Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype

Authors: Lisa Vermunt[a], Sietske Sikkes[a,b], Ardo van den Hout[c], Ron Handels[d], Isabelle Bos[d], Wiesje M. van der Flier[a], Silke Kern[e], Pierre-Jean Ousset[f], Paul Maruff[g], Ingmar Skoog[e], Frans RJ Verhey, Yvonne Freund-Levi, Magda Tsolaki, Asa Wallin, Marcel Olde-Rikkert, Hilkka Soininen, Henrik Zetterberg, Kaj Blennow, Philip Scheltens[a], Graciela Muniz-Terrera[h], Pieter Jelle Visser[a,d], for the Alzheimer Disease Neuroimaging Initiative*, AIBL Research Group**, and ICTUS/DSA study groups***.

* Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

****AIBL**

*** *ICTUS study Group*: Vellas B., Reynish E., Ousset PJ., Andrieu S. (Toulouse), Burns A. (Manchester),Pasquier F. (Lille), Frisoni G.(Brescia), Salmon E. (Liège), Michel J.P., Zekry D.S. (Geneva), Boada M. (Barcelona), Dartigues J.F. (Bordeaux), Olde-Rikkert M.G.M. (Nijmejen), Rigaud A.S. (Paris), Winblad B. (Huddinge), Malick A., Sinclair A. (Warwick), Frölich L.(Mannheim), Scheltens P. (Amsterdam), Ribera C.(Madrid), Touchon J. (Montpellier), Robert P. (Nice), Salva A.(Barcelona), Waldmar G. (Copenhagen), Bullock R.(Swindon), Costa-Tsolaki M. (Thessaloniki), Rodriguez G. (Genoa), Spiru L. (Bucharest), Jones R.W. (Bath), Stiens G., Stoppe G. (Goettingen), Eriksdotter Jönhagen M. (Stockholm), Cherubini A. (Perugia), Lage P.M., Gomez-Isla T. (Pamplona), Camus V. (Tours), Agüera-Morales E., Lopez F.(Cordoba).
DSA Group: Andrieu S., Savy S., Cantet C., Coley N.

Corresponding Author: Lisa Vermunt, MD, Alzheimercentrum Amsterdam, Amsterdam UMC, PO Box 7057, 1007 MB, Amsterdam, the Netherlands (l.vermunt@vumc.nl).

Email adressess co-authors:

s.sikkes@vumc.nl,

ardo.vandenhout@ucl.ac.uk,

ron.handels@maastrichtuniversity.nl,

isabelle.bos@maastrichtuniversity.nl,

WM.vdFlier@vumc.nl,
silke.kern@neuro.gu.se,
ousset.pj@chu-toulouse.fr,
pmaruff@cogstate.com,
ingmar.skoog@neuro.gu.se,
F.Verhey@maastrichtuniversity.nl
Yvonne.Freund-Levi@ki.se,
tsolakim1@gmail.com,
Asa.k.wallin@skane.se,
lsaslan@brainaging.ro,
hilkka.soininen@uef.fi,
M.Olde-Rikkert@ger.umcn.nl,
henrik.zetterberg@clinchem.gu.se,
Kaj.Blennow@neuro.gu.se
p.scheltens@vumc.nl,
G.Muniz@ed.ac.uk,
PJ.Visser@vumc.nl
Target journal: JAMA neurology (try Lancet Neurology)
Word count: 3648 (max 3500)
Tables/figures: 3/2 (max 5) Refs:
Word count abstract:

Abstract (max 300, nu 311 zonder funding):

Background Alzheimer disease (AD) is a slowly progressive disorder with preclinical, prodromal and dementia stages. Little information is available on their respective duration. Therefore, the aim was to estimate the age-specific duration of the disease stages of AD, taking sex, *APOE* genotype, setting (clinical vs. research), and cerebrospinal fluid (CSF) total tau (t-tau) into account.

Methods Data of international cohort studies performed in a clinical or research setting, was combined in a multistate model analysis with four AD stages (preclinical (n=438), prodromal (n=729), mild AD dementia (n=xx), and moderate to severe AD dementia (n=2169)) and death as the end stage and different covariates, from which stage durations were estimated by XXX. The mean baseline age was 73 years (SD=8) and mean follow-up time 2.8 years (SD=1.9, range 0.3-20).

Findings The estimated overall disease duration for individuals with preclinical AD at age 70 was 20 years, of which 10 years (95% CI, 8-11) were predicted to be spent in preclinical AD, followed by 4 years (95% CI, 3-5) in prodromal AD, 3 years (95% CI 2-3) in mild dementia and 3 years (95% CI 2-3) in the moderate to severe dementia stage. The duration of the preclinical stage was estimated to be longer in the research (11 years [95% CI, 9-13]) than the clinical setting (3 years [95% CI, 2-5]). The dementia stage was 2 years longer in females than males. *APOE* ε4 genotype and abnormal CSF t-tau associated with a shorter pre-dementia, but not dementia duration.

Interpretation Age-specific estimates for the disease duration of AD, including the preclinical stage, were generated based on short-term longitudinal data. The setting of preclinical AD seems of major influence on the prognosis. These estimates can inform expectations of patients, caregivers, and doctors, and contribute to optimal clinical study design and the extrapolation of trial results.

Funding

IMI

Introduction

Alzheimer disease (AD) is highly prevalent and a major cause of death in elderly individuals [1]. Accumulation of amyloid in the brain is the first sign of the disease and can precede clinical diagnoses of dementia by up to 20 years [2-4]. AD has three stages in which amyloid accumulation is present: the preclinical stage, characterized by normal cognitive ability, the prodromal stage, characterized by mild cognitive impairment (MCI), and the dementia stage [5-8]. It is still unclear how long individuals with amyloid pathology spend in each disease stage of AD [2, 4]. Attempts to quantify the duration of AD should include age into the estimates, because age imposes the greatest risk for both dementia and mortality. In addition, it is unknown how the duration of the AD is influenced by factors such as sex and the ε4 variant of the apolipoprotein E (*APOE*) gene, the major genetic risk factor for AD [9, 10]. Better knowledge on the duration of AD will be important to inform patients, their caregivers, and their doctors. Furthermore, this information will be useful for clinical study design, as well as provide context for the interpretation of trial results. For example, while a future treatment may slow disease progression in the preclinical AD stage, the clinical benefit of such a treatment lies in preventing the onset of downstream stages. Therefore, a complete understanding of the total duration of AD is necessary for a reliable expectation of treatment effects.

Previous studies on the length of the dementia stage in AD reported a duration of 3 to 10 years [11-13]. Younger age, female sex and lower CSF total tau (t-tau) were found to be associated with a longer duration of the AD dementia stage, while the effect of *APOE* genotype was equivocal [11-16]. The duration of prodromal AD was estimated in one study to be 3 years in a pooled memory clinic cohort, although no age-specific estimates were provided [17]. Patients with prodromal AD who besides amyloid accumulation also showed

increased CSF t-tau levels tend to convert sooner to dementia. These estimates may need to be considered carefully as individuals studied in a research setting could show differences in disease duration than individuals seeking treatment in memory clinics [18]. The duration of the preclinical AD stage duration has only been estimated in combination with the prodromal AD stage, which was 17 to 30 years, based on prevalence data or extrapolations of change in positron emission tomography (PET) amyloid load over time [19, 20].

Disease stage duration estimates can be generated by applying a multistate modeling approach. Multistate modeling can offer an estimate of disease duration based on stage progression and mortality rates in the absence of very long term follow-up studies and was previously applied in AD research [21-23]. The aim of this study was therefore to estimate the disease duration for preclinical, prodromal and AD dementia stage taking age, sex, *APOE* genotype, setting (clinical vs research), and baseline CSF t-tau levels into account.

Methods

Participants

Six longitudinal cohort studies, including three memory clinic cohorts, Amsterdam Dementia cohort (ADC), DESCRIPA, and ICTUS, and three research cohorts, Alzheimer Disease Neuroimaging Initiative (ADNI), Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) and Prospective Population Study of Women in Gothenburg H70 (Gothenburg H70) provided data for the study [24-29]. All studies were approved by an ethical review board and their participants gave informed consent. From these cohorts, we selected participants aged 50 years and older with evidence of amyloid accumulation (Supplement 1), and with information on diagnosis and/or mortality at follow-up available. In absence of amyloid measures for the ICTUS cohort, we included from this cohort patients with a clinical diagnosis of AD-type dementia and analyses were repeated without this cohort [30].

Disease stages

AD was categorized into four disease stages: preclinical AD, prodromal AD, mild AD dementia, and moderate to severe AD dementia (shortened to moderate AD dementia). Preclinical AD was defined by amyloid accumulation and normal cognition, irrespective of subjective complaints. Prodromal AD was defined by amyloid accumulation and a diagnosis of MCI, amnestic and non-amnestic (Supplement 1) [31, 32]. AD dementia was diagnosed according to the NINCDS-ADRDA criteria and subdivided in mild AD (Clinical Dementia Rating (CDR) below 2, or CDR sum of boxes (CDR-SOB) <10 or (if no CDR was available) a MMSE >20) and moderate AD dementia (CDR>1, CDR-SOB > 9, or (if no CDR was available) a MMSE<21) [33-35]. Few participants with preclinical or prodromal AD received

a clinical diagnosis of non-AD dementia at follow-up (n=10), and were classified as AD-type dementia stage in the analysis.

Mortality assessment

The ADC cohort mortality data were obtained from the Dutch population register, while the other studies provided mortality data recorded during the study. In AIBL the exact mortality date was unknown and therefore set at the next planned visit, which is 1.5 years after last follow-up. In others cases of a missing mortality date (n=3), the date was set 2 years after last follow-up.

Amyloid markers

Evidence of amyloid pathology was defined by at least one abnormal marker of amyloid accumulation. The amyloid PET scans were visually rated or a published threshold was applied [36]. For CSF amyloid-beta 1-42 (Aβ1-42) cohort-specific thresholds were applied (Supplement 1) [37, 38].

Predictor variables

For all participants, age, sex and setting were available. The setting was classified as clinical for ADC, DESCRIPA and ICTUS and research for ADNI, AIBL and Gothenburg H70. *APOE* genotype was dichotomized according to presence or absence of the AD-associated ε4 allele of *APOE* and was available in all studies except ICTUS. Baseline CSF t-tau was classified as normal or abnormal by applying the cohort-specific cut-off and available for the ADC, DESCRIPA, ADNI and Gothenburg H70 studies (Supplement 1).

Statistical analyses

Baseline characteristics between diagnostic groups were compared using Chi-square, Kruskal-Wallis and ANOVA tests with Tukey post-hoc, where appropriate. To estimate the disease duration, the first step was fitting a multistate model (MSM) with four disease stages of AD and death as the end-stage [39]. All transition rates between stages were incorporated in one model, including the mortality risk. Reversions from prodromal to preclinical AD were included in the model, and therefore a duration in a preclinical AD stage for participants with prodromal AD at baseline was reported. Reversion in the dementia stages were fitted as misclassification (details in supplement 2). The rate was estimated for each transition shown in Figure 1. Age was a time-dependent covariate, and centered at age 70. For each covariate a hazard ratio was calculated for each transition. Most covariate effects on mortality were not estimable; therefore, a restricted model was applied (see Supplement 2 for additional methods and specifications multistate model analysis).

Five multistate models were fitted to the data with different numbers of covariates. The first model included only age, then, for the second model we also included sex and setting as covariates. The third model included age, setting, and *APOE*, while the fourth model had age, setting, and tau as covariates, and the fifth model was fully adjusted for all covariates. As not all covariates were available for all participants, the number of participants varied between models. The resulting transition rates and hazard ratios are based on every observation of every participant in combination with the time in between the observations. Using the MSM maximum likelihood estimate as input the duration for every stage was predicted, where 95% confidence interval were derived by simulation using the asymptotic properties of the maximum likelihood estimation. That allowed comparison between age-specific estimates for the different covariates. R-packages *msm* for the multistate transition model and *ELECT*

version 0.3 (Estimating Life-Expectancies for interval censored data) were used to estimate the duration estimates [39, 40]. Sensitivity analyses included, aside of fitting all covariates in one model, sequentially removing cohorts from the analysis.

Role of the funding source

Funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors had full access to the data and the corresponding author takes final responsibility for the decision to submit for publication.

Results

A total of 3.336 participants were included in the analysis across the six cohorts combined. The mean (SD) age at baseline was 73 (8) years. The mean (SD) number of follow-up years was 2.8 (1.9) with a range of 0.3 to 20 years, and a median (IQR) of 4 (3-5) visits. Progression to at least one consecutive stage was apparent in 998 (32% of 3099) participants. Table 1 shows how participants in the different disease stages at baseline compared in sex, *APOE* ε4 genotype, abnormal CSF t-tau, follow-up length and mortality (Supplement S2.7 and S2.8 for subgroups with data on *APOE* and CSF t-tau available).

Multistate model

In the model with age, sex and setting as covariates, all transition rates were influenced significantly by age, except for mortality in the preclinical AD stage and for progression from prodromal AD to mild AD dementia (Table S2.5 for all estimates, including model with age only). Compared to males, females had a higher progression rate to moderate AD dementia (HR=1.25 [95% CI, 1.05, 1.49]), while their mortality risk in moderate AD dementia was decreased (HR=0.60 [95% CI, 0.45,0.79]). When compared to data collected in a research setting, data from clinical settings provided an increased progression rate (HR=4.41 [95% CI, 2.80, 6.95]) and reversion rate (HR=1.97 [95% CI, 1.15,3.39]) between preclinical to prodromal AD. Additionally, in the clinical setting the progression rates from the prodromal AD to the mild AD dementia stage (HR=1.48 [95% CI, 1.14,1.93]) and from the mild AD to the moderate AD dementia stage (HR=1.42 [95% CI,1.16-1.72]) were increased.

AD stage duration according to age, sex, and setting

The predicted mean total disease duration, based on the model with age, for an individual with preclinical AD at age 70 was 10 years (95% CI, 8-11) in the preclinical AD stage, followed by

4 years (95% CI, 3-5) in the prodromal AD stage, followed by 3 (95% CI, 2-3) in mild AD dementia and 3 years (95% CI, 2-3) in the moderate AD dementia stage (Table 2). Estimates for age 60 and 80 for individuals with preclinical AD at baseline are provided in Figure 2A, showing that the overall disease duration declined with older age, ranging from 24 years at age 60 to 15 years at age 80. In females, the pre-dementia stages were similar, and the dementia stage duration was 2 years longer than in males (Figure 2C, Table S2.6). The duration of preclinical AD was shorter in a clinical setting (3 years [95% CI, 2-5]) than in a research setting (11 years [95% CI, 9-13]).

APOE effect

APOE ε4 carriers had an increased rate of progression from the preclinical AD to prodromal AD stage (HR=1.63 [95% CI, 1.11, 2.41]) and from the prodromal AD to mild AD dementia stage (HR=1.50 [95% CI, 1.18-1.90]), and a trend for slower decline from the mild to the moderate AD dementia stage (HR 0.77 [95% CI, 0.60-1.00]) compared to non-carriers. The estimated duration of the preclinical AD stage for an *APOE* ε4 carrier aged 65 would be around 3 years shorter, and the prodromal AD stage 1 year shorter, when compared to non-carriers, though with overlapping confidence intervals (Figure 2B and Table S2.6).

CSF total tau effect

As normal CSF t-tau level may become abnormal over time only the estimated duration of the starting stages are presented in Table 3. Individuals with preclinical AD and abnormal CSF t-tau showed a trend for an increased progression rate from preclinical to prodromal AD (HR=1.494 [95% CI, 0.95-2.35]). In prodromal AD, abnormal tau associated with decreased reversion rate to preclinical AD stage (HR=0.41 [95% CI, 0.23-0.71]) and increased progression rate to the mild AD dementia stage (HR=1.91 [95% CI, 1.48-2.48]), shortening

the estimated prodromal AD stage by around 2.5 years (Table S2.5). The estimated prodromal AD stage was 2.5 years shorter, while there was no association of baseline abnormal t-tau with the dementia stage durations.

Sensitivity analyses

Consecutively removing each of the cohorts did not affect the estimates (Table S2.8 and S2.9). When all variables were combined in one model, most estimates remained unchanged (Table S2.5).

Discussion

We estimated the duration of the preclinical, prodromal, mild dementia, and moderate to severe dementia stages of AD using a multistate model. Depending on age, sex, *APOE* genotype, baseline CSF t-tau and setting, the total disease duration varied between 12 and 25 years, the preclinical stage between 3 and 13, the prodromal stage between 3 to 7, mild AD dementia stage between 2 and 6 and moderate to severe AD dementia stage between 1 and 7 years.

Effects of age

Age had the strongest effect on the duration of the preclinical and mild dementia stages. The preclinical AD stage was primarily shorter at higher age due to higher progression rates. The mild AD dementia was shorter at higher age due to both higher progression and mortality rates. In prodromal AD, higher age related to increased mortality, but progression rates were the same. Combining the preclinical and prodromal stage, the pre-dementia duration was respectively 17 and 14 years for a 60- and 70-year-old, an estimate equivalent to the 17 years estimated based on differential equation modeling of the amyloid accumulation rate [20]. The reason for the shorter duration of the preclinical stage at higher age could be that older individuals were in a preclinical stage for a longer period before inclusion in the study (also referred to as left-censoring). Alternatively, at an older age there may be less resilience to AD pathology, leading to a faster clinical progression [41].

Effects of setting

The duration of preclinical stage was 8 years shorter in the clinical compared to the research setting, suggesting that memory clinic patients presenting with preclinical AD are in a more advanced phase of the preclinical stage. As a setting effect was also observed in the

symptomatic disease stages, it is also conceivable that clinical monitoring leads to earlier identification of progression. Another explanation is that those individuals with a more aggressive disease course would be more likely to visit the clinic, whereas a slower progressive disease would be picked up in the research setting.

Effects of *APOE* genotype

A shorter age-specific duration of the preclinical stage in *APOE* ε4 carriers is consistent with the earlier onset of AD dementia observed in epidemiological studies [42-45]. *APOE* ε4 carriers also progressed faster from prodromal AD to dementia, but may be longer in the mild dementia stage, which could mean the symptomatic disease duration is similar, but divided differently over the stages. No evidence for increased mortality in the dementia stage was found [15].

Effects of sex

The duration of the dementia stage was longer in women, which was driven by lower mortality. The study did not reveal sex differences in the duration of preclinical and prodromal AD. The direction of our estimates fits with a recent report in which the investigators observed a higher progression rate from preclinical to prodromal AD in men and then a higher progression rate from prodromal AD to AD dementia in women [44, 46].

Effects of tau pathology

The presence of increased CSF t-tau was associated with a shorter pre-dementia disease duration. This effect was partly driven by a decreased rate of reversion from prodromal AD to preclinical AD. An increased total tau in individuals with amyloid accumulation seems to certainty that the cognitive impairment is due to AD. Unlike a previous study, no effects of

tau on mortality and duration of the AD dementia stage were found, which may be due to dichotomization of total tau in our analysis [16].

Duration and mortality

Comparing the total duration estimates for the starting stages preclinical AD and mild dementia, with residual life-expectancies of community-dwelling elderly in Europe and the USA, our estimated life-expectancies were longer [47]. Explanations include that disease duration could have been overestimated, because mortality had not been checked systematically in all studies. Mortality rates in our study cohorts may also be lower, because both volunteers participating in studies and memory clinic patients will be relatively healthy at study entry. This means for the interpretation of the estimates that the more severe stages of AD may not be reached, and if so, are of shorter duration before death.

On the other hand, compared to progression rates between clinical disease stages in population based studies, our estimates were higher than generally reported in those studies [44]. This would lead to a shorter estimated duration of the stages. The finding most likely reflects that our sample is not representative of the general population. However, given the nature of recruitment and ascertainment, the sample studied here may actually be more representative of the patients that attend memory clinic clinics, and of the participants that enroll in clinical trials of treatments designed to slow or halt AD.

Strengths and limitations

A strength of the study is the large sample of participants with amyloid accumulation. The multistate model approach incorporates individuals that fluctuate between clinical stages in a data driven manner, as well as the competitive risk of death. A limitation of the approach is

the assumption in the model that progression risk is independent on the previous time spend in a stage, while progression risk may actually change after being in a stage for a longer period of time. This was at least partly taken into account with age as the time-dependent covariate, which is common practice [22, 48]. To create the model, we had to combine data of multiple cohorts across the disease spectrum. As such, the sample consisted of over 3000 individuals, of which more than 400 with preclinical AD; yet, some effects were still difficult to estimate. Combing cohort data could have led to heterogeneity, i.e. due to different application of diagnostic criteria, cognitive testing and amyloid status. To diminish potential bias we have used robust clinically relevant endpoints and stratified by setting. For the ICTUS dementia patient cohort, amyloid status and *APOE* genotype were not known but sensitivity analysis without ICTUS had no major effect on the results.

Implications

Our findings can help to inform patients, clinicians and research participants on their prognoses. For example a 60 year-old memory clinic patient may be likely to survive until the onset of dementia, and therefore clinical monitoring and treatment may be appropriate [49]. In the topic of disclosure of amyloid status to prevention trial participants, these estimates can give an indication of the prognosis. In terms of strategy for finding participants for clinical trials our results need to be validated, was we did not include them in the study, but it would be interesting to learn how populations currently recruited into prevention trials, such as A4 study, compare to our results [50]. The presented estimates can also be used to simulate the design and extrapolate results of clinical trials in different populations, in particular those aimed to prevent dementia.

Conclusion

We provide age-specific disease duration estimates for the AD stages and according to sex, setting, *APOE* and tau, with setting being the strongest predictor in the preclinical AD stage. These generated estimates are most useful for doctors who can interpret them in the light of informing patients on disease progression, as well as for deciding on target populations for clinical prevention trials and extrapolating the clinical trial outcomes.

Role of the Authors

Name	Role	Contribution
L. Vermunt, MD	Author	Design and conceptualized study; data analysis; wrote the manuscript.
S. Sikkes, PhD	Co-author	Supervision of project; revised the manuscript
A. van Den Hout, PhD	Co-author	Methodological teaching and advise; revised the manuscript
R. Handels, PhD	Co-author	Methodological advise; revised the manuscript
I. Bos, PhD	Co-author	Collected and provided data; revised the manuscript
W.M. vna de Flier, PhD	Co-author	Collected and provided data; revised the manuscript
S. Kern, MD, PhD	Co-author	Collected and provided data; revised the manuscript
P-J Ousset, MD, PhD	Co-author	Collected and provided data; revised the manuscript
P. Maruff, PhD	Co-author	Collected and provided data; revised the manuscript
I. Skoog, MD, PhD	Co-author	Collected and provided data; revised the manuscript
Frans RJ Verhey	Co-author	Collected and provided data; revised the manuscript
Yvonne Freund-Levi	Co-author	Collected and provided data; revised the manuscript
Magda Tsolaki	Co-author	Collected and provided data; revised the manuscript
Asa Wallin	Co-author	Collected and provided data; revised the manuscript
Luiza Spiru	Co-author	Collected and provided data; revised the manuscript
Hilkka Soininen	Co-author	Collected and provided data; revised the manuscript
Marcel Olde-Rikkert	Co-author	Collected and provided data; revised the manuscript
Henrik Zetterberg	Co-author	Analysed data; revised the manuscript
Kaj Blennow	Co-author	Analysed data; revised the manuscript
Ph. Scheltens, MD, PhD	Co-author	Collected and provided data; revised the manuscript
G. Muniz-Terrera, PhD	Co-author	Supervision of project; Data analysis; Methodological advise; revised the manuscript
P.J. Visser, MD, PhD	Senior author	Design and conceptualized study; Supervision of project; revised the manuscript

Declaration of interests

Vermunt, Kern and Bos reports no disclosures. Skoog reports consultant for Takeda. Handels reports the following to conduct this study: grants from European Brain Council (VoT project; 2017); Ron Handels reports the following outside this study: grants from BIOMARKAPD (EU JPND; 2012-2016); grants from Actifcare (EU JPND; 2014-2017); grants from Dutch

Flutemetamol Study (2012-2017); grants from ROADMAP (IMI2; 2016-2019); grants from SNAC (Sweden public funding; 2016-2018); grants from MIND-AD (EU JPND; 2017-2018); grants from Alzheimer association Nederland (NL fellowship; 2017-2019); grants from Economic and policy implications new treatment for AD (ARUK; 2017-2018); grants from various ZonMw projects (NL public funding; 2017-2022); grants from RECAGE (EU H2020; 2018-2022); personal fees from Piramal (advisory; 2016); personal fees from Roche (advisory; 2017). Research programs of Dr van der Flier have been funded by ZonMW, the Netherlands Organization of Scientific Research, Seventh European Framework Programme, Alzheimer Nederland, Cardiovascular Onderzoek Nederland, Stichting Dioraphte, Gieskes-Strijbis fonds, Boehringer Ingelheim, Piramal Imaging, Roche BV, Janssen Stellar, and Combinostics. All funding is paid to her institution. Dr Scheltens has acquired grant support (for the institution) from GE Healthcare, Danone Research, Piramal, and Merck. In the past 2 years, he has received consultancy/speaker fees (paid to the institution) from Lilly, GE Healthcare, Novartis, Sanofi, Nutricia, Probiodrug, Biogen, Roche, Avraham, and EIP Pharma. HZ has served at scientific advisory boards for Roche Diagnostics, Wave, Samumed and CogRx and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg (not related to this study). No other disclosures are reported.

Funding

The work was supported by the IALSA (Integrative Analysis of Longitudinal Studies of Aging and Dementia) network, which received support by NIH grant P01AG043362; 2013-2018; from the Innovative Medicines Initiative Joint Undertaking under grant agreement n115736, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution; and the European Brian Council. HZ is a Wallenberg Academy Fellow supported by grants from the Swedish Research Council and the European Research Council.

Studies:
ADC: The VU University Medical Center (VUMC) Alzheimer Center is supported by Alzheimer Nederland and Stichting VUMC funds. This study was performed within the framework of the Dutch ABIDE project and was supported by a ZonMW-Memorabel grant (project No 733050201) in the context of the Dutch Deltaplan Dementie and through a grant of Piramal Imaging (positron emission tomography scan costs) to the Stichting Alzheimer & Neuropsychiatrie, Amsterdam. Research of the VUMC Alzheimer Center is part of the neurodegeneration research program of Amsterdam Neuroscience. The clinical database structure was developed with funding from Stichting Dioraphte.
ADNI: Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical

Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California
AIBL:
DESCRIPA:
Gothenburg H70: The Swedish Research Council (2015-02830, 2013-8717), Swedish Research Council for Health, Working Life and Wellfare (no 2013-2496, 2013-2300, 2010-0870, 2012-1138), Sahlgrenska University Hospital (ALF 716681), The Alzheimer's Association Zenith Award (ZEN-01-3151), The Alzheimer's Association Stephanie B. Overstreet Scholars (IIRG-00-2159), Alzheimerfonden, Hjärnfonden, Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse
ICTUS/DSA The ICTUS study was partially supported by a grant from the European Commission within the 5th framework programme (QLK6-CT-2002-02645) and partially from an unrestricted equal grant from each of Eisai, Janssen, Lundbeck, and Novartis pharmaceutical companies. The pharmaceutical companies had no role in study design, data collection, data analysis, data interpretation. Promotion of the ICTUS study was supported by the University Hospital Centre of Toulouse. The data sharing activity was supported by the "Association Monegasque pour la recherche sur la maladie d'Alzheimer"(AMPA) and the UMR 1027 Unit INSERM – University of Toulouse III

Dr Bos has received research support from the Innovative Medicines Initiatives Joint Undertaking under EMIF grant agreement number 115372 resources that are composed of financial contributions from EU FP7 (FP7/2007-2013) and in-kind EFPIA.

References

1. Group, A.S. *A National Alzheimer's Strategic Plan: The Report of the Alzheimer's Study Group*. [cited 2018 Aug 8]; Available from: https://www.alz.org/documents/national/report_ASG_alzplan.pdf.
2. Scheltens, P., et al., *Alzheimer's disease.* Lancet, 2016. **388**(10043): p. 505-17.
3. Winblad, B., et al., *Defeating Alzheimer's disease and other dementias: a priority for European science and society.* Lancet Neurol, 2016. **15**(5): p. 455-532.
4. Jack, C.R., et al., *Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers.* The Lancet Neurology, 2013. **12**(2): p. 207-216.
5. McKhann, G.M., et al., *The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.* Alzheimers Dement, 2011. **7**(3): p. 263-9.
6. Albert, M.S., et al., *The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.* Alzheimers Dement, 2011. **7**(3): p. 270-9.

7. Sperling, R.A., et al., *Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.* Alzheimers Dement, 2011. **7**(3): p. 280-92.
8. Jack, C.R., Jr., et al., *NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease.* Alzheimers Dement, 2018. **14**(4): p. 535-562.
9. Neu, S.C., et al., *Apolipoprotein E Genotype and Sex Risk Factors for Alzheimer Disease: A Meta-analysis.* JAMA Neurol, 2017. **74**(10): p. 1178-1189.
10. Lim, Y.Y., et al., *Association of beta-Amyloid and Apolipoprotein E epsilon4 With Memory Decline in Preclinical Alzheimer Disease.* JAMA Neurol, 2018. **75**(4): p. 488-494.
11. Brodaty, H., K. Seeher, and L. Gibson, *Dementia time to death: a systematic literature review on survival time and years of life lost in people with dementia.* Int Psychogeriatr, 2012. **24**(7): p. 1034-45.
12. Wattmo, C., E. Londos, and L. Minthon, *Risk factors that affect life expectancy in Alzheimer's disease: a 15-year follow-up.* Dement Geriatr Cogn Disord, 2014. **38**(5-6): p. 286-99.
13. Larson, E.B., et al., *Survival after initial diagnosis of Alzheimer disease.* Ann Intern Med, 2004. **140**(7): p. 501-9.
14. Rhodius-Meester, H.F.M., et al., *Disease-related determinants are associated with mortality in dementia due to Alzheimer's disease.* Alzheimers Res Ther, 2018. **10**(1): p. 23.
15. van der Flier, W.M., et al., *Early-onset versus late-onset Alzheimer's disease: the case of the missing APOE ε4 allele.* The Lancet Neurology, 2011. **10**(3): p. 280-288.
16. Degerman Gunnarsson, M., et al., *High tau levels in cerebrospinal fluid predict nursing home placement and rapid progression in Alzheimer's disease.* Alzheimers Res Ther, 2016. **8**(1): p. 22.
17. Vos, S.J., et al., *Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage.* Brain, 2015. **138**(Pt 5): p. 1327-38.
18. Farias, S.T., et al., *Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts.* Arch Neurol, 2009. **66**(9): p. 1151-7.
19. Jansen, W.J., et al., *Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis.* JAMA, 2015. **313**(19): p. 1924-38.
20. Villemagne, V.L., et al., *Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study.* Lancet Neurol, 2013. **12**.
21. Robitaille, A., et al., *Transitions across cognitive states and death among older adults in relation to education: A multistate survival model using data from six longitudinal studies.* Alzheimers Dement, 2018. **14**(4): p. 462-472.
22. Jack, C.R., Jr., et al., *Transition rates between amyloid and neurodegeneration biomarker states and to dementia: a population-based, longitudinal cohort study.* Lancet Neurol, 2016. **15**(1): p. 56-64.
23. Coley, N., et al., *A Longitudinal Study of Transitions Between Informal and Formal Care in Alzheimer Disease Using Multistate Models in the European ICTUS Cohort.* J Am Med Dir Assoc, 2015. **16**(12): p. 1104 e1-7.
24. Weiner, M.W., et al., *The Alzheimer's disease neuroimaging initiative: progress report and future plans.* Alzheimers Dement, 2010. **6**(3): p. 202-11 e7.

25. van der Flier, W.M., et al., *Optimizing patient care and research: the Amsterdam Dementia Cohort.* J Alzheimers Dis, 2014. **41**(1): p. 313-27.
26. Reynish, E., et al., *The ICTUS Study: A Prospective longitudinal observational study of 1,380 AD patients in Europe. Study design and baseline characteristics of the cohort.* Neuroepidemiology, 2007. **29**(1-2): p. 29-38.
27. Visser, P.J., et al., *Development of screening guidelines and clinical criteria for predementia Alzheimer's disease. The DESCRIPA Study.* Neuroepidemiology, 2008. **30**(4): p. 254-65.
28. Rowe, C.C., et al., *Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging.* Neurobiol Aging, 2010. **31**.
29. Gustafson, D.R., et al., *Cerebrospinal fluid beta-amyloid 1-42 concentration may predict cognitive decline in older women.* J Neurol Neurosurg Psychiatry, 2007. **78**(5): p. 461-4.
30. Dubois, B., et al., *Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria.* The Lancet Neurology, 2007. **6**(8): p. 734-746.
31. Petersen, R.C., et al., *Mild cognitive impairment: clinical characterization and outcome.* Arch Neurol, 1999. **56**(3): p. 303-8.
32. Winblad, B., et al., *Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment.* J Intern Med, 2004. **256**(3): p. 240-6.
33. O'Bryant, S.E., et al., *Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study.* Arch Neurol, 2008. **65**(8): p. 1091-5.
34. Perneczky, R., et al., *Mapping scores onto stages: mini-mental state examination and clinical dementia rating.* Am J Geriatr Psychiatry, 2006. **14**(2): p. 139-44.
35. McKhann, G., et al., *Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease.* Neurology, 1984. **34**(7): p. 939-44.
36. Landau, S.M., et al., *Amyloid-beta imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods.* J Nucl Med, 2013. **54**(1): p. 70-7.
37. Bertens, D., et al., *Unbiased estimates of cerebrospinal fluid beta-amyloid 1-42 cutoffs in a large memory clinic population.* Alzheimers Res Ther, 2017. **9**(1): p. 8.
38. Shaw, L.M., et al., *Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects.* Ann Neurol, 2009. **65**(4): p. 403-13.
39. Jackson Ch, L., *Multi-State Models for Panel Data: The msm Package for R* Journal of Statistical Software, 2011. **38** ((8)): p. 1-29.
40. Van den Hout, A., *Multi-State Survival Models for Interval-Censored Data. Boca Raton:*
CRC/Chapman & Hall. 2017.
41. Vemuri, P., et al., *Evaluation of Amyloid Protective Factors and Alzheimer Disease Neurodegeneration Protective Factors in Elderly Individuals.* JAMA Neurol, 2017. **74**(6): p. 718-726.
42. Mormino, E.C., et al., *Amyloid and APOE epsilon4 interact to influence short-term decline in preclinical Alzheimer disease.* Neurology, 2014. **82**(20): p. 1760-7.
43. Corder, E.H., et al., *Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families.* Science, 1993. **261**(5123): p. 921-3.

44. Roberts, R.O., et al., *Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting.* JAMA Neurol, 2018.
45. van der Lee, S.J., et al., *The effect of APOE and other common genetic variants on the onset of Alzheimer's disease and dementia: a community-based cohort study.* Lancet Neurol, 2018. **17**(5): p. 434-444.
46. Buckley, R.F., et al., *Sex, amyloid, and APOE epsilon4 and risk of cognitive decline in preclinical Alzheimer's disease: Findings from three well-characterized cohorts.* Alzheimers Dement, 2018.
47. Database., H.M.; Available from: University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). Available at www.mortality.org or www.humanmortality.de.
48. Brookmeyer, R., et al., *Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States.* Alzheimers Dement, 2018. **14**(2): p. 121-129.
49. Brookmeyer, R. and N. Abdalla, *Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease.* Alzheimers Dement, 2018.
50. Sperling, R.A., et al., *The A4 Study: Stopping AD before Symptoms Begin?* Science translational medicine, 2014. **6**(228): p. 228fs13-228fs13.

TABLES AND FIGURES

Table 1. Baseline characteristics according to diagnosis

	Preclinical AD (N = 438)	Prodromal AD (N = 729)	Mild AD dementia (N= 1932)	Moderate to severe AD dementia (N = 237)	p-value overall group difference
Age, years	73 (7)	72 (7)	73 (9)	75 (10)	<0.01[a]
Male, No. (%)	204 (47%)	417 (57%)	813 (42%)	80 (34%)	<0.01
MMSE (0-30), median (IQR) (N=3320)	29 (28-30)	27 (26-29)	22 (19-24)	15 (13-19)	<0.01[b]
APOE ε4 genotype^, No. (%) (N=1984)	210 (49%)	466 (66%)	554 (71%)	35 (51%)	<0.01
Abnormal CSF total tau^, No. (%) (N=1563)	87 (38%)	348 (57%)	538 (81%)	47 (82%)	<0.01
Follow-up, years median (IQR)	3.8 (2-4.5)	3.9 (2.5-4.8)	2 (1.5-2.5)	2 (1.2-2.2)	<0.01[c]
Progression to next stage, No. (%)	87 (20%)	325 (45%)	586 (30%)	NA	NA
Death at follow-up, No. (%)	12 (3%)	76 (10%)	228 (12%)	55 (23%)	NA

Mean (SD), unless otherwise specified. In Tukey posthoc: [a] Moderate to severe AD dementia older than the MCI and Mild AD dementia group; [b] All groups significantly different from each other; [c] Normal cognition and MCI longer follow-up than dementia groups; [d] MCI higher median visits and moderate to severe AD dementia lower compared to the other groups. ^ Available in subset of cohorts.

Table 2. Estimated stage-specific duration of Alzheimer Disease

Starting stage	*Duration, time in years (CI, 95%)*	Age 60	Age 70	Age 80
Preclinical AD	***Preclinical AD***	13 (10.6-14.9)	9.9 (8.3-11.4)	7.6 (5.6-9.7)*
	Prodromal AD	4.4 (3.7-4.8)	4 (3.3-4.7)	3.5 (2.3-4.5)
	Mild AD dementia	3.5 (3-3.8)	2.9 (2.4-3.3)	2.1 (1.4-2.5)*
	Moderate AD dementia	3.5 (2.8-4.1)	2.6 (2.1-3.2)	1.7 (1.1-2.3)*
	Total duration	***~ 24***	***~ 19***	***~ 15***
Prodromal AD	***Preclinical AD***	3.2 (2.3-4.1)	1.6 (1.1-2.1)*	0.7 (0.4-1.2)*
	Prodromal AD	4.6 (3.9-5.3)	4.4 (4-4.8)	4 (3.4-4.8)
	Mild AD dementia	4.5 (4-4.9)	3.9 (3.5-4.2)	3 (2.5-3.3)*
	Moderate AD dementia	4.8 (4.2-5.4)	3.8 (3.2-4.4)	2.7 (2.1-3.3)*
	Total duration	***~ 18***	***~ 14***	***~ 10***
Mild AD dementia	***Mild AD dementia***	4.9 (4.3-5.6)	4.3 (4-4.6)	3.5 (3.2-3.9)*
	Moderate AD dementia	5.9 (5.2-6.7)	4.7 (4.1-5.4)	3.5 (2.9-4.2)*
	Total duration	***~ 11***	***~ 9***	***~ 7***
***Moderate* AD dementia**	***Moderate AD dementia***	6.5 (5.5-7.6)	5.2 (4.5-5.9)	4.1 (3.4-5)*

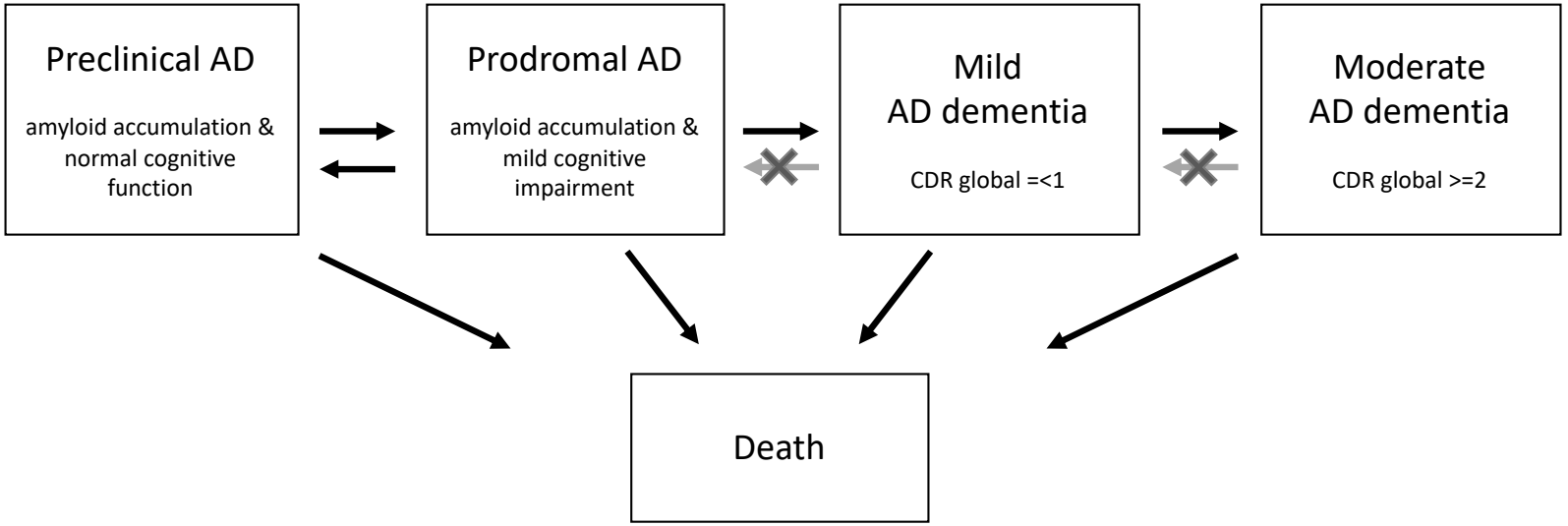
*Estimates different from estimates of persons aged 60. Estimates based on model with age as covariate. Moderate to severe AD dementia is shortened to moderate AD dementia for readability.

Table 3. Estimated stage-specific duration stratified for baseline CSF total tau by setting

		Age 70			
		Clinical setting		Research setting	
Starting stage	***Duration, time in years (CI, 95%)***	**Tau normal**	**Tau abnormal**	**Tau normal**	**Tau abnormal**
Preclinical AD	***Preclinical AD***	5.6 (3.7-8.9)	3 (1.9-4.3)	11.6 (8.3-14.3)	7.7 (5.6-9.9)^
Prodromal AD	***Prodromal AD***	5.4 (4.0-7.0)	3 (2.3-3.7)*	6.8 (5.5-8.1)	3.9 (3.3-4.6)*
Mild AD dementia	***Mild AD dementia***	4.4 (3.2-5.9)	3.6 (2.9-4.4)	6.4 (4.7-7.9)	5.4 (4.2-6.5)
Moderate AD dementia	***Moderate AD dementia***	4.9 (3.1-7.7)	5.9 (4.1-8.7)	2.8 (1.8-4.1)	3.5 (2.5-4.7)

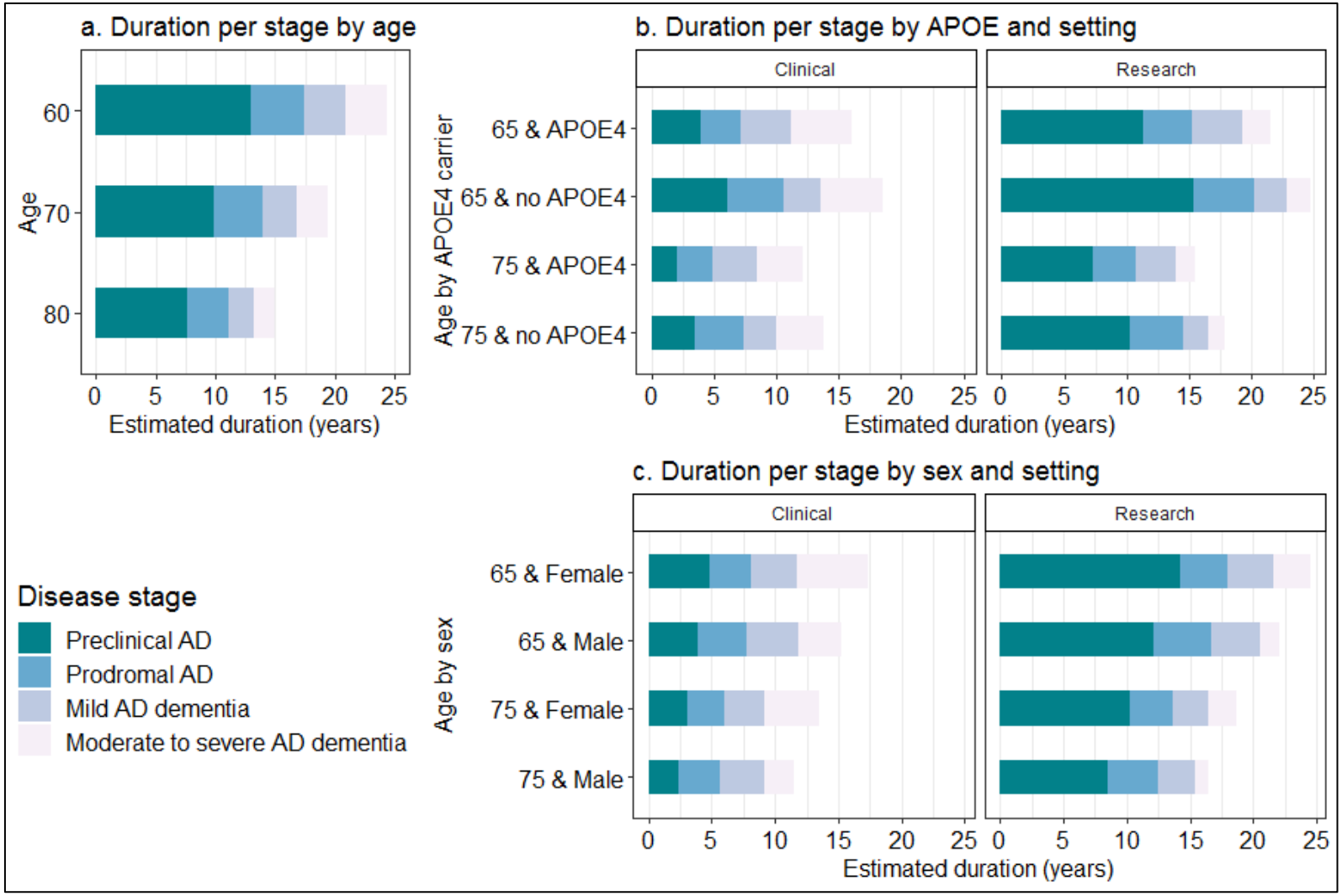
Tau = baseline CSF total tau. Abbreviations: Severe AD = moderate to severe AD dementia. ^non-overlapping 95% confidence intervals between setting, same tau classification. *non-overlapping 95% confidence intervals between tau classification, same setting. Model includes age as continues and baseline CSF tau and setting as dichotomous covariates. Moderate to severe AD dementia is shortened to moderate AD dementia for readability.

Figure 1. Multistate Model



Arrows indicate fitted progression and reversion rates between disease stages in the multistate model. Moderate to severe AD dementia is shortened to moderate AD dementia for readability.

Figure 2. Estimated Stage-specific Duration for Starting Stage Preclinical AD



The panels show the predicted time spend in each stage stacked and stratified for (a) age (model 1); for (b) age, APOE genotype, and setting (model 3); and for (c) age, sex, and setting (model 2). Models include age as continues, and (b) and (c) sex or APOE, and setting a dichotomous covariates.

The age is the preclinical stage at baseline and the estimated duration the predicted duration in the subsequent stages in years.

The 95% confidence intervals for each prediction can be found for (a) in table 2, for panel (b in table S2.7, and for panel (c) in table S2.6)

Supplement 1. Cohort information

Table S1.1 Eligibility, diagnostic criteria and amyloid measures for all cohorts

Cohort	ADC	ADNI	AIBL	DESCRIPA	Gothenburg	ICTUS
Age range	>50	55-90	>60	>55	70-84	>50
Participants	Consecutive memory clinic patients	Research volunteers and memory clinics	Research volunteers and memory clinics	Consecutive memory clinic patients	Population based women study	Consecutive GP and memory clinic patients
Relevant exclusion criteria	None	Other disorder causing cognitive impairment; medication causing cognitive impairment, Hachinski >4, GDS>6	Good general health with no history of stroke or other neurological disease	Other disorder causing cognitive impairment	None	MMSE <10, nursing home at entry, pathology leading to < 2 years' life expectancy, no caregiver.
Dementia diagnosis	According to criteria NINCDS-ADRDA criteria applied in clinical work-up	Consensus committee applies criteria NINCDS-ADRDA criteria	NINCDS-ADRDA criteria for probable AD and CDR of 1 or more	NINCDS-ADRDA criteria, checked by consensus committee	NINCDS-ADRDA	Probable AD according NINCDS-ADRDA criteria
Criteria for MCI	Petersen's criteria until 2012, thereafter National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for MCI.	Memory complaint by subject or study partner, verified by a study partner; below cut-off on Logical Memory II DR Wechsler Memory Scaled (LMII-DR of WMS), education adjusted; MMSE 24-30 (inclusive); CDR = 0.5, Memory score >= 0.5; diagnosis of AD dementia is not met.	Subjective and objective cognitive difficulties in the absence of significant functional loss and had a CDR of < 1 (Petersen et al., 1999; Winblad et al., 2004).	Cognitive test score <1.5 SD, dementia criteria not met.	Winblad criteria	NA
Criteria for Cognitively normal	Criteria for MCI and dementia not met and no current psychiatric illness.	Normal scoring on Logical Memory II subscale (delayed Paragraph Recall) Wechsler Memory Scaled (LMII-DR of WMS), education adjusted, MMSE 24-30, CDR = 0; no significant impairment in cognitive functions or ADL.	Criteria for MCI and dementia not met, enrichment with: wide age range, 50% memory complaints, 50% APOE ε4	No cognitive test score <1.5 SD, dementia criteria not met.	Criteria for MCI and dementia not met.	NA
Amyloid pathology measures	Visually rated positive on amyloid PET (PiB or Florbetaben) by experienced raters, or CSF Aβ1-42 below 640 ng/L on the Innotest assay.	Positive on amyloid PET scans by cut-offs were for PiB 1.5 SUVR for Florbetapir 1.11 SUVR (ref) or CSF Aβ1-42 below Aβ1-42 192 ng/L of the xx assay	Positive on amyloid PET PIB SUVR > 1.5	CSF Aβ1-42 below 550 ng/L on the Innotest assay.	CSF Aβ1-42 below 640 ng/L cut-off on Innotest assay.	No amyloid measures available
Tau pathology measures	Above CSF total tau> 375 pg/ml on the Innotest assay.	Above CSF total tau> 92 pg/ml on the xx assay	NA	Above CSF total tau> 375 pg/ml on the Innotest assay.	Above CSF total tau> 375 pg/ml on the Innotest assay.	NA

Table S1.2. Participants numbers and baseline characteristics of participants by cohort

	ADC (N=751)	ADNI (N=854)	AIBL (N=336)	DESCRIPA (N=72)	Gothenburg (N=23)	ICTUS (N=1300)
Baseline Diagnosis						
Normal cognition, No.	40	180	191	23	4	0
Mild Cognitive Impairment, No.	140	449	73	49	18	0
Mild AD dementia, No.	507	224	69	0	1	1131
Moderate to severe AD dementia, No.	64	1	3	0	0	169
Follow-up, y median (IQR)	3 (1.5-4.5)	3 (2-4.2)	4.5 (1.5-4.5)	2.5 (2-3)	12 (8-16)	2 (1.5-2)
Age, y mean (SD)	66 (7)	74 (7)	74 (7)	69 (8)	74 (4)	76 (8)
Female. %	50	45	51	46	100	64

ADC=Amsterdam Dementia Cohort; ADNI = Alzheimer's Disease Neuroimaging Initiative; AIBL = Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing; Gothenburg = Prospective Population Study of Women in Gothenburg.

ADNI methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

Supplement 2. Methods and specifications multistate model analysis and estimations of disease duration

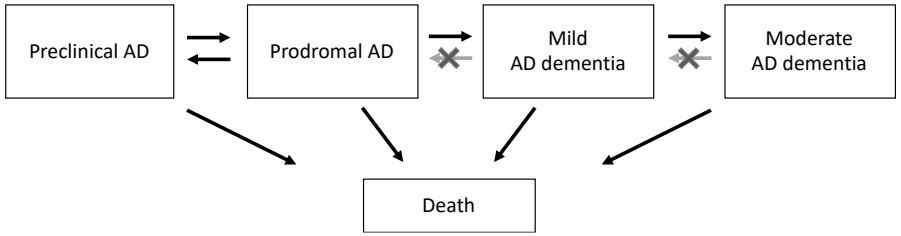
Background multistate model and disease duration

A multistate model is a Markov model in which multiple transition rates can be estimated in a single model, while also allowing non-linear rates over time with age as a time-dependent covariate (i.e. being age-specific). This technique was previously used in AD research to estimate age-related AD biomarker abnormality prevalence and to extrapolate the effect on the prevalence if a preventive treatment would come available [Jack et al. 2016, Brookmeyer et al.2018]. After determining the transition rate with the *msm*-package in R, the maximum likelihood estimate can be used as input for predicting the duration for every stage, as well as to derive 95% confidence intervals by simulation using the asymptotic properties of the maximum likelihood estimation, using the R-package created by Ardo van den Hout called *Estimating Life-Expectancies for interval censored data* (*ELECT*) [van den Hout 2017, Jackson 2011]. We build up several models with the goal to estimate disease durations and investigate the effects of certain covariates. This supplement describes the data input and the choices in more detail.

Rationale of model choice

Data on clinical diagnosis and survival at every follow-up visit were used to fit a multistate model that included five stages. This model contained four living stages: preclinical AD, prodromal AD, mild dementia, and moderate to severe dementia. Death was the end-stage (Figure S2.1).

Figure S2.1. Five stage multistate model



Reversion from prodromal AD to preclinical AD was kept in the model as MCI is a clinically defined syndrome based on test scores, from which a participant can at least temporary improve, even in the presence of amyloid pathology (n=62 in this dataset). As a result, we report a duration in the preclinical stage for

participants with prodromal AD at baseline. Reversions from mild dementia to prodromal AD or from moderate to mild dementia were treated as being misclassified in the more severe stage previous to the reversion, because it was considered that these reversions were due to variability in clinical scores rather than improvement of the disease. The probabilities for misclassifications were low; with 0.014 (95% CI, 0.010-0.021) of true state prodromal AD being misclassified as mild AD dementia and 0.041 (95% CI, 0.036-0.048) of true state mild AD being misclassified as moderate to severe AD dementia.

Specifics of data

Table S2.1 shows the state table of the dataset. This table contains all observations. Each individual can have multiple observations. 'From' does not refer to baseline diagnosis, but to diagnosis at previous visit. The time interval between visits varies. Table S2.2 and S2.3 and S2.4 present the number observations at each moment in time, the number of observations per individual and the number of observations per stage.

Table S2.1. Summary of all transitions – Multistate model state table

From \ To	CN	MCI	Mild AD- dementia	Moderately severe AD	Death	End of follow-up
CN	1094	105	9	0	13	70
MCI	72	1819	344	11	31	133
Mild AD dementia	0	17	3944	701	187	630
Moderately severe AD	0	0	125	801	140	193

Table S2.2. Number of observations per follow-up time

Follow-up, y	0	<0.3	0.5	1	2	3	4	5	6	7	8	9	10-20
Observations, No.	3336	21	2135	2473	3281	1038	537	511	190	100	80	35	38

Table S2.3. Number of observations per individual

Observations, No.	2	3	4	5	6	7	8	9	10	11	12	13
Participants, No.	666	507	825	905	216	107	41	20	17	17	8	7

Table S2.4. Number of observations per stage

Stage	CN	MCI	Mild AD dementia	Moderate to severe AD dementia	Death	Last known alive, diagnosis unknown
Observations, No.	1604	2670	6354	1750	371	1026

Basic model specifications

The baseline estimates were centered at age 70. First the hazard ratios per year increase in age were estimated in Model 1 of which the estimates are in table S2.5 below. Based on these models, we estimated the duration of stages in table 2 according to age using the ELECT package.

Models with covariates sex and setting

We build up the model by adding the effects of sex and setting (Model 2 in table S2.5). For the preclinical AD duration per setting reported in the text, estimates were based on only age and setting, which had very similar estimates to model 2. As there is a covariate effect on every transition, the number of parameters increases rapidly when adding covariates to a model. In particular the point estimates of effect of covariates on the transitions from preclinical AD, prodromal AD and mild AD dementia to death were not estimable, leading to incredibly large or small hazard ratios with confidence intervals of more than 3 times the hazard ratios. The only exception was the transition from mild AD dementia to death for sex in model 2. The others were omitted.

Table S2.5. All five models with baseline transition rates and hazard ratios

	Preclinical AD to prodromal AD	Preclinical AD to death	Prodromal AD to preclinical AD	Prodromal AD to mild dementia	Prodromal AD to death	Mild AD to moderately severe AD dementia	Mild AD dementia to death	Moderately severe AD dementia to death
Model 1 AGE								
Transition rate, at age 70	0.083 (0.066,0.104)	0.002 (0.001,0.010)	0.049 (0.039, 0.062)	0.199 (0.176,0.224)	0.003 (0.001,0.011)	0.200 (0.182,0.220)	0.005 (0.002,0.016)	0.164 (0.140,0.192)
Age, per year increase	**1.026 (1.001,1.053)**	1.058 (0.897,1.248)	**0.951 (0.923,0.979)**	1.004 (0.990,1.018)	**1.128 (1.026,1.240)**	**1.011 (1.0001,1.02)**	**1.144 (1.059,1.237)**	**1.024 (1.011,1.039)**
Model 2 AGE/SEX/SETTING								
Transition rate, at age 70	0.0681 (0.049,0.094)	0.003 (0.001,0.010)	0.040 (0.027,0.059)	0.166 (0.137,0.199)	0.003 (0.001,0.011)	0.135 (0.110,0.167)	0.008 (0.002,0.027)	0.257 (0.188,0.351)

Age, per year increase	**1.047 (1.020,1.074)**	1.051 (0.900,1.228)	**0.965 (0.934,0.997)**	1.014 (0.998,1.029)	**1.127 (1.019,1.247)**	**1.011 (1.001,1.022)**	**1.143 (1.055,1.238)**	**1.026 (1.011,1.041)**
Sex = female	0.772 (0.536,1.113)	-	1.022 (0.636,1.642)	1.154 (0.930,1.432)	-	**1.248 (1.048,1.486)**	0.405 (0.158,1.036)	**0.597 (0.451,0.790)**
Setting = clinic	**4.409 (2.797,6.950)**	-	**1.972 (1.149,3.385)**	**1.482 (1.138,1.930)**	-	**1.415 (1.161,1.724)**	-	0.804 (0.593,1.090)
Model 3 AGE/APOE/SETTING								
Transition rate, at age 70	0.043 (0.032,0.062)	0.002 (0.001,0.009)	0.0427 (0.030,0.066)	0.133 (0.106,0.167)	0.004 (0.001,0.011)	0.196 (0.151,0.255)	0.001 (0.000,0.020)	0.193 (0.127,0.293)
Age, per year increase	**1.061 (1.033,1.090)**	1.0638 (0.906,1.249)	**0.963 (0.932,0.996)**	**1.017 (1.001,1.033)**	**1.124 (1.025,1.232)**	1.004 (0.987,1.021)	**1.292 (1.086,1.538)**	**1.022 (1.0003,1.04)**
APOE ε4 genotype = yes	**1.632 (1.106,2.408)**	-	0.932 (0.566,1.534)	**1.495 (1.178,1.897)**	-	0.781 (0.608,1.003)	-	1.132 (0.796,1.611)
Setting = clinic	**4.501 (2.786,7.273)**	-	**1.890 (1.088,3.284)**	**1.444 (1.101,1.894)**	-	**1.481 (1.133,1.935)**	-	0.704 (0.468,1.060)
Model 4 AGE/TAU/SETTING								
Transition rate, at age 70	0.068 (0.046,0.099)	0.001 (0.000,0.022)	0.0487 (0.033,0.071)	0.115 (0.09,0.145)	0.004 (0.001,0.012)	0.137 (0.099,0.189)	0.001 (0.0004,0.02)	0.284 (0.018,0.450)
Age, per year increase	**1.035 (1.001,1.071)**	1.073 (0.810,1.422**)**	0.973 (0.940,1.007)	1.011 (0.994,1.028)	**1.112 (1.014,1.219)**	1.003 (0.984,1.021)	**1.274 (1.072,1.513)**	1.016 (0.993,1.040)
Baseline CSF total tau = abnormal	1.494 (0.949,2.352)	-	**0.407 (0.234,0.709)**	**1.914 (1.481,2.475)**	-	1.225 (0.901,1.664)	-	0.843 (0.557,1.276)
Setting = clinic	**3.166 (1.876,5.342)**	-	**2.811 (1.563,5.057)**	**1.332 (1.006,1.764)**	-	**1.513 (1.125,2.035)**	-	**0.606 (0.388,0.946)**
Model 5 AGE/SEX/APOE/TAU/SETTING								
Transition rate, at age 70	0.079 (0.047,0.134)	0.001 (0.0001,0.02)	0.044 (0.025,0.077)	0.096 (0.071,0.130)	0.004 (0.001,0.012)	0.159 (0.109,0.231)	0.0006 (0.000,0.032)	0.302 (0.176, 0.531)
Age, per year increase	**1.042 (1.005,1.080**)	1.079 (0.825,1.410)	0.976 (0.941,1.013)	1.016 (0.998,1.035)	**1.120 (1.017,1.234)**	1.005 (0.986,1.024)	**1.294 (1.053,1.589)**	1.015 (0.991,1.039)
Sex = female	**0.562 (0.359,0.878)**	-	1.072 (0.625,1.838)	0.997 (0.778,1.279)	-	1.120 (0.853,1.444)	-	0.700 (0.487,1.007)
APOE ε4 genotype = yes	1.201 (0.756,1.909)	-	1.197 (0.681,2.105)	**1.318 (1.010,1.720)**	-	**0.749 (0.568,0.988**)	-	1.117 (0.766,1.628)
Baseline CSF total tau = abnormal	1.470 (0.923,2.340)	-	**0.358 (0.199,0.643)**	**1.846 (1.417,2.405)**	-	1.189 (0.866,1.632)	-	0.928 (0.603,1.427)
Setting = clinic	**3.335 (1.884,5.905**)		**2.801 (1.522,5.157)**	**1.368 (1.022,1.830)**	-	**1.559 (1.1501,2.11)**	-	**0.587 (0.370,0.931)**

Hazard ratios that are different from 1 in bold.

Table S2.6. Estimated stage-specific duration for current preclinical AD stratified by sex and setting

Starting stage	*Duration, time in years (CI, 95%)*	Age 65				Age 75			
		Clinical setting		Research setting		Clinical		Research setting	
		Female	Male	Female	Male	Female	Male	Female	Male
Preclinical AD	***Preclinical AD***								
	Prodromal AD								
	Mild AD dementia								
	Moderate AD dementia								
	Total duration								

Model with APOE

We next performed the analysis with APOE ε4 as predictor. In the subset of individuals with APOE data the effects of age, sex and setting on stage transitions were not different from those in the full dataset. Sex did no longer predict transition from mild dementia to death. The sample demographics are shown in table S2.7 and the prediction of the age only model in table S2.9. The effects of the covariates on death in the preclinical, prodromal and mild AD dementia stage were again omitted from the model. Model 3 for APOE and setting was used to generate the estimates in Figure 2 and Table S2.6 (S2.5).

Model with CSF total tau

We next performed the analysis with baseline CSF total tau as predictor. In the subset of individuals with baseline CSF total tau (n=1563) data (table S2.7), the effect of age and sex, setting on stage transitions were similar to those in the full dataset (table S2.5 and S2.8). The confidence intervals were wider, and the effect of age and sex on mild AD dementia to moderate AD dementia lost significance. Model 4 for tau and setting was used to generate the estimates in table 3. Model 5 includes all covariates and was part of the sensitivity analysis showing similar estimates.

Table S2.7. Estimated stage-specific duration for current preclinical AD stratified by APOE and setting

Starting stage	*Duration, time in years (CI, 95%)*	Age 65				Age 75			
		Clinical setting		Research setting		Clinical		Research setting	
		No APOE ε4	APOE ε4	No APOE ε4	APOE ε4	No APOE ε4	APOE ε4	No APOE ε4	APOE ε4
Preclinical AD	***Preclinical AD***	6.1 (4.0-8.6)	3.9 (2.7-5.5)	15.4 (13-18)^	11.3 (9.3-13)^	3.5 (2.2-5.4)	2.1 (1.3-3.2)	10.3 (8.3-13)^	7.3 (5.9-8.8)^
	Prodromal AD	4.5 (3.4-5.8)	3.3 (2.7-4)	4.8 (3.7-5.6)	3.9 (3.3-4.5)	3.9 (2.9-5.1)	2.8 (2.2-3.6)	4.2 (3-5.3)	3.4 (2.7-4.1)
	Mild AD dementia	3.0 (2.2-3.8)	4.0 (3.2-4.8)	2.6 (1.9-3.4)	4.1 (3.2-4.9)	2.6 (1.8-3.4)	3.5 (2.6-4.3)	2.0 (1.3-2.9)	3.2 (2.4-4)
	Moderate AD dementia	4.9 (3.3-7.3)	4.8 (3.4-6.5)	1.9 (1.1-2.9)^	2.2 (1.5-2.9)^	3.8 (2.2-5.9)	3.7 (2.2-5.9)	1.4 (0.8-2.2)	1.6 (1-2.3)
	Total duration	*~ 19*	*~ 16*	*~ 25*	*~ 22*	*~14*	*~12*	*~18*	*~16*

Abbreviations: Moderate AD dementia = moderate to severe AD dementia. ^non-overlapping 95% confidence intervals between setting, same APOE ε4 genotype. Model includes age as continues and APOE ε4 and setting as dichotomous covariates.

Table S2.8. Baseline characteristics of participants with APOE data classified by baseline disease stage

	Normal Cognition (N = 431)	Mild Cognitive Impairment (N = 709)	Mild AD dementia (N= 776)	Moderate to severe AD dementia (N = 68)	P-value
Age, year mean (SD)	73 (7)	72 (8)	69 (9)	66 (8)	<0.01
Male, No. (%)	200 (46%)	407 (57%)	394 (51%)	25 (37%)	<0.01
MMSE (0-30), median (IQR)	29 (2)	28 (3)	22 (5)	13 (8.2)	<0.01
APOE ε4 genotype, No. (%)	210 (49%)	466 (66%)	554 (71%)	35 (51%)	<0.01
Abnormal CSF tau^, No. (%)	85 (37%)	328 (56%)	517 (80%)	47 (82%)	<0.01
Follow-up, years median (IQR)	4 (2.5)	3.9 (2.3)	2.5 (3)	3.5 (3)	<0.01
Visits, No. median (IQR)	4 (2)	5 (2)	3 (2)	2 (1)	<0.01
Progression to next stage, No. (%)	86 (20%)	320 (45%)	200 (26%)	NA	NA
Death at follow-up, No. (%)	11 (2%)	68 (10%)	106 (14%)	23 (34%)	NA

^ Available in subset of cohorts.

Table S2.9. Baseline characteristics of participants with baseline CSF tau classified by baseline disease stage

	Normal Cognition (N = 231)	Mild Cognitive Impairment (N = 607)	Mild AD dementia (N= 668)	Moderate to severe AD dementia (N = 57)	P-value
Age, years mean (SD)	73 (7)	72 (7)	68 (8)	66 (8)	<0.01
Male, No. (%)	98 (42%)	352 (58%)	343 (51%)	22 (39%)	<0.01
MMSE (0-30), median (IQR)	29 (2)	28 (3)	22 (4)	14 (7)	<0.01
APOE ε4 genotype, No. (%)	117 (52%)	383 (65%)	464 (72%)	30 (53%)	<0.05
Abnormal CSF tau, No. (%)	87 (38%)	346 (57%)	535 (80%)	47 (82%)	<0.01
Follow-up, years median (IQR)	3 (2)	3.8 (2.4)	2.5 (3)	3.5 (2.5)	<0.01
Visits, No. median (IQR)	4 (2)	5 (3)	3 (2)	2 (1)	<0.01
Progression to next stage, No. (%)	57 (24%)	270 (44%)	166 (25%)	NA	NA
Death at follow-up, No. (%)	10 (4%)	63 (10%)	98 (15%)	21 (37%)	NA

Moderate AD dementia = moderate to severe AD dementia.

Table S2.10. Predicted stage-specific disease duration – subset with APOE or baseline CSF total tau

		Subset with APOE (n=1984)*			Subset with CSF total tau (n=1563)^		
Starting stage	***Duration, time in years (CI, 95%)***	**Age 60**	**Age 70**	**Age 80**	**Age 60**	**Age 70**	**Age 80**
Preclinical AD	***Preclinical AD***	13.2 (11-15)	10 (8.6-11.5)	7.5 (5.5-9.6)	9.8 (6.9-11.9)	8.1 (6.6-9.7)	6.6 (4.4-9)
	Prodromal AD	4.4 (3.8-4.8)	4.1 (3.3-4.7)	3.6 (2.4-4.6)	4.8 (3.9-5.4)	4.4 (3.5-5)	3.7 (2.3-4.6)
	Mild AD dementia	3.8 (3.1-4.4)	3.2 (2.6-3.8)	2 (1.3-2.9)	4.2 (3.2-4.8)	3.5 (2.7-4.2)	2.1 (1.3-3)
	Moderate AD dementia	3 (2.3-3.8)	2 (1.4-2.6)	1 (0.6-1.7)	3.3 (2.4-4.1)	2.1 (1.5-2.9)	1 (0.5-1.7)
Prodromal AD	***Preclinical AD***	3.2 (2.2-4.3)	1.5 (1.2-2)	0.7 (0.4-1.2)	2.5 (1.6-3.4)	1.3 (0.9-1.8)	0.6 (0.3-1)
	Prodromal AD	4.7 (4-5.4)	4.5 (4-4.9)	4.1 (3.4-4.8)	5 (4.1-5.7)	4.7 (4.1-5.1)	4.2 (3.4-5)
	Mild AD dementia	4.5 (3.9-5)	4.4 (3.8-4.9)	3.4 (2.6-4.1)	4.5 (3.9-5.1)	4.4 (3.8-5.1)	3.4 (2.6-4.1)
	Moderate AD dementia	4.6 (3.9-5.3)	3.3 (2.6-4)	1.9 (1.3-2.7)	4.4 (3.6-5.2)	3.1 (2.4-4)	1.8 (1.2-2.7)
Mild AD dementia	***Mild AD dementia***	4.5 (3.8-5.3)	4.8 (4.2-5.3)	4.3 (3.6-5.1)	4.4 (3.7-5.1)	4.8 (4-5.5)	4.4 (3.5-5.2)
	Moderate AD dementia	6 (5.1-6.9)	4.4 (3.6-5.2)	2.8 (2.1-4)	5.7 (4.8-6.6)	4.2 (3.4-5)	2.7 (1.9-3.7)
Moderate AD dementia	***Moderate AD dementia***	6.5 (5.4-7.7)	4.9 (4.1-5.8)	3.7 (2.9-5)	6.2 (5.1-7.3)	4.7 (4-5.6)	3.5 (2.7-4.7)

Time in years. *No estimates are significantly different from analysis with all data. In these subsets no ICTUS data, i.e. only confirmed amyloid positive individuals. ^In this subset no ICTUS and AIBL data. Model with age as covariate. Moderate AD dementia = moderate to severe AD dementia.

Table S2.11. Predicted stage-specific disease duration – subsequently removing cohorts

		Subset without ADNI (n=2482)			Subset without ADC (n=2585)			Subset without DESCRIPA (n=3264)			Subset without Gothenburg (n=3313)		
		Age 60	**Age 70**	**Age 80**	**Age 60**	**Age 70**	**Age 80**	**Age 60**	**Age 70**	**Age 80**	**Age 60**	**Age 70**	**Age 80**
Current preclinical AD	***Time in preclinical AD***	12.9 (10-15.6)	11 (8.5-13)	8.6 (5.6-12)	15 (12.6-17)	10.4 (9-12)	7.1 (5.4-8.9)	13.6 (11-15.6)	10.2 (8.6-12)	7.6 (5.4-10)	12.9 (10.7-15)	10.1 (8.4-12)	7.9 (5.7-10)
	Time in prodromal AD	3.2 (2.5-3.7)	2.5 (1.7-3)	1.6 (0.8-2.5)	4.4 (3.6-4.9)	4.1 (3.4-4.8)	3.6 (2.4-4.5)	4.4 (3.7-4.8)	4.1 (3.3-4.7)	3.6 (2.2-4.4)	4.4 (3.8-4.8)	4.1 (3.3-4.8)	3.7 (2.5-4.6)
	Time in mild AD dementia	3.5 (2.7-3.7)	2.7 (1.8-3.2)	1.7 (0.8-2.4)	3.4 (2.8-3.7)	2.8 (2.2-3.1)	2 (1.3-2.5)	3.4 (2.9-3.8)	2.8 (2.3-3.2)	2 (1.3-2.5)	3.6 (3.1-3.9)	2.9 (2.4-3.3)	2.1 (1.4-2.6)
	Time in moderately severe AD dementia	3.9 (3-4.6)	2.8 (1.9-3.5)	1.7 (0.8-2.5)	3.1 (2.4-3.6)	2.5 (1.9-3.2)	1.9 (1.2-2.6)	3.4 (2.7-4)	2.6 (2-3.1)	1.7 (1-2.2)	3.6 (3-4.2)	2.7 (2.1-3.4)	1.8 (1.1-2.4)
Current prodromal AD	***Time in preclinical AD***	3.8 (2.5-5.6)	2.1 (1.3-3.2)	1 (0.4-1.8)	4.4 (3-6.1)	1.8 (1.3-2.3)	0.7 (0.4-1.1)	2.6 (1.7-3.7)	1.3 (0.9-1.7)	0.6 (0.3-1)	3.1 (2.2-4.1)	1.5 (1.1-2)	0.7 (0.4-1.2)
	Time in prodromal AD	3.8 (3-4.4)	3.1 (2.6-3.6)	2.5 (1.9-3.3)	4.9 (4-5.7)	4.6 (4-5)	4.1 (3.4-4.8)	4.7 (4-5.4)	4.5 (4.1-4.9)	4.1 (3.4-4.8)	4.6 (4-5.3)	4.4 (4-4.9)	4.1 (3.4-4.9)
	Time in mild AD dementia	4.3 (3.6-4.6)	3.7 (3.3-4)	3 (2.3-3.5)	5 (4.3-5.5)	3.9 (3.6-4.2)	2.8 (2.4-3.2)	4.5 (4-4.9)	3.9 (3.5-4.1)	3 (2.5-3.3)	4.5 (4.1-4.9)	3.9 (3.6-4.2)	3 (2.6-3.4)
	Time in moderately severe AD dementia	5.1 (4.1-5.8)	4.2 (3.4-4.9)	3.1 (2.2-4)	4.4 (3.7-5.2)	3.6 (3-4.1)	2.6 (2-3.3)	4.9 (4.3-5.5)	3.8 (3.3-4.4)	2.6 (2-3.2)	5 (4.3-5.5)	3.9 (3.3-4.6)	2.8 (2.2-3.4)
Current mild AD dementia	***Time in mild AD dementia***	4.7 (4.1-5.2)	4.1 (3.7-4.4)	3.4 (3-3.7)	6.3 (5.2-7.3)	4.7 (4.3-5.1)	3.4 (3-3.7)	4.9 (4.2-5.5)	4.3 (3.9-4.6)	3.5 (3.2-3.9)	4.9 (4.3-5.5)	4.3 (4-4.6)	3.6 (3.3-4)
	Time in moderately severe AD dementia	6.2 (5.3-7.2)	5 (4.3-5.8)	3.8 (3.1-4.7)	5.7 (4.5-7.1)	4.4 (3.8-5.1)	3.3 (2.8-4)	6 (5.2-6.8)	4.7 (4.1-5.3)	3.5 (2.9-4.1)	6 (5.2-6.8)	4.8 (4.2-5.5)	3.6 (3-4.4)
Current moderately severe AD dementia	***Time in moderately severe AD dementia***	6.8 (5.5-8.1)	5.5 (4.7-6.4)	4.4 (3.7-5.5)	6.7 (4.7-9.1)	5.1 (4.1-6.1)	3.8 (3.3-4.7)	6.5 (5.3-7.6)	5.2 (4.6-5.9)	4.1 (3.4-4.9)	6.5 (5.4-7.7)	5.3 (4.5-6.1)	4.2 (3.5-5.2)

Time in years. *No estimates are significantly different from analysis with all data. In these subsets no ICTUS data, i.e. only confirmed amyloid positive individuals. Model with age as covariate.

References supplement 2

Brookmeyer ….

Jack, C. R., Jr., T. M. Therneau, H. J. Wiste, S. D. Weigand, D. S. Knopman, V. J. Lowe, M. M. Mielke, P. Vemuri, R. O. Roberts, M. M. Machulda, M. L. Senjem, J. L. Gunter, W. A. Rocca and R. C. Petersen (2016). "Transition rates between amyloid and neurodegeneration biomarker states and to dementia: a population-based, longitudinal cohort study." Lancet Neurol 15(1): 56-64.

Jackson

Van den Hout, A. (2017). "Multi-State Survival Models for Interval-Censored Data. Boca Raton: CRC/Chapman & Hall.".

Acknowledgements:

The authors are very thankful to all patients and participants in the studies included in the paper, as well as to all staff that were involved in the data collection and data sharing. We also thank Michele Potashman and Hans Berkhof for the discussions on AD disease progression modelling.