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RESEARCH ARTICLE

Short-Term Response to Cholinesterase Inhibitors in Alzheimer's Disease Delays Time to Nursing Home Placement

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Abstract: ***Background:*** A varying response to cholinesterase inhibitor (ChEI) treatment has been reported among patients with Alzheimer's disease (AD). Whether the individual-specific response directly affects time to nursing home placement (NHP) was not investigated.

Objective: We examined the relationship between the 6-month response to ChEI and institutionalization.

Methods: In a prospective, observational, multicenter study, 881 outpatients with a clinical AD diagnosis and a Mini-Mental State Examination score of 10-26 at the start of ChEI therapy (baseline) were included. The participants were evaluated using cognitive, global, and activities of daily living (ADL) scales at baseline and semiannually over 3 years. The date of NHP was recorded.

Results: During the study, 213 patients (24%) were admitted to nursing homes. The mean ± standard deviation time from baseline (AD diagnosis) to NHP was 20.8 ± 9.3 months. After 6 months of ChEI treatment, the improved/unchanged individuals had longer time to NHP than those who worsened. The prolonged time to NHP was 3 months for cognitive response (P=0.022), 4 months for global response (P=0.004), 6 months for basic ADL response (P<0.001), and 8 months for response in all three scales (P<0.001). No differences were detected between the improved and unchanged groups in any scales.

Conclusion: Patients who exhibit a positive short-term response to ChEI can expect to stay in their own home for 3-8 months longer. These findings underline the importance of a comprehensive clinical examination including various assessment scales to evaluate treatment response and provide a more accurate prognosis.

Keywords: Alzheimer's disease, cholinesterase inhibitors, treatment effect, activities of daily living, cognition, nursing home placement, predictors, statistical models.

1. INTRODUCTION

1.1. Background

After a long, insidious, neurodegenerative disease process with diminishing cognitive and functional capacities and escalating need of community-based services, 30%-50% of people with Alzheimer's disease (AD) in high-income countries receive care in nursing homes (NHs). Among the chronic diseases, dementia is by far the most important contributor to nursing home placement (NHP). Compared with nondemented long-term care users, the residents with AD need more personal care, a greater amount of care, and more supervision, all of which are related to greater caregiver burden and higher costs of care [1]. Institutionalization might also have negative effects on the demented individual's quality of life, activity level, and intake of antipsychotics [2]. In Sweden, admission to NHs is based solely on the person's needs and is not dependent on their socioeconomic status or insurance coverage. The costs of NHs are predominantly funded by the social security system; the annual cost in 2016 was SEK 655,000 (USD ~80,800, EUR ~68,200) per care recipient [3]. Our group reported that on average, 72% (4.1 years) of the period from AD diagnosis to death was spent in NHs [4].

The reasons for NHP are likely multifactorial and depend on both patient and caregiver characteristics. For example, older age [5, 6], living alone [7, 8], lower cognitive and functional performance [6, 7], and poor health of the caregiver [7] have been observed to precipitate institutionalization. Conflicting results regarding sex have been demonstrated [5, 7]; however, the interaction effect of sex and solitary living might affect this result. We showed that males living alone had an almost fourfold risk of NHP compared with males living with family, while the corresponding risk for females was threefold [9].

After two decades, the predominant symptomatic AD therapy is still cholinesterase inhibitors (ChEI; donepezil, rivastigmine, and galantamine). ChEIs prevent the degrada-

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tion of acetylcholine by the acetylcholinesterase enzyme, resulting in increased amounts in the synaptic cleft available for receptor absorption. This improves cholinergic transmission and enhances the communication between neurons. Nevertheless, remarkably few AD studies over the years have investigated the association between various aspects of ChEI treatment and time to NHP. Some observational studies suggested that the use of ChEIs delays admission to NHs [10, 11]. A follow-up of participants earlier enrolled in clinical trials of donepezil reported that effective dosages and sustained use might postpone institutionalization [12]. Previously, we found that a higher mean dose of ChEI over the study period prolonged the average time to NHP by 7 months [9].

In randomized clinical trials, ChEIs have exhibited short-term response in both cognitive abilities and activities of daily living (ADL) [13]; however, the response differed between the AD patients [14]. After 6 months of therapy, 49%-63% of the individuals had improved or were unchanged as measured by cognitive scales [15], while the corresponding percentages were 49% for instrumental ADL and 74% for basic ADL [16]. Studies from our group and others have described that the protective factors for better cognitive response to ChEI were lower cognitive status [14, 17], male sex [17, 18], older age [17, 19], and absence of the apolipoprotein E (APOE) ε4 allele [17, 20]. In contrast, better cognitive performance and younger age at the initiation of ChEI treatment predicted a more positive ADL response after 6 months [16]. No study has shown whether different levels of short-term response to ChEI directly affect the time to NHP.

Knowledge about aspects of ChEI therapy and other factors that might alter the time to NHP is necessary for clinicians to optimize the effects of treatment and for counselling of patients and their family about the future, thereby allowing the individual to stay in their home for as long as possible. The identification of persons with AD who are expected to experience a more rapid disease progression is important because they might have a more urgent need for institutionalization, which is essential information for community-based services.

The aims of this study were 1) to examine the relationship between time to NHP and the 6-month response to ChEI therapy using cognitive, global, and functional measures and 2) to identify potential predictors that might influence these outcomes.

2. METHODS

2.1. Study and Subjects

The Swedish Alzheimer Treatment Study (SATS) was commenced in 1997 to assess the longitudinal effectiveness of ChEI treatment in AD patients in routine clinical practice. SATS is a 3-year, open-label, observational, nonrandomized, multicenter study and various results have been reported in several publications *e.g.,* [4, 9, 15-17]. Considered for enrollment were outpatients aged ≥40 years who had been clinically diagnosed with dementia, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [21], and with possible or probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [22]. Additional inclusion criteria in the SATS were living at home at the time of AD diagnosis, having a responsible caregiver, and possible evaluation using the Mini-Mental State Examination (MMSE) [23] at the start of ChEI therapy (baseline). The participants were diagnosed by specialists in dementia disorders. In total, 1,258 patients were prospectively enrolled from 14 memory clinics situated in different geographical areas of Sweden. Among these, all 881 individuals who had MMSE scores at baseline ranging from 10-26 (indicating mild-to-moderate AD) and who had fulfilled the 6-month post-baseline visit were included in this study.

All procedures performed in studies involving the SATS participants were in accordance with the Helsinki Declaration. The SATS protocol and the current analysis of data from the SATS presented in this manuscript were submitted to and approved by the Regional Ethical Review Board, Lund University, Sweden (no. 2014/658, dated December 9, 2014). Written informed consent was obtained from all patients included in the SATS. If an individual was not able to provide consent for him/herself, consent was obtained from their closest relative.

The AD patients were investigated in a structured follow-up program, which assessed cognition, global status, and instrumental and basic ADL immediately before the initiation of ChEI treatment and then semiannually over 3 years. After inclusion and baseline evaluations, the participants were prescribed ChEIs according to the approved product recommendations. The choice of drug agent and dose for each individual was left entirely up to the dementia specialist's discretion and professional judgment, *i.e.*, the standard in a routine clinical setting. The ChEI dose was recorded after 2 months of therapy, and every 6 months after baseline during the 3-year study. Research nurses specialized in dementia care obtained the ADL assessment from an interview with the caregiver (usually the spouse or an adult child). Concomitant medications other than ChEI were permitted, with the exception of memantine, and were documented at baseline. If memantine was initiated, the patient dropped out from the SATS at that time point.

The date of NHP was obtained from medical records and institutionalization was defined as the permanent entry to a licensed skilled-nursing facility with 24 h care; *i.e.*, rehabilitative or respite care was excluded. If hospitalization occurred or was prolonged because of a lack of nursing home beds at the time of the study, the date of application to the nursing home was used.

2.2. Assessment Scales

Cognitive ability was investigated using the MMSE scale, which ranges from 0 to 30, where a lower score indicates more impaired cognition. The Clinician Interview-Based Impression of Change (CIBIC) [24] was used as a global measure of "change from the baseline". The evaluations of change in global performance from the start of ChEI treatment were performed at all intervals using a 7-point scale from 1 (very much improved) to 7 (marked worsening), with 4 indicating no change. No guidelines or descriptors

were provided to define the individual ratings. The classification between, *e.g.,* minimally improved or very much improved, was left to the physician's clinical judgment.

Functional capacity was assessed using the Instrumental Activities of Daily Living (IADL) scale [25], comprising eight items: telephone use, shopping, food preparation, housekeeping, doing laundry, mode of transportation, responsibility for own medications, and ability to handle finances. Each item was scored from 1 (no impairment) to 3-5 (severe impairment), allowing a total range of 8-31 points. Basic ADL were measured using the Physical Self-Maintenance Scale (PSMS) [25], comprising six items: toilet use, feeding, dressing, grooming, physical ambulation, and bathing. Each item was scored from 1 (no impairment) to 5 (severe impairment), giving a total range of 6-30 points.

2.3. Statistical Analyses

The IBM Statistical Package for the Social Sciences (SPSS) for Windows (version 24.0; IBM Corporation, Armonk, NY, USA) was used to perform statistical analyses. The level of significance was defined as $P < 0.05$ if not otherwise specified, and all tests were two-tailed. Parametric tests were used because of the large sample size and the approximately normally distributed continuous variables. A one-way analysis of variance (ANOVA) was performed to compare the differences between the means obtained for three or more independent groups, such as positive response to ChEI on the number of assessment scales. A *t* test was used to analyze two independent groups, *e.g.,* improved/unchanged *vs.* worsened. Chi-squared tests were computed for analyses of categorical variables, and median tests for comparisons of CIBIC score at baseline between the groups. Kaplan-Meier graphs were used to illustrate the differences in time to NHP in the figures. The distribution of time was compared using the log-rank test.

2.3.1. Cox Proportional Hazards Models

Backward stepwise elimination Cox regression models were used to simultaneously estimate the effect of all potential factors mentioned below including the 6-month response to ChEI in each model (MMSE, CIBIC, IADL, or PSMS scale). The dependent variable was the time to NHP (in months) after the initiation of treatment. Variables with $P > 0.05$ were removed from the stepwise models. No violation of the assumption of proportional hazards was detected.

Based on prior knowledge of risk factors of disease progression and institutionalization in AD, several sociodemographic and clinical characteristics as well as specific medications were concomitantly included in each of the aforementioned models. The independent variables were: age at baseline; clinician's estimate of duration of AD; sex by solitary living; years of education; presence of the APOE ε4 allele (no/yes); cognitive, instrumental and basic ADL capacities at baseline (or global rating in the CIBIC model); specific medications used (no/yes for each group: antihypertensive/cardiac therapy, antidiabetic drugs, asthma medication, thyroid therapy, lipid-lowering agents, estrogens, non-steroidal anti-inflammatory drugs/acetylsalicylic acid, antidepressants, antipsychotics, and anxiolytics/sedatives/hypnotics); type of ChEI agent (coded as dummy variables); drug dose; and the 6-month response to ChEI measured by the MMSE, CIBIC, IADL, or PSMS score.

The ChEI dose could vary during the treatment period for an individual participant and between participants. Therefore, the mean dose used during the first 6 months of therapy was calculated for each patient. Furthermore, to obtain a similar metric of percent maximum dosage for the three ChEI agents, the mean dose was divided by the maximum recommended dose for each drug agent, *i.e.*, 10 mg of donepezil, 12 mg of rivastigmine (oral therapy), and 24 mg of galantamine.

Response was calculated as the change in score between the 6-month visit after the start of ChEI treatment and the baseline for each scale (MMSE, IADL, or PSMS). To facilitate comparisons between the scales, changes in the scores calculated as positive values should be interpreted as indicating improvement, and those calculated as negative values interpreted as indicating decline. The evaluations of change in global status (CIBIC) after 6 months were scored as 1-3 (improved), 4 (unchanged), and 5-7 (worsened).

3. RESULTS

3.1. Response After 6 Months of ChEI Treatment

The sociodemographic and clinical characteristics of the 881 SATS participants at the initiation of ChEIs (baseline) are described in Table **1**. Of these, 213 (24%) were admitted to NHs over the study period; their mean (95% confidence interval [CI]) time from baseline to NHP was 20.8 (19.5-22.0) months. Table **2** demonstrates the sociodemographic and clinical characteristics of the improved/unchanged *vs.* worsened groups measured by the MMSE, CIBIC, IADL, and PSMS scales, respectively, after 6 months of ChEI therapy.

Improvement/no change (≥ 0 point change) in MMSE score after 6 months of treatment was shown in 565 (64%) of the individuals. Fig. (**1A**) displays a Kaplan-Meier graph of the distribution of time from baseline to NHP for the improved/unchanged *vs.* worsened groups measured by MMSE score after 6 months (log-rank test, $P < 0.001$). A multivariate Cox proportional hazards regression model showed a 1.59-fold risk of institutionalization for the worsened patients compared with those who were improved/unchanged ($P = 0.002$). Other independent factors in the MMSE model that significantly decreased the risk of NHP were better cognitive and IADL abilities at baseline, and living with family irrespective of sex (Table **3**). During the study, 22% of the improved/unchanged participants and 29% of those who worsened ($\chi^2(1) = 5.03$; $P = 0.026$) were admitted to NHs. The mean (95% CI) time from baseline to NHP was 22.1 (20.5-23.7) months and 19.1 (17.2-21.1) months ($t_{(209)} = 2.30$; $P = 0.022$) for the improved/unchanged and worsened groups, respectively. No differences were observed between the improved and unchanged patients in any of the aforementioned analyses.

Global improvement/no change (CIBIC score, 1−4) after 6 months of ChEI therapy was found in 669 (76%) of the participants. Fig. (**1B**) illustrates a Kaplan-Meier graph of the distribution of time from baseline to NHP for the im-

Table 1. Sociodemographic and clinical characteristics (*n* = 881).

Variable	*n*/%
Female sex	566/64%
APOE ε4 carrier, (*n* = 865)	586/68%
Solitary living at baseline	303/34%
Nursing home placement during the study	213/24%
Antihypertensive/cardiac therapy	358/41%
Antidiabetics	38/4%
Asthma medication	34/4%
Thyroid therapy	67/8%
Lipid-lowering agents	98/11%
Estrogens	60/7%
NSAIDs/acetylsalicylic acid	264/30%
Antidepressants	224/25%
Antipsychotics	37/4%
Anxiolytics/sedatives/hypnotics	120/14%
Variable	**Mean ± Standard Deviation**
Estimated age at onset of AD, years	72.1 ± 7.4
Estimated duration of AD, years	3.0 ± 2.1
Age at the start of ChEI treatment (baseline), years	75.1 ± 7.1
Education, years	9.4 ± 2.5
MMSE score at baseline	21.4 ± 3.7
IADL score at baseline	15.9 ± 5.4
PSMS score at baseline	7.5 ± 2.2
Mean dose of ChEI during the first 6 months of therapy, mg	
Donepezil (*n* = 453)	6.2 ± 1.6
Rivastigmine (*n* = 180)	4.9 ± 1.3
Galantamine (*n* = 248)	12.1 ± 3.1
Number of concomitant medications at baseline	2.9 ± 2.4
Time from baseline to nursing home placement, months, (*n* = 213)	20.8 ± 9.3

AD, Alzheimer's disease; APOE, apolipoprotein E; ChEI, cholinesterase inhibitor; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; NSAIDs, nonsteroidal anti-inflammatory drugs; PSMS, Physical Self-Maintenance Scale.

proved/unchanged *vs.* worsened patients measured by CIBIC score after 6 months (log-rank test, $P < 0.001$). A multivariate Cox regression model showed a 2.13-fold risk of institutionalization for the worsened *vs.* the improved/unchanged group ($P < 0.001$). Other independent factors in the CIBIC model that significantly decreased the risk of NHP were younger age and a more positive global performance at baseline, and living with family regardless of sex (Table **3**). The proportion of participants admitted to NHs during the study was 22% of the improved/unchanged individuals and 32% of those who worsened ($\chi^2(1) = 10.16$; $P = 0.002$). The mean (95% CI) time from baseline to NHP was 22.1 (20.6-23.6) months and 18.3 (16.1-20.5) months ($t_{(209)} = 2.88$; $P = 0.004$) for the improved/unchanged and worsened patients, respectively. No differences were detected between the improved and unchanged groups in any of the analyses.

Improvement/no change (≥ 0 point change) in IADL score after 6 months of ChEI treatment was observed in 410 (47%) of the individuals. Fig. (**1C**) displays a Kaplan-Meier graph of the distribution of time from baseline to NHP for the improved/unchanged *vs.* worsened groups measured by IADL score after 6 months (log-rank test, $P = 0.017$). A multivariate Cox regression model exhibited a 1.62-fold risk of institutionalization for the worsened participants compared with the improved/unchanged individuals ($P = 0.002$). Other independent factors in the IADL model that decreased the risk of NHP were better cognitive and IADL capacities at baseline. In addition, males living with a family member showed a significantly lower risk of admission than the other groups (Table **4**). During the study, 21% of the improved/unchanged patients and 26% of those who worsened ($\chi^2(1) = 2.74$; $P = 0.098$) were institutionalized. However, IADL status at the start of ChEI therapy differed between the participants: the worsened group was less impaired, ($t_{(860)} = -2.42$; $P = 0.016$), Table **2**. After adjusting for baseline IADL scores as an independent variable in a logistic regression model, a significant difference in time to NHP between the two groups was found ($P = 0.016$). The mean (95% CI) time from baseline to institutionalization was 21.8 (20.0-23.7) months and 20.6 (18.8-22.3) months ($t_{(200)} = 0.98$; $P = 0.328$) for the improved/unchanged and worsened patients, respectively. After adjusting for baseline IADL scores in a general linear model, a trend toward significance ($P = 0.068$) in time to NHP between the groups was detected. No differences were observed between the improved and unchanged individuals in any of the analyses.

Improvement/no change (≥ 0 point change) in basic ADL (PSMS) score after 6 months of ChEI treatment was shown in 625 (71%) of the participants. Fig. (**1D**) illustrates a Kaplan-Meier graph of the distribution of time from baseline to NHP for the improved/unchanged *vs.* worsened patients measured by the PSMS scale after 6 months (log-rank test, $P < 0.001$). A multivariate Cox regression model demonstrated a 2.13-fold risk of institutionalization for the worsened *vs.* the improved/unchanged group ($P < 0.001$). Other independent factors in the PSMS model that significantly decreased the risk of NHP were absence of the APOE ε4 allele, better cognitive and basic ADL performance at baseline, and living with family regardless of sex (Table **4**). The proportion of patients who were admitted to NHs during the study was 20% of the improved/unchanged individuals and 35% of those who worsened ($\chi^2(1) = 20.82$; $P < 0.001$). The mean (95% CI) time from baseline to NHP was 23.4 (22.0-24.8) months and 17.4 (15.3-19.5) months ($t_{(200)} = 4.82$; $P <$

Table 2. Sociodemographic and clinical characteristics according to response after 6 months of ChEI therapy.

MMSE	**Improved/Unchanged (*n* = 565, 64%)**	**Worsened (*n* = 316, 36%)**	***P* Value**
Female sex	351/62%	215/68%	0.079
Solitary living at baseline	191/34%	112/35%	0.624
Age at the start of ChEI treatment (baseline), years	74.9 ± 7.1	75.5 ± 6.9	0.239
MMSE score at baseline	21.3 ± 3.7	21.5 ± 3.9	0.316
CIBIC score at baseline, median (q1 - q3)	4 (3 - 4)	4 (3 - 4)	0.185
IADL score at baseline	15.4 ± 5.4	16.7 ± 5.2	0.001
PSMS score at baseline	7.4 ± 2.1	7.7 ± 2.3	0.073
Mean dose of ChEI during the first 6 months of therapy, mg			
Donepezil[a]	6.2 ± 1.6 (52%)	6.2 ± 1.6 (50%)	0.681
Rivastigmine[a]	4.9 ± 1.3 (19%)	4.8 ± 1.1 (22.5%)	0.726
Galantamine[a]	12.2 ± 3.1 (29%)	11.9 ± 3.1 (27.5%)	0.439
CIBIC	**Improved/Unchanged (*n* = 669, 76%)**	**Worsened (*n* = 212, 24%)**	***P* Value**
Female sex	422/63%	144/68%	0.200
Solitary living at baseline	217/32%	86/41%	0.030
Age at the start of ChEI treatment (baseline), years	75.3 ± 7.1	74.6 ± 7.1	0.249
MMSE score at baseline	21.6 ± 3.5	20.6 ± 4.3	0.002
CIBIC score at baseline, median (q1 - q3)	4 (3 - 4)	4 (3 - 4)	0.006
IADL score at baseline	15.5 ± 5.3	17.1 ± 5.5	<0.001
PSMS score at baseline	7.4 ± 2.1	7.8 ± 2.4	0.021
Mean dose of ChEI during the first 6 months of therapy, mg			
Donepezil[a]	6.2 ± 1.6 (50%)	6.3 ± 1.6 (57%)	0.454
Rivastigmine[a]	5.0 ± 1.3 (21%)	4.6 ± 1.1 (18%)	0.105
Galantamine[a]	12.2 ± 3.1 (29%)	11.6 ± 3.1 (25%)	0.175
IADL	**Improved/Unchanged (*n* = 410, 47%)**	**Worsened (*n* = 471, 53%)**	***P* Value**
Female sex	252/61%	314/67%	0.108
Solitary living at baseline	123/30%	180/38%	0.010
Age at the start of ChEI treatment (baseline), years	75.0 ± 7.0	75.3 ± 7.1	0.489
MMSE score at baseline	21.6 ± 3.7	21.2 ± 3.7	0.063
CIBIC score at baseline, median (q1 - q3)	3 (3 - 4)	4 (3 - 4)	0.910
IADL score at baseline	16.4 ± 5.9	15.5 ± 4.8	0.016
PSMS score at baseline	7.5 ± 2.3	7.5 ± 2.1	0.992
Mean dose of ChEI during the first 6 months of therapy, mg			
Donepezil[a]	6.1 ± 1.6 (56%)	6.3 ± 1.6 (47%)	0.241
Rivastigmine[a]	4.8 ± 1.3 (16%)	4.9 ± 1.3 (24%)	0.419
Galantamine[a]	12.4 ± 3.3 (28%)	11.8 ± 2.9 (29%)	0.196

(Table 2) contd….

PSMS	Improved/Unchanged (*n* = 625, 71%)	Worsened (*n* = 256, 29%)	*P* Value
Female sex	394/63%	172/67%	0.244
Solitary living at baseline	197/32%	106/41%	0.005
Age at the start of ChEI treatment (baseline), years	74.7 ± 7.3	76.2 ± 6.4	0.003
MMSE score at baseline	21.9 ± 3.5	20.1 ± 4.0	<0.001
CIBIC score at baseline, median (q1 - q3)	3 (3 - 4)	4 (3 - 4)	<0.001
IADL score at baseline	15.1 ± 5.3	18.1 ± 5.1	<0.001
PSMS score at baseline	7.4 ± 2.2	7.7 ± 2.3	0.086
Mean dose of ChEI during the first 6 months of therapy, mg			
Donepezil[a]	6.2 ± 1.6 (51%)	6.2 ± 1.6 (52%)	0.939
Rivastigmine[a]	4.9 ± 1.2 (21%)	4.8 ± 1.3 (20%)	0.629
Galantamine[a]	12.3 ± 3.1 (28%)	11.6 ± 3.1 (28%)	0.155

Values are presented as n/% or mean ± standard deviation.

[a]Percentage of patients in each group that received the specific ChEI agent in parentheses, χ^2 test: (MMSE, $p = 0.532$); (CIBIC, $p = 0.220$); (IADL, $p = 0.008$); (PSMS, $p = 0.978$).

ChEI, cholinesterase inhibitor; CIBIC, Clinician Interview-Based Impression of Change; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; PSMS, Physical Self-Maintenance Scale.

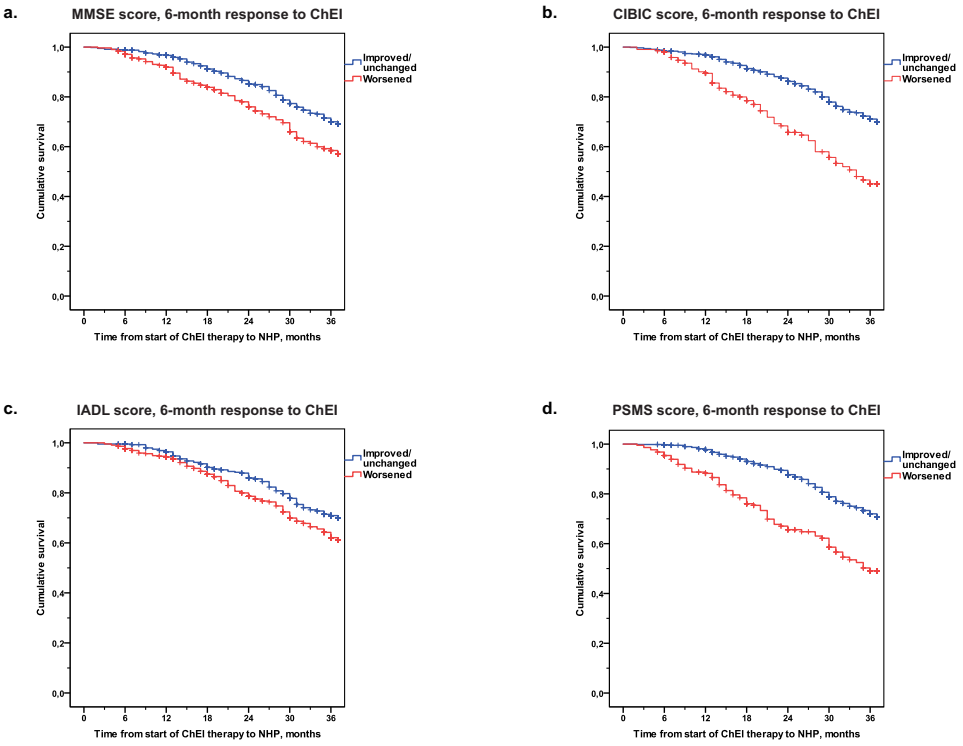

Fig. (1). Time from the start of ChEI therapy (baseline) to the endpoint NHP. (**A**) Kaplan-Meier graph of the distribution of time from baseline to NHP according to cognitive response to ChEI after 6 months of treatment. A log-rank test showed a longer time to NHP for the improved/unchanged SATS participants ($P < 0.001$). (**B**) Kaplan-Meier graph of the distribution of time from baseline to NHP according to global response to ChEI after 6 months of therapy. A log-rank test demonstrated a longer time to NHP for the improved/unchanged patients ($P < 0.001$). (**C**) Kaplan-Meier graph of the distribution of time from baseline to NHP according to IADL response to ChEI after 6 months of treatment. A log-rank test exhibited a longer time to NHP for the improved/unchanged group ($P = 0.017$). (**D**) Kaplan-Meier graph of the distribution of time from baseline to NHP according to basic ADL response to ChEI after 6 months of therapy. A log-rank test showed a longer time to NHP for the improved/unchanged individuals ($P < 0.001$).

ADL, activities of daily living; ChEI, cholinesterase inhibitor; CIBIC, Clinician Interview-Based Impression of Change; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; NHP, nursing home placement; PSMS, Physical Self-Maintenance Scale; SATS, Swedish Alzheimer Treatment Study.

Table 3. Factors that affected the time to nursing home placement of AD patients after the start of ChEI treatment (Cox proportional hazards cognitive, global, and all scales models).

	MMSE		CIBIC		All Scales (MMSE, CIBIC, IADL, PSMS)	
Significant Predictors	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
MMSE score at baseline	0.91 (0.87−0.95)	<0.001	na		0.92 (0.88−0.96)	<0.001
Worsening in MMSE score after 6 months of ChEI therapy (no = 0, yes = 1)	1.59 (1.18−2.14)	0.002	na		na	
CIBIC score at baseline	na		1.70 (1.41−2.06)	<0.001	na	
Worsening in CIBIC (score 5−7) after 6 months of ChEI therapy (no = 0, yes = 1)	na		2.13 (1.57−2.89)	<0.001	na	
Worsening in number of scales[a]	na		na			
1 scale					1.09 (0.70−1.68)	0.710
2 scales					1.87 (1.25−2.82)	0.002
3 scales					2.74 (1.73−4.35)	<0.001
4 scales					4.10 (2.26−7.43)	<0.001
Sex by living status[b]						
Females living with family	1.52 (0.98−2.36)	0.061	1.46 (0.95−2.25)	0.084	1.56 (1.01−2.42)	0.047
Females living alone	2.81 (1.83−4.32)	<0.001	2.46 (1.63−3.71)	<0.001	2.89 (1.88−4.44)	<0.001
Males living alone	3.69 (2.02−6.73)	<0.001	2.78 (1.53−5.06)	0.001	3.63 (1.98−6.64)	<0.001
Age at the start of ChEI treatment (baseline), years		ns	1.03 (1.01−1.05)	0.019		ns
IADL score at baseline	1.06 (1.02−1.11)	0.001	na		1.06 (1.02−1.11)	0.001

APOE genotype, duration of AD, years of education, basic ADL ability, type of ChEI agent, drug dose, and specific concomitant medications (antihypertensive/cardiac therapy, antidiabetics, asthma medication, thyroid therapy, lipid-lowering agents, estrogens, nonsteroidal anti-inflammatory drugs/acetylsalicylic acid, antidepressants, antipsychotics, and anxiolytics/sedatives/hypnotics) used at the start of ChEI treatment (baseline) were not significant. However, carrier of APOE ε4 allele showed a trend toward significance in the MMSE model; hazard ratio 1.37 (0.98−1.92), $P = 0.064$, and in the all scales model, hazard ratio 1.36 (0.97−1.90), $P = 0.074$.

Hazard ratios are expressed per 1 unit increase for continuous variables and for the condition present in categorized variables.

[a]Improvement/no change in all 4 scales (MMSE, CIBIC, IADL, and PSMS) was the reference category.

[b]Males living with family were the reference category.

AD, Alzheimer's disease; ADL, activities of daily living; APOE, apolipoprotein E; ChEI, cholinesterase inhibitor; CI, confidence interval; CIBIC, Clinician Interview-Based Impression of Change; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; na, not applicable; ns, not significant; PSMS, Physical Self-Maintenance Scale.

0.001) for the improved/unchanged and worsened groups, respectively. No differences were found between the improved and unchanged individuals.

The percentage of SATS participants who were improved/unchanged after 6 months of ChEI therapy was 26% ($n = 227$) measured by all four scales (MMSE, CIBIC, IADL, and PSMS), 30% ($n = 266$) measured by three of the scales, 26% ($n = 231$) measured by two of the scales, 12% ($n = 101$) measured by one of the scales, and 6% ($n = 56$) were worsened in all scales. Fig. (**2**) displays a Kaplan-Meier graph of the distribution of time from the initiation of ChEI to NHP according to improvement/no change after 6 months of treatment on the number of assessment scales. A relationship between the individuals' number of scales with positive response to ChEI and delays in the time to institutionalization was found ($P < 0.001$). The log-rank test also exhibited significant differences for all pairwise comparisons ($0.001 < P \leq 0.039$), except for the combination of "improvement/no change on three of the scales—improvement/no change on all four scales." A multivariate Cox regression model showed a decreased risk of NHP depending on the AD patients' positive 6-month responses to ChEI on the number of scales (MMSE, CIBIC, IADL, and PSMS); however, no difference was observed between the individuals who exhibited improvement/no change measured by three or by four of the scales. Other independent factors in the model that significantly decreased the risk of institutionalization were better cognitive and IADL capacities at baseline. Moreover, males

Table 4. Factors that affected the time to nursing home placement of AD patients after the start of ChEI treatment (Cox proportional hazards functional models).

	IADL		PSMS	
Significant Predictors	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
IADL or PSMS score at baseline	1.09 (1.06−1.13)	<0.001	1.10 (1.04−1.17)	0.001
Worsening in IADL or PSMS score after 6 months of ChEI therapy (no = 0, yes = 1)	1.62 (1.20−2.19)	0.002	2.13 (1.57−2.88)	<0.001
Sex by living status[a]				
Females living with family	1.60 (1.04−2.47)	0.034	1.48 (0.96−2.28)	0.078
Females living alone	2.85 (1.86−4.37)	<0.001	2.47 (1.62−3.77)	<0.001
Males living alone	4.24 (2.33−7.70)	<0.001	3.90 (2.14−7.08)	<0.001
Carrier of APOE ε4 allele (no = 0, yes = 1)		ns[b]	1.45 (1.03−2.03)	0.033
MMSE score at baseline	0.93 (0.89−0.97)	<0.001	0.91 (0.87−0.94)	<0.001

Age at the start of ChEI treatment (baseline), duration of AD, years of education, type of ChEI agent, drug dose, and specific concomitant medications (antihypertensive/cardiac therapy, antidiabetics, asthma medication, thyroid therapy, lipid-lowering agents, estrogens, nonsteroidal anti-inflammatory drugs/acetylsalicylic acid, antidepressants, antipsychotics, and anxiolytics/sedatives/hypnotics) used at baseline were not significant.

Hazard ratios are expressed per 1 unit increase for continuous variables and for the condition present in categorized variables.

[a]Males living with family were the reference category.

[b]Carrier of APOE ε4 allele showed a trend toward significance in the IADL model; hazard ratio 1.39 (0.99−1.94), $P = 0.056$.

AD, Alzheimer's disease; APOE, apolipoprotein E; ChEI, cholinesterase inhibitor; CI, confidence interval; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; ns, not significant; PSMS, Physical Self-Maintenance Scale.

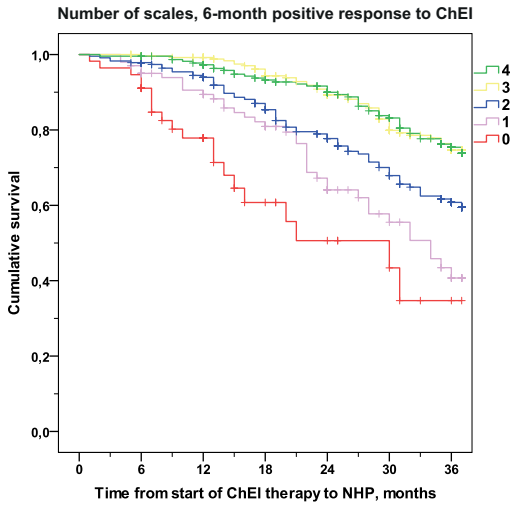

Fig. (2). Time from the start of ChEI treatment to the endpoint NHP. Kaplan-Meier graph of the distribution of time from baseline to NHP according to improvement/no change after 6 months of therapy as measured by the number of assessment scales (MMSE, CIBIC, IADL, and PSMS). A log-rank test demonstrated a relationship between the SATS patients' number of scales with positive response to ChEI and delays in the time to NHP ($P < 0.001$). All pairwise comparisons were significant ($0.001 < P \leq 0.039$), except for the combination of "improvement/no change on three of the scales—improvement/no change on all four scales."

ChEI, cholinesterase inhibitor; CIBIC, Clinician Interview-Based Impression of Change; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; NHP, nursing home placement; PSMS, Physical Self-Maintenance Scale; SATS, Swedish Alzheimer Treatment Study.

living with a family member demonstrated less risk of NHP compared with the other groups (Table **3**). The proportion of participants who were admitted to NHs during the study was 19% of the improved/unchanged patients measured by all four scales, 17% measured by three of the scales, 29% measured by two of the scales, 38% measured by one of the scales, and 36% of those who did not respond positively to ChEI therapy using any scale ($\chi^2(4) = 26.73$; $P < 0.001$). From the three scales (MMSE, CIBIC, and PSMS) that using *t* tests independently exhibited significant differences between the improved/unchanged *vs.* worsened groups regarding the time from initiation of ChEI to NHP, the mean (95% CI) period differed between individuals with the various 6-month responses to treatment: improved/unchanged measured by three of the scales, 23.8 (21.8-25.9) months; measured by two of the scales, 22.9 (20.8-24.9) months; measured by one of the scales, 17.6 (15.0-20.2) months; and worsened in all scales, 15.4 (11.4-19.5) months; ($F_{3,\ 209} = 10.64$, $P < 0.001$). Improvement/no change measured by the IADL scale did not affect the time to institutionalization in this analysis.

4. DISCUSSION

This observational AD study performed in a routine clinical setting showed that 3-8 months longer time to NHP was independently associated with a more positive response in cognitive, global, instrumental and basic ADL ability after 6 months of ChEI therapy (regardless of drug agent). The Cox regression models were consistent and controlled for sociodemographics, clinical factors, and concomitant medications. Improvement/no change in global performance and basic ADL capacity, respectively, exhibited the greatest de-

crease in risk of institutionalization, whereas improvement/no change in cognition or IADL demonstrated the weakest (but still significant) decrease in risk. Other factors in the multivariate models that significantly lowered the risk of NHP were better cognitive and IADL (or global) status at baseline, living with a family member (particularly in males), younger age (global model only), and absence of the APOE ε4 allele (basic ADL model only).

No previous studies have focused on the direct relationship between short-term treatment response to ChEI and time to NHP. Our results suggest that different levels of response can predict the time to admission with high accuracy. In particular, worsening in global outcome or basic ADL may increase the risk of NHP. A significantly lower risk of institutionalization was found in the SATS patients who were improved/unchanged after 6 months of therapy, which was 64% of the cohort in cognition, 76% in global performance, 47% in IADL, and 71% in basic ADL. Earlier placebo-controlled, randomized clinical trials of donepezil showed that 79.7%-81.1% of the participants with AD were improved/unchanged in cognitive ability and 57%-63% in global rating after 24 weeks [26, 27]. A 6-month clinical trial of galantamine reported that 64%-65% of the study group exhibited improvement/no change in cognition and 68%-69% in global performance [28]. The percentage of responders in ADL was not addressed. The differences in proportion of responders between the studies might depend on the sociodemographic and clinical composition of the cohorts.

Few AD studies have investigated patient characteristics that might affect the short-term effect of ChEI therapy on various capacities and endpoints. Previous publications from our group and others [17, 28, 29] observed that the more cognitively impaired participants demonstrated a better 6-month cognitive response to ChEI, highlighting the importance of also giving these individuals treatment opportunities. However, a more pronounced deterioration in cognition was detected in this group after the initial therapeutic response [17]. Other predictors that have been associated with more favorable cognitive response in AD were male sex [17, 18], older age [17, 19], and absence of the APOE ε4 allele [17, 20]; however, these findings were not conclusive: sex [30], age [31], APOE genotype [30]. We earlier reported a weak linear relationship between cognitive and functional response after 6 months of ChEI treatment; thus, the predictors of response might differ between these measures. In contrast to the responders in cognition, better cognitive ability and younger age at the initiation of ChEI, but not APOE genotype, predicted a more positive functional 6-month response. Moreover, the individuals who responded also showed a significantly higher ADL performance after 3 years of therapy [16]. To increase the understanding of the heterogeneous response to ChEI in AD, more research is needed to be able to identify positive responders and increase the drug efficacy and its cost benefits.

Improvement/no change in any of the capacities after 6 months of ChEI treatment significantly delayed NHP in the Cox regression models in the present study. Well-known factors that have been suggested to influence the time to admission were also included in the multivariate models, such as severity of AD, sex, age, living alone, and concomitant medications [7]. Better MMSE and IADL scores (or CIBIC score in the global model) at baseline and living with family, especially for males, independently postponed institutionalization in all our models, which gives creditability to the results. Age exhibited significance in the global model only; however, in the cognitive and ADL models where MMSE and IADL scores at baseline were included, these measures of AD severity were stronger predictors of time to NHP than age. In longer-term follow-ups, the possible effect of age might diminish with increasing worsening of the disease [32]. Earlier dementia studies have described varying associations between age and time to institutionalization, which led to inconsistent conclusions between two systematic reviews [32, 33]. Carriers of the APOE ε4 allele demonstrated a 45% increased risk of NHP in our basic ADL model, while in the other models, this characteristic showed a similar but nonsignificant trend. Some AD studies [17, 34, 35], but not all [36], found that presence of the ε4 allele could lead to a faster cognitive decline. Hence, like the aforementioned reports of predictors of response to ChEI, the significant predictors of longitudinal outcomes and endpoints in AD have been mixed and conflicting between studies. Explanations for these inconclusive observations might involve different patient characteristics in the cohorts under study and various independent predictors included in the multivariate models. Nevertheless, the heterogeneous results complicate comparisons between publications and the understanding of the course of the disease. Knowledge of the role of predictors can facilitate the interpretation of results in new clinical trials of AD therapies.

Concomitant medications were not significant in this study indicating that the other variables were more important factors for admission in persons with AD. In agreement with our results, dementia has been suggested as the strongest chronic-disease predictor of NHP in earlier publications. No other health condition predicted risk of NHP among participants with dementia; thus, it is the consequences of dementia itself, such as deterioration in various abilities, that seem to precipitate institutionalization [37, 38].

In the current AD study, worsening in global performance or basic ADL after 6 months of ChEI therapy had the strongest influence on NHP, with more than a doubled risk of admission compared with the individuals who were improved/unchanged. The clinician's global assessment can serve as a useful measure of the clinical relevance of drug effects. In addition, global measures, being in general more unspecified, allow detection whatever changes occur within treatment [39]. An alteration in this more clinically meaningful measure might have a marked impact on institutionalization. Furthermore, many dementia studies have reported that deficits in both instrumental and basic ADL are strong predictors of NHP [7, 32], in particular, the consequences of the loss of the crucial functions that may lead to malnutrition, incontinence, limited mobility, and falls [32].

Our Cox regression model showed that worsening in IADL after 6 months of treatment implied a 62% higher risk of NHP; however, the *t* test failed to show significance between the responder groups in number of months to NHP. One explanation for this inconsistent finding might be that the proportion of patients who were categorized as im-

proved/unchanged according to IADL was lower (47%) compared with that categorized using the other scales (64%-76%). Moreover, the responders in IADL demonstrated a lower IADL capacity at the start of ChEI therapy than those who worsened, which might have affected the result. Lower IADL status at baseline, but not basic ADL, was a significant factor for increased risk of NHP in all multivariate models in this study of a cohort with mild-to-moderate AD. A decline in IADL is typically observed before that of basic ADL in AD. Previously, our group has reported that better IADL ability at the initiation of ChEI and a slower rate of IADL deterioration over a longer time were independent predictors of postponed institutionalization. Hence, the AD patients' rate of functional change showed a stronger association than the rate of cognitive change on time to NHP [9]. These findings stress the importance for the clinician to evaluate IADL performance to detect AD and start treatment at an earlier stage to enable improved prognosis and longer stay at home. Furthermore, a thorough assessment after 6 months of ChEI therapy using cognitive, global, and functional measures to evaluate the patient's level of response to treatment may better predict the rate of progression and the time until the need of NHP. Clinically, ADL might be the most useful measure in AD to assess the individual's abilities to manage themselves independently. The well-known scales used in this report are reliable, easily administered, and not too time-consuming for physicians and nurses working in a routine clinical setting for dementia. Knowledge of persons with AD who are expected to show a worse response to ChEIs and faster deterioration, and to require more informal/formal care and a shorter time to NHP, is important information for family members, clinicians, and community-based services.

Socioeconomic characteristics had no influence on time to NHP in this Swedish study. Admission to NHs is based on an assessment of the individual's level of impairment and need for care *via* the social services system, in a similar way irrespective of municipality. The costs of NHs are publicly financed and not dependent on the resident's socioeconomic situation [40]. Consistently, years of education had no effect on time to institutionalization in any of the models in the present study. In some countries, *e.g.,* the USA, the person's education level, the family's income, and/or insurance coverage can have a great impact on admission to NHs [7, 41]. Our SATS has the advantage of analyzing the time to NHP focusing on the patient's actual disabilities without the influence of socioeconomic factors.

The result in this study-that initial response to ChEI, regardless of drug agent, delays NHP by 3-8 months-supports our previous observations that the responders exhibit slower disease progression and postponed endpoints in AD [15, 16]. In agreement with other publications, no differences in effectiveness were demonstrated between the three types of ChEI [17, 36]. We recently reported that improvement/no change after 6 months of therapy in cognitive, global, or functional capacities implied 0.5 years longer life-span on average [15]. However, no relationships were detected between response to ChEI and the survival time in NHs, *i.e.*, the period of NH care was not altered [4]. These findings indicate a positive ~6-month shift in AD; thus, the individuals were able to stay longer in their own homes before admission to NHs, while the end stage of the disease was not prolonged.

The strengths of the observational, prospective SATS are the large sample and well-structured, semiannual evaluations of different aspects of the course of AD including community-based services over 3 years after the initiation of ChEI treatment. Everyday AD outpatients with concomitant disorders and medications from 14 memory clinics across Sweden were enrolled. Compliance in the cohort was high, which was investigated *via* an analysis of the level of the plasma concentration of the drug [42]. The publicly funded Swedish health care and social service systems assume a representative selection of participants as discussed above. Similar to other long-term naturalistic studies of AD, the limitations are that the SATS was not placebo controlled because of ethical concerns, or randomized with respect to ChEI agent. Specialists in dementia disorders decided on the type of ChEI drug and dose for each individual, in agreement with the standards used in routine clinical practice. In addition, the time to NHP might be affected by other factors that do not originate from the patient's AD, such as specific concomitant somatic diseases or disabilities and the health status or circumstances of the caregiver, which were not recorded in the SATS. Therefore, the number of medications was used as an indicator of comorbidity.

This is the first AD study to investigate the association between short-term response to ChEI therapy and institutionalization. Few studies have assessed potential predictors that may influence the short-term response to ChEI and the results are inconsistent. Additional observational studies are required to advance our understanding of the possible characteristics that independently affect response to AD treatment. Other aspects that were not evaluated in the SATS but that need to be examined include the participants' quality of life and the strain on caregivers during this extended time to NHP. An increased understanding of the response to ChEI is important for the estimation of the patient's outcome by the treating clinician. Detailed information regarding factors that affect NHP in AD might be a valuable tool for the health authorities to analyze the effects and costs of the disease from a societal perspective. In addition, the sociodemographic and clinical composition of an AD cohort under study may be one of the explanations for the different responses to ChEI therapy reported in clinical trials.

CONCLUSION

The current study of response to ChEI after 6 months of treatment showed 3-8 months delayed NHP among the improved/unchanged AD patients regarding cognition, global performance, and instrumental and basic ADL. The more scales the individual demonstrated positive response to, the longer was the time to NHP. Lack of short-term response to ChEI therapy implied a higher risk of institutionalization. In particular, worsening in the more clinically relevant global measure or in basic ADL tasks more than doubled the risk of NHP compared with those who were improved/unchanged. These findings underline the importance of a thorough examination using different tools to assess short-term therapeutic response to ChEIs and hence be able to provide a more accurate patient prognosis over a longer time, as well as the prediction of end points, such as NHP. Our results may be generalizable for health care systems where institutionalization is dependent on the individuals' need of care as opposed

to their financial status. Milder disease severity (regardless of scale used) at the initiation of ChEI and living with family, especially among males, were protective factors for lower risk of NHP in all Cox regression models. These observations are consistent with those of other dementia reports, which suggest stability in our multivariate models. Various sociodemographic and clinical characteristics may lead to alterations in treatment response and rate of decline among participants with AD. In addition, significant predictors of response can differ depending on the capacity or endpoint evaluated. These discrepancies may affect the outcome and interpretation of results in trials of new AD therapies. Knowledge of individuals who are expected to exhibit a worse response to therapy and more rapid disease progression-and thus require more care resources and earlier NHP-is important information for family members, physicians, and the community-based services. In summary, several months of longer stay in their own home can be expected for AD patients whose short-term response to ChEI is positive.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
ADL	=	Activities of Daily Living
APOE	=	Apolipoprotein E
ChEI	=	Cholinesterase Inhibitor
CI	=	Confidence Interval
CIBIC	=	Clinician Interview-Based Impression of Change
IADL	=	Instrumental Activities of Daily Living scale
MMSE	=	Mini-Mental State Examination
NH	=	Nursing Home
NHP	=	Nursing Home Placement
PSMS	=	Physical Self-Maintenance Scale
SATS	=	Swedish Alzheimer Treatment Study

AVAILABILITY OF DATA AND MATERIALS

Currently, we are unable to share the SATS data because data collection, such as dates of death, is presently taking place and the data analysis process is ongoing.

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AUTHORS' CONTRIBUTIONS

Carina Wattmo participated in the SATS, supervised the data collection, was responsible for the statistical design, performed the statistical analyses, interpreted the results, and drafted the manuscript. Elisabet Londos participated in the study, assisted in the analysis and interpretation of the data, and revised the manuscript critically. Lennart Minthon was responsible for the design of the study, was the principal investigator, and revised the manuscript critically. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The SATS protocol and the current analysis of data from the SATS presented in this manuscript were submitted to and approved by the Regional Ethical Review Board, Lund University, Sweden (no. 2014/658, dated December 9, 2014).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving the SATS participants were in accordance with the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written informed consent was obtained from all patients included in the SATS. If an individual was not able to provide consent for him/herself, consent was obtained from their closest relative.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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