Received: 1 March 2023 | Revised: 2 August 2023 | Accepted: 1 September 2023

DOI: 10.1002/alz.13488

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Predicting sojourn times across dementia disease stages, institutionalization, and mortality

Ashley E Tate[1] | Vincent Bouteloup[2,3] | Ingrid S. van Maurik[4,5,6] | Delphine Jean[2,3] | Arenda Mank[4,5,6] | Andreja Speh[7,8] | Valerie Boilet[2,3] | Argonde van Harten[4,5] | Maria Eriksdotter[9,10] | Anders Wimo[1] | Carole Dufouil[2,3] | Wiesje M. van der Flier[4,5,6] | Linus Jönsson[1]

[1]Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden

[2]Univ, Bordeaux, Inserm U1219, PHARes team, Institut de Santé Publique, d'Epidémiologie et de Développement (ISPED), Bordeaux, France

[3]CHU Bordeaux, CIC 1401 EC, Pôle Santé Publique, Bordeaux, France

[4]Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, The Netherlands

[5]Amsterdam Neuroscience, Neurodegeneration, Amsterdam, The Netherlands

[6]Amsterdam UMC location Vrije Universiteit Amsterdam, Epidemiology and Data Science, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, The Netherlands

[7]Department of Neurology, University Medical Center Ljubljana, Ljubljana, Slovenia

[8]Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

[9]Theme Inflammation and Aging, Karolinska University Hospital, Huddinge, Sweden

[10]Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden

Correspondence
Ashley Tate, Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet 171 77, Stockholm, Sweden.
Email: Ashley.tate@ki.se

Funding information
Swedish Research Council for Health, Working Life and Welfare (FORTE), Grant/Award Number: 2018-01887

Abstract

INTRODUCTION: Inferring the timeline from mild cognitive impairment (MCI) to severe dementia is pivotal for patients, clinicians, and researchers. Literature is sparse and often contains few patients. We aim to determine the time spent in MCI, mild-, moderate-, severe dementia, and institutionalization until death.

METHODS: Multistate modeling with Cox regression was used to obtain the sojourn time. Covariates were age at baseline, sex, amyloid status, and Alzheimer's disease (AD) or other dementia diagnosis. The sample included a register (SveDem) and memory clinics (Amsterdam Dementia Cohort and Memento).

RESULTS: Using 80,543 patients, the sojourn time from clinically identified MCI to death across all patient groups ranged from 6.20 (95% confidence interval [CI]: 5.57–6.98) to 10.08 (8.94–12.18) years.

DISCUSSION: Generally, sojourn time was inversely associated with older age at baseline, males, and AD diagnosis. The results provide key estimates for researchers and clinicians to estimate prognosis.

KEYWORDS
Alzheimer's disease, dementia, epidemiology, institutionalization, mortality, multistate modeling, multi-state modeling, sojourn times

1 | INTRODUCTION

In line with the aging population, the prevalence of dementia is rapidly increasing, with a projected 152.8 million Alzheimer's disease (AD) cases in 2050.[1] Consequently, the cost of dementia is set to rise; direct costs already comprise 1% of the total global gross domestic product.[2] Previous studies have indicated that the cost of care increases as the disease progresses (e.g.,[3]). Given the expected rise in prevalence and cost to society, it is critical to understand the precise timing of the progression to inform clinical decision making, prognosis, and health economic models. We aim to determine the sojourn times for the different dementia stages by creating a disease progression model in clinically identified patients.

Receiving a dementia diagnosis represents profound stress for the patient and their loved ones.[4] Typically, one of their foremost concerns is the amount of time a patient has until the severe stage of dementia.[5] The cognitive decline of dementia occurs in a continuum of stages. The earliest stage of cognitive decline may manifest itself as subjective cognitive decline (SCD), in which a person experiences cognitive decline without having cognitive impairment. Importantly, an individual with SCD has a hazard ratio of around 2 for developing any further symptoms of cognitive impairment.[6] In the next stage, mild cognitive impairment (MCI), most functional cognitive aspects are preserved, and mild symptoms exist in one or more domains; however, many MCI patients report never experiencing an SCD stage. Following the MCI stage, the loss of independence and decreasing cognitive capacity indicate the onset of dementia, which progresses relatively continuously until death.

Providing patients and their loved ones with a detailed, individualized prediction of how long a patient will spend in each stage, for example, MCI, mild-, moderate-, or severe dementia, and institutionalization, until death, can provide a much needed road map in the face of uncertainty. The results can also inform clinical decision making and policy decisions around the implementation of disease-modifying treatment and prevention programs. Thus, beyond economic models, the sojourn time represents a clinical necessity for both medical professionals and patients.

Most dementia progression studies rely on data from simulations or multiple data sources and, as a result, must make assumptions about data parametrics.[7] Additionally, many studies have used parametric modeling which may not capture the nuance and flexibility of the true disease course.[8] Therefore, a semi-parametric model using recently collected, uniform, generalizable data could provide more accurate estimates for cost-effectiveness studies.

Key efforts have been made to provide dementia stage durations, such as a systematic review published in 2012,[9] and given that the treatment and diagnostic landscape have changed dramatically, these estimates must be updated.[10] A more recent systematic review identified few updated studies in which the time spent in dementia disease states was the primary aim. Most of the included studies consisted of smaller samples (e.g., <1000 participants), which may have led to underpowered samples. To illustrate, one epidemiological study used six longitudinal data sources to determine the sojourn time for each disease state.[11] However, with just over 3000 participants, they were unable to fully examine the later stages of AD and mortality. Thus, an update is sorely needed to understand the time spent in disease status, especially until death and the severe disease states. Thus, we aim to create a multi-state survival model to determine the sojourn time spent across dementia disease stages using a multi-national cohort.

2 | METHODS

2.1 | Participants

2.1.1 | SveDem

SveDem—the Swedish national quality registry for cognitive disorders—began in 2007.[12] Patients with any dementia diagnosis are followed up annually from the date of diagnosis until death. Mini-Mental State Examination (MMSE) scores are used to determine cognition, and national register data are used to determine institutionalization and death.[13] Currently, the register comprises more than 81,844 patients. Coverage is fairly high, with data from 75% of primary care clinics, more than 600 nursing homes, and all Swedish dementia specialization clinics.[14]

2.1.2 | Amsterdam Dementia Cohort

The Amsterdam Dementia Cohort (ADC) consists of patients from the Alzheimer Center Amsterdam, Amsterdam UMC from 2008 and onward. A battery of assessments, including the MMSE, is used to determine cognition, and biomarker data are available in the form of PET, MRIs, and other biomaterials.[15] The cohort contains information on over 2800 patients with SCD, MCI, and dementia.

2.1.3 | Memento Cohort

The Memento Cohort contains detailed data from 2,323 participants collected from 28 memory clinics across France. Patients with either SCD or MCI were recruited from the clinics between 2011 and 2014 and were followed every 6 months for 5 years. Memento contains

RESEARCH IN CONTEXT

1. **Systematic review**: Relevant literature on multistate modeling and disease progression in dementia and Alzheimer's disease was obtained through PubMed. Few epidemiology studies which examined sojourn times were identified.
2. **Interpretation**: In the largest disease progression modeling study to date, we present the sojourn times across disease severity and institutionalization until death. The full disease course from mild cognitive impairment (MCI) to institutionalized severe dementia lasted between 6.2 and 10.1 years. The results show that a younger age at baseline, amyloid negative status, and being female were associated with a slower disease course.
3. **Future direction**: Further research is needed to better understand the transition from subjective cognitive decline (SCD) to MCI. Providing a sojourn time could give reassurance to patients in the face of uncertainty. Including more dementia sub-types and alternative biomarkers, for example„ p-tau or hippocampal volume would help to better stratify patients and provide more precise estimates.

data across biomarkers, various cognitive assessments, and lifestyle factors.

All individuals with available MMSE data were included in the study, no exclusion criteria were applied.

2.2 | Measures

2.2.1 | Outcome

MCI and dementia diagnoses were determined based on diagnosis in the respective clinical settings. In Memento, all dementia cases were validated by an expert committee panel, blinded to genetic and biological markers, with the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria. Similarly, SveDem used DSM-IV criteria prior to 2013 and DSM-5 criteria following. ADC diagnosed individuals based on the National Institute on Aging-Alzheimer's criteria.[16]

Once patients were diagnosed with dementia, their latest MMSE score was used to determine disease severity. The MMSE measures cognitive impairment on a scale of 0–30 and is one of the most widely used measures for dementia. The scores were broken down into mild (30–20), moderate (19–10), and severe (9–0) stages.[13]

In the SveDem, the Swedish national registers captured institutionalization and mortality. While Memento and ADC obtained information from clinical follow-up with patients and caregivers. We decided to create separate states for institutionalization given that the costs and mortality rates differ widely compared to those living in the community.[17,18]

2.2.2 | Predictors

To create the binary variable AD dementia diagnosis, we used the first specified dementia diagnosis given by a clinician, once the patient passed the MCI state; thus, patients were considered to have either an AD dementia diagnosis or another form of dementia. No MCI data were available for SveDem participants as follow-up began after dementia diagnosis.

Amyloid positive status was evaluated through cerebral spinal fluid (CSF) obtained via lumbar puncture as well as through positron emission tomography (PET) scans. Further information on the tests and cutoffs can be found in the supplemental material.

2.3 | Analysis

2.3.1 | Data handling

In the Svedem data, we imputed a new MMSE every 6 months following participants' last score until death or the end of follow-up using a non-linear mixed effects model from the r package progmod,[19] and a time lag was added (Figure S1). This step was not completed in the other cohorts due to incomplete mortality data, as Memento and ADC rely on regular follow-up information for death rather than the national register data available for SveDem. In all cohorts, if a participant's recorded transition skipped a stage, for example, a transition from mild to severe, we imputed the time of the missing state by using the date halfway between the two recorded stages. As a sensitivity analysis, we repeated the analysis for the individuals who skipped a stage.

We separated individuals into a training and hold out sample using a 10:1 split to validate our findings. The data split was stratified by cohort and based on preserving an equal distribution of MCI, mild, and severe states between the sets.

2.3.2 | Estimating disease progression

To model the progression of dementia, we constructed a multistate model using Cox regression. A multistate model represents multiple survival curves, where each state has its own model. As each possible state is modeled, the multistate model inherently accounts for competing risks. A transition matrix was created based on the states MCI, mild, moderate, severe, institutionalized -mild, -moderate, -severe, and death leading to 17 transitions and models. A flow chart of the possible transition pathways can be found in Figure 1. All participants were included in each model, the exposure was considered the dementia stage specified at the transition starting state (e.g., Moderate); thus, patients were considered non-exposed (i.e., not at risk) if they did not enter that particular dementia stage during the study

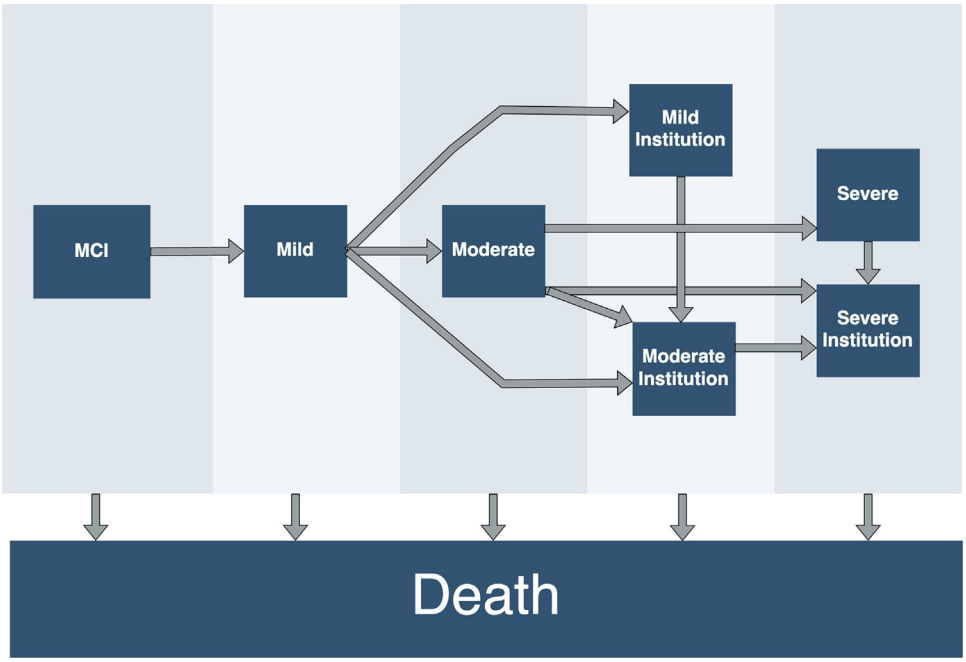

FIGURE 1 Possible pathways through the disease severity states. MCI = mild cognitive impairment. Participants can begin in any state. Transition into death is possible from all states. MCI was determined through clinical diagnosis. After patients were diagnosed with dementia by a clinician, Mini-Mental State Examination (MMSE) scores were used to break down the disease states into mild (30–20), moderate (19–10), and severe (9–0) stages.

duration. Days since entry into the study were used as the underlying time scale, for example, clock forward. Due to data availability, only Memento and ADC data were used to model the MCI transitions. The resulting sojourn times can be interpreted as the predicted disease duration based on an individual with the same specified patient profile.

Models were individually trained using backward elimination, and variables with a *p*-value lower than 0.05 were included in the final models.[20] The candidate variables were sex, age at study entry, amyloid positive status (only for models with the starting state in MCI), and AD dementia diagnosis (i.e., a binary variable indicating (1) being diagnosed with AD dementia or (0) another form of dementia; only included in models with the starting state in mild or later stages). We reported results by the average and 1 standard deviation ± for each age, separated by sex and AD dementia diagnosis. In order to prevent borrowing from the future, (i.e., using information collected following the exposure, in this case the "from" transitioning state), we did not include AD dementia diagnosis in models that started in the MCI state, and the biomarkers were only included that were obtained before a dementia diagnosis. To internally validate the results, the models were then created using the validation dataset, the sojourn time estimates from the main dataset were considered robust if they fell within the confidence intervals (CIs) of estimates from the validation dataset. This method tests the reliability of the estimates as well as the internal validity of the study, as the validation set is not a resampling of the data (i.e., simply repeating the analysis) but data new to the model. Moreover, the method has been shown to reduce bias in survival analysis in large community-level studies.[21]

Data were analyzed in R using the package Mstate.[22]

3 | RESULTS

A total of 80,543 participants (58.2% female; 50.9% diagnosed with AD dementia) were included in the study (Table 1). SveDem was the largest cohort with 76,747 participants, followed by Memento (N = 1119), and ADC (N = 1942). The amyloid data were available for a subset of patients from Memento and ADC (N = 2,336). The median follow-up time was between 3 and 6 years (SveDem = 3.08 years; ADC = 4.44 years; Memento = 6 years). The total follow-up time varied between the cohorts (SveDem = 17.2 years; ADC = 12.3 years; Memento = 6.5 years), with a total person-time of 255,906 years. The training set (N = 72,490) and the test set (N = 8053) split were uniform (Table S1). Proportions were similar between the sexes across entry states. The majority of participants of both sexes entered in the mild stage (65.3% of all females; 68.0% of all males) and the moderate stage (23.6% of all females; 22.0% of all males).

Few participants had skipped stages (e.g., those with recorded mild and severe stages but not moderate) (mild N = 68; moderate N = 241; institutional moderate N = 106), and we imputed these values using the date halfway between the two recorded values (mild = 698 days; moderate = 790 days; and institutional moderate = 797 days). When we repeated the analysis with the imputed individuals removed, we found similar estimates to the main analysis (Table S2).

A Spearman correlation matrix was created for the covariates (Table S3).

TABLE 1 Demographic information for the total sample.

	SveDem	Memento	Amsterdam Dementia Cohort
N	76,747	1854	1942
Female	44,854 (58.4%)	1119 (60.4%)	905 (46.6%)
Mean age (range)	80 (35–105)	70.5 (32–93)	65.6 (50–86)
Diagnosed with AD N	39,550 (51.5%)	224 (13.2%)	1264 (65.1%)
Amyloid available N (proportion positive)	NA	655 (12.5%)	1,681 (83.10%)
Total N			
Mild cognitive impairment	0	1,842	647
Mild	52,706	291	966
Moderate	41,095	153	727
Severe	12,027	21	113
Institutionalized mild	14,478	25	9
Institutionalized moderate	25,839	24	18
Institutionalized severe	17,189	10	4
N at study entry (proportion)			
Mild cognitive impairment	0	1842 (99.4%)	647 (33.30%)
Mild	52,706 (68.70%)	11 (0.6%)	794 (40.90%)
Moderate	18,017 (23.50%)	0	443 (22.80%)
Severe	1738 (2.26%)	0	55 (2.83%)
Institutionalized mild	2070 (2.70%)	1 (0.05%)	2 (0%)
Institutionalized moderate	1878 (2.40%)	0	0
Institutionalized severe	338 (0.44%)	0	1 (0.06%)
N death	37,879 (49.4%)	88 (4.8%)	872 (44.9%)
N institutionalization	34,516 (45.0%)	47 (2.5%)	43 (2.21%)

3.1 | Multi-state modeling

A full list of the variables and coefficients used in each transition model can be found in Table 2. Figures S2–S18 contain the survival curves. Results from the cohort distribution indicated that many patients with MCI did not transition to dementia status during the study period (Figure 2, Figure S19–S21). Indeed, 297 patients with MCI (16%) from Memento and 1467 patients with MCI (84%) from ADC transitioned to dementia. Moreover, there was a steep decline at year 7, which matched the maximum follow-up time for Memento, in other words, these individuals were censored due to end of follow-up.

The range of the full disease course from MCI to death was between 10.08 (8.94–12.18) years for females 71 years at study entry who were diagnosed with AD dementia and 6.20 (5.57–6.98) years for males aged 87 who were diagnosed with AD dementia (Figure 3). The age categories were derived based on the mean age of the sample ± 1 standard deviation. Generally, the individuals who were amyloid positive and later diagnosed with AD dementia spent less time in the MCI state (sojourn time in years [95% CI]; for example, MCI, females 79 years at study entry 5.51 [4.78–6.25]) compared to those negative and diagnosed with another form of dementia (MCI, females 79 years at study entry 7.03 [6.23–7.83]). Likewise, males tended to progress faster than females and spent less time in the MCI state (MCI, males diagnosed with AD dementia, 79 years old 4.15 [3.71–4.59]). The length of time spent in each state decreased with participant age at study entry (e.g., mild, females diagnosed with AD dementia, 71 years old 1.28 [0.87–1.70]; 79 years old 1.18 [0.81–1.55]; 87 years old 1.03 [0.67–1.40]). The

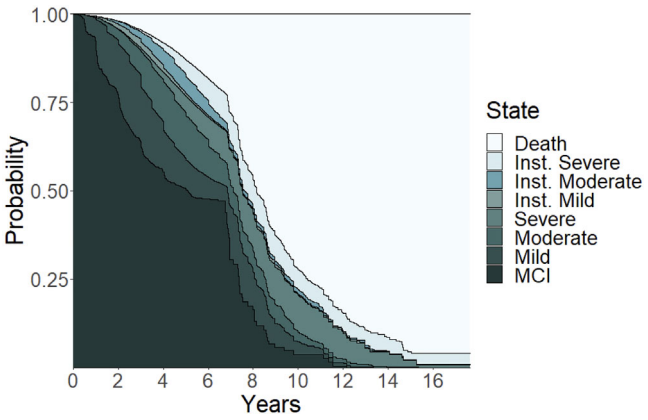

FIGURE 2 The cohort distribution based on the predictions for females, aged 79, with Alzheimer's disease (AD). Years represents days since study entry. The predicted probability for being in each state over time for females starting in mild cognitive impairment, aged 79 at study entry, diagnosed with AD dementia, and amyloid positive.

TABLE 2 Transition models.

Transition number	From	To	N at risk (N in transition)	Median survival time (years)	Variables included	HR (CI)	Z	*p*
1	MCI	Mild	2240 (409)	Median not reached[a]	Amyloid positive	4.50 (3.7–5.47)	5.83	<0.001
-	-	-	-	-	Age at baseline (age)	1.04 (1.02–1.05)	15.07	<0.001
2	MCI	Death	2240 (143)	7.53 (7.35–8.56)	Age	1.06 (0.04–0.08)	5.39	<0.001
-	-	-	-	-	Female	0.40 (0.28–0.57)	4.98	<0.001
3	Mild	Moderate	48,537 (21,145)	3.00 (3.00–3.00)	Age	1.02 (1.02–1.02)	18.92	<0.001
-	-	-	-	-	Female	1.12 (1.09–1.15)	8.30	<0.001
4	Mild	Inst. Mild	48,537 (11,170)	7.04 (6.57–8.27)	Diagnosed with Alzheimer's disease dementia (AD)	0.75 (0.72–0.78)	15.08	<0.001
-	-	-	-	-	Age	1.06 (1.06–1.07))	42.47	<0.001
-	-	-	-	-	Female	1.27 (1.22–1.32)	11.89	<0.001
5	Mild	Inst. moderate	48,537 (276)	Median not reached[a]	Age	1.02 (1.00–1.04)	2.51	0.012
6	Mild	Death	48,537 (4578)	7.33 (7.04–7.52)	AD	0.75 (0.71–0.8))	9.57	<0.001
-	-	-	-	-	Age	1.08 (1.07–1.08)	31.87	<0.001
-	-	-	-	-	Female	0.62 (0.59–0.66)	15.90	<0.001
7	Moderate	Severe	37,746 (9349)	4.5 (4.50–4.50)	AD	0.93 (0.89–0.97)	3.32	0.001
-	-	-	–		Age	1.01 (1.01–1.01))	6.21	<0.001
8	Moderate	Inst. moderate	37,746 (12,214)	3.10 (2.99–3.24)	AD	0.92 (0.88–0.95)	4.79	<0.001
-	-	-	-	-	Age	1.04 (1.04–1.04)	31.71	<0.001
-	-	-	-	-	Female	1.12 (1.08–1.17)	6.22	<0.001
9	Moderate	Inst. severe	37,746 (97)	Median not reached[a]	No variables included			
10	Moderate	Death	37,746 (5,310)	5.28 (5.04– 5.48)	AD	0.86 (0.81–0.9)	5.59	<0.001
-	-	-	-	-	Age	1.06 (1.05–1.06)	28.28	<0.001
-	-	-	-	-	Female	0.61 (0.57–0.64))	18.04	<0.001
11	Severe	Inst. severe	10,939 (3,431)	2.05 (1.89–2.26)	AD	1.12 (1.04–1.19)	3.15	0.002
-	-	-	-	-	Age	1.03 (1.02–1.03)	11.79	< 0.001
12	Severe	Death	10,939 (2,204)	4.37 (4.15–4.72)	Age	1.06 (1.06–1.07)	20.47	< 0.001
-	-	-	-	-	Female	0.64 (0.59–0.69)	10.54	< 0.001
13	Inst. mild	Inst. moderate	13,058 (9,088)	2.5 (2.50–2.50)	AD	1.05 (1.00–1.09)	2.17	0.030
-	-	-	-	-	Age	1.01 (1.01–1.02)	9.86	< 0.001
14	Inst. mild	Death	13,058 (3,348)	2.63 (2.51–2.76)	AD	0.88 (0.82–0.94)	3.77	< 0.001
-	-	-	-	-	Age	1.04 (1.04–1.05)	16.01	< 0.001
–	-	-	-	-	Female	0.61 (0.57–0.65)	14.13	< 0.001
15	Inst. moderate	Inst. severe	23,273 (11,641)	3.50 (3.50–3.50)	Age	1.00 (1.00-1.01)	2.59	0.010
-	-	-	-	-	Female	1.04 (1.00–1.09)	2.08	0.037
16	Inst. moderate	Death	23,273 (9180)	2.25 (2.16–2.34)	AD	0.94 (0.90–0.97)	3.18	0.002
-	-	-	-	-	Age	1.05 (1.04–1.05) 0	27.81	< 0.001
-	-	-	-	-	Female	0.62 (0.59–0.65)	22.23	< 0.001
17	Inst. severe	Death	15,482 (10,143)	2.13 (1.96–2.28)	Age	1.04 (1.04–1.05)	29.18	< 0.001
-	-	-	-	-	Female	0.68 (0.66–0.71)	17.93	< 0.001

[a]Median not reached at the end of follow-up, 16 years.

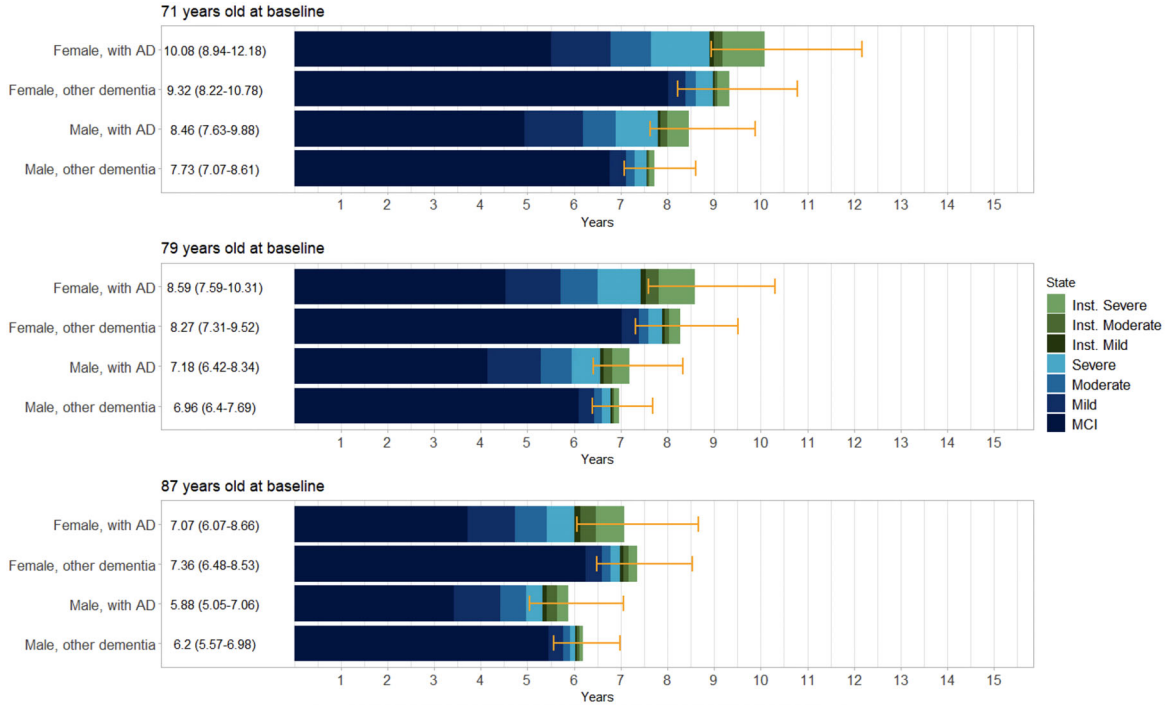

FIGURE 3 Sojourn times for each disease state, separated by age at study entry, years represents years since entry into the study. Orange bars indicate the 95% confidence intervals for the total disease time; "with AD" signifies being amyloid positive and diagnosed with Alzheimer's disease dementia; "other dementia" signifies being amyloid negative and diagnosed with another form of dementia. Ages were broken down based on the average age at study entry (79 years) ± 1 standard deviation. the figure can be interpreted as the predicted disease duration based on an individual with the patient profile specified on the x-axis. This graph represents an individual who begins clinical follow-up in a mild cognitive impairment (MCI) state; while the sections of the bar represents the transitioning state. In other words, the mild section represents how long a patient who originally presents with MCI is expected to spend in the mild state.

years spent in each disease state decreased as severity worsened and after institutionalization (Figure 3; Tables S4–S13).

The time spent in each disease state increased for patients that entered the study at a later disease stage (e.g., males aged 79, diagnosed with AD dementia, time in severe state: starting in MCI 0.36 years [0.27–0.44]; starting in mild 0.65 [0.57–0.73]; starting in moderate 0.83 [0.76–0.90]; starting in severe 1.69 [1.56–1.82]).

3.2 | Validation

After completing the analysis using the validation dataset, the sojourn time from the training set fell within the CI of the test set in all but 9 models (out of 300). All failures occurred in individuals who entered the study in the MCI state and six occurred in the youngest age group (Tables S4–S15).

4 | DISCUSSION

4.1 | Sojourn time

This study sought to chart the timeline of disease progression, mortality, and institutionalization in a multi-national sample of 80,543 patients with cognitive decline. We found that patients' full disease course from clinically identified MCI to death can be expected to last between 6.20 (5.57–6.98) years for males 87 years old at study entry, amyloid positive, and diagnosed with AD dementia and 10.08 (8.94–12.18) years for females 71 years at study entry, amyloid positive, and diagnosed with AD dementia. There was a noticeable steep decline at year 7, which coincided with the maximum follow-up time with the Memento cohort, indicating a wave of censoring end of follow-up.

Our sojourn times were slightly longer compared to the average estimates found by systematic reviews. Brück et al.[23] found an average duration of 5.12 years from MCI to death for patients with all types of dementia and 6.30 years for patients with AD. While an older review identified a wider range of 1.1 to 8.5 years from mild dementia to death depending on the patient profile.[9] It is likely that the discrepancy partially arises from the age of the studies included in past reviews, as mortality in dementia patients has reduced over time.[10] This could reflect the improvement in overall age-adjusted survival and health in the general population leading to a spillover effect for reduced mortality for dementia patients, as well as the increase in early diagnosis of dementia. Indeed, our sojourn aligned but attenuated compared to those presented in Vermunt et al.'s more recent study (also included in Brück et al.'s review).[11] They found a total disease duration of 12.2 years and 9.6 years for individuals age 70 and 80 at study entry, respectively (not including their preclinical, i.e., SCD, phase), compared to our

total duration range of 7.73–10.08 years across all patient groups aged 71 at baseline and 6.96–8.59 years across all patients groups aged 79 years at baseline.

Our results should also be interpreted in the context of a study by Mooldijk, et al.[24] which sought to chart the life expectancy in a sample of community-dwelling MCI patients from the beginning of first symptoms. Within individuals aged 70 and 80, they found the disease course to last between 13.8 and 8.0 years, respectively. While our study aimed to capture patients at the time when patients first began clinical follow-up or time at the first clinician visit, our results are attenuated. Thus, this is likely due to a difference in study design, as well as sample differences between the community and those within clinical care, arising from self-selection biases and perhaps poorer general health.

Using covariates, amyloid status, age, sex, and AD dementia diagnosis, we were able to present results for patient subgroups commonly seen by clinicians. Amyloid positive patients who were later diagnosed with AD dementia transitioned from clinically identified MCI to dementia more quickly (5.51 years) compared to those who were negative and later diagnosed with another form of dementia (7.03). Participants who were older at study entry tended to progress more quickly through each stage (e.g., mild state for individuals 87 at study entry: 1.03 years) compared those younger individuals (71 at study entry: 1.28 years). This fits within previous literature, which has consistently found increased mortality and disease severity for older dementia patients.[25–27]

Males had a shorter disease duration (on average 7.07 years) compared to females (on average 8.44 years). Previous literature identified males with dementia as having a greater mortality and worse cognition compared to females,[9,27] perhaps arising from sex hormone differences[28] or a greater number of comorbidities.[29] Moreover, institutionalization was associated with more rapid disease progression across all patient subgroups, aligning with findings from a previous Swedish study.[17] This association could be due, in part, to the relationship between poorer overall health and being institutionalized.[30] Finally, individuals who entered the study beginning in mild or later state, stayed longer in each state; this held true for all progressive stages. This could be due to participants' time in each state being fully captured, as follow-up for patients' entering in an earlier state may end before the transition to a new state, indicating an underestimation of time in later disease states. The finding could also be partially due to differences in patients who begin treatment in the later stage of the disease, for example, less comorbidities or clinician interaction.

4.2 | Validation

Our results were internally validated through use of a holdout sample (i.e., test set), only 9 out of 300 models had sojourn times that fell outside of the test set CIs. All failures occurred in individuals who entered the study in the MCI state, and all except for two failures occurred in patients aged 71 years at study entry. Given that younger patients at baseline as well as individuals who entered the study at an earlier stage may have been more likely to be censored due to end of follow-up before reaching the severe stage, it is likely that low-power limited the certainty of the results for this patient group. Moreover, our youngest cohort, ADC, had fewer patients that entered into severe states, which also may have limited our power for this group.

4.3 | Strengths and weaknesses

The primary strength of this study is the sample. To the authors' knowledge this is the largest study to date on dementia progression. We had access to large cohorts from across Europe consisting of a national population register and almost 30 memory clinics. The use of the population register, SveDem, gave us nearly complete coverage of all deaths and institutionalizations. Moreover, we used a semi-parametric modeling method and Cox regression for our multi-state models, meaning fewer assumptions were made about the data compared to parametric methods. Finally, the use of a holdout sample to internally validate our results gives some confidence to the stability of our findings.

The study was hampered by limited overlap and the datasets as well as potential differences in the samples, for example, national register data versus specialized memory clinics. For example, the lack of biomarkers in our largest cohort, SveDem, and as a result, we were unable to use the amyloid data in any state other than MCI. Additionally, MCI data were not available in SveDem, as a result our estimates may lead to an underestimation of the time spent in the MCI state compared to the general population.[24] We have used the phrase "diagnosed with AD dementia" deliberately, as the diagnosis may not reflect reality due to misdiagnosis or a delay in diagnosis. The misdiagnosis or delay in diagnosis may lead to an underestimation of the time spent in each stage, especially in the early stages, when a patient may not notice symptoms. To this end, we have used the phrase "clinically identified" to account for biases that lead to underestimation of the early disease stages. Further, the models that were not able to be validated using the test set occurred in the participants who were younger at study entry, potentially spelling that, even with our large sample sizes, we were still underpowered in some models. With this, we did not have a large enough sample to investigate diagnosis of other types of dementia, for example, Lewy body dementia, as well as patients experiencing SCD. Finally, our analysis had a clock forward assumption, meaning that the risk of progression was related to the total follow-up time, rather the time spent in a disease state (e.g., clock reset).[31] This leads to more naïve estimates than if we would have accounted for both avenues.

5 | CONCLUSION

Future studies should examine SCD and the time to transition. Finally, other forms of dementia besides AD are understudied and this study, unfortunately, is not an exception. Cohorts with a larger sample of individuals with other types of dementia should include individual estimates when possible.

In conclusion, we found that individuals with dementia and clinical care, or follow-up can expect the disease course of dementia from MCI

to death to last from 6.20 to 10.08 years, depending on amyloid status, sex, AD dementia or other dementia diagnosis, and age. The estimates given in this study are of particular use to health economists who wish to estimate treatment effects and for clinicians to calculate patient prognosis.

ACKNOWLEDGEMENTS

The authors warmly thank Professor Hein Putter for his input and guidance on the use of the Mstate package.

The project is supported through EU Joint Programme- Neurodegenerative Disease Research (JPND) ADDITION project. The project is supported through the following funding organization under the aegis of JPND, www.jpnd.edu and a research grant from the Swedish Research Council for Health, Working Life and Welfare (FORTE), 2018-01887.

Research of Alzheimer center Amsterdam is part of the neurodegeneration research program of Amsterdam Neuroscience. Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting Steun Alzheimercentrum Amsterdam. The chair of Wiesje van der Flier is supported by the Pasman stichting. The clinical database structure was developed with funding from Stichting Dioraphte.

CONFLICTS OF INTEREST STATEMENT

L. Jönsson was previously employed by H. Lundbeck, but this work was unrelated to the present study. He is a minority shareholder in H. Lundbeck and has received license fees for the data collection instrument Resource Utilization in Dementia. I.S. van Maurik received a consultancy fee (paid to the university) from Roche unrelated to this study. A. Wimo has received license fees for the data collection instrument Resource Utilization in Dementia. W. van der Flier (W.F.) has been an invited speaker at Boehringer Ingelheim, Biogen MA Inc, Danone, Eisai, WebMD Neurology (Medscape), NovoNordisk, Springer Healthcare, European Brain Council. All funding is paid to her institution. W.F. is consultant to Oxford Health Policy Forum CIC, Roche, and Biogen MA Inc. All funding is paid to her institution. W.F. participated in advisory boards of Biogen MA Inc, Roche, and Eli Lilly. All funding is paid to her institution. W.F. is member of the steering committee of PAVE, and Think Brain Health. W.F. was associate editor of Alzheimer, Research & Therapy in 2020/2021. W.F. is associate editor at *Brain*. All work was unrelated to this study. All other authors report no conflict of interest that are directly relevant to the content of this study. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The Amsterdam Dementia center data were collected on ethical grounds and approved by the local boards of the Medical Ethics Committee (Amsterdam UMC (approval no.2019.282); all the participants provided informed consent.

In Svedem, no informed consent was needed because study participants were not identifiable on the basis of our study question. Ethical permission for this study was obtained from the Stockholm regional ethics review board (DNR: 2016/2244-31).

The MEMENTO study protocol has been approved by the local ethics committee ("Comité de Protection des Personnes Sud-Ouest et Outre Mer III"; approval number 2010-A01394-35). All participants provided written informed consent.

ORCID

Ashley E Tate https://orcid.org/0000-0002-4523-6960
Linus Jönsson https://orcid.org/0000-0001-5751-6292

REFERENCES

1. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7:e105-e125.
2. Wimo A, Seeher K, Cataldi R, et al. The worldwide costs of dementia in 2019. *Alzheimers Dement*. 2023;19(7):2865-2873.
3. Gustavsson A, Brinck P, Bergvall N, et al. Predictors of costs of care in Alzheimer's disease: a multinational sample of 1222 patients. *Alzheimer Dement*. 2011;7:318-327.
4. Cooper C, Balamurali T, Livingston G. A systematic review of the prevalence and covariates of anxiety in caregivers of people with dementia. *Int Psychogeriatr*. 2007;19:175-195.
5. Smith AL, Lauret R, Peery A, Mueller T. Caregiver needs: a qualitative exploration. *Clin Gerontol*. 2001;24:3-26.
6. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. *Lancet Neurol*. 2020;19:271-278.
7. Commenges D, Joly P. Multi-state model for dementia, institutionalization, and death. *Commun Theory Methods*. 2004;33:1315-1326.
8. Sheskin DJ. *Handbook of Parametric and Nonparametric Statistical Procedures*. Chapman and Hall/CRC; 2003.
9. Brodaty H, Seeher K, Gibson L. Dementia time to death: a systematic literature review on survival time and years of life lost in people with dementia. *Int Psychogeriatr*. 2012;24:1034-1045.
10. Dufouil C, Beiser A, Chêne G, Seshadri S. Are trends in dementia incidence associated with compression in morbidity? Evidence from the Framingham Heart Study. *J Gerontol Ser B*. 2018;73:S65-S72.
11. Vermunt L, Sikkes SA, Van Den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. *Alzheimer Dement*. 2019;15:888-898.
12. Religa D, Fereshtehnejad S-M, Cermakova P, et al. SveDem, the Swedish Dementia Registry–a tool for improving the quality of diagnostics, treatment and care of dementia patients in clinical practice. *PLoS One*. 2015;10:e0116538.
13. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40:922-935.
14. Handels R, Jönsson L, Garcia-Ptacek S, Eriksdotter M, Wimo A. Controlling for selective dropout in longitudinal dementia data: application to the SveDem registry. *Alzheimer Dement*. 2020;16:789-796.
15. Van Der Flier WM, Scheltens P. Amsterdam dementia cohort: performing research to optimize care. *J Alzheimer's Dis*. 2018;62:1091-1111.
16. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med*. 2014;275:214-228.
17. Lagergren M, Hallberg IR, Holst G, Wimo A. Behov och insatser för de äldre i SNAC-kommunerna. Faculty of Medicine, Lund University in Region Skåne; 2003.
18. Jönsson L, Tate A, Frisell O, Wimo A. The costs of dementia in Europe: an updated review and meta-analysis. *Pharmacoeconomics*. 2023;41:59-75.
19. Raket LL. Statistical disease progression modeling in Alzheimer disease. *Front Big Data*. 2020;3:24.

20. Chowdhury MZI, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. *Fam Med Community Health*. 2020;8(1):e000262.
21. Halloran ME, Longini Jr IM. Using validation sets for outcomes and exposure to infection in vaccine field studies. *Am J Epidemiol*. 2001;154:391-398.
22. Putter H. Tutorial in biostatistics: competing risks and multi-state models analyses using the mstate package. Leiden University Medical Center, Department of Medical Statistics and Bioinformatics; 2011.
23. Brück CC, Wolters FJ, Ikram MA, de Kok IM. Heterogeneity in reports of dementia disease duration and severity: a review of the literature. *J Alzheimer's Dis*. 2021;84:1515-1522.
24. Mooldijk SS, Yaqub A, Wolters FJ, et al. Life expectancy with and without dementia in persons with mild cognitive impairment in the community. *J Am Geriatr Soc*. 2022;70:481-489.
25. Agüero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B. Mortality from dementia in advanced age: a 5-year follow-up study of incident dementia cases. *J Clin Epidemiol*. 1999;52:737-743.
26. Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST. Alzheimer disease and mortality: a 15-year epidemiological study. *Arch Neurol*. 2005;62:779-784.
27. Garcia-Ptacek S, Farahmand B, Kåreholt I, Religa D, Cuadrado ML, Eriksdotter M. Mortality risk after dementia diagnosis by dementia type and underlying factors: a cohort of 15,209 patients based on the Swedish Dementia Registry. *J Alzheimer's Dis*. 2014;41:467-477.
28. Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinol*. 2014;35:385-403.
29. Corrao S, Argano C, Natoli G, et al. Sex-differences in the pattern of comorbidities, functional independence, and mortality in elderly inpatients: evidence from the RePoSI register. *J Clin Med*. 2019;8:81.
30. Miller EA, Weissert WG. Predicting elderly people's risk for nursing home placement, hospitalization, functional impairment, and mortality: a synthesis. *Med Care Res Rev*. 2000;57:259-297.
31. Iacobelli S, Carstensen B. Multiple time scales in multi-state models. *Stat Med*. 2013;32:5315-5327.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tate AE, Bouteloup V, van Maurik IS, et al. Predicting sojourn times across dementia disease stages, institutionalization, and mortality. *Alzheimer's Dement*. 2023;1-10. https://doi.org/10.1002/alz.13488