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Long-term course of Alzheimer's disease in patients treated according to the Dutch dementia guideline at a memory clinic: a 'real-life' study

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Running title

Long-term course of Alzheimer's disease

Abstract

Introduction: There is little knowledge of the long-term course of Alzheimer's disease (AD) in light of current pharmacological and non-pharmacological interventions provided in a 'real-life' setting.

Methods: The Frisian Alzheimer's Disease Cohort study is a 'real-life' study of the course of AD in patients (n=576) treated with pharmacological (i.e. cholinesterase inhibitors (ChEIs)) and non-pharmacological (i.e. case management, respite care) interventions. Disease course was described by changes in cognition (MMSE, clock-drawing test (CDT)) and number of types of professional care applying a repeated measures analysis using a marginal model (population based average model). In addition, behavioural and psychological symptoms (BPS), proportions of nursing home admissions and deaths were investigated.

Results: During 3.5 years, the average MMSE decreased from 22.24 to 18.91, the CDT score increased from 3.38 to 4.05, the number of types of professional care increased from 0.85 to 2.64 and the patients with BPS increased from 29.0% to 70.2%. The proportion of patients admitted to a nursing home was 40.8% and 41.0% died.

Conclusion: Cognition and behaviour of AD patients deteriorated accompanied with an increase in care-dependency during 3.5 years. Nevertheless, compared to the pre-ChEI-era, current pharmacological and non-pharmacological interventions appear to slow cognitive decline, which emphasizes that they seem to have a favorable effect.

Key words: Alzheimer disease, community-dwelling, 'real-life' setting, memory clinic, cholinesterase inhibitors, disease course

1. Introduction

Alzheimer's disease (AD), the most frequent cause of dementia¹, is characterized by cognitive impairment, functional decline, and neuropsychiatric symptoms². Consequently, AD has substantial effects on the quality of life of patients and their caregivers³.

There is no curative treatment for AD. Since the 1990s, two types of symptomatic pharmacologic treatments are available: the N-Methyl-D-aspartate glutamate receptor antagonist memantine (approved in 2002) and the cholinesterase inhibitors (ChEIs) rivastigmine, galantamine and donepezil^{4,5}. ChEIs are recommended for the management of mild to moderate AD, memantine for moderate to severe AD^{5,6}. Randomised controlled trials (RCTs) have shown beneficial effects of ChEIs on cognition, global clinical state, activities of daily living and behaviour⁷. However, it is difficult to draw firm conclusions about the long term effectiveness as most trials lasted on average six months^{4,7}. In addition, RCTs are performed in selected groups of patients with strict inclusion and exclusion criteria. Consequently, AD patients enrolled in RCTs may not be representative of AD patients treated in a 'real-life' setting, limiting the external validity of the results^{8,9}.

In the past years, it is not just the pharmacological treatment that has changed the management of AD. Drugs are given in addition to multiple non-pharmacological interventions such as dementia case management, respite care and occupational therapy⁶. In the Netherlands, memory clinics have been established to provide and monitor these pharmacological and non-pharmacological interventions. They provide care according to the Dutch dementia guideline, and ChEIs and memantine are reimbursed if patients are treated accordingly⁶.

Knowledge of the long-term course of AD in light of current pharmacological and non-pharmacological interventions provided in a 'real-life' setting, i.e. outside of clinical trials, is scarce. A better understanding of the long-term course is of great importance as it gives the possibility to assess the effect of these interventions and to plan future needs for care. This may contribute to an improvement of outcomes for AD patients. This 'real-life' study aims to describe the long-term course of AD in patients treated with pharmacological and non-pharmacological interventions according to the Dutch dementia guideline at a memory clinic.

2. Methods

2.1. Study design & setting

The Frisian Alzheimer's Disease Cohort study is a retrospective longitudinal 'real-life' study of the long-term course of AD in patients treated with pharmacological and non-pharmacological interventions according to the Dutch Dementia guideline at our memory clinic. Patients were evaluated by a physician and a specialized geriatric nurse. A comprehensive geriatric assessment (CGA)¹⁰ was performed including cognitive screening tests such as the Mini Mental State Examination (MMSE) and the clock-drawing test (CDT). When a diagnosis could not be established, additional tests were ordered such as neuropsychological testing and brain imaging. When the diagnosis probable or possible AD, according to the criteria of the National Institute of Neurological and Communicative Diseases –Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA)¹¹, mild to moderate (MMSE ≥ 10) was established, patients were offered treatment with a ChEI. During the first three months of treatment, a specialized nurse had contact by telephone with the patient and/or his caregiver to discuss possible ChEI related side-effects. After the diagnosis, most patients were referred to dementia case management. When appropriate, other forms of non-pharmacological interventions were implemented. The guideline recommendation to evaluate patients every six months was adjusted to yearly evaluations due to our large patient population. If required, the frequency of visits was increased for certain patients. During outpatient visits, the overall condition of the patient was assessed based on the oral information provided and the outcomes of the MMSE and CDT. When necessary, care was arranged, counselling provided and medications adjusted. Outpatient visits ended when treatment with ChEIs and/or memantine was terminated or in case of nursing home admission.

2.2. Participants

AD patients who visited the memory clinic between 2002 to 2012, aged 65 years or older, living at home or in residential care at the time of diagnosis and who started with a ChEI, were included. Patients were naïve to ChEIs at baseline and were not treated with a ChEI before AD diagnosis. Patients were excluded if they did not meet the inclusion criteria. Data were retrospectively collected and entered into a database by a research fellow. Disease course was described by changes in cognition, number of types of professional care and behavioural and psychological symptoms (BPS) of dementia for a period of 3.5 years. In addition, the number and characteristics of patients admitted to a nursing home and the number of deaths were investigated. The study was approved by the local ethics committee of the Medical Center Leeuwarden.

2.3. Measurements

2.3.1. Socio-demographic characteristics

Age, gender, living status, and use of informal care were recorded. Comorbidity was evaluated by the Cumulative Illness Rating Scale (CIRS) with a total score ranging from 0 (no impairment) to 56 (extremely severe impairment)¹². AD as index disease was not included in the CIRS score. The number of medications beside the ChEI was recorded. Polypharmacy was defined as use of 4 or more medications beside the ChEI.

2.3.2. Cognitive functioning

Cognitive functioning was assessed by the MMSE¹³ and the CDT. We used the scoring system of Shulman 1993, in which the total score ranges from 1 to 6, and a score of 3 or more indicates cognitive impairment¹⁴.

2.3.3. Use of professional care

For research purposes, Instrumental Activities of Daily Living (IADL) would ideally be operationalized with a measurement instrument. However, in our memory clinic, IADL was not measured with an instrument. Therefore, for this study, we used the number of types of professional care as indirect measure of IADL, since loss of ability to perform (I)ADLs is associated with increased need for

professional care^{15,16}. Five types were distinguished: dementia case management, domestic help, homecare, respite care (i.e. daycare center) and meals at home services.

2.3.4. Behavioral and psychological symptoms (BPS) of dementia

Based on self reported patient and caregiver information, we recorded whether BPS were present or absent. Since BPS was not operationalized with a measurement instrument, it was not possible to report the severity, nature nor frequency of BPS.

2.3.5. Type and dosage of ChEI

At each outpatient visit, type and dosage of ChEI, and if applicable memantine, were recorded. At our memory clinic, galantamine retard is the treatment of choice for patients with mild to moderate AD. The retard form of galantamine is prescribed since 2005, before 2005, galantamine was given twice daily. Patients start with 8 milligram (mg) galantamine per day for at least four weeks, followed by 16 mg/day for at least four weeks and, if necessary, the dose was increased to the maintenance dose of 24 mg/day.

2.3.6. Nursing home admission and mortality

At one point in time, December 2012, we checked the place of residency (i.e. at home or nursing home) of all patients included in our cohort and whether the patient had died. If possible, the date of nursing home admission and/or death was recorded.

2.4 Statistical Analysis

Data were analysed with Statistical Package for the Social Sciences (SPSS) 16.0 and Statistical Analysis Software (SAS) 9.2. All hypothesis tests were two-tailed. A probability (p) value of less than 0.05 was considered statistically significant. Descriptive statistics are presented as means $\pm$ standard deviations for normally distributed variables. For skewed distributed variables, median and 25th – 75th percentiles are given. We used the Kolmogorov Smirnov test to establish the normality of distribution of the variables. Number and proportion are given for categorical variables.

The course of cognition and professional care were assessed applying a repeated measures analysis using a marginal model (population based averaged model) and SAS proc mixed procedure with time as repeated statement and unstructured covariance structure. The repeated measures analysis has been developed for the analysis of longitudinal, continuous, dependent data. It gives an estimate of change in the dependent variable over time. The analyses were performed with all available data from patients with a baseline assessment and at least one follow-up assessment, over a period of maximally 3.5 years (five measurements). From the 6th measurement moment, it was not possible to give a reliable estimate of change in the dependent variable due to the small number of patients at that moment. Three analyses were performed, with MMSE score, CDT score and the number of types of professional care as dependent variable. Within these analyses, time (i.e. the number of measurement moments) was included as independent variable. Because BPS is a dichotomous variable, no repeated measures analysis could be performed. Therefore, the course of BPS was described by comparing the percentage of patients with BPS at each measurement moment to the percentage of patients with BPS at baseline, using the McNemar test.

Various characteristics were compared between patients admitted to a nursing home vs. patients who were not admitted to a nursing home, respectively between patients who died vs. those who survived and between patients who dropped out in the first six months (i.e. who did not complete the first assessment) versus patients who completed at least one follow-up assessment. The independent sample t-test was performed to compare normally distributed variables. We employed the Mann-Whitney U test to compare skewed distributed variables. The Pearson Chi-square or Fisher's exact test was used to compare categorical variables.

3. Results

3.1. Patient characteristics

Table 1 shows the patient characteristics of the 576 enrolled patients at the time of AD diagnosis. At baseline, median age was 80 years, median MMSE score 23 and median CDT score 3. More than half of the patients (51.4%) were dependent of professional care and 83% were dependent of informal care. Nearly a third (29%) of the patients had BPS. Of all patients, 96.4% started with galantamine and 3.6% with rivastigmine. During follow-up, memantine was added in 81 patients (14.1%) and 18 patients (3.1%) switched to monotherapy with memantine.

3.2. Follow-up

The number of outpatient visits per patient ranged from 1 to 11, the median number was 3 (25th – 75th percentile 2 – 5). Median time from starting a ChEI to the first subsequent outpatient visit was 6.3 months (25th – 75th percentile 5.5 – 7.3). Median time between subsequent visits was 10.6 months (25th – 75th percentile 10.1 – 11.7). Although the first patient was included in 2002, most patients were diagnosed with AD between 2006 and 2010 (87.3%). Median follow-up time between the date of diagnosis and December 2012 was 49 months (4.1 years) (25th – 75th percentile 37 – 66 months).

3.3. Drop-out

The number of patients that remained in the study at the different visits was: 576 at visit 1 (baseline), 447 patients at visit 2, 344 at visit 3, 242 at visit 4, 149 at visit 5, 73 at visit 6, 30 at visit 7, 11 at visit 8, 4 at visit 9, 1 at visit 10 and 1 at visit 11, respectively. Of the 576 patients that started using a ChEI, 171 patients (29.7%) are still waiting for their next outpatient clinic visit. 405 Patients (70.3%) did not show up at the next clinic visit at a given moment during follow-up. The main reasons patient did not show up were nursing home admission (n = 151, 37.3%) and discontinuation of treatment with a ChEI (n = 90, 22.2%). Most of the patients who discontinued ChEI treatment did so because of gastrointestinal side effects (n = 28, 31.1%). Of the 576 patients, 125 dropped out in the first six months and 451 patients completed at least one follow-up assessment. Patients who dropped out in the first six months were older, had a higher score on the CDT, had more often BPS and were more dependent on professional and informal care, compared to patients who had a least one follow-up assessment. There were no differences between the two groups with regard to gender, social status, MMSE score, comorbidity, ChEI which was used and the number of medications beside the ChEI (see Table, Supplemental Digital Content 1) .

3.4. Course of cognition expressed by MMSE and CDT score

The course of the MMSE score is presented in table 2 and figure 1. There was no interaction between baseline MMSE score and time. Mean MMSE score at baseline was 22.24. During the first 6 months, the MMSE score remained stable. During the following three years, the MMSE score decreased to 18.91. The decrease in MMSE score equals to an average decrease of 1.1 points/year.

At baseline, the mean CDT score was 3.38 (table 2 and figure 1). The score did not change in the first 6 months. After 3.5 years, the score increased with 0.67 points compared to baseline.

Over the follow-up period of 3.5 years, AD patients deteriorated on cognition, operationalized with both the MMSE (p<0.001) and the CDT (p=0.009).

3.5. Course of IADL expressed by use of professional care

At baseline the mean number of types of professional care was 0.85 (table 2, figure 2). The increase in number of types of care was the greatest during the first 6 months (i.e. 1.08) and increased more gradually thereafter with a mean number of types of professional care of 2.64 after 3.5 years (p<0.001).

3.6. Course of behavioural functioning expressed by BPS

During 3.5 years of follow-up, the prevalence of BPS increased from 29.0% at baseline to 41.4% at 6 months, to 54.3% at 18 months, to 59.6% at 30 months and to 70.2% at 42 months (p<0.001).

3.7. Course of AD expressed by proportions of nursing home admissions and deaths

For 476 patients (83.6%), the place of residency could be determined. Of these patients, 194 (40.8%) were admitted to a nursing home during a median follow-up time of 4.1 years. The date of nursing home admission was available for 39 patients (20.1%). Median time to nursing home placement for these patients was 24 months (25th – 75th percentile 8.0 – 33.0). Patients admitted to a nursing home had poorer cognition, more BPS and used more professional care at baseline compared to those who remained at home (see Table, Supplemental Digital Content 2) . In addition, the proportion of deaths was higher in patients admitted to a nursing home. Median follow-up time for patients admitted to a nursing home was 5.5 months longer compared to patients who were not admitted ($p=0.002$) (see Table, Supplemental Digital Content 2) .

For 478 patients, it was possible to determine whether they died or not. Of these patients, 196 (41.0%) died during a median follow-up time of 4.1 years. Median time until death after diagnosis was 32.2 months (25th – 75th percentile 17.3 – 45.5). Patients who died had poorer cognition, used more types of professional care, had more comorbidity and more polypharmacy at baseline than survivors (see Table, Supplemental Digital Content 2) . Median follow-up for patients who died was 15 months longer compared to those who survived ($p=0.000$).

4. Discussion

To our knowledge, this is one of the largest ‘real-life’ studies of the long-term disease course of newly diagnosed AD patients treated at a memory clinic, and the first from the Netherlands. Our results show that, with the pharmacological and non-pharmacological interventions, provided according to the Dutch dementia guideline, cognition and behaviour deteriorated accompanied with an increase in care-dependency during 3.5 years of follow-up.

The estimated rate of decline in MMSE score (1.1 point/year) was lower than in historical pre-ChEI-era cohorts, with an estimated rate of decline of 3.3 point/year (95% confidence interval 2.9 – 3.7)¹⁷ (figure 1). The mean annual decline in our study was also lower compared to other long-term, ‘real-life’ ChEI-era cohorts, where the decline in MMSE score ranged from 1.3 to 2.5 points/year¹⁸⁻²⁰.

However, the interpretation of these comparisons must be performed with caution, because of differences in patient characteristics and study methodology. In the ‘Swedish Alzheimer Treatment Study’ (SATS) cohort, mean annual decline in MMSE score was 1.3 points¹⁸. These patients were younger compared to the patients in our cohort, which might have contributed to the faster decline in MMSE score in the SATS cohort²¹. In ‘The REseau sur la maladie d’Alzheimer Français’ (REAL.FR) cohort, mean annual decline in MMSE score was 2.4¹⁹. However, these patients had been diagnosed with AD over a year, while we investigated newly-diagnosed patients. In addition, differences in geographical position, reflecting differences in cultural and health care system can influence the outcome. We do not know details on how the care for people with dementia in France and Sweden is organized. Although, ‘The Impact of Cholinergic Treatment Use’ (ICTUS) study showed that the progression of AD was similar across 12 European countries (including France, Sweden and the Netherlands), despite different health care systems²⁰. Patients from the ICTUS cohort were diagnosed with AD for 0.4 years. The MMSE declined in the first year 1.5 points and in the second year 2.5 points²⁰. However, 10% of the patients from the ICTUS cohort received not continuous treatment with a ChEI after inclusion. This may have contributed to the difference in mean annual decline in MMSE score between the ICTUS cohort and our cohort. Irrespective of possible differences, the results of the SATS¹⁸, REAL.FR¹⁹ and ICTUS²⁰ cohort are in line with our finding that the rate of decline in MMSE score is slower than in historical pre-ChEI-era cohorts¹⁷, suggesting that long-term treatment with pharmacological and non-pharmacological interventions in a ‘real-life’ setting appears to slow cognitive decline in AD patients.

Little is known about changes in CDT score over time. Shulman et al. reported an increase in CDT score with 0.33 points in demented patients from the pre-ChEI-era during 18 months of follow-up. This is less compared to our increase with 0.67 points in 18 months. The lower increase in CDT score

reported by Shulman et al. could be explained by a ceiling effect since their patients had severe dementia (MMSE score 15.77), though their baseline score on the CDT was 3.30¹⁴. Shulman et al. concluded that the CDT can be helpful in the monitoring of dementia¹⁴. To our knowledge, there are no studies that investigated the responsiveness of the CDT. Our results suggest that the CDT is able to detect changes over time in AD patients. The decrease in MMSE score and increase in CDT score in the present study, demonstrate that cognitive functions as measured by the MMSE deteriorate over time, but also as measured by the CDT, including executive functions.

Describing the use of professional care provides valuable information as it might help to plan the use of professional care and estimate future health care costs. To our knowledge, the use of professional care was investigated in one other ChEI-era AD cohort¹⁶. In this cohort, the use of professional care increased gradually over time¹⁶. In our study, the increase in use of professional care was the greatest during the first six months of ChEI treatment. This is most likely explained by the fact that we investigated newly diagnosed patients for whom pharmacological and non-pharmacological interventions, including professional care, were initiated after the diagnosis. Thus, the steep rise in number of professional types of care in the first six months is not a reliable measure for the severity of IADL limitations in our cohort.

The long-term course of BPS has been investigated in three other ChEI-era cohorts^{19,20,22}. They reported similar results, namely that BPS gradually increased over time^{19,20,22}. We have found no studies on the course of BPS from the pre-ChEI-era. Based on our results, we can not be conclusive whether treatment with ChEIs, in addition to non-pharmacological interventions, reduces behavioural problems. Though, there is evidence showing some benefit of ChEIs with regard to BPS⁷.

The proportion of patients admitted to a nursing home (40.8%) is higher than in other ChEI-era cohorts, with proportions of 12.4% in 2 years²⁰ and 34% in 4 years¹⁹. The higher proportion in our cohort is possibly explained by our longer follow-up time, which could be as long as 10 years for some patients, though the median follow-up time was 4.1 years. To our knowledge, the proportion of patients admitted to a nursing home was investigated in two pre-ChEI-era cohorts^{23,24}. In the pre-ChEI-era cohort of Yaffe et al., the proportion of patients admitted to a nursing home was higher, i.e. 52% after 3 years²³. However, this proportion is based on patients with more advanced dementia²³. Smith et al. concluded that proportions of nursing home admission of approximately 10% per year could be expected in pre-ChEI-era dementia patients²⁴, which equals the proportion of our cohort. Therefore, based on our results, it is not possible to be conclusive as to whether the current interventions reduce nursing home admission. Though, the proportion of patients admitted to a nursing home in the other ChEI-era cohorts is lower compared to the pre-ChEI-era cohorts of Yaffe et al. and Smith et al., possibly reflecting the benefits of the pharmacological and non-pharmacological interventions with regard to nursing home admission. Patients admitted to a nursing home were characterized by a more severe AD at baseline compared to patients who remained at home. This finding is consistent with other studies^{19,25,26}. In addition, the proportion of deaths was higher in patients admitted to a nursing home, which is in agreement with other studies²⁷. Our finding that BPS is associated with nursing home admission is also in line with other studies^{23,28} and emphasizes the importance of more research to treatment options for BPS in AD.

The proportion of deaths in our study (41%) is higher than in other ChEI-era cohorts, with proportions of 3.6% in 3 years²⁹ and 23% in 4 years¹⁹. The higher proportion in our cohort is possibly explained by our longer follow-up time. In addition, the patients in the cohort where the proportion of deaths was 3.6%²⁹, were seven years younger than our patients. As far as we know, the proportion of deaths was investigated in two pre-ChEI-era cohorts^{30,31}. In one of these cohorts, the proportion of deaths was 17% during 4 years of follow-up³⁰. In the pre-ChEI study of Holmes et al., the proportion of deaths was 70.5% after 3 years of follow-up³¹. Because of differences in patient characteristics between these cohorts and the present study, it is not possible to be conclusive about the effect of ChEIs, in addition to non-pharmacological interventions, on mortality. For example, patients in the cohort from Holmes et al. had advanced dementia with mean baseline MMSE score of 9.9. However, there is some evidence that galantamine reduces mortality. A recent trial in 2051 AD patients

showed that galantamine was associated with lower mortality compared to placebo³². Patients who died during our study were characterized by a more severe AD at baseline. In addition, they had more comorbidity and polypharmacy. This suggests that mortality is related to the overall health status of AD patients, whereas admission to a nursing home is related to the dementia itself.

Strengths of our study are that we investigated patient-relevant outcomes in a relatively large group of AD patients with a long follow-up. In addition, the 'real-life' setting avoids the limitations of most AD clinical trials, increasing the external validity of the results. Another strength is that the disease course was described by a wide spectrum of domains. In addition, we investigated the course of cognition by change in the CDT. Statistical analysis of longitudinal data is primarily complicated because of intra-individual correlation and, particularly in older AD patients, drop out of patients³³. A repeated measures analysis is specifically developed for the analysis of longitudinal dependent data. All data contribute to the longitudinal analysis and even data from patients who dropped out can be used. By applying a repeated measures analysis in our study we could maximize the use of all available data of a large number of patients with a long follow-up.

Some limitations of the study must be considered. Firstly, all our AD patients were treated with a ChEI. Therefore, we compared our results with data derived from historical pre-ChEI-era AD cohorts. These comparisons have shortcomings because of differences in methodology and clinical characteristics. A placebo-controlled study is the ideal way to assess the effect of long-term treatment with ChEIs embedded in the current package of care. However, such a study can no longer be performed because of ethical reasons and would not reflect a 'real-life' setting. Furthermore, the decision to start the patient on a ChEI was made by the physicians of the memory clinic. This may have contributed to selection bias. A third limitation is the retrospective design of our study. Hence, IADL and BPS were not measured using validated questionnaires. In addition, not all the non-pharmacological interventions were recorded (for example, it was not recorded if patients used occupational therapy). Moreover, for some patients data regarding nursing home admission and mortality could not be determined. Hence, it was not possible to perform a survival analysis, which thoroughly estimates incidences of nursing home admission and mortality and takes into account differences in follow-up, as was the case in our study. The fourth limitation is that the disease course was described by various rating scales for which a definition of a worthwhile clinical response is lacking. We can not assume that the statistically significant changes in test scores would be considered clinically relevant by patients, caregivers or health care professionals. Development of scales that can describe the course of AD for all relevant domains and provides worthwhile clinical changes are needed. Recently, such a scale was developed: the Relevant Outcome Scale for Alzheimer's Disease (ROSA)³⁴, which may be a promising tool for the future.

In conclusion, the present 'real-life' study provides insight in the long-term course of AD patients treated according to the Dutch dementia guideline at a memory clinic. Despite pharmacological and non-pharmacological interventions, cognition and BPS deteriorated accompanied with an increase in care-dependency during 3.5 years of follow-up. Compared to the disease progression in the period before ChEIs were available, long-term treatment appears to slow cognitive decline. This emphasizes that the combination of pharmacological and non-pharmacological interventions seem to have a favorable effect on the long-term course of AD.

More data regarding the course of AD should be collected in well established registries using appropriate and validated scales. This offers the opportunity to use 'benchmarking' in order to improve the care for AD patients. With benchmarking, the clinical approaches of institutions with excellent clinical outcomes can be identified and used for the improvement of the quality of care and outcomes of other institutions³⁵.

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6. Figure legends

Figure 1. Course of cognition: results from the repeated measures analysis.

(a) Course of the Mini Mental State Examination (MMSE) score in the Frisian Alzheimer's Disease Cohort.

(b) Course of the score on the clock-drawing test in the Frisian Alzheimer's Disease Cohort.

(c) Course of the MMSE score in the Frisian Alzheimer's Disease Cohort vs. in historical pre-ChEI-era cohorts.

CI: Confidence Interval, ★: significant compared to baseline.

Figure 2. Course of the number of types of professional care: results from the repeated measures analysis.

CI: Confidence Interval, ★: significant compared to baseline.

7. List of Supplemental Digital Content

Supplemental Digital Content 1: Table: Patient characteristics of patients who dropped out in the first six months vs. patients who completed at least one follow-up assessment.

Supplemental Digital Content 2: Table: Patient characteristics of patients admitted to a nursing home vs. patients not admitted to a nursing home, respectively patients who died vs. who survived.

8. Abbreviations

(I)ADL	: Instrumental Activities of Daily Living
AD	: Alzheimer's disease
BPS	: Behavioral and psychological symptoms
CDT	: Clock-drawing test
ChEI	: Cholinesterase inhibitor
CI	: Confidence interval
CIRS	: Cumulative Illness Rating Scale
mg	: Milligram
MM	: Measurement moment
MMSE	: Mini Mental State Examination
NINCDS-ADRDA	: National Institute of Neurological and Communicative Diseases – Alzheimer's Disease and Related Disorder Association
n	: Number of patients
p	: Probability
RCT	: Randomized controlled trial
ROSA	: Relevant Outcome Scale for Alzheimer's Disease
SAS	: Statistical Analysis Software
SD	: Standard deviation
SE	: Standard error
SPSS	: Statistical Package for the Social Sciences