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Chapter 2

Clinical course of Alzheimer disease

Chapter 2.1

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

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Abstract

INTRODUCTION: We estimated the age-specific duration of the preclinical, prodromal and dementia stages of AD, and the influence of sex, setting, *APOE*, and CSF tau on disease duration.
METHODS: We performed multi-state modeling in a combined sample of 6 cohorts (n=3,268) with death as the end-stage, and estimated the preclinical, prodromal and dementia stage duration.
RESULTS: The overall AD duration varied between 24 years (age 60) and 15 years (age 80). For individuals presenting with preclinical AD, age 70, the estimated preclinical AD duration was 10 years, prodromal AD 4 years, and dementia 6 years. Male sex, clinical setting, *APOE* ε4 genotype and abnormal CSF tau were associated with a shorter duration and these effects depended on disease stage.
DISCUSSION: Estimates of AD disease duration become more accurate if age, sex, setting, *APOE* and CSF tau are taken into account. This will be relevant for clinical practice and trial design.

1 Introduction

Alzheimer disease (AD) is highly prevalent, and a major cause of dementia and death in elderly individuals [1-3]. Accumulation of amyloid in the brain is believed to be the first sign of the disease and can precede a clinical diagnosis of dementia by up to 20 years [1, 4, 5]. Based on the degree of cognitive impairment, AD is often divided into three stages: the preclinical stage, characterized by normal cognitive ability, the prodromal stage, characterized by mild cognitive impairment (MCI), and the dementia stage, with functional impairment [6-9], but it is unclear how long individuals with amyloid pathology spend in each stage. A better understanding of the stage-specific duration of AD is needed to inform patients, caregivers, and clinicians. This information is also useful for the design of clinical studies, as well as to provide context for the interpretation of trial results, in particular the clinical trials that include individuals in pre-dementia stages and aim to slow down progression to AD dementia.

Attempts to quantify the duration of AD should be age-specific, because age imposes the greatest risk for both dementia and mortality, and take into account *APOE* genotype, sex, and cerebrospinal fluid (CSF) tau levels [4, 6, 10-12]. Setting is also important, as progression from MCI to dementia was longer in research settings than in clinical settings [13]. Previous studies on the length of the AD dementia stage reported a duration of 3 to 10 years [14, 15]. Younger age, female sex and lower CSF total tau (tTau) were found to be associated with a longer duration of the AD dementia stage, while the effect of *APOE* genotype was equivocal [14-17]. The median duration of prodromal AD was three years in a pooled memory clinic cohort study, but no age-specific estimates were provided and mortality was not taken into account [18]. The patients with prodromal AD and increased CSF tTau levels tended to

convert sooner to AD dementia [19, 20]. The duration of the preclinical AD stage has been estimated in combination with the prodromal AD stage, which was 17 years, based on extrapolations of change in positron emission tomography (PET) amyloid load over time [21].

We estimated disease duration by applying a multi-state modeling approach, which has been previously used in AD research [22-25], and can offer an estimate of disease duration based on stage progression and mortality rates in the absence of very long follow-up duration. The aim of this study was therefore to estimate the disease duration for preclinical, prodromal and AD dementia stage according to age, setting (clinical versus research), sex, *APOE* genotype, and baseline CSF tTau levels.

2 Methods

2.1 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 (Supplement A for more cohort information) [26-31]. From these cohorts, we selected participants aged 50 years and older with evidence of amyloid accumulation, and with information on diagnosis and/or mortality at follow-up available. Evidence of amyloid pathology was an inclusion criterion for this study, defined by at least one abnormal marker of amyloid accumulation. The amyloid PET scans were visually rated or a published threshold was applied and for CSF amyloid-beta 1-42 ($A\beta_{42}$) cohort-specific thresholds were applied (Supplement A). In absence of amyloid measures for the ICTUS cohort, only the patients with a clinical diagnosis of AD-type dementia were included and analyses repeated without this cohort. All studies were approved by an ethical review board and their participants gave informed consent.

2.2 AD stages

AD was categorized into four clinical stages: preclinical AD, prodromal AD, mild AD dementia, and moderate to severe AD dementia (from here on shortened to moderate AD dementia). Preclinical AD was defined by amyloid accumulation and normal cognition (Supplement A). Prodromal AD was in this study defined by amyloid accumulation and a diagnosis of MCI, amnestic and non-amnestic [9, 32, 33]. AD dementia was diagnosed according to the NINCDS-ADRDA criteria, and if an amyloid evaluation was available this had to be confirmative [7]. AD dementia was subdivided in mild AD dementia (Clinical Dementia Rating (CDR) below 2, or CDR sum of boxes (CDR-SOB) <10, or (if no CDR was available) MMSE>20), and moderate AD dementia (CDR>1, CDR-SOB>9, or (if no CDR was available) MMSE<21) [34, 35].

2.3 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 of those who died was unknown (n=19) and therefore set at the next planned visit, which is 1.5 years after the last follow-up. In others cases of a missing mortality date (n=4), the date was set 2 years after last follow-up.

2.4 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 the presence or absence of the AD-associated ε4 allele of *APOE* and was available in all cohorts except ICTUS. Baseline CSF tTau 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 A).

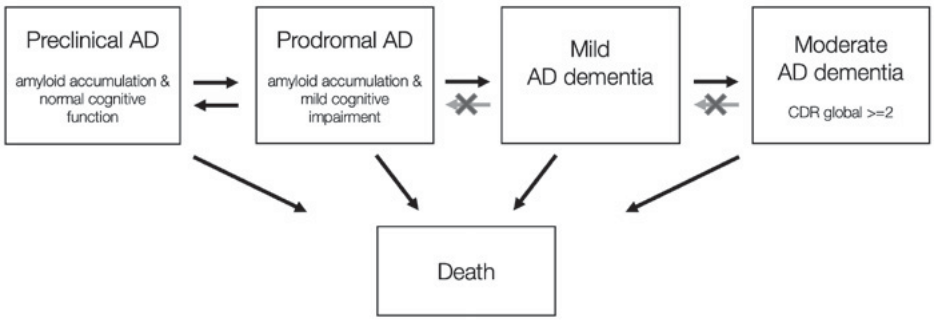

Figure 1 Multi-state Model
Arrows indicate fitted progression and reversion rates between stages in the multi-state model. Moderate to severe AD dementia is shortened to moderate AD dementia for readability.

2.5 Statistical analyses

Baseline characteristics between diagnostic groups were compared using Chi-square, Kruskal-Wallis or ANOVA tests with Tukey post-hoc, where appropriate. To estimate the disease duration, a multi-state model (MSM) with the four stages of AD and death as the end-stage was fitted [36]. All transition rates between stages were incorporated in one model (Figure 1). Reversions from prodromal to preclinical AD were also included in the model. Reversion in the dementia stages were fitted using misclassification (see Supplement B for additional methods and specifications of multi-state model analysis).

Multi-state models with different numbers of covariates were fitted to the data. Age was a time-dependent covariate, and centered at age 70. For each covariate a hazard ratio was calculated for each transition. As most covariate effects on mortality

were not estimable; a restricted model was applied. The first model included only age as covariate, the second model included setting as well, and the third model had age, setting, and sex as covariates. The fourth model included age, setting, and *APOE*, while the fifth model had age, setting, and tau as covariates, and the sixth model included all five 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.

In a second step, using the MSM maximum likelihood estimate as input, the duration for every stage was estimated. Confidence intervals of 95% were derived by simulation using the asymptotic properties of the maximum likelihood estimation, which allowed comparison between age-specific estimates for the different covariates. R-packages msm for the multi-state transition model and ELECT version 0.3 (Estimating Life-Expectancies for interval censored data) were used to estimate the duration estimates and confidence intervals [36, 37]. Sensitivity analyses included, aside of fitting all covariates in one model, sequentially removing cohorts from the analysis to ensure results were not driven by a single cohort. We also reran all models in the subset with data on all covariates (n=1518).

3 Results

A total of 3,268 participants were included in the analyses across the six cohorts combined. The mean (SD) age at baseline was 73 (8) years with a range of 50 to 96 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) number of 4 (3-5) visits. Progression to at least one consecutive stage was apparent in 981 (32% of 3,034) participants. Table 1 shows how participants in the baseline stages differed in sex, *APOE* ε4 genotype, abnormal CSF tTau, follow-up length and mortality (Suppl. table B.5 for subgroups with data on *APOE* and CSF tTau available).

3.1 Transition rates

In the model that included age, sex and setting, all transition rates to subsequent disease were significantly influenced by age, except mortality in the preclinical AD stage and progression from prodromal AD to mild AD dementia (Suppl. table B.2 for all estimates of the models). Compared to data collected in a research setting, data from clinical settings was associated with a higher progression rate (HR=4.40 [95% CI, 2.80-6.94]) and reversion rate (HR=1.98 [95% CI, 1.15-3.39]) between preclinical and 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, 1.34-1.92]) and from the mild AD to the moderate AD dementia stage (HR=1.41 [95% CI,1.16-1.72]) were higher. Females had a higher progression rate from mild AD to moderate AD dementia, compared to males (HR=1.24 [95% CI, 1.04-1.47]), while their mortality risk in moderate AD dementia was lower (HR=0.60 [95% CI, 0.46-0.80]).

Table 1 Baseline characteristics according to diagnosis

	Preclinical AD (n = 438)	Prodromal AD (n = 729)	Mild AD dementia (n = 1867)	Moderate to severe AD dementia (n = 234)	p-value overall group difference
Age (years)	73 (7)	72 (7)	73 (9)	75 (10)	<0.01[a]
Male (n)	204 (47%)	417 (57%)	781 (42%)	74 (33%)	<0.01
MMSE (0-30, median (IQR)) (n=3252)	29 (28-30)	27 (26-29)	22 (19-24)	16 (13,19)	<0.01[b]
APOE e4 genotype* (n) (n=1984)	210 (49%)	466 (66%)	554 (71%)	35 (51%)	<0.01
Abnormal CSF total tau* (n) (n=1563)	87 (38%)	346 (57%)	535 (80%)	47 (82%)	<0.01
Follow-up years (median (IQR))	3.8 (2-4.5)	3.9 (2.5-4.8)	2.0 (1.5-2.5)	2.0 (1.2-2.3)	<0.01[c]
Progression to next clinical disease stage (n)	87 (20%)	325 (45%)	569 (30%)	NA	NA
Death at follow-up (n)	12 (3%)	76 (10%)	215 (12%)	54 (23%)	NA
Participants by cohort (n ADC/ ADNI/ AIBL/ DESCRIPA/ Gothenburg/ ICTUS)	40/ 180/ 191/ 23/ 4/ 0	140/ 449/ 73/ 49/ 18/ 0	507/ 224/ 69/ 0/ 1/ 1066	64/ 1/ 3/ 0/ 0/ 166	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 * Available in subset of cohorts, *APOE* not for ICTUS.

3.2 AD stage duration according to age, sex, and setting

The predicted total disease duration, based on the model with age, for an individual with preclinical AD at age 70 was 20 years (95% CI, 17-21), consisting of a preclinical stage of 10 years (95% CI, 8-11), followed by a prodromal stage of 4 years (95% CI, 3-5), mild AD dementia for 3 years (95% CI, 2-3), and moderate AD dementia for 3 years (95% CI, 2-3, Table 2). Figure 2A shows for those with preclinical AD a lower predicted overall disease duration at older age, which ranged from 24 years (95% CI, 22-25) at age 60 to 15 years (95% CI, 11-17) at age 80. The duration of preclinical AD at age 70 was shorter in a clinical setting (4 years [95% CI, 3-5]) than in a research setting (11 years [95% CI, 9-13]). In the clinical setting, for individuals with prodromal AD, the stage duration of prodromal AD was also shorter, and while the dementia stage duration for these individuals was equal between settings, more time was spent

in the moderate AD stage (Suppl. table B.7a and b). The estimated total duration with starting stage preclinical AD ranged in the clinical setting 19 years (95% CI, 17-20) at age 60 to 11 years (95% CI, 10-12) at age 80 and in the research setting from 26 years (95% CI, 23-28) at age 60 to 15 years (95% CI, 12-17) at age 80. In females the moderate AD dementia stage duration was longer than in males (e.g. 2.1 years (95% CI, 1.1-3.2, p<0.0001 at age 70 in a clinical setting; Figure 2B, Suppl. table B.3).

Table 2 Estimated stage-specific duration of Alzheimer Disease

Starting stage	Duration, time in years (95% CI)	Age 60	Age 70	Age 80
Preclinical AD	Preclinical AD	13 (10.4, 14.9) †	9.9 (8.4, 11.5)	7.6 (5.6, 9.7) †
	Prodromal AD	4.4 (3.7, 4.8)	4.0 (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, 3.3)	1.7 (1.1, 2.4) §
	Total duration	24.1 (21.8, 25.4)	19.5 (17.3, 20.8)	15.0 (11.0, 16.9)
Prodromal AD	Preclinical AD	3.2 (2.2, 4.3) ‡	1.6 (1.1, 2.1)	0.7 (0.4, 1.2) §
	Prodromal AD	4.6 (4.0, 5.3)	4.4 (3.9, 4.8)	4.0 (3.4, 4.7)
	Mild AD dementia	4.5 (4.0, 4.9) ‡	3.9 (3.5, 4.2)	3.0 (2.5, 3.4) §
	Moderate AD dementia	4.9 (4.2, 5.5) §	3.9 (3.3, 4.5)	2.7 (2.2, 3.5) §
	Total duration	17.2 (15.8, 18.3)	13.6 (12.7, 14.5)	10.3 (9.3, 11.5)
Mild AD dementia	Mild AD dementia	5.0 (4.3, 5.7)†	4.3 (4.0, 4.7)	3.6 (3.2, 3.9) §
	Moderate AD dementia	6.0 (5.1, 6.7) ‡	4.8 (4.2, 5.5)	3.6 (3.0, 4.5) §
	Total duration	10.9 (10.1, 11.8)	9.0 (8.4, 9.7)	7.1 (6.4, 7.9)
Moderate AD dementia	Moderate AD dementia	6.5 (5.4, 7.5) ‡	5.2 (4.0, 6.0)	4.1 (3.5, 5.1) ‡

Estimates based on model including age as covariate (Model 1 in suppl. table B.2). Moderate AD dementia = Moderate to severe AD dementia. Stage estimates significantly different from estimates at age 70: * p<0.05 † p<0.01; ‡ p<0.001; § p<0.0001.

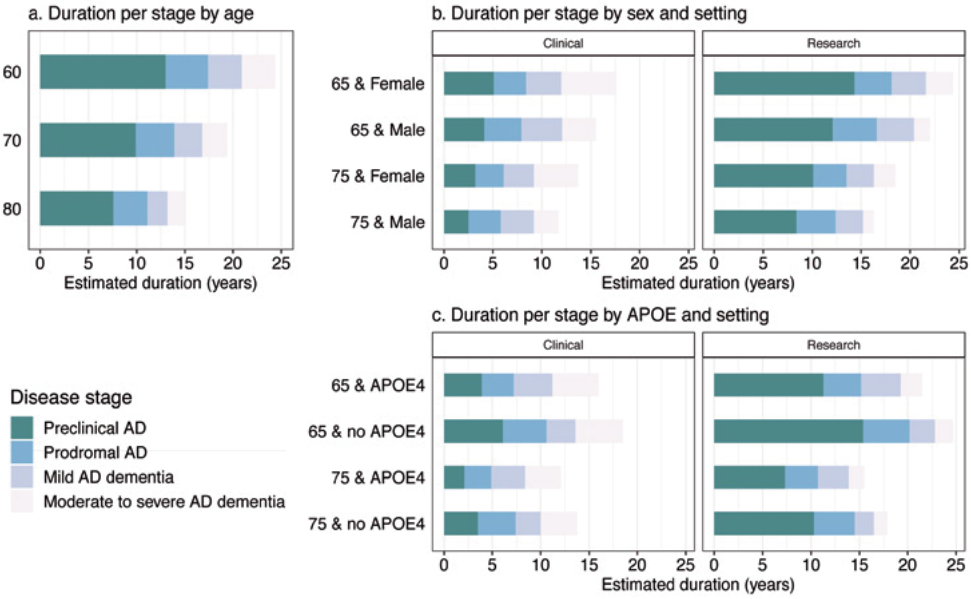

Figure 2 Estimated Stage-specific Duration for Starting Stage Preclinical AD
The panels show the predicted time spend in each stage stacked and stratified for (a) age (model 1); for (b) age, sex, and setting (model 3); and for (c) age, *APOE* genotype, and setting (model 4). Models include age as continues, and (b) sex or (c) *APOE*, and setting as dichotomous covariates. The age refers to the starting stage with preclinical AD and the estimated duration the predicted duration in the subsequent stages in years. The 95% confidence intervals and p-values for estimate comparison can be found for (a) in table 2, for panel (b) in suppl. table B.3, and for panel (c) in suppl. table B.4)

3.3 *APOE* effect

APOE ε4 carriers had, compared to non-carriers, 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]). When compared to a non-carrier, an *APOE* ε4 carrier aged 70 in the clinical setting had a 1.6 years (95% CI, 0.4-3.3; p=0.0295) shorter estimated preclinical AD stage duration, and 1.1 years (95% CI, 0.3-2.1; p=0.0110) shorter prodromal AD stage duration, but 1.0 year (95% CI, 0.3-1.8; p=0.0050) longer mild dementia stage duration (Suppl. table B.4). Figure 2C shows how the total predicted disease duration ranged from 12 to 25 years depending on *APOE* ε4 genotype, age and setting.

3.4 Tau effect

As normal CSF tTau 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 tTau showed a trend for an increased progression rate from preclinical to prodromal AD (HR=1.49 [95% CI, 0.95-2.35]). In prodromal AD, abnormal tau associated with a 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]). The estimated preclinical AD stage was shortened by around 3 years and the prodromal AD stage by around 2.5 years (Table 3). There was no association of baseline abnormal tTau with the duration of the dementia stages.

Table 3 Estimated stage-specific duration stratified for baseline CSF total tau by setting at age 70 years

		Clinical setting			Research setting		
Starting stage	Duration, in years (95% CI)	Tau normal	Tau abnormal	Difference (95% CI; p-value)	Tau normal	Tau abnormal	Difference (95% CI; p-value)
Preclinical AD	Preclinical AD	5.6 (3.7, 8.9)	3 (1.9, 4.3)	2.6 (0.7, 5.5; p=0.034)	11.6 (8.3, 14.3)	7.7 (5.6, 9.9)	3.7 (0.4, 7.3; p=0.033)
Prodromal AD	Prodromal AD	5.4 (4.0, 7.0)	3 (2.3, 3.7)	2.4 (1.2, 3.7; p=0.0002)	6.8 (5.5, 8.1)	3.9 (3.3, 4.6)	2.9 (1.4, 4.2; p=0.0001)
Mild AD dementia	Mild AD dementia	4.4 (3.2, 5.9)	3.6 (2.9, 4.4)	0.8 (-0.4, 2.2; p=0.230)	6.4 (4.7, 7.9)	5.4 (4.2, 6.5)	1.1 (-0.5, 2.7; p=0.197)
Moderate AD dementia	Moderate AD dementia	4.9 (3.1, 7.7)	5.9 (4.1, 8.7)	-0.9 (-3.0,1.6; p=0.439)	2.8 (1.8, 4.1)	3.5 (2.5, 4.7)	-0.6 (-2.0, 1.0; p=0.438)

Tau = baseline CSF total tau. Abbreviations: Moderate AD = moderate to severe AD. Estimates based on model including age as continues and baseline CSF tTau and setting as dichotomous covariates (Model 5 in suppl. table B.2).

3.5 Sensitivity analyses

Consecutively removing each of the cohorts did not affect the estimates (Suppl. table B.6). When all variables were combined in one model, most estimates remained unchanged. In the additional analysis of the same models in the subset of individuals with all covariates (n=1518, see Suppl. Table B.8), the effects were similar. Varying the mortality assumptions for unknown mortality dates of those who died, did not change the results.

4 Discussion

We estimated the duration of the preclinical, prodromal, mild dementia, and moderate dementia stages of AD using a multi-state model. Depending on age, sex, *APOE* genotype, baseline CSF tTau and setting, the total disease duration varied between 12 and 25 years, the preclinical stage between 2 and 15, the prodromal stage between 3 to 7, mild AD dementia stage between 2 and 6 and moderate AD dementia stage between 1 and 7 years.

4.1 Effect of age

Age had the strongest effect on the duration of the preclinical and dementia stages, which could be explained by higher progression and mortality rates. The decrease of disease duration of the preclinical AD stage could also be due to a reduction in resilience to AD pathology at higher age, for example due to co-morbid brain disorders, resulting in a faster clinical progression [38]. Alternatively, older individuals may have spent a longer period in the preclinical AD stage before inclusion in the study. Our estimated duration of the combined preclinical and prodromal stage for a 70-year-old (17 years) was very similar to the estimated duration of 17 years pre-dementia AD based on differential equation modeling of the amyloid accumulation rate in individuals aged 72 years on average [21].

4.2 Effect of setting

The shorter duration of the preclinical and prodromal stage in the clinical compared to the research setting could be explained by the fact that individuals who present in a clinical setting are in a more advanced stage of the disease. An alternative explanation is that individuals who present in a clinical setting have a more aggressive disease form of the disease, whereas those with a slower progressive variant would be picked up in the research setting [39]. The estimated differences between settings may be underestimated in the current study, as part of the individuals from the AIBL and ADNI research cohorts were recruited in memory clinics. The effects of setting on disease progression are consistent with other AD studies [40, 41].

4.3 Effect of *APOE* genotype

The shorter age-specific duration of the preclinical stage in *APOE* ε4 carriers is consistent with the observed earlier onset of dementia due to AD in epidemiological studies and the faster cognitive decline of *APOE* ε4 carriers with preclinical AD in research studies [11, 42-44]. While the prodromal stage was shorter in *APOE* ε4 carriers, the dementia stage was longer which would imply that the total symptomatic disease duration is similar, but differently divided over the stages. These findings are important for clinical trials. For example, exclusion of ε4 carriers during a trial, what happened in the high-dose group of the BAN2401 trial, may affect rate of progression and possibly the power of the study [45].

4.4 Effect of sex

The dementia stage duration was longer in women, which was driven by lower mortality in this group. The study did not reveal significant sex differences in the duration of preclinical and prodromal AD stages.

4.5 Effect of tau

The presence of increased CSF tTau was associated with a shorter pre-dementia disease duration, which confirms that increased tau is associated with faster disease progression. Unlike previous studies, no effect of tau on mortality and duration of the AD dementia stage were found, which may be explained by dichotomization of CSF tTau in our analysis [16, 17].

4.6 Duration and mortality

The estimation of total disease duration estimates were in some cases longer than the residual life expectancies of population data [46]. For example, the residual life expectancy at age 80 was reported to be 8-10 years in the USA and Australia (data from 2010-2012), while in our study this ranged from 4 years for those with moderate AD to 15 years for individuals with preclinical AD. One explanation for the longer duration is that we may have overestimated disease duration because mortality had not been checked systematically in all studies. On the other hand, mortality rates in our study cohorts may also be lower because both volunteers participating in studies and memory clinic patients may be healthier at study entry than individuals not participating in research or attending memory clinics.

4.7 Strengths and limitations

A strength of the study is the large sample of participants with amyloid accumulation. The multi-state model approach is another strength, because it enabled the incorporation of multiple clinical stages, including fluctuations between stage, and the mortality risk in a data driven manner. A limitation of the modeling approach is the underlying assumption 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 addressed by taking age as the time-dependent covariate, which has been applied before to overcome this issue [22, 47]. To estimate the disease duration, we had to combine data of multiple cohorts across the disease spectrum. As such, the sample consisted of over 3000 individuals, still not all the effects were estimable. Combining cohort data leads to heterogeneity, i.e. due to different application of diagnostic criteria, cognitive testing and amyloid status. Another limitation was that amyloid status and *APOE* genotype were unknown for AD-type dementia patients of the ICTUS study, but the sensitivity analysis without the ICTUS, yielded very similar results. Additionally, we used the old criteria for the preclinical AD definition, while the recent research criteria also require tau

positivity [8]. Finally, our sample is not representative of the general population, but may be representative of the patients who physicians need to inform, and volunteers that participate in clinical trials.

4.8 Implications

Our estimates are of practical use to clinicians needing to provide prognostic information to research participants and patients. For instance, in a research study with disclosure of abnormal amyloid status, these estimates can give an indication of the prognosis, often asked for by the trial participants before joining the study. The estimates of AD duration are also useful to define target populations for trials. Furthermore, these estimates can be used to indicate how a preventive treatment in the early stage of the disease could impact total disease duration.

4.9. Conclusion

We provided age-specific disease estimates of the duration of AD, including the long pre-dementia stage, according to setting, sex, *APOE* genotype, and presence of tau pathology. Our findings will be useful to provide patients a prognosis, to inform clinical trial design, and can help to model how interventions in early stage AD may influence long-term outcome.

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Alzheimer Disease Neuroimaging Initiative refers to: Data used in preparation of this article were obtained from the Alzheimer 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 Research Group refers to: https://aibl.csiro.au/about/aibl-research-team
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Declarations

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Supplemental data Chapter 2.1

Supplementary file A. Cohort Information

Table A1 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.[4,5]	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 [4,5]	Cognitive test score <1.5 SD, dementia criteria not met.	Winblad criteria[5]	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 $A\beta_{42}$ below 640 ng/L on the Innotest assay.[2]	Positive on amyloid PET scans by cut-offs were for PiB 1.5 SUVR for Florbetapir 1.11[1] SUVR or CSF $A\beta_{42}$ below $A\beta_{42}$ 192 ng/L of the Luminex assay[1,3]	Positive on amyloid PET PIB SUVR > 1.5	CSF $A\beta_{42}$ below 550 ng/L on the Innotest assay.	CSF $A\beta_{42}$ below 640 ng/L cut-off on Innotest assay.	No amyloid measures available
Tau pathology measures	Above CSF tTau> 375 pg/ml on the Innotest assay.	Above CSF tTau> 92 pg/ml on the Luminex assay	NA	Above CSF tTau> 375 pg/ml on the Innotest assay.	Above CSF tTtau> 375 pg/ml on the Innotest assay.	NA

Table A2 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=1232)
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	1066
Moderate to severe AD dementia, No.	64	1	3	0	0	166
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)	77 (7)
Female, %	50	45	51	46	100	65

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.

Table A3 Total amyloid positive participants and numbers excluded by cohort

	ADC	ADNI	AIBL	DESCRIPA	Gothenburg	ICTUS
Amyloid positive	751	882	418	101	23	n/a
After removal duplicate cases of ADC or no Dx	n/a	n/a	418	83	n/a	1301
N included with FU	751	854	336	72	23	1232

For ADNI number of individuals is at download date. ADC is a clinical database, which was recently updated, so numbers cannot be traced back

Table A4 Overview characteristics included versus not included due to no follow-up by cohort and baseline diagnosis

		CN		MCI		Dementia	
		No follow-up	With follow-up	No follow-up	With follow-up	No follow-up	With follow-up
ADNI	N	2	180	11	449	15	225
	Age	75.3 (1.1)	74.8 (6.0)	72.0 (9.1)	73.3 (7.2)	77.8 (9.9)	74.2 (7.9)
	Female, N (%)	2 (100%)	101 (56%)	6 (55%)	185 (41%)	6 (40%)	97 (43%)
	MMSE	29.5 (0.7)	29.0 (1.2)	27.3 (2.3)	27.5 (1.8)	22.9 (2.1)	23.3 (2.0)
AIBL	N	24	191	35	73	23	72
	Age, mean (SD)	71 (4.5)	73.4 (7.0)	73.3 (5.8)	76 (6.4)	75.7 (7.7)	73.4 (8.1)
	Female, N (%)	13	94	13	35	10	41
	MMSE, mean (SD)	28.6 (1.1)	28.6 (1.3)	26.3 (2.5)	26.6 (2.3)	20.7 (5.2)	20.8 (4.9)
DESCRIPA	N	2	23	9	49	n/a	n/a
	Age, mean (SD)	71 (6)	69 (9)	71 (8)	70 (8)	n/a	n/a
	Female, N (%)	0 (0%)	14 (61%)	5 (56%)	19 (39%)	n/a	n/a
	MMSE, mean (SD)	28.5 (0.7)	28.7 (1.3)	26.0 (2.5)	26.5 (2.8)	n/a	n/a
ICTUS	N	n/a	n/a	n/a	n/a	69	1232
	Age	n/a	n/a	n/a	n/a	75.5 (7.7)	76.7 (7.4)
	Female, N (%)	n/a	n/a	n/a	n/a	52 (75%)	802 (65%)
	MMSE	n/a	n/a	n/a	n/a	19.8 (4.2)	20.4 (4.0)

Not relevant for ADC and Gothenburg, because all had follow-up data.

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).

References supplement A

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Supplement B.
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). The multistate model was fit with the R-package msm (Jackson, 2011). After determining the transition rates, 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. These calculations were done with the R-package created by Ardo van den Hout called Estimating Life-Expectancies for interval censored data (ELECT) (van den Hout 2017, Jackson 2011). P-values of differences of the duration estimates between covariates specified in a model were obtained with the same software. More specifically each of the simulations were subtracted between two groups of a fitted model (i.e. male vs female) to derive a 95% confidence interval of the difference, and then calculate the p-value of the estimate. The same seed was set for all simulations to assure the same samples were drawn from the same multivariate distribution. 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.

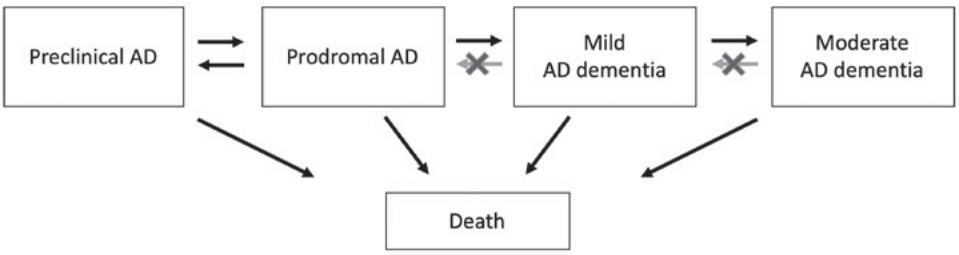

Figure B.1 Five stage multistate model

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 B1). 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 0.043 (95% CI, 0.037-0.049) of true state mild AD being misclassified as moderate to severe AD dementia. Few participants with preclinical or prodromal AD received during follow-up a clinical diagnosis of non-AD dementia at follow-up (n=10), and were classified as having mild or moderate to severe dementia based on the global CDR score.

Specifics of data

Table B.1a 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 B.1b-d present the number observations at each moment in time, the number of observations per individual and the number of observations per stage.

Basic model specifications

The baseline estimates (transition rates) 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 B.2 below. Here the transition rates are defined for age in years. Based on these models, we estimated the duration of stages in Table 2 according to age. In the multistate model the rate for transitioning out of a state can be based on more than one rate. For instance the rate for moving from preclinical AD is based on the rates of preclinical AD to prodromal AD and of preclinical AD to death. In this case, the rate for preclinical AD to prodromal AD should not be interpreted in isolation. Interpretation of a fitted model is typically done using hazard ratios, as presented in the manuscript.

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

To / From	CN	MCI	Mild AD dementia	Moderate AD dementia	Death	End of follow-up
CN	1094	105	9	0	13	70
MCI	72	1819	344	11	31	133
Mild AD dementia	0	17	3787	684	187	620
Moderate AD dementia	0	0	124	782	135	192

Table B.1b Number of observations per follow-up time
Table B.1c Number of observations per individual
Table B.1d Number of observations per stage

B.1b

Follow-up, y	0	<0.3	0.5	1	2	3	4	5	6	7	8	9	10-20
Observations, No.	3268	20	2071	2381	3228	1034	535	508	190	100	80	35	38

B.1c

Observations, No.	2	3	4	5	6	7	8	9	10	11	12	13
Participants, No.	658	497	813	870	213	107	41	20	17	17	8	7

B.1d

Stage	CN	MCI	Mild AD dementia	Moderate AD dementia	Death	Last known alive, diagnosis unknown
Observations, No.	1604	2670	6131	1711	357	1015

Models with covariates sex and setting

We build up the model by adding the effects setting and then of sex, shown in Table B.2, model 2 and 3. 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 3. The others were omitted.

Model with APOE

We next performed the analysis with *APOE* ε4 as predictor (Table B.2, model 4). In the subset of individuals with *APOE* data (n=1984) 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 B.5a and the prediction of the age only model in table B.6a. The effects of the covariates on death in the preclinical, prodromal and mild AD dementia stage were again omitted because they were not estimable. Model 4 with age, *APOE* and setting was used to generate the estimates with starting stage preclinical AD in Figure 2 and Table B.4.

Model with CSF total tau

We next performed the analysis with baseline CSF total tau as predictor (Table B.2, model 5). In the subset of individuals with baseline CSF total tau (n=1563) data (table B.5a), the effect of age and sex, setting on stage transitions were similar to those in the full dataset. The confidence intervals were wider, and the effect of age and sex on mild AD dementia to moderate AD dementia lost significance. The sample demographics are shown in table B.5b and the prediction of the age only model in table B.6b. Model 5 with age, setting and tau was used to generate the estimates in Table 3. Model 6 includes all covariates and was part of the sensitivity analysis showing similar estimates (Table B.2).

Table B.3a Estimated stage-specific duration for starting stage preclinical AD stratified by sex and setting

Duration in years (CI, 95%)	Age 65 Clinical setting		Age 65 Research setting		Age 75 Clinical setting		Age 75 Research setting	
	Female	Male	Female	Male	Female	Male	Female	Male
Preclinical AD	5.1 (3.6-7.3)	4.1 (3-5.8)	14.3 (11.8-16.8)	12.1 (9.8-14.3)	3.2 (2-5.1)	2.5 (1.6-3.8)	10.1 (7.9-12.4)	8.4 (6.6-10.4)
Prodromal AD	3.3 (2.6-4.1)	3.8 (3-4.6)	3.8 (3-4.5)	4.5 (3.8-5.2)	2.9 (2.2-3.8)	3.3 (2.6-4.3)	3.4 (2.5-4.2)	4.0 (3-4.8)
Mild AD dementia	3.6 (3.1-3.9)	4.2 (3.6-4.7)	3.5 (2.7-4.1)	3.8 (3-4.5)	3.1 (2.6-3.5)	3.4 (2.8-3.9)	2.8 (1.9-3.6)	2.8 (2.1-3.7)
Moderate AD dementia	5.6 (4.5-6.8)	3.4* (2.7-4)	2.8 (2-3.7)	1.6* (1.1-2.1)	4.5 (3.3-5.7)	2.5* (1.8-3.3)	2.2 (1.3-3)	1.1* (0.7-1.5)
Total duration	18 (16-20)	16 (14-17)	24 (22-26)	22 (20-24)	14 (12-15)	12 (11-13)	18 (15-20)	16 (14-18)

Table B.2 All six models with baseline transition rates and hazard ratios (HR)

	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 moderate AD dementia	Mild AD dementia to death	Moderate AD dementia to death
Model 1 AGE								
Transition rate, at age 70	0.083 (0.066,0.103)	0.002 (0.001,0.010)	0.049 (0.039, 0.062)	0.199 (0.176,0.223)	0.004 (0.001,0.011)	0.200 (0.181,0.220)	0.004 (0.001,0.014)	0.164 (0.140,0.191)
HR Age, per year increase	1.027 (1.001,1.053)	1.057 (0.897,1.245)	0.951 (0.923,0.979)	1.004 (0.990,1.018)	1.126 (1.027,1.240)	1.011 (1.0001,1.022)	1.163 (1.068,1.268)	1.024 (1.010,1.038)
Model 2 AGE/SETTING								
Transition rate, at age 70	0.060 (0.046, 0.078)	0.003 (0.001,0.010)	0.0407 (0.0300,0.05)	0.1783 (0.1538,0.2068)	0.003 (0.001,0.011)	0.151 (0.125, 0.182)	0.005 (0.002, 0.015)	0.206 (0.1548, 0.274)
HR Age, per year increase	1.047 (1.020,1.073)	1.049 (0.894,1.230)	0.963 (0.933,0.994)	1.011 (0.996,1.027)	1.128 (1.024,1.243)	1.012 (1.001,1.022)	1.148 (1.065,1.238)	1.022 (1.008,1.036)
HR Clinic setting (ref=research setting)	4.832 (3.106,7.519)	-	2.132 (1.259,3.61)	1.450 (1.114,1.887)	-	1.446 (1.188,1.760)	-	0.750 (0.554,1.014)
Model 3 AGE/SEX/SETTING								
Transition rate, at age 70	0.0682 (0.049,0.094)	0.003 (0.001,0.010)	0.040 (0.027,0.058)	0.166 (0.138,0.199)	0.003 (0.001,0.011)	0.137 (0.111,0.168)	0.005 (0.001,0.022)	0.263 (0.193,0.357)
HR Age, per year increase	1.046 (1.020,1.074)	1.054 (0.903,1.231)	0.965 (0.934,0.997)	1.013 (0.998,1.029)	1.127 (1.020,1.245)	1.011 (1.001,1.023)	1.164 (1.067,1.227)	1.025 (1.010,1.040)
HR Female (ref=male)	0.769 (0.534,1.107)	-	1.028 (0.639,1.651)	1.154 (0.930,1.431)	-	1.237 (1.039,1.473)	0.446 (0.169,1.174)	0.602 (0.456,0.795)
Model 4 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)
HR 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)

Clinic setting (ref=research setting)	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 5 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)
HR 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)
HR Abnormal baseline CSF tau (ref=normal baseline CSF tau)	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)
Clinic setting (ref=research setting)	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 6 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)
HR 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)
HR Female (ref=male)	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)
HR *APOE* ε4 carrier (ref=non-carrier)	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)
HR Abnormal baseline CSF tau (ref=normal baseline CSF tau)	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)
HR Clinic setting (ref=research setting)	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)
HR Clinic setting (ref=research setting)	4.403 (2.793,6.943)	-	1.975 (1.150,3.389)	1.477 (1.134,1.924)	-	1.410 (1.158,1.718)	-	0.771 (0.570,1.045)

Hazard ratios that are different from 1 in bold. Moderate = moderate to severe. ' - ' = the HR was not estimable.

Table B.3b P-values and estimated difference in duration

Difference in years (CI, 95%)	Age 65 Clinical setting Female vs male	p-value	Age 65 Research setting Female vs male	p-value	Age 75 Clinical setting Female vs male	p-value	Age 75 Research setting Female vs male	p-value
Preclinical AD	0.97 (-0.41-2.47)	0.1880	2.13 (-0.83- 5.25)	0.1700	0.67 (-0.27- 1.78)	0.2028	1.68 (-0.53- 4.25)	0.1692
Prodromal AD	-0.53 (-1.28- 0.19)	0.1577	-0.74 (-1.65- 0.03)	0.0842	-0.45 (-1.07- 0.16)	0.1530	-0.63 (-1.38- 0.02)	0.0802
Mild AD dementia	-0.6 (-1.21- 0.04)	0.0590	-0.33 (-1.23- 0.47)	0.4501	-0.28 (-0.86- 0.24)	0.3274	0 (-0.82- 0.69)	0.9911
Moderate AD dementia	2.27 (1.14- 3.37)	0.0001	1.24 (0.54- 1.91)	0.0004	1.99 (1.1- 2.93)	<0.0001	1.06 (0.44- 1.65)	0.0006

Abbreviations: Moderate AD dementia = moderate to severe AD dementia. Model includes age as continues and sex and setting as dichotomous covariates. Based on model 4 in table B.2. Significant difference between estimates between sex, same age and setting: *p<0.0. P-values based on confidence intervals of differences for each stratification based on 500 simulation with the same seed.

Table B.4a Estimated stage-specific duration for starting stage preclinical AD stratified by *APOE* and setting

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	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	18 (16-21)	16 (14-18)	25 (22-26)	22 (20-23)	14 (12-16)	12 (10-14)	18 (15-20)	16 (14-18)

Table B.4b P-values and estimated difference in duration

Difference in years (CI, 95%)	Age 65 Clinical setting No *APOE* ε4 vs *APOE*	p-value	Age 65 Research setting No *APOE* ε4 vs *APOE*	p-value	Age 75 Clinical setting No *APOE* ε4 vs *APOE*	p-value	Age 75 Research setting No *APOE* ε4 vs *APOE*	p-value
Preclinical AD	2.08 (0.53- 4.06)	0.0210	3.97 (0.98- 6.72)	0.0067	1.26 (0.29- 2.67)	0.0383	2.96 (0.69- 5.08)	0.0083
Prodromal AD	1.24 (0.33- 2.26)	0.0117	0.93 (-0.11- 1.90)	0.0698	1.09 (0.31- 1.96)	0.0100	0.81 (-0.13-1.73)	0.0889
Mild AD dementia	-1.06 (-1.86- -0.32)	0.0070	-1.56 (-2.33- -0.79)	0.0001	-0.94 (-1.56- -0.34)	0.0025	-1.21 (-1.77- -0.64)	<0.0001
Moderate AD dementia	0.15 (-1.35- 2.03)	0.8608	-0.27 (-0.99- 0.66)	0.5195	0.14 (-1.11- 1.62)	0.8437	-0.19 (-0.78-0.49)	0.5669

Abbreviations: Moderate AD dementia = moderate to severe AD dementia. Model includes age as continues and *APOE* ε4 and setting as dichotomous covariates. Based on model 5 in table B.2. Significant difference between estimates between genotype, same age and setting: *p<0.05. P-values based on confidence intervals of differences for each stratification based on 500 simulation with the same seed.

Table B.5a Baseline characteristics of participants with *APOE* data classified by baseline AD stage

	Preclinical AD (N = 431)	Prodromal AD (N = 709)	Mild AD dementia (N= 776)	Moderate 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

Table B.5b Baseline characteristics of participants with baseline CSF tau classified by baseline AD stage

	Preclinical AD (N = 231)	Prodromal AD (N = 607)	Mild AD dementia (N= 668)	Moderate 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

^ Available in subset of cohorts. Moderate AD dementia = moderate to severe AD dementia.

Table B.6a 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 (6.9-12)	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)

Models with age as covariate. Moderate AD dementia = moderate to severe AD dementia. *All estimates have overlapping confidence intervals with confidence intervals based on the full dataset Table 2. In these subsets no ICTUS data, i.e. only confirmed amyloid positive individuals. ^In this subset no ICTUS and AIBL data.

Table B.6b Predicted stage-specific disease duration – subsequently removing cohorts

		Subset without ADNI (n=2414)			Subset without ADC (n=2517)			Subset without DESCRIPA (n=3196)			Subset without Gothenburg (n=3245)		
Starting stage	Duration, time in years (CI, 95%)	Age 60	Age 70	Age 80	Age 60	Age 70	Age 80	Age 60	Age 70	Age 80	Age 60	Age 70	Age 80
Preclinical AD	Preclinical AD	12.9 (10-15.2)	11 (8.5-14)	8.6 (5.5-13)	15 (12-17)	10.4 (9-12)	7.1 (5.3-8.9)	13.6 (11-15.5)	10.2 (8.7-12)	7.6 (5.6-9.7)	13 (11-14.8)	9.9 (8.4-11)	7.6 (5.7-9.5)
	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 (3.2-4.7)	3.6 (2.4-4.5)	4.4 (3.6-4.9)	4.1 (3.3-4.7)	3.6 (2.5-4.6)	4.4 (3.7-4.8)	4 (3.3-4.7)	3.5 (2.4-4.5)
	Mild AD dementia	3.5 (2.8-3.8)	2.7 (1.8-3.2)	1.7 (0.8-2.4)	3.4 (2.8-3.8)	2.7 (2.2-3.1)	2 (1.3-2.4)	3.4 (2.9-3.7)	2.8 (2.3-3.2)	2 (1.3-2.5)	3.5 (3.1-3.8)	2.9 (2.4-3.3)	2 (1.3-2.6)
	Moderate AD dementia	4 (3.1-4.7)	2.9 (1.9-3.7)	1.7 (0.8-2.6)	3.1 (2.5-3.7)	2.6 (1.9-3.1)	1.9 (1.2-2.7)	3.4 (2.8-3.9)	2.6 (2-3.2)	1.7 (1.1-2.4)	3.5 (2.9-4.1)	2.7 (2.1-3.4)	1.7 (1.1-2.4)
Prodromal AD	Preclinical AD	3.8 (2.4-5.3)	2.1 (1.3-3)	1 (0.4-1.9)	4.4 (3.1-6.2)	1.8 (1.4-2.3)	0.7 (0.4-1.1)	2.6 (1.7-3.6)	1.3 (0.9-1.8)	0.6 (0.3-1.1)	3.2 (2.3-4.4)	1.6 (1.2-2.1)	0.7 (0.4-1.1)
	Prodromal AD	3.8 (2.9-4.5)	3.1 (2.6-3.6)	2.5 (1.7-3.2)	4.9 (4-5.7)	4.6 (4.1-5.1)	4.1 (3.4-4.8)	4.7 (4-5.4)	4.5 (4-5)	4.1 (3.5-4.8)	4.6 (4-5.3)	4.4 (3.9-4.9)	4 (3.4-4.7)
	Mild AD dementia	4.3 (3.6-4.7)	3.7 (3.2-4)	3 (2.2-3.4)	5.1 (4.4-5.7)	4 (3.6-4.2)	2.8 (2.4-3.1)	4.5 (4-4.8)	3.9 (3.5-4.2)	2.9 (2.5-3.3)	4.5 (4.1-4.9)	3.9 (3.5-4.2)	3 (2.5-3.4)
	Moderate AD dementia	5.2 (4.2-5.9)	4.3 (3.4-5)	3.2 (2.2-4)	4.5 (3.7-5.2)	3.6 (3.1-4.3)	2.7 (2-3.5)	5 (4.4-5.6)	3.9 (3.3-4.5)	2.7 (2.1-3.4)	4.9 (4.3-5.5)	3.9 (3.3-4.6)	2.7 (2.1-3.4)
Mild AD dementia	Mild AD dementia	4.7 (4-5.3)	4.1 (3.7-4.4)	3.4 (3-3.7)	6.5 (5.4-7.5)	4.8 (4.4-5.2)	3.4 (3.1-3.8)	4.9 (4.3-5.5)	4.3 (3.9-4.6)	3.5 (3.2-3.9)	5 (4.4-5.6)	4.3 (4-4.7)	3.6 (3.2-4)
	Moderate AD dementia	6.3 (5.4-7.2)	5.1 (4.4-5.9)	3.9 (3.2-4.9)	5.8 (4.5-7.2)	4.5 (3.9-5.2)	3.4 (2.8-4.2)	6 (5.2-6.8)	4.8 (4.3-5.4)	3.6 (3-4.4)	6 (5.2-6.8)	4.8 (4.2-5.5)	3.6 (2.9-4.4)
Moderate AD dementia	Moderate AD dementia	6.8 (5.6-7.9)	5.6 (4.8-6.6)	4.5 (3.7-5.7)	6.8 (4.7-9.2)	5.2 (4.2-6.2)	3.9 (3.3-4.8)	6.5 (5.4-7.6)	5.2 (4.6-5.9)	4.2 (3.4-5)	6.5 (5.5-7.6)	5.2 (4.6-6)	4.2 (3.4-5.1)

Moderate AD dementia = moderate to severe AD dementia. Model with age as covariate. *All estimates have overlapping confidence interval with confidence intervals based on the full dataset Table 2, model 2 in table B2.

Table B.7a Estimated difference in duration and p-values between setting

Starting stage	Duration, time in years (CI, 95%)	Age 60 Research vs clinical setting	p-value	Age 70 Research vs clinical setting	p-value	Age 80 Research vs clinical setting	p-value
Preclinical AD	Preclinical AD	10.08 (7.45,12.63)	<0.0001	7.7 (5.87,9.88)	<0.0001	5.62 (3.91,7.52)	<0.0001
	Prodromal AD	0.61 (-0.47,1.51)	0.2287	0.58 (-0.44,1.41)	0.2253	0.46 (-0.58,1.21)	0.3167
	Mild AD dementia	-0.14 (-0.92,0.59)	0.7351	-0.25 (-0.9,0.39)	0.4580	-0.38 (-0.98,0.15)	0.1797
	Moderate AD dementia	-2.62 (-3.58,-1.66)	<0.0001	-2.19 (-3.04,-1.4)	<0.0001	-1.70 (-2.48,-1.11)	<0.0001
Prodromal AD	Preclinical AD	1.6 (0.31,3.14)	0.0268	0.82 (0.21,1.46)	0.0099	0.39 (0.1,0.67)	0.0075
	Prodromal AD	1.5 (0.4,2.53)	0.0059	1.36 (0.4,2.22)	0.0035	1.14 (0.34,1.82)	0.0026
	Mild AD dementia	1.22 (0.36,2.16)	0.0079	0.97 (0.29,1.7)	0.0068	0.57 (0.1,1.17)	0.0385
	Moderate AD dementia	-1.86 (-2.95,-0.64)	0.0017	-1.55 (-2.59,-0.58)	0.0026	-1.25 (-2.06,-0.5)	0.0017
Mild AD dementia	Mild AD dementia	1.90 (0.89,3.05)	<0.0001	1.57 (0.75,2.48)	0.0001	1.13 (0.57,1.8)	0.0010
	Moderate AD dementia	-1.67 (-3.02,-0.18)	0.0208	-1.42 (-2.6,-0.22)	0.0196	-1.19 (-2.16,-0.23)	0.0161
Moderate AD dementia	Moderate AD dementia	-1.59 (-3.11,0.16)	0.0569	-1.33 (-2.66,0.14)	0.0635	-1.10 (-2.28,0.12)	0.0713

Moderate AD dementia = moderate to severe AD dementia. Model includes age as continues and setting as dichotomous covariates. Based on model 2 in table B.2. P-values based on confidence intervals of differences based on 500 simulation with the same seed. To interpret as positive is longer for research and negative is longer for the clinical setting.

Table B.7b Estimated duration by setting

Starting stage	Duration, time in years (CI, 95%)	Age 60		Age 70		Age 80	
	Setting	Research	Clinical	Research	Clinical	Research	Clinical
Preclinical AD	Preclinical AD	15.6 (12.9-17.5)	5.8 (4.1-7.6)	11 (9.5-12.6)	3.5 (2.5-5)	7.5 (5.8-9.4)	2.1 (1.4-3.3)
	Prodromal AD	4.4 (3.6-5)	3.8 (3.1-4.5)	4 (3.2-4.6)	3.4 (2.8-4.3)	3.5 (2.3-4.3)	3 (2.2-4)
	Mild AD dementia	3.9 (3.2-4.6)	4.1 (3.6-4.5)	3.3 (2.6-3.9)	3.5 (3.1-3.9)	2.3 (1.6-3)	2.7 (2.2-3.2)
	Moderate AD dementia	2.4 (1.8-3.1)	5.1 (4.3-6)	1.9 (1.4-2.6)	4.2 (3.5-5.2)	1.3 (0.8-1.9)	3.1 (2.4-4)
	Total duration	26 (23-28)	19 (17-20)	20 (18-22)	15 (13-16)	15 (12-17)	11 (10-12)
Prodromal AD	Preclinical AD	3.2 (2.2-4.6)	1.6 (1-2.5)	1.5 (1.1-2.1)	0.7 (0.4-1.2)	0.7 (0.4-1.1)	0.3 (0.1-0.6)
	Prodromal AD	5.3 (4.3-6.2)	3.8 (3-4.6)	4.7 (4.2-5.2)	3.4 (2.7-4.2)	4 (3.5-4.7)	2.9 (2.2-3.9)
	Mild AD dementia	5.6 (4.7-6.4)	4.4 (3.9-4.9)	4.8 (4.2-5.4)	3.8 (3.5-4.2)	3.5 (2.9-4.1)	3 (2.6-3.4)
	Moderate AD dementia	3.7 (2.9-4.7)	5.7 (4.9-6.6)	2.9 (2.3-3.7)	4.6 (3.9-5.5)	2 (1.5-2.7)	3.4 (2.7-4.4)
	Total duration	18 (16-19)	16 (14-17)	14 (13-15)	13 (12-14)	10 (9-11)	10 (9-11)
Mild AD dementia	Mild AD dementia	6.5 (5.4-7.6)	4.6 (4-5.3)	5.6 (4.8-6.5)	4 (3.6-4.3)	4.4 (3.7-5)	3.2 (2.9-3.6)
	Moderate AD dementia	4.6 (3.6-5.9)	6.4 (5.6-7.4)	3.7 (2.9-4.6)	5.3 (4.5-6.1)	2.7 (2.1-3.6)	4.1 (3.3-5.1)
	Total duration	11 (10-13)	11 (10-12)	9 (8-10)	9 (8-10)	7 (6-8)	7 (6-8)
Moderate AD dementia	Moderate AD dementia	5 (3.7-6.7)	6.8 (5.8-8.2)	4.1 (3.2-5.2)	5.6 (4.8-6.5)	3.3 (2.5-4.3)	4.6 (3.8-5.7)

Moderate AD dementia = moderate to severe AD dementia. Model includes age as continues and setting as dichotomous covariates. Based on model 2 in table B.2. P-values based on confidence intervals of differences based on 500 simulation with the same seed.

Table B.8 All six models with baseline transition rates and hazard ratios, sensitivity analysis in those with complete covariate data (= reduced sample size, n=1518)

Model 1 AGE

	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 moderate AD dementia	Mild AD dementia to death	Moderate AD dementia to death
Main analysis								
Transition rate, at age 70	0.083 (0.066,0.103)	0.002 (0.001,0.010)	0.049 (0.039, 0.062)	0.199 (0.176,0.223)	0.004 (0.001,0.011)	0.200 (0.181,0.220)	0.004 (0.001,0.014)	0.164 (0.140,0.191)
Age, per year increase	1.027 (1.001,1.053)	1.057 (0.897,1.245)	0.951 (0.923,0.979)	1.004 (0.990,1.018)	1.126 (1.027,1.240)	1.011 (1.0001,1.022)	1.163 (1.068,1.268)	1.024 (1.010,1.038)
Sample all variables (n=1518)								
Transition rate, at age 70	0.119 (0.091, 0.155)	0.002 (0.000, 0.017)	0.048 (0.037, 0.062)	0.185 (0.162, 0.211)	0.004 (0.002,0.012)	0.196 (0.171,0.225)	0.001 (0.000, 0.018)	0.178 (0.148,0.214)
Age, per year increase	1.012 (0.980,1.045)	1.104 (0.874,1.393)	0.945 (0.915,0.976)	1.004 (0.988,1.020)	1.115 (1.018,1.220)	0.990 (0.973,1.006)	1.258 (1.083,1.461)	1.030 (1.010,1.051)

Model 2 AGE/SETTING

	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 moderate AD dementia	Mild AD dementia to death	Moderate AD dementia to death
Main analysis								
Transition rate, at age 70	0.060 (0.046, 0.078)	0.003 (0.001,0.010)	0.0407 (0.0300,0.05)	0.1783 (0.1538,0.2068)	0.003 (0.001,0.011)	0.151 (0.125, 0.182)	0.005 (0.002, 0.015)	0.206 (0.1548, 0.274)
Age, per year increase	1.047 (1.020,1.073)	1.049 (0.894,1.230)	0.963 (0.933,0.994)	1.011 (0.996,1.027)	1.128 (1.024,1.243)	1.012 (1.001,1.022)	1.148 (1.065,1.238)	1.022 (1.008,1.036)
Clinic setting (ref=research setting)	4.832 (3.106,7.519)	-	2.132 (1.259,3.61)	1.450 (1.114,1.887)	-	1.446 (1.188,1.760)	-	0.750 (0.554,1.014)
Sample all variables (n=1518)								
Transition rate, at age 70	0.072 (0.050,0.103)	0.002 (0.000,0.018)	0.036 (0.026,0.051)	0.159 (0.135,0.189)	0.004 (0.002,0.012)	0.151 (0.117,0.196)	0.001 (0.000,0.076)	0.175 (0.144,0.211)
Age, per year increase	1.050 (1.016,1.085)	1.097 (0.867,1.388)	0.964 (0.930,0.999)	1.014 (0.997,1.032)	1.116 (1.019,1.222)	1.003 (0.982,1.025)	1.257 (0.995,1.588)	1.030 (1.009,1.052)
Clinic setting (ref=research setting)	4.278 (2.546,7.187)		2.384 (1.346, 4.223)	1.586 (1.191,2.111)		1.568 (1.088, 2.259)		0.493 (0.000,37651)

	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 moderate AD dementia	Mild AD dementia to death	Moderate AD dementia to death
Main analysis								
Transition rate, at age 70	0.0682 (0.049,0.094)	0.003 (0.001,0.010)	0.040 (0.027,0.058)	0.166 (0.138,0.199)	0.003 (0.001,0.011)	0.137 (0.111,0.168)	0.005 (0.001,0.022)	0.263 (0.193,0.357)
Age, per year increase	1.046 (1.020,1.074)	1.054 (0.903,1.231)	0.965 (0.934,0.997)	1.013 (0.998,1.029)	1.127 (1.020,1.245)	1.011 (1.001,1.023)	1.164 (1.067,1.227)	1.025 (1.010,1.040)
Female (ref=male)	0.769 (0.534,1.107)	-	1.028 (0.639,1.651)	1.154 (0.930,1.431)	-	1.237 (1.039,1.473)	0.446 (0.169,1.174)	0.6021 (0.456,0.795)
Clinic setting (ref=research setting)	4.403 (2.793,6.943)	-	1.975 (1.150,3.389)	1.477 (1.134,1.924)	-	1.410 (1.158,1.718)	-	0.771 (0.570,1.045)
Sample all variables (n=1518)								
Transition rate, at age 70	0.098 (0.064,0.150)	0.002 (0.000,0.018)	0.037 (0.024,0.056)	0.153 (0.124,0.188)	0.004 (0.001, 0.012)	0.142 (0.109, 0.186)	0.001 (0.000,0.045)	0.307 (0.205,0.460)
Age, per year increase	1.046 (1.012,1.082)	1.103 (0.883,1.378)	0.964 (0.930,0.9996)	1.015 (0.998,1.033)	1.118 (1.021,1.224)	1.006 (0.987,1.025)	1.268 (1.044,1.539)	1.013 (0.989,1.038)
Female (ref=male)	0.568 (0.365, 0.883)		0.947 (0.561, 1.599)	1.089 (0.851,1.393)		1.146 (0.881,1.491)	0.110 (0.000,31.177)	0.693 (0.486,0.990)
Clinic setting (ref=research setting)	4.125 (2.424,7.020)		2.476 (1.392,4.404)	1.597 (1.199,2.128)		1.605 (1.185,2.173)		0.581 (0.366,0.924)

Model 4 AGE/*APOE*/SETTING

	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 moderate AD dementia	Mild AD dementia to death	Moderate AD dementia to death
Main analysis								
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 carrier (ref=non-carrier)	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)
Clinic setting (ref=research setting)	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)
Sample all variables (n=1518)								
Transition rate, at age 70	0.063 (0.041,0.098)	0.001 (0.000,0.019)	0.037 (0.022,0.060)	0.126 (0.097,0.162)	0.004 (0.001, 0.012)	0.185 (0.136,0.252)	0.001 (0.000,0.028)	0.226 (0.142,0.359)
Age, per year increase	1.053 (1.019,1.088)	1.097 (0.856,1.406)	0.964 (0.930,0.999)	1.019 (1.001,1.037)	1.118 (1.020,1.224)	1.004 (0.986,1.023)	1.303 (1.066,1.593)	1.016 (0.992,1.040)
APOE ε4 carrier (ref=non-carrier)	1.271 (0.804,2.009)		0.973 (0.563,1.683)	1.425 (1.095,1.855)		0.760 (0.577,1.002)		1.192 (0.820,1.732)
Clinic setting (ref=research setting)	4.087 (2.413,6.921)		2.417 (1.364,4.284)	1.546 (1.161,2.059)		1.588 (1.170,2.155)		0.592 (0.374,0.938)

	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 moderate AD dementia	Mild AD dementia to death	Moderate AD dementia to death
Main analysis								
Transition rate, at age 70	0.068 (0.046,0.099)	0.001 (0.000,0.022)	0.049 (0.033,0.071)	0.115 (0.092,0.145)	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)
Abnormal baseline CSF tau (ref=normal baseline CSF tau)	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)
Clinic setting (ref=research setting)	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)
Sample all variables (n=1518)								
Transition rate, at age 70	0.064 (0.044,0.095)	0.001 (0.000,0.020)	0.050 (0.034,0.072)	0.113 (0.090, 0.143)	0.004 (0.001,0.012)	0.134 (0.097,0.186)	0.001 (0.000,0.024)	0.295 (0185,0.469)
Age, per year increase	1.043 (1.008,1.079)	1.080 (0.817,1.428)	0.971 (0.938,1.006)	1.012 (0.994,1.030)	1.115 (1.014,1.226)	1.005 (0.986,1.024)	1.280 (1.072,1.529)	1.015 (0.991,1.039)
Abnormal baseline CSF tau (ref=normal baseline CSF tau)	1.430 (0.908,2.252)		0.387 (0.221,0.680)	1.905 (1.470,2.468)		1.187 (0.870,1.620)		0.832 (0.548,1.265)
Clinic setting (ref=research setting)	3.915 (2.281,6.720)		2.977 (1.643,5.393)	1.386 (1.038,1.850)		1.572 (1.158,2.134)		0.592 (0.373,0.940)

Model 6 subsample with all variables (n=1518) AGE/SEX/*APOE*/ TAU/ SETTING

	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 moderate AD dementia	Mild AD dementia to death	Moderate AD dementia to death
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)
Female (ref=male)	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 carrier (ref=non-carrier)	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)
Abnormal baseline CSF tau (ref=normal baseline CSF tau)	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)
Clinic setting (ref=research setting)	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. Moderate = moderate to severe

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Chapter 2.2

Alzheimer Disease biomarkers may aid in the prognosis of MCI cases initially reverted to normal

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Abstract

OBJECTIVE: To identify potential predictors for outcome in individuals with mild cognitive impairment (MCI) who have reverted to normal cognition (NC).
METHODS: We selected individuals with MCI, who reverted at follow-up to NC, with follow-up after reversion from ADNI. Common clinical markers, AD biomarkers, and neurodegeneration imaging markers were used to compare MCI reverters based on subsequent clinical outcome (i.e. subsequent decline or stable reversion). For independent comparison, findings of the clinical Amsterdam Dementia Cohort are presented.
RESULTS: Seventy-seven (10%) out of 757 individuals with MCI reverted to NC and 61 individuals of these had follow-up data available. After 3.2±2.2 years 16 (24%) progressed to MCI, and 3 (5%) to dementia. Those who declined were older and had a higher amyloid PET burden and higher cerebrospinal fluid (CSF) tau levels.
CONCLUSION: In MCI reverters, abnormal biomarkers for AD pathology are associated with subsequent decline. AD biomarkers may aid in the prognosis of reverting MCI.

1 Introduction

Individuals with mild cognitive impairment (MCI) are at increased risk to develop dementia [1]. Yet, up to 25% of individuals with MCI revert to normal cognition (NC) [2, 3]. Although improved cognition seems to be a positive event, individuals reverting from MCI remain at increased risk to develop dementia compared to NC individuals [1, 4, 5]the Sydney Memory and Ageing Study. RESULTS While prevalence of MCI and different MCI subtypes remains relatively stable across all assessments, reversion from MCI and transitions between different MCI subtypes were common. Up to 46.5% of participants classified with MCI at baseline reverted at some point during follow-up. The majority (83.8%. Timely identification of individuals with a higher risk will increase prognostic certainty for patients and be useful for health care planning.

In individuals with NC and MCI, low memory function, abnormal biomarkers for Alzheimer Disease (AD), and neurodegeneration predict dementia [6, 7]. While MCI reverters deviate from the common clinical trajectory, the same disease processes may be underlying. Our aim was to investigate whether MCI reverters who subsequently showed clinical decline have more abnormal AD markers than MCI reverters who remain stable.

2 Methods

2.1 Participants

Data analyzed were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu, downloaded at 2017/8/9). From the individuals with at least two years clinical follow-up, we selected all individuals with prevalent and incident MCI reverting to NC with additional follow-up after reversion [8]. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The 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 measure progression to MCI and early AD. Next to the primary analyses in ADNI, we selected from the Amsterdam Dementia Cohort (ADC) all MCI reverters with follow-up after reversion. Similar clinical and biomarker assessments are presented for this small, independent clinical sample for illustration purposes only (for cohort and biomarker methods [9]).

2.2 Standard protocol approvals, registrations, and participant consents

All protocols were approved by an ethical review board and participants signed informed consent.

2.3 Clinical markers and *APOE*

All individuals had baseline data on age, sex and education. *APOE* genotype was dichotomized into ε4 carriers and non-carriers. Overall cognitive status was assessed by the MMSE, memory by the Rey Auditory Verbal Learning Test (RAVLT) immediate

(0-75) and delayed total recall (0-15), executive function by the Trial making test (TMT) A and B (seconds) and depressive symptoms by the Geriatric Depression Scale (GDS) (0-15). Subthreshold depression was classified as GDS>4 [10].

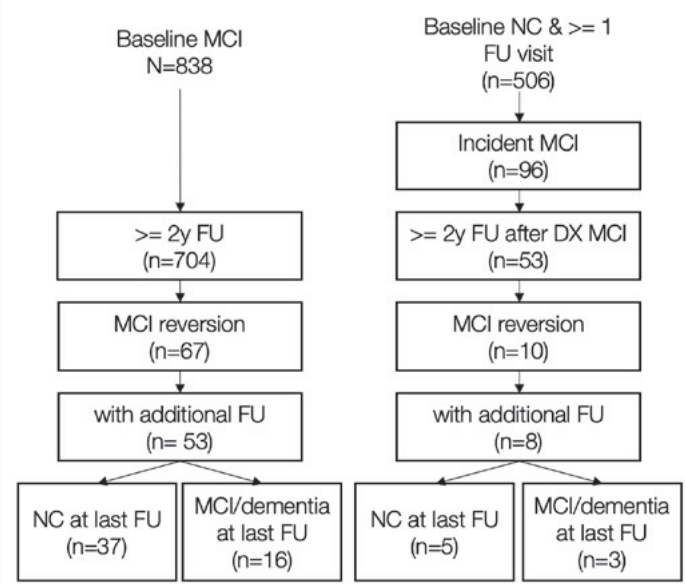

Figure 1 Flow diagram sample selection ADNI
N = number of individuals; MCI = Mild cognitive impairment; NC = cognitively normal; FU= follow-up visit; DX= diagnosis

2.4 Biomarkers of AD and neurodegeneration

We studied CSF amyloid beta 1-42 (Aβ1-42) and total tau (tTau) (Luminex in ADNI [11]; Innotest in ADC [12]), and amyloid PET (Florbetapir and PIB) as markers for AD pathology. PIB scans were harmonized to Florbetapir by: new value=PIB standard uptake value ratio (SUVr)*.67+.15[13]. For imaging markers of neurodegeneration, we studied FDG-PET, hippocampal volume (HV, UCSF in Freesurfer v4.4/v5.1), normalized to total intracranial volume, and white matter hyperintensity volume (WMH [14]2 and the primary goal of ADNI, the lifetime risk for stroke equals and may exceed the risk of AD in some circumstances 3. In addition, MRI evidence of asymptomatic cerebrovascular disease (CVD). Cut points for abnormality for dichotomized analysis in ADNI were: CSF Aβ1-42<192 pg/ml, CSF tTau>93pg/ml, amyloid PET SUVr>1.10, FDG-PET SUVr METAROI<1.21 and raw HV<6732 mm^3 ([11, 12, 15, 16] for procedures and processing). Data collected within one year before or after MCI diagnosis were included.

Table 1 MCI reverters with follow-up of ADNI and ADC

	ADNI MCI reverters				Amsterdam Dementia Cohort MCI reverters	
	Persistent normal cognition (n = 42)	Decline to MCI or dementia (n = 19)	p-value ADNI group comparison	p-value adjusted for age, sex, education, *APOE* ε4	Persistent normal cognition (n = 24)	Decline to MCI or dementia (n = 2)
Baseline characteristics						
Age, y	69 (8)	74 (8)	0.016	NA	65 (7)	71 (7)
Female, %	50%	26%	0.146	NA	29%	100%
Education, ADNI, y ADC, Verhage scale	17.2 (2.6)	16.3 (2.0)	0.095	NA	5 (1.4)	5 (1.4)
APOE E4 carrier, %	38%	32%	0.839	NA	46%	50%
Follow-up						
Total follow-up y, median (IQR)	4 (2.3)	5 (2.5)	0.109	NA	3.0 (1.8)	5.3 (1.6)
Time to reversion y, median (IQR)	1 (1.8)	2 (2)	0.462	NA	1.3 (1.0)	1.8 (0.7)
Follow-up after reversion y, median (IQR)	2 (1.8)	3 (2)	0.265	NA	1.4 (0.9)	3.6 (1.0)
Time to progression after reversion y, median (IQR)	NA	1 (1)	NA	NA	NA	1 (0)
N with > 1 reversion	4	2	>0.99	NA	2	1
Clinical						
MMSE	28.7 (1.4)	28.3 (1.8)	0.573	0.904	27.5 (1.6)	29
RAVLT immediate total recall	43 (11)	47 (12)	0.262	0.002	36 (10)	19
RAVLT delayed total recall	6.6 (4.2)	8.3 (4.6)	0.185	0.002	5.6 (1.6)	3
Trial making test A	31 (10)	34 (11)	0.496	0.700	38 (11)	44 (1)
Trial making test B	72 (24)	80 (31)	0.362	0.973	90 (36)	94 (30)
Geriatric depression scale (GDS)	1.1 (1)	1.6 (2)	0.138	0.018	3.7 (3)	3.5 (2)
GDS > 4, n (%)	2 (5%)	1 (5%)	>0.99	0.508	7 (32%)	1 (50%)

	ADNI MCI reverters				Amsterdam Dementia Cohort MCI reverters	
	Persistent normal cognition (n = 42)	Decline to MCI or dementia (n = 19)	p-value ADNI group comparison	p-value adjusted for age, sex, education, *APOE* ε4	Persistent normal cognition (n = 24)	Decline to MCI or dementia (n = 2)
AD biomarkers						
Amyloid PET, SUVR	1.08 (0.15)	1.21 (0.21)	0.026	0.016	-	-
Amyloid PET, n SUVR > 1.10 (%)	10 (30%)	9 (64%)	0.065	0.018	-	-
Luminex CSF Aβ1-42, pg/mL^	218 (45) ^	190 (65) ^	0.214	0.213	-	-
Innotest CSF Aβ1-42, pg/mL^	-	-			1047 (243)^	780 (5) ^
Abnormal CSF Aβ1-42, n (%)^	9 (31%)	5 (45%)	0.629	0.455	4 (20%)	2 (100%)
Luminex CSF total tau, pg/mL^	53 (17) ^	84 (42) ^	0.042	0.020	-	-
Innotest CSF total tau, pg/mL^	-	-			284 (140) ^	955 (24) ^
Abnormal CSF total tau, n (%)^	0 (0%)	3 (27%)	0.024	0.009	3 (15%)	2 (100%)
Imaging markers of neurodegeneration						
FDG PET METAROI, SUVR	1.34 (0.11)	1.27 (0.14)	0.051	0.458	-	-
FDG PET METAROI, SUVR < 1.21, n (%)	5 (13%)	6 (35%)	0.126	0.627	-	-
Hippocampus/Intracranial volume, cm^3	0.48 (0.07)	0.42 (0.09)	0.092	0.591	-	-
Hippocampus volume < 6673 mm^3, n (%)	6 (27%)	5 (56%)	0.280	0.731	-	-
White matter hyperintensities volume, cm^3	1.80 (2.69)	4.29 (6.24)	0.263	0.054	-	-

Data are mean (SD) unless otherwise specified; Bold = significant level < 0.05; Italic < 0.10; * if no biomarker data was available at the first MCI visit the data within 12 months was used. ^for ADNI: Luminex assay abnormality threshold: CSF Aβ1-42 <192 pg/mL, total tau >93 pg/mL; in ADC Innotest values corrected for upwards drift with abnormality thresholds CSF Aβ1-42 <813 pg/mL; total tau >375 pg/mL; Verhage scale range 1 to 7. MMSE=Mini-mental state examination. RAVLT=Rey auditory verbal learning test. Sample sizes in ADNI: Amyloid PET: n = 47; FDG PET: n = 55; MR hippocampal volumes n = 31; White matter hyperintensities: n = 58; CSF: n = 40. Sample sizes in Amsterdam Dementia Cohort: RAVLT: n=24; GDS: n=24; CSF: n =22.

2.5 Statistical analysis

MCI reverters with NC at last follow-up and MCI reverters with subsequent decline were compared on clinical and biomarkers using Chi-square, Wilcoxon and t-tests when appropriate. We report results unadjusted and adjusted for age, sex, education, and *APOE* ε4 genotype with univariate linear regression models, and scaling of continuous outcomes, to facilitate comparability of effects.

2.6 Data-sharing statement

Data used for this study are available from the corresponding author, upon reasonable request.

3 Results

In ADNI, 757 individuals with prevalent or incident MCI had been followed for at least two years (Figure 1). Of these, 77 (10%) reverted to NC, and 61 (79%) had additional follow-up available. After 3.2±2.2 years (mean±SD) 16 (24%) had converted to MCI, and 3 (5%) to dementia. One individual was excluded, due to missing data.

MCI reverters who showed subsequent clinical decline were on average 5 years older than reverters remaining NC, and had, adjusted for age, sex, education and *APOE*, higher and more often abnormal AD biomarkers (amyloid PET and CSF tTau), less impaired memory and higher GDS scores (Table 1/Figure 2). Follow-up after reversion seemed slightly shorter for stable MCI reverters (p=0.11). Repeating analyses including this covariate did not essentially changed the results (Table S1).

Post-hoc analyses further showed that biomarkers of MCI reverters were on average more similar to NC than non-reverting MCI, except for amyloid, which was more often abnormal in MCI reverters than in NC (Table S2). Still, MCI reverters showed higher clinical progression rates (110/1000 person-years) compared to baseline NC (52/1000 person-years, hazard ratio [95% CI] = 2.3 [1.4-4.0], p=0.002, Table S3/ Figure S1). The biomarker associations with progression were similar for NC and MCI reverters, whereas associations with progression and cognitive test scores were less consistent (Table S4/Figure S2).

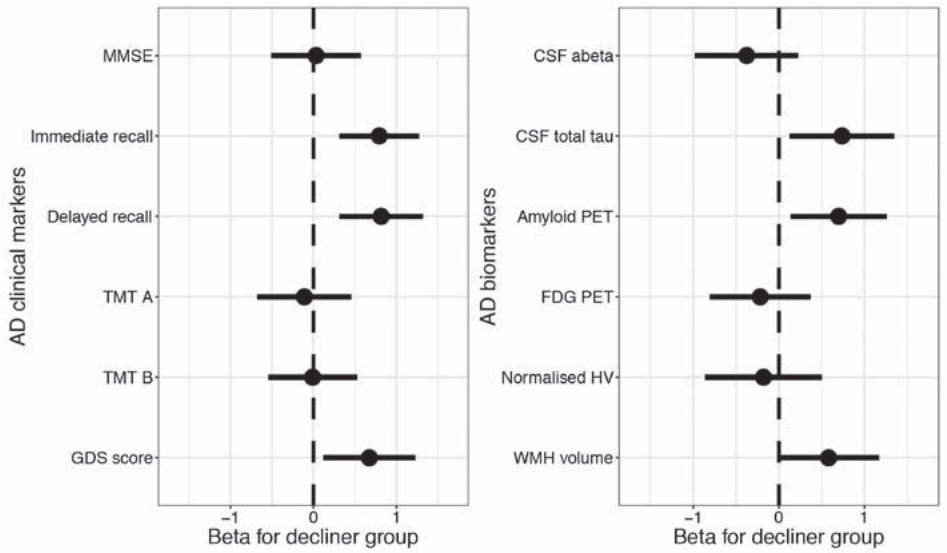

Figure 2 Standardized beta's AD clinical and biomarker for decliner group
Immediate and delayed recall of the RAVLT (Rey auditory verbal learning test); TMT = Trail making test; GDS = Geriatric depression scale; WMH = white matter hyperintensities; HV = hippocampal volume. Models were adjusted for age, sex, education and *APOE* ε4.

3.1 Outcome of MCI reverters in clinical ADC cohort

In the ADC, of 735 patients with MCI and a follow-up visit, 75 (10%) reverted to NC. Twenty-six (35%) patients had 1.6±0.8 years (mean±SD) follow-up available after reversion, after which 24 (92%) remained NC and 2 (8%) had dementia. Small group size precluded formal statistical testing. The two decliners had abnormal CSF Aβ1-42 and tTau (Table 1). The majority of individuals remaining NC had normal CSF Aβ1-42 (80%) and tTau (85%). Thirty-two percent of the stable reverters showed baseline subthreshold depression.

4 Discussion

Age and AD biomarkers are associated with decline in MCI patients who initially reverted to normal cognition. MCI reverters showed higher clinical progression rates than NC individuals, which is in line with previous reports [1, 4]. MCI reverters with subsequent decline had an increased amyloid PET burden and CSF tau compared to reverters remaining normal. Between amyloid markers, amyloid PET showed a significant association with the subsequent decline group in MCI reverters, while this association was significant for CSF $A\beta_{42}$ in NC. Although previous research suggests that CSF amyloid becomes abnormal before PET [17, 18], the findings are in line with other reports that this may not apply to all individuals [19, 20], which contributes to the

notion that CSF Aβ42 and amyloid PET may represent different AD-related processes.

An outstanding question is why individuals with underlying AD temporarily improved. Our results suggest that at baseline MCI reverters were more similar to NC than non-reverting MCI. Furthermore, biomarker values associated with subsequent decline were similar for reverting MCI and NC, while cognitive measures were less consistent. Possibly, reverters with decline received an MCI diagnosis very early in their clinical disease course, as their biomarker profiles was alike the non-reverting MCI. A modest improvement e.g., due to learning effects, resolving of (subthreshold) depressive symptoms or measurement error, may have contributed to reclassification as normal. Here we observed that when AD is present, such improvement is often not lasting.

Furthermore, it remains unclear as to why individuals who reverted and remained NC over time were initially diagnosed with MCI. Aside neurodegenerative diseases, depressive symptoms are a common cause of MCI. Low depressive symptoms scores in ADNI reflect inclusion criteria. In the ADC subthreshold depression was more common. Another possibility is that distress or insecurity led to a suboptimal performance. The question remains how to deal with the classification of these individuals in the context of AD disease progression research, when MCI is often regarded as an intermediate disease stage. A practical implementation could be to classify reverting MCI with normal biomarkers as NC. Alternatively, including stability of the diagnosis in the classification has been suggested [4].

A limitation of this study is the relatively short follow-up time, and so we cannot exclude the possibility that some individuals in the stable group may progress again. Compared to population-based studies, reversion rates in both cohorts were low [3]. Possibly, this reflects that clinicians will not easily reverse a known diagnosis. Reversion rates may even be lower, because we based reversion rates on individuals with MCI that met our inclusion criteria. Individuals with MCI excluded from these analyses as they were lost to follow-up were somewhat older and more cognitively impaired, which are characteristics that associate with decline [1] (Table S5). Although further replication in large population-based studies is necessary, our results suggest that AD biomarkers aid in the prognosis of MCI reverters, and could help to identify those with a good short term prognosis and those likely to decline again in the longer term.

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Declarations

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Supplemental data Chapter 2.2

Table S1 MCI reverters stable versus decliner adjusted for follow-up time after revision.

	ADNI MCI reverters
	p-value adjusted for age, sex, education, *APOE* ε4, and duration FU after reversion
Clinical	
MMSE	0.915
RAVLT immediate total recall	0.003
RAVLT delayed total recall	0.003
Trial making test A	0.817
Trial making test B	0.979
Geriatric depression scale (GDS)	0.023
GDS > 4, n (%)	0.540
AD biomarkers	
Amyloid PET, SUVR	0.017
Amyloid PET, n SUVR > 1.10 (%)	0.019
Luminex CSF $A\beta_{42}$, pg/mL	0.219
Abnormal CSF $A\beta_{42}$, n (%)	0.461
Luminex CSF total tau, pg/mL	0.020
Abnormal CSF total tau, n (%)	0.008
Imaging markers of neurodegeneration	
FDG PET METAROI, SUVR	0.980
FDG PET METAROI, SUVR < 1.21, n (%)	0.879
Hippocampus/Intracranial volume, cm^3	0.605
Hippocampus volume < 6673 mm^3, n (%)	0.743
White matter hyperintensities volume, cm^3	0.030

Table S2 Baseline NC and non-reverting MCI compared to baseline MCI reverters

	NC	MCI Non-reverting	MCI reverters	NC vs MCI reverters		Non-reverting MCI vs reverters	
	(n = 460)	(n = 637)	(n = 67)	p-value	Adjusted for age, sex, education, APOE ε4	p-value	Adjusted for age, sex, education, APOE ε4
Baseline characteristics							
Age, y	74 (6)	73 (7)	69 (8)	<0.001	-	<0.001	-
Female, %	51%	40%	43%	0.327	-	0.738	-
Education, y	16.4 (2.7)	15.9 (2.8)	16.8 (2.3)	0.306	-	0.018	-
APOE ε4 carrier, %	28%	51%	39%	0.102	-	0.089	-
Total follow-up, y	5 (3)	4 (2)	5 (2)	<0.001	-	<0.001	-
Follow-up after reversion, y (n=53)	-	-	3 (2)	-	-	-	-
Average % yearly progression to MCI or dementia	4.4%	-	9.8%	-	-	-	-
Average % yearly progression to dementia	1.2%	9.7%	1.5%	-	-	-	-
Clinical							
MMSE	29.1 (1.2)	27.5 (1.8)	28.7 (1.3)	0.025	0.012	<0.001	<0.001
RAVLT immediate total recall	45 (10)	34 (10)	43 (11)	0.282	0.006	<0.001	<0.001
RAVLT delayed total recall	7.6 (4)	3.6 (3.7)	7.1 (4)	0.368	0.068	<0.001	<0.001
Trail making test A	34 (12)	42 (19)	32 (10)	0.085	0.828	<0.001	0.003
Trail making test B	83 (40)	117 (66)	76 (23)	0.022	0.868	<0.001	<0.001
GDS	0.8 (1)	1.7 (1)	1.3 (1)	0.002	0.003	0.024	0.013
GDS>4	8 (2%)	30 (5%)	3 (4%)	0.312	0.328	>0.99	0.836

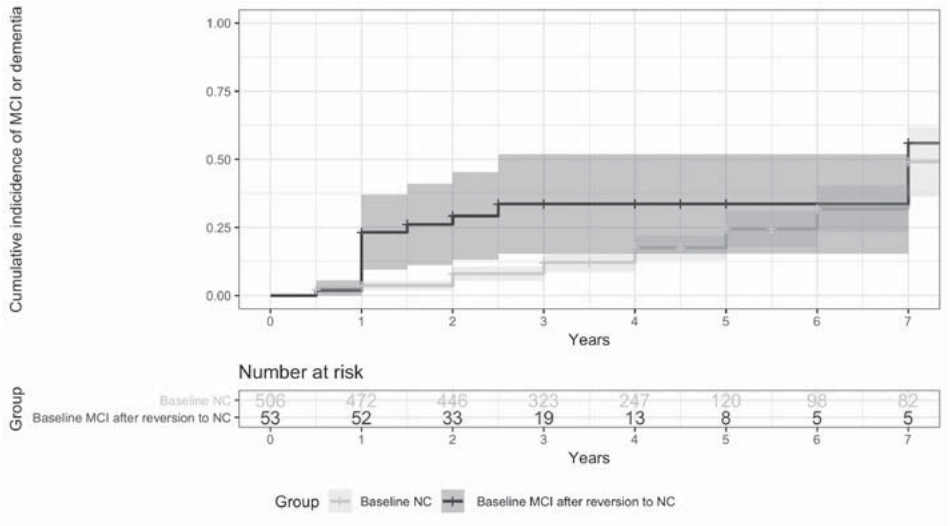
	NC	MCI Non-reverting	MCI reverters	NC vs MCI reverters		Non-reverting MCI vs reverters	
	(n = 460)	(n = 637)	(n = 67)	p-value	Adjusted for age, sex, education, APOE ε4	p-value	Adjusted for age, sex, education, APOE ε4
AD biomarkers							
Amyloid PET, SUVR	1.11 (0.18)	1.22 (0.22)	1.12 (0.16)	0.362	0.203	0.005	0.025
Amyloid PET SUVR > 1.11, %	87 (35%)	202 (58%)	22 (41%)	0.240	0.021	0.038	0.167
Luminex CSF $A\beta_{42}$, pg/mL^	204 (52)	168 (52)	206 (47)	0.708	0.934	<0.001	<0.001
Abnormal CSF $A\beta_{42}$, n (%)^	133 (40%)	327 (68%)	19 (37%)	0.801	0.950	<0.001	<0.001
Luminex CSF total tau, pg/mL^	67 (32)	92 (53)	62 (27)	0.203	0.892	<0.001	<0.001
Abnormal CSF total tau, n (%)^	63 (19%)	188 (39%)	3 (6%)	0.037	0.178	<0.001	<0.001
Imaging of neurodegeneration							
FDG PET METAROI, SUVR	1.31 (0.12)	1.24 (0.13)	1.32 (0.12)	0.535	0.575	<0.001	0.001
FDG PET METAROI, SUVR < 1.21, %	65 (19%)	195 (40%)	11 (17%)	0.929	0.594	0.001	<0.001
Hippocampus/ Intracranial volume, cm^3	0.46 (0.1)	0.39 (0.1)	0.48 (0.1)	0.214	0.918	<0.001	<0.001
Hippocampus volume < 6673 mm^3, %	132 (41%)	305 (72%)	9 (26%)	0.131	0.826	<0.001	<0.001
WMH volume, cm^3	3.5 (7.7)	4.0 (6.9)	2.6 (4.1)	0.791	0.925	0.487	0.333

All >=2yr FU after baseline visit. Baseline CN includes the CN with incident MCI and then reversion. MCI reverters includes all MCI reverters with MCI at the baseline visit, also those without additional FU, but not the incident MCI who reverted. Available sample: amyloid PET n=651, CSF n=865, FDG n=894, HV=779, WMH=1139.

Table S3 Hazard ratio's for progression of MCI reverters to MCI or dementia compared to NC

		HR [95% CI]	p-value
Model 1 (unadjusted)	NC vs MCI reverters	2.34 (1.38-3.99)	0.002
Model 2 (adjusted)	NC vs MCI reverters	2.30 (1.33-3.92)	0.003
	Age at baseline or reversion	1.04 (1.01-1.07)	0.010
	Sex - male	1.39 (0.95-2.04)	0.088
	Education	0.95 (0.89-1.02)	0.137
	APOE e4	1.59 (1.08-2.34)	0.019

Figure S1 Cumulative incidence of MCI or dementia in NC (green) compared to baseline MCI who reverted (orange).



Model 1 of table above. The groups include all baseline NC (n=506, progression n=101 (5 immediate to dementia) and MCI reverters (n=53, progression n=16) with follow-up visits. For the MCI only those with baseline MCI to avoid overlapping subjects. Progression to MCI or dementia for NC was 52 per 1000 person-years, and for the MCI reverters 110 per 1000 person-years.

Table S4 ADNI Predictors of progression in baseline NC compared to the MCI reverters

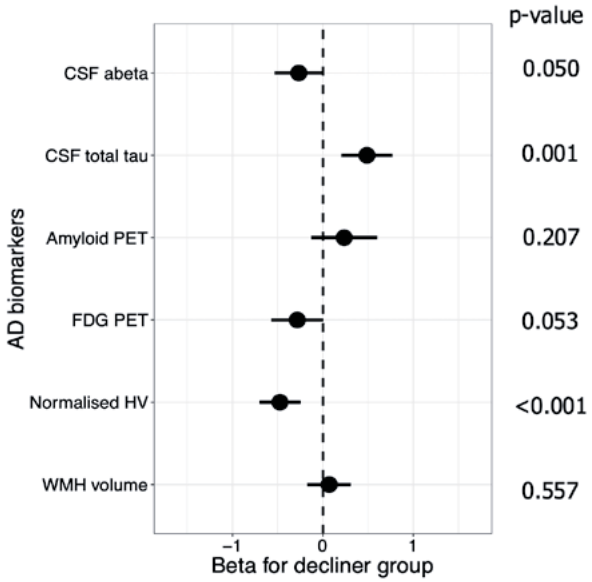
	Baseline CN stable vs progression			MCI reverters (copy table 1)		
	Persistent normal cognition (n = 377)	Decline to MCI or dementia (n = 83)	CN stable vs CN decline p-value^	Persistent normal cognition (n = 42)	Decline to MCI or dementia (n = 19)	p-value^
Baseline characteristics						
Age, y	74 (6)	76 (5)	<0.001	69 (8)	74 (8)	0.016
Female, %	52%	45%	0.281	50%	26%	0.146
Education, y	16.5 (2.7)	16.1 (2.5)	0.216	17.2 (2.6)	16.3 (2.0)	0.095
APOE ε4 carrier, %	27%	34%	0.270	38%	32%	0.839
Total follow-up y, median (IQR)	4 (2)	5.5 (7)	<0.001	4 (2.3)	5 (2.5)	0.109
Clinical						
MMSE	29.1 (1.2)	29.1 (1.1)	0.262	28.7 (1.4)	28.3 (1.8)	0.904
RAVLT immediate total recall	46 (10)	41 (10)	0.003	43 (11)	47 (12)	0.002
RAVLT delayed total recall	8 (3.8)	6 (3.9)	0.001	6.6 (4.2)	8.3 (4.6)	0.002
Trail making test A	34 (11)	38 (13)	0.042	31 (10)	34 (11)	0.700
Trail making test B	82 (40)	88 (37)	0.998	72 (24)	80 (31)	0.973
GDS	0.8 (1)	1.1 (1)	0.009	1.1 (1)	1.6 (2)	0.018
GDS>4	5 (1%)	3 (4%)	0.085	2 (5%)	1 (5%)	0.508
AD biomarkers						
Amyloid PET, SUVR	1.11 (0.17)	1.17 (0.21)	0.207	1.08 (0.15)	1.21 (0.21)	0.016
Amyloid PET SUVR > 1.11, %	70 (32%)	16 (55%)	0.070	10 (30%)	9 (64%)	0.018
Luminex CSF $A\beta_{42}$, pg/mL^	207 (51)	188 (51)	0.050	218 (45)	190 (65)	0.213
Abnormal CSF $A\beta_{42}$, n (%)^	105 (38%)	30 (54%)	0.094	9 (31%)	5 (45%)	0.455
Luminex CSF total tau, pg/mL^	64 (30)	82 (35)	0.001	53 (17)	84 (42)	0.020
Abnormal CSF total tau, n (%)^	42 (15%)	21 (38%)	<0.001	0 (0%)	3 (27%)	0.009
Imaging markers of neurodegeneration						
FDG PET METAROI, SUVR	1.32 (0.11)	1.28 (0.13)	0.053	1.34 (0.11)	1.27 (0.14)	0.458
FDG PET METAROI, SUVR < 1.21, %	46 (16%)	18 (31%)	0.053	5 (13%)	6 (35%)	0.627
Hippocampus/Intracranial volume, cm^3	0.47 (0.07)	0.43 (0.05)	<0.001	0.48 (0.07)	0.42 (0.09)	0.591
Hippocampus volume < 6673 mm^3, %	92 (36%)	40 (61%)	0.002	6 (27%)	5 (56%)	0.731
WMH volume, cm^3	3.32 (6.47)	4.28 (11.95)	0.577	1.80 (2.69)	4.29 (6.24)	0.054

All baseline NC with >= 2y follow-up (n=460). ^Clinical, AD and imaging markers comparisons are adjusted for age, sex, education, and *APOE* ε4.

Table S5 Included and excluded MCI individuals based at least 2 years of follow-up time

	Included sample of MCI individuals	Excluded MCI individuals	Included vs Excluded	
	(n = 757)	(n = 177)	p-value	Adjusted for age, sex, education, *APOE* ε4
Baseline characteristics				
Age, y	73 (8)	76 (8)	<0.001	-
Female, %	41%	41%	0.985	-
Education, y	16.0 (2.8)	15.6 (2.9)	0.149	-
APOE ε4 carrier, %	48%	54%	0.209	-
Clinical				
MMSE	27.7 (1.8)	27.4 (2.0)	0.090	0.426
RAVLT immediate total recall	35 (11)	32 (11)	0.002	0.058
RAVLT delayed total recall	4.0 (3.9)	3 .2(3.5)	0.006	0.090
Trail making test A	40 (18)	44 (22)	0.027	0.014
Trail making test B	112 (63)	131 (71)	0.001	0.014
GDS	1.6 (1)	1.9 (2)	0.187	0.033
AD biomarkers				
Amyloid PET, SUVR	1.21 (0.22)	1.25 (0.24)	0.159	0.788
Amyloid PET, n SUVR > 1.10 (%)	55%	64%	0.106	0.646
Luminex CSF $A\beta_{42}$, pg/mL	172 (54)	165 (49)	0.196	0.734
Abnormal CSF $A\beta_{42}$, n (%)	352 (65%)	65 (71%)	0.262	0.814
Luminex CSF total tau, pg/mL	89 (51)	98 (59)	0.155	0.612
Abnormal CSF total tau, n (%)	229 (36%)	57 (37%)	0.824	0.464
Imaging markers of neurodegeneration				
FDG PET METAROI, SUVR	1.25 (0.13)	1.20 (0.14)	0.001	0.007
FDG PET METAROI, SUVR < 1.21, n (%)	217 (38%)	53 (49%)	0.053	0.246
Hippocampus/Intracranial volume, cm^3	0.40 (0.08)	0.40 (0.08)	0.943	0.479
Hippocampus volume < 6673 mm^3, n (%)	328 (69%)	91 (72%)	0.529	0.909
White matter hyperintensities volume, cm^3	3.94 (7.04)	3.96 (6.77)	0.306	0.598

Figure S2 Biomarkers beta's for progression group vs stable group in normal cognition.



WMH = white matter hyperintensities; HV = hippocampal volume. Univariate analysis.