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Association Between Proxy- or Self-Reported Cognitive Decline and Cognitive Performance in Memory Clinic Visitors

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Abstract.

Background: It is uncertain whether self- and proxy-reported cognitive decline in older adults reflect an actual objective cognitive dysfunction in the clinical sense, and if these are predictive for developing dementia.

Objective: The aim of the present study is to investigate the cross-sectional and longitudinal relation between subjective cognitive decline and objective cognitive performance, depressive symptoms, and to determine the predictive value for development of dementia.

Methods: We included 405 patients without dementia at first visit from the Maastricht memory clinic participating in a longitudinal cohort study. Subjective cognitive decline was measured using a self- and proxy-report questionnaire. All patients underwent a standardized neuropsychological assessment. Follow-up assessments were performed yearly for three consecutive years, and once after five years.

Results: Subjective cognitive decline was associated with lower cognitive performance and more depressive symptoms. When comparing self- ($n = 342$, 84%) and proxy-reported decline ($n = 110$, 27%), it was shown that proxy reports were associated with a more widespread pattern of lower cognitive performance. In participants without cognitive impairment proxy-reported decline was not associated with depressive symptoms. In contrast, self-reported decline was associated with a stable course of depressive symptoms at follow-up. Proxy-reported cognitive decline (HR = 1.76, 95%CI = 1.12–2.78), and mutual complaints (HR = 1.73, CI: 1.09–2.76) predicted incident dementia while self-reported decline did not reach statistical significance (HR = 1.26, 95%CI = 0.65–2.43).

Conclusion: Proxy-reported cognitive decline was consistently associated with lower cognitive performance and conversion to dementia over 5 years. Self-reported cognitive decline in patients without cognitive impairment might indicate underlying depressive symptoms and thus deserve clinical attention as well.

Keywords: Cognition, dementia, depressive symptoms, mild cognitive impairment, proxy-report, subjective cognitive decline

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INTRODUCTION

Subjective cognitive decline is defined as self-perceived worsening of cognition over time, which is common in older adults [1]. It is often a reason for concern, resulting in visits to healthcare facilities, such as memory clinics. There is increasing evidence that the experience of cognitive decline is related to a greater risk of conversion to mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia [2–4]. A meta-analysis shows that elderly people experiencing cognitive decline are twice as likely to develop dementia [3]. However, previous studies have generated inconsistent findings with regard to the relation with objective cognitive performance and risk of conversion to dementia [2, 5, 6]. Some studies have shown that subjective cognitive decline reflects worse objective cognitive performance both at baseline and over time [7–10], whereas other studies found no associations with cognition [11–14]. On the other hand, cognitive complaints have also been shown to be closely associated with personality traits, depressive symptoms, and other psychiatric conditions [2, 11–14]. Differences in study design might explain this heterogeneity, as studies that found an association between subjective cognitive decline and objective cognitive performance have generally adopted a longitudinal and community-based design in a cognitively healthy sample while studies focusing on a memory-clinic population have not always demonstrated differences in cognitive performance [15, 16].

The differential prognostic value of self- as compared with proxy-reported cognitive decline is another unresolved issue. Indeed, some studies indicate that proxy-reported decline has a higher accuracy of indicating subsequent objective cognitive performance and predict future cognitive decline in comparison to self-reported decline [17, 18]. Proxy-reported decline has also been shown to differentiate normal aging from future conversion to dementia, while self-reported decline did not [19, 20]. In contrast, other studies found weak associations between proxy-reported decline and cognitive test performances [14, 21]. These discrepancies could be explained by methodological differences, variability in terminology, and a focus on subjective memory complaints and not on other cognitive domains, such as attention. Consequently, the clinical significance and prognostic value of self- and proxy-reported cognitive decline remain unclear. More insight into subjective cognitive decline might

allow for identification of an at-risk population for developing AD dementia that is easily implemented in clinical practice. It would also facilitate the implementation of early interventions [2]. This study will extend evidence from predominantly cognitively healthy subjects to a clinical population of memory clinic visitors who actively sought help using a large memory-clinic cohort and a long follow-up period. In addition, we will explicitly focus on contrasting proxy- and self-reported cognitive decline, which includes reports of both memory and attention complaints and is based on a standardized instrument asking for the decline compared to one year prior to the assessment. To our knowledge, only a few studies have studied this in memory-clinic visitors, usually focusing on current subjective complaints. Our primary aim is to investigate the cross-sectional and longitudinal association between self- and proxy-reported cognitive decline and objective cognitive performances in nondemented memory clinic visitors. The secondary aim is to determine the association with conversion to dementia in patients with and without self- and proxy-reported cognitive decline at baseline. The third aim is to investigate the cross-sectional and longitudinal association between self- and proxy-reported cognitive decline and depressive symptoms, and to repeat this analysis separately in patients with and without cognitive impairment.

MATERIALS AND METHODS

Study design and participant selection

Participants were selected from the Bio-Bank Alzheimer Center Limburg (BBACL) study, which is an ongoing prospective cohort study of patients referred to the memory clinic of the Maastricht University Medical Center in the Netherlands for an evaluation of their cognitive complaints. Patients were included if they were 55 years or older, had no cognitive impairment (NCI), or mild cognitive impairment (MCI) in the absence of dementia. Participants were classified as having MCI when they had an objectified impairment on one or more cognitive tests [22], had a Clinical Dementia Rating (CDR) score of ≤ 0.5 , and no significant interference in daily life. Performance on a cognitive test was considered impaired if the score was more than 1.5 Standard Deviation (SD) below the age-, sex-, and education-adjusted normative mean [23–25]. Participants were excluded if they had dementia at

baseline, and medical disorders, which could result in cognitive impairment. This includes Normal Pressure Hydrocephalus, Huntington's disease, recent cerebrovascular disorders (Transient Ischemic Attack [TIA] or stroke < 2 years prior to the assessment or cognitive decline within 3 months after a TIA or stroke), brain tumor, epilepsy or encephalitis. Participants were also excluded if they had a history (<12 months) of or current treatment for major depressive disorder, bipolar disorder, or psychotic disorder based on DSM-IV-TR criteria. Cognitive problems as a result of excessive use of alcohol (clinician judgement) and the expectation that the participant would not reach the first-year follow-up also led to exclusion. For the present study, we selected participants who completed the self- and proxy questionnaires on cognitive decline. This resulted in a sample size of $N=405$ at baseline. Figure 1 shows the flow chart of this study. Ethical approval was given by the Medical Ethics Review Committee of Maastricht University Medical Center. Participants gave written informed consent.

Baseline assessment

Standard clinical assessment as part of the diagnostic procedure at baseline included a detailed medical history of the patient, demographic information, neurological, psychiatric, and physical examinations. Furthermore, a standardized interview based on the Disability Assessment for Dementia Scale (DAD) [26] was conducted with a proxy to evaluate significant interference in daily life which was also based on clinical judgement. Also, self- and proxy-reported information of cognitive decline, and a neuropsychological assessment were part of the baseline assessment.

Self- and proxy reported cognitive decline

Self-reported cognitive decline was measured by the Subjective Cognitive Functioning (SCF) questionnaire [27]. Participants had to rate their cognitive change in the past year on a scale from -3 (very strong decline) to $+3$ (very strong improvement) in the domains of memory and attention. Two groups were identified: those who reported a cognitive decline (in memory or in concentration, or in both) ($SCF < 0$), and those who reported no change or an improvement in these domains ($SCF \geq 0$). The Dutch translation of the *Détérioration Cognitive Observée* (DECO) [28] was used to measure proxy-reported cognitive

decline. It consists of 19 items concerning the degree of change in cognitive functioning in the past year on a scale from 2 (no change) to 0 (great decline). It has been shown to be highly sensitive for changes in cognitive functioning [28]. Furthermore, it shows high discriminability, with a sensitivity of 79% and specificity of 90% for detecting dementia using a cut-off score of ≤ 24 , which is not influenced by level of education [29]. This cutoff was used to identify two groups: those who reported a greater decline in cognitive functioning (DECO ≤ 24), and those who did not (DECO > 24).

Neuropsychological assessment

All participants underwent neuropsychological assessment by use of a standardized test battery. The following cognitive domains were measured: general cognitive functioning (MMSE) [30], episodic memory, both for verbal (Dutch version of the verbal learning test; VLT) [31] and visual information (Visual Association Test; VAT) [32], information processing speed (Stroop Color-Word Test part I; SCWT-I [33], and Trail Making Test part A; TMT-A [34] or Concept Shifting Task part A; CST-A) [35], executive functioning (interference index of the SCWT) [33], concept shifting (CST-C) [35], and semantic word fluency (1-minute animal naming) [36]. All cognitive performances were translated to z-scores adjusted for age, education and, if appropriate, sex [23–25, 37]. Extreme z-scores were found for SCWT-I (4.7% of all scores), SCWT interference (5.3% of all scores), CSTA/TMTA (1.1% of all scores), and concept shifting (1.9% of all score). These scores were winsorized at a lower (-5) and upper ($+5$) boundary. Presence and severity of depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS-15) [38].

Follow-up assessments

Follow-up (FU) assessments took place one, two, three, and five years (FU1, FU2, FU3, FU5) after baseline. Comparable to baseline, every follow-up assessment included a medical history and neuropsychological assessment using parallel versions to reduce material-specific test-retest effects. The consultation with a family member, based on the DAD, was also taken again to evaluate interference in daily living and decline from a previous level of functioning (social or occupational). The DECO, SCF, and GDS questionnaires were also included at the follow-

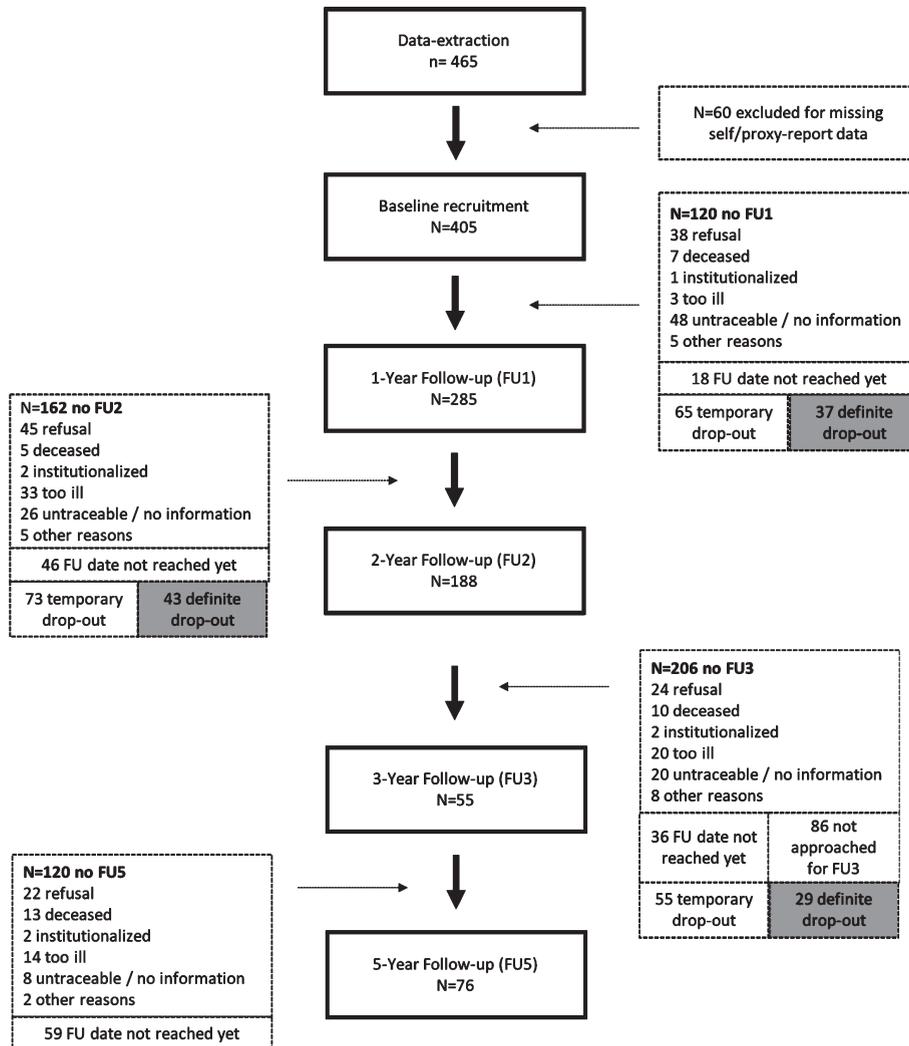


Fig. 1. Flowchart of ongoing longitudinal BBACL cohort.

up assessments. Dementia diagnosis was reviewed at every assessment according to DSM-IV-TR criteria using all available information (outcome of the neuropsychological assessment, medical history, family history, and evaluation of interference in daily live) [39]. In the case of significant interference in daily life was suspected, the medical specialist (psychiatrist) from the memory clinic was consulted. After reviewing all data (e.g., earlier brain scans, current new information), the medical specialist made the dementia diagnosis.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 for Mac OS X. Differences in baseline

characteristics between the self- and proxy-reported cognitive decline groups and dementia converters and non-converters were compared using independent-sample *t*-tests (or Mann-Whitney U tests in case of no normal distribution), and χ^2 -tests (categorical variables). To estimate associations between self- or proxy-reported cognitive decline with objective cognitive performance over time, linear mixed models were used with a random intercept and random slope to account for correlated repeated measurements within individuals. The unstructured covariance structure type was chosen as this gave the best model fit using likelihood ratio testing. The cognitive test *z*-scores were used as dependent variables in the model with a separate model for each subtest. The independent terms included the self-reported cogni-

tive decline group, time (categorical: baseline, FU1, FU2, FU3, FU5), and group by time interaction. The interaction term was added to explore future cognitive decline or improvement between the groups. The null hypothesis of no difference in course of cognitive performance was tested with an F test to examine whether there was a significant group effect and group-by-time interaction across all time points. Furthermore, estimated means were calculated in this analysis for group by time. All models were adjusted for age, sex, education (low, middle, high), and depressive symptoms. The same model was run with the proxy-reported group as independent term. Because time was added as a categorical variable the differences between the groups could be identified at each measurement. To explore the association between subjective cognitive decline and depressive symptoms the linear mixed model analysis was also run with the GDS-15 score as dependent term and the same independent terms as described above. This model was adjusted for age, sex, and education. Cox regression analyses adjusted for age, sex, education, and depressive symptoms were performed to evaluate if proxy- and self-reported cognitive decline were associated with conversion to dementia. Cause-specific hazard ratios were calculated with competing risk of death ($n = 35$, 9.6%). The outcome was dementia converters versus non-converters. The survival time was time to diagnosis of dementia (converters) or last available follow-up diagnosis (non-converters). The alpha-level was set at 0.05 in two-sided tests throughout.

RESULTS

Baseline characteristics

At baseline, 84.4% of the patients were identified as having self-reported cognitive decline (SCF < 0) and 27.2% as having proxy-reported cognitive decline (DECO ≤ 24). The combination of both self- and proxy reported cognitive decline was present in 23.5% of the patients, while in 11.5% no subjective cognitive decline was reported by either the patient or family member. The baseline demographic characteristics are shown in Table 1. Most proxies were partners (71.4%). Other proxies included children (20%), acquaintances (3%), siblings (2.2%), other family members (2.2%), and ex-partners (1.2%). Overall, most proxies had daily (75.6%) or at least once a week (21.4%) contact with the patient. Patients with self- or proxy-reported cog-

nitive decline showed no significant differences with respect to demographic features (Table 1). The prevalence of MCI was comparable between participants with and without self- ($\chi^2(1) = 0.64$, $p = 0.425$) or proxy-reported ($\chi^2(1) = 1.63$, $p = 0.202$) cognitive decline. In addition, patients with self- or proxy-reported cognitive decline had significantly higher mean scores of depressive symptoms than those without (self-report: $U = 7853$, $p = 0.002$, proxy-report: $U = 11691$, $p < 0.001$).

Association between self- and proxy-reported cognitive decline and cognitive performance

The differences in course of cognitive performance for patients with and without self- or proxy-reported cognitive decline are shown in Table 2 and Fig. 2. In these analyses, we did not differentiate between patients with and without cognitive impairment. At baseline, linear mixed models, corrected for age, sex, education, and depressive symptoms, showed no significant differences regarding cognitive performance between patients with and without self-reported decline. In addition, no significant overall interaction effect was found with time. However, averaged over all time points together, patients with self-reported cognitive decline at baseline had a lower performance on the VLT immediate recall ($F(1, 475) = 11.68$, $p = 0.001$), VLT delayed recall ($F(1, 463) = 15.50$, $p < 0.001$), semantic fluency ($F(1, 473) = 7.59$, $p = 0.006$), and SCWT-I ($F(1, 456) = 10.10$, $p = 0.002$) (Fig. 2 and Table 2) in comparison to patients who did not report a subjective cognitive decline.

Patients with proxy-reported cognitive decline had a lower performance on the CSTA/TMTA and SCWT-I at baseline compared to those without (Table 2). However, no differences were found on the other cognitive tests. Averaged over all time points, while accounting for correlated measures within individuals, patients with proxy-reported cognitive decline had a lower performance on the VLT delayed recall ($F(1, 448) = 4.63$, $p = 0.032$), VAT ($F(1, 435) = 23.75$, $p < 0.001$), semantic fluency ($F(1, 464) = 11.14$, $p = 0.001$), CSTA/TMTA ($F(1, 460) = 12.72$, $p \leq 0.001$), concept shifting ($F(1, 376) = 5.53$, $p = 0.019$), SCWT-1 ($F(1, 463) = 25.62$, $p < 0.001$), and SCWT-interference ($F(1, 420) = 11.13$, $p = 0.001$), and higher scores on GDS-15 ($F(1, 478) = 9.60$, $p = 0.002$). Also, a significant overall interaction with time shows that the cognitive performance of patients with proxy-

Table 1
Comparison of demographic characteristics in patients with and without self- or proxy-reported cognitive decline ($n = 405$)

	Self-reported cognitive decline		Proxy-reported cognitive decline	
	Present	Absent	Present	Absent
n (%)	342 (84.4)	63 (15.6)	110 (27.2)	295 (72.8)
Age, y	70.0 \pm 8.3	70.1 \pm 8.9	71.1 \pm 9.0	69.6 \pm 8.2
Sex, n female (%)	128 (37.4)	29 (46.0)	42 (38.2)	115 (39.0)
Education n (%)				
Low	128 (37.4)	30 (47.7)	47 (42.7)	111 (37.6)
Middle	128 (37.4)	21 (33.3)	37 (33.6)	112 (38.0)
High	86 (25.2)	12 (19.0)	26 (23.7)	72 (24.4)
Diagnosis n (%)				
NCI	139 (40.6)	29 (46.0)	40 (36.4)	128 (43.4)
MCI	203 (59.4)	34 (54.0)	70 (63.6)	167 (56.6)
GDS-15 score	3.6 \pm 3.0 ^a	2.6 \pm 2.8	4.6 \pm 3.6 ^b	3.1 \pm 2.6
MMSE score	27.6 \pm 2.4	27.2 \pm 2.5	26.7 \pm 2.6 ^a	27.8 \pm 2.2

Demographics are represented in mean \pm SD unless stated otherwise. Education was stratified following the Dutch education system in low (primary), average (lower secondary or vocational), and high (higher secondary education, higher vocational, university) education. Groups were compared using Student's t -tests, Mann-Whitney U-tests and Pearson's chi-squared tests where appropriate. ^a $p \leq 0.05$. ^b $p \leq 0.001$. NCI, no cognitive impairment; MCI, mild cognitive impairment; GDS, Geriatric Depression Scale; MMSE, Mini-Mental Status Examination.

reported cognitive decline significantly decreased over time on the VAT ($F(4, 389) = 3.75, p = 0.005$), CSTA/TMTA ($F(4, 411) = 4.18, p = 0.003$), SCWT-I ($F(4, 406) = 5.42, p < 0.001$), and SCWT interference ($F(4, 357) = 5.37, p < 0.001$). No significant overall interaction was found on the other cognitive tests.

Self- and proxy-reported cognitive decline and conversion to dementia

As shown in Table 3, 23.3% of the participants at baseline converted to dementia within five years. Converters had a higher age ($U = 8110, p < 0.001$), had more often MCI ($\chi^2(1) = 44.7, p < 0.001$) and proxy-reported decline ($\chi^2(1) = 6.28, p = 0.012$) than nonconverters. Converters were also characterized by lower GDS-15 ($U = 10680, p = 0.001$) and MMSE scores ($U = 8928, p < 0.001$). Cox regression, adjusted for age, sex, education, and depressive symptoms, were conducted separately for self- and proxy-reported cognitive decline at baseline to investigate the association with conversion to dementia. Table 4 shows that patients with proxy-reported cognitive decline and mutual self- and proxy-reported cognitive decline at baseline were significantly associated with developing dementia compared to patients who did not report proxy-reported cognitive decline or mutual complaints. Patients with self-reported decline also were related with developing dementia compared to patients without self-reported decline, however statistical significance could not be reached. If neither the patient nor a family member reported cognitive decline, patients developed dementia less

often, but statistical significance could not be reached (Table 4).

Association between self- and proxy reported cognitive decline and depressive symptoms

Taking together the group as a whole (NCI and MCI) linear mixed models, corrected for age, sex, and education showed that participants with self reported cognitive decline had more depressive symptoms averaged over all time points together ($F(1, 462) = 31.50, p < 0.001$) and level of symptoms were significantly higher at FU1, FU2, and FU5 (Table 5). Participants with proxy-reported cognitive decline also had reported more depressive symptoms averaged across all time points ($F(1, 478) = 9.60, p = 0.002$), and these were significantly higher at baseline and follow-up one (Table 5) compared to no proxy-reported decline. No interaction with time was found for both self- and proxy-reported cognitive decline.

Table 5 and Fig. 3 show the results of the separate linear mixed model analyses in patients with NCI or MCI. In NCI patients, self-reported decline was significantly associated with more depressive symptoms at each follow-up, but not at baseline. A significant overall interaction with time showed that the depressive symptoms in participants who experienced self-reported cognitive decline remained stable over time, while the depressive symptoms decreased over time in the group without self-reported decline. In contrast, no significant differences at each measurement or overall interaction with time were

Table 2
Differences in cognitive performances between participants with or without self- or proxy-reported cognitive decline per follow-up

Parameter	Baseline		FU1		FU2		FU3		FU5		Group by time ^c	
	β	95% CI	F	p								
Self-reported decline												
VLT IR	-0.17	-0.47, 0.12	-0.13	-0.36, 0.10	-0.39 ^b	-0.64, -0.13	-0.54 ^a	-1.03, -0.05	-0.25	-0.66, 0.17	0.99	0.411
VLT DR	-0.09	-0.36, 0.19	-0.32 ^b	-0.56, -0.08	-0.45 ^b	-0.73, -0.18	-0.32	-0.84, 0.21	-0.60 ^b	-1.05, -1.6	1.33	0.259
VAT	0.15	-0.26, 0.56	-0.21	-0.57, 0.15	-0.25	-0.71, 0.20	-0.23	-1.30, 0.83	-0.29	-0.95, 0.38	0.64	0.636
Semantic fluency	-0.10	-0.30, 0.11	-0.12	-0.30, 0.06	-0.24 ^a	-0.43, -0.04	-0.09	-0.46, 0.29	-0.36 ^a	-0.68, -0.05	0.73	0.572
CST-A / TMT-A	-0.02	-0.35, 0.31	0.05	-0.24, 0.34	-0.00	-0.33, 0.32	-0.43	-1.04, 0.17	-0.49	-1.01, 0.04	1.22	0.302
Concept shifting	-0.15	-0.61, 0.32	-0.28	-0.59, 0.04	0.06	-0.27, 0.40	-0.55	-1.20, 0.09	0.21	-0.31, 0.74	1.52	0.195
SCWT – I	-0.21	-0.70, 0.29	-0.37	-0.73, 0.01	-0.16	-0.57, 0.25	-0.33	-1.10, 0.44	-0.56	-1.23, 0.10	0.37	0.832
SCWT interference	-0.25	-0.88, 0.37	-0.24	-0.76, 0.27	0.10	-0.44, 0.63	-0.26	-1.26, 0.74	0.25	-0.59, 1.08	0.49	0.743
Proxy-reported decline												
VLT IR	-0.02	-0.27, 0.22	-0.10	-0.40, 0.21	-0.17	-0.54, 0.21	-0.01	-0.57, 0.56	-0.47	-1.00, 0.07	0.64	0.635
VLT DR	-0.01	-0.25, 0.22	-0.23	-0.55, 0.08	-0.23	-0.62, 0.17	-0.40	-1.00, 0.20	-0.35	-0.92, 0.22	0.75	0.557
VAT	-0.17	-0.52, 0.18	-0.60 ^b	-1.05, -0.15	-0.93 ^b	-1.57, -0.29	-2.39 ^b	-3.62, -1.15	-0.57	-1.44, 0.30	3.75	0.005 ^b
Semantic fluency	0.09	-0.26, 0.08	-0.05	-0.28, 0.18	-0.27	-0.57, 0.03	-0.60 ^b	-1.04, -0.15	-0.38	-0.79, 0.03	1.87	0.115
CST-A / TMT-A	-0.30 ^a	-0.57, -0.03	0.01	-0.36, 0.37	-0.16	-0.62, 0.29	-0.61	-1.28, 0.05	-1.46 ^b	-2.12, -0.81	4.18	0.003 ^b
Concept shifting	-0.07	-0.44, 0.30	-0.12	-0.53, 0.29	-0.48	-0.98, 0.03	-0.63	-1.38, 0.11	-0.53	-1.26, 0.20	1.05	0.383
SCWT – I	-0.48 ^a	-0.89, -0.07	-0.37	-0.84, 0.10	-0.26	-0.83, 0.31	-1.13 ^b	-1.98, -0.29	-2.30 ^b	-3.11, -1.49	5.42	<0.001 ^b
SCWT interference	0.38	-0.12, 0.88	-0.25	-0.91, 0.42	0.36	-0.41, 1.13	-1.70 ^b	-2.77, -0.63	-1.58 ^b	-2.66, -0.50	5.37	<0.001 ^b

Groups were compared using linear mixed models. Model: cognitive z score (dependent), time, group, group by time, sex, age, education, and depressive symptoms. Groups were compared using linear mixed models and differences are represented in β . FU, follow up; CI, confidence interval; VLT, verbal learning test; IR, immediate recall; DR, delayed recall; VAT, Visual Association Test; CST, Concept Shifting Test; TMT, Trail Making Test; SCWT, Stroop Color and Word Test. ^a $p < 0.05$. ^b $p < 0.01$. ^cOverall interaction between group and time.

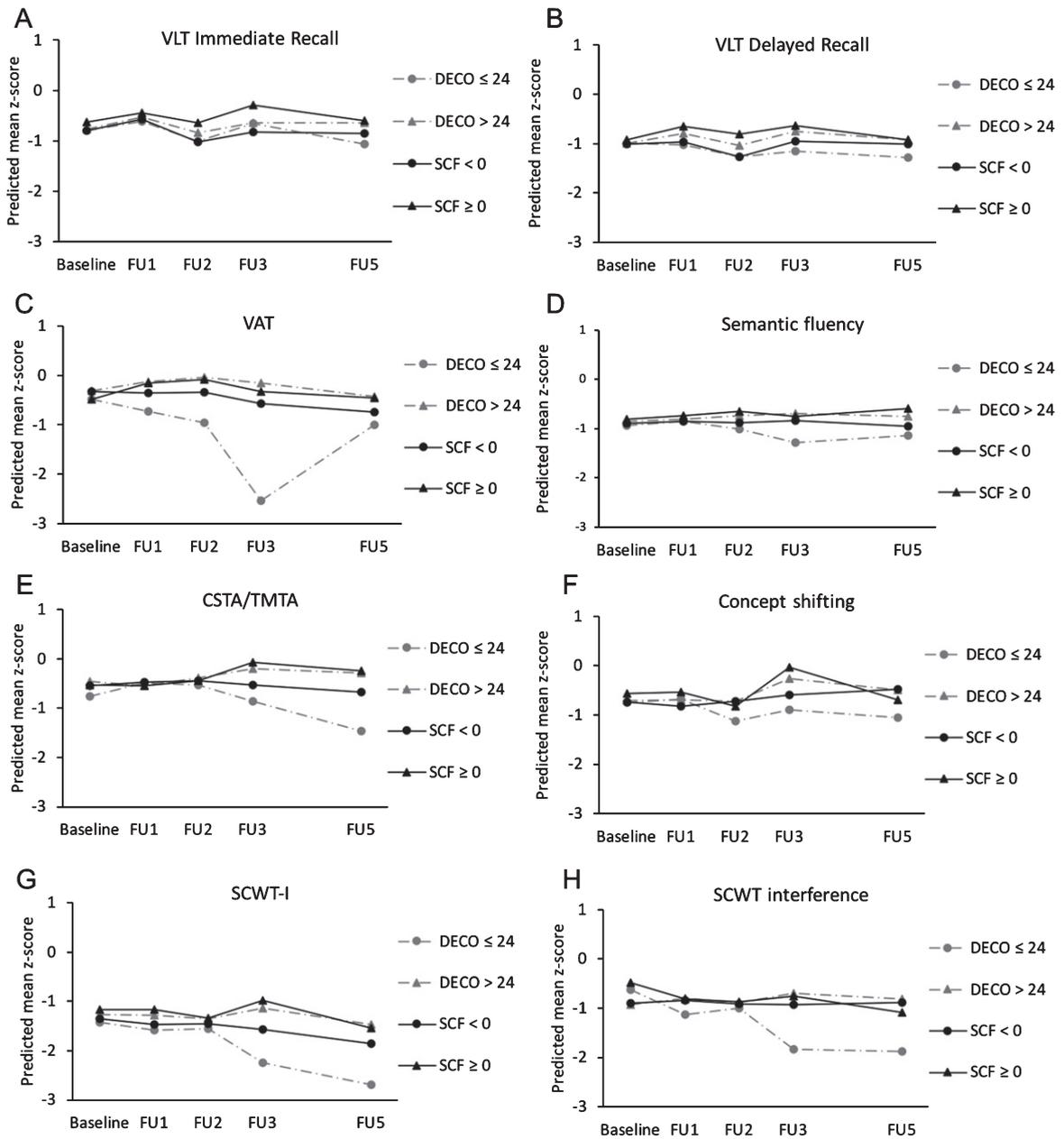


Fig. 2. Course of cognitive performances by subjective cognitive decline groups. DECO \leq 24: proxy-reported cognitive decline, DECO $>$ 24: no proxy-reported cognitive decline, SCF $<$ 0: self-reported cognitive decline, SCF \geq 0: no self-reported cognitive decline. A) Course of VLT IR scores. B) Course of VLT DR. C) Course of VAT scores. D) Course of fluency scores. E) Course of CSTA/TMTA scores. F) Course of concept shifting scores. G) Course of SCWT-I scores. H) Course of SCWT interference scores. The groups were compared using random-effects analysis with random intercept, random slope and unstructured covariance structure, adjusted for age, gender, education, and depressive symptoms. Predicted mean scores are estimated marginal means of subjective cognitive decline group by time. Higher mean scores represent a better cognitive performance (z-score). SCF, subjective cognitive functioning; DECO, *Détérioration Cognitive Observée*; VLT, 15-Word Learning Test; DR, delayed recall; IR, immediate recall; VAT, Visual Association Test; CST, Concept Shifting Test; TMT, Trail Making Test; SCWT, Stroop Color and Word Test.

Table 3
Summary characteristics of patients with and without conversion to dementia

	Converters (n = 94)	Nonconverters (n = 311)	p
Age, y	75.1 ± 6.8	68.5 ± 8.3	<0.001
Sex, n female (%)	44 (46.8)	113 (36.3)	0.068
Education n (%)			0.171
Low	31 (33.0)	127 (40.8)	
Middle	37 (39.3)	112 (36.0)	
High	26 (27.7)	72 (23.2)	
Diagnosis n (%)			0.001
NCI	11 (11.7)	157 (50.5)	
MCI	83 (88.3)	154 (49.5)	
Subjective cognitive decline n (%)			0.012
Self-reported	83 (88.3)	259 (83.3)	
Proxy-reported	35 (37.2)	75 (24.1)	
GDS-15 score	2.5 ± 2.1	3.8 ± 3.1	0.001
MMSE score	26.2 ± 2.8	27.9 ± 2.1	<0.001

Demographics are represented in mean ± SD unless stated otherwise. Education was stratified following the Dutch education system in low (primary), average (lower secondary or vocational), and high (higher secondary education, higher vocational, university) education. Groups were compared using Student's *t*-tests, Mann-Whitney U-tests and Pearson's chi-squared tests where appropriate. NCI, no cognitive impairment; MCI, mild cognitive impairment; GDS, Geriatric Depression Scale; MMSE, Mini-Mental Status Examination.

Table 4
Cox regression models for time to dementia diagnosis.

	No of cases	Hazard ratio (95% CI)	p
Self-reported cognitive decline versus no self-reported decline	83/342 (24%) 11/63 (18%)	1.26 (0.65 to 2.43)	0.489
Proxy-reported cognitive decline versus no proxy-reported decline	35/110 (32%) 59/295 (20%)	1.76 (1.12 to 2.78)	0.015 ^a
No self or proxy reported cognitive decline versus self- or proxy-reported decline	8/48 (17%) 86/357 (24%)	0.68 (0.32 to 1.43)	0.307
Both self and proxy reported cognitive decline versus no self and proxy reported decline	32/95 (34%) 62/310 (20%)	1.73 (1.09 to 2.76)	0.021 ^a

Each row represents a separate cox regression analysis adjusted for sex, age, education, and depressive symptoms. Number of cases indicates how many participants of the group were diagnosed with dementia. CI, confidence interval. ^a*p* < 0.05.

found for the proxy-reported decline group as compared to no proxy-reported decline. In MCI patients, self-reported decline was associated with more depressive symptoms at baseline, FU1 and FU5. Proxy-reported decline was associated with more depressive symptoms at baseline and FU1. No significant interaction with time was found for either self- or proxy reported cognitive decline.

DISCUSSION

This study aimed to gain further insight into the association between self- and proxy-reported cognitive decline and objective cognitive performance, depressive symptoms, and dementia conversion in memory clinic visitors. At baseline, self-reported cognitive decline was not associated with lower cognitive performance, while proxy-reported decline was

associated with a lower performance on two subtests. However, averaged over the course of five years, both self- and proxy-reported decline were associated with generalized lower objective cognitive performance. Proxy-reported decline also related to a significant decline over time on cognitive tests and to developing dementia, while self-reported decline did not reach statistical significance. Participants more often developed dementia when self-reported decline was confirmed by a proxy. Furthermore, both self- and proxy reported decline were associated with higher rates of depressive symptoms. In patients without cognitive impairment self-reported decline was significantly associated with more depressive symptoms while proxy-reported decline was not.

Our findings are in line with previous studies that found an association with subjectively perceived cognitive decline and objective cognitive perfor-

Table 5
Differences between participants with and without self or proxy-reported decline in depressive symptoms per follow-up moment

Parameter	Baseline		FU1		FU2		FU3		FU5		Group by time ^c	
	β	95% CI	F	<i>p</i>								
Both NCI and MCI												
Self-reported decline												
GDS-15	0.55	-0.12, 1.22	1.30 ^b	0.75, 1.85	1.00 ^b	0.38, 1.63	1.08	-0.12, 2.28	1.78 ^b	0.77, 2.80	1.27	0.282
Proxy-reported decline												
GDS-15	0.90 ^b	0.34, 1.46	1.06 ^b	0.34, 1.78	0.68	-0.24, 1.60	0.37	-1.02, 1.76	1.01	-0.32, 2.35	0.27	0.895
NCI patients only												
Self-reported decline												
GDS-15	-0.47	-1.43, 0.49	1.41 ^b	0.59, 2.23	1.52 ^b	0.63, 2.41	1.85 ^a	0.09, 3.62	2.20 ^b	0.75, 3.65	3.45	0.009 ^b
Proxy-reported decline												
GDS-15	0.80	-0.05, 1.66	0.30	-1.12, 1.72	0.86	-0.62, 2.34	0.41	-1.88, 2.69	1.85	-0.60, 4.31	0.38	0.822
MCI patients only												
Self-reported decline												
GDS-15	1.50 ^b	0.58, 2.41	1.14 ^b	0.39, 1.90	0.64	-0.23, 1.50	0.58	-1.04, 2.20	1.46 ^b	0.07, 2.85	0.71	0.587
Proxy-reported decline												
GDS-15	0.99 ^b	0.34, 1.46	1.23 ^b	0.38, 2.08	0.49	-0.69, 1.67	0.38	-1.40, 2.16	0.66	-0.98, 2.30	0.39	0.815

Groups were compared using linear mixed models. Model: depressive symptoms (dependent), time, group, group by time, sex, age, and education. Groups were compared using linear mixed models and differences are represented in β . FU, follow up; CI, confidence interval; GDS, Geriatric Depression Scale. ^a $p < 0.05$. ^b $p < 0.01$. ^cOverall interaction between group and time.

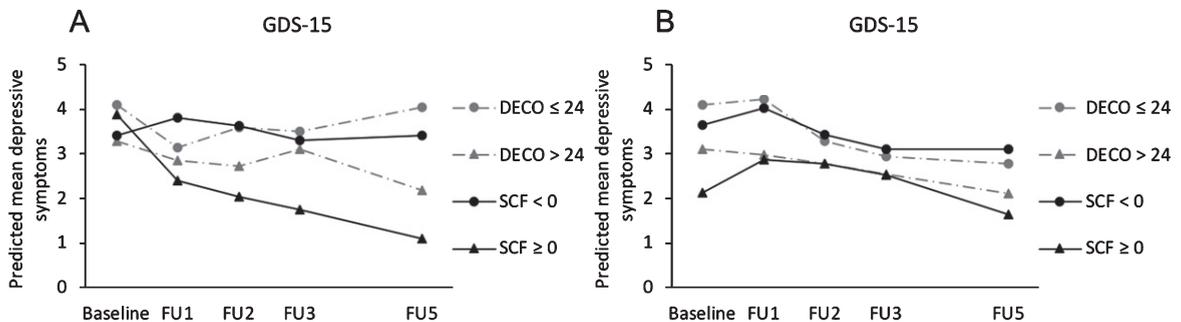


Fig. 3. Course of depressive symptoms by subjective cognitive decline groups. DECO \leq 24: proxy-reported cognitive decline, DECO $>$ 24: no proxy-reported cognitive decline, SCF $<$ 0: self-reported cognitive decline, SCF \geq 0: no self-reported cognitive decline. A: Course of depressive symptoms in patients with NCI. B: Course of depressive symptoms in patients with MCI. These figures are based on random-effects analyses adjusted for age, gender, and education. The predicted mean scores are estimated marginal means of time by group. Higher mean scores represent a higher level of depressive symptoms. SCF, subjective cognitive functioning; DECO, *Détérioration Cognitive Observée*; GDS, Geriatric Depression Scale.

mance, but contrasts with other studies [8–11, 17]. An explanation for these conflicting findings could be the differences in methodology, such as use of different populations, questionnaires and conceptual discrepancies [2, 40]. We found that proxy reported decline was more often associated with a lower performance on cognitive tests, cognitive decline, and conversion to dementia than self-reported decline. This is consistent with earlier studies that showed that proxy-reported cognitive decline is a better predictor of cognitive performance and development of dementia than self-reported decline in patients with no cognitive impairment and mild AD dementia [19, 21]. Only a handful studies, however, have contrasted self- and informant reported cognitive decline in a memory clinic population. Studies conducted in a memory-clinic population reported that experiencing more mutual complaints were associated with a worse cognitive trajectory, while other cross-sectional studies demonstrated that self- or proxy-reported decline did not result in any cognitive differences [16, 41, 42]. This study extends evidence to a clinical population from a memory clinic ranging from no cognitive disorders to MCI with a longer follow-up period. The lack of association between cognition and self- and proxy-reported decline at baseline might be explained by the difference between subjective and objective measurements. The questionnaires (SCF and DECO) require a subjective judgment of cognitive complaints in the past year, while cognitive performance is an objective measure at a single time point in which the premorbid level cannot be taken into account. The cross-sectional objective measurements might not be sensitive enough to determine subtle intra-individual changes as reflected in the subjective report

of the complaints, as proposed by a recent review [2]. Although proxy-reported cognitive decline was related to almost all cognitive test performances, it was shown that self-reported decline was related to a lower performance on selective cognitive tests only. Patients with self-reported cognitive decline performed worse on tasks concerning episodic memory and verbal fluency. These cognitive domains have been extensively described in the literature as one of the first characteristics of cognitive decline in prodromal AD [43, 44]. Decreased episodic memory scores could be a first sign of underlying AD pathology, such as medial temporal lobe damage or elevated amyloid- β burden, which in turn is also associated with self-reported decline [45]. These findings contrast with recent studies in memory-clinic visitors in which self-reported decline was not associated with cognitive differences [15, 42]. This could, however, be explained by smaller sample sizes, the use of a non-standardized way to measure self-reported cognitive decline or cross-sectional analyses. Recently, more evidence has become available showing that the combination of self-reported cognitive decline with AD positive biomarkers improves the ability of predicting objective cognitive decline and dementia [15, 46].

In both proxy- and self-reported cognitive decline an association with depressive symptoms was found. The finding that participants without cognitive impairment reported more depressive symptoms remained significant for the self-reported cognitive decline group, while this was not found for proxy-reported decline. Depressive symptoms have been considered one of the most influential factors associated with subjective cognitive decline in the absence of cognitive impairment [11, 47]. The question

remains what underlies the co-existence of subjective complaints and depressive symptoms. On one hand, the “cognitive model of depression” emphasizes that depressed patients often view themselves, others, and their future in a negatively distorted way [48]. This negative cognitive bias has been thought to mediate the impaired ability to accurately self-assess cognitive functioning [49]. A recent study shows an underestimation of cognitive functioning in depressed patients and an overestimation in healthy participants [50]. On the other hand, previous studies have found that depressive symptoms and major depression are related to lower hippocampal volumes and increased vascular brain lesions, which could cause cognitive impairment [51, 52]. The DSM-IV criteria of a Major Depressive Disorder also include having difficulties concentrating and an impaired ability to make decisions [53]. Conversely, it is also debated that depressive symptoms could be the result of realizing cognitive decline [54]. It is highly likely that these theories play a role in the association between subjective cognitive decline and depressive symptoms. Another explanation of the association between self-reported decline and depressive symptoms could be the high prevalence of depressive symptoms among patients referred to a memory clinic [55]. Since the memory clinic in this study is embedded within the psychiatric department, the prevalence could be even higher. Therefore, depressive symptoms might indicate underlying depressive symptomatology in memory clinic visitors which asks for a multidisciplinary approach in the evaluation of cognitive complaints.

Our study shows that proxy-reported cognitive decline is predictive for cognitive decline and developing dementia, while statistical significance was not reached for self-reported cognitive decline. This is in line with previous studies suggesting that informant report may enable identification of very early decline and that only a small proportion of participants with self-reported decline in a memory clinic develop dementia [2, 15]. In turn, other findings pointing towards a higher risk of conversion to MCI or dementia for memory clinic patients with self-reported decline [3, 56] However, our findings should be carefully interpreted because participants with self-reported cognitive decline seems to be a heterogeneous group and therefore less sensitive and discriminative for decline in cognitive performance. The high prevalence might have led to lack of contrast when comparing those with and without subjective cognitive decline to the cognitive outcomes.

For the dementia outcome, large standard errors and wide 95% confidence intervals indeed suggest large variability, which might have led to a relatively high and non-significant *p*-value despite an HR around 1.5 (and similar to the one found for proxy-reported decline). Obviously, subjective cognitive decline denotes a still very heterogeneous group of patients that was of limited predictive value. In contrast, proxy-reported decline seems to have a higher sensitivity for cognitive outcome and for conversion to dementia. This could be explained by less influence of reporting bias [57]. Proxy-reports have also been described as a more objective measure because they can give insight into more implicit processes which are often not noticed by the patient due to subtle changes [58]. When both self- and proxy-reported cognitive decline was present, this identified a group that more often converted to dementia than those with proxy-reported decline alone. This is in line with diagnostic criteria, which often includes cognitive complaints corroborated by family members [22]. In addition, mutual proxy- and self-reported cognitive decline have been shown to be associated with AD neuropathology [41]. These findings underline the importance of taken informant-based information into account in diagnostics at memory clinic settings.

For the current study, both strengths and limitations have to be kept in mind when interpreting the findings. The strengths of this study are the large sample size and the long follow-up period of up to five years. In addition, not many studies have focused on subjective cognitive decline in memory clinic visitors with and without cognitive impairment. In addition, a broad range of inclusion criteria were chosen to maximize generalizability in a clinical population. However, some limitations should be mentioned. Self-reported cognitive decline was measured using a new questionnaire that needs further psychometric evaluation. This questionnaire consists of two questions in which patients could indicate the range of the experienced change (from strong decline to strong improvement) on both memory and attention. This is likely to have a better validity and reliability than the use of one single question in which the patients only answers with yes or no, which has been used in several other studies [59]. Other studies have used more extensive questionnaires, such as the Cognitive Failures Questionnaire, but this does not include the opportunity to report improvements and focuses on memory complaints. Nonetheless, standardization of measurements for self-reported cognitive decline is important, which is also highlighted in the recently

proposed framework for subjective cognitive decline [2, 40] In addition, we should consider that only 67 participants could be included in the five-year follow-up measurement, which is partly due to the ongoing nature of this cohort study. For example, 159 participants (39.6%) were included in the study after 2013 and therefore did not reach their fifth-year assessment yet. In addition, the number of participants at the three-year follow-up was relatively small due to the study design, which did not include a regular three-year follow-up assessment initially. This resulted in less data for cognitive tests and therefore could have led to less robust findings (e.g., VAT follow-up 3, Fig. 2). The drop-outs may have resulted in non-differential attrition bias. When comparing groups at baseline, the drop-outs were frailer, that is, older and performing worse on most cognitive tests, leaving a less impaired sample in the analyses. This might have led to an underestimation of group differences due to the attrition of patients with cognitive impairment. However, the maximum likelihood estimation in the repeated-measures design takes this into account and is relatively robust against missing data points when covariates related to missing data are included [60]. It is also important to note that this study has been conducted in memory clinic visitors, and its outcome can therefore not be generalized to the general population.

In summary, the present study shows that both self- and proxy-reported cognitive decline was related to lower cognitive performance and more depressive symptoms. Proxy-reported decline indicated future cognitive decline and conversion to dementia. When subjective cognitive decline is confirmed by both the patient and informant it showed the strongest relation with subsequent dementia onset. The current findings may be useful for earlier identification of patients at-risk for dementia. This could lead to a larger time frame to implement interventions, guidance, and an increased understanding of the disease process. It has been shown that early interventions can be beneficial for caregivers in the pre-dementia phase when levels of stress and burden are still relatively low [61–63]. Our findings suggest that when a patient is referred to a memory clinic, the role of both depressive symptomatology and proxy-reported cognitive decline is very important to take into account.

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