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ORIGINAL ARTICLE

The Italian version of Cognitive Function Instrument (CFI) for tracking changes in healthy elderly: results at 1-year follow-up

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Abstract

Cognitive Function Instrument (CFI) is a questionnaire aimed at detecting very early changes in cognitive and functional abilities and useful for monitoring cognitive decline in individuals without clinical impairment. The Italian version has been recently validated. The aim of the present study was to investigate the utility of the Italian version of CFI in tracking early cognitive changes in a cohort of healthy elderly subjects. A consecutive series of 257 cognitively healthy and functionally independent subjects, recruited either among relatives of patients attending our Memory Clinic or as volunteers after advertisement, underwent a baseline neuropsychological assessment. Of them, 157 subjects performed a 1-year follow-up assessment. All subjects completed the CFI, a short questionnaire composed of 14 items administered to both the subject and the referent (study-partner). Cognitive performance was assessed by Mini-Mental State Examination (MMSE) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). At 1-year follow-up, Cronbach's α was 0.79 (95% CI, 0.74–0.84) in self-report and 0.83 (95% CI, 0.79–0.87) for partner-report. CFI self-report correlated with MMSE ($rS = -0.22$, $p = 0.006$) and RBANS ($rS = -0.23$, $p = 0.004$). CFI partner-report showed negative correlation with MMSE ($rS = -0.17$, $p = 0.037$) and RBANS ($rS = -0.20$, $p = 0.014$). CFI 1-year follow-up score correlated with baseline both in self-report ($rS = 0.56$, $p < 0.001$) and partner-report ($rS = 0.66$, $p < 0.001$). Baseline CFI partner-report ($p = 0.014$) and CFI self+partner report ($p = 0.023$) were associated with RBANS total score less than 85 at 1-year follow-up, while only a trend was found considering baseline CFI self-report. Our results support the suitability of the Italian version of CFI for tracking cognitive changes along aging.

Keywords Alzheimer's disease · Cognitive Function Instrument · Subjective cognitive decline · Italian version · Questionnaire

Introduction

Recent research on Alzheimer's disease (AD) is increasingly focused on the long preclinical phase that precedes mild cognitive impairment (MCI) [1, 2]. Accumulating evidences suggest that subjective cognitive decline (SCD) may indicate subtle cognitive decline characteristic of individuals with preclinical AD and that it may be an early indicator of AD pathology [3–5]. Therefore, individuals with SCD may have an increased likelihood of biomarker abnormalities consistent with AD and an increased risk for future pathologic cognitive decline and dementia [6].

In view of treating AD in prevention trials, the identification of older individuals who manifest earliest cognitive signs represents a major issue. Targeting clinically normal adults at risk of cognitive decline requires sensitive tools to detect subtle changes in large cohorts of clinically normal adults.

The Alzheimer's Disease Cooperative Study (ADCS)-Cognitive Function Instrument (CFI) is a simple questionnaire composed of 14 items administered to the subject and the referent [7, 8]. In a longitudinal study with a 4-year follow-up [8], the questionnaire was highly predictive of cognitive decline and it was considered useful to detect early changes in cognitive abilities in individuals without clinical impairment. The Italian version of CFI has been recently validated [9], showing that acceptability, internal consistency, and construct validity were comparable to the original version of the instrument.

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The aim of the present study was to investigate the utility of the Italian version of CFI in detecting early cognitive changes in a cohort of healthy and functionally independent elderly subjects followed-up for 1 year.

Methods

Participants

A consecutive series of 257 cognitively healthy and functionally independent subjects (age 60–85; mean 71; M 98, F 158), recruited among the relatives of the patients referring to our Memory Clinic ($n = 72$) or as volunteers ($n = 185$), were enrolled over the course of 2015 in a longitudinal cohort as part of the project "NeuroPsySCD" at the Centre for Memory Disturbances in Perugia. They were recruited through advertisements in pharmacies, GPs clinics, and Senior Centers. The announcements were seeking for healthy and functionally independent elderly subjects available to participate in a 4-year longitudinal study evaluating cognitive functions. Of 185 volunteers, 19 were recruited from pharmacies, 44 from GPs clinics, and 122 from Seniors Centers. Subjects were included if they met the following inclusion criteria: (i) age between 60 and 85, (ii) good physical and mental health, (iii) no concomitant uncontrolled medical diseases, (iv) Mini Mental State Examination score ≥ 24, and (v) presence of a study partner available to answer CFI partner-report. A group of 157 subjects (age 60–85; mean 70.9; M 96, F 61) performed a 1-year follow-up assessment; 96 subjects were females (61.1%) while 61 were males (38.9%), with a mean of 12.8 ± 3.9 years of education (Table 1).

Assessment procedure

The CFI is a questionnaire composed of 14 items, administered in written form both to subjects and study-partners separately. The purpose of the answers is to investigate, compared with 1 year before, the presence of memory decline, appraisal of cognitive difficulties, and functional abilities. The score ranges from 0 to 14, codified with answer yes = 1, maybe = 0.5, and no = 0 and summed to calculate a total score (Table 2).

The Italian version of the CFI has been recently validated [9] and was independently administered by expert neuropsychologists.

For the assessment of global cognitive functioning, the MMSE [10] and the RBANS [11], Italian version [12], were administered. MMSE is a worldwide-recognized screening tool, but it is relatively insensitive to detect minimal or mild cognitive alteration [13]. We included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which represents a simple and brief measure of global cognitive functioning, suitable for longitudinal studies [12, 14]. It has been extensively used to identify cognitive change in individuals with normal cognition [15], Mild Cognitive Impairment (MCI) [14], and Alzheimer's disease (AD) [16, 17], confirming its suitability as neurocognitive battery for diagnosis and follow-up of cognitive dysfunctions [14]. Recently, RBANS has been also used as primary outcome in clinical trials (ClinicalTrials.gov Identifier: NCT02484547) and observational longitudinal studies (e.g., European Prevention of Alzheimer's Dementia Longitudinal Cohort Study) [18]. RBANS is composed of 12 sub-tests exploring five cognitive domains (Immediate Memory – List Learning and Story Memory; Visuospatial/Constructional – Figure Copy and Line Orientation; Language – Picture naming and Semantic Fluency; Attention – Digit Span and Coding; Delayed Memory – List Recall, List Recognition, Story Memory, and Figure Recall). For each domain, an index score is obtained (standardized mean 100 ± 15). A score of 85 or lower is indicative of objective cognitive impairment. The total score is given by the sum of all index scores and expressed as standardized mean as well. The Clinical Dementia Rating (CDR), a rating scale for dementia staging, representing an inclusion criteria at baseline (CDR 0), was also re-administered. The same assessment was performed at baseline and at follow-up.

The study was approved by the local Ethics Committee (CEAS Umbria), and all participants signed the informed consent.

Statistical analysis

For the difference between the mean total score of CFI self- and partner-report, MMSE and RBANS were calculated at baseline and after 1-year follow-up. Psychometric properties

Table 1 Cohort characteristics by age groups

Variable	60–64, $n = 9$	65–69, $n = 51$	70–74, $n = 59$	> 75, $n = 35$	All, $n = 157$
Gender (M/F)	1/8	12/39	28/31	18/17	61/96
Education	12.7 ± 2.4	12.4 ± 3.9	13.2 ± 4.0	12.5 ± 4.1	12.8 ± 3.9
MMSE	28.8 ± 1.1	29.0 ± 0.9	28.6 ± 1.1	28.6 ± 1.3	28.7 ± 1.1
RBANS	102.3 ± 13.2	96.0 ± 11.7	95.4 ± 10.8	90.2 ± 10.1	94.8 ± 11.4

Table 2 Percentages of answers "yes" and corrected-correlations with total score for each item in self- and partner-report

Item	Self-report		Partner-report	
	Yes (%)	Item total correlation	Yes (%)	Item total correlation
1 - Subjective memory decline	8	0.57	6	0.58
2 - Questions repetition	13	0.49	14	0.52
3 - Misplacing things	18	0.43	15	0.49
4 - Use of written reminders	43	0.40	25	0.52
5 - Remember appointments	13	0.53	12	0.73
6 - Recalling names and words	31	0.47	21	0.49
7 - Driving	10	0.46	7	0.37
8 - Managing money	3	0.41	1	0.55
9 - Social activities	12	0.36	9	0.45
10 - Work performance	6	0.54	3	0.42
11 - Following news or the plots of books, movies	6	0.57	3	0.57
12 - Hobbies	4	0.44	3	0.62
13 - Spatial disorientation	9	0.53	6	0.49
14 - Using household appliances	3	0.44	3	0.40

of the CFI were evaluated at 1-year follow-up. We assessed the internal consistency of the Italian version of CFI by means of Cronbach's α and item-score correlations. Criterion validity was assessed by means of Spearman correlation coefficients between CFI and MMSE and RBANS (Table 3). Mann-Whitney *U* test was used for comparing test scores between groups. A multivariate logistic regression model was used to assess reason for drop-out at 1-year follow-up. Statistical analyses have been performed using R (www.r-project.org). A *p* value less than 0.05 has been considered statistically significant.

Results

Demographic characteristics are given in Table 1. The mean age was 70.9 ± 5.1 years (mean ± standard deviation (SD); range 60–85). Ninety-six subjects were females (61.1%) while 61 were males (38.9%), with a mean of 12.8 ± 3.9 years of education. Our population was comparable in terms of gender distribution with the elderly population of Umbria, but the participants in our study were younger and more educated. In fact, the elderly in Umbria have a female proportion of 57% (61% in our study) and a mean age of 76 years (71 in our cohort). Furthermore, subjects in our sample hold a slightly higher level of education with a proportion of 77% of subjects having 13 years of education years or less compared to the 69% in the general population [dati.istat.it accessed 2019-05-07]. Mean MMSE was 28.7 ± 1.1 (range 25–30) and mean Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was 94.8 ± 13.4 (range 74–125). The CDR score was unchanged (CDR 0) in all participants.

The mean CFI self-score was 3.24 ± 2.43 at baseline while it was 2.72 ± 2.36 at 1-year follow-up. The mean CFI partner-report was 2.29 ± 2.13 at baseline; at 1-year follow-up, it was 1.99 ± 2.26. The mean RBANS total score was 98.66 ±

Table 3 Spearman correlation coefficients with 95% CI of CFI self- and CFI partner-report with RBANS and MMSE

	CFI self-report		CFI partner-report		CFI self+partner report	
	r (95% CI)	*p* value	*r* (95% CI)	*p* value	*r* (95% CI)	*p* value
RBANS immediate memory	− 0.13 (− 0.28 to 0.02)	0.098	− 0.16 (− 0.31 to − 0.01)	0.044	− 0.18 (− 0.39 to − 0.02)	0.030
RBANS delayed memory	− 0.20 (− 0.35 to − 0.05)	0.011	− 0.16 (− 0.31 to 0)	0.048	− 0.27 (− 0.42 to − 0.11)	0.001
RBANS visuospatial	− 0.11 (− 0.27 to 0.04)	0.158	− 0.04 (− 0.2 to 0.12)	0.609	− 0.10 (− 0.26 to 0.07)	0.242
RBANS linguistic	− 0.13 (− 0.28 to 0.03)	0.106	− 0.22 (− 0.37 to − 0.07)	0.006	− 0.17 (− 0.33 to − 0.01)	0.043
RBANS attention	− 0.08 (− 0.23 to 0.08)	0.352	0.01 (− 0.14 to 0.17)	0.864	− 0.09 (− 0.25 to 0.08)	0.287
RBANS total	− 0.23 (− 0.37 to − 0.07)	0.004	− 0.2 (− 0.34 to − 0.04)	0.014	− 0.31 (− 0.45 to − 0.15)	< 0.001
MMSE	− 0.22 (− 0.36 to − 0.06)	0.006	− 0.17 (− 0.32 to − 0.01)	0.037	− 0.26 (− 0.41 to − 0.09)	0.002

12.04 at baseline while it was 94.8 ± 13.4 at 1-year follow-up. At baseline, 139 participants performed a RBANS total error > 85 at baseline. Of these, 21 progressed to a RBANS < 85 at 1-year follow-up. The mean MMSE total score was 28.42 ± 1.27 at baseline, while at 1-year follow-up, it was 28.7 ± 1.1. Acceptability was appropriate due to the low rate of missing values in each item, which ranges from 0 to 3% in self-report and from 4 to 5% in partner-report. CFI self- and partner-report scores were correlated ($rS = 0.31$, $p < 0.001$). One hundred participants dropped-out from the study at 1-year follow-up visit due to personal reasons. For eighteen of them, the reason of withdrawal was the occurrence of medical conditions requiring diagnostic and therapeutic actions that would interfere with study participation. Sixty-five lost interest in participating, three participants died, and fourteen had other impediments (i.e., illness of a family member, change of residence). Lower MMSE (OR = 1.048, $p = 0.023$) and RBANS (OR = 1.013, $p < 0.001$) at baseline were independent predictors of drop-out. CFI scores and gender were not associated to drop-out either in the univariate or in the multivariate analysis. Age was associated with drop-out in the univariate analysis but was not significant in the multivariate model.

CFI self-report

Corrected item–total correlations were satisfactory, ranging between 0.36 and 0.57. The proportion of no answers ranged from 33% (item 6th) to 96% (item 8th). (Table 2) The total CFI score ranged between 0 and 14, with a mean ± SD of 2.7 + 2.3 and a median (q1–q3) of 2 (1–4). Seventeen (10.8%) responders scored zero while one reached the maximum score of 14. Reliability, measured by standardized alpha based upon the correlations, was 0.79 (95% CI, 0.74–0.84). The analysis of the relationship between the CFI and other cognitive assessments revealed a correlation with MMSE ($rS = -0.22$, $p = 0.006$) and RBANS ($rS = -0.23$, $p = 0.004$). (Table 3) CFI self-report at baseline and follow-up correlates ($rS = 0.56$, $p < 0.001$). The correlation between CFI self-report and neuropsychological measures increased slightly from baseline to follow-up both for MMSE (rS from −0.14 to −0.22) and RBANS (rS from −0.22 to −0.23) (Fig. 1). Furthermore, considering only participants who performed RBANS > 85 at baseline, we found that baseline CFI self-report showed a trend towards an association with 1-year RBANS < 85 (2.18 ± 2.08 vs 2.88 ± 2.41; $p = 0.174$).

CFI partner-report

Corrected item–total correlations ranged between 0.37 and 0.73. The proportion of no answers ranged from 63% (item 3rd) to 93% (item 8th). (Table 2) The total CFI score ranged between 0 and 11, with a mean ± SD of 1.92 ± 2.26 and a median (q1–q3) of 1 (0.0–2.5). Forty-six (29.3%) informants scored zero while nobody reached the maximum score. The percentage of zero scores was significantly higher in the partners than that in the subjects ($p < 0.001$). Reliability, measured by standardized alpha based upon the correlations, was 0.83 (95% CI, 0.79–0.87). The analysis of the relationship between the CFI and other cognitive assessments confirmed a negative correlation with MMSE ($rS = -0.17$, $p = 0.037$) and RBANS ($rS = -0.20$, $p = 0.014$). (Table 3) CFI partner-report at baseline and follow-up correlates ($rS = 0.66$, $p < 0.001$).

The correlation between CFI partner-report and neuropsychological measures increased slightly, from baseline to follow-up both for MMSE (rS from −0.10 to −0.17) and RBANS (rS from −0.17 to −0.20) (Fig. 1).

Considering only participants who performed RBANS > 85 at baseline, we found that baseline CFI partner-report was significantly associated with 1-year RBANS < 85 (3.03 ± 2.41 vs 4.17 ± 2.06; $p = 0.014$).

CFI self+partner report

The analysis of the relationship between the CFI self+partner report and other cognitive assessments resulted in a negative correlation with MMSE ($rS = -0.26$, $p = 0.002$) and RBANS ($rS = -0.31$, $p < 0.001$) (Table 3).

The correlation between CFI self+partner report and neuropsychological measures increased slightly, from baseline to follow-up both for MMSE (rS from −0.16 to −0.24) and RBANS (rS from −0.25 to −0.26) (Fig. 1).

Furthermore, considering only participants who performed RBANS > 85 at baseline, we found that baseline CFI self+partner report showed a significant association with 1-year RBANS < 85 (5.67 ± 4.43 vs 7.76 ± 4.19; $p = 0.023$).

Discussion

Current evidence suggests that Alzheimer's disease (AD) is a continuum and that the positivity of biomarkers of Alzheimer's disease (AD) begun a decade or more before the emergence of clinical impairment [1, 19]. In order to successfully prevent progression by means of disease-modifying agents, it is necessary to detect the subtle cognitive decline from a previous level of cognition that may occur in the preclinical AD phase. Thus, it is mandatory to use intra-individual measures able to track decline of cognitive performance even if still within a "normal" range.

The Cognitive Function Instrument (CFI) seems to be a sensitive tool for tracking early changes of cognitive and functional abilities in a cohort of healthy elderly individuals [8]. Recently, the Italian version of the CFI has been validated [9] showing statistical properties comparable to the original version. Therefore, we aimed to validate the usefulness of the questionnaire in tracking cognitive changes in a cohort of

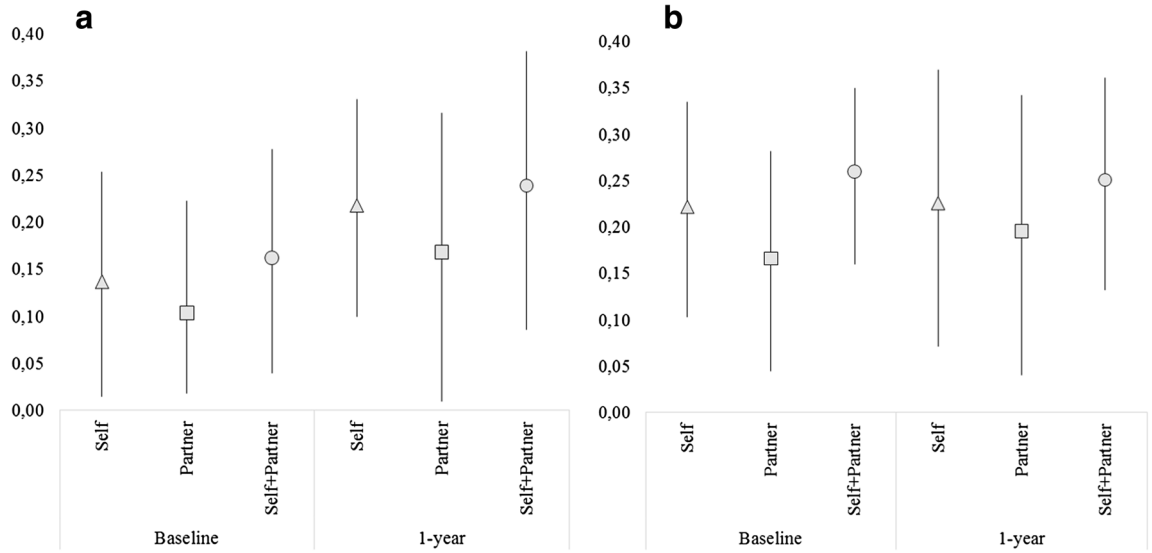

Fig. 1 **a** Correlation between CFI self-, partner-, self+partner report and MMSE over time. **b** Correlation between CFI self-, partner-, self+partner report and RBANS over time

Italian healthy elderly followed over time. The present study reports the validation at 1-year follow-up of the Italian version of CFI.

Our findings may be considered to be generalizable to the target population. In fact, our validation study was tailored to healthy elderly subjects. Participants were gender-matched compared with the general population (dati.istat.it) and, as expected, they were younger and attained a higher level of education. Characteristics such as education level or socioeconomic status can affect participation in studies. Individuals with these characteristics may find easier to understand study information, to participate in a longitudinal study and to learn about research opportunity [20, 21]. Cronbach's α was comparable to the baseline results and to the original version both in self-report and partner-report [8]. We found that CFI self- and partner-report total mean score were both lower at follow-up compared to baseline. Furthermore, the MMSE and RBANS scores were substantially stable between baseline and 1-year follow-up. These findings' result could be due to a selection bias in our follow-up sample, where only healthier subjects were motivated to remain in the study. Further follow-up of our cohort may be of help on addressing this issue.

Criterion validity is confirmed for CFI self- and partner-report by the correlation with both MMSE and RBANS. Although significant, the correlation between total self- and partner-report scores was not strong. This might be due to the asynchrony between the perception of disturbances by subjects and their partners, usually earlier in subjects. Study partners do not spend all the time with the subjects. The combination of self- and partner-report may be more reliable in tracking changes in healthy subjects [8].

CFI self-report demonstrated stronger correlations with cognitive measures than partner CFI in both baseline and follow-up assessments. Results suggest that the first perception of slight changes of cognitive impairments in functionally intact elderly subjects may be mainly detected in first person. Therefore, CFI self-report could be more reliable for slight changes in cognitive function, whereas CFI partner-report could be useful in detecting cognitive impairment in an advanced phase of decline [8, 22–24]. To find confirmation, it would be necessary to have the possibility of monitoring the same subjects for a longer period of time.

Moreover, baseline CFI partner-report ($p = 0.014$) and CFI self+partner report ($p = 0.023$) were associated with RBANS total score less than 85 at 1-year follow-up, while only a trend was found when we considered baseline CFI self-report. This result may suggest the predicted value of the CFI in tracking cognitive changes over time.

Our findings suggest the ability of the CFI to correlate with other neuropsychological tests similar to the results of the original paper [8]. This represents a first sign to consider the Italian version of CFI suitable in identifying and monitoring the cognitive functioning in a cohort of healthy and functionally independent elderly subjects. However, it is mandatory to check in future studies if the CFI variation showed by our cohort is representative of the general population. This important issue needs to be further validated throughout the longitudinal study when changes in neuropsychological tests and CDR will be more pronounced.

Our study has two limitations: (1) short follow-up period (1 year). Although our results at 1-year follow-up confirm a trend in prediction of slight cognitive decline, longer periods of observation may confirm the utility of CFI in tracking cognitive changes. (2) High proportion of subjects dropped-out

from baseline to follow-up due to personal reasons (i.e., novel medical conditions, loss of motivation, death, other reasons). The greatest number of drop-out depended on interest's loss and it could be connected to the difficulty of maintaining a large cohort of healthy volunteers in a longitudinal study. Moreover, we saw that poorly functioning subjects were more likely to be lost at follow-up compared with well-functioning subjects [25, 26]. (3) The use of the Italian version of RBANS could suffer from some limitations. Normative data were obtained from a heterogeneous group of subjects, aged from 20 to 80 years, including psychiatric diseases and dementia. Since no data in subjects > 80 years are available, correction was invariably made using the normative values of the groups 70–79 years. These limitations should be considered in future prospective studies aimed at improving the Italian normative data of this battery.

In conclusion, the results of the present study support the use of the Italian version of CFI. However, it is necessary to continue the longitudinal study with annual follow-up in order to fully validate the results obtained so far, supporting the suitability of the Italian version of CFI for tracking cognitive changes along aging.

Compliance with ethical standards

The study was approved by the local Ethics Committee (CEAS Umbria), and all participants signed the informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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