Received: 7 November 2023 | Revised: 7 February 2024 | Accepted: 1 March 2024

DOI: 10.1002/dad2.12578

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Prediction of dementia risk from multimodal repeated measures: The added value of brain MRI biomarkers

Ariane Bercu[1] | **Carole Dufouil**[1,2] | **Stéphanie Debette**[1,3] | **Marc Joliot**[4] | **Ami Tsuchida**[1,4] | **Catherine Helmer**[1] | **Anthony Devaux**[1,5,6] | **Vincent Bouteloup**[1,2] | **Cécile Proust-Lima**[1] | **Hélène Jacqmin-Gadda**[1]

[1]University of Bordeaux, Inserm, Bordeaux Population Health Research Center U1219, Bordeaux Cedex, France

[2]Pôle de santé publique, Centre Hospitalier Universitaire (CHU) de Bordeaux, Bordeaux Cedex, France

[3]Department of Neurology, Institute of Neurodegenerative Diseases, Bordeaux University Hospital, Bordeaux Cedex, France

[4]Groupe d'Imagerie Neurofonctionelle-Institut des maladies neurodégénératives (GIN-IMN), UMR 5293, Bordeaux University, CNRS, CEA, Bordeaux Cedex, France

[5]The George Institute for Global Health, Newtown NSW 2042, New South Wales, Australia

[6]School of Population Health, UNSW Kensington Campus Sydney, Sydney, Australia

Correspondence
Ariane Bercu, University of Bordeaux, Inserm, Bordeaux Population Health Research Center, Bordeaux cedex, France.
Email: ariane.bercu@u-bordeaux.fr

Abstract: The utility of brain magnetic resonance imaging (MRI) for predicting dementia is debated. We evaluated the added value of repeated brain MRI, including atrophy and cerebral small vessel disease markers, for dementia prediction. We conducted a landmark competing risk analysis in 1716 participants of the French population-based Three-City Study to predict the 5-year risk of dementia using repeated measures of 41 predictors till year 4 of follow-up. Brain MRI markers improved significantly the individual prediction of dementia after accounting for demographics, health measures, and repeated measures of cognition and functional dependency (area under the ROC curve [95% CI] improved from 0.80 [0.79 to 0.82] to 0.83 [0.81 to 0.84]). Nonetheless, accounting for the change over time through repeated MRIs had little impact on predictive abilities. These results highlight the importance of multimodal analysis to evaluate the added predictive abilities of repeated brain MRI for dementia and offer new insights into the predictive performances of various MRI markers.

KEYWORDS
brain volume, cognition, competing risks, dementia, hippocampal volume, landmark, mixed model, survival, white matter hyperintensities

Highlights

- We evaluated whether repeated brain volumes and cSVD markers improve dementia prediction.
- The 5-year prediction of dementia is slightly improved when considering brain MRI markers.
- Measures of hippocampus volume are the main MRI predictors of dementia.
- Adjusted on cognition, repeated MRI has poor added value over single MRI for dementia prediction.
- We utilized a longitudinal analysis that considers error-and-missing-prone predictors, and competing death.

1 | BACKGROUND

Given the aging of the population worldwide and the expected growth in dementia burden, prevention of dementia is a major challenge for the next years.[1] As dementia is a long process with a phase of progressive cognitive decline accompanied by brain modifications, including atrophy, before symptoms are obvious,[2] early detection of persons at high risk of dementia is key to anticipating clinical management. It is well-recognized that dementia is caused by a mix of neurodegenerative processes and vascular brain injury.[3] The most frequent vascular brain disease is cerebral small vessel disease (cSVD) which is characterized by the presence of subcortical and cortical lesions observed on brain magnetic resonance imaging (MRI), such as white matter hyperintensities (WMH), dilated perivascular spaces (PVS), lacunae, cerebral microbleeds or microinfarcts,[4,5] as well as concomitant brain atrophy.[6]

In recent studies, performances of prediction models have been improved by leveraging fluid and MRI biomarkers. However, only a limited number of studies have assessed the efficacy of various MRI indicators of brain aging, such as global and regional brain volumes or cSVD markers, in predicting dementia beyond commonly utilized factors, and their findings vary.[7–11]

The research hypotheses of this work are that dementia risk prediction could be improved by incorporating, in addition to established risk predictors, (1) MRI markers, including both atrophy and cSVD markers; and (2) repeated measurements of MRI markers compared to a single measurement.

Two potential flaws need to be better addressed in prediction models. First, there is the competing risk of death: Since many predictors of dementia risk are also predictors of death, it is possible that the best predictors of the instantaneous risk of dementia as selected by standard survival analysis (ie, Cox model) are different from the best predictors of the cumulative risk to develop dementia before death over a period of time that could be identified using a model for competing risks. Second, although the natural history of dementia is characterized by a progressive cognitive/functional deterioration, most prediction models have relied on single time point measures of MRI biomarkers or cognitive and functional levels. The added value of repeated measures and whether accounting for the markers' dynamic change could improve dementia risk prediction are unclear.[12]

The objective of this work was to identify the best predictors of the 5-year cumulative incidence function (CIF) of dementia among cognitive and functional measures, MRI measures including brain atrophy measures, and cSVD markers (repeated or single measure), along with other standard risk factors considering repeated measures of the time-dependent markers.

RESEARCH IN CONTEXT

1. **Literature review**: The authors reviewed the literature using traditional sources (eg, Google Scholar, PubMed). The usefulness of MRI markers of brain aging in the prediction of dementia has been widely described. Nonetheless, few studies have focused on its added value, in particular of cSVD markers, after accounting for cognitive and functional predictors, and none of them evaluated predictive abilities of repeated MRI.
2. **Interpretation**: This manuscript proposes a methodological framework for building prediction models for dementia based on repeated measures of numerous multimodal predictors, avoiding selection biases and accounting for competing risk of death. Our findings highlight that MRI markers of brain aging measures can improve predictive abilities over cognitive and functional assessments.
3. **Future directions**: Future work could focus on replicating the analysis on other cohort data and exploring the role of other cSVD markers such as lacunae and microbleeds.

2 | METHODS

2.1 | Three-City cohort

The Three-City Study (3C) is a population-based cohort study conducted in the French elderly population that aims at investigating the relationship between vascular risk factors and dementia.[13] Participants over 65 years old and living at home in three French cities (Bordeaux, Dijon, Montpellier) were randomly selected from electoral rolls and invited to enroll in the study between 1999 and 2001. After baseline visits, participants underwent follow-up visits at 2, 4, 7, 10, and 12 years. At each visit, a trained neuropsychologist completed a standardized medical and neuropsychological evaluation. Brain MRI scans were carried out on subsamples at baseline and at the 4-year follow-up visit (Visit_4y).

As MRI markers were not available in the center at Montpellier, the current study was restricted to participants of Bordeaux and Dijon, still at risk of dementia at the Visit_4y. Among the 7035 participants enrolled in the cohort from Bordeaux and Dijon, 2210 had at least one measure of MRI markers, and among them 1757 participants were seen and at risk (ie, not demented) at Visit_4y. After exclusion of 39 participants with missing information on at least one predictor, the final analytical sample was composed of 1716 participants (see flow chart in supplementary Figure S1).

2.2 | Sociodemographic, cognitive, functional, and health data collected

Sex is considered binary, female or male. Education level is classified as low if the participants reached secondary school or less, and long otherwise.

Functional impairment was characterized by three binary indicators: (1) mobility impairment, from the Rosow and Breslau mobility scale,[14] which is defined as any restrictions in "walking between 500 m and 1 km" or "stair climbing" up to Visit_4y; (2) the basic activities of daily living (ADL); and (3) the instrumental activities of daily living

(IADL). The latter two were assessed by the Katz and Lawton scale.[15,16] A participant was labeled *IADL-impair* if not independent for four activities up to Visit_4y: telephone, transportation, medication, and budget. A participant had an ADL impairment if not independent for five activities up to Visit_4y: bathing, dressing, going to the toilet, transferring, and feeding.

Repeated indicators of health condition from the clinical examinations included systolic blood pressure (SBP, mean of two evaluations in seated position), body mass index (BMI, weight/height^2), depressive symptomatology score using the Center for Epidemiologic Studies–Depression (CES-D) scale,[17] medication intake (number of drugs [#DRUGS]) as the number of regular drugs taken in the last month before the follow-up visit, and the binary incontinence indicator defined from the ADL scale.[18]

History of the following comorbidities at Visit_4y was considered. A person was considered diabetic if under treatment or if blood glucose was ≥7 mmol/L at least one visit up to Visit_4y. Coronary disease history was defined as self-reported myocardial infarction or angina pectoris or coronary surgery at least one time up to Visit_4y. Stroke was self-reported up to Visit_4y.

Genetic determinant of dementia was defined by the apolipoprotein E (*APOE*) gene, as carrying at least one $\varepsilon 4$ allele.

Cognition was assessed through four cognitive tests, with higher scores reflecting better cognitive functions: the Benton Visual Retention Test (BVRT)[19] for visual memory and attention; the Mini-Mental State Examination (MMSE)[20] for global cognitive functioning; the Trail Making Test A and B (TMT A and B)[21] for visual scanning/processing speed and executive function; and Isaacs's Set Test[22] (IST) for verbal fluency (15 seconds for the semantic categories of animals, cities, fruit, and colors). These cognitive tests were administered at baseline, 2- and 4-year follow-up examinations, excluding TMT at 2-year follow-up.

2.3 | MRI examination

The detailed MRI acquisition process is outlined in Appendix A.[23,24] Total white matter volume (WMV), total gray matter volume (GMV), hippocampus volume (HIPP), and total cerebrospinal fluid volume (CSFV) were obtained by automated procedures using Statistical Parametric Mapping and FreeSurfer software. Total intracranial volume (TIV) was calculated as (WMV + GMV)/(WMV + GMV + CSFV). An automated procedure for the assessment of WMH by multispectral (T1, T2, PD) MRI was implemented.[24] WMH volume was calculated as the sum of the volumes of detected lesions in the WM. Perivascular space burden in deep white matter and basal ganglia (DWM-PVS and BG-PVS), that is, the number of PVS clusters, was obtained using the SHIVA-PVS deep learning algorithm.[25,26]

2.4 | Diagnosis of dementia and death

Potential dementia cases were ascertained at each visit according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition revised (DSM IV-R) criteria, using a three-step procedure. The psychologist initially screened participants based on neuropsychological performance and decline. Participants suspected of having dementia underwent examination by a senior neurologist for clinical diagnosis. Final diagnosis was established by consensus of a classification committee of experts.[27] Clinical dementia onset time was defined as the midpoint between the last visit with a confirmed absence of dementia ("negative diagnosis") and the diagnosis visit.

Vital status and exact date of death were recorded throughout the follow-up. The competing dementia-free-death was defined as a death within 3 years following a negative diagnosis. Otherwise, the time to dementia-free-death was censored at the last negative diagnosis time.

2.5 | Statistical analysis: A landmark regularized survival approach

We aimed at predicting the risk of dementia before death, from a landmark time of 4 years after baseline (ie, Visit_4y), to a horizon of prediction of 5 years, among participants free of dementia at the landmark time, using all the information collected up to the landmark time (ie, baseline, Visit_2y, and Visit_4y). To avoid the bias due to the selection of the subjects with complete measures of all predictors at Visit_4y and the bias due to the measurement error on the predictors,[28] the trajectories of most of the repeated markers were first modeled using a mixed effects model and their predicted values and slopes at Visit_4y were then included as explanatory variables in a regularized Fine and Gray (F&G) model to predict the 5-year risk of dementia. Note that the quantitative values of the regression parameters cannot be interpreted in F&G models.[29,30]

The trajectories of 16 markers were modeled from baseline to Visit_4y. This set of predictors included five cognitive test scores (MMSE, IST, BVRT, TMT A and B), six MRI variables (WMH, DWM- and BG-PVS, HIPP, GMV, WMV), and five health indicators (SBP, #DRUGS, BMI, CES-D, and incontinence). The trajectories were estimated by curvilinear mixed models which extend the linear mixed model theory to quantitative outcomes that are not necessarily Gaussian (eg, MMSE or CES-D).[31] The trajectories over time in the curvilinear mixed models were assumed quadratic or linear with individual random effects depending on the number of repeated measures for each time-dependent variable. Backward selection based on p-value ($\alpha = 0.05$) was performed to optimize trajectories prediction (see supplementary Table S1).

The analyses were carried out in R with the packages lcmm,[32] Hdlandmark,[33] and crrp[34] for mixed models estimation, individual predictions, and the F&G regularized model, respectively.

2.6 | Strategy of analysis

The full set of predictors was composed of 40 variables, including four time-fixed variables observed at inclusion (sex, education level, *APOE4*, and TIV), seven time-dependent variables observed at Visit_4y (Age, Mobility, IADL and ADL impairment, history of diabetes, coronary

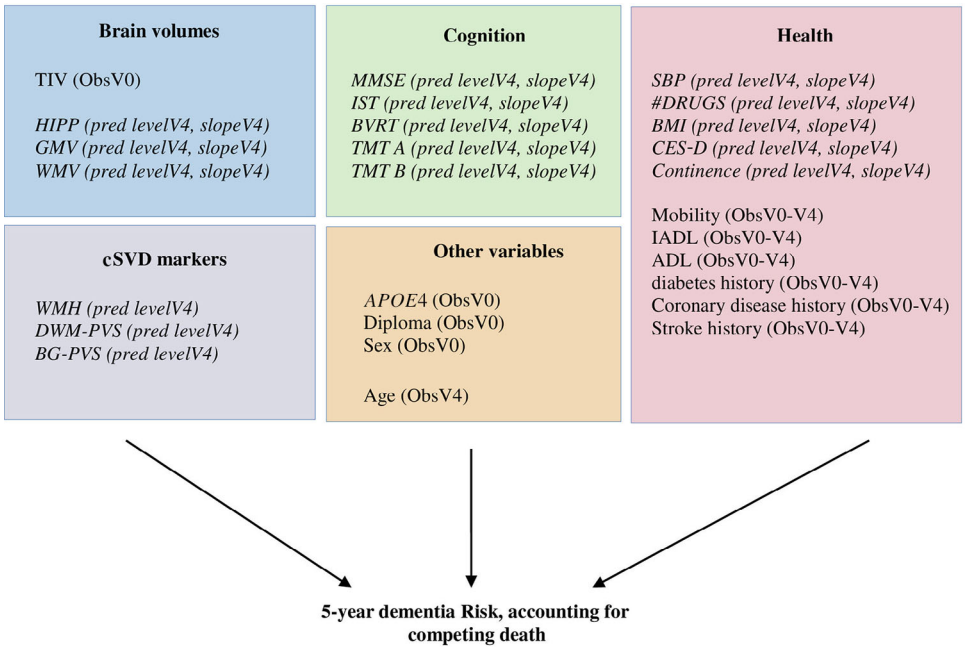

FIGURE 1 Exhaustive list of the multimodal candidate covariates for 5-year prediction of dementia risk in the Three-City Study cohort ($n = 1716$). The candidates are presented by their affiliation to cognition, health indicators, brain volumes, cSVD markers, or as other variables. Parenthetical notations indicate whether the candidate is defined as an observation at inclusion or at landmark time (ObsV0 and ObsV4, respectively; in roman), or if its value is predicted at landmark time (predlevelV4) in addition to its slope (slopeV4), both in italics. PredlevelV4 and slopeV4 were predicted from the curvilinear mixed model; ObsV0, ObsV0-V4, and ObsV4 were directly observed. ADL, activities of daily living; BG, basal ganglia; BMI, body mass index; BVRT, Benton Visual Retention; CES-D, Center for Epidemiologic Studies–Depression score; #DRUGS, number of drugs; DWM, deep white matter; GMV, gray matter volume; HIPP, hippocampus volume; IADL, instrumental activities of daily living; IST, Isaacs's Set Test; MMSE, Mini-Mental State Examination; PVS, perivascular space; SBP, systolic blood pressure; TIV, total intracranial volume; TMT, Trail Making Test; WMH, white matter hyperintensities; WMV, white matter volume.

disease, and stroke), sixteen predicted values and thirteen predicted slopes of time-dependent variables at Visit_4y (listed above, Figure 1). Note that predicted slopes in linear mixed models are defined as the value of the first derivative at Visit_4y. The slopes of the three cSVD markers were not considered because the Pearson's correlation matrix (supplementary Figure S2) showed that the predicted values and slopes of cSVD markers brought the same information (correlation of >0.95).

We first considered the full set of predictors and identified the predictors associated with better estimation of the CIF of dementia in a penalized F&G model. Minimax concave penalty (MCP) was chosen because it provides a postselection Wald test for the regression parameters.[35] We then applied the same approach to select the most predictive variables from three reduced sets of candidate predictors: (1) excluding MRI measures, (2) excluding only cSVD markers, and (3) excluding predicted slopes at Visit_4y (slopeV4) of MRI measures (to quantify the improvement in predictive abilities when using repeated MRI measures vs a single measure). To account for brain reserve,[36,37] the analyses were adjusted for TIV.

The 5-year predictive abilities of the four models were compared using the time-dependent area under the (receiver operating characteristic [ROC]) curve (AUC) and the time-dependent Brier Score (BS).[38] The AUC quantifies the probability at 5 years that a random subject with dementia has a higher predicted dementia probability than a random dementia-free subject.[38] BS is the mean squared error between dementia status and the predicted probability to develop dementia within the 5-year window.[39] Censoring was accounted for by an inverse probability of censoring weighting estimator (timeROC R package).[38] To avoid overfitting, the AUC and BS were estimated by repeated 5-fold cross-validation. Standard error of the AUC, BS, and differences of the AUC and BS between models were estimated empirically over the 50 repetitions in order to compute 95% confidence intervals (CIs). The predictive abilities of two models were significantly different if zero was not in the 95%CI of the difference of AUC or BS.

3 | RESULTS

3.1 | Sample description

Tables 1 and 2 display characteristics of the 1716 participants included in the analysis. Participants' mean age at Visit_4y was 76 years (SD 4.0 years), 62% were female, 58% had a low educational level, 20% had at least one *APOE* ε4 allele. Few participants were dependent at Visit_4y (5%, 4%, and 1% for mobility, IADL, and ADL, respectively), 10% of the participants had a history of diabetes or coronary artery disease, and 3% had a history of stroke at Visit_4y.

During the 5 years following Visit_4y, 111 participants were diagnosed with dementia (86 with Alzheimer's disease [AD], 10 mixed, 15

TABLE 1 Characteristics of participants at landmark time (Visit_4y).

Variables[a]	Incident dementia cases ($n = 111$)	Incident death dementia-free ($n = 109$)	No event ($n = 1\,496$)	All ($n = 1716$)
Measured at enrollment in cohort				
Female sex (*n*, %)	74 (67)	45 (41)	948 (63)	1067 (62)
Short educational level (*n*, %)	68 (61)	71 (65)	854 (57)	993 (58)
At least one *APOE* ε4 allele (*n*, %)	35 (32)	21 (19)	295 (20)	351 (20)
Total intracranial volume (in cm^3)	1249 (137)	1290 (155)	1329 (147)	1314 (149)
Measured at landmark time				
Age (in years)	78 (3.92)	77 (3.90)	75 (3.76)	76 (3.96)
Dependent in mobility (*n*, %)	16 (14)	16 (15)	56 (4)	88 (5)
Dependent in instrumental activities of daily living (*n*, %)	16 (14)	18 (17)	32 (2)	66 (4)
Dependent in activities of daily living (*n*, %)	3 (3)	7 (6)	13 (1)	23 (1)
History of diabetes (*n*, %)	16 (14)	20 (18)	136 (9)	172 (10)
History of stroke (*n*, %)	4 (4)	4 (4)	39 (3)	47 (3)
History of coronary disease (*n*, %)	17 (15)	11 (10)	145 (10)	173 (10)

Notes: The 3C cohort, $n = 1716$. 3C-Patients' characteristics observed at landmark time are defined per subgroups of events and globally ($n = 1716$). Categorical variables are only binary and described in terms of number of subjects and percentage per subgroups. Continuous variables are described in terms of mean and standard deviation. *APOE*, apolipoprotein E.

[a]Continuous data are the mean and standard deviation in parentheses; binary data are the numbers of patients and percentages in parentheses (from subgroups of event).

other type), and 109 participants died dementia-free. The mean time to onset of dementia after Visit_4y was 2.55 years (SD 1.21; range 1.37 to 4.76 years). Participants who died during this 5-year period were followed 2.35 years on average (SD 1.31; range 0.29 to 4.98 years). Participants alive and without dementia diagnosis were followed on average for 4.85 years (SD 0.48; range 2.60 to 5 years).

3.2 | Selected variables for predicting dementia

From the full set of 40 predictors (Figure 1), the MCP-regularized F&G model selected 17 predictors of 5-year dementia risk. Since quantitative values of parameters do not have a meaningful interpretation, we reported in Figure 2 the direction of the association with a deleterious/protective association with the CIF of dementia (ie, higher/lower incidence) indicated by bars showing positive/negative values, and the strength of evidence indicated by the height of each bar which corresponded to the log (*p*-value) (ie, the higher the bar, the more significant the association). The evolution of parameter values as the intensity of the penalization increases is displayed in supplementary Figure S3. The selected predictors among cognitive, functional, health, and MRI markers were age, sex, *APOE* gene, educational level, MMSE, IST, depressive symptomatology, SBP, #DRUGS, mobility, IADL and ADL impairment, TIV, GMV, HIPP, and WMH volume. Higher cognitive test scores at Visit_4y were significantly associated with a lower CIF of dementia. *APOE* genotype and IADL dependency at Visit_4y were significantly associated with a higher CIF of dementia. Age, sex, educational level, depressive symptomatology, SBP, #DRUGS, mobility, and ADL were selected but not significantly associated with the CIF of dementia at the 5% level. Among MRI markers, both higher volumes and slower atrophy (less negative slope) of HIPP were associated with a lower CIF of dementia. Although TIV and GMV were selected in the final model, they were poorly associated with dementia risk in the adjusted model. Finally, among cSVD markers, only WMH volume at Visit_4y was selected, higher volume being associated with a higher CIF of dementia but this association was not significant.

To assess the impact of MRI measures in the prediction models, we performed the same analysis excluding all MRI measures from the initial set of predictors (Figure 2, top panel). The selected variables among cognitive, functional, and health indicators were identical with and without including MRI markers although significance levels for age, *APOE*, and education were deeply reduced when adjusting on MRI.

3.3 | Predictive abilities

To evaluate the respective contribution of MRI, repeated MRI, and cSVD markers to the prediction of the CIF of dementia, we compared the repeated 5-fold cross-validated AUC (the higher the value, the more discriminative) and BS (the lower the value, the more accurate) of models built by MCP regression (Table 3). All models showed good performance in predictive abilities with a mean AUC above 0.80. However, considering MRI measures in addition to cognition and health indicators led to slightly but significantly better predictive performances (eg,

TABLE 2 Characteristics of participants for time-dependent variables at inclusion and landmark time (Visit_4y).

Time-dependent variables[a]	Incident dementia cases ($n = 111$)	Incident death dementia-free ($n = 109$)	No event ($n = 1\,496$)	All ($n = 1\,716$)
Health indicators				
Incontinence (*n*, %)				
At enrollment	25 (23)	16 (15)	299 (20)	340 (20)
At 4-year follow-up	28 (25)	18 (17)	244 (16)	290 (17)
Depressive symptomatology score using Center for Epidemiologic Studies–Depression scale				
At enrollment	10.6 (10.2)	8.0 (6.9)	8.9 (8.3)	8.9 (8.4)
At 4-year follow-up	11.7 (8.8)	9.3 (7.7)	8.3 (7.7)	8.6 (7.8)
Body mass index (in kg/m^2)				
At enrollment	25.7 (3.9)	26.3 (3.7)	25.5 (3.7)	25.6 (3.7)
At 4-year follow-up	25.4 (3.9)	25.7 (3.6)	25.4 (3.7)	25.4 (3.7)
Number of drugs used (/month)				
At enrollment	4.8 (3.1)	4.5 (3.0)	3.9 (2.8)	4.0 (2.8)
At 4-year follow-up	5.9 (3.3)	5.3 (3.2)	4.8 (3.2)	4.9 (3.2)
Systolic blood pressure (mmHg)				
At enrollment	148.1 (23.2)	151.9 (25.9)	146.3 (22.1)	146.7 (22.4)
At 4-year follow-up	136.6 (19.2)	141.0 (25.5)	136.6 (20.0)	136.8 (20.3)
Cognition				
Benton Visual Retention				
At enrollment	11.05 (1.94)	11.57 (1.89)	11.95 (1.77)	11.87 (1.80)
At 4-year follow-up	10.61 (2.00)	11.27 (1.95)	11.64 (1.86)	11.55 (1.89)
Mini-Mental State Examination				
At enrollment	27.19 (1.90)	27.83 (1.72)	27.95 (1.64)	27.89 (1.67)
At 4-year follow-up	26.68 (2.01)	27.53 (1.99)	27.97 (1.70)	27.85 (1.77)
Isaacs's Set Test				
At enrollment	30.34 (5.82)	31.98 (6.77)	34.33 (6.56)	33.92 (6.61)
At 4-year follow-up	29.50 (6.06)	32.15 (7.28)	35.84 (6.20)	35.19 (6.50)
Trail Making Test A (# good moves/time)				
At enrollment	26.94 (8.87)	29.69 (12.40)	30.85 (9.47)	30.53 (9.69)
At 4-year follow-up	24.85 (8.51)	28.01 (11.78)	30.95 (9.65)	30.38 (9.85)
Trail Making Test B (# good moves/time)				
At enrollment	11.54 (5.94)	13.64 (7.07)	14.77 (7.03)	14.49 (7.00)
At 4-year follow-up	9.97 (6.47)	11.85 (6.94)	14.10 (7.13)	13.70 (7.16)
Magnetic resonance imaging (MRI)				
White matter hyperintensities (in cm^3)				
At enrollment	5.77 (5.30)	5.09 (3.83)	4.86 (3.76)	4. 93 (3.89)
At 4-year follow-up	7.63 (5.75)	6.38 (5.33)	5.83 (4.68)	5.96 (4.80)
White matter—perivascular spaces (# of)				
At enrollment	295.47 (101.33)	306.99 (105.89)	306.86 (110.35)	306.13 (109.49)
At 4-year follow-up	306.36 (108.17)	299.56 (105.97)	308.86 (106.74)	308.26 (106.73)
Basal ganglia—perivascular spaces (# of)				
At enrollment	20.43 (9.29)	22.06 (10.35)	18.69 (8.14)	19.02 (8.42)
At 4-year follow-up	22.52 (11.43)	23.36 (10.54)	20.83 (9.48)	21.05 (9.68)

(Continues)

TABLE 2 (Continued)

Time-dependent variables[a]	Incident dementia cases ($n = 111$)	Incident death dementia-free ($n = 109$)	No event ($n = 1\,496$)	All ($n = 1\,716$)
Hippocampus volume (in cm^3)				
At enrollment	6.21 (0.86)	6.51 (0.90)	6.71 (0.78)	6.67 (0.80)
At 4-year follow-up	5.82 (0.91)	6.28 (0.90)	6.51 (0.83)	6.46 (0.85)
Gray matter volume (in cm^3)				
At enrollment	488.46 (42.23)	493.19 (51.91)	502.29 (49.74)	500.82 (49.56)
At 4-year follow-up	470.72 (40.41)	475.79 (56.19)	491.15 (48.88)	489.23 (49.09)
White matter volume (in cm^3)				
At enrollment	459.96 (45.96)	468.48 (55.69)	466.35 (52.25)	466.07 (52.90)
At 4-year follow-up	448.27 (50.48)	460.55 (68.23)	469.19 (64.73)	467.56 (64.33)

Notes: The 3C cohort, $n = 1716$. 3C-Patients' characteristics observed at enrollment and landmark time are defined per subgroups of events and globally ($n = 1716$). These characteristics will be summarized at landmark time through predicted value and slope. Categorical variables are only binary and described in terms of number of subjects and percentage per subgroups. Continuous variables are described in terms of mean and standard deviation.
[a]Continuous data are the mean and standard deviation in parentheses; binary data are the numbers of patients and percentages in parentheses (from subgroups of event).

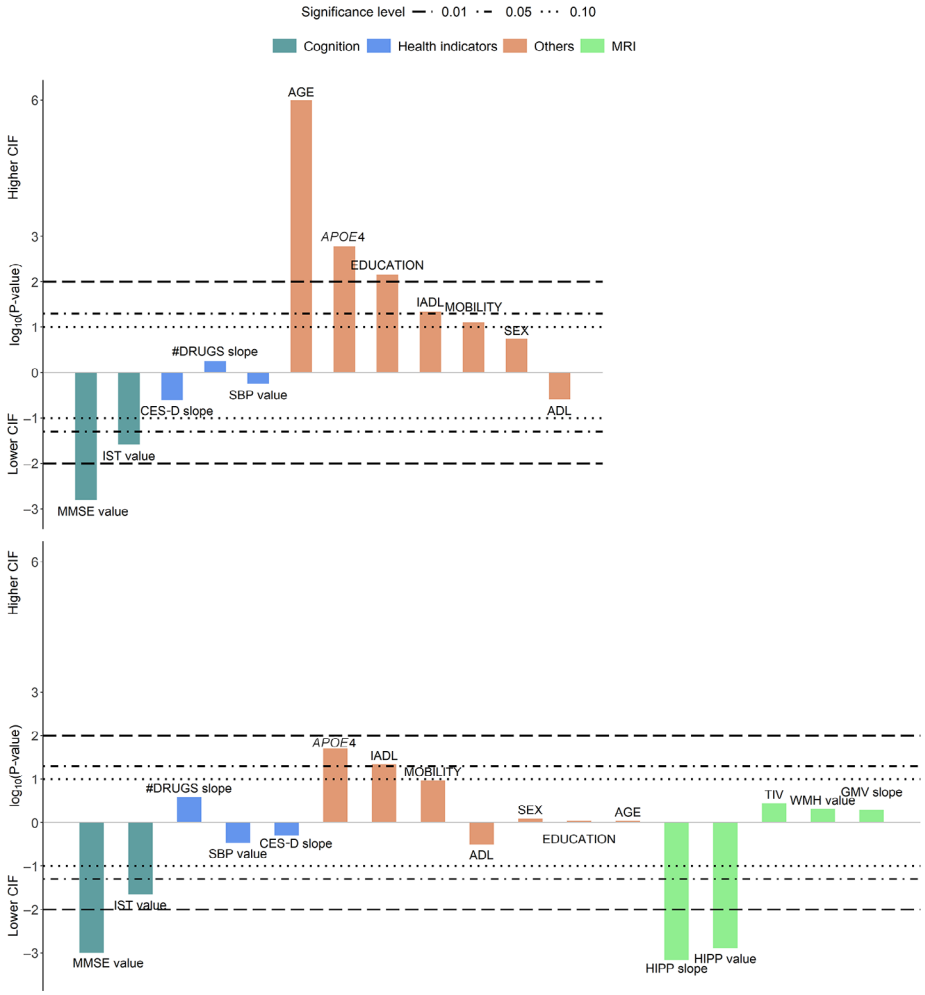

FIGURE 2 Direction of associations and significance level between the variables selected by minimax concave penalty regression and cumulative incidence function (CIF) of dementia among the whole set of potential predictors including MRI (bottom panel) and excluding MRI (top panel), $n = 1716$. The figure presents the log (p-value) and the direction of the association with cumulative incidence of dementia (positive bars if higher cumulative incidence for higher predictor value; negative bars if lower cumulative incidence for higher predictor value) for all the predictors selected in the final model. ADL, activities of daily living; CES-D, Center for Epidemiologic Studies–Depression score; CIF, cumulative incidence function; #DRUGS, number of drugs; GMV, gray matter volume; HIPP, hippocampus volume; IADL, instrumental activities of daily living; IST, Isaacs's Set Test, MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; SBP, systolic blood pressure; TIV, total intracranial volume; WMH, white matter hyperintensities.

TABLE 3 Performances of different models based on the inclusion of magnetic resonance imaging (MRI) markers to predict incident dementia from landmark time to the next 5 years.

Models[a]	Area under the curve [95% CI]	Brier score [95% CI]
1 – Full model	0.828 [0.813 to 0.842]	0.047 [0.045 to 0.048]
2 – without MRI markers	0.802 [0.788 to 0.817]	0.050 [0.049 to 0.051]
3 – without slopes of MRI markers at 4 years follow-up	0.821 [0.805 to 0.836]	0.048 [0.047 to 0.049]
4 – without cSVD markers	0.827 [0.814 to 0.841]	0.047 [0.046 to 0.048]

Notes: The 3C cohort, $n = 1716$. The performance of the models for 5-year prediction of dementia are compared by area under the curve and Brier Score computed by 5-fold cross-validation on the 3C cohort ($n = 1716$). Four different models are presented. Variable selection for each model is performed by minimax concave penalty (MCP) regularization using four different sets of initial candidate predictors. The set of candidate predictors for Model 1 includes the 40 variables. The set of candidate predictors for Model 2 excludes MRI markers (thus it is composed of 30 variables); the set of candidate predictors for Model 3 excludes only slopes of MRI markers (thus it includes 37 variables)s the set of candidate predictors for Model 4 excludes only cerebral small vessel disease (cSVD) markers (37 variables).
Abbreviations: cSVD: cerebral small vessel disease; MRI: magnetic resonance imaging.
[a]Full model is composed of 40 predictors: sex, education level, apolipoprotein E (*APOE*) ε4 allele, total intracranial volume, age, mobility, instrumental activities of daily living (IADL) and activities of daily living (ADL) impairment, history of diabetes, coronary disease and stroke, predicted values and slopes of cognitive tests, health indicators, and MRI markers.

AUC [95% CI] = 0.83 [0.81 to 0.84] with MRI vs 0.80 [0.79 to 0.82] without MRI). Differences of AUC and BS between models are displayed in Figure 3. Among models with MRI markers, excluding cSVD markers (ie, predicted value at Visit_4y of WMH and PVS) did not significantly alter the predictive performances since the 95% CIs of the difference included 0 (ΔAUC = −0.0003 [−0.006 to 0.005], ΔBS = −0.0000 [−0.0005 to 0.0005]). Excluding the slopes of all MRI markers did not significantly modify the AUC (ΔAUC = −0.007 [−0.015 to 0.002]) but slightly increased the BS (ΔBS = 0.0009 [0.0001 to 0.002]).

4 | DISCUSSION

Adding MRI markers to a prediction model that includes classical dementia risk factors, along with repeated cognitive and functional assessments, improved the accuracy of 5-year prediction of dementia. Given that cognitive and functional markers are good predictors of dementia,[12] it was not obvious that the inclusion of MRI markers would significantly improve the predictive abilities. Our findings suggest that low volume and steeper atrophy of the hippocampus increase the 5-year risk. Conversely, cSVD markers (WMH volume and PVS burden) did not improve significantly the individual prediction of the cumulative dementia risk in a prediction model that includes demographics, health measures, and repeated measures of cognition, functional dependency, and brain volumes.

This work also aimed to address the utility of repeated measures of MRI. Accounting for the change over time of hippocampal volume through repeated MRIs had only a minor impact on predictive abilities: This slightly increased the prediction accuracy but did not improve significantly the discrimination between future cases of dementia and other participants.

Few studies have focused on the added value of repeated measures of brain volumes and cSVD markers on the prediction of dementia while considering both known risk factors and measures of cognitive and functional decline. Most of these studies are not population-based and/or focused only on the transition from mild cognitive impairment (MCI) to AD or dementia,[40,41] In the 3C cohort, Stephan et al.[7] showed that HIPP and WMH at baseline were significantly associated with the instantaneous risk of dementia after adjusting on conventional factors but it did not significantly improve the discrimination (C-index). We note that factors associated (possibly causally) with both dementia risk and mortality may not be predictive of the cumulative incidence of dementia before death. Indeed, factors that increase the risk of death reduce the time at risk of dementia and thus tend to reduce the CIF of dementia. Studies that have investigated the link between cSVD and mortality suggest that stroke and dementia explain only partly the increased mortality observed in elderly individuals with extended WMH volumes. cSVD is also a marker of vascular damages in other territories than the brain such as coronary arteries.[42] To further explore the role of cSVD in the prediction of dementia, it would be useful to include more markers such as lacunae and microbleeds (not yet available in 3C data) and to include more repeated measures. The two measures of WMH and PVS showed an increase over time of these markers but they were too highly correlated to capture the individual variability.

The strengths of the study include the population-based design of the 3C cohort with a large number of participants, a standardized clinical diagnosis of dementia, and a large set of potential predictors measured with standardized methods. From a methodological point of view, this analysis handled the competing risk of death, which is a major issue in the elderly population, particularly for dementia prediction, given that most of the risk factors for dementia are also associated with an increased risk of death. Using the F&G model, we were able to predict directly the probability to develop dementia before dying within the next 5-years, which is a clinically meaningful indicator. Secondly, repeated 5-fold cross-validation permitted the analysis to validate and compare the predictive abilities of models avoiding over optimistic results in AUC and BS. Finally, the landmark approach has three main advantages. First, this approach is similar to the clinical setting where the specialist uses all past and current information to assess a patient's future risk. Second, it accounts for repeated measures of the predictors in order to evaluate if the change over time of the predictors brings additional information to their current value. Third, using mixed models to obtain predicted value and slope of the repeated predictors limits the selection bias since participants without measures of the predictors at the landmark time can be included in the analysis.

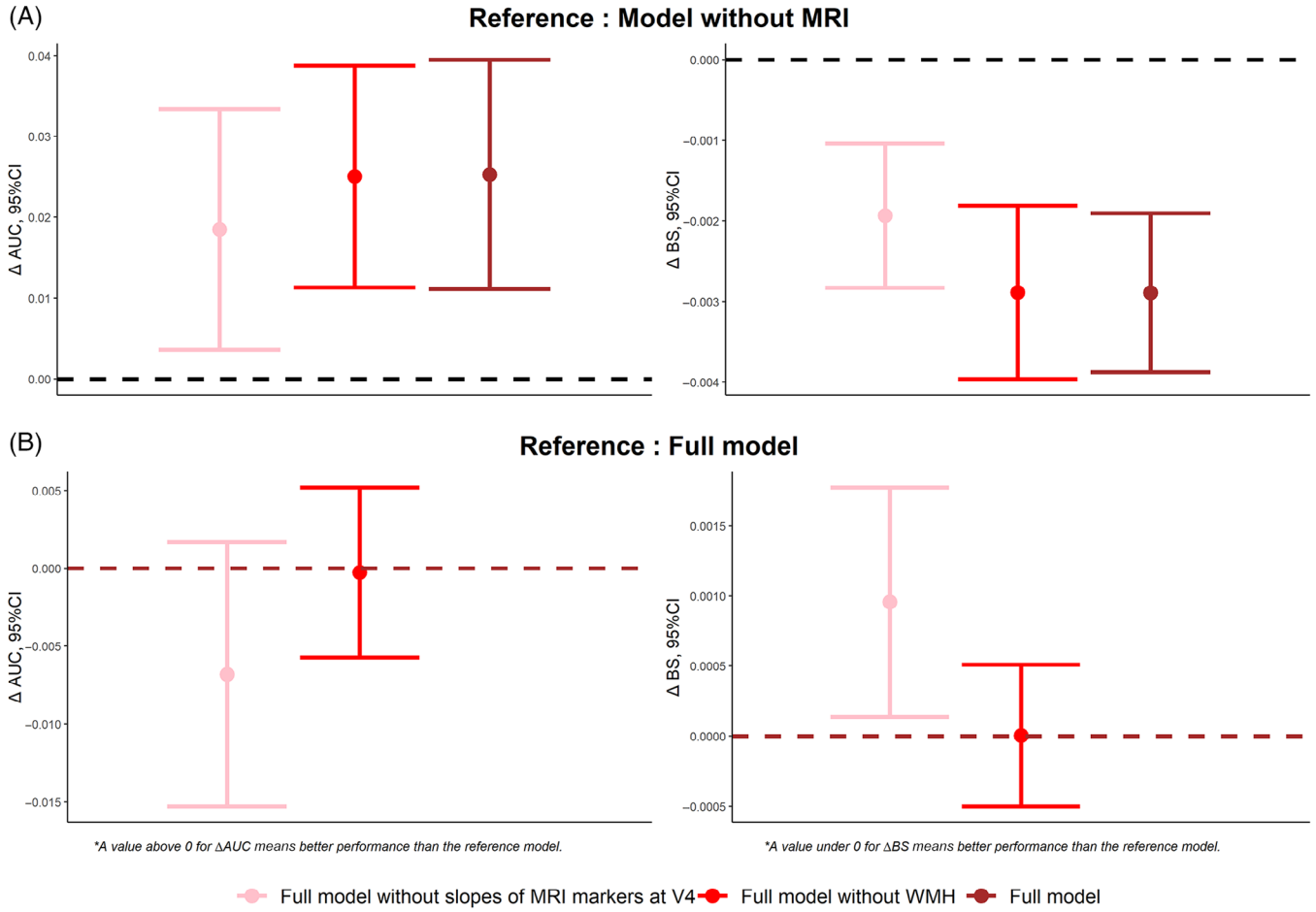

FIGURE 3 The performances of the models in comparison with two reference models—without magnetic resonance imaging (MRI; top panel) or full model (bottom panel)—were computed by 50 repeated 5-fold cross-validation in the Three-City Study cohort, $n = 1716$. The performance of the models at the next 5 years after landmark time are analyzed through discrimination (differences in area under the curve—ΔAUC) and calibration index (differences in Brier Score—ΔBS) in the 3C cohort ($n = 1716$). A value above 0 for ΔAUC and under 0 for ΔBS are associated with better discrimination and calibration in comparison to the reference model. The full model is composed of 40 predictors: sex, education level, apolipoprotein E allele, total intracranial volume, age, mobility, instrumental activities of daily living and activities of daily living impairment, history of diabetes, coronary disease, and stroke, predicted values and slopes of cognitive test, health indicators, and MRI markers. V4, 4-year follow-up; WMH, white matter hyperintensities.

Using predicted values instead of the observed ones also reduces bias due to measurement error on the predictors.[43,44] This was confirmed by a sensitivity analysis restricted to the 1108 participants with complete data, where we replicated the landmark analysis by considering the observed values and slopes rather than the predicted ones (see web Appendix B with Table S2 and Figures S4-5).

Some limitations should be considered when interpreting the results. The 3C population-based cohort is composed of volunteers who tend to have better global health than the general population, especially for those who completed MRI.[45] Thus, the incidence of dementia may be lower compared to the general population, limiting the power of the study. Nonetheless, the association between MRI markers and CIF of dementia should be similar among all subgroups. Bias in population could also have been introduced by the selection process. All participants must have at least 4 years of follow-up, this can lead to exclusion of participants with poor health. A limitation in the methodology is the clinical interpretation of the parameters. While this model is well adapted for building a prediction model in the framework of competing risks, the quantitative values of its parameters have no meaningful interpretation.[30] We can only interpret the direction of the association and the level of significance.

To conclude, we have demonstrated that combining MRI markers with neuropsychological tests, functional evaluations, and established and known demographic and clinical risk factors for dementia can slightly but significantly improve the 5-year prediction of dementia accounting for mortality. Especially, atrophy of the hippocampus is the most useful predictor while cSVD markers and repeated MRI are not necessary for individual prediction when cognitive trajectories are considered. Future work including more cSVD markers with several repeated measures could be useful to confirm these results.

ACKNOWLEDGMENTS

The Three-City Study is conducted under a partnership agreement between the National Institute of Health and Medical Research (INSERM), the University Bordeaux 2 Victor Segalen, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The Three-City Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Conseils Régionaux d'Aquitaine et Bourgogne, Fondation de France, Ministry of Research-INSERM Programme "Cohortes et collections de données biologiques," Agence Nationale de la Recherche ANR PNRA 2006 and LongVie 2007, the "Fondation Plan Alzheimer" (FCS 2009-2012), the Caisse Nationale de Solidarité pour l'Autonomie (CNSA) and Roche. This project is supported by a grant overseen by the French National Research Agency (ANR) as part of the France 2030 plan ANR-18-RHUS-0002. This study was also carried out in the framework of the University of Bordeaux's France 2030 program/RRI PHDS.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest. This paper has not been published previously in whole or in part. Author disclosures are available in the Supporting Information

CONSENT STATEMENT

All human subjects provided informed consent.

REFERENCES

1. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M, World Alzheimer Report 2015, The Global impact of dementia: an analysis of prevalence, incidence, cost and trends. Alzheimer's Disease International; 2015.
2. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119-128. doi:10.1016/S1474-4422(09)70299-6
3. Viswanathan A, Rocca W, Tzourio C. Vascular risk factors and dementia how to move forward. *Neurology*. 2009;72(4):368-374.
4. Deramecourt V, Slade JY, Oakley AE, et al. Staging and natural history of cerebrovascular pathology in dementia. *Neurology*. 2012;78(14):8. doi:10.1212/WNL.0b013e31824e8e7f
5. Mortamais M, Artero S, Ritchie K. Cerebral white matter hyperintensities in the prediction of cognitive decline and incident dementia. *Int Rev Psychiatry*. 2013;25(6):686-698. doi:10.3109/09540261.2013.838151
6. Duering M, Biessels GJ, Brodtmann A, et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol*. 2023;22(7):602-618. doi:10.1016/S1474-4422(23)00131-X
7. Stephan BCM, Tzourio C, Auriacombe S, et al. Usefulness of data from magnetic resonance imaging to improve prediction of dementia: population based cohort study. *BMJ*. 2015;350(jun22 8):h2863-h2863. doi:10.1136/bmj.h2863
8. Kuller LH, Lopez OL, Newman A, et al. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology*. 2003;22(1):13-22. doi:10.1159/000067109
9. Meguro K, Ishii H, Kasuya M, et al. Incidence of dementia and associated risk factors in Japan: the Osaki-Tajiri Project. *J Neurol Sci*. 2007;260(1-2):175-182. doi:10.1016/j.jns.2007.04.051
10. Hou XH, Feng L, Zhang C, Cao XP, Tan L, Yu JT. Models for predicting risk of dementia: a systematic review. *J Neurol Neurosurg Psychiatry*. 2019;90(4):373-379. doi:10.1136/jnnp-2018-318212
11. Tang EYH, Harrison SL, Errington L, et al. Current developments in dementia risk prediction modelling: an updated systematic review. Forloni G, ed. *PLOS ONE*. 2015;10(9):e0136181. doi:10.1371/journal.pone.0136181
12. Ben-Hassen C, Helmer C, Berr C, Jacqmin-Gadda H. Five-year dynamic prediction of dementia using repeated measures of cognitive tests and a dependency scale. *Am J Epidemiol*. 2022;191(3):453-464. doi:10.1093/aje/kwab269
13. 3C Study Group. Vascular factors and risk of dementia: design of the three-city study and baseline characteristics of the study population. *Neuroepidemiology*. 2003;22(6):316-325. doi:10.1159/000072920
14. Rosow I, Breslau N. A guttman health scale for the aged. *J Gerontol*. 1966;21(4):556-559. doi:10.1093/geronj/21.4.556
15. Lawton MP. Scales to measure competence in everyday activities. *Psychopharmacol Bull*. 1988;24(4):609-614.
16. Katz S, Downs T, Cash H, Grotz R. Progress in development of the index of ADL. *The gerontologist*. 1970;10:20-30. Part 1.
17. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385-401. doi:10.1177/014662167700100306
18. Katz S. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. 1963;185(12):914. doi:10.1001/jama.1963.03060120024016
19. Lechevallier-Michel N, Fabrigoule C, Lafont S, Letenneur L, Dartigues JF. Normes pour le MMSE, le test de rétention visuelle de Benton, le set test d'Isaacs, le sous-test des codes de la WAIS et le test de barrage de Zazzo chez des sujets âgés de 70 ans et plus : données de la cohorte PAQUID. *Rev Neurol (Paris)*. 2004;160(11):1059-1070. doi:10.1016/S0035-3787(04)71143-1
20. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6
21. Amieva H, Le Goff M, Stoykova R, et al. Trail Making Test : a et B (version sans correction des erreurs) : normes en population chez des sujets âgés, issues de l'étude des trois Cités. *Rev Neuropsychol*. 2009;1(3):210. doi:10.3917/rne.013.0210
22. Isaacs B, Kennie AT. The set test as an aid to the detection of dementia in old people. *Br J Psychiatry*. 1973;123(575):467-470. doi:10.1192/bjp.123.4.467
23. Godin O, Dufouil C, Maillard P, et al. White matter lesions as a predictor of depression in the elderly: the 3c-Dijon study. *Biol Psychiatry*. 2008;63(7):663-669. doi:10.1016/j.biopsych.2007.09.006
24. Maillard P, Delcroix N, Crivello F, et al. An automated procedure for the assessment of white matter hyperintensities by multispectral (T1, T2, PD) MRI and an evaluation of its between-centre reproducibility based on two large community databases. *Neuroradiology*. 2008;50(1):31-42. doi:10.1007/s00234-007-0312-3
25. Boutinaud P, Tsuchida A, Laurent A, et al. 3D segmentation of perivascular spaces on T1-weighted 3 tesla MR images with a convolutional autoencoder and a U-shaped neural network. *Front Neuroinform*. 2021;15:641600. doi:10.3389/fninf.2021.641600
26. Duperron MG, Knol MJ, Le Grand Q, et al. Genomics of perivascular space burden unravels early mechanisms of cerebral small vessel disease - 2023.pdf. *Nat Med*. 2023;29:950-962. doi:10.1038/s41591-023-02268-w
27. Vahia V. Diagnostic and statistical manual of mental disorders 5: a quick glance. *Indian J Psychiatry*. 2013;55(3):220. doi:10.4103/0019-5545.117131
28. Andersen PK, Liestøl K. Anderson—attenuation caused by infrequently updated covariates in survival analysis. *Biostatistics*. 2003;4(4):633-649. doi:10.1093/biostatistics/4.4.633
29. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144

30. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol*. 2012;41(3):861-870. doi:10.1093/ije/dyr213
31. Proust-Lima C, Amieva H, Jacqmin-Gadda H. Analysis of multivariate mixed longitudinal data: a flexible latent process approach. *Br J Math Stat Psychol*. 2012;66(3):470-487. doi:10.1111/bmsp.12000
32. Proust-Lima C, Philipps V, Liquet B. Estimation of extended mixed models using latent classes and latent processes: the R package lcmm. *J Stat Softw*. 2017;78(2):1-56. doi:10.18637/jss.v078.i02
33. Devaux A, Genuer R, Peres K, Proust-Lima C. Individual dynamic prediction of clinical endpoint from large dimensional longitudinal biomarker history: a landmark approach. *BMC Med Res Methodol*. 2022;22(1):188. doi:10.1186/s12874-022-01660-3
34. Fu Z, Parikh CR, Zhou B. Penalized variable selection in competing risks regression. *Lifetime Data Anal*. 2017;23(3):353-376. doi:10.1007/s10985-016-9362-3
35. Zhang CH. Nearly unbiased variable selection under minimax concave penalty. *Ann Stat*. 2010;38(2):894-942. doi:10.1214/09-AOS729
36. Foubert-Samier A, Catheline G, Amieva H, et al. Education, occupation, leisure activities, and brain reserve: a population-based study. *Neurobiol Aging*. 2012;33(2):423.e15-423.e25. doi:10.1016/j.neurobiolaging.2010.09.023
37. Barnes J, Ridgway GR, Bartlett J, et al. Head size, age and gender adjustment in MRI studies: a necessary nuisance? *NeuroImage*. 2010;53(4):1244-1255. doi:10.1016/j.neuroimage.2010.06.025
38. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med*. 2013;32(30):5381-5397. doi:10.1002/sim.5958
39. Mogensen UB, Ishwaran H, Gerds TA. Evaluating random forests for survival analysis using prediction error curves. *J Stat Softw*. 2012;50(11):1-23. doi:10.18637/jss.v050.i11
40. Korolev IO, Symonds LL, Bozoki AC. Predicting progression from mild cognitive impairment to Alzheimer's dementia using clinical, MRI, and plasma biomarkers via probabilistic pattern classification. Herholz K, ed. *PLoS One*. 2016;11(2):e0138866. doi:10.1371/journal.pone.0138866. Alzheimer's Disease Neuroimaging Initiative.
41. Gomar JJ, Bobes-Bascaran MT, Conejero-Goldberg C, Davies P, Goldberg TE. Alzheimer's disease neuroimaging initiative. utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. *Arch Gen Psychiatry*. 2011;68(9):961-969. doi:10.1001/archgenpsychiatry.2011.96
42. Debette S, Beiser A, DeCarli C, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham offspring study. *Stroke*. 2010;41(4):600-606. doi:10.1161/STROKEAHA.109.570044
43. Ferrer L, Putter H, Proust-Lima C. Individual dynamic predictions using landmarking and joint modelling: validation of estimators and robustness assessment. *Stat Methods Med Res*. 2019;28(12):3649-3666. doi:10.1177/0962280218811837
44. Sweeting MJ, Barrett JK, Thompson SG, Wood AM. The use of repeated blood pressure measures for cardiovascular risk prediction: a comparison of statistical models in the ARIC study. *Stat Med*. 2017;36(28):4514-4528. doi:10.1002/sim.7144
45. Den Heijer T, Van Der Lijn F, Koudstaal PJ, et al. A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline. *Brain*. 2010;133(4):1163-1172. doi:10.1093/brain/awq048

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: Bercu A, Dufouil C, Debette S, et al. Prediction of dementia risk from multimodal repeated measures: The added value of brain MRI biomarkers. *Alzheimer's Dement*. 2024;16:e12578. https://doi.org/10.1002/dad2.12578