*Research article*

# Temporal modeling and AT profiles in the early phase of Alzheimer's disease

Journal of Alzheimer's Disease Reports
Volume 9: 1–17

DOI: 10.1177/25424823241306097
journals.sagepub.com/home/alr

**Carlos Platero**[1]

## Abstract

**Background:** Identifying markers that have predictive value for disease progression and clinical manifestations, such as mild cognitive impairment (MCI), is important to detect Alzheimer's disease (AD) early.
**Objective:** In this study, we combined biomarkers from amyloid and tau pathologies (AT profiles) with the prediction of diagnosis and the temporal evolution of clinical symptoms.
**Methods:** Multiple disease progression models were developed through supervised and unsupervised techniques via a two-stage data-driven approach. Models whose natural histories most closely resembled the diagnostic predictions were selected. Finally, various hypotheses regarding the progression of cognitive decline were tested using longitudinal patient data and AT profiles.
**Results:** At baseline, 22.5% of the cognitively unimpaired (CU) individuals and 46.2% of the CU converters (who progressed to MCI during the first four years) in the studied population had amyloid pathology (A+). Only a small subset of neuropsychological measures was used to predict cognitive decline and its timeline. The study revealed that amyloid pathology occurred approximately 5 years after cognitive decline in the population under investigation. Additionally, patients who were A+ at baseline experienced a more accelerated progression toward cognitive decline than those who were not (A−).
**Conclusions:** Based on the proposed natural histories and cross-sectional and longitudinal analysis of AD markers, the results indicate that only a single cerebrospinal fluid sample is necessary during the early phase of AD. The progression from CU to MCI and its timeline can be predicted exclusively through neuropsychological measures.

## Keywords

Alzheimer's disease, Alzheimer's disease continuum, Alzheimer's Disease Neuroimaging Initiative, cognitively unimpaired, core AD biomarkers, disease progression modeling, mild cognitive impairment, predictive models

Received: 19 December 2023; accepted: 11 November 2024

## Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder in elderly individuals. It is characterized by a progressive loss of cognitive ability and specific neuropathological alterations, including the accumulation of amyloid-β plaques (Aβ deposition), neurofibrillary tangles (pathological tau), and neurodegeneration. These changes lead to impairments in memory and other cognitive domains, ultimately resulting in dementia syndrome.[1]

The revised criteria to diagnose and stage AD, proposed by the National Institute on Aging and the Alzheimer's Association (NIA-AA), distinguish between syndrome (clinically identified impairment) and biology (etiology).[2] AD is characterized by its underlying biology, with the disease initially becoming apparent through the emergence of Aβ plaques and subsequently manifesting with neocortical tau tangles, even when individuals remain asymptomatic. In living individuals, the disease is diagnosed via specific core biomarkers. Unimpaired individuals with abnormal biomarkers are at risk for symptoms due to AD. Symptoms are a result of the disease process and are not necessary to diagnose AD. Clinical syndromes commonly associated with AD can also be caused by disorders

[1]Grupo de Tecnologías para Ciencias de la Salud, Escuela Técnica Superior de Ingeniería y Diseño Industrial, Universidad Politécnica de Madrid, Madrid, España

**Corresponding author:**
Carlos Platero, Grupo de Tecnologías para Ciencias de la Salud, Escuela Técnica Superior de Ingeniería y Diseño Industrial, Universidad Politécnica de Madrid, Ronda de Valencia, 3, 28040 Madrid, España..
Email: carlos.platero@upm.es

other than AD; thus, relying solely on clinical presentation is insufficient for an AD diagnosis.

Core AD biomarkers are categorized into A (Aβ) and T (tau) groups. T biomarkers are further divided into T1, which detects soluble tau fragments, and T2, which measures paired helical filament tau aggregates. Collectively, they form the AT profile, which indicates the presence of the two key pathological hallmarks of AD. Core 1 and Core 2 AD biomarkers are introduced to distinguish patients based on the timing of abnormality onset and their intended use.[2] Core 1 biomarkers show abnormalities at approximately the same time as amyloid positron emission tomography (PET) scans and primarily fall under the A category. In contrast, Core 2 biomarkers exhibit abnormalities later in AD progression and are more closely associated with the onset of symptoms than Core 1 biomarkers. Combining Core 2 biomarkers with Core 1 biomarkers provides insights into the likelihood that symptoms are related to AD, disease staging, the risk of progression in asymptomatic individuals, and the likely rate of progression in symptomatic individuals.[2] Core 1 biomarkers are sufficient for diagnosing AD and include amyloid PET, cerebrospinal fluid (CSF) $A\beta_{42/40}$, CSF pTau/$A\beta_{42}$, and CSF tTau/$A\beta_{42}$. Although Core 2 biomarkers have many uses, they are typically not used as standalone diagnostic tests for AD.

Several risk factors have been identified for progression from cognitively unimpaired (CU) to mild cognitive impairment (MCI). These include nonmodifiable factors, such as age, sex, and genetics, as well as modifiable factors, such as years of education or patient and family medical history.[3–5] Recent studies have shown that AD biomarkers may be particularly useful in predicting the risk of progression in CU individuals. Abnormal amyloid, abnormal tau, and signs of neurodegeneration are associated with an increased risk of cognitive decline.[6–10] However, the link between AD biomarkers and cognitive ability is less clear.

Although several studies have been conducted to examine the risk of progression from CU to MCI at the group level,[11–13] others have used the same measures to predict progression at the individual level.[9,14–22] Many proposed models require multiple measures that are not easily available, limiting their use in clinical practice. The fewer markers required from patients, the easier it is to implement predictive models. One objective of this study is to build predictive models that select an optimal combination of different markers that are easily extractable.

A new machine learning framework represents AD progression as a continuous process and derives long-term pathological trajectories from short-term clinical data.[23–27] Disease progression models (DPMs) order markers from normal to pathological stages along the disease time axis, providing a data-driven description of the natural evolution of AD and enabling automatic diagnosis. One class of DPMs, such as growth models by alternating conditional expectation (GRACE), models longitudinal trajectories via self-modeling regression and iteratively estimates long-term progression curves.[23]

It is important to consider the use of clinical diagnosis in the construction of predictive models. First, the use of clinical categories can lead to the overestimation of prediction performance due to circularity. Many of the measures used in predictive models were originally either explicitly or implicitly used for clinical diagnosis. Second, identifying patient conversion times from CU to MCI and their use in predictive models are sources of error. An alternative approach to overcome these limitations is the use of unsupervised learning methods.[22] GRACE is an algorithm that does not rely on clinical group information or the conversion time of patients. However, each set of the selected markers builds a DPM in GRACE, which determines a timeline in the natural history of disease progression. In this study, we propose a combination of supervised and unsupervised techniques to improve the prediction of progression from CU to MCI. Longitudinal survival analysis provides feature selections for use by GRACE. Subsequently, we evaluated GRACE models by using implicit classification of patients and estimation of conversion time for subjects progressing to MCI.

Therefore, following the methodology proposed above[28] and applying the new framework for the diagnosis of AD,[2] it has been suggested to monitor clinical symptoms. These DPMs could be implemented exclusively with neuropsychological measures (NMs), leaving AD CSF biomarkers for the definition of AT profiles. In this study, we combined AT profiles with the prediction of diagnosis and the temporal evolution of clinical symptoms. The markers that best predict progression from CU to MCI were identified, and a natural history of cognitive decline was proposed. The evolution of CU individuals who progressed on the AD continuum was analyzed and compared to those of individuals without amyloid pathology. Relationships among NMs, AD CSF biomarkers, and T1-MRI markers of cognitive decline were also explored.

## Methods

### *Alzheimer's Disease Neuroimaging Initiative*

The Alzheimer's Disease Neuroimaging Initiative (ADNI) database was used to carry out this study.[29] Initially, participants with a normal cognitive state at baseline, a range of neuropsychological measures, and at least one T1-MRI scan from any of their visits were selected. This group consisted of 323 individuals with a total of 2423 visits. Additionally, to construct the DPMs and characterize cognitive decline, participants from the ADNI cohort with MCI at baseline, who maintained this diagnosis throughout their follow-up, were also included. This group comprised 403 individuals with a total of 2590 visits. On the other hand, in order to analyze the AT profiles of these clinical

groups, it is necessary for patients to have certain CSF data during their visits. A total of 227 CU subjects with 565 visits and 333 MCI patients with 581 visits had AD CSF biomarkers. Additional information on the inclusion and exclusion criteria, schedule of assessments, and other details can be found at http://adni.loni.usc.edu/.

Data were extracted from the ADNIMERGE R package,[30] which focuses on various neuropsychological measures, such as the Assessment-Cognitive 13-item scale (ADAS13), Clinical Dementia Rating-Sum of Boxes (CDRSB), Preclinical Alzheimer's Cognitive Composite (PACC), and Functional Assessment Questionnaire (FAQ). MRI brain imaging data were also included and computed with FreeSurfer via cross-sectional processing (https://surfer.nmr.mgh.harvard.edu/).

## AT profiles

In our study, we conducted a second analysis of individuals with measures of AD neuropathology, specifically AD CSF biomarkers. CSF samples were measured via specific assays,[31] and the data were collected only from a subset of ADNI volunteers. The core 1 AD CSF biomarkers are $A\beta_{42}$, pTau/$A\beta_{42}$, and pTau. Within the framework previously defined by the NIA-AA for AD,[32] amyloid pathology (A+) was correlated with low $A\beta_{42}$ values. Furthermore, tau pathology (T+) was defined as high levels of pTau, and even neurodegeneration (N+) was assessed based on high values of total tau. Hansson et al.[33] established thresholds for AD CSF biomarkers to define amyloid and tau pathologies in the ADNI and BIOCARD cohorts. In the population studied here, values of pTau/$A\beta_{42} > 0.028$ indicated A+, similar to $A\beta_{42} < 880$ pg/mL. For T+, pTau > 27 pg/mL was defined. These CSF biomarkers are adapted to the new revision of the Core 1 AD biomarkers in both A and T1.[2]

## Clinical groups

To predict conversion from CU to MCI, individuals classified as CU at baseline were monitored for progression to MCI. ADNIMERGE provides a clinical diagnosis for each subject visit, considered in this study as unquestionable, indicating whether the patient presents a stage of CU, MCI or dementia during each visit.[30] CU individuals who progress to MCI status during the follow-up period were classified as CU progressing to MCI (pCU). On the other hand, those who maintained their CU diagnosis throughout the study were referred to as stable CU (sCU). Patients were assigned to a clinical group (sCU or pCU) based on their diagnosis at the first and last visit, without accounting for changes in cognitive status that may have occurred at intermediate visits. As a result, any partial improvements or deteriorations observed in cognitive assessments during these intermediate visits were disregarded. The conversion time for a pCU subject, that is, the time taken to reach cognitive decline, was measured from the beginning of the study to the first diagnosis of MCI, if this diagnosis was confirmed at the final visit. In the case of sCU subjects, the interval between their first and last visit was designated as the censoring time. The CU individuals were classified into 238 sCU and 85 pCU individuals based on clinical follow-up data from the 323 CU participants. For the AT profiles analysis, which included population with AD CSF biomarkers, 227 CU individuals were also divided into 172 sCU and 55 pCU individuals. Approximately 30% of pCU individuals (n = 27/85 or n = 16/55) progressed not only to MCI during their follow-up but also to dementia. Approximately 12% of the CU population (n = 38/323 or n = 26/227) were individuals who converted in the first four years. These individuals constituted approximately 45% of all pCU subjects (see Supplemental Materials, S1, S2, S3). We classified these individuals as fast-converting pCU individuals. Conversely, pCU patients who converted later were categorized as slow converters. Similarly, sCU individuals who were followed for less than 4 years were classified as fast stable, whereas those whose sCU was censored for more than 48 months were classified as slow stable (see Supplemental Materials, S1, S2, S3).

## Statistical analysis

Two types of data were collected from the participants: (1) AT profiles and (2) the severity of cognitive impairment. The AT profiles indicated whether the patient had normal or abnormal core AD biomarker values. By using cutoff scores for the AT markers, subject profiles were obtained both at baseline and longitudinally. For the second type of data, temporal progression from CU to MCI was assessed based on clinical symptoms. To predict categorical diagnosis and DPM, both supervised and unsupervised learning techniques were combined using a two-stage data-driven approach.[28] Because the natural history of AD estimated by GRACE depends on the choice of marker vector, a survival analysis was applied to identify good markers from longitudinal data that showed good performance in detecting a high risk of progression to cognitive impairment. These proposed markers were then used to build DPMs using the GRACE approach. Finally, the DPM with the best timeline toward MCI was selected by using three proposed measures of the plausibility of the suggested natural history.

## Predictive models

First, we analyzed the link between longitudinal data and cognitive decline progression using survival models that

consider conversion times and finite follow-up.[34–36] Briefly, within the population of CU individuals, longitudinal measurements were obtained from the studied cohort. These outcomes were modeled using linear mixed effects (LME) models, which incorporate both fixed effects and subject-specific random effects to capture the longitudinal trajectories.[37] Consequently, this modeling approach allowed the estimation of marker values for each subject over time. Furthermore, information regarding the progression of symptoms from CU to MCI during the follow-up period was available, i.e. conversion and censorship times. An extended Cox model was constructed for each significant discrete time.[36] To build each of these predictive models, hazard ratios were calculated and transformed into probabilistic terms of conversion from CU to MCI using a logistic regression model. By utilizing a set of markers derived from NMs and T1-MRI data, feature selection and model building were carried out using a nested cross-validation (CV) procedure, which prevented overfitting and biased performance estimates.[38,39] The procedure consisted of two nested CV loops: an inner loop, designed to select the optimal feature subsets for the proposed predictive models, and an outer loop, designed to obtain an unbiased estimate of model performance. Within each inner CV loop, diverse combinations of markers with varying dimensions were proposed and subsequently evaluated in the outer CV loop. A feature ordering stage that uses the minimal-redundancy-maximal-relevance (mRMR) algorithm[40] to propose good subsets of markers to predict the progression from CU to MCI was used. A resampling method was employed to identify the top subsets of features based on mutual information differences in mRMR. Then, predictive models were constructed using training data with the identified feature subsets, selecting the highest-performing combinations based on classification quality metrics such as sensitivity (SEN), specificity (SPE), accuracy (ACC), and area under the curve (AUC), evaluated on the test data.[41] For a more detailed description, including the theoretical framework for building predictive models, see.[28] A MATLAB implementation is available at https://www.nitrc.org/projects/twogrsurvana/.

## DPM with GRACE

Several markers were subsequently selected based on their ability to yield the highest classification scores during the development of the predictive models. These markers were then used to train and evaluate the GRACE approach. The proposal by Donohue et al.[23] aims to estimate time shift parameters and short-term and long-term curves in a self-modeling regression model with linear subject level effects and nonparametric monotone smoothing. For $p$ markers measured from $n$ individuals at different follow-up times, we denote the measured outcome $k$ for individual $i$ at time $j$ as $y_{ijk}$, where $i = 1, \ldots, n$, $i = 1, \ldots, p$ and $j = 1, \ldots, q_{ik}$. The sample is expressed as follows:

$$y_{ijk} = g_k(t^c_{ijk} + \delta_i) + \alpha_{0ik} + \alpha_{1ik} \cdot t^c_{ijk} + e_{ijk},$$

where $g_k$ represents a continuously differentiable and monotonic function, whereas $\delta_i$ is the unknown subject-specific time shift, which follows a normal distribution with mean zero and variance $\sigma^2_\delta$. The short-term observation time is denoted by $t^c_{ijk}$, which represents the centered years relative to the temporal evolution of the visits. Specifically, $t^c_{ijk} = t_{ij} - (t_{i_1} + t_{i_{end}})/2$, where $t_{ij}$ is the visit time, and $i_1$ and $i_{end}$ indicate the first and last visit indices of the $i$-th subject, respectively. The long-term progression time is computed from $t^c_{ijk} + \delta_i$. The parameters $\alpha_{0ik}$ and $\alpha_{1ik}$ represent the subject- and outcome-specific random intercept and slope, respectively. The vector $(\alpha_{0ik}, \alpha_{1ik})$ follows a bivariate Gaussian distribution with mean zero and covariance matrix $\Sigma_k$, which reflects how the subset of regression parameters for the $i$-th subject deviates from those of the population. The measurement error term, $e_{ijk}$, follows a zero-mean Gaussian distribution with variance $\sigma_k$.

The GRACE method does not utilize follow-up clinical diagnostic information in its development. Before fitting GRACE to the data, the outcomes were transformed into percentiles using a weighted empirical cumulative distribution function to ensure a common scale. The resulting scale was percentile-normalized to range from 0 (least severe observed value) to 1 (most severe observed value). Finally, bootstrapping was used to obtain confidence intervals for the DPM evaluation parameters and to analyze the long-term trajectories of markers in patient groups with and without amyloid pathology. Figure 1 shows a flowchart of the applied methodology.

As mentioned, GRACE estimates the temporal displacement of each $i$-th patient in the progression of the disease, $\delta_i$. For an initial year of cognitive impairment or zero time, denoted as $t_{onset}$, the short-term trajectories from sCU individuals should be to the left of $t_{onset}$, indicating that the markers evolve before $t_{onset}$. In contrast, for pCU individuals, the marker trajectories should cross $t_{onset}$ and increase thereafter. Therefore, when estimating temporal ordering using GRACE with a proposed subset of markers, certain scores can be suggested. The first score we defined is the percentage of sCU individuals whose last visit, $t^c_{i_{end}} + \delta_i$, was less than $t_{onset}$, relative to the total number of sCU subjects:

$$SCORE_1 = \frac{\#\{i | (i \in sCU) \cap ((t^c_{i_{end}} + \delta_i) < t_{onset})\}}{\#sCU}$$

For pCU individuals, two measures were established. The first measure was the proportion of pCU individuals who, at baseline, had a time less than $t_{onset}$, $(t^c_{i_1} + \delta_i) < t_{onset}$.

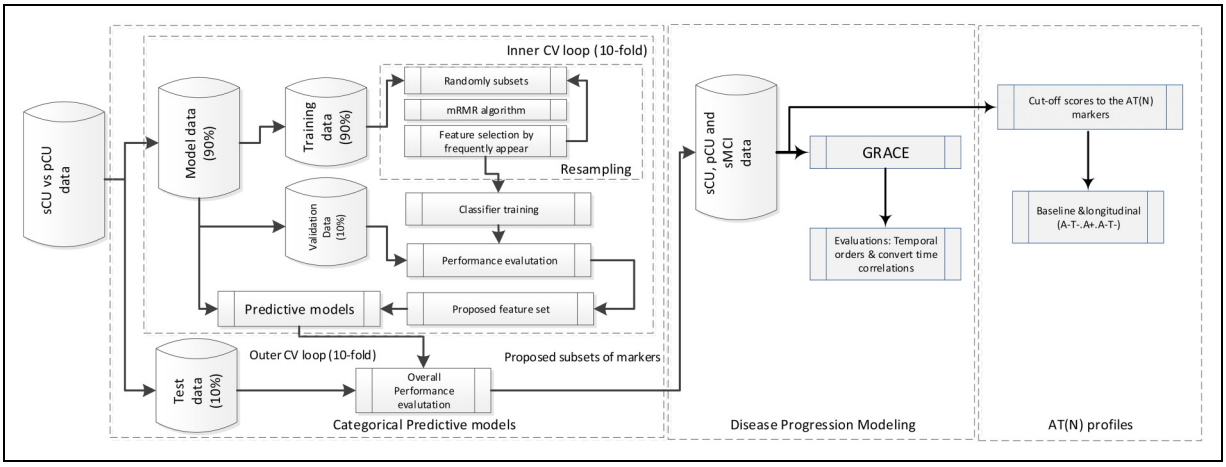


**Figure 1.** This flowchart provides an overview of the interaction between the three key components of the data processing pipeline for CU and MCI patients: (a) categorical predictive models, (b) disease progression modeling, and (c) AT profiles.

This number was compared to the total number of pCU individuals:

$$SCORE_2 = \frac{\#\{i|(i \in pCU) \cap ((t^c_{i_1} + \delta_i) < t_{onset})\}}{\#pCU}$$

The second measure was the ratio of pCU individuals whose last visit had a value greater than $t_{onset}$ compared with the total number of pCU individuals:

$$SCORE_3 = \frac{\#\{i|(i \in pCU) \cap ((t^c_{i_{end}} + \delta_i) > t_{onset})\}}{\#pCU}$$

Thus, we maximized the top three ranking scores to estimate a zero time. As $t_{onset}$ increases, $SCORE_1$ and $SCORE_2$ increase, whereas $SCORE_3$ decreases. An optimal time is one that achieves the maximum score for all $SCORE_i$ values and ensures their similarity. To obtain the optimum, we propose minimizing the absolute differences in $SCORE_i$ values among individuals classified as CU at baseline:

$$\hat{t}_{onset} = \arg\min_{t_{onset}} \sum_{r=1}^{2} \sum_{s=r+1}^{3} |SCORE_r(t_{onset}) - SCORE_s(t_{onset})|$$

### Criteria for validation of the proposed DPM

A timeline of the disease is proposed for each vector used to train GRACE. To select the most likely natural history, three criteria were used to measure the reliability of the suggested DPM: a) We considered the three scores from the previous subsection, denoted as $SCORE_i$. b) We performed a linear regression analysis between the conversion times of pCU individuals and their times estimated by the proposed DPM, denoted as $t_{onset} - (t^c_{i_1} + \delta_i)$, for all $i \in pCU$. c) We compared the values of the long-term trajectories of the markers at $t_{onset}$ with their cutoff values used in clinical practice to diagnose patients with cognitive impairment. Therefore, based on the predictive models, a set of markers that most effectively detect the risk of progression to cognitive impairment was selected. DPMs were subsequently constructed using combinations of these selected measures, and the quality of the estimates of the proposed natural histories was subsequently evaluated based on the three previously defined criteria. Finally, among the DPMs that best estimate the natural history, the one with the smallest number of measures was selected to facilitate its implementation in clinical practice.

## Results

### AT profiles

Table 1 displays the distribution of the AT profiles in the two cognitive groups studied at baseline and by using longitudinal data: sCU and pCU (refer to the Supplemental Material for more details, S4). Two proposed criteria for amyloid pathology (A+) were compared using CSF biomarkers: a) pTau/A$\beta_{42} > 0.028$ and b) A$\beta_{42} < 880$ pg/mL.[33] Individuals with pTau $> 27$ pg/mL[33] were classified as T+.

At baseline, 75% and 65% of the sCU individuals had A−T− profiles according to the first and second criteria, respectively. For pCU individuals, these percentages were 40% and 36%, respectively. Additionally, the individuals in the AD continuum, i.e. they had an A+ profile (A+T− and A+T+), were 42% and 40% of the pCU individuals compared to 16% and 22% of the sCU individuals, depending on the criterion used. Furthermore, the A−T+ group was smaller in the two clinical groups (sCU and pCU), with the first criterion for A+. Therefore, the first A+ criterion was more discriminative between sCU and pCU individuals with respect to AT profiles. Moreover, the first

**Table 1.** Percentages of AT profiles in sCU and pCU individuals based on the criteria for A+ status: a) pTau/$A\beta_{42}$ > 0.028 or b) $A\beta_{42}$ < 880 pg/mL and pTau > 27 pg/mL for T+.

| Group | Criterion for A+ | Time | A−T− | A−T+ | A+ (A+T−, A+T+) | A+T− | A+T+ |
|---|---|---|---|---|---|---|---|
| sCU, n = 172 | pTau/$A\beta_{42}$ > 0.028 | Baseline | 75.0% | 8.7% | 16.3% | 7.6% | 8.7% |
| | | Long | 68.0% | 10.5% | 21.5% | 9.3% | 12.2% |
| | $A\beta_{42}$ < 880 pg/mL | Baseline | 65.1% | 12.8% | 22.1% | 17.4% | 4.7% |
| | | Long | 58.1% | 12.8% | 29.1% | 22.1% | 7.0% |
| pCU, n = 55 | pTau/$A\beta_{42}$ > 0.028 | Baseline | 40.0% | 18.2% | 41.8% | 16.3% | 25.5% |
| | | Long | 34.6% | 18.2% | 47.3% | 14.6% | 32.7% |
| | $A\beta_{42}$ < 880 pg/mL | Baseline | 36.4% | 23.7% | 40.0% | 20.0% | 20.0% |
| | | Long | 30.9% | 21.8% | 47.2% | 23.6% | 23.6% |

These profiles are assessed at baseline or through longitudinal analysis. *n* represents the number of subjects.

criterion showed greater agreement with amyloid PET measurements (AV45) than the second criterion.[33]

In this longitudinal study, the maximum value of pTau/$A\beta_{42}$ or the minimum value of $A\beta_{42}$ from each subject's visit was selected. For the visit with the selected value of the amyloid biomarker, the value of pTau was used. For either of the two A+ criteria, a slight increase in amyloid pathology and a slight decrease in A−T− profiles were observed compared with the percentages at baseline for the two clinical groups. In contrast, individuals with A−T+ profiles remained constant over time. Thus, the longitudinal study mostly occurred within normality (A−T−) or in the AD continuum (A+T− or A+T+), whereas the individuals with the A−T+ profile were mostly detected at baseline and remained constant over time (see Supplemental Material, S4).

## Risk factors

At baseline, the variables that best discriminated between the sCU and pCU groups were age and NMs, highlighting the ADAS13, LDELTOTAL and PACC tests (see Supplemental Materials, S2, S5). The CSF biomarkers of amyloid pathology, both $A\beta_{42}$ and the pTau/$A\beta_{42}$ ratio, also showed the ability to discriminate between the selected clinical groups. Table 2 shows the analysis of the risk factors for the conversion from CU to MCI. For the studied population, the risk factors that showed significant differences were age and amyloid pathology and, to a lesser extent, *APOE4* carrier status. No significant differences were found between the stable subjects and converters in terms of sex or level of education.

## Predictive models

Table 3 presents the predictive model scores for detecting pCU-fast subjects based on our proposal at baseline, month 12, and month 24.

Over time, these predictive scores improved. The cognitive and functional scores of the ADAS13, CDRSB, DIGITSCORE, FAQ, LDELTOTAL, and PACC were suggested as measures to be used in the different proposed predictive models. However, when T1 MRI markers were added to the feature set to propose new predictive models, their classification scores did not improve (see Supplemental Material, S5).

Using the proposed methodology and once the set of markers selected by the predictive models was obtained, the DPMs were implemented with a combination of these proposed markers. The DPMs that best estimated pCU patients' conversion times and diagnoses at each visit were then selected (see subsection Criteria for Validation of the Proposed DPM). Various combinations were evaluated, each with a different number of markers (see subsection Consistency of the Proposed Natural History). The resulting DPMs demonstrated similar performance and indicated comparable trajectories of cognitive decline progression. Among these options, the model with the fewest markers was chosen to facilitate clinical implementation:

{ADAS13, CDRSB, AGE}

Constructing the predictive model with this proposed vector yielded good sensitivity and specificity in detecting pCU-fast subjects at baseline, with SEN = 66.2% (63.3%–69.1%), SPE = 66.5% (64.7%–68.3%), ACC = 66.5% (65.0%–67.9%), and AUC = 0.770 (0.751–0.788). While these scores were slightly lower than those achieved by other proposed vectors (see Table 3), training this vector with GRACE and considering the quality criteria established in the suggested timelines (see subsection Criteria for Validation of the Proposed DPM) produced a DPM that proposed one of the best natural histories of progression toward cognitive impairment, using the fewest features.

Table 4 shows a comparison of the predictive model results for estimating progression to cognitive decline at baseline (converted or not in the next four years) for each clinical group. This comparison was made in relation to the positivity of the two most important risk factors: age and amyloid positivity (see Supplemental Material for

**Table 2.** Comparison of risk factors between sCU and pCU individuals in the study population.

| Factor | pCU | pCU(fast/slow) | sCU | sCU(fast/slow) | p-value |
|---|---|---|---|---|---|
| Age (y) | 76.3 (4.9) | 77.5 (5.3)<br>75.1 (4.3) | 73.6 (5.9) | 73.5 (6.0)<br>73.6 (5.9) | 0.004 |
| Female | 43.5% | 36.8% 48.9% | 52.5% | 55.8%<br>50.9% | 0.155 |
| Years of education | 16.1 (2.7) | 16.0 (2.9)<br>16.2 (2.6) | 16.6 (2.6) | 16.6 (2.6)<br>16.6 (2.6) | 0.147 |
| *APOE4* | 35.3% | 26.3% 42.6% | 23.9% | 23.4%<br>24.2% | 0.043 |
| A+ | 41.8% | 46.2%<br>37.9% | 16.3% | 19.7%<br>14.4% | <0.001 |

For quantitative variables, the mean is presented with the standard deviation in parentheses. For binary categorical variables, the percentage of positivity is shown. A+ indicates amyloid positivity.

**Table 3.** Predictive scores for fast CU-to-MCI conversion (within the first four years of follow-up).

| Data | SEN (%) | SPE (%) | ACC (%) | AUC | Frequency | Optimal feature subsets |
|---|---|---|---|---|---|---|
| *Bl* | 75.3<br>(73.9 76.4) | 70.5<br>(70.0 71.1) | 70.8<br>(70.3 71.3) | 0.797<br>(0.788 0.804) | 1391–1078 | *A, D, F, L*<br>*D, F, P*<br>*C, P* |
| *m*12 | 84.2<br>(83.0 85.5) | 71.0<br>(70.3 71.6) | 72.2<br>(71.6 72.8) | 0.847<br>(0.840 0.854) | 1246–1052 | *A, D, F, L*<br>*D, F, P*<br>*C, P* |
| *m*24 | 83.0<br>(81.6 84.4) | 77.4<br>(76.7 78.1) | 77.6<br>(76.9 78.2) | 0.877<br>(0.869 0.884) | 1326–1009 | *A, F, L*<br>*D, F, P*<br>*C, P* |

A predictive model was built using the extended Cox approach for each visit (Baseline, bl; Month 12, m12; Month 24, m24). Numbers in parentheses represent the 95% confidence interval, except in the frequency column. A: ADAS13; C: CDRSB; D: DIGITSCORE; F: FAQ; L: LDELTOTAL; P: PACC; AUC: Area Under the Curve; ACC: Accuracy; SEN: Sensitivity; SPE: Specificity; Frequency: Minimum and maximum number of times the combination of proposed features was evaluated during the cross-validation procedure.

**Table 4.** Comparison of the proposed predictive model's results for baseline cognitive decline conversion (using binary classification: convert or not) against the three highest risk factors (Age, A+, PACC) at baseline.

| Clinical | *time* ≤ *month*48? | n | *Age* > 75 | A+ | *PACC* < 0.0 | model |
|---|---|---|---|---|---|---|
| sCU | Slow | 161 | 38.5% | 14.4% | 36.6% | 29.8% |
| | Fast | 77 | 42.9% | 19.7% | 50.6% | 39.0% |
| pCU | Slow | 47 | 44.7% | 37.9% | 48.9% | 51.1% |
| | Fast | 38 | 63.3% | 46.2% | 78.9% | 68.4% |

*n* represents the number of subjects.

more details, S2, S5). The prediction of conversion to MCI by using a $PACC < 0.0$ is also included, as this composite score has been shown to detect the first signs of cognitive deterioration.[42]

The pCU-fast population corresponded to the oldest groups, and approximately 50% had amyloid pathology at baseline. On the other hand, the sCU-slow population had the lowest percentage of elderly individuals and amyloid pathology. The proposed predictive model had the highest success rates in estimating conversion to MCI in the next four years for these two groups (pCU-fast and sCU-slow), with close to 70% accuracy for converters and a classification error below 30% for stable individuals at baseline. We observed that the proposed marker vector discriminated between stable and progressive individuals in a manner similar to that of PACC. Although age or amyloid pathology did not significantly differ between the sCU-slow and sCU-fast groups, the classification of the risk of conversion to MCI did differ when both the PACC and the proposed predictive model were used. This finding indicates a greater probability of MCI conversion to sCU-fast than to sCU-slow (see Supplemental Material, S3).

## *DPM with GRACE*

The proposed vector was used to train the GRACE algorithm on the studied population. Figure 2 displays the number of subjects as a function of the time shift, $\delta_i$, categorized by their clinical group (shown in the first three columns). It also illustrates the relationship between the

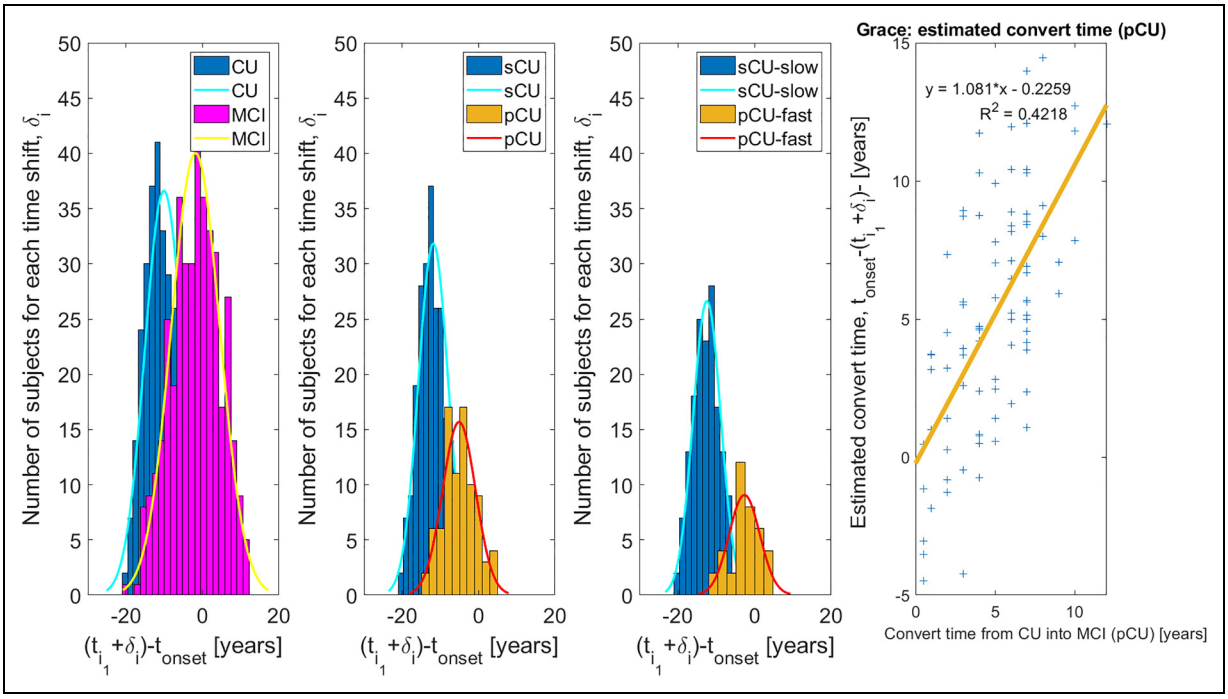


**Figure 2.** Subject classification is determined by the time shift $\delta_i$ . The first three columns present histograms showing the number of subjects according to the temporal ordering proposed by GRACE, $(t^c_{i_1} + \delta_i) - t_{onset}$, across different clinical groups: (a) CU versus MCI, (b) sCU versus pCU, and (c) sCU-slow versus pCU-fast. The fourth column illustrates the conversion time, in years, for pCU individuals, relative to GRACE's estimates, $t_{onset} - (t^c_{i_1} + \delta_i)$.

conversion times of the pCU subjects ($t_{convert}$) and their estimates by GRACE ($\hat{t}_{convert}$) in the last column.

It can be observed that that the time shift distribution between the sCU-slow and pCU-fast groups exhibits less overlap compared to the distribution between the sCU and pCU patients. This suggests that individuals in the pCU-fast group are the closest to progressing to the MCI state. Additionally, the $\delta_i$ values for the sCU-fast and pCU-slow groups are more comparable, with sCU-fast individuals displaying higher $\delta_i$ values than those in the sCU-slow group. These findings are consistent with the varying risks of MCI conversion among CU individuals at baseline, as predicted by the model presented in Table 4. For the conversion times of the pCU subjects, the regression line had a unit slope and an intercept near zero. In other words, the estimated times and the cognitive decline timelines were very similar ($\hat{t}_{convert} = 1.08 \cdot t_{convert} - 0.23$) and had a Pearson correlation coefficient of $R = 0.654$ (0.642 − 0.666). By optimizing the classification scores of the subjects based on $t^c_i + \delta_i$ and the clinical groups, the onset time of cognitive decline was estimated to be approximately $\hat{t}_{onset} \approx 2.6$ years.

Figure 3 displays the individual observed trajectories for each marker in the original scale, ordered in the progression timeline using the DPM approach. The first two columns show the short-term trajectories colored according to the clinical group or amyloid pathology, whereas the third column shows the long-term trajectories of the markers that were subjected to bootstrap analysis to obtain confidence intervals. This visualization shows that the ordering proposed by estimating $\delta_i$ was consistent both in the clinical classification and in A−/A+. We note that the GRACE approach was blind to the information of the clinical group or AT profiles of the subjects. The short-term trajectories of the markers belonging to the sCU subjects occurred in times less than $t_{onset}$, whereas those of the MCI subjects occurred in times greater than $t_{onset}$. Additionally, patients with amyloid pathology had trajectories with higher $\delta_i$ times than those who were A −. For the estimated onset time $\hat{t}_{onset} \approx 2.6$ years, $SCORE_1 = 86.0\%(85.4\% - 86.5\%)$ of the sCU subjects met the condition $t^c_{i_{end}} + \delta_i < t_{onset}$, whereas $SCORE_2 = 89.2\%(88.5\% - 90.0\%)$ of the pCU patients at baseline $t^c_{i_1} + \delta_i < t_{onset}$ and $SCORE_3 = 74.2\%(73.1\% - 75.2\%)$ at the end of the visits $t^c_{i_{end}} + \delta_i > t_{onset}$ of the converters were correctly classified.

After the progression timeline from CU to cognitive decline was defined based on the $\delta_i$ values, the long-term trajectories of any marker acquired from the studied population could be inferred. Figure 4 displays the short-term and long-term trajectories of the AD CSF biomarkers ($A\beta_{42}$, pTau/$A\beta_{42}$, and pTau) and normalized hippocampal volume (NHV), along with the ADAS13 measurement. The short-term trajectories of the AD CSF biomarkers and NHV were found to be much more dispersed than their long-term trends, unlike neuropsychological measures, such as the

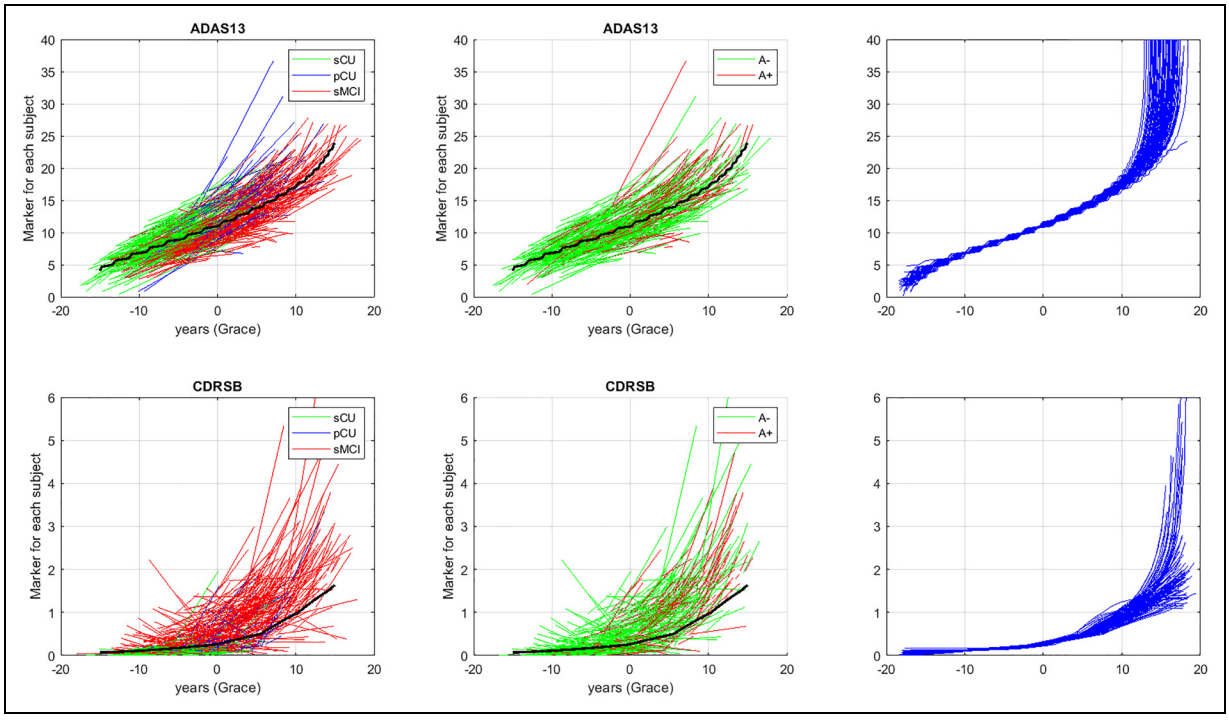


**Figure 3.** For each selected marker, the long-term trajectories (black lines) are overlaid on the subject-level observations in their original scale, with colors indicating diagnosis (sCU in green, pCU in blue, and sMCI in red) or AT profiles (A− in green and A+ in red). The third column displays the long-term trajectories of the selected markers derived from the bootstrapping technique, shown in blue.

ADAS13. By coloring the AD CSF marker trajectories with the suggested temporal ordering, better grouping between A+ and A− subjects was observed than when clinical diagnosis labels (sCU, pCU, and sMCI) were used. We once again confirmed that A+ subjects at baseline had greater cognitive decline than A− subjects because patients with amyloid pathology had greater temporal displacement.

The long-term trajectories of $A\beta_{42}$, pTau/$A\beta_{42}$, and pTau were combined with the cutoff values used to define the amyloid pathology and T+ of the AT profiles to yield the following event times in the progression of cognitive impairment: a) $t_{A\beta 42=880pg/ml} - t_{onset} = 4.6\ years$, b) $t_{\frac{pTau}{A\beta_{42}}=0.028} - t_{onset} = 4.8 years$ and c) the event $t_{pTau=27\frac{pg}{ml}} - t_{onset}$ was not reached at this stage of AD.

Table 5 presents a comparison of the mean values of NMs at baseline for sCU, pCU and sMCI participants with values estimated based on the long-term trajectories at the onset of MCI. The calculated NM values at $\hat{t}_{onset} \approx 2.6\ years$ were found to be similar to the cutoff points used in clinical practice to determine the progression from CU to MCI. Additionally, these NM scores at $t_{onset}$ fall between the mean values of the pCU and sMCI populations at baseline. Conversely, AD CSF biomarker values from DPM at $t_{onset}$ were found to be between the values of the sCU population and pCU/sMCI subjects.

Figure 5 illustrates the application of bootstrap techniques to the long-term trajectories of markers between populations with A+ and A−. We observed that cognitive decline accelerated among A+ individuals compared with A− individuals. These A+ individuals are on the AD continuum. Using cutoff points from CU to MCI in the scores of the NMs (the ADAS13 threshold was 12[43] and with a CDRSB of 0.5[44]), we observed that A+ individuals converted to MCI between −7 and −3 years, whereas A− subjects progressed to MCI within 2 to 4 years. In other words, the time of conversion differed by more than five years between subjects who had amyloid pathology and those who did not present with amyloid pathology at baseline. With respect to the AD CSF biomarkers, we observed that the AT profiles of the two populations remained constant over time, which is consistent with the conclusion previously obtained in the analysis of the AT profiles. For pTau/$A\beta_{42}$ and pTau, the long-term trajectories exhibit flat behavior over time in the A− population. In contrast, for $A\beta_{42}$, the difference between the values of the A+ and A− subpopulations was maintained over time.

## Consistency of the proposed natural history

Other DPMs can be constructed using our methodology. We selected several models that were built using better

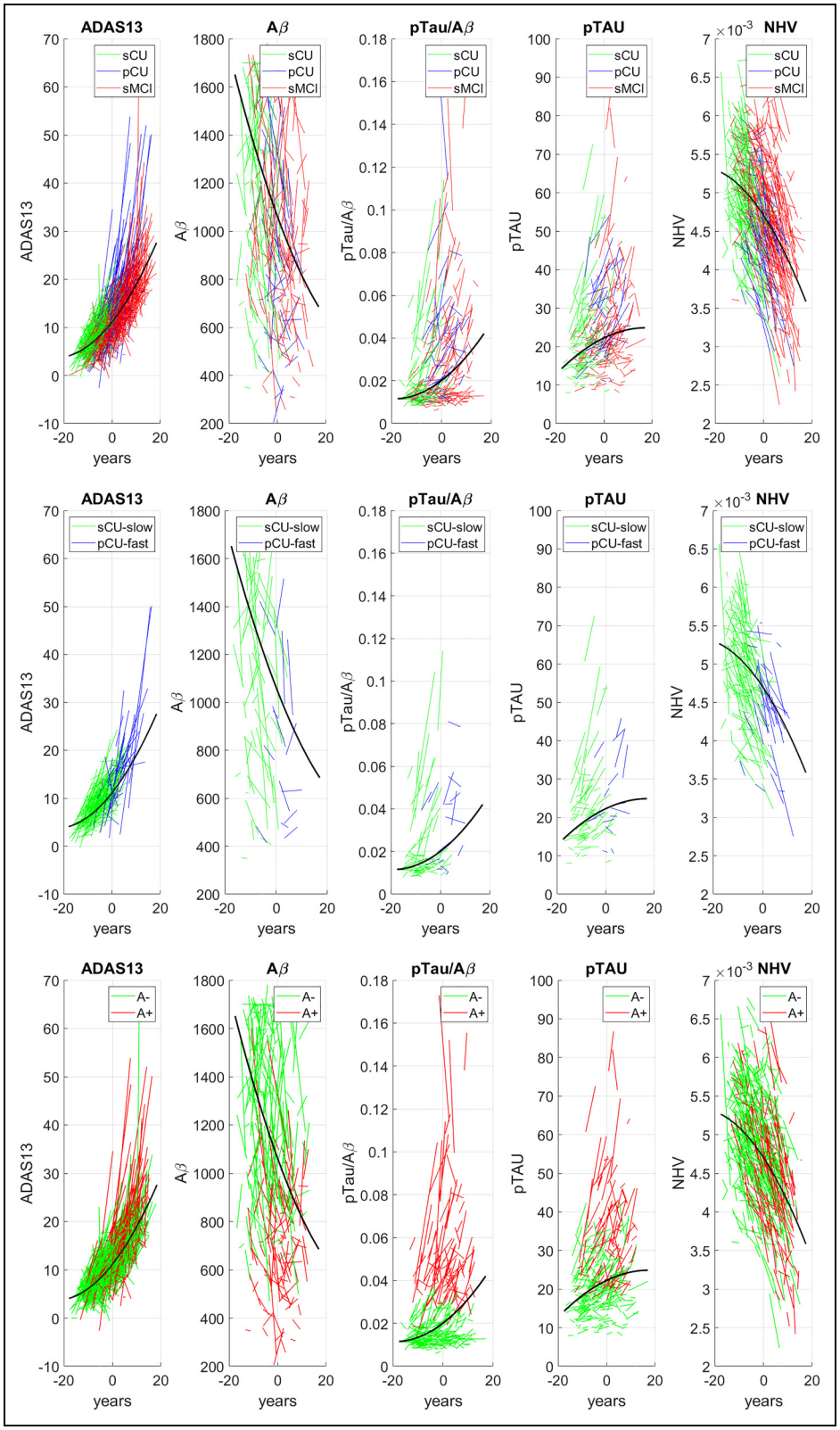


**Figure 4.** Long-term trajectories (black curves) for each selected marker are overlaid on subject-level observations in their original scale. In the first row, colors indicate diagnosis (sCU in green, pCU in blue, and sMCI in red); in the second row, colors distinguish between sCU-slow (green) and pCU-fast (blue); and in the third row, colors represent AT profiles at baseline (A− in green and A+ in red).

**Table 5.** For each selected marker, we present a comparison of the mean values across clinical groups (sCU, pCU, sMCI) at baseline in our cohort.

| Demographic and clinical characteristics | | | | | |
|---|---|---|---|---|---|
| Subjects | sCU | pCU | sMCI | clinical cutoff | DPM $t_{onset} \approx 2.6$ *years* |
| Cognitive outcomes | | | | | |
| ADAS13 | 8.33 | 11.04 | 12.92 | 12[43] | 12.6 |
| CDRSB | 0.03 | 0.04 | 1.24 | 0.5[44] | 0.37 |
| AD CSF biomarkers | | | | | |
| $A\beta_{42}$ | 1275.64 | 1064.99 | 1117.42 | 880[33] | 992 |
| pTau | 20.75 | 25.48 | 23.08 | 27[33] | 22.9 |
| pTau/$A\beta_{42}$ | 0.019 | 0.032 | 0.026 | 0.028[33] | 0.023 |

This comparison includes the clinical practice cut-off values used to determine progression to cognitive decline, as well as the values estimated by long-term trajectories at the onset time.

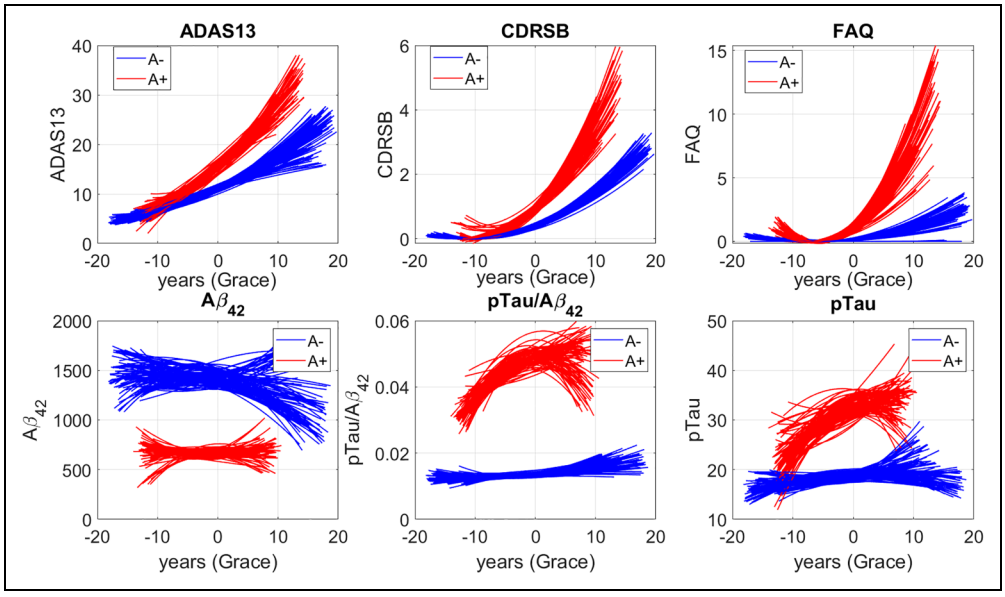


**Figure 5.** Long-term trajectories of markers during the early AD stage, comparing A+ and A− individuals, with amyloid pathology defined at baseline. Confidence intervals for these trajectories were inferred using the bootstrap technique.

marker combinations. These models have shown the highest degree of correlation between the conversion times of pCU individuals and their estimations when GRACE is used. Table 6 displays the linear regression equations, Pearson coefficients, and proposed scores based on the onset time of cognitive decline. All of the proposals had similar scores for diagnosis classification and $t_{onset}$.

Table 7 displays the values of the markers that define the onset of cognitive decline from their long-term trajectories. These values show that the various DPM proposals were consistent in identifying the time when cognitive decline begins.

After the proposed timeline was obtained by each DPM, some relevant temporal intervals were inferred. For this purpose, the cutoff of some markers used in clinical practice to define an event was used. Next, these threshold values were placed on the long-term trajectories of the DPMs, and the elapsed time between two events was estimated. Although the onset times of the DPMs were similar (see Table 7), the ADAS13 with 12 points was used to set the reference time. Table 8 shows estimates of the times, in years, between $t_{ADAS13=12}$ and the onset time of cognitive decline and amyloid pathology.

## Discussion

A combination of cross-sectional analysis of AD CSF biomarkers with the estimated progression of cognitive decline, obtained by constructing a DPM in the context of the early phase of Alzheimer's disease, was proposed. This approach aims to a) analyze the risk factors associated with amyloid pathology, b) verify various hypotheses about the evolution of the symptoms of cognitive decline and AT

**Table 6.** Set of features used to construct the proposed DPMs and their performance in relation to correlations and scores.

| Features | *tonset* | regression equations | R | $SCORE_1$ | $SCORE_2$ | $SCORE_3$ |
|---|---|---|---|---|---|---|
| A,C,Ag | 2.6 | 1.08t-2.83 | 0.65 | 86.0% | 89.2% | 74.2% |
| A,C,L,Ag | 2.8 | 1.09t-2.95 | 0.65 | 81.5% | 89.4% | 75.3% |
| C,L,P,Ag | 2.5 | 1.24t-3.52 | 0.65 | 85.5% | 78.8% | 70.6% |
| C,F,I,L,M,Ag | 2.8 | 1.26t-3.67 | 0.64 | 87.8% | 80.0% | 69.4% |

The features include: A: ADAS13; Ag: Age; C: CDRSB; F: FAQ; I: RAVLT Immediate; L: RAVLT Learning; M: MMSE; P: PACC.

**Table 7.** Stage of cognitive decline according to the selected DPMs, based on the values of relevant markers at onset time from their long-term trajectories.

| Features | *tonset* | A13($t_{onset}$) | CDRSB($t_{onset}$) | Aβ42($t_{onset}$) | pTau/Aβ42($t_{onset}$) | pTau($t_{onset}$) |
|---|---|---|---|---|---|---|
| A, C, Ag | 2.6 | 12.87 | 0.375 | 992 | 0.023 | 23.0 |
| A, C, L, Ag | 2.8 | 12.81 | 0.349 | 975 | 0.023 | 23.2 |
| C, L, P, Ag | 2.5 | 12.81 | 0.341 | 998 | 0.022 | 22.8 |
| C, F, I, L, M, Ag | 2.8 | 12.98 | 0.362 | 1020 | 0.022 | 22.7 |

A: ADAS13; Ag: Age; C: CDRSB; F: FAQ; I: RAVLT Immediate; L: RAVLT Learning; M: MMSE; P: PACC.

**Table 8.** Estimation of relevant events in years using the proposed DPMs, starting from $t_{ADAS13=12}$.

| Features | $t_{A\beta=880} - t_{A13=12}$ | $t_{pTau/A\beta=0.027} - t_{A13=12}$ | $t_{onset} - t_{A13=12}$ |
|---|---|---|---|
| A, C, Ag | 5.8 | 6.0 | 1.2 |
| A, C, L, Ag | 5.1 | 5.4 | 1.6 |
| C, L, P, Ag | 5.8 | 9.7 | 1.1 |
| C, F, I, L, M, Ag | 7.0 | 7.2 | 1.5 |

A: ADAS13; Ag: Age; C: CDRSB; F: FAQ; I: RAVLT Immediate; L: RAVLT Learning; M: MMSE; P: PACC.

profiles, c) facilitate the automated diagnosis and prognosis of patients, and d) obtain relevant conclusions to improve clinical practice.

## AT profiles

At baseline, 22.5% of the CU population had A+ with the pTau/$A\beta_{42} > 0.028$ criterion and 26.4% had $A\beta_{42} \leq$ 880 pg/mL. The second result was closer to those in other publications that indicated that one-third of CU patients were A+ in the studied age range.[32,45,46] This finding is reasonable because the second criterion was used in these references. However, with the first criterion, AT profiles for CU individuals were more discriminative between sCU and pCU individuals and showed more agreement with amyloid PET.[33]

When the first criterion was applied, 66.5% of the CU population was A−T−, 22.5% was on the AD continuum, and 11% was A−T+. These percentages of AT profiles were in concordance with those reported by other authors.[6,7,47]

## Risk factors

In this study, we identified age and amyloid pathology as two significant risk factors for cognitive decline. AD is the leading cause of dementia, and the risk of developing it increases with age.[48] According to Evans et al.,[49] age was associated with the most significant risk factor for progression from the CU state to MCI. However, the effect of age on the transition from MCI to dementia is unclear.

According to numerous studies, individuals with abnormal amyloid biomarkers in the CU state experience a more rapid progression of atrophy, hypometabolism, and cognitive decline than individuals without biomarker evidence of Aβ deposition.[32,50] After four years of follow-up, 24% of the CU-A+ individuals progressed to MCI, which was double the percentage observed in the general population (12%). This finding is consistent with those of other authors.[10,46,50] The population with the highest percentage of amyloid positivity was the pCU-fast group (46.2%), which was close to the rate observed in MCI individuals with A+.[7,51] Previous studies have shown that 40–60% of MCI patients are A+ on PET.[51] In contrast, the sCU-slow individuals had a lower percentage of A+ at 14.4%.

Strong evidence supports that amyloid pathology increases with age.[52,53] According to a meta-analysis, the frequency of amyloid pathology gradually increases from 10% at 50 years of age to 44% at 90 years of age in CU participants based on PET and CSF data.[53]

The results regarding *APOE4* are more contradictory. While the percentages of *APOE4* carriers differed between the pCU and sCU subjects, the pCU slow population surprisingly showed a greater increase in *APOE4* carriers than the pCU fast population. This finding may simply be due to the limited sample size. Several authors have indicated that *APOE4* is not a significant predictor of MCI among CU individuals.[12,21]

## Predictive models

Several biomarkers, such as pTau or tTau, and measures such as NHV or FDG, have been proposed for predicting cognitive decline in AD patients.[9,14,15] However, at baseline, these measures neither classified well nor had correlations with the NMs, such as the PACC (see Supplemental Material, S5). Although Aβ is a specific pathology of AD, its burden is not linearly correlated with the severity of symptoms.[51] At baseline, the ADAS13 was found to be the most effective measure for predicting cognitive decline. However, multivariate approaches, such as the combined PACC measure or the proposed multivariate models, significantly improved the predictive results.

Episodic memory, orientation, and executive function are the prominent domains of AD-related cognitive dysfunction.[46] Among the different cognitive domains considered, memory measures are the most sensitive to early AD stages.[12,20] The proposed multivariate predictive models consist of different NMs formed by combinations of ADAS13, logical memory delayed recall (LDELTOTAL), and the digit symbol substitution test (DIGITSCORE). These NMs cover global cognitive domains, memory, language, visuospatial processing speed, and attention. Functional tests for FAQ and CDRSB were also included. Han et al.[54] reported that neuropsychological tests can identify changes in the course of the disease in the presymptomatic phase. Battista et al.[55] reported that some tests were more frequently the best predictors for automatic classification, namely, Logical Memory, ADASCog, RAVLT, and FAQ. Additionally, their classification performance was similar to the scores reported here.

Ansart et al.[56] reported that including cognitive scores, and CSF or FDG variables significantly improved predictive performance compared with not including them. However, including other modalities, particularly T1 MRI, did not have a significant effect. In this study, we combined AD CSF biomarkers with NMs, which were used to describe AT profiles and clinical symptoms, respectively. Some authors[15,20] have indicated that the addition of MRI measures and AD CSF biomarkers provides relatively little predictive power compared with the above NMs. These conclusions are in line with our results. When we added T1-MRI markers to the pool of features to propose new predictive models, we did not observe any improvement in the classification scores (see Supplemental Material, S5).

## DPM with GRACE

Most researchers developing DPMs typically trained these models using all available features,[23,26] assuming that each marker contributes positively to the model. However, some researchers have applied ablation techniques to determine whether certain groups of markers influence the performance of the DPM.[57,58] Alternatively, we propose the following: 1) AT profiles should be separated from clinical symptoms in the early diagnosis of AD; 2) Markers suitable to exclusively analyze the progression from CU to MCI differ between the preclinical and prodromal phases; 3) Compared with other types of markers, the DPMs developed in this study demonstrated that neuropsychological measures better capture the progression of cognitive decline; 4) To implement a DPM in clinical practice, a minimum number of measures should be used, and noninvasive markers are preferred to improve feasibility.

With this in mind, a two-stage data-driven approach was proposed. First, the markers that best detect the risk of conversion to MCI were selected. The DPM that best estimates the natural history was subsequently selected. The selected vector consisted of only two NMs, ADAS13 and CDRSB, plus the patient's age. Although this vector was not optimal for predicting the diagnosis over time, it inferred a natural history that is easy to implement in clinical practice and has high reliability in both estimating the conversion times of the pCU individuals and classifying the individuals using the proposed temporal ordering. On this basis, a longitudinal follow-up of these NMs combined with a single AD CSF sample has been proposed.

Other authors have proposed combining ADAS13 and CDRSB to obtain a reliable MCI classification with high specificity and sensitivity.[16,59,60] Moreover, predictive models require the addition of the age variable to maintain high levels of diagnostic reliability in the transition from CU to MCI.[49] van Maurik et al.[14] also reported that the effects of MRI markers lost significance when age was included in the model. The DPM performed well with the suggested combination because the selected markers coincided with those used to determine each patient's clinical group.[44] However, GRACE does not rely on clinical diagnostic information to construct the proposed cognitive decline timeline. These results indicate that the proposed natural history of early AD based on unsupervised machine learning (and excluding follow-up diagnostic information) significantly captures the underlying disease burden. The DPM may be portable to other cohorts and may be applicable over wide age ranges.

The proposed natural history of the progression from CU to MCI was analyzed based on three different aspects: a) The conversion times of pCU individuals and their values estimated by GRACE strongly and linearly correlated ($R = 0.654$ $(0.642 - 0.666)$). Furthermore, the regression line shows that the times estimated by GRACE are practically coincident with the times of natural history. b) The clinical classification (sCU versus pCU) of the individuals with the proposed temporal ordering had good scores: $SCORE_1 = 95.3\%$ $(95.1\% - 95.6\%)$, $SCORE_2 = 80.6\%$ $(79.7\% - 81.6\%)$ and $SCORE_3 = 74.5\%$ $(73.8\% - 75.2\%)$. c) The cutoff points of the ADAS13 and CDRSB, which are used in clinical practice to determine cognitive impairment,

are similar to their long-term trajectories at the $t_{onset}$ (see Table 5).

The proposed temporal ordering of the studied CU/MCI population allowed inference of the long-term trajectories of AT markers. The results suggest that amyloid pathology (A+) is present approximately 5 years after the onset of cognitive impairment ($t_{A\beta 42 = 880} - t_{onset}$ or $t_{pTau/A\beta 42 = 0.028} - t_{onset}$), whereas T+ is not reached at this stage of AD. These findings are consistent with previous research indicating that 40–60% of MCI individuals had A+,[51] whereas only 22.5% of CU individuals had amyloid pathology. Additionally, previous studies have shown that CSF $A\beta_{42}$ levels are unequivocally abnormal 5–10 years or more prior to dementia diagnosis,[61] while both CSF tTau and pTau levels become increasingly abnormal as the time to diagnosis of dementia increases.[62]

To describe how CU individuals transition into cognitive decline, we analyzed the long-term trajectories of the NMs and AT markers on a common scale (see Supplemental Material, S6). Our results revealed that the progress of AD CSF biomarkers was much slower than that of cognitive measures and that the first measures to become abnormal in progression into AD were those of Aβ.[32] These findings support the dual use of AT profiles and predictive models of clinical symptom progression. The AT profile at baseline allowed discrimination among normal AD biomarkers, the AD continuum, and other forms of dementia. Moreover, the presented predictive models estimated the time to reach cognitive impairment. Furthermore, our findings suggest that estimating the progression to cognitive decline only requires the exclusive use of NMs.

The conclusion that amyloid pathology at baseline accelerates cognitive decline was already obtained from the cross-sectional analysis of the population (see Table 2) and now also from the longitudinal analysis based on the long-term trajectories between the A+ population with respect to the A− population (see Figure 5). In this context, Han et al.[54] reported that an A+ profile was associated with poorer performance in the domains of global cognitive function, memory, language, visuospatial ability, processing speed, and attention/working memory/executive functions when compared to an A− profile. However, no correlations were observed between AD CSF biomarkers and neuropsychological measures (see Supplemental Material, S5). Although Aβ is an AD-specific pathology, the Aβ burden is not linearly correlated with symptom severity.[51]

The bootstrap analysis also indicated that the AT profiles of patients remained relatively stable in the early stages of AD. Additionally, A+ individuals at baseline converted to MCI approximately eight years before A− individuals based on the cutoff points of the ADAS13 and CDRSB for conversion from CU to MCI. These findings were consistent with those of other authors.[4,63]

Several DPMs were built by using different marker combinations. The results of the various temporal orderings proposed by each DPM were similar. The various inferred natural histories indicated the following: a) The onset times of cognitive decline ($t_{onset}$) were approximately one and a half years after $t_{ADAS13 = 12}$. b) The time interval between $t_{ADAS13 = 12}$ and the onset of amyloid pathology was approximately 6 years ($t_{A\beta 42 = 880} - t_{ADAS13 = 12}$ and $t_{pTau/A\beta 42 = 0.027} - t_{ADAS13 = 12}$).

## Limitations, future and new ideas

The present study has several limitations that need to be acknowledged. Participants were recruited from a single database. Moreover, the ADNI patients were mostly well educated and Caucasian. Further validation studies with larger and more generalizable populations are needed. Furthermore, the performance of predictive models and DPMs may vary in other cohorts due to the variability of CU and MCI diagnoses. Although dementia is a relatively definitive endpoint, MCI patients may remain stable or convert to CU, and the variability in this diagnosis among centers may be greater than that in the case of dementia.[14]

Although we highlighted the importance of amyloid pathology and age as risk factors in this study, other factors that might explain differences in cognitive scores, such as cardiovascular risk and socioeconomic status,[54] or sex and its interaction with the *APOE4* genotype,[64] still need to be analyzed.

Further investigations are needed to examine the relationships between the core AD biomarkers and the risk of cognitive decline in CU patients with subjective complaints.[6] A comparison between this group and CU subjects is still pending.

AD CSF biomarkers are binarized when AT profiles are used, meaning that a single cutoff value is applied, resulting in a loss of information. However, a two-cutoff approach may be more effective. A moderate cutoff may be appropriate for detecting early symptoms, whereas conservative cutoffs may provide high diagnostic certainty.[10,32]

Because AD CSF biomarkers are derived from an invasive technique, alternative methods need to be identified. A possible turning point has emerged with the recent development of blood-based biomarkers.[15] Future research should analyze the results of this study by using new markers of the core AD biomarkers.

Although GRACE has demonstrated superiority in estimating disease progression compared with alternative approaches,[28] new DPM training algorithms have emerged in recent years,[65,66] including proposals based on recurrent neural networks.[57,67] Thus, a comparison between GRACE and these new approaches remains pending.

## Conclusions

The purpose of this study was to integrate information from core AD CSF biomarkers with the description of a proposed natural history obtained through the construction of a DPM. This approach showed the following: a) In the CU population, cognitive decline was more pronounced in individuals who presented with amyloid pathology (A+) at baseline than those who did not (A−). b) Hypotheses about the progression of cognitive decline were verified. Amyloid pathology manifested approximately 5 years after cognitive decline, and T+ was not present in this early stage of AD. c) By projecting the long-term trajectories of the biomarkers onto a common scale, our results indicated that the temporal progression of the AD CSF biomarkers was significantly slower than that of the cognitive measures. This finding supports the combined use of cross-sectional analysis of AT profiles and longitudinal analysis for clinical symptom progression. d) Moreover, DPMs alone, in addition to being a tool for automatic diagnosis and prognosis, allowed us to analyze whether a marker captures the progression of the disease, in this case, the evolution of cognitive decline.

Supported by the proposed natural histories and cross-sectional and longitudinal analyses of AD markers, we suggest that 1) only a single CSF sample is necessary during the early phase of AD and that 2) the prediction of cognitive decline syndrome and its timeline can be achieved exclusively through NMs. By using AD CSF biomarkers, the baseline AT profile enables discrimination among various stages of the AD continuum and other dementias. Patients' AT profiles remained approximately constant in the first few years of follow-up, as was also observed from the long-term trajectories of AD CSF biomarkers. In terms of predicting cognitive decline, the inclusion of T1-MRI markers did not significantly improve the results. Finally, short-term trajectories from some NMs, compared with their long-term trajectories, capture the evolution of cognitive decline with fidelity.

## Acknowledgments

Data collection for this study was funded by the ADNI (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering and and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; IXICO Ltd; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. 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.ucla.edu/wp-content/uploads/how to apply/ADNI Acknowledgement List.pdf We are especially grateful to Michael Donohue, who provided code for the disease progression model (https://bitbucket.org/mdonohue/grace).

## ORCID iD

Carlos Platero https://orcid.org/0000-0003-3712-8297

## Statements and declarations

### Author contributions

Carlos Platero (Conceptualization; Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing – original draft; Writing – review & editing).

### Funding

This work is part of the MINA-CM program (number S2022/BMD-7236), funded by the call for the implementation of programs of R&D activities between research groups of the Community of Madrid in Biomedicine 2022 (Order 1171/2022).

### Declarations of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Supplemental material

Supplemental material for this article is available online.

## References

1. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement* 2012; 8: 1–13.
2. Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement* 2024; 20: 5143–5169.
3. Roberts R and Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med* 2013; 29: 753–772.
4. Vermunt L, Sikkes SAM, 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. *Alzheimers Dement* 2019; 15: 888–898.
5. Porsteinsson AP, Isaacson RS, Knox S, et al. Diagnosis of early Alzheimer's disease: clinical practice in 2021. *J Prev Alzheimers Dis* 2021; 8: 371–386.
6. Ebenau JL, Timmers T, Wesselman LMP, et al. ATN Classification and clinical progression in subjective cognitive decline: the SCIENCe project. *Neurology* 2020; 95: e46–e58.

7. Bucci M, Chiotis K and Nordberg A. Alzheimer's disease profiled by fluid and imaging markers: tau PET best predicts cognitive decline. *Mol Psychiatry* 2021; 26: 5888–5898.
8. Yu JT, Li JQ, Suckling J, et al. Frequency and longitudinal clinical outcomes of Alzheimer's AT(N) biomarker profiles: a longitudinal study. *Alzheimers Dement* 2019; 15: 1208–1217.
9. Song R, Wu X, Liu H, et al. Prediction of cognitive progression in individuals with mild cognitive impairment using radiomics as an improvement of the ATN system: a five-year follow-up study. *Korean J Radiol* 2022; 23: 89–100.
10. van der Kall LM, Truong T, Burnham SC, et al. Association of β-amyloid level, clinical progression, and longitudinal cognitive change in normal older individuals. *Neurology* 2021; 96: e662–e670.
11. Soldan A, Pettigrew C, Lu Y, et al. Relationship of medial temporal lobe atrophy, APOE genotype, and cognitive reserve in preclinical Alzheimer's disease. *Hum Brain Mapp* 2015; 36: 2826–2841.
12. Chen Y, Denny KG, Harvey D, et al. Progression from normal cognition to mild cognitive impairment in a diverse clinic-based and community-based elderly cohort. *Alzheimers Dement* 2017; 13: 399–405.
13. Parnetti L, Chipi E, Salvadori N, et al. Prevalence and risk of progression of preclinical Alzheimer's disease stages: a systematic review and meta-analysis. *Alzheimers Res Ther* 2019; 11: 7.
14. van Maurik IS, Slot RER, Verfaillie SCJ, et al. Personalized risk for clinical progression in cognitively normal subjects-the ABIDE project. *Alzheimers Res Ther* 2019; 11: 33.
15. Palmqvist S, Tideman P, Cullen N, et al. Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures. *Nat Med* 2021; 27: 1034–1042.
16. Gross AL, Hassenstab JJ, Johnson SC, et al. A classification algorithm for predicting progression from normal cognition to mild cognitive impairment across five cohorts: the preclinical AD consortium. *Alzheimers Dement (Amst)* 2017; 8: 147–155.
17. Luo W, Wen H, Ge S, et al. Development of a sex-specific risk scoring system for the prediction of cognitively normal people to patients with mild cognitive impairment (SRSS-CNMCI). *Front Aging Neurosci* 2022; 13: 774804.
18. Cho SH, Woo S, Kim C, et al. Disease progression modelling from preclinical Alzheimer's disease (AD) to AD dementia. *Sci Rep* 2021; 11: 4168.
19. Gavidia-Bovadilla G, Kanaan-Izquierdo S, Mataró-Serrat M, et al. Early prediction of Alzheimer's disease using null longitudinal model-based classifiers. *PLoS One* 2017; 12: e0168011.
20. Albert M, Zhu Y, Moghekar A, et al. Predicting progression from normal cognition to mild cognitive impairment for individuals at 5 years. *Brain* 2018; 141: 877–887.
21. Steenland K, Zhao L, John SE, et al. A 'Framingham-like' algorithm for predicting 4-year risk of progression to amnestic mild cognitive impairment or Alzheimer's disease using multidomain information. *J Alzheimers Dis* 2018; 63: 1383–1393.
22. Wang Z, Tang Z, Zhu Y, et al. AD Risk score for the early phases of disease based on unsupervised machine learning. *Alzheimers Dement* 2020; 16: 1524–1533.
23. Donohue MC, Jacqmin-Gadda H, Le Goff M, et al. Estimating long-term multivariate progression from short-term data. *Alzheimers Dement* 2014; 10: S400–S410.
24. Guerrero R, Schmidt-Richberg A, Ledig C, et al. Instantiated mixed effects modeling of Alzheimer's disease markers. *Neuroimage* 2016; 142: 113–125.
25. Schmidt-Richberg A, Ledig C, Guerrero R, et al. Learning biomarker models for progression estimation of Alzheimer's disease. *PLoS One* 2016; 11: e0153040.
26. Li D, Iddi S, Thompson WK, et al. Bayesian Latent time joint mixed effect models for multicohort longitudinal data. *Stat Methods Med Res* 2019; 28: 835–845.
27. Lorenzi M, Filippone M, Frisoni GB, et al. Probabilistic disease progression modeling to characterize diagnostic uncertainty: application to staging and prediction in Alzheimer's disease. *Neuroimage* 2019; 190: 56–68.
28. Platero C. Categorical predictive and disease progression modeling in the early stage of Alzheimer's disease. *J Neurosci Methods* 2022; 374: 109581.
29. Wyman BT, Harvey DJ, Crawford K, et al. Standardization of analysis sets for reporting results from ADNI MRI data. *Alzheimers Dement* 2013; 9: 332–337.
30. ADNI Team. *ADNIMERGE: Alzheimer's Disease Neuroimaging Initiative*, 2021.
31. Bittner T, Zetterberg H, Teunissen CE, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement* 2016; 12: 517–526.
32. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018; 14: 535–562.
33. Hansson O, Seibyl J, Stomrud E, et al. CSF Biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimers Dement* 2018; 14: 1470–1481.
34. Kleinbaum DG and Klein M. *Survival analysis*. New York: Springer, 2010.
35. Sabuncu MR, Bernal-Rusiel JL, Reuter M, et al. Event time analysis of longitudinal neuroimage data. *Neuroimage* 2014; 97: 9–18.
36. Platero C and Tobar MC. Longitudinal survival analysis and two-group comparison for predicting the progression of mild cognitive impairment to Alzheimer's disease. *J Neurosci Methods* 2020; 341: 108698.
37. Bernal-Rusiel JL, Greve DN, Reuter M, et al. Statistical analysis of longitudinal neuroimage data with linear mixed effects models. *Neuroimage* 2013; 66: 249–260.

38. Kuhn M and Johnson K. *Applied predictive modeling*. New York: Springer, 2013.
39. Korolev IO, Symonds LL, Bozoki AC, et al. Predicting progression from mild cognitive impairment to Alzheimer's dementia using clinical, MRI and plasma biomarkers via probabilistic pattern classification. *PLoS One* 2016; 11: e0138866.
40. Peng H, Long F and Ding C. Feature selection based on mutual information criteria of max-dependency, max-relevance, and min-redundancy. *IEEE Trans Pattern Anal Mach Intell* 2005; 27: 1226–1238.
41. Cuingnet R, Gerardin E, Tessieras J, et al. Automatic classification of patients with Alzheimer's disease from structural MRI: a comparison of ten methods using the ADNI database. *Neuroimage* 2011; 56: 766–781.
42. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol* 2014; 71: 961–970.
43. Ulbl J and Rakusa M. The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog): validation of Slovenian version for detecting mild cognitive impairment or Alzheimer's dementia. *Alzheimers Dement* 2021; 17: e056177.
44. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's disease neuroimaging initiative (ADNI): clinical characterization. *Neurology* 2010; 74: 201–209.
45. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7: 280–292.
46. Donohue MC, Sperling RA, Petersen R, et al. Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. *JAMA* 2017; 317: 2305–2316.
47. Kern S, Zetterberg H, Kern J, et al. Prevalence of preclinical Alzheimer disease: comparison of current classification systems. *Neurology* 2018; 90: e1682–e1691.
48. Hou Y, Dan X, Babbar M, et al. Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol* 2019; 15: 565–581.
49. Evans S, McRae-McKee K, Hadjichrysanthou C, et al. Alzheimer's disease progression and risk factors: a standardized comparison between six large data sets. *Alzheimers Dement (N Y)* 2019; 5: 515–523.
50. Papp KV, Buckley R, Mormino E, et al. Clinical meaningfulness of subtle cognitive decline on longitudinal testing in preclinical AD. *Alzheimers Dement* 2020; 16: 552–560.
51. Jang H, Park J, Woo S, et al. Prediction of fast decline in amyloid positive mild cognitive impairment patients using multimodal biomarkers. *Neuroimage Clin* 2019; 24: 101941.
52. Rowe CC, Ellis KA, Rimajova M, et al. Amyloid imaging results from the Australian imaging, biomarkers and lifestyle (AIBL) study of aging. *Neurobiol Aging* 2010; 31: 1275–1283.
53. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA* 2015; 313: 1924–1938.
54. Han SD, Nguyen CP, Stricker NH, et al. Detectable neuropsychological differences in early preclinical Alzheimer's disease: a meta-analysis. *Neuropsychol Rev* 2017; 27: 305–325.
55. Battista P, Salvatore C and Castiglioni I. Optimizing neuropsychological assessments for cognitive, behavioral, and functional impairment classification: a machine learning study. *Behav Neurol* 2017; 2017: 1850909.
56. Ansart M, Epelbaum S, Bassignana G, et al. Predicting the progression of mild cognitive impairment using machine learning: a systematic, quantitative and critical review. *Med Image Anal* 2021; 67: 101848.
57. Nguyen M, He T, An L, et al. Predicting Alzheimer's disease progression using deep recurrent neural networks. *Neuroimage* 2020; 222: 117203.
58. Karaman BK, Mormino EC, Sabuncu MR, et al. Machine learning based multi-modal prediction of future decline toward Alzheimer's disease: an empirical study. *PLoS One* 2022; 17: e0277322.
59. Zhou B, Nakatani E, Teramukai S, et al. Risk classification in mild cognitive impairment patients for developing Alzheimer's disease. *J Alzheimers Dis* 2012; 30: 367–375.
60. Yang Y, Hsu K, Wei C, et al. Operational determination of subjective cognitive decline, mild cognitive impairment, and dementia using sum of boxes of the Clinical Dementia Rating scale. *Front Aging Neurosci* 2021; 13: 705782.
61. Buchhave P, Minthon L, Zetterberg H, et al. Cerebrospinal fluid levels of β-amyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. *Arch Gen Psychiatry* 2012; 69: 98–106.
62. Fagan AM, Mintun MA, Shah AR, et al. Cerebrospinal fluid tau and ptau181 increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer's disease. *EMBO Mol Med* 2009; 1: 371–380.
63. Insel PS, Weiner M, Mackin RS, et al. Determining clinically meaningful decline in preclinical Alzheimer disease. *Neurology* 2019; 93: e322–e333.
64. Ishida T, Tokuda K, Hisaka A, et al. A novel method to estimate long-term chronological changes from fragmented observations in disease progression. *Clin Pharmacol Ther* 2019; 105: 436–447.
65. Ghazi MM, Nielsen M, Pai A, et al. Robust parametric modeling of Alzheimer's disease progression. *Neuroimage* 2021; 225: 117460.
66. Koval I, Bône A, Louis M, et al. AD Course map charts Alzheimer's disease progression. *Sci Rep* 2021; 11: 8020.
67. Ghazi MM, Sorensen L, Ourselin S, et al. CARRNN: a continuous autoregressive recurrent neural network for deep representation learning from sporadic temporal data. *IEEE Trans Neural Netw Learn Syst* 2024; 35: 792–802.