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Original Research Article

The Progression of Alzheimer's Disease Can Be Assessed with a Short Version of the CERAD Neuropsychological Battery: The Kuopio ALSOVA Study

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Key Words

Dementia · Cognition · Clinical Dementia Rating · Follow-up studies · Mini-Mental State Examination · Executive function

Abstract

Background/Aims: Measuring and predicting Alzheimer's disease (AD) progression is important in order to adjust treatment and allocate care resources. We aimed to identify a combination of subtests from the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) that best correlated with AD progression in follow-up as well as to predict AD progression. ***Method:*** A total of 236 participants with very mild [Clinical Dementia Rating (CDR) = 0.5] or mild AD (CDR = 1.0) at baseline were followed up for 3 years. The CERAD-NB and Mini-Mental State Examination (MMSE) were used to assess cognition, and the CDR scale sum of boxes (CDR-sb) was employed to evaluate AD progression. Generalized estimating equations were used to develop models to predict and follow up disease progression. ***Results:*** Performance declined on all CERAD-NB subtests. The ability of the separate subtests to distinguish between groups (baseline CDR = 0.5 or 1.0) diminished during

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follow-up. The best combination of subtests that explained 62% of CDR-sb variance in follow-up included verbal fluency, constructional praxis, the clock drawing test, and the MMSE. Baseline values of the same combination predicted 37% of the CDR-sb change. ***Conclusion:*** A short version of the CERAD-NB subtests provides a promising and time-efficient alternative for measuring cognitive deterioration during AD follow-up. Although the initial signs of AD include memory difficulties, it may be useful to assess non-memory tasks in follow-up.

Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disease characterized by cognitive decline. As worldwide populations age and the proportion of individuals suffering from memory disorders increases, society and health care systems are faced with challenges. Several studies have suggested that the rate of cognitive decline can vary among individuals with AD [1–4], although the decline may occur at a slower rate than previously thought [3, 5].

Many baseline factors can predict the risk of rapid AD progression, including young age [6–8], male gender [8], deteriorated cognition [6, 8–10], behavioral symptoms [6, 7, 10, 11], poor awareness of impairment [10], impaired activities of daily living [8, 10], and delirium [12].

Although many neuropsychological tests have been used to predict disease progression, studies describing these tests are often outdated, and newer diagnostics and treatments have been developed in the meantime. For example, predictors of rapid AD progression include impairment in executive function [13], mental control abilities, performance of tasks that demand attention [14], performance in verbal memory tests, aphasia [14–17], and apraxia [17]. Atchison et al. [18] reported that the best cognitive predictor of AD progression after 1 year of follow-up was the global severity of cognitive impairment measured at the time of diagnosis.

Rapid cognitive decline is often defined as a reduction in Mini-Mental State Examination (MMSE) [19] score [8, 9, 11, 13, 14, 18, 20] or an increase in Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) score [6, 21]. However, the MMSE has been criticized for being insensitive to AD progression [18] due to large error associated with measurement and year-to-year variation [22].

Other indicators of disease progression include global measures such as the Clinical Dementia Rating (CDR) scale [10] and the CDR scale sum of boxes (CDR-sb) [21]. McLaughin et al. [23] proposed that global measures (e.g., the CDR) provided a better characterization of AD progression than the MMSE.

The Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) is a more sensitive and reliable measure for evaluating cognition in AD than the MMSE [24, 25]. The CERAD-NB was originally developed for screening cognitive impairment in the early stages of AD [24, 25]. Studies [26–28] have shown that the entire CERAD-NB and the later developed total score [29] constitute an accurate, reliable screening tool. In Finland, among some other countries, the CERAD-NB is widely used in screening, and therefore information obtained when this measure is used in persons with AD at the time of diagnosis is largely available. Recent studies have confirmed that the CERAD total score is also suitable for monitoring the progression of AD [4, 30]. However, using the whole CERAD-NB as a follow-up tool of AD progression in clinical settings is often too time-consuming. Individual CERAD-NB subtests have been used to distinguish stages of AD dementia, but memory tasks were not found to be effective [31, 32]. Cross-sectional studies have identified verbal fluency [28, 31, 33] and praxis [28, 31] as the best individual subtests for distinguishing AD

stages. Recognition memory [28] and the Boston Naming Test [33] have also effectively classified stages of AD in cross-sectional studies. However, less is known about the long-term changes in CERAD-NB subtest scores during AD progression.

More information about cognitive deterioration in long-term follow-up is needed, as well as brief and accurate tools to monitor and predict cognitive decline in AD. For example, Handels et al. [34] supported the use of empirical models to simulate the natural disease course in evaluating long-term disease progression.

The present study utilizes longitudinal follow-up data (1) to identify which CERAD-NB subtests and subtest combination are best correlated with AD progression (CDR-sb) during annual visits over a 3-year follow-up and (2) to determine whether AD progression can be predicted with baseline CERAD-NB subtest information as measured by changes in CDR-sb scores assessed during annual visits over a 3-year follow-up.

Methods

The data analyzed in this study were collected as part of the ALSOVA follow-up study [4, 35–37].

Participants

A total of 241 volunteer patient-caregiver dyads from 3 hospital districts in Finland were recruited into the ALSOVA study after receiving an AD diagnosis in 2002–2006. Although the participants were followed up annually for up to 5 years, the present study was based on 3-year follow-up data. Persons with AD were diagnosed by a geriatrician or neurologist according to the NINCDS-ADRDA [38] and DSM-IV [39] guidelines.

Participants were eligible for inclusion in the ALSOVA study if they were diagnosed with very mild or mild AD at baseline and were fluent in Finnish, community-dwelling, free of comorbid conditions that could have affected cognition at baseline, and capable of performing the CERAD subtests at baseline. Participants were also required to have a family caregiver who could participate in the ALSOVA study. The endpoints of the study were institutionalization and death. Of the 241 screened potential participants, 1 was excluded at the randomization visit (baseline visit) due to unconfirmed AD, 3 were excluded as they had moderate AD (CDR = 2) at baseline, and 1 was excluded due to inability to perform all the required CERAD baseline tests because of impaired vision. The final ALSOVA study group comprised 236 persons with very mild (CDR = 0.5, n = 128) or mild AD (CDR = 1.0, n = 108) at baseline.

Data Collection

Participation in the ALSOVA study involved attending annual visits to local memory clinics, where persons with AD were evaluated and caregivers were interviewed. A trained study nurse or a psychologist evaluated AD progression using the above-mentioned measures. The covariates used in this study included age, gender, and education (measured as total years of schooling).

Outcome Measures

Severity of AD was measured with the CDR and was an outcome measure in the analyses [40, 41]. The CDR is a structured interview that evaluates 6 areas (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). Scores obtained from this measure are combined to produce a CDR-sb score (range 0–18) and a global score (CDR stages: 0 = no dementia, 0.5 = very mild, 1 = mild, 2 = moderate, and 3 = severe dementia). The CDR-sb was used as an outcome measure in this study.

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Table 1. Number of study participants with available data at each visit by scale

	Baseline	Visit 1	Visit 2	Visit 3	At all visits
Participated	236	198	168	131	130
CDR stage	236	198	168	129	128
CDR-sb	236	198	168	128	128
MMSE	236	198	166	125	124
CERAD total	234	194	163	125	123
All data	234	194	163	125	123

Independent Variables

The CERAD-NB and MMSE were used to evaluate cognition. For each participant, the total CERAD-NB score was calculated using the subtest addition method (range 0–100) [29]. The Finnish version of the CERAD-NB included all subtests from the original English test battery, including the Boston Naming Test (15-item version; range 0–15), category fluency (animals; range from 0 to no limit), word list learning (range 0–30), word list recall (range 0–10), word list recognition (range 0–20), and constructional praxis (range 0–11). In addition, the Finnish version included the clock drawing test (range 0–6) and the constructional praxis delayed recall test (range 0–11) [24]. All 8 subtests included in the Finnish CERAD-NB and the MMSE were used as independent variables in the analyses to meet aim 1. To achieve aim 2 (prediction), only the baseline values of the subtests that best correlated with AD progression at follow-ups (for aim 1) were used.

Even if participants were not able or willing to perform all the CERAD-NB subtests or the MMSE during the annual follow-up visits, we still collected applicable parts of the CERAD-NB and the MMSE as well as the CDR caregiver interview data. Table 1 summarizes the available data.

Statistical Analysis

Descriptive statistical methods (i.e., means, percentages, etc.) were used to characterize the longitudinal CDR stage, CDR-sb, CERAD-NB, and the MMSE scores. An independent-samples t test or nonparametric Mann-Whitney U test was used to compare participants with very mild (CDR = 0.5) and those with mild AD (CDR = 1) at baseline, males and females, and participants who completed the 3-year follow-up and those who dropped out. The Spearman rank correlation coefficient was used to analyze correlations between age, education, CERAD-NB subtests, MMSE scores, CERAD-NB total scores, and CDR-sb scores during the 3-year follow-up.

Due to relatively high attrition rates, patterns in possibly missing data were analyzed. Generalized estimating equation (GEE) analyses were conducted step by step, and the GEE models used were specified with gaussian distribution, identity link function, and unstructured correlation matrix. First, to meet aim 1, associations between AD severity (CDR-sb at the annual visits over the 3-year follow-up) and the repeated measures of MMSE, CERAD-NB total score, and each CERAD-NB subtest were analyzed separately with and without the selected covariates of age at baseline, gender, education, and time. Variables were then added and removed using repeated measures of these variables to find the best subtest combination to explain the variance of the repeated measures of CDR-sb. We evaluated the goodness of the combination in terms of goodness-of-fit diagnostics and pseudo-R^2 statistics [42], which measured how much of the outcome variable's variation was explained by the model at hand. Finally, to meet study aim 2, the same variables that were included in the best subtest combination, but only the baseline values, were used to predict disease progression over time.

Table 2. Baseline demographics and baseline MMSE, CERAD-NB total, and CERAD-NB subtest scores

	All (n = 236)	CDR 0.5 group (n = 128)	CDR 1 group (n = 108)	p[a]
Female, n (%)	121 (51.3)	73 (57.0)	48 (44.4)	0.054
Age, years	75.15 (6.52)	74.50 (6.26)	75.92 (6.78)	0.097
Education, years	7.55 (3.29)	8.11 (3.51)	6.89 (2.90)	0.004*
CDR-sb	4.14 (1.47)	3.10 (0.85)	5.37 (1.05)	0.001*
MMSE	21.50 (3.44)	22.65 (3.07)	20.15 (3.38)	0.001*
CERAD-NB total	51.58 (11.85)	54.64 (11.73)	47.95 (10.98)	0.001*
Verbal fluency	13.49 (5.19)	14.48 (4.99)	12.31 (5.97)	0.001*
Constructional praxis	8.36 (1.86)	8.56 (1.78)	8.12 (1.94)	0.138
Clock drawing test	4.00 (1.73)	4.39 (1.56)	3.55 (1.81)	0.001*

Data are shown as means (SD) unless otherwise specified. Independent-samples t tests and Pearson's χ^2 test were used in comparisons between groups. * $p < 0.05$. [a] Group comparisons.

With the GEE models, the relationship between the variables of the model at different time points could be analyzed simultaneously to reflect the longitudinal relationship between the outcome variable and the time-independent and/or time-dependent covariates using all available longitudinal data.

Statistical significance was defined as $p < 0.05$. Analyses were performed with the IBM SPSS statistics software (version 19.0; SPSS Inc., Chicago, Ill., USA) or STATA (version 12.0; StataCorp, College Station, Tex., USA).

Ethical Considerations

The Ethics Committee of the Kuopio University Hospital approved the ALSOVA study (opinion No. 64/00). Potential participants were informed about the study in both oral and written form, with an emphasis on the voluntary nature of participation and the confidentiality of the collected data. The informed consent forms were signed by both the persons with AD and by their caregivers. The caregivers also provided proxy consent on behalf of the persons with AD.

Results

At baseline, 53.8% of the participants had very mild AD (CDR = 0.5; group CDR 0.5), and 46.2% had mild AD (CDR = 1; group CDR 1). All the participants who attended follow-up visits used AD-specific medication. At baseline, the CDR 0.5 and the CDR 1 group did not differ significantly in age, but the CDR 0.5 group was slightly more educated, and differences in the proportion of female subjects came close to reaching significance (table 2).

During the 3-year follow-up, both groups showed a high prevalence of mild AD (CDR = 1). A total of 130 participants were followed up for 3 years. Reasons for participant dropout included institutionalization (34/236), death (20/236), health deterioration (15/236), caregiver-related reasons (health, burden, death or refusal; 20/236), and patients' refusal to participate (8/236). Although there was no significant difference in baseline AD severity (CDR-sb) between the participants who dropped out and those who did not drop out ($p = 0.155$), those who dropped out had more severe cognitive impairments (CERAD-NB total $p = 0.047$, MMSE $p = 0.033$) and achieved lower scores in the clock drawing test ($p = 0.003$) at

baseline. Furthermore, there was no significant difference in education ($p = 0.667$), baseline age ($p = 0.407$), or other CERAD-NB subtest scores (data not shown) between those who remained in the study and those who dropped out.

AD Progression Measured with CERAD-NB Subtests

Performance on all CERAD-NB subtests declined during the 3-year follow-up period (fig. 1). At baseline, the CDR 0.5 group outperformed the CDR 1 group on the MMSE, the CERAD-NB total, the CDR-sb, and most of the CERAD-NB subtests. However, at baseline, the groups were not significantly different in their scores for naming or constructional praxis. Then, at follow-up visits 1 and 2, the groups showed significant differences in constructional praxis. At follow-up visit 3, the verbal fluency, word list learning, CERAD-NB total, and CDR-sb scores remained significantly different between the CDR 0.5 and the CDR 1 group. Throughout all the visits, the groups were distinguished by differences in verbal fluency, CERAD-NB total, and CDR-sb scores. In the CDR 1 group, word list recall, constructional praxis, and clock drawing test scores were higher at visit 3 than at visit 2.

Spearman's correlation values were used to analyze the associations between age, education, the MMSE, the CERAD-NB subtests, and the CERAD-NB total (data not shown). The verbal fluency and clock drawing tests, both of which measure executive function skills, were the only subtests that did not correlate with education at any visit. Age was only correlated with the naming test scores. The global cognitive measures, CERAD-NB total and MMSE were correlated with all subtests at baseline and all follow-up visits. Men outperformed women on the Boston Naming Test at baseline ($p < 0.001$), at follow-up visit 1 ($p = 0.022$), and at follow-up visit 3 ($p = 0.015$). Men also outperformed women on the word list recognition test at follow-up visit 3 ($p = 0.031$). On the other hand, women outperformed men on the word list learning test at baseline ($p = 0.022$) and on constructional praxis at follow-up visit 3 ($p = 0.044$). Women also had lower (better) CDR-sb scores than men at follow-up visit 1 ($p = 0.026$) and at follow-up visit 2 ($p = 0.028$).

Modeling AD Severity (CDR-sb) with the CERAD-NB Subtests

Table 3 presents the results for aim 1, GEE models that incorporated the MMSE (model 1), the CERAD-NB total (model 2), both the MMSE and CERAD-NB tests (model 3), and the best CERAD-NB subtest combination (model 4) for the purpose of modeling AD severity. The best explorative model included gender, time, verbal fluency, word list learning, word list recall, constructional praxis, and the clock drawing test (data not shown), which explained CDR-sb better than the model including all subtests. Next, we limited the number of tests in the model in an attempt to decrease the burden associated with test administration. The resulting model included gender, time, verbal fluency, constructional praxis, and the clock drawing test. Education and age were included in the model. The model that included verbal fluency, constructional praxis, and the clock drawing test with the covariates produced nearly the same pseudo-R^2 as the above-mentioned battery, which included 5 subtests. Addition of the MMSE boosted the pseudo-R^2.

With this method, we determined that model 4 provided the best results (table 3). Although model 3 (the combined MMSE and CERAD-NB total) provided a better explanation for the CDR-sb variance than either model 1 or model 2, model 4 produced a higher pseudo-

Fig. 1. Progression of CERAD-NB subtest, MMSE, and CERAD-NB total scores of participants with very mild (group CDR 0.5) or mild AD (group CDR 1) at baseline during the 3-year follow-up. Significant differences ($p < 0.05$) between the CDR 0.5 and the CDR 1 group at baseline are shown.

(For figure see next page.)

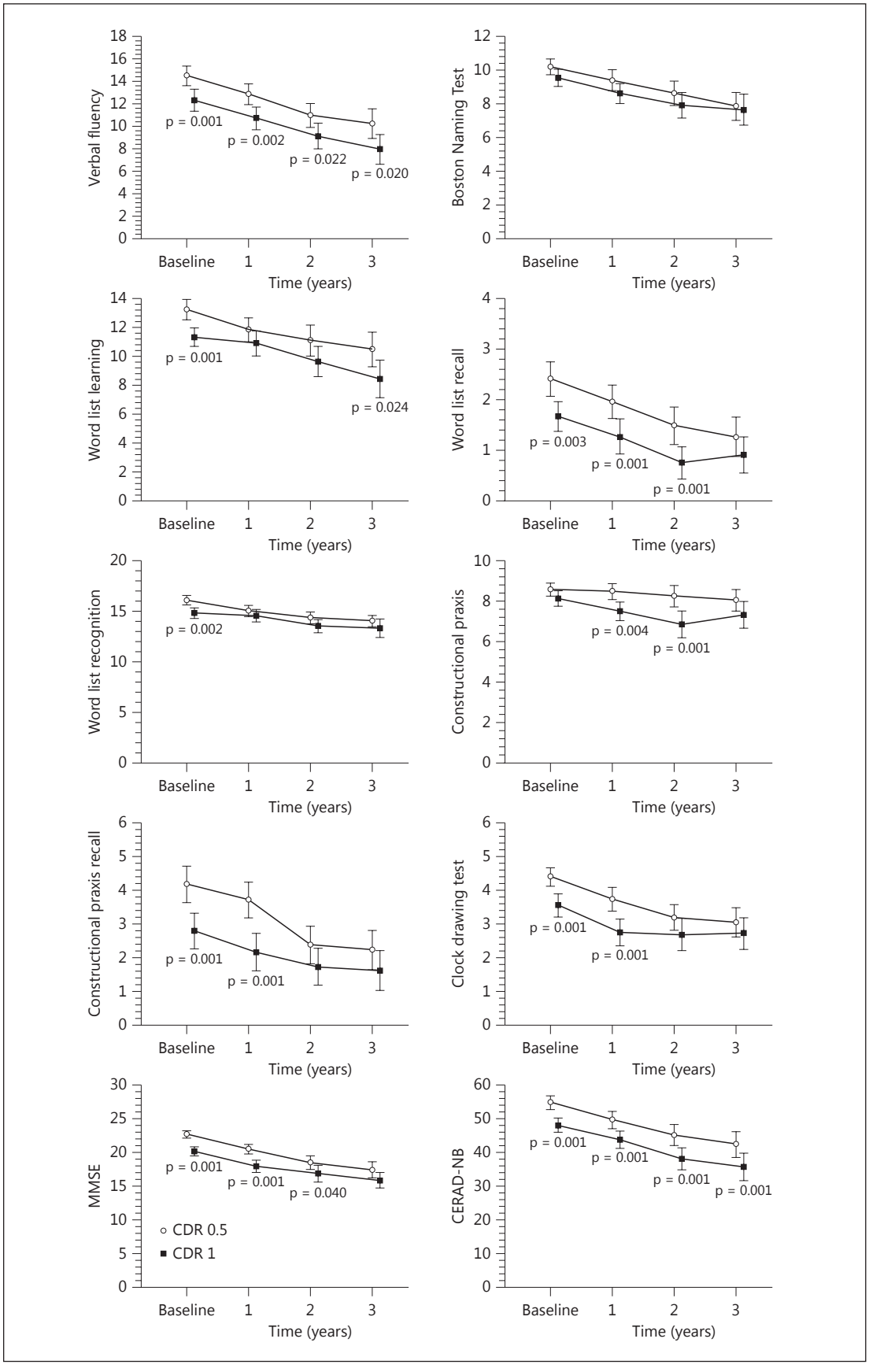
Verbal fluency
p = 0.001
p = 0.002
p = 0.022
p = 0.020
Boston Naming Test
Word list learning
p = 0.001
p = 0.024
Word list recall
p = 0.003
p = 0.001
p = 0.001
Word list recognition
p = 0.002
Constructional praxis
p = 0.004
p = 0.001
Constructional praxis recall
p = 0.001
p = 0.001
Clock drawing test
p = 0.001
p = 0.001
MMSE
p = 0.001
p = 0.001
p = 0.040
CDR 0.5
CDR 1
CERAD-NB
p = 0.001
p = 0.001
p = 0.001
p = 0.001
Baseline
1
2
3
Time (years)

Table 3. Association of demographic variables, CERAD-NB subtests, CERAD-NB total score, and the MMSE with AD progression (CDR-sb)

Parameter	Model 1	Model 2	Model 3	Model 4
Intercept	11.51 (8.87, 14.15)*	10.54 (7.77, 13.32)*	11.84 (9.29, 14.40)*	11.74 (9.21, 14.27)*
Time				
Baseline	–2.70 (–3.16, –2.24)*	–3.31 (–3.72, –2.89)*	–2.41 (–2.81, –2.01)*	–2.45 (–2.84, –2.05)*
Year 1	–1.90 (–2.26, –1.54)*	–2.22 (–2.62, –1.83)*	–1.68 (–2.02, –1.33)*	–1.72 (–2.06, –1.38)*
Year 2	–0.99 (–1.31, –0.68)*	–1.22 (–1.57, –0.86)*	–0.88 (–1.19, –0.57)*	–0.89 (–1.21, –0.58)*
Year 3	0[a]	0[a]	0[a]	0[a]
Gender				
Female	–0.64 (–1.01, –0.28)*	–0.60 (–0.99, –0.22)*	–0.63 (–0.99, –0.27)*	–0.58 (–0.93, –0.24)*
Male	0[a]			0[a]
Age	0.03 (–0.00, 0.06)	0.02 (–0.01, 0.06)	0.03 (0.00, 0.06)	0.04 (0.01, 0.07)*
Education	0.02 (–0.04, 0.08)	–0.01 (–0.07, 0.05)	0.04 (–0.02, 0.10)	0.03 (–0.03, 0.09)
MMSE	–0.32 (–0.38, 0.26)*	–	–0.26 (–0.31, –0.21)*	–0.26 (–0.31, –0.21)*
CERAD-NB total	–	–0.08 (–0.10, –0.07)	–0.04 (–0.05, –0.02)*	–
Verbal fluency	–	–	–	–0.04 (–0.08, –0.01)*
Constructional praxis	–	–	–	–0.14 (–0.21, –0.06)*
Clock drawing test	–	–	–	–0.10 (–0.20, –0.01)*
Scale	3.55	3.89	3.35	3.24
Pseudo-R^2	58.47	54.52	60.77	62.07
QIC	2,533.40	2,769.76	2,390.86	2,310.24
QICC	2,524.05	2,762.58	2,383.40	2,302.28

Data denote B regression coefficients (95% CI) unless otherwise specified. GEE models with repeated values of each variable were used. All GEE models were specified with gaussian distribution, identity link function, and unstructured correlation matrix. Model 1: time, gender, age, education, and MMSE. Model 2: time, gender, age, education, and CERAD-NB total. Model 3: time, gender, age, education, MMSE, and CERAD-NB total. Model 4: time, gender, age, education, MMSE, verbal fluency, constructional praxis, and clock drawing test. Pseudo-R^2: coefficient of determination, calculated as 1 – [unexplained variance by model/overall variance of dependent variable (CDR-sb)]. QIC = Quasi likelihood under independence model criterion; QICC = corrected quasi likelihood under independence model criterion, interpreted with the-smaller-the-better principle. * $p < 0.05$. [a] Set to 0 because this parameter is redundant.

R^2 estimate (i.e., had better explanatory power) (table 3). Thus, the MMSE, 3 CERAD-NB subtests, and a selected set of covariates could explain 62.1% of the variance in dementia severity (measured in terms of CDR-sb) during the 3-year follow-up period.

Predicting the Progression of AD with the Proposed Model Using the Baseline Measurements

Finally, we tested our explorative models for predicting AD progression to assist with addressing aim 2 of the study. The model that included baseline values of the MMSE, verbal fluency, constructional praxis, the clock drawing test scores, and the covariates predicted CDR-sb progression during the 3-year follow-up period better than the MMSE alone, the CERAD-NB total alone, or the combination of MMSE and CERAD-NB (table 4). The model that included only baseline measurements had a pseudo-R^2 value of 36.6%.

Discussion

To the best of our knowledge, this is the first study to examine potential combinations of CERAD-NB subtests in evaluating or predicting AD progression. We also report 3-year follow-up data on CERAD-NB subtests of persons with very mild or mild AD at baseline. In

Table 4. Demographic variables, CERAD-NB subtests, CERAD-NB total score, and the MMSE at baseline used to predict AD progression (CDR-sb) during the 3-year follow-up

Parameter	Model 1	Model 2	Model 3	Model 4
Intercept	15.43 (10.96, 19.91)*	14.14 (9.92, 18.37)*	16.01 (11.83, 20.19)*	15.49 (11.44, 19.53)*
Time				
Year 1	–3.30 (–3.76, –2.84)*	–3.30 (–3.76, –2.84)*	–3.29 (–3.75, –2.83)*	–3.31 (–3.77, –2.86)*
Year 2	–1.79 (–2.17, –1.41)*	–1.78 (–2.16, –1.40)*	–1.77 (–2.15, –1.39)*	–1.78 (–2.16, –1.40)*
Year 3	0[a]	0[a]	0[a]	0[a]
Gender				
Female	–0.99 (–1.62, –0.36)*	–0.94 (–1.58, –0.31)*	–0.97 (–1.59, –0.35)*	–0.91 (–1.50, –0.31)*
Male	0[a]		0[a]	0[a]
Age	0.02 (–0.04, 0.07)	0.00 (–0.05, 0.05)	0.01 (–0.04, 0.06)	0.02 (–0.03, 0.06)
Education	–0.01 (–0.11, 0.10)	–0.02 (–0.13, 0.08)	0.02 (–0.08, 0.13)	–0.00 (–0.11, 0.10)
MMSE	–0.33 (–0.43, –0.22)*	–	–0.21 (–0.33, –0.10)*	–0.17 (–0.28, –0.06)*
CERAD-NB total	–	–0.09 (–0.12, –0.06)*	–0.06 (–0.09, –0.03)*	–
Verbal fluency	–	–	–	–0.05 (–0.12, 0.01)
Constructional praxis	–	–	–	–0.18 (–0.35, 0.00)
Clock drawing test	–	–	–	–0.37 (–0.57, –0.17)*
Scale	6.57	6.59	6.25	5.89
Pseudo-R^2	29.21	29.02	32.62	36.55
QIC	3,187.98	3,195.98	3,032.11	2,852.76
QICC	3,180.25	3,188.97	3,023.80	2,840.32

Data denote B regression coefficients (95% CI) unless otherwise specified. GEE were used for modeling with the baseline values of each variable. All GEE models were specified with gaussian distribution, identity link function, and unstructured correlation matrix. Model 1: time, gender, age, education, and MMSE. Model 2: time, gender, age, education, and CERAD-NB total. Model 3: time, gender, age, education, MMSE, and CERAD-NB total. Model 4: time, gender, age, education, MMSE, verbal fluency, constructional praxis, and clock drawing test. Pseudo-R^2: coefficient of determination, calculated as 1 – [unexplained variance by model/overall variance of dependent variable (CDR-sb)]. QIC = Quasi likelihood under independence model criterion; QICC = corrected quasi likelihood under independence model criterion, interpreted with the-smaller-the-better principle. * $p < 0.05$. [a] Set to 0 because this parameter is redundant.

the current study, we created an explorative model that could explain the majority of variance in AD severity (the CDR-sb). The findings from this study suggest that a combination of the MMSE and 3 CERAD-NB subtests (verbal fluency, constructional praxis, and the clock drawing test) including the covariates age, gender, and education could explain over 60% of the variance in the CDR-sb during follow-up. Furthermore, if only baseline data were used, the same set of variables could explain approximately 37% of the variance in AD severity (measured with the CDR-sb). This study showed that the CERAD-NB subtests were able to detect the participants' cognitive decline during the 3-year follow-up period. However, the ability of each CERAD-NB subtest to separately distinguish between the study groups (CDR = 0.5 and 1.0 at baseline) declined during follow-up. At the beginning of the follow-up period, almost all the CERAD subtests and the MMSE differed between the groups. Up to the 2-year follow-up visit, the original study groups could be distinguished by word list recall, constructional praxis, and the MMSE. During the entire 3-year follow-up period, the study groups only significantly differed in verbal fluency and the CERAD total score. Although memory problems are typically the first sign of AD, other aspects of cognition, such as executive function and visual perception, may provide better AD staging information as discussed by Welsh et al. [28].

A previous study [43] showed that verbal fluency declined more in persons with AD than in controls and persons with preclinical AD. In cross-sectional studies, verbal fluency [28, 31,

33] and praxis [28, 31] were the best CERAD-NB subtests for distinguishing between AD stages. In our study sample, verbal fluency distinguished the study groups at all visits, and it was not subject to a ceiling or floor effect. Furthermore, as is consistent with previous cross-sectional studies, the findings from this study suggested that constructional praxis was a good subtest for modeling AD progression, and it could distinguish between groups during the first 2 years following AD diagnosis. However, constructional praxis scores remained stable in the CDR 0.5 group throughout follow-up and in the CDR 1 group after 2 years of follow-up. The findings of the study also suggest that the clock drawing test is a viable tool for modeling AD progression; however, the observed deterioration in this test slowed after the 1-year follow-up visit (especially in the CDR 1 group). The clock drawing test has been found to test executive control [44] and can characterize the degree of cognitive deterioration [45]; however, the studies in which these results were obtained relied on an elaborate scoring system for classifying different types of errors.

In contrast, the delayed memory task (delayed word list recall and delayed constructional praxis recall) scores approached a floor effect during the last visit, consistent with previous observations of delayed recall measures [28]. However, it was also found that word list recall could distinguish between the study groups during the first 2 years of follow-up. Previously, only memory recognition tasks were found to be effective at distinguishing between CDR stages [28, 31, 32].

Although memory tasks are used for the early detection of AD, this study, in line with previous studies [28, 32], suggests that non-memory tasks appear to be better tools for evaluating AD progression. The subtests included in our follow-up model, such as verbal fluency, constructional praxis, and the clock drawing test, assessed executive function and visual perception. In a recent meta-analysis, an association was found between executive function and activities of daily living in dementia [46]. This study also found that verbal fluency and the clock drawing test were the only subtests that did not correlate with education at any visit. Additionally, since education did not predict AD progression in the predictive models, the model used in this study is unlikely to be biased by patients' education. Fluency was not correlated with education in the study of Welsh et al. [25], either. However, in contrast to our findings, a previous review suggests a correlation between education and the clock drawing test [47]. As opportunities for education have been limited in Finland in the past, the level of education is typically low for members of this age group. Consequently, the educational level of the persons with AD in this study group was not necessarily a good indicator of cognitive capacity. Furthermore, both verbal fluency and the clock drawing test have been correlated with education in a Finnish normative population [48]. A possible explanation for these discrepancies might be that the influence of education is different in normally aging individuals and in persons with AD.

As suggested by earlier reports [8], it was found that male gender was associated with an increased AD progression rate. However, in contrast to several previous studies, the findings from this study suggest that age was not a significant predictor of AD progression [6–8]. This discrepancy may be explained by the fact that participants in this study were already of advanced age at disease onset (mean age at onset 75.2 years).

Although the model proposed in this study explained the major part of the variance in AD severity as a follow-up tool, it was not as successful in predicting AD progression over the 3-year follow-up period. Baseline cognitive and demographic characteristics explained only one third of the variance in AD progression. However, using only baseline values, the model proposed in this study predicted the progression of AD better than either the MMSE or the CERAD-NB alone or both together. Furthermore, the predictive accuracy of the proposed models on an individual level is to be examined in the future.

In clinical settings, the MMSE has often been used as the only measure to evaluate cognitive deterioration and AD progression, despite the fact that it has been reported to be insensitive to longitudinal follow-ups [18, 22] and is subject to floor and ceiling effects [49]. In this study, the MMSE progressed linearly relative to the CERAD-NB total and the CDR-sb but lost its ability to distinguish between the study groups 2 years after the AD diagnosis. The new model including the MMSE and 3 subtests is more comprehensive than the MMSE alone, but it remains brief and easy to administer. It has been shown that the CERAD-NB total score is a good measure of AD progression [4], consistent with previous study findings [30]. However, the whole CERAD-NB is often too time-consuming to assess in clinical settings as a follow-up tool – even if it is recommended for use as a screening tool. The new, shorter version proposed in this study may facilitate the follow-up of AD progression by providing a promising alternative to the MMSE and the longer CERAD-NB in research and clinical practice. Additionally, it may be an easier-to-learn and more objective measure than the CDR-sb. However, this explorative model must be tested in other populations to determine its generalizability as well as to examine its predictive accuracy and reliability.

Our study has both strengths and limitations. We followed up medicated persons with AD in normal care for up to 3 years after AD diagnosis. Validated and respected measures that have been used in other study populations and cultures were also used in this study. However, only persons with very mild or mild AD at baseline were included, which limits the generalizability of the results.

The use of volunteers as study participants may have limited the generalizability of the study findings. Additionally, almost half the participants dropped out during follow-up, although this was to be expected in this group [50]. Dropouts may lead to bias in statistical analyses and may influence the results. However, we used GEE modeling, one remarkable advantage of which was the possibility to use all available longitudinal data including those from the participants who dropped out. If conventional analysis of variance methods for repeated measurements had been applied instead, complete data would have been required on every subject (on every visit over the follow-up period) or else they would have been dropouts from the analysis, which in turn could have led to a significant loss of statistical power and could have been a potential source of sample bias (i.e., individuals with complete data may not have been representative of the entire cohort). In the original ALSOVA study, institutionalization and death were endpoints because we wanted to study AD progression in patients with early AD who lived at home with the help of caregivers, as is often the case in real-life settings all over the world.

In conclusion, the brief model proposed in this study, which includes the MMSE and verbal, visual, and executive function CERAD-NB subtests, could explain over 60% of the variance in dementia severity during a 3-year follow-up period. The model's predictive capacity was also better than that of the MMSE or CERAD-NB alone, even if a model that included only baseline demographic and cognitive measures explained less than 40% of the variance in dementia progression. A recent review has called for the use of a multivariate approach [51] to model long-term AD progression, and, in the future, our results can be connected with other clinical symptoms and health-related factors such as comorbidities, activities of daily living, and neuropsychiatric symptoms.

Appendix

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R. Lahoz is a paid employee of Novartis Pharma AG. J. Martikainen is a senior partner of ESiOR Oy, which provides health economic and outcome research services to pharmaceutical and medical device companies. S. Väätäinen is a paid employee of ESiOR Oy.

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