We previously showed that this scoring method results in a valid CFC score that is in line with clinical manifestations of different diagnostic groups and not affected by range restrictions in scoring.[28]

2.3 | Reference measures

As previously reported,[22] commonly employed AD clinical trial measures were administered, including the ADAS-Cog-13 (total score range 0-85),[5] ADCS-ADL (total score range 0-78),[29] and the CDR-SB (total score range 0-18).[18] The study partner version of the Cognitive Function Instrument (CFI) was administered as anchor measure of clinical decline. The CFI includes 14 items that enquire about decline in day-to-day cognitive and functional abilities, compared with 1 year ago (score range 0-14, higher scores reflecting more decline).[39] It was originally developed to track decline in preclinical stages of AD, but the study partner version was also found to be useful to assess decline individuals with subtle cognitive impairment.[40]

2.4 | Procedures

Study visits took place at the hospital or the participant's home, depending on the participant's preference. At baseline, a number of 74 participants (43%) chose testing at home, and we aimed to keep assessment location constant within participants over time. CFC and traditional tests were administered at each follow-up time-point, so that head-to-head comparisons could be made between all measures. A trained rater administered the cognitive tests according to standardized instructions, starting with the MMSE and followed by the cognitive part of the CFC and the remaining ADAS-Cog-13 tests. In the meantime, the study partner completed the A-IADL-Q and CFI independently on an iPad. Finally, the rater completed the ADCS-ADL and CDR interview with the study partner. The content of each study visit was similar, except that existing, validated parallel versions were used for Word Recognition and Word Recall, specifically List 1, 2, 4, and 5.[5]

A shortened protocol was used in the SCD and DLB participants, as it was not our purpose to compare the CFC to traditional tests that were not designed for these groups. Therefore, SCD and DLB participants who only underwent the MMSE and cognitive battery of the CFC while their study partner completed the functional component of the CFC.

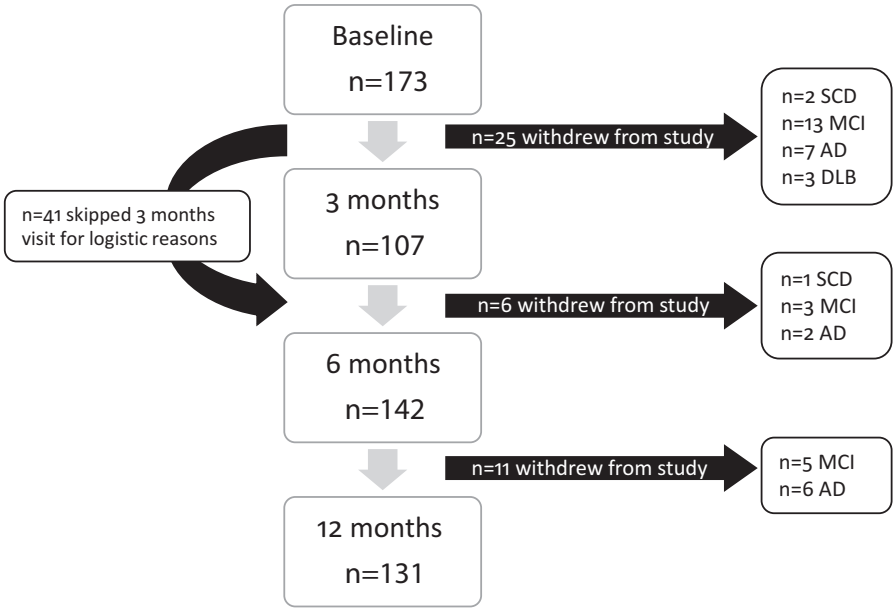

FIGURE 1 Flow diagram providing an overview of the sample size at each time point

2.5 | Statistical analyses

Statistical analyses were performed using R version 3.5.3 (R Core Team, 2016). Statistical significance was set at $P < .05$. Baseline differences between groups were investigated using χ^2 or Fisher's exact tests when appropriate, one-way analyses of variance followed by Hochberg's post-hoc tests, and independent t-tests for measures only available for the MCI and AD groups.

Sensitivity to change over time of the CFC was investigated using linear mixed models (LMM) with random effects for subject (intercept and slope) and center (intercept). All subjects with at least one follow-up assessment available were included in these models. We ran separate models with CFC, CC, and A-IADL-Q scores as dependent variable and time as independent variable (measured on a continuous level). Second, we repeated these models while adjusting for age, sex, education, diagnosis, and the interaction between time and diagnosis. If a significant effect of the time*diagnosis term was found, analyses were repeated stratified per diagnosis. In our sample of MCI and mild AD subjects, separate LMM models adjusting for age, sex, and education were also performed with the ADAS-Cog, ADCS-ADL, and CDR-SB as dependent variables and time as independent variable. To control for the different scaling properties and to allow for proper head-to-head comparisons, the ADAS-Cog and CDR-SB total scores were reversed so that higher scores reflected better performance, and subsequently z-transformed using total group baseline means and SDs of the combined sample of MCI and AD subjects. ADCS-ADL scores were standardized using the same approach.

To compare the sensitivity of the CFC and traditional tests at different time points, r^2 effect sizes of change were calculated from baseline to each follow-up point (3, 6, and 12 months). Effect sizes were evaluated based on predefined cut-offs, with .01 defined as small, .09 as medium, and .25 as large effects.

To assess the clinical meaningfulness of observed change on the CFC and traditional tests, separate linear regression analyses were performed for each test in our combined sample of MCI and AD participants. The CFI score obtained at 12 months follow-up was used as dependent variable, and annual CFC change scores were inserted as independent variable while adjusting for age, sex, and education.

Sensitivity analyses. To explore whether change on the CFC was specific to AD-related decline as opposed to change over time in general, we repeated the LMM analyses for the CFC in a subset of amyloid positive participants. Second, differences among study cohorts were explored by repeating the LMM analyses for the CFC and traditional test scores separately for each study center.

3 | RESULTS

3.1 | Study sample characteristics

A total of 173 subjects were included (age = 71.3 ± 8.5, 42% female, n = 14 SCD; n = 75 MCI; n = 72 AD; n = 12 DLB) in the Catch-Cog study, of which n = 131 (76%) subjects completed the 12-month assessment (Figure 1). Subjects that withdrew during the study (n = 42; age = 72.7 ± 8.4; 39% female; n = 3 SCD, n = 21 MCI, n = 15 AD, n = 3 DLB) did not differ regarding age, sex, education, and clinical severity at baseline from those who completed the study.

A number of n = 148 participants (86%) had at least one follow-up available and were included in the current study. Table 1 presents the baseline characteristics for this sample as well as separately for each clinical group, revealing that groups did not differ regarding age, sex, and education. Mean baseline CFC scores differed among groups (SCD = .91 ± .61; MCI = .28 ± .50; AD = −.34 ± .65; DLB = −.51 ± .75, $F = 25.84$, $P < .001$), with post-hoc comparisons showing a significantly

TABLE 1 Demographic and clinical characteristics at baseline, for the total included sample (N = 148) and separately for each clinical group

		Total (N = 148)						
			SCD (n = 12)	MCI (n = 62)	AD (n = 65)	DLB (n = 9)	*P* –Value	Post-hoc comparisons[a]
Demographics	Age	71.3 (8.4)	68.3 (7.0)	73.6 (8.1)	71.2 (9.0)	69.3 (6.4)	.106	n.a.
	Female (%)	66 (45%)	8 (66.7%)	23 (37.1%)	33 (50.8%)	2 (22.2%)	.087	n.a.
	Education	13.8 (3.9)	15.2 (5.1)	14.0 (3.8)	13.3 (3.9)	14.4 (3.1)	.40	n.a.
	MMSE	25.7 (3.2)	29.2 (1.3)	26.9 (2.3)	24.2 (3.4)	24.0 (3.0)	<.001	SCD > AD; SCD > DLB; MCI > AD; MCI > DLB
CFC measures	CC	.00 (.66)	.84 (.53)	.20 (.51)	–.27 (.61)	–.49 (.70)	<.001	SCD > MCI > AD; SCD > DLB; MCI > DLB
	A-IADL-Q	.00 (.92)	.99 (.80)	.37 (.66)	–.42 (.89)	–.66 (.60)	<.001	SCD > AD; MCI > AD; SCD > DLB; MCI > DLB
	CFC score	.00 (.72)	.91 (.61)	.28 (.50)	–.34 (.65)	–.51 (.75)	<.001	SCD > MCI > AD; SCD > DLB; MCI > DLB
Traditional tests	ADAS-Cog	24.9 (7.6)	n.a.	22.0 (6.8)	28.2 (7.0)	n.a.	.106	n.a.
	ADCS-ADL	66.4 (8.5)	n.a.	67.8 (7.0)	64.3 (9.4)	n.a.	<.001	n.a.
	CDR-SB	3.8 (2.3)	n.a.	2.8 (1.9)	4.9 (2.0)	n.a.	<.001	n.a.

ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperation Study–Activity of Daily Living; A-IADL-Q, Amsterdam IADL Questionnaire; CC, Cognitive Composite; CDR-SB, Clinical Dementia Rating Sum of Boxes; CFC, Cognitive-Functional Composite; MMSE, Mini-Mental State Examination; n.a., not applicable.
[a]Based on Hochberg's post-hoc tests.

higher score for SCD compared to MCI, as well as for MCI compared to AD and DLB dementia (Table 1). A similar pattern was observed on the traditional tests, except that no significant differences were found in the ADAS-Cog scores between the MCI and AD group (Table 1).

3.2 | Sensitivity to change over time of the CFC in the total sample

Overall, CFC scores declined over time ($\beta = -.15$, 95%CI [–.10 to –20], $P < .001$), and we found that this association was independent of age, sex, education, and diagnosis at baseline (corrected $\beta = -.16$, 95% confidence interval [CI; –.10 to –22], $P < .001$). However, a significant time*diagnosis interaction was found ($\beta = -.18$, $P < .001$), and therefore analyses were repeated stratified per clinical group. The results are presented in Figure 2, showing that decline on the CFC was only significant in the mild AD group ($\beta = -.25$, 95% CI [–.33 to –18], $P < .001$). A steeper decline was observed in DLB; however, this effect did not reach statistical significance ($\beta = -.47$, $P = .096$).

3.3 | Comparison between the CFC and traditional measures in MCI and mild AD

Figure 3 displays change on the CFC components and the traditional tests adjusted for age, sex, and education, separately for the MCI and AD groups. Tables S1 and S2 in supporting information show the corresponding regression coefficients. We found a significant decline in A-IADL-Q score in MCI ($\beta = -.15$, $P = .03$), whereas none of the traditional measures declined in MCI (Table S2).

All CFC scores and traditional tests scores declined over 1 year in AD (Figure 3, Tables S1 and S2). Effect sizes of change at all follow-up time-points on the CFC and traditional tests are presented in Figure 4. The CFC showed a small-to-medium effect after 3 months ($r^2 = .08$), a medium effect after 6 months ($r^2 = .12$), and a large effect ($r^2 = .42$) after 12 months, thereby exhibiting greater change than the CDR-SB all follow-up time points (r^2 ranging from .02–.12).

3.4 | Association with an anchor measure of clinical progression in MCI and mild AD

Figure 5 shows the associations between the CFI score obtained at 12-month follow-up and annual decline on the CFC, CDR-SB, ADCS-ADL, and ADAS-Cog in our combined sample of MCI and mild AD subjects (n = 127). Linear regression analyses showed that decline on the CFC was significantly associated with decline in cognitive functioning as reported on the CFI ($\beta = .38$, 95% CI [.20-.56], $P < .001$). Among the traditional tests, only decline on the ADCS-ADL was significantly related to the CFI score at 12-month follow-up ($\beta = .26$, 95% CI [.07-.45], $P = .009$).

3.5 | Sensitivity analyses

Sensitivity analyses in amyloid positive participants (n = 37; n = 1 SCD, n = 7 MCI, and n = 29 dementia) showed that CFC scores declined over time ($\beta = -.21$, 95% CI [–.11 to –.33], $P < .001$), with decline observed on both the cognitive and functional component (CC score: $\beta = -.16$,

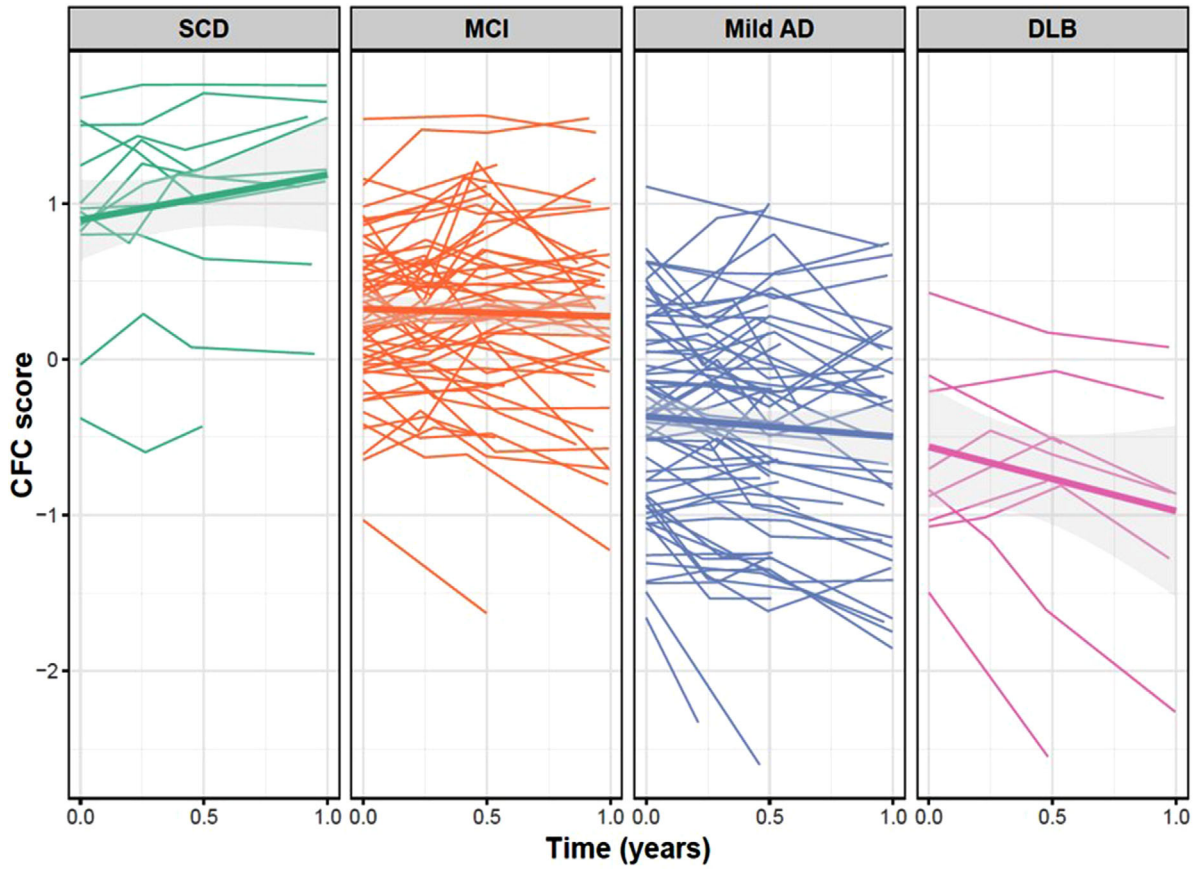

FIGURE 2 Annual change on the Cognitive-Functional Composite, separately for each clinical group

95% CI [−.29 to −.04], $P < .001$; A-IADL-Q score: $\beta = -.30$, 95% CI [−.47 to −.14], $P < .001$).

Table S3 in supporting information shows the regression coefficients obtained from LMM stratified per study center. These results show that CFC scores declined over time in the AC, EMC, and EDI cohorts, whereas a slight improvement on the CFC ($\beta = .11$, $P = .049$) was observed in the UMCG cohort that seemed driven by the cognitive component ($\beta = .19$, $P < .001$). This was in agreement with results on the traditional tests, as an improvement on the ADAS-Cog was also observed in UMCG cohort ($\beta = .39$, $P = .003$).

4 | DISCUSSION

In this longitudinal construct validation study, we demonstrated that the CFC is sensitive to clinical progression. In MCI, the functional component of the CFC detected decline over 1 year, whereas the CDR-SB, ADAS-Cog, and ADCS-ADL failed to do so. In mild AD dementia, the CFC captured decline over 1 year, and effect sizes of change suggested greater sensitivity than the traditional measures within 1 year (ie, after 3 and 6 months). Furthermore, annual change on the CFC was associated with informant reports of cognitive decline.

Worldwide, researchers have addressed the need for outcome measures that are capable of detecting clinically meaningful change in early AD.[14,41] Regulatory agencies have further elevated this importance, as their guidelines state that evidence of clinically meaningful change is required for approval of novel therapeutic interventions.[15,16] Previous studies on the CFC already demonstrated its good test-retest reliability, feasibility of use, construct validity, and suitability for the target population (ie, MCI and mild dementia due to AD).[26–28] Additionally, separate studies on the cognitive and functional component previously showed their sensitivity to change over time.[23,42] By performing an independent longitudinal validation of the CFC, the current study provides further evidence the CFC meets the requirements for a clinically meaningful outcome measure in early clinical stages of AD.

The current study results bear crucial implications for AD clinical trials, because the CDR-SB is currently still widely applied as primary clinical endpoint of efficacy. Previous studies have already indicated limitations of the CDR-SB as outcome measure of change, relating to its poor inter-rater reliability,[21] and ceiling effects in scoring in MCI and mild dementia.[28] Our current study findings suggest that the CFC could offer advantages over the use of the CDR-SB as measure to evaluate clinical progression, by providing a concise and more objective measure of clinically meaningful cognitive decline.

With regard to other recently developed composites for disease progression in AD, it is important to consider that CDR performance is also a key component of the recently employed Alzheimer's Disease Composite Score (ADCOMS).[43] However, this measure has

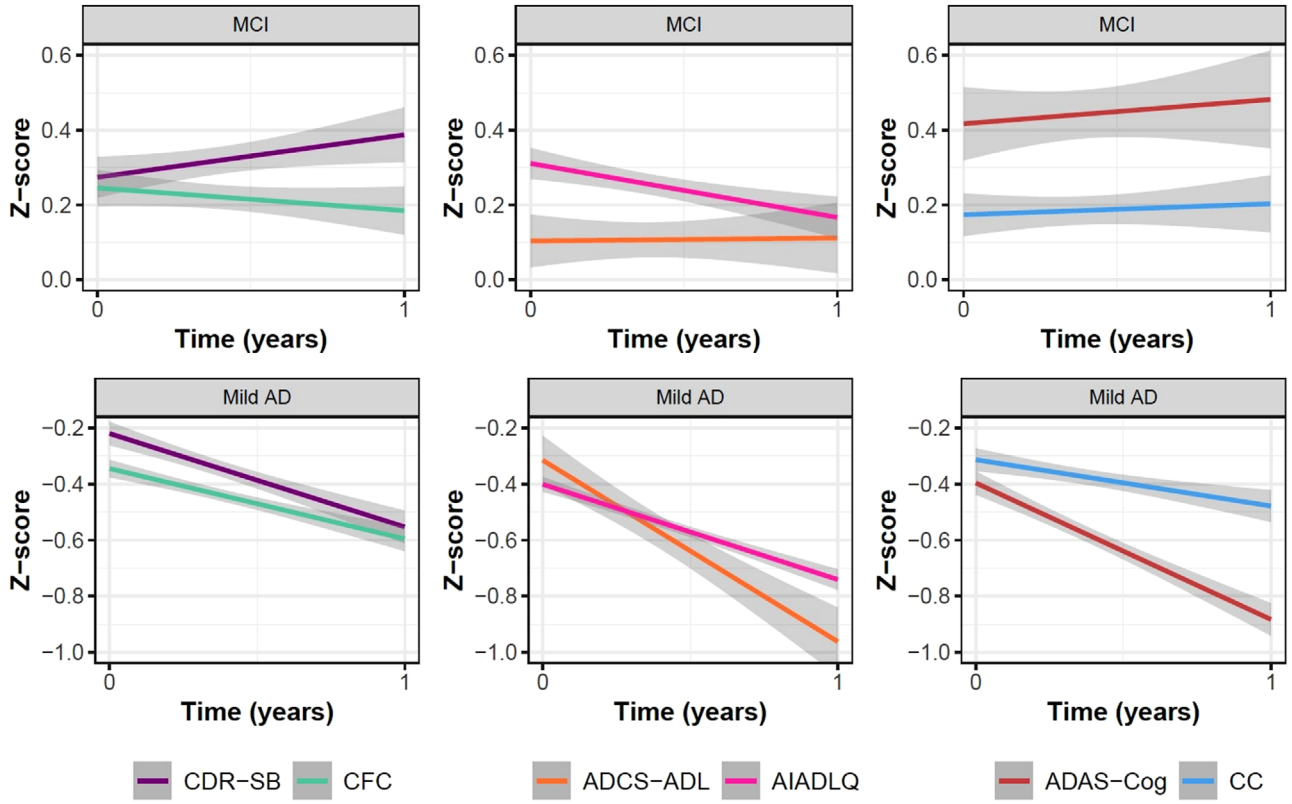

FIGURE 3 Annual decline (corrected for age, sex, and education) on the Cognitive-Functional Composite measures versus traditional tests, separately in mild cognitive impairment and Alzheimer's disease

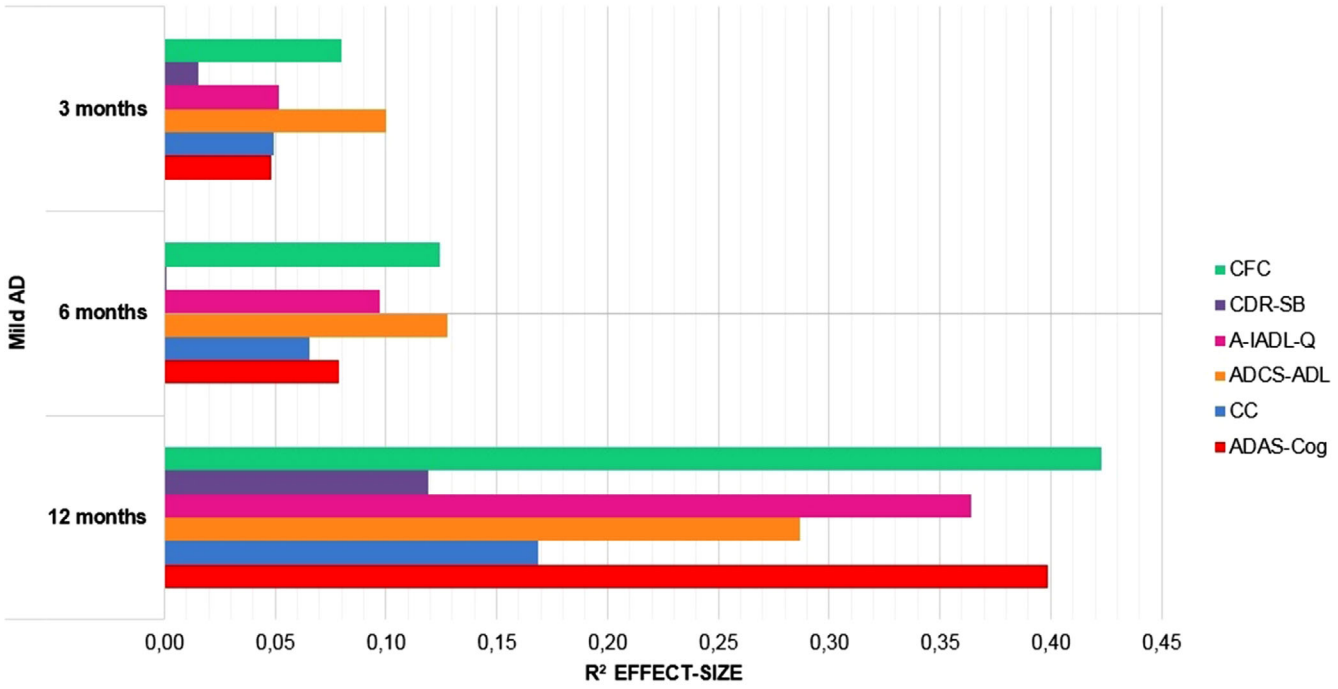

FIGURE 4 Effect sizes of the Cognitive-Functional Composite measures and traditional tests at all follow-up time points

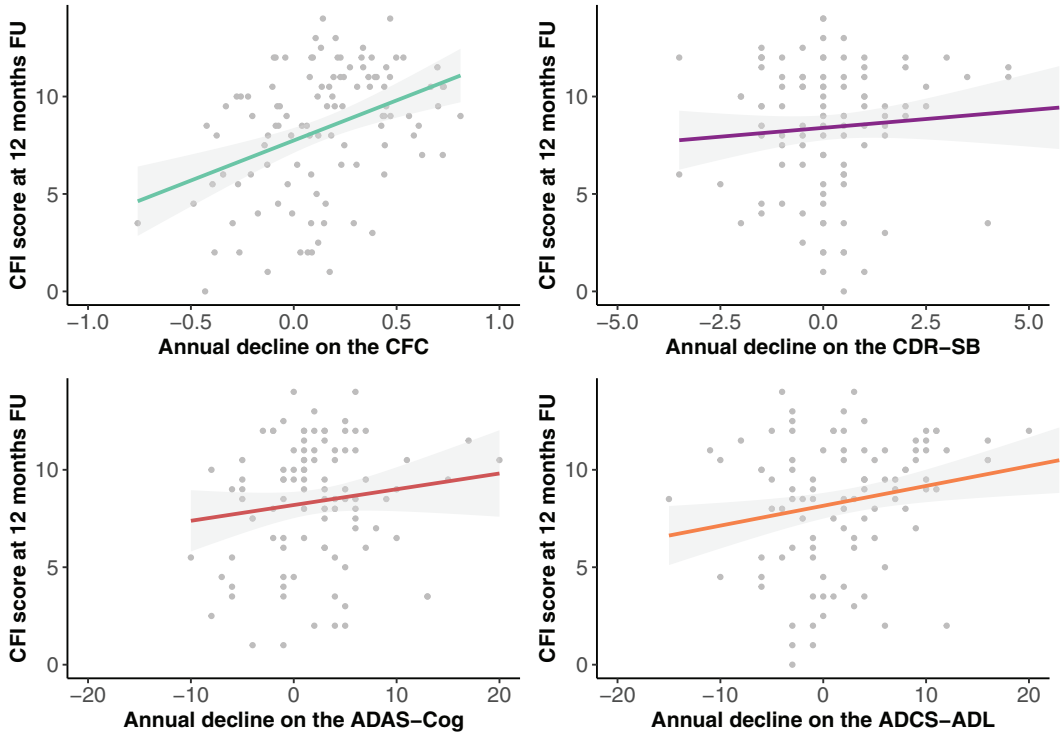

FIGURE 5 Associations between Cognitive Function Instrument score at 12-month follow-up and annual decline in Cognitive-Functional Composite, Clinical Dementia Rating Sum of Boxes, Alzheimer's Disease Assessment Scale–Cognitive subscale, and Alzheimer's Disease Cooperation Study–Activity of Daily Living scores. N.B. All *x*-axis scales represent annual change scores with positive scores reflecting decline compared to baseline

been statistically derived, and its clinical meaningfulness has not been demonstrated yet. The same holds true for proposed cognitive composites,[44,45] that have been developed to detect change in preclinical AD. Because those composites do not include a functional component, they are probably less useful to track clinical progression in MCI and mild dementia stages, in which evolving functional impairment plays a key role.[26]

Comparisons between the CFC subcomponents and traditional cognitive and functional tests revealed that the A-IADL-Q already captured decline in MCI, whereas the ADCS-ADL did not. This implies that the A-IADL-Q is more focused on those activities that are prone to decline in earlier clinical stages.[26] Interestingly, comparable sensitivity to change was observed for the CC and ADAS-Cog. This could be explained by the fact that those measures partially overlap, and that changes on the ADAS-Cog score seemed driven by the three memory subtests that are also included in the CC. This is line with previous studies showing that the ADAS-Cog subtests that focus on praxis, language, and confrontation were found to be insensitive to change in MCI and mild dementia.[7] As such, the CC can be considered a more concise measure, as it has a shorter administration time and focuses on the cognitive domains that are vulnerable to early cognitive decline.[46]

Our finding that the functional component of the CFC detected clinical progression in individuals with MCI, whereas the cognitive component did not, may seem counterintuitive as the assumed clinical trajectory of AD entails that cognitive impairment induces and thereby precedes functional impairment.[47] However, our findings do not argue against this conceptual understanding of cognitive impairment preceding functional change, but rather imply that existing paper-and-pencil cognitive tests may not provide the right tools to capture subtle cognitive decline. This is in line with previous studies that pointed toward the limited sensitivity of existing cognitive tests in early clinical stages of AD.[4,48] A functional measure, on the other hand, may be capable of capturing meaningful decline as reflected by increasing difficulties in complex activities of daily living.

There are some limitations that should be considered. First, our results might have been biased by heterogeneity in our sample due to differences in recruitment strategies employed across the centers. The majority of the UMCG cohort included community-based SCD and MCI participants, who are presumed to be at less risk for developing dementia compared to those recruited in a memory clinic setting.[49] It is therefore likely that those community-based participants showed less progression in cognition and function over time, as also reflected by our sensitivity analyses after stratification by study center. As such, our main analyses on the CFC's sensitivity to clinical progression may have been underestimated, especially in the MCI group. The fact that those community-based individuals did also not decline on the traditional tests indicates that this limitation was not specific for the CFC. Second, the sample size of the SCD and DLB groups were relatively small and thus the power to detect statistical significance was limited. Hence, no strong interferences can yet be drawn for the utility of the CFC in these groups. Third, it could be argued that a follow-up period of 1 year is relatively short to observe evident

cognitive decline in individuals with MCI or mild AD. However, we think it is a relevant timeframe as it corresponds to regular follow-up periods in clinical practice and clinical trial designs, and therefore it is crucial to know whether the CFC can capture clinical changes within this timeframe. Finally, it should be noted that the same rater completed all assessments within one visit and was therefore not blind for the cognitive assessments when performing the study partner interview, and that our CDR-SB assessment was slightly different than in other studies. However, we do not think that this has affected our CDR-SB scores, nor our comparisons between the CDR-SB and CFC.

Strengths of this study include our study design that enabled us to perform an independent validation of the CFC. Furthermore, the direct comparisons between the CFC and traditional measures is an important and unique aspect of this study. Additionally, our comparison with an anchor measure of everyday functioning strengthened the clinical meaningfulness of our findings. This additional investigation has been founded on the concern that statistically significant effects observed on cognitive tests do not self-evidently demonstrate clinically meaningful effects.[9] It should be acknowledged that our approach of establishing clinical meaningfulness has limitations, and that more sophisticated, qualitative methods involving patients and expert focus groups exist.[50] However, we think that the current study provides a first step to assess the CFC's clinical meaningfulness. Finally, sensitivity analyses in the amyloid-positive group enabled us to explore whether the CFC would be sensitive to AD-specific decline. However, these findings should be interpreted with caution due to the relatively small sample size of participants with biomarker data available, and thus need to be replicated in a larger sample. Altogether, these aspects will likely enhance future implementation of the CFC in both AD research and clinical practice.

Future directions include the optimization of the CFC's sensitivity to change in MCI, for example by exploring different weights for the CFC components to create a more sensitive score. Additionally, applying IRT scoring to the cognitive component might yield more precise measurement and thereby aid the detection of change over time.[51] IRT has already been applied in the scoring of the A-IADL-Q, which showed the highest sensitivity to change. Furthermore, IRT would enable us to use anchor-based bookmarking methods to determine the minimal important change, which could further establish the clinical meaningfulness of the CFC. Additionally, it would be interesting to investigate the sensitivity of the CFC beyond 1 year of follow-up, with a particular focus on the SCD and MCI groups. This would allow us to investigate whether the sensitivity of the CFC could be improved, and whether the CFC could predict conversion to dementia. To further facilitate the implementation of the CFC in clinical practice and research, it would be relevant to develop norms based on CFC performance in cognitively normal individuals.

Last, it would be interesting to further investigate the utility of CFC to measures progression in DLB, given the increasing number of DLB clinical trials[52] and the limited understanding on the clinical course of DLB so far.[53]

In conclusion, the current study provides evidence that the CFC yields an efficient and clinically meaningful measure of AD disease progression, and thereby has the potential to serve as efficacy endpoint for use in AD clinical trials.[15,16] By providing a concise measure of clinically meaningful cognitive decline, the CFC could contribute to the monitoring of disease progression, which is of relevance for both research and clinical practice.

ACKNOWLEDGMENTS

The authors would like to thank Philippe Lee Meeuw Kjoe, Mandy Ter Haar, Larissa Masselink, Judith Meurs, Mieke Geertsma, Nina Schimmel, Ilya de Groot, Judy van Hemmen, Kate Forsyth, Sarah Gregory, Neil Fullerton, Clare Dolan, and Matthew Hunter for their help with the data collection. Additionally, we would like to acknowledge Stichting Buytentwist for their support. Research of the Alzheimer Center Amsterdam is part of the neurodegeneration research program of Amsterdam Neuroscience. The Alzheimer Center Amsterdam is supported by Alzheimer Nederland and Stichting VUmc Fonds. The present study is supported by a grant from Memorabel (grant no. 733050205), which is the research program of the Dutch Deltaplan for 2 Dementia.

CONFLICTS OF INTEREST

R.J.J., A.B., R.V., R.A.J.D, F.J.J, C.W.R., E.O.M., and A.A. report no relevant disclosures. In the past 2 years, J.H. has received honoraria and paid consultancy from 23andMe, Abbvie, A2Q, AlzCure, Amgen, Anavex, Aptinyx, Astellas, AstraZeneca, Avraham, Axon, Axovant, Biogen, Boehringer Ingelheim, Bracket, Catenion, Cognition Therapeutics, CRF Health, Curasen, DeNDRoN, Enzymotec, Eisai, Eli Lilly, GfHEu, Heptares, Johnson & Johnson, Kaasa Health, Lysosome Therapeutics, Lundbeck, Merck, MyCognition, Mind Agilis, Neurocog, Neurim, Neuroscios, Neurotrack, Novartis, Nutricia, Pfizer, PriceSpective, Probiodrug, Regeneron, Rodin Therapeutics, Roche, Sanofi, Servier, Shire, Takeda, and vTv Therapeutics. P.S. has acquired grant support (for the institution) from GE Healthcare and Piramal. In the past 2 years, he has received consultancy/speaker fees (paid to the institution) from Novartis, Probiodrug, Biogen, Roche, and EIP Pharma, LLC. S.A.M.S. is supported by grants from JPND and Zon-MW, and has provided consultancy services in the past 2 years for Nutricia and Takeda. All funds were paid to her institution.

REFERENCES

1. Scheltens P, Blennow K, Breteler MM, et al. Alzheimer's disease. *The Lancet*. 2016;388(10043):505-517.
2. Sabbagh MN, Hendrix S, Harrison JE. FDA position statement "Early Alzheimer's disease: developing drugs for treatment, Guidance for Industry" *Alzheimers Dement*. 2019;5:13-19.
3. Harrison J, Maruff P. Measuring the mind: assessing cognitive change in clinical drug trials. *Expert Rev Clin Pharmacol*. 2008;1(4):471-473.
4. Mortamais M, Ash JA, Harrison J, et al. Detecting cognitive changes in preclinical Alzheimer's disease: a review of its feasibility. *Alzheimers Dement*. 2017;13(4):468-492.
5. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356-1364.
6. Karin A, Hannesdottir K, Jaeger J, et al. Psychometric evaluation of ADAS-Cog and NTB for measuring drug response. *Acta Neurol Scand*. 2014;129(2):114-122.

7. Cano SJ, Posner HB, Moline ML, et al. The ADAS-cog in Alzheimer's disease clinical trials: psychometric evaluation of the sum and its parts. *J Neurol Neurosurg Psychiatry*. 2010;81(12):1363-1368.
8. Kueper JK, Speechley M, Montero-Odasso M. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): modifications and Responsiveness in Pre-Dementia Populations. *A Narrative Review J Alzheimers Dis*. 2018;63(2):423-444.
9. Rockwood K, Fay S, Gorman M, et al. The clinical meaningfulness of ADAS-Cog changes in Alzheimer's disease patients treated with donepezil in an open-label trial. *BMC Neurol*. 2007;7(1):26.
10. Royall DR, Lauterbach EC, Kaufer D, et al. The cognitive correlates of functional status: a review from the Committee on Research of the American Neuropsychiatric Association. *J Neuropsychiatry Clin Neurosci*. 2007;19(3):249-265.
11. Jekel K, Damian M, Wattmo C, et al. Mild cognitive impairment and deficits in instrumental activities of daily living: a systematic review. *Alzheimers Res Ther*. 2015;7(1):17.
12. Sikkes SA, de Lange-de Klerk ES, Pijnenburg YA, et al. A systematic review of Instrumental Activities of Daily Living scales in dementia: room for improvement. *J Neurol Neurosurg Psychiatry*. 2009;80(1):7-12.
13. Kaur N, Belchior P, Gelinas I, et al. Critical appraisal of questionnaires to assess functional impairment in individuals with mild cognitive impairment. *Int Psychogeriatr*. 2016;28(9):1425-1439.
14. Snyder PJ, Kahle-Wrobleski K, Brannan S, et al. Assessing cognition and function in Alzheimer's disease clinical trials: do we have the right tools?. *Alzheimers Dement*. 2014;10(6):853-860.
15. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation. Early Alzheimer's Disease: Developing Drugs For Treatment, Guidance for Industry. 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/alzheimers-disease-developing-drugs-treatment-guidance-industy.
16. Committee for Medicinal Products for Human Use (CHMP). Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease. 2018. http://www.amge.it/wp/wp-content/uploads/2018/03/Alzheimer1.pdf.
17. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140:566-572.
18. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43:2412-2414.
19. Williams MM, Storandt M, Roe CM, Morris JC. Progression of Alzheimer's disease as measured by Clinical Dementia Rating Sum of Boxes scores. *Alzheimers Dement*. 2013;9(1 Suppl):S39-44.
20. Evans S, McRae-McKee K, Wong MM, Hadjichrysanthou C, De Wolf F, Anderson R. The importance of endpoint selection: how effective does a drug need to be for success in a clinical trial of a possible Alzheimer's disease treatment?. *Eur J Epidemiol*. 2018;33:1-10.
21. Tractenberg RE, Schafer K, Morris JC. Interobserver disagreements on clinical dementia rating assessment: interpretation and implications for training. *Alzheimer Dis Assoc Disord*. 2001;15(3):155-161.
22. Jutten RJ, Harrison J, de Jong FJ, et al. A composite measure of cognitive and functional progression in Alzheimer's disease: design of the Capturing Changes in Cognition study. *Alzheimers Dement*. 2017;3(1):130-138.
23. Harrison J, Dgetluck N, Gawryl M, et al. Validation of a novel cognitive composite assessment for mild and prodromal Alzheimer's disease. *Alzheimers Dement*. 2013;9(4):P661.
24. Sikkes SA, de Lange-de Klerk ES, Pijnenburg YA, et al. A new informant-based questionnaire for instrumental activities of daily living in dementia. *Alzheimers Dement*. 2012;8(6):536-543.
25. Sikkes SA, Knol DL, Pijnenburg YA, de Lange-de Klerk ES, Uitdehaag BM, Scheltens P. Validation of the Amsterdam IADL Questionnaire(c), a new tool to measure instrumental activities of daily living in dementia. *Neuroepidemiology*. 2013;41(1):35-41.
26. Jutten RJ, Peeters CFW, Leijdesdorff SMJ, et al. Detecting functional decline from normal aging to dementia: development and validation of a short version of the Amsterdam IADL Questionnaire. Alzheimer's & Dementia: diagnosis. *Assess Dis Monit*. 2017;8:26-35.
27. Jutten RJ, Harrison J, Lee Meeuw Kjoe P, et al. A novel cognitive-functional composite measure to detect changes in early Alzheimer's disease: test-retest reliability and feasibility. Alzheimer's & Dementia: diagnosis. *Assess Dis Monit*. 2018;10:153-160.
28. Jutten RJ, Harrison JE, Lee Meeuw Kjoe PR, et al. Assessing cognition and daily function in early dementia using the cognitive-functional composite: findings from the Catch-Cog study cohort. *Alzheimers Res Ther*. 2019;11(1):45.
29. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11(Suppl 2):S33-S39.
30. Tijms BM, Willemse EAJ, Zwan MD, et al. Unbiased Approach to Counteract Upward Drift in Cerebrospinal Fluid Amyloid-beta 1-42 Analysis Results. *Clin Chem*. 2018;64(3):576-585.
31. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement*. 2014;10(6):844-852.
32. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:270-279.
33. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263-269.
34. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
35. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1983;17(1):37-49.
36. Lezak MD. Neuropsychological assessment. USA: Oxford University Press; 2004.
37. Wechsler D. Wechsler memory scale–fourth edition (WMS-IV). San Antonio, TX: Pearson; 2009.
38. Wechsler D. Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). San Antonio, TX: NCS Pearson; 2008:498.
39. Amariglio RE, Donohue MC, Marshall GA, et al. Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: the Alzheimer's disease cooperative study cognitive function instrument. *JAMA Neurol*. 2015;72(4):446-454.
40. Li C, Neugroschl J, Luo X, et al. The Utility of the Cognitive Function Instrument (CFI) to Detect Cognitive Decline in Non-Demented Older Adults. *J Alzheimers Dis*. 2017;60(2):427-437.
41. Weintraub S, Carrillo MC, Farias ST, et al. Measuring cognition and function in the preclinical stage of Alzheimer's disease. *Alzheimers Dement*. 2018;4:64-75.
42. Koster N, Knol DL, Uitdehaag BM, Scheltens P, Sikkes SA. The sensitivity to change over time of the Amsterdam IADL Questionnaire. *Alzheimers Dement*. 2015;11:1231-1240.
43. Wang J, Logovinsky V, Hendrix SB, et al. ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials. *J Neurol Neurosurg Psychiatry*. 2016;87(9):993-999.
44. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71:961-970.
45. Langbaum JB, Hendrix SB, Ayutyanont N, et al. An empirically derived composite cognitive test score with improved power to track and

evaluate treatments for preclinical Alzheimer's disease. *Alzheimers Dement*. 2014;10:666-674.
46. Vellas B, Andrieu S, Sampaio C, Coley N, Wilcock G, European Task Force Group. Endpoints for trials in Alzheimer's disease: a European task force consensus. *Lancet Neurol*. 2008;7(5):436-450.
47. Liu-Seifert H, Siemers E, Price K, et al. Cognitive Impairment Precedes and Predicts Functional Impairment in Mild Alzheimer's Disease. *J Alzheimers Dis*. 2015;47(1):205-214.
48. Rentz D, Parra MA, Amariglio RE, Stern Y, Sperling R, Ferris SH. Promising developments in neuropsychological approaches for the detection of preclinical Alzheimer's disease: a selective review. *Alzheimers Res Ther*. 2013;5(6):58.
49. Slot RER, Sikkes SAM, Berkhof J, et al. Subjective cognitive decline and rates of incident Alzheimer's disease and non–Alzheimer's disease dementia. *Alzheimers Dement*. 2019;15(3):465-476.
50. Edgar CJ, Vradenburg G, Hassenstab J. The 2018 Revised FDA Guidance for Early Alzheimer's Disease: establishing the Meaningfulness of Treatment Effects. *J Prev Alzheimers Dis*. 2019;6:227-227.
51. Edelen MO, Reeve BB. Applying item response theory (IRT) modeling to questionnaire development, evaluation, and refinement. *Qual Life Res*. 2007;16(Suppl 1):5-18.
52. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. 2017;89(1):88-100.
53. Mueller C, Ballard C, Corbett A, et al. The prognosis of dementia with Lewy bodies. *Lancet Neurol*. 2017;16(5):390-398.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Jutten RJ, Harrison JE, Brunner AJ, et al. The Cognitive-Functional Composite is sensitive to clinical progression in early dementia: longitudinal findings from the Catch-Cog study cohort. *Alzheimer's Dement*. 2020;6:e12020. https://doi.org/10.1002/trc2.12020