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RESEARCH ARTICLE

Cerebrospinal Fluid Biomarker Levels as Markers for Nursing Home Placement and Survival Time in Alzheimer's Disease

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Abstract: Background: Cerebrospinal Fluid (CSF) biomarkers are associated with conversion from mild cognitive impairment to Alzheimer's Disease (AD), but their predictive value for later end-points has been less evaluated with inconsistent results.

Objective: We investigated potential relationships between CSF amyloid- β_{1-42} ($A\beta_{42}$), Phosphorylated tau (P-tau), and Total tau (T-tau) with time to Nursing Home Placement (NHP) and life expectancy after diagnosis.

Methods: This prospective observational study included 129 outpatients clinically diagnosed with mild-to-moderate AD who underwent a lumbar puncture. The CSF biomarkers were analysed with xMAP technology. Dates of institutionalisation and death were recorded.

Results: After 20 years of follow-up, 123 patients (95%) were deceased. The participants with abnormal P-tau and T-tau (A+ T+ (N)+) died earlier than those with normal P-tau/abnormal T-tau (A+ T- (N)+) (mean, 80.5 vs. 85.4 years). Linear associations were demonstrated between lower $A\beta_{42}$ and shorter time to NHP ($p = 0.017$), and higher P-tau and younger age at death ($p = 0.016$). No correlations were detected between survival after AD diagnosis and CSF biomarkers. In sex- and age-adjusted Cox regression models, higher P-tau and T-tau were independent predictors of shorter lifespan after diagnosis. In multivariate Cox models, older age and lower baseline cognitive status, but not elevated tau, significantly precipitated both institutionalisation and death.

Conclusion: These findings suggest that CSF biomarker levels plateau in the dementia phase of AD, which may limit their possible relationships with clinical end-points, such as NHP and survival time. However, the biomarkers reflect the central pathophysiologies of AD. In particular, pathologic tau is associated with more advanced disease, younger age at onset, and earlier death.

Keywords: Alzheimer's disease, nursing home placement, mortality, longitudinal study, predictors, CSF biomarkers, AT(N), Tau.

1. INTRODUCTION

After a long neurodegenerative disease process with decreasing cognitive ability and a continuous loss of instrumental and basic activities of daily living (ADL) performance, patients with Alzheimer's disease (AD) reach the end-points of nursing home placement (NHP) and finally death [1]. Factors affecting both the institutionalisation process and survival in AD are complex and depend on socio-demographic and clinical features. Previous studies of dementia have reported several characteristics that precipitate NHP, such as older age [2, 3], living alone, and lower cognitive and

functional capacities [3-5]. Conflicting results regarding sex have been described [2, 4]. Shorter life expectancy in AD has been related to, for *e.g.* male sex, older age [6-8], lower cognitive status and comorbid medical disorders, such as cardiovascular disease and diabetes [6, 8]. In contrast, an earlier study showed that the presence of the apolipoprotein E (*APOE*) $\epsilon 4$ allele was associated with excess 5-year mortality [9], while a 16-year follow-up from our group observed no relationship between *APOE* genotype and risk of death [8].

The AD pathological processes can be monitored by biomarkers, but a large variation in the CSF biomarker levels exists across persons with AD. A previous study demonstrated that the CSF levels of phosphorylated tau (P-tau) and total tau (T-tau) become pathological later in the course of AD compared with amyloid- β_{1-42} ($A\beta_{42}$) [10]. A research frame-

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work for the classification of biomarkers has been recently reported. The biomarkers were grouped into those of β -amyloid deposition “A”, pathologic tau “T” and neurodegeneration/neuronal injury “(N)” (non-AD specific; thus, labeled in parentheses). With the application of cut points, each of the A, T or (N) can be classified as abnormal (+) or normal (-), resulting in different AT(N) biomarker profiles [11].

It is unclear if higher tau levels are associated with the individuals’ time to NHP or survival after diagnosis. Few studies have investigated the possible relationships between the end-points of AD and the levels of CSF biomarkers, and the outcomes are inconsistent. Only three earlier AD studies analysed the relationship between biomarkers and time to institutionalisation; however, two found no correlations between those variables [12, 13], while the other study described a greater risk of NHP among participants with higher levels of T-tau [14]. No studies have evaluated the potential associations between biomarkers and the survival time in nursing homes (NHs).

In some long-term studies, high T-tau and P-tau have been correlated with shorter lifespan [15, 16], whereas others have observed no associations between CSF biomarkers and mortality [17, 18]. A recent study showed that lower $A\beta_{42}$, but not abnormal tau, predicted a shorter time to death [13].

The current AD study aims to investigate the possible relationships between patients with different AT(N) biomarker profiles and (1) time to institutionalisation, (2) survival time in NHs and (3) life expectancy after diagnosis.

2. MATERIAL AND METHODS

2.1. Study and Subjects

The AD cohort of 129 participants was prospectively recruited from the Memory Clinic, Skåne University Hospital, Malmö, Sweden. A subgroup of these individuals using the same run and batch of reagents was enrolled in a previous study that defined CSF biomarker cut-off values [19]. At the start of Cholinesterase Inhibitor (ChEI) therapy (baseline), the patients in the present study underwent a Lumbar Puncture (LP) and exhibited a Mini-Mental State Examination (MMSE) [20] score ranging from 10 to 26, *i.e.*, mild-to-moderate AD. These 129 participants were included in a previous publication that assessed the rates of change in cognitive, global, and functional performance, longitudinal prognosis, short-term response to ChEIs, and *APOE* genotype between groups with different AT(N) biomarker profiles [21]. This cohort is a subset of the Swedish Alzheimer Treatment Study (SATS), which is a 3-year, open-label, non-randomized, multicentre study implemented in clinical practice. No significant differences in sex, *APOE* genotype, age at onset or at baseline, years of education, cognitive and functional abilities, and the number of medications at baseline were detected between the subgroup who underwent a LP and the other individuals.

The SATS was started in 1997 to evaluate the longitudinal effectiveness of ChEIs in naturalistic outpatients on dif-

ferent aspects of AD (*e.g.*, cognitive, ADL, use of community-based services). Various results from this study have been published in several articles, for example [5, 8, 15, 21, 22]. Before inclusion, all patients underwent a thorough clinical investigation, including medical history, physical and neurological examinations, cognitive assessments, laboratory tests, and cerebral computed tomography to rule out other causes of dementia. Moreover, in some centres, they were investigated further through CSF tap, measurement of regional cerebral blood flow (Cortexplorer using 133 -xenon inhalation or single-photon emission computed tomography), electroencephalography, and neuropsychological tests. Individuals fulfilling the clinical criteria of dementia, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) [23], and those of probable or possible AD, according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) [24], were enrolled in the SATS. The participants were diagnosed by specialists in dementia disorders. Additional inclusion criteria were older than 40 years, living in their own home at the time of diagnosis, having a responsible caregiver (usually the spouse or an adult child), and to be assessable with MMSE at the initiation of ChEIs (baseline). Patients not fulfilling the diagnostic criteria for AD, those already undergoing active treatment with any ChEI drug or persons with contra-indications for ChEI therapy were excluded from the study.

Shortly after their AD diagnosis, the participants were enrolled in the study and completed the baseline evaluations. They were then prescribed ChEI treatment according to the approved product labelling as in routine clinical practice. All decisions regarding drug agent and dose were left to the physicians who were dementia specialists, and all dose adjustments were documented throughout the study. Medications other than ChEI therapy were recorded at baseline and allowed during the SATS, with the exception of memantine. If the patient stopped taking ChEI, or if memantine was initiated, he/she dropped out from the study at that time point, and no further information regarding NHP was documented. Regarding participants who dropped out for other reasons, information regarding whether they continued with ChEI treatment after discontinuing the SATS was not available.

The date of NHP was obtained from medical records and institutionalisation was defined as the permanent entry to a licensed skilled nursing facility with 24 h care; *i.e.*, rehabilitative or respite care was excluded. Using the 12-digit personal identity number assigned to each Swedish resident, we determined whether each individual in the SATS was still alive on 31st December 2017 with the help of the Swedish population register (Swedish Tax Agency). If not, the date of death was recorded.

2.2. Ethics Approval and Consent to Participate

All procedures performed in studies involving the SATS participants were in accordance with the Declaration of Helsinki. The SATS protocol and the current analyses of da-

ta were submitted to and approved by the Regional Ethical Review Board, Lund University, Lund, Sweden (no. 2014/658, dated 9th December 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.

2.3. Assessment Scales

The SATS patients were investigated in a well-structured, follow-up program using cognitive and functional rating scales at the start of ChEI therapy, after 2 months (MMSE only) and every 6 months over 3 years. Cognitive status was assessed using the MMSE, with scores ranging from 0 to 30 (a higher score indicating less impaired cognition).

The Instrumental Activities of Daily Living (IADL) scale [25] consists of 8 different items: The ability to use the telephone, shopping, food preparation, housekeeping, 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), which allowed a total range of 8-31 points. The Physical Self-Maintenance Scale (PSMS) [25] consists of 6 different items: toilet, feeding, dressing, grooming, physical ambulation and bathing. Each item was scored from 1 (no impairment) to 5 (severe impairment), which yielded a total range of 6-30 points. Trained dementia nurses obtained the ADL evaluations from interviews with the caregiver.

2.4. Analysis of Baseline CSF

CSF was collected in polypropylene tubes, stored at -80°C and analysed after the clinical follow-up of the study was completed. LP was only performed at the baseline visit. The procedure followed The Alzheimer's Association Flow Chart for LP and CSF sample processing [26]. The levels of A β ₄₂, P-tau phosphorylated at Thr₁₈₁ and T-tau were determined using xMAP technology [27]. Abnormal levels of CSF biomarkers were defined as A β ₄₂ <209 pg/mL (A+), P-tau >51 pg/mL (T+) and T-tau >100 pg/mL (N)+ [19].

2.5. 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 the statistical analyses. The level of significance was defined as $p < 0.05$ if not otherwise mentioned, and all tests were two-tailed. Observed-case analyses were used to avoid overestimation of the treatment effect by imputing earlier superior outcome scores in a long-term study of a progressively deteriorating disease. One-way Analysis of Variance (ANOVA) with Bonferroni correction was used to compare the difference between the mean scores calculated from, e.g. the continuous assessment scales, time to NHP or survival and the four AT(N) biomarker profiles. Independent-sample t -tests were used to compare the differences between the means obtained for two groups, and chi-square tests were computed to analyse categorical variables. Spearman's non-parametric corre-

lation coefficient was calculated to evaluate the presence of any associations between the CSF biomarker values and time to institutionalisation or lifespan.

Backward stepwise elimination Cox proportional hazards regression models were used to simultaneously estimate the effect of all the possible predictors mentioned below on the time to NHP or death. Variables with $p > 0.05$ were removed from the stepwise models. No violation of the assumption of proportional hazards was detected. Classical risk factors such as sex, age at baseline, the clinician's estimation of age at onset, years of education, and APOE genotype were included in the Cox regression model. Measures of AD severity, i.e., cognitive, instrumental and basic ADL capacities at baseline, were also included as independent variables. Comorbidities were investigated as the presence of specific medications used by $\geq 10\%$ of the participants (no/yes for each group), i.e., antihypertensive/cardiac therapy, thyroid therapy, lipid-lowering agents, non-steroidal anti-inflammatory drugs (NSAIDs)/acetylsalicylic acid, antidepressants, anxiolytics/sedatives/hypnotics, and vitamin B12/folate. Antidiabetic drugs, asthma medication, oestrogens and anti-psychotics were used by less than 10% of the patients and are therefore not included in the models. The impact of CSF biomarkers on institutionalisation and mortality, respectively, was analysed in two separate Cox models together with the aforementioned potential predictors: (1) dichotomously coded as normal/abnormal and (2) continuous values.

3. RESULTS

3.1. Baseline Characteristics According to AT(N) Biomarker Profiles

All 129 SATS participants had abnormal (low) CSF A β ₄₂ (A+), suggesting that they had brain amyloidosis. The socio-demographic and clinical characteristics of the patients were divided into four biomarker profiles and are displayed in Table 1: normal P-tau and T-tau (A+ T- (N)-), $n = 58$ (45%); abnormal (high) P-tau and normal T-tau (A+ T+ (N)-), $n = 12$ (9%); normal P-tau and abnormal (high) T-tau (A+ T- (N)+), $n = 17$ (13%); and both abnormal P-tau and T-tau (A+ T+ (N)+), $n = 42$ (33%). Some of the data in Table 1 have been previously reported in another study [21]. Post hoc tests (Bonferroni) demonstrated that the individuals with A+ T+ (N)+ were younger at the estimated onset of AD ($F_{3,125} = 4.78$, $p = 0.003$) and at the initiation of ChEI therapy (baseline) ($F_{3,125} = 4.46$, $p = 0.005$) than those with A+ T- (N)+. The levels of P-tau ($F_{3,125} = 73.68$, $p < 0.001$) and T-tau ($F_{3,125} = 68.57$, $p < 0.001$), but not A β ₄₂, differed between the AT(N) biomarker profiles as expected. Post hoc tests showed significant differences for all pairwise comparisons of P-tau with the exception of the combination of A+ T- (N)- and A+ T- (N)+, and for all pairwise comparisons of T-tau except for the combination of A+ T- (N)- and A+ T+ (N)-. No differences regarding the use of concomitant medications were exhibited between the four AT(N) profiles (Table 1).

Table 1. Socio-demographic and clinical characteristics by AT(N) biomarker profiles ($n = 129$).

-	A+ T- (N)- ($n = 58, 45\%$)	A+ T+ (N)- ($n = 12, 9\%$)	A+ T- (N)+ ($n = 17, 13\%$)	A+ T+ (N)+ ($n = 42, 33\%$)	<i>p</i> value
Variable	<i>n</i> / <i>%</i>	<i>n</i> / <i>%</i>	<i>n</i> / <i>%</i>	<i>n</i> / <i>%</i>	-
Female sex	34/59%	10/83%	14/82%	30/71%	0.139
Living alone	19/33%	7/58%	8/47%	16/38%	0.345
Carrier of the <i>APOE</i> $\epsilon 4$ allele	41/71%	8/67%	10/59%	34/81%	0.340
Antihypertensive/cardiac therapy	20/34%	3/25%	8/47%	8/19%	0.143
Thyroid therapy	8/14%	0/0%	2/12%	5/12%	0.605
Lipid-lowering agents	7/12%	2/17%	1/6%	2/5%	0.465
NSAIDs/acetysalicylic acid	27/47%	3/25%	7/41%	10/24%	0.098
Anti-depressants	20/34%	4/33%	8/47%	15/36%	0.805
Anxiolytics/sedatives/hypnotics	7/12%	0/0%	5/29%	6/14%	0.138
Vitamin B12/folate	22/38%	1/8%	5/29%	12/29%	0.229
Variable	Mean \pm Standard Deviation				<i>p</i> value
Estimated age at onset, years	72.9 \pm 7.2	74.5 \pm 4.8	77.1 \pm 5.7	70.3 \pm 6.2	0.003
Estimated duration of AD at baseline, years	3.2 \pm 2.4	2.3 \pm 1.4	2.2 \pm 1.3	3.0 \pm 1.9	0.228
Age at baseline, years	76.1 \pm 6.2	76.8 \pm 4.6	79.2 \pm 6.2	73.3 \pm 6.0	0.005
Education, years	10.2 \pm 3.1	9.4 \pm 1.9	9.1 \pm 2.0	9.0 \pm 2.0	0.116
MMSE score at baseline	21.7 \pm 3.8	19.5 \pm 3.7	20.6 \pm 4.6	20.2 \pm 4.0	0.181
IADL score at baseline	17.2 \pm 5.7	14.6 \pm 5.9	15.9 \pm 5.7	15.9 \pm 4.9	0.403
PSMS score at baseline	7.9 \pm 2.9	7.2 \pm 1.9	8.3 \pm 3.1	7.4 \pm 2.2	0.568
A β_{42} , pg/mL	122 \pm 22	116 \pm 12	118 \pm 19	115 \pm 14	0.274
T-tau, pg/mL	72 \pm 15	82 \pm 11	122 \pm 19	155 \pm 46	<0.001
P-tau, pg/mL	30 \pm 13	61 \pm 8	40 \pm 9	79 \pm 24	<0.001

Note: Antidiabetic drugs, asthma medication, oestrogens, and anti-psychotics were used by <10% of the patients and therefore not presented. **Abbreviations:** A+, abnormal CSF A β_{42} ; A β_{42} , amyloid- β_{1-42} ; AD, Alzheimer's disease; *APOE*, apolipoprotein E; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; (N)-, normal CSF T-tau; (N)+, abnormal CSF T-tau; NSAIDs, non-steroidal anti-inflammatory drugs; PSMS, Physical Self-Maintenance Scale; P-tau, phosphorylated tau; T-, normal CSF P-tau; T+, abnormal CSF P-tau; T-tau, total tau.

Table 2. End-points by AT(N) biomarker profiles.

Variable	A+ T- (N)-	A+ T+ (N)-	A+ T- (N)+	A+ T+ (N)+	<i>p</i> value
Deceased patients after 20 years of follow-up ($n = 123$), <i>n</i> / <i>%</i>	54/93%	12/100%	16/94%	41/98%	0.617
Time from baseline to death, years ($n = 123$) ^a	6.8 (5.8, 7.8)	5.3 (3.9, 6.7)	5.7 (4.6, 6.8)	7.3 (6.2, 8.4)	0.184
Age at death, years ($n = 123$) ^a	83.3 (81.5, 85.0)	82.3 (79.5, 85.2)	85.4 (82.7, 88.2)	80.5 (78.8, 82.3)	0.024
Variable	A+ T- (N)-	A+ T+ (N)- / A+ T- (N)+ / A+ T+ (N)+	-	-	<i>p</i> value
Nursing home placement during the study ($n = 31$), <i>n</i> / <i>%</i>	13/22%	18/25%	-	-	0.698
Time from baseline to nursing home placement, months ($n = 31$) ^a	21.2 (15.3, 27.1)	18.8 (13.4, 24.2)	-	-	0.535
Survival time in nursing homes, years ($n = 31$) ^a	4.3 (2.7, 5.9)	4.1 (3.1, 5.1)	-	-	0.807

Note: ^aMean (95% confidence interval).

Abbreviations: A+, abnormal CSF amyloid- β_{1-42} ; (N)-, normal CSF total tau; (N)+, abnormal CSF total tau; T-, normal CSF phosphorylated tau; T+, abnormal CSF phosphorylated tau.

3.2. End-Points During the SATS

During the study, 31 individuals (24%) were admitted to NHs. This frequency, the mean (95% Confidence Interval [CI]) time from the initiation of ChEIs to institutionalisation (19.8 [16.0-23.5] months) or the survival time in NHs (4.2 [3.4-5.0] years) did not differ between the groups with normal/abnormal levels of tau (Table 2).

Using the continuous CSF biomarker values, a linear relationship was demonstrated between shorter time to NHP

and lower A β_{42} ($r_s = 0.426$, $p = 0.017$) (Fig. 1); the correlation was still significant after controlling for age and MMSE score at baseline.

No linear associations were observed between time to institutionalisation and P-tau ($r_s = -0.251$, $p = 0.173$) or T-tau ($r_s = -0.245$, $p = 0.184$), and between survival time in NHs and A β_{42} ($r_s = 0.001$, $p = 0.995$), P-tau ($r_s = -0.112$, $p = 0.548$), or T-tau ($r_s = -0.131$, $p = 0.483$). The above-mentioned results were not affected by *APOE* genotype. The

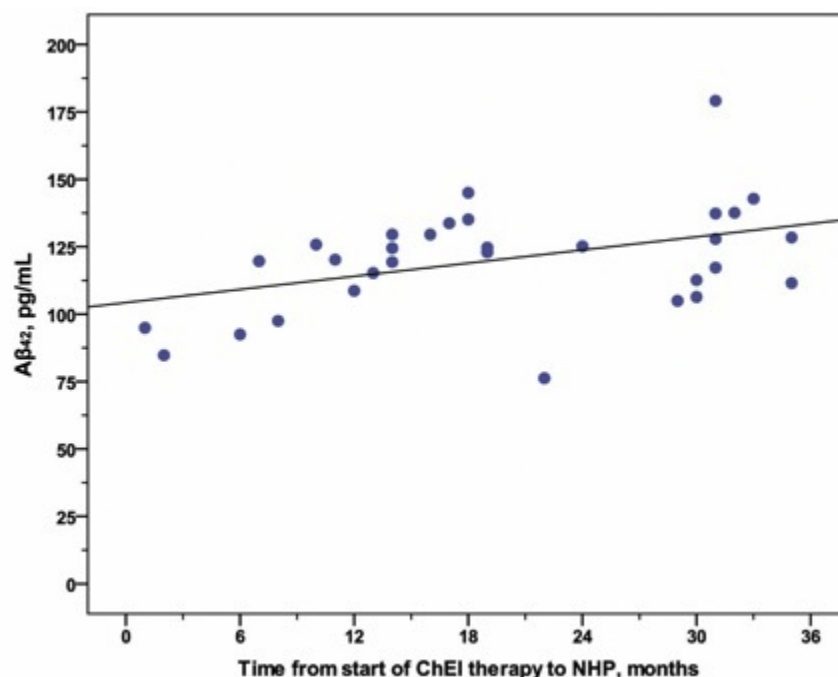


Fig. (1). Relationship between CSF biomarkers and the end-point NHP. A positive linear association between higher levels of $A\beta_{42}$ at baseline and prolonged time to institutionalisation was observed ($r_s = 0.426$, $p = 0.017$). Abbreviations: $A\beta_{42}$, Amyloid- β_{1-42} ; ChEI, cholinesterase inhibitor; CSF, cerebrospinal fluid; NHP, Nursing home placement.

CSF biomarkers (as continuous or dichotomized variables) were not significant predictors in multivariate general linear models with survival time in NHs as the dependent variable.

After 20 years of follow-up, 123 of the 129 SATS patients (95%) had died. Their mean (95% CI) lifespan after the start of ChEI therapy was 6.7 (6.1-7.3) years, and no difference among the AT(N) biomarker profiles was found (Table 2). Fig. (2) illustrates the percentage of deceased persons per year according to AT(N) profile after the initiation of ChEIs (time of AD diagnosis).

The mean age at death was 82.5 (81.5-83.6) years; however, individuals with A+ T+ (N)+ died at a younger age than those with A+ T- (N)+ ($F_{3,119} = 3.25$, $p = 0.024$) (Table 2). Using the continuous CSF biomarker values, no correlations were observed between life expectancy after the start of ChEIs and $A\beta_{42}$ ($r_s = -0.076$, $p = 0.402$), P-tau ($r_s = -0.001$, $p = 0.996$) or T-tau ($r_s = -0.042$, $p = 0.644$). A linear relationship was demonstrated between younger age at death and higher P-tau ($r_s = -0.216$, $p = 0.016$) (Fig. 3a), but not between age at death and $A\beta_{42}$ ($r_s = -0.123$, $p = 0.174$) or T-tau ($r_s = -0.135$, $p = 0.135$). The correlation was still significant after controlling for MMSE score at baseline. The above-mentioned results were not affected by *APOE* genotype.

In a Kaplan-Meier analysis with pairwise log-rank tests, the individuals with A+ T+ (N)- exhibited shorter survival after initiation of ChEI treatment than those with A+ T- (N)- ($p = 0.032$) or A+ T+ (N)+ ($p = 0.016$) (Fig. 3b). The interac-

tion effects of normal/abnormal levels of tau with the presence/absence of the *APOE* $\epsilon 4$ allele on life expectancy were also investigated. No difference in mean survival time after baseline was found between the four groups when examined by an ANOVA or using a Kaplan-Meier analysis. The proportion of deaths did not differ between the groups.

3.3. Cox Regression Models for NHP and Time to Death

Univariate Cox proportional hazards modelling adjusted for sex and age demonstrated that a shorter time from the start of ChEI therapy to institutionalisation was related to older age and lower cognitive performance at baseline. The hazard ratios with 95% CI and p values are listed in Table 3. When subjected to multivariate backward elimination modelling, these two variables were also retained in the Cox model for a shorter time to NHP. The actual continuous values of the CSF biomarkers or dichotomously coded normal/abnormal, respectively, were not significant predictors in the Cox regression models (Table 3).

Univariate Cox proportional hazards modelling controlled for sex and age showed some risk factors to be associated with mortality. Shorter time from the initiation of ChEI treatment to death was related to older age, lower cognitive and functional capacities at baseline and higher P-tau or T-tau. The hazard ratios with 95% CI and p values are listed in Table 4. When subjected to multivariate backward elimination modelling, three variables, *i.e.*, older age, lower cognitive ability and usage of anxiolytics/sedatives/hypnotics (the dichotomously coded tau model only), were retained in the

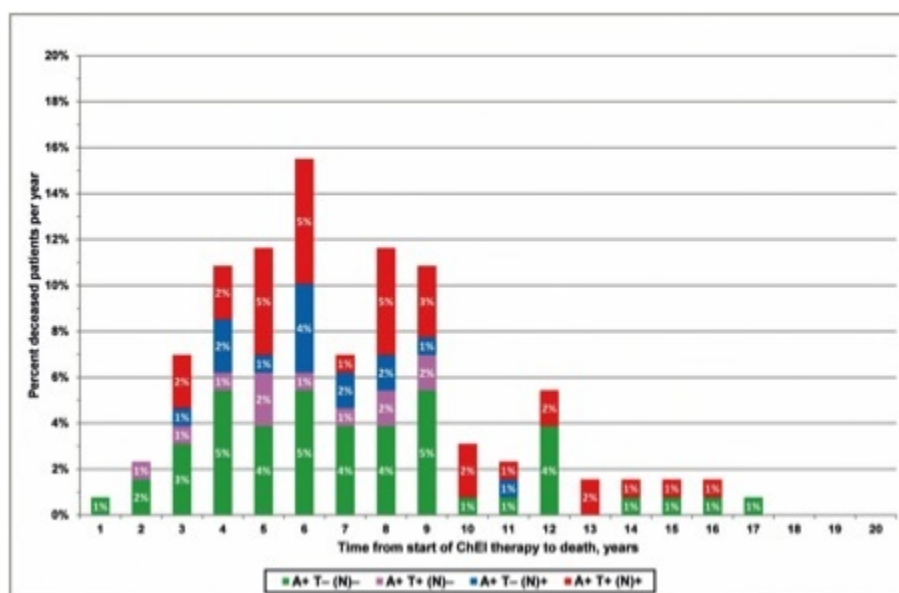


Fig. (2). Mortality over 20 years in AD. Proportion of deceased patients per year by AT(N) biomarker profile after the initiation of ChEI treatment (approximately the time of AD diagnosis). After up to 20 years of follow-up, 123 (95%) of the 129 SATS participants had died. The percentages of deceased individuals were 10% after 3 years, 33% after 5 years, 55% after 7 years, and 81% after 10 years. Year 1 indicates a lifespan after baseline of up to 1 year, year 2 indicates >1 to ≤2 years, year 3 indicates >2 to ≤3 years, etc. Abbreviations: A+, abnormal CSF Aβ₄₂; AD, Alzheimer's disease; ChEI, cholinesterase inhibitor; CSF, cerebrospinal fluid; (N)-, normal CSF T-tau; (N)+, abnormal CSF T-tau; SATS, Swedish Alzheimer Treatment Study; T-, normal CSF P-tau; T+, abnormal CSF P-tau. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 3. Cox proportional hazards modelling of time to nursing home placement.

-	Univariate ^a	-	Multivariate, Significant Predictors	-
Independent Variables	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
Sex (male = 0, female = 1)	1.19 (0.53-2.66)	0.676	-	-
Living alone (no = 0, yes = 1)	1.47 (0.66-3.26)	0.341	-	-
Carrier of the APOE ε4 allele (no = 0, yes = 1)	1.13 (0.51-2.51)	0.769	-	-
Antihypertensive/cardiac therapy (no = 0, yes = 1)	0.74 (0.33-1.63)	0.455	-	-
Thyroid therapy (no = 0, yes = 1)	0.72 (0.21-2.43)	0.599	-	-
Lipid-lowering agents (no = 0, yes = 1)	1.59 (0.55-4.55)	0.391	-	-
NSAIDs/acylsalicylic acid (no = 0, yes = 1)	1.01 (0.46-2.23)	0.976	-	-
Anti-depressants (no = 0, yes = 1)	0.85 (0.40-1.84)	0.689	-	-
Anxiolytics/sedatives/hypnotics (no = 0, yes = 1)	1.24 (0.52-2.94)	0.630	-	-
Vitamin B12/folate (no = 0, yes = 1)	1.11 (0.53-2.32)	0.781	-	-
Estimated age at onset, years	0.92 (0.78-1.09)	0.361	-	-
Age at baseline, years	1.12 (1.04-1.19)	0.001	1.09 (1.02-1.17)	0.011
Education, years	0.89 (0.75-1.06)	0.208	-	-
MMSE score at baseline	0.89 (0.83-0.96)	0.004	0.89 (0.83-0.96)	0.004
IADL score at baseline	1.06 (0.99-1.14)	0.084	-	-
PSMS score at baseline	1.10 (0.98-1.24)	0.116	-	-
Aβ ₄₂ , pg/mL ^b	1.00 (0.98-1.02)	0.870	-	-
T-tau, pg/mL ^b	1.00 (0.99-1.01)	0.664	-	-
P-tau, pg/mL ^b	1.00 (0.99-1.01)	0.928	-	-

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

^aAdjusted (if applicable) for the baseline variables sex and age. ^bDichotomously coded T-tau and P-tau (normal/abnormal), instead of the continuous values, were not significant in a multivariate Cox regression model adjusted for the above-mentioned predictors. The variables (hazard ratio, 95% CI) age (1.09, 1.02-1.17, $p = 0.011$) and MMSE score at baseline (0.89, 0.83-0.96, $p = 0.004$) were also significant predictors of time to institutionalisation in that model.

Abbreviations: Aβ₄₂, amyloid-β₁₋₄₂; APOE, apolipoprotein E; CI, confidence interval; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; NSAIDs, non-steroidal anti-inflammatory drugs; PSMS, Physical Self-Maintenance Scale; P-tau, phosphorylated tau; T-tau, total tau.

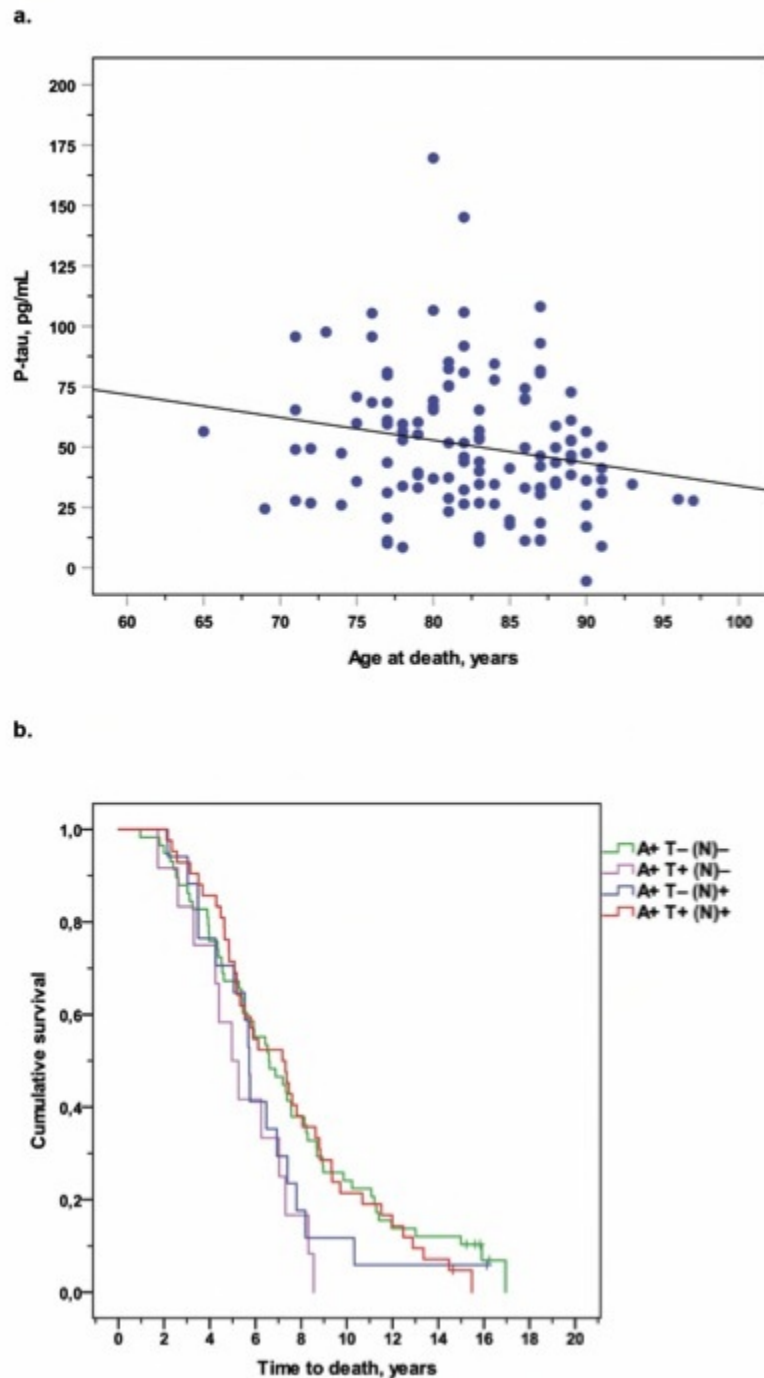


Fig. (3). Associations between CSF biomarkers and the end-point death. (a) A linear relationship was found between higher levels of P-tau and younger age at death ($r_s = -0.216$, $p = 0.016$). The correlation was still significant after controlling for MMSE score at baseline. (b) Kaplan-Meier graph of the distribution of time from the start of ChEI therapy (approximately the time of AD diagnosis) to death according to AT(N) biomarker profile. Using pairwise log-rank tests, the SATS patients with A+ T+ (N)- showed a shorter life expectancy than those with A+ T- (N)- ($p = 0.032$) or A+ T+ (N)+ ($p = 0.016$).

Abbreviations: A+, abnormal CSF $A\beta_{42}$; AD, Alzheimer's disease; ChEI, cholinesterase inhibitor; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; (N)-, normal CSF T-tau; (N)+, abnormal CSF T-tau; P-tau, phosphorylated tau; SATS, Swedish Alzheimer Treatment Study; T-, normal CSF P-tau; T+, abnormal CSF P-tau. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 4. Cox proportional hazards modelling of time to death.

-	Univariate ^a	-	Multivariate, Significant Predictors	-
Independent Variables	Hazard Ratio (95% CI)	<i>p</i> value	Hazard Ratio (95% CI)	<i>p</i> value
Sex (male = 0, female = 1)	0.96 (0.65-1.41)	0.839	-	-
Living alone (no = 0, yes = 1)	1.02 (0.69-1.52)	0.925	-	-
Carrier of the <i>APOE</i> $\epsilon 4$ allele (no = 0, yes = 1)	0.85 (0.57-1.26)	0.415	-	-
Antihypertensive/cardiac therapy (no = 0, yes = 1)	1.09 (0.73-1.63)	0.681	-	-
Thyroid therapy (no = 0, yes = 1)	1.41 (0.80-2.47)	0.238	-	-
Lipid-lowering agents (no = 0, yes = 1)	0.72 (0.38-1.35)	0.299	-	-
NSAIDs/acetysalicylic acid (no = 0, yes = 1)	0.84 (0.57-1.24)	0.374	-	-
Anti-depressants (no = 0, yes = 1)	1.08 (0.75-1.58)	0.671	-	-
Anxiolytics/sedatives/hypnotics (no = 0, yes = 1)	1.63 (0.97-2.73)	0.063	-	-
Vitamin B12/folate (no = 0, yes = 1)	1.08 (0.73-1.61)	0.699	-	-
Estimated age at onset, years	1.04 (0.95-1.14)	0.392	-	-
Age at baseline, years	1.06 (1.03-1.10)	<0.001	1.06 (1.03-1.09)	<0.001
Education, years	0.97 (0.90-1.04)	0.345	-	-
MMSE score at baseline	0.90 (0.86-0.94)	<0.001	0.90 (0.87-0.95)	<0.001
IADL score at baseline	1.05 (1.01-1.09)	0.008	-	-
PSMS score at baseline	1.08 (1.01-1.16)	0.036	-	-
A β_{42} , pg/mL ^b	1.001 (0.992-1.011)	0.763	-	-
T-tau, pg/mL ^b	1.004 (1.000-1.008)	0.030	-	-
P-tau, pg/mL ^b	1.007 (1.000-1.014)	0.048	-	-

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

^aAdjusted (if applicable) for the baseline variables sex and age.

^bDichotomously coded T-tau and P-tau (normal/abnormal), instead of the continuous values, were not significant in a multivariate Cox regression model adjusted for the above-mentioned predictors. The variables (Hazard Ratio, 95% CI) age (1.06, 1.02-1.09, $p = 0.001$) and MMSE score at baseline (0.91, 0.87-0.95, $p < 0.001$), and use of anxiolytics/sedatives/hypnotics (1.73, 1.01-2.95, $p = 0.046$), were significant predictors of survival time in that model.

Abbreviations: A β_{42} , amyloid- β_{1-42} ; *APOE*, apolipoprotein E; CI, confidence interval; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; NSAIDs, non-steroidal anti-inflammatory drugs; PSMS, Physical Self-Maintenance Scale; P-tau, phosphorylated tau; T-tau, total tau.

Cox model for a shorter lifespan. A trend towards significance was detected for the usage of anxiolytics/sedatives/hypnotics in the continuously coded tau model ($p = 0.063$). The actual continuous values of CSF tau or dichotomously coded normal/abnormal, respectively, were not significant predictors of time to death in the multivariate Cox regression models (Table 4).

4. DISCUSSION

In this longitudinal, observational study, we demonstrated that the participants with A+ T+ (N)+ (pathologic tau and neurodegeneration) died 5 years earlier on average than those with A+ T- (N)+ (normal tau but with neurodegeneration). The time from the start of ChEIs (AD diagnosis) to NHP, survival time in NHs, frequency of deaths and life expectancy after diagnosis did not differ between the AT(N) biomarker profiles. Linear associations were shown between lower A β_{42} and shorter time to institutionalisation, and between higher P-tau and younger age at death. No correlations between any of the CSF biomarkers and survival time in NHs or lifespan after AD diagnosis were found. Higher P-tau and T-tau were independent predictors of shorter survival after diagnosis in sex- and age-adjusted univariate Cox regression models. However, only the variables, older age and lower cognitive status, at baseline significantly precipitated NHP and death in the multivariate Cox models. In addition,

the usage of anxiolytics/sedatives/hypnotics predicted shorter life expectancy.

The relationships between the levels of CSF biomarkers and the severity of AD or its end-points are inconsistent and not well understood. Previous studies have assumed that A β_{42} mirrors the amount of amyloid plaque load in the brain, which results in decreased secretion of A β_{42} to the CSF, *i.e.*, a lower clearance. T-tau has been suggested to reflect the intensity of axonal degeneration and brain injury, while the more specific AD marker P-tau mirrors the formation of neurofibrillary tangles [26]. Therefore, correlations between more advanced severity of AD, lower levels of A β_{42} and higher levels of T-tau and P-tau, are expected. However, the biomarker levels, particularly A β_{42} , seem to be noticeably changed very early in the course of AD, many years before the symptoms appear [10], which could imply low associations between disease severity and the biomarker values at later stages of AD [28]. Inconsistently, increased T-tau values and more impaired cognitive performance at follow-up were observed in some studies [29, 30], whereas one study using a small-sample mild AD cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI) demonstrated a decreased annual change of P-tau, but not of T-tau. A diminishing neurodegenerative process could reflect neuronal death, *i.e.*, fewer amounts of neurons remain in the brain

[31]. In a recent study from our group, no differences in cognitive and functional rates of progression were detected between the AT(N) biomarker profiles [21].

A moderate linear correlation was found in the current study between shorter time to NHP and a lower level of $A\beta_{42}$ suggesting a greater brain amyloid load ($r_s = 0.43$); however, this relationship was not significant in the multivariate Cox regression models. Only three publications have evaluated the possible associations between institutionalisation and CSF biomarkers in AD. One previous small-sample study from our group [12] and a recent French larger-sample study [13] observed no correlation between time to NHP and the biomarkers. The third study reported a higher risk of admission to NHs for individuals in the highest quartile of T-tau (but not $A\beta_{42}$ or P-tau), also using multivariate Cox models [14]. In the SATS, no difference in NHP between the quartiles of T-tau was detected. One explanation for the inconsistent findings might be differences in socio-demographic and clinical characteristics between the cohorts. The participants in Gunnarsson *et al.* [14] study were younger (median, 70 vs. 76 years), had higher education level (mean/median years was not addressed in that study) and better cognitive performance (mean MMSE score, 24 vs. 21 points) at baseline than in our study, indicating a higher cognitive reserve capacity and possibly a more intense and advanced disease in relation to their results on cognitive tests [32]. This could imply a faster and greater burden of neurodegeneration in the brain, expressed as increased tau values, which might contribute to worse AD progression. In addition, a higher percentage of the patients was living alone in the SATS compared with Degerman Gunnarsson's study (39% vs. 24%). Since solitary living and older age are strong risk factors of institutionalisation [3], reduced cognitive reserve among the older individuals could lead to sooner detection and diagnosis of AD, and more pronounced $A\beta_{42}$ but less tau pathology. However, the inconsistent associations between CSF biomarkers and NHP, an important event in AD with enormous societal costs, need further investigation.

After up to 20 years of follow-up with 95% deceased participants, the SATS is the longest study of mortality in AD. We observed no significant relationships between survival time after AD diagnosis and any of the CSF biomarkers in the multivariate Cox regression models. Consistently, Nägga *et al.* [17] demonstrated in a large-sample 13-year follow-up (89% deceased patients) from the Malmö Alzheimer Study that cerebral inflammation, but not CSF biomarkers, is independently associated with early death in AD. Another study from our group with 7 years of follow-up (52-55% deceased individuals) showed that increased levels of T-tau were related to a shorter lifespan in dementia with Lewy bodies, but not in AD [18]. In contrast, a 6-year follow-up of a tacrine-treated small-sample cohort at our Memory Clinic (52% deceased participants) was described previously using univariate analyses that low levels of $A\beta_{42}$, as well as elevated levels of T-tau (but not P-tau), may lead to a higher risk of mortality [12]. Moreover, a subgroup of AD patients with very high levels of T-tau and P-tau, and shorter survival after 5

years of follow-up (30% deceased individuals), was found in a cluster analysis from our clinic. The outcome was still significant after controlling for demographics and cognitive status [15]. High T-tau, especially in the highest quartile, was also associated with a higher risk of dying in severe dementia after up to 9 years of follow-up (34% deceased participants) [16]. No difference in life expectancy between the patients in the highest quartile of P-tau or T-tau and the other individuals was detected in the present study. Two recent AD studies reported contradictory results: a French follow-up (median period 3.9 years, 18% deceased participants) suggested CSF $A\beta_{42}$, but not tau, as a strong prognostic marker of survival time, whereas a Dutch study (mean 4.9 years, 35% deceased participants) described a trend towards higher P-tau and earlier death ($p = 0.058$) in one of their multivariate statistical models, but the other models exhibited no relationships between any of the biomarkers and lifespan. The patients in this study and in most of the other publications mentioned above had similar mean ages (75-76 years) [15, 17, 18] and cognitive ability at baseline (MMSE score, 20-22) [13, 15, 17, 18, 33]. Therefore, age and cognitive performance, which are common predictors of survival, cannot explain the different observations. Furthermore, our study and the majority of the others used the same statistical method, *i.e.*, multivariate Cox regression models [13, 16-18, 33]. Based on these mixed findings of the length of study periods, the proportion of deaths, and potential predictors included in the statistical models, the association between the levels of biomarkers and life expectancy in AD is inconsistent and not well understood.

Various comorbidities and concomitant medications among the participants in different studies might also affect mortality. In this study, the use of anxiolytics/sedatives/hypnotics was an independent risk factor for a shorter time to death. The use of anxiolytics/sedatives/hypnotics has been related to impaired cognitive and physical functioning, daytime sleepiness, increased falls and fractures, and decreased survival [34]. In the aforementioned studies of lifespan in AD, the analyses regarding comorbidity demonstrated inconsistent outcomes. Hypertension, cardiovascular drugs and anti-psychotics/sedatives were independent predictors of earlier death in all-cause mortality, but none of these variables were significant in deaths caused specifically by dementia [17]. The other studies discussed above showed no impact on coronary heart disease/heart failure or number of medications on survival time [16, 33], or did not include comorbidities in the statistical models [13, 15, 18]. Different comorbidities and medications might influence life expectancy and complicate analyses of the AD-associated variables' direct influence on death [35]. Taking the various findings together, it is not possible to conclude that a high level of tau reflects a worse prognosis and predicts shorter survival in the dementia phase of AD.

The advantages of the SATS are its semi-annual, prospective, well-organized assessments of cognitive and functional capacities and use of community-based services (which is less commonly documented in most studies) after the initiation of ChEI therapy. However, CSF biomarkers

were only measured at baseline. The biomarkers were analysed after the clinical follow-up was completed, yet all individuals had abnormal $A\beta_{42}$ indicating the accuracy of the AD diagnosis. The diagnosis and subsequent follow-ups were performed by specialists in dementia disorders. The mortality of this large Memory Clinic cohort of ordinary AD patients with comorbidities and concomitant medications has now been followed over 20 years. Community-based services, including NHs in Sweden, are publicly funded and accessible to all residents, regardless of their socio-economic status [36]. Therefore, we assume that the participants were representative of the general population and that their need for NHs reflected their actual disabilities. A limitation is that the time to institutionalisation 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 evaluated in the SATS. Therefore, the medication categories were used as indicators of comorbidity. Dietary factors were not recorded in the study. Similar to other longitudinal observational studies of AD, the SATS is not placebo-controlled (because of ethical concerns) or randomized with respect to ChEI agents.

Few studies have investigated the relationships between CSF biomarkers and end-points during the course of AD, such as NHP and survival, and reported inconsistent results. Thus, future studies are needed to increase the knowledge of these still unclear associations. AD is a heterogeneous condition, and it is essential to identify characteristics including biomarkers that can estimate the malignancy of the disease process. The efficacy of different treatments may vary between patient subgroups (e.g., severity of AD, pattern of biomarkers, *APOE* genotype). Currently, there is an enhanced interest in the tau protein and its role in pathophysiology, and clinical trials of immunization with anti-tau antibodies are now ongoing.

CONCLUSION

In this longitudinal study in a routine clinical setting, we found that the individuals with both pathologic tau and neuronal injury died at a younger age than those without pathologic tau but with neurodegeneration, suggesting a subtype of AD with earlier onset and a more aggressive disease. A linear correlation was observed between shorter time to institutionalisation and a lower level of $A\beta_{42}$, which reflects the higher levels of amyloid deposits in the brain; however, this association was not significant in the multivariate Cox regression model. In the sex- and age-adjusted univariate (but not multivariate) Cox models, higher P-tau and T-tau were independent predictors of shorter life expectancy after AD diagnosis. The significant variables in the multivariate Cox regression models of both NHP and death were older age, lower cognitive ability at baseline and use of anxiolytics/sedatives/hypnotics (mortality model only), which are commonly related to lifespan, and provide creditability to the results. Our findings indicate that CSF biomarker levels plateau in the dementia phase of AD, which may limit their possible associations with clinical end-points, such as time

to NHP, survival time in NHs and life expectancy. The AT(N) biomarker profiles might not be useful to predict events or subtypes of AD in the later stages of the disease. However, the biomarkers reflect the central pathophysiology of AD, and particularly pathologic tau relates to more advanced disease with younger age at onset and earlier death. Continued investigations of the AD pathologies and their suggested downstream effects are essential to increase the understanding of the disease process, and hence, to enable improved development of new therapies.

LIST OF ABBREVIATIONS

A+	= Abnormal CSF $A\beta_{42}$
$A\beta_{42}$	= Amyloid- β_{1-42}
AD	= Alzheimer's Disease
ADL	= Activities of Daily Living
ANOVA	= One-way Analysis of Variance
<i>APOE</i>	= Apolipoprotein E
ChEI	= Cholinesterase Inhibitors
CI	= Confidence Interval
CSF	= Cerebrospinal Fluid
IADL	= Instrumental Activities of Daily Living Scale
LP	= Lumbar Puncture
MMSE	= Mini-Mental State Examination
(N)-	= Normal CSF T-tau
(N)+	= Abnormal CSF T-tau
NH	= Nursing Home
NHP	= Nursing Home Placement
NSAIDs	= Non-Steroidal Anti-Inflammatory Drugs
PSMS	= Physical Self-Maintenance Scale
P-tau	= Phosphorylated tau
SATS	= Swedish Alzheimer Treatment Study
T-	= Normal CSF P-tau
T+	= Abnormal CSF P-tau
T-tau	= Total tau

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The SATS protocol and the current analyses of data were submitted to and approved by the Regional Ethical Review Board, Lund University, Lund, Sweden (no. 2014/658, dated 9th December 2014).

HUMAN AND ANIMAL RIGHTS

No animal were used in this study. All procedures performed in studies involving the SATS participants were in

accordance with the Declaration of Helsinki.

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.

AVAILABILITY OF DATA AND MATERIALS

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

FUNDING

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CONFLICT OF INTEREST

CW has no competing interests. KB has served as a consultant or on advisory boards for Alzheon, Biogen, Eli Lilly, Fujirebio Europe, IBL International and Roche Diagnostics and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg. OH has received research support (for the institution) from Roche, GE Healthcare, Biogen, AVID Radiopharmaceuticals, Fujirebio, and Euroimmun. In the past 2 years, he has received consultancy/speaker fees (paid to the institution) from Eli Lilly, Roche and Fujirebio. The sponsors had no involvement in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the manuscript.

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