






OPEN ACCESS

Original research

# Plasma phosphorylated tau 181 predicts amyloid status and conversion to dementia stage dependent on renal function

Sylvain Lehmann <sup>1</sup>, Susanna Schraen-Maschke,<sup>2</sup> Jean-Sébastien Vidal <sup>3</sup>, Constance Delaby <sup>1,4</sup>, Frédéric Blanc,<sup>5</sup> Claire Paquet,<sup>6</sup> Bernadette Allinquant,<sup>7</sup> Stéphanie Bombois,<sup>2,8</sup> Audrey Gabelle,<sup>9</sup> Olivier Hanon <sup>3</sup>

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jnnp-2022-330540>).

For numbered affiliations see end of article.

## Correspondence to

Professor Sylvain Lehmann, LBPC-PPC, Montpellier Université d'Excellence, Montpellier 34295, France; [sylvain.lehmann@umontpellier.fr](mailto:sylvain.lehmann@umontpellier.fr)

Received 10 October 2022  
Accepted 15 December 2022  
Published Online First 3 April 2023



► <http://dx.doi.org/10.1136/jnnp-2022-330619>



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Lehmann S, Schraen-Maschke S, Vidal J-S, et al. *J Neurol Neurosurg Psychiatry* 2023;**94**:411–419.

## ABSTRACT

**Objectives** Plasma P-tau181 is an increasingly established diagnostic marker for Alzheimer's disease (AD). Further validation in prospective cohorts is still needed, as well as the study of confounding factors that could influence its blood level.

**Methods** This study is ancillary to the prospective multicentre Biomarker of Amyloid peptide and Alzheimer's disease Risk cohort that enrolled participants with mild cognitive impairment (MCI) who were examined for conversion to dementia for up to 3 years. Plasma P-tau-181 was measured using the ultrasensitive Quanterix HD-X assay.

**Results** Among 476 MCI participants, 67% were amyloid positive (Aβ+) at baseline and 30% developed dementia. Plasma P-tau181 was higher in the Aβ+ population (3.9 (SD 1.4) vs 2.6 (SD 1.4) pg/mL) and in MCI that converted to dementia (3.8 (SD 1.5) vs 2.9 (SD 1.4) pg/mL). The addition of plasma P-tau181 to a logistic regression model combining age, sex, APOEε4 status and Mini Mental State Examination improved predictive performance (areas under the curve 0.691–0.744 for conversion and 0.786–0.849 for Aβ+). The Kaplan-Meier curve of conversion to dementia, according to the tertiles of plasma P-tau181, revealed a significant predictive value (Log rank  $p < 0.0001$ ) with an HR of 3.8 (95% CI 2.5 to 5.8). In addition, patients with plasma P-Tau(181)  $\leq 2.32$  pg/mL had a conversion rate of less than 20% over a 3-year period. Using a linear regression approach, chronic kidney disease, creatinine and estimated glomerular filtration rate were independently associated with plasma P-tau181 concentrations.

**Conclusions** Plasma P-tau181 effectively detects Aβ+ status and conversion to dementia, confirming the value of this blood biomarker for the management of AD. However, renal function significantly modifies its levels and may thus induce diagnostic errors if not taken into account.

## INTRODUCTION

Alzheimer's disease (AD) accounts for 60%–70% of dementia and is thus a major public health problem and socioeconomic burden that is only increasing with the ageing of the population. For a long time, diagnostic efforts have been minimal, due to the lack of preventive measures or curative treatment. However, in recent years, it has been demonstrated

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The clinical use of plasma phosphorylated tau 181 (P-tau181) for Alzheimer's disease is being considered but further validation and study of confounding factors are still needed.

## WHAT THIS STUDY ADDS

⇒ In our large prospective cohort, P-tau181 predicts brain amyloidopathy and conversion to dementia in patients with mild cognitive impairment, but renal function significantly alters plasma levels and thus may induce diagnostic errors if not taken into account.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study suggests that measurement of creatinine or estimation of glomerular filtration rate, which are easy and standardisable ways to provide information on renal function, will contribute to optimal interpretation of plasma P-tau181 results in routine clinical practice.

that modifiable risk factors account for 40% of AD.<sup>1</sup> Furthermore, many potential treatments are in the final stages of study.<sup>2</sup> Early diagnosis will be the key to further understanding of AD and successfully treating it.

The development of biological biomarkers, linked to amyloid and tau pathology, has greatly contributed to the understanding of the presymptomatic and postsymptomatic AD 'continuum', in which, thanks to genetic forms, it has been shown that the disease was present from a biological point of view decades before its clinical appearance.<sup>3</sup> This opens up therapeutic perspectives and allows us to use these biomarkers in early diagnosis and even in risk assessment. Their relevance has already been proven in cerebrospinal fluid (CSF) justifying their implementation in clinical routine.<sup>4,5</sup> Furthermore, the blood is now amenable to diagnostic assays, thanks to ultrasensitive techniques, including mass spectrometry.

The first analytes used in blood were amyloid peptides. Their levels in serum can detect amyloid positive (Aβ+) patients, as defined by amyloid PET or CSF analysis, and predict evolution of patients within the AD continuum, including conversion of

patients, with mild cognitive impairment (MCI), to dementia.<sup>6</sup> While the detection of total tau in blood was not so discriminating,<sup>7</sup> detection of its phosphorylated forms at position threonine 181 was a real breakthrough.<sup>8</sup> P-tau181 concentration is predictive of amyloid or tau PET findings and is significantly higher in AD and MCI compared with subjects without cognitive impairment or compared with other causes of dementia.<sup>8–10</sup> Its prognostic value has also been established in some longitudinal studies<sup>11–13</sup> and its overall performance allow to consider a clinical application. To reach this milestone, we will need additional prospective data, in vitro diagnostic certified kits and sufficient information on preanalytical stability.<sup>14,15</sup> It will equally be paramount to identify any confounding factors that may alter clinical performance in routine use.<sup>14</sup>

In this work, we used the prospective multicentre Biomarker of Amyloid peptide and Alzheimer's disease Risk (BALTAZAR) cohort<sup>16</sup> to confirm the ability of plasma P-tau181 to detect brain amyloidopathy and also to predict the conversion of MCI patients to dementia stage. As plasma biomarkers are soon to be implemented in routine practice, we also investigated potential confounding factors that must be considered to interpret the results adequately.

## MATERIALS AND METHODS

### Study population

The BALTAZAR study is a multicentre prospective cohort study (ClinicalTrials.gov Identifier #NCT01315639) that enrolled patients with MCI or AD, according to a previously described protocol.<sup>16</sup> All participants had clinical, neuropsychological, brain MRI and biological assessments (see below). Right and left hippocampal volume was obtained for each participant using automatic segmentation of the hippocampus. The hippocampal volume was normalised using the following calculation: hippocampal volume/total brain volume × mean total brain volume. CSF samples were collected only in accepting participants. APOE was genotyped in a single centralised laboratory. MCI subjects were selected according to the Petersen's criteria<sup>17</sup> and then they were dichotomised into amnesic (aMCI) and non-amnesic (naMCI) phenotypes, based on the presence of memory impairment on the free and cued selective reminding test related to age, sex and educational level. The characteristic of the aMCI/naMCI population is fully described elsewhere.<sup>16</sup> Patients had visits every 6 months for 3 years. MCI participants were reassessed for conversion to dementia at each visit by the clinician.<sup>6</sup> The progression from MCI to dementia was defined by evaluating the following parameters: (1) decline in cognitive function (measured by changes from the baseline in scores of the Mini Mental State Examination (MMSE)), (2) disability in activities of daily living (ADL) (instrumental ADL (IADL) >1) and (3) clinical dementia rating sum of boxes (>1). The conversions were reviewed by an adjudication committee.

In this study, we analysed 476 available baseline plasma samples from patients with MCI diagnosis (365 aMCI and 111 naMCI).

### Biological biomarker measurements

To minimise preanalytical and analytical problems, identical collection tubes were used across centres to collect plasma (EDTA BD Vacutainer K2E, ref 367 525, Becton Dickinson, USA) and for CSF (10 mL polypropylene tube, ref 62.610.201, Sarstedt, Germany). Blood and CSF samples were collected on the same day. All aliquots were stored in the same low-binding Eppendorf LoBind microtubes (Eppendorf, ref 022431064, Hamburg,

Germany). Baseline blood samples were used to measure fasting glycaemia, cholesterol (total, high-density lipoproteins (HDL), low-density lipoprotein (LDL)), prealbumin, albumin, creatinine.<sup>16</sup> Estimated glomerular filtration rate (eGFR), based on creatinine, age and sex, was computed using the chronic kidney disease (CKD)-Epidemiology Collaboration (CKD-EPI) equation<sup>18</sup>. CSF biomarkers were measured in a single centralised laboratory using commercially available Innostest assays for tau and phosphorylated tau at position T181 (P-tau181) or Euroimmun for amyloid peptides Aβ1–42 and Aβ1–40. Positive amyloid status (Aβ+) was defined, as previously, when the CSF Aβ1–42/Aβ1–40 ratio was below 0.1.<sup>19</sup>

Plasma P-tau181 was determined using a commercial P-tau181 assay kit (Quanterix, USA) based on ultrasensitive Simoa technology<sup>20</sup> on an HD-X analytical platform. All samples were fourfold diluted with the provided dilution buffer to minimise matrix effects. After dilution, the lowest limit of detection was 0.019 pg/mL and the limit of quantification was of 0.085 pg/mL. Quality controls with low (QC 1 with mean concentration of 3.82 pg/mL) or high (QC 2–52.4 pg/mL) P-tau181 known concentration were provided in the kits. Inter-assay variation for QC 1 and QC 2 was low, with coefficient of variation (CV) of 7% and 5%, respectively. We also used two serum pools (average P-tau181 of 4.47 pg/mL and 2.81 pg/mL) as internal QCs run at the beginning and end of each sample plate. These had low inter-assay CV of 3% and 6%, respectively.

### Statistical analyses

General characteristics were analysed in the whole MCI sample, according to MCI subtype (aMCI and naMCI), conversion to dementia and to plasma P-tau181 tertile. Categorical variables are presented as percentages and counts (% (N)); continuous variables, as mean and SD (M (SD)), or median (25–75th percentile), and comparisons were assessed by  $\chi^2$  tests, t-tests, Mann-Whitney U test and analysis of variance (ANOVA, Kruskal-Wallis test). The relationship between conversion and plasma P-tau181 was assessed using regression models with age, sex and baseline presence of APOE  $\epsilon 4$  allele as covariables.

Kaplan-Meier curves were drawn for conversion according to plasma P-tau181 tertile and overall differences between tertiles was calculated by log rank test. We also examined how plasma P-tau181 improved dementia risk prediction using logistic regression with age, sex, APOE  $\epsilon 4$  and MMSE score at baseline and by calculating continuous net reclassification improvement (NRI).<sup>21</sup> Receiving operator characteristic (ROC) curves, using conversion as a dependent variable, were also used to compute for different factors. The corresponding areas under the curve (AUCs) were compared using the Delong method.<sup>22</sup> Logistic regression model (enter model), Kaplan Meier and ROC curves were generated with MedCalc (V20.111) software. In all analyses, the two-sided  $\alpha$ -level of 0.05 was used for significance testing.

## RESULTS

### Characteristics of the MCI participants at baseline

Of the 539 MCI participants enrolled in the BALTAZAR study, 63 were excluded due to missing data or absence of plasma P-tau181 biomarkers. In this study, we analysed, 476 MCI participants (mean age 77.7 (SD 5.5) years, 61.4% women) with 365 aMCI (77%) and 111 naMCI (23%) at baseline (table 1, online supplemental table 1). Average MMSE score was 26.4 (SD 2.5) and 39.8% (n=185) were APOE  $\epsilon 4$  carriers. During the clinical follow-up period of 6 to 36 months, 30% (n=144) of

**Table 1** Characteristics in the whole MCI population and between MCI participants who converted, or not, to dementia within 3 years

	All MCI N=476	MCI non-converters N=332	MCI converters N=144	P value	P\$
Patient characteristics					
Age (years)	77.7 (5.5)	77.3 (5.4)	78.5 (5.7)	0.048	0.003
Women (%)	292 (61.4)	205 (61.7)	60.4	0.78	0.67
BMI (kg/m <sup>2</sup> )	25 (3.8)	25.1 (3.8)	24.8 (3.8)	0.39	0.95
MMSE (/30)	26.4 (2.5)	26.7 (2.5)	25.6 (2.5)	<0.0001	0.0002
1 or 2 APOE4 alleles	185 (39.8)	105 (31.6)	80 (55.5)	<0.0001	<0.0001
Hippocampal volume (R+L) (cm <sup>3</sup> )	4.55 (1.12)	4.79 (1.05)	4.01 (1.09)	<0.0001	<0.0001
CSF biomarkers*					
Aβ1–40 (pg/mL)	7434 (2241)	7458 (2298)	7389 (2143)	0.83	0.64
Aβ1–42 (pg/mL)	766 (384)	857 (398)	593 (288)	<0.0001	<0.0001
Aβ1–42/Aβ1–40	0.104 (0.045)	0.116 (0.045)	0.082 (0.036)	<0.0001	<0.0001
Tau (pg/mL)	578 (254)	376.1 (185.2)	547 (223.4)	<0.0001	<0.0001
p-tau181 (pg/mL)	76.7 (30.2)	58.58 (24.47)	80.3 (33.58)	<0.0001	<0.0001
Blood biomarkers					
Fasting glycaemia (mmol/L)	5.37 (1.19)	5.34 (1.21)	5.45 (1.14)	0.34	0.20
Triglycerides (mmol/L)	1.21 (0.59)	1.2 (0.58)	1.24 (0.6)	0.54	0.82
Cholesterol total (mmol/L)	5.5 (1.16)	5.48 (1.2)	5.53 (1.07)	0.67	0.91
Cholesterol HDL (mmol/L)	1.74 (0.52)	1.75 (0.53)	1.72 (0.48)	0.66	0.98
Cholesterol LDL (mmol/L)	3.2 (1)	3.19 (1.01)	3.24 (0.98)	0.65	0.90
Prealbumin (mg/dl)	27.6 (5.4)	28.1 (6.2)	27.7 (5.8)	0.53	0.52
Albumin (g/L)	40.3 (3.9)	40.5 (3.5)	39.8 (4.5)	0.09	0.11
Creatinine (μmol/L)	78.2 (21.3)	79.4 (22.2)	73.7 (13.6)	0.10	0.82
eGFR (mL/min/1.73 m <sup>2</sup> )	76.9 (14.7)	77.0 (14.8)	76.7 (14.7)	0.85	0.80
Plasma P-tau181 (pg/mL)	3.19 (1.49)	2.9 (1.4)	3.8 (1.5)	<0.0001	<0.0001

P: Comparison between the three groups, by ANOVA or  $\chi^2$ ; P\$: comparison between the three groups by linear regression adjusted for age, sex and the presence of the APOE  $\epsilon$ 4 allele; % (number) were used to describe categorical variable, mean $\pm$ SD for continuous variables.  
 \*CSF biomarkers were available in 140 and 74 MCI non-converters and converters, respectively.  
 ANOVA, analysis of variance; APOE, apolipoprotein E; BMI, body mass index; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; R+L, right+left.

the MCI participants developed dementia, on average 14.6 (SD 8.2) months after the baseline visit and in 95% of the cases, they converted to clinically probable AD.<sup>6</sup>

### Comparison between MCI converters and non-converters: P-tau predicts conversion to AD

At baseline, the MCI converters to dementia were older, had a lower MMSE score, were more often APOE  $\epsilon$ 4 carriers and had more severe hippocampal atrophy (table 1). As lumbar puncture was optional in our cohort, CSF values were available in 214 subjects. CSF Aβ1–40, Aβ1–42, tau and p-tau181 values were highly differential between MCI that converted or not.

We next turned our attention to the efficacy of markers in the blood, as these samples were available from all participants. We have previously described differential levels of plasma amyloid biomarkers in the BALTAZAR cohort.<sup>6</sup> Here we found plasma P-tau181 increased significantly, on average by 30%, between MCI non-converters at 2.9 (SD 1.4) pg/mL and converters at 3.8 (SD 1.5) pg/mL ( $p < 0.0001$ ). Plasma P-tau remained significant after adjustment for age, sex and APOE  $\epsilon$ 4 status (table 1). No difference was observed between MCI converters and non-converters for metabolic or renal function blood biomarkers: fasting blood glucose (glycaemia), triglycerides, cholesterol (total, HDL, LDL), prealbumin, albumin and creatinine or eGFR.

### Comparison between Aβ+ and Aβ– patients: tau predicts amyloid status

The amyloid status, Aβ+ corresponding to the (A+) ATN classification,<sup>3</sup> was defined based on the CSF Aβ1–42/Aβ1–40 ratio.<sup>23</sup>

Almost half of the MCI participants had a lumbar puncture and 117 of them were Aβ+ and 97 were Aβ–. At baseline, Aβ+ patients were older, had a lower MMSE score and were more often APOE  $\epsilon$ 4 carriers. However, unlike MCI converters, Aβ+ patients did not have a lower hippocampal volume (table 2). CSF Aβ1–42, Tau and p-tau181 values were also highly differential between Aβ+ and Aβ– patients. Plasma P-tau181 was significantly higher on average by 50% in Aβ+ than in Aβ– (3.9 (SD 1.4) vs 2.6 (SD 1.4) pg/mL,  $p < 0.0001$ ). This difference remained significant after adjustment for age, sex and APOE  $\epsilon$ 4 status (table 2).

### P-tau181 improves predictive power of age, sex, APOE $\epsilon$ 4 status and MMSE for MCI conversion and amyloid status detection

Using a logistic regression approach with conversion as a dependent variable and age, sex, APOE $\epsilon$ 4 status and MMSE as independent variables, it was possible to predict conversion ( $p < 0.0001$ ) with an AUC of the model fit of 0.691 (95% CI 0.655 to 0.741). The addition of plasma P-tau181 resulted in a significant increase of the AUC to 0.744 (95% CI 0.702 to 0.784) (online supplemental table 3). The added value of plasma P-tau181 was further documented by computing the NRI of the two models. This revealed a 12.8% improvement in patient classification between MCI converters and non-converters due to plasma P-tau181. Since blood biomarkers are intended to replace CSF biomarkers, we compared the respective values of plasma and CSF P-tau181 for amyloid status detection in the subcohort where patients had undergone a lumbar puncture. The addition

**Table 2** Characteristics in the whole population and between A $\beta$ - and + patients

	All N=214	A $\beta$ - N=97	A $\beta$ + N=117	P value	P value <sup>\$</sup>
Patient characteristics					
Age (years)	77.4 (5.6)	76.6 (5.1)	78 (5.9)	0.073	0.0122
Women (%)	127 (59.3)	53 (54.6)	74 (64.9)	0.20	0.36
BMI (kg/m <sup>2</sup> )	24.7 (3.7)	25.4 (3.7)	24.2 (3.6)	0.024	0.26
MMSE (/30)	26.4 (2.4)	27.1 (2)	25.8 (2.5)	<0.0001	0.0007
One or 2 APOE4 alleles	78 (36.4)	15 (15.5)	63 (57.3)	<0.0001	<0.0001
Hippocampal volume (R+L) (cm <sup>3</sup> )	4.56 (1.09)	4.64 (1.23)	4.5 (0.96)	0.41	0.91
CSF biomarkers					
A $\beta$ 1-40 (pg/mL)	7434 (2241)	7421 (1896)	7446 (2499)	0.93	0.62
A $\beta$ 1-42 (pg/mL)	766 (385)	1095 (287)	494 (196)	<0.0001	<0.0001
A $\beta$ 1-42/A $\beta$ 1-40	0.104 (0.045)	0.149 (0.022)	0.068 (0.018)	<0.0001	<0.0001
Tau (pg/mL)	433 (213)	320 (133)	533 (222)	<0.0001	<0.0001
p-tau181 (pg/mL)	66.4 (30.2)	51.3 (15.1)	79 (33.8)	<0.0001	<0.0001
Blood biomarkers					
Fasting glycaemia (mmol/L)	5.4 (1.1)	5.4 (1.1)	5.4 (1.2)	0.99	0.71
Triglycerides (mmol/L)	1.17 (0.6)	1.18 (0.48)	1.15 (0.69)	0.70	0.62
Cholesterol total (mmol/L)	5.5 (1.2)	5.5 (1.3)	5.5 (1.1)	0.78	0.29
Cholesterol LDL (mmol/L)	1.7 (0.5)	1.8 (0.5)	1.7 (0.5)	0.58	0.81
Cholesterol HDL (mmol/L)	3.2 (1)	3.3 (1.1)	3.2 (0.9)	0.92	0.21
Prealbumin (mg/dL)	28.4 (6.4)	28.5 (7.6)	28.3 (5.1)	0.77	0.77
Albumin (g/L)	40.1 (4.3)	39.9 (3.6)	40.2 (4.9)	0.60	0.38
Creatinine ( $\mu$ mol/L)	79.0 (23.0)	80.1 (24.9)	78.2 (21.5)	0.54	0.76
eGFR (mL/min/1.73 m <sup>2</sup> )	76.9 (14.7)	76.9 (15.5)	77.5 (15.5)	0.62	0.45
Plasma P-tau181 (pg/mL)	3.3 (1.5)	2.6 (1.4)	3.9 (1.4)	<0.0001	<0.0001

P: Comparison between the three groups, by ANOVA or  $\chi^2$ ; P<sup>\$</sup>: comparison between the three groups by linear regression adjusted for age, sex and the presence of the APOE  $\epsilon$ 4 allele; % (number) were used to describe categorical variables, mean $\pm$ SD for continuous variables. HDL, high-density lipoproteins; LDL, low-density lipoproteins. ANOVA, analysis of variance; APOE, apolipoprotein E; A $\beta$ +, amyloid positive; BMI, body mass index; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; R+L, right+left.

in the model of plasma or CSF P-tau181 resulted in a significant increase of the AUC from 0.786 (95% CI 0.723 to 0.84) for age, sex, APOE $\epsilon$ 4 status and MMSE to 0.849 (95% CI 0.792 to 0.895) and 0.857 (95% CI 0.801 to 0.902), respectively (P(difference)=0.00075 and 0.0002). AUCs obtained by the addition of plasma or CSF P-tau181 for conversion or amyloid status detection (0.750 and 0.752, respectively) were not different (P(difference)=0.81). Importantly, when creatinine or eGFR were associated with P-tau181 using logistic regression, they did not give in better performance models.

### Association of plasma P-tau181 with other biomarkers and cohort characteristics

The relationships and correlations between plasma P-tau181 concentration and the other biomarkers and cohort characteristics were analysed after splitting the population by tertile (table 3). Age, body mass index (BMI) and APO  $\epsilon$ 4 were significantly different between tertile. Patient conversion rate was also clearly correlated with plasma P-tau181, with values of 16.4%, 26.1% and 47.8% in the first, second and third tertile, respectively. Distribution of A $\beta$ + patients was also greatly increased along with tertile, a relationship that was confirmed by the high correlation observed between plasma P-tau181 and CSF A $\beta$ 1-42/A $\beta$ 1-40 use to define the A $\beta$ + status (correlation coefficient=-0.4428,  $p$ <0.0001). eGFR decreased ( $p$ =0.017) while creatinine very significantly increased ( $p$ <0.0001) in the higher plasma P-tau181 tertiles. All these results remained significant after adjustment for age, sex and APOE  $\epsilon$ 4 status (table 3). The relationship between plasma P-tau181 and MCI conversion

was further documented by plotting the Kaplan-Meier curve of conversion to dementia according to the tertiles (figure 1A). A very significant overall difference was observed (Log rank  $p$ <0.0001) and the HR between the first and the third tertile was 3.8 (95% CI 2.5 to 5.8).

### Impact of comorbidities and covariates on P-tau181 concentration and diagnostic performance

The relationship between plasma P-tau181 concentration and comorbidities, demographic factors and biological information collected at baseline in the BALTAZAR cohort was investigated using a linear regression approach. We identified APOE status, creatinine and eGFR as strongly connected to plasma P-tau181 (figure 1B). To a lesser degree, age and BMI also affected plasma P-tau181 levels. Among comorbidities we tested, chronic kidney disease (CKD) appeared strongly linked to P-tau181 levels. All these results remained very similar after adjustment for age, sex and APOE  $\epsilon$ 4 status. To further evaluate the impact of these covariates, we plotted the correlation between creatinine, eGFR, BMI and age in the population stratified by amyloid status (figure 2A-D). The correlation in the BALTAZAR subpopulation with lumbar puncture ( $n$ =214) remained significant only for eGFR and creatinine (online supplemental table 2). We observed higher values of plasma P-tau181 in the A $\beta$ + population. P-tau181 levels were also correlated with low and high values of eGFR and creatinine. To confirm this observation, we stratified the population based on tertile of creatinine or eGFR levels (figure 2E,F, table 4). The ANOVA confirmed that the mean level of plasma

**Table 3** Characteristics in the different P-tau181 tertiles

	First tertile N=158	Second tertile N=157	Third tertile N=161	P value	P value\$
Plasma P-tau181					
Age (years)	76.9 (5.4)	77.9 (5.1)	78.3 (5.9)	0.06	0.0009
Women (%)	101 (63.9)	96 (61.1)	95 (59.0)	0.66	0.32
BMI (kg/m <sup>2</sup> )	25.8 (3.7)	24.9 (3.9)	24.4 (3.7)	0.004	0.01
MMSE (/30)	26.7 (2.4)	26.4 (2.5)	26.1 (2.7)	0.16	0.19
1 or 2 APOE4 alleles (%)	38 (17.7)	63 (40.1)	84 (52.2)	<0.0001	<0.0001
Hippocampal volume (R+L) (cm <sup>3</sup> )	4.75 (1.13)	4.38 (1.16)	4.5 (1.04)	0.02	0.28
Aβ+ status (%)	13 (19.1)	40 (62.5)	64 (78.0)	<0.0001	<0.0001
Conversion MCI (%)	26 (16.4)	41 (26.1)	77 (47.8)	<0.0001	<0.0001
Blood biomarkers					
Fasting glycaemia (mmol/L)	5.46 (1.28)	5.4 (1.1)	5.26 (1.18)	0.32	0.12
Triglycerides (mmol/L)	1.2 (0.6)	1.3 (0.7)	1.2 (0.5)	0.26	0.23
Cholesterol (mmol/L)	5.52 (1.19)	5.48 (1.23)	5.5 (1.06)	0.94	0.82
Cholesterol HDL (mmol/L)	1.72 (0.47)	1.76 (0.56)	1.75 (0.52)	0.85	0.29
Cholesterol LDL (mmol/L)	3.25 (1.03)	3.15 (1.07)	3.21 (0.9)	0.69	0.59
Prealbumin (mg/dL)	27.5 (6.2)	28 (6.7)	28.4 (5.4)	0.47	0.17
Albumin (g/L)	40.4 (3.7)	40.2 (4.8)	40.3 (3.1)	0.87	0.90
Creatinine (μmol/L)	73.5 (16.5)	78.6 (19)	82.1 (26.1)	0.002	0.0005
eGFR (mL/min/1.73 m <sup>2</sup> )	80.3 (13.5)	76 (14.1)	74.4 (15.9)	0.02	0.01
Plasma P-tau181 (pg/mL)	1.75 (0.38)	2.93 (0.36)	4.86 (1.19)	NA	NA

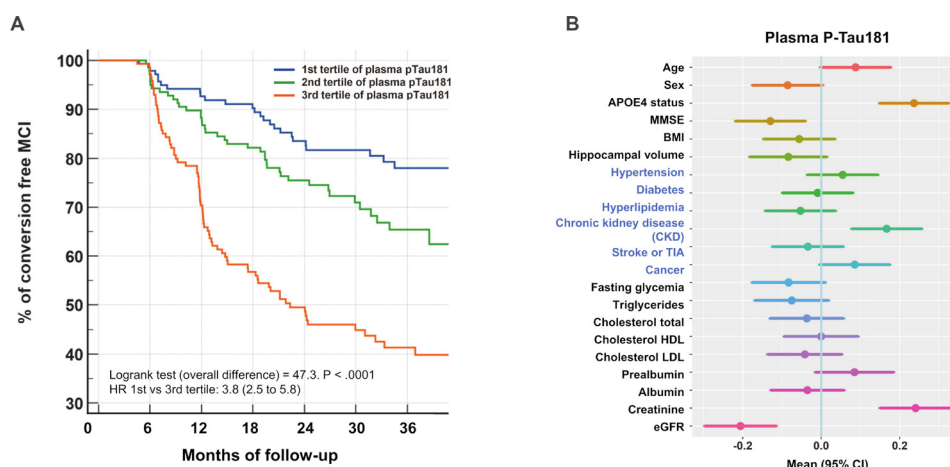
P: Comparison between the three groups, by ANOVA or  $\chi^2$ ; P\$: comparison between the three groups with linear regression adjusted for age, sex and the presence of the APOE  $\epsilon$ 4 allele; % (number) were used to describe categorical variables, mean $\pm$ SD for continuous variables.  
ANOVA, analysis of variance; APOE, apolipoprotein E; BMI, body mass index; eGFR, estimated glomerular filtration rate; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; NA, not available; R+L, right+left.

P-tau181 was globally differential among both creatinine or eGFR tertiles ( $p < 0.001$ ). Finally, to evaluate the impact on P-tau181 on the detection of amyloid status, we computed the ROC curves and determined best cutpoints and corresponding performance for Aβ+ (table 4).

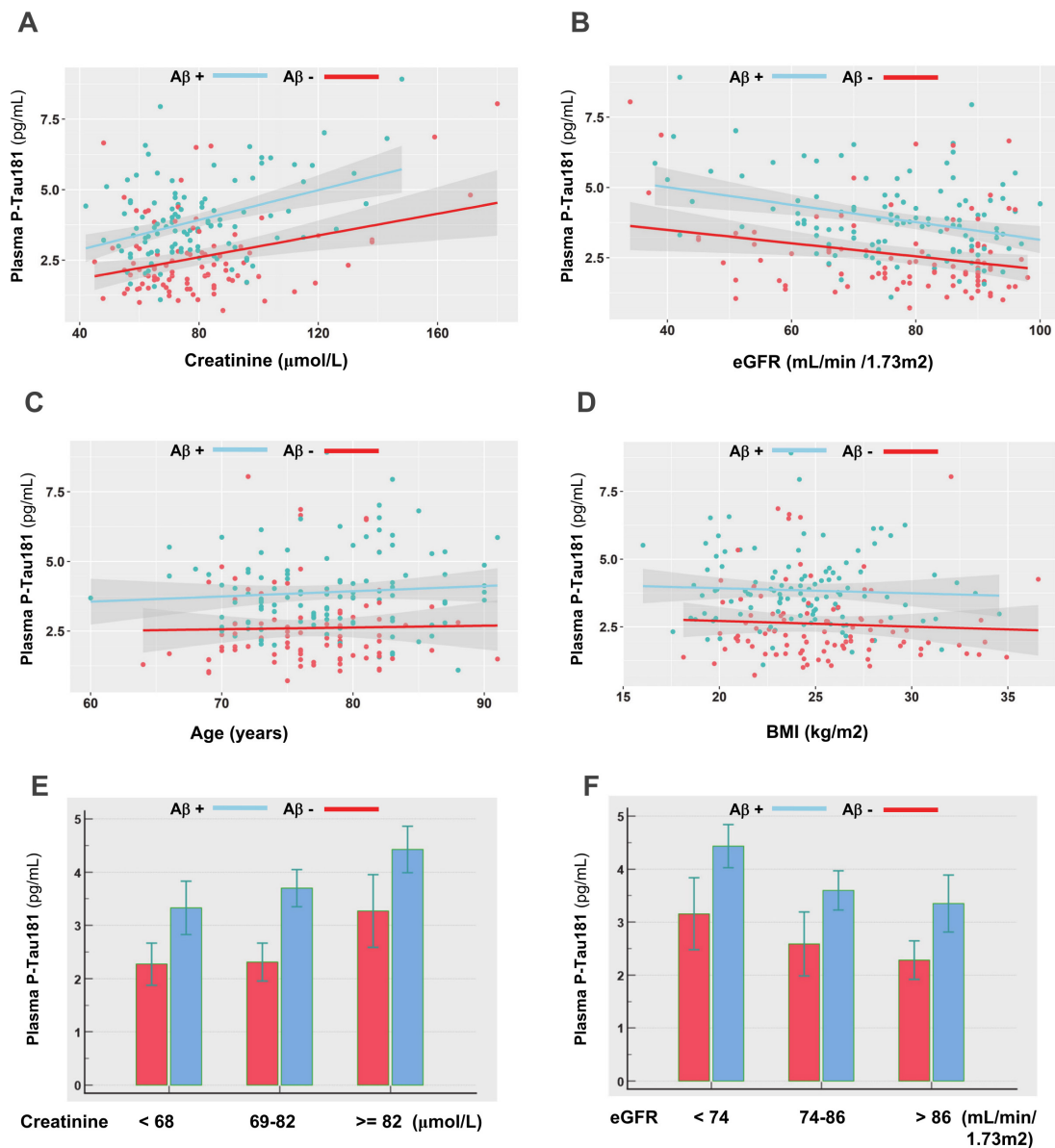
## DISCUSSION

Here, we present results from a large-scale multicentre prospective longitudinal cohort of clinically defined MCI participants, referred to memory centre, with a follow-up of 3 years. Our principal finding is that patients who convert to dementia

have 30% higher levels of plasma P-tau181 independently of age, sex or APOE  $\epsilon$ 4. Importantly, 48% of MCI participants among the highest tertile of plasma P-tau181 ( $>3.61$ ) converted to dementia and thus had a fourfold higher risk. In addition, patients in the first P-tau(181) tertile (ie, with a value  $\leq 2.32$  pg/mL) have a conversion rate of 19.8% over a 3-year period. It is likely that combining P-tau(181) with other blood biomarkers such as plasma amyloid peptides could improve this prediction. This information is valuable for patient management and for using therapeutic strategies to prevent progression. In this



**Figure 1** (A): Kaplan-Meier curve of conversion to dementia according to the tertiles of plasma P-tau181 in MCI subjects. (B): Associations between multiple factors and plasma P-tau181 concentrations. Forest plots of associations between demographic, comorbidities (in blue) and biological variables and plasma P-tau181, using linear regression. Means and 95% CIs are provided. Z-scores are used to compare the factors between them. APOE, apolipoprotein E; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; TIA, transient ischaemic attack; HDL, high-density lipoproteins; LDL, low-density lipoproteins.



**Figure 2** (A–D): Correlation between plasma P-tau181 and creatinine, eGFR, age and BMI in the amyloid negative and positive populations. (E, F): Levels of plasma P-tau181 in the amyloid negative and positive populations, by tertiles of creatinine or eGFR. Concentrations of plasma P-tau181 were significantly different between amyloid negative and positive patients in all cases, as tested using a Mann-Whitney U test ( $p < 0.05$ ). Aβ+, amyloid positive; BMI, body mass index; eGFR, estimated glomerular filtration rate (unit: mL/min/1.73 m<sup>2</sup>).

MCI population, plasma P-tau181 also predicted amyloid status (based on the CSF Aβ<sub>1–42</sub>/Aβ<sub>1–40</sub> ratio), with Aβ+ patients having 50% higher P-tau181 levels than their Aβ– counterparts.

One important element that raises the interest of using this plasma biomarker in the future is its added value above that of just using a combination of age, sex, APOEε4 status and MMSE. It is noteworthy that adding plasma P-tau181 significantly improved the detection of both Aβ+ patients and MCI converters. Even more striking is that this added value of plasma P-tau181 was equivalent to that of CSF P-tau181. This finding will impact future clinical use of the approach, as it might avoid the need for lumbar puncture. The capacity of plasma P-tau181 to detect Aβ+ patients as well as AD and MCI when compared with control and to other diseases has been described.<sup>8,9 11–13 24–27</sup> However, the only previous other large study focusing on MCI conversion was that of Karikari *et al*<sup>11</sup> who observed that baseline concentrations of plasma

P-tau181 accurately predicted future dementia and Aβ+ status (as defined by PET). As well as validating this previous study, our study has the added value of the biological data collected in the BALTAZAR cohort. These include metabolic blood biomarkers: fasting glycaemia, triglycerides, cholesterol (total, HDL, LDL), prealbumin, albumin, creatinine and eGFR, which can be used to monitor diabetes, cardiovascular risk, nutritional status or kidney function. None of these factors were differential, either in comparing MCI converters to non-converters, or when comparing Aβ+ and Aβ– patients. However, when we investigated factors influencing P-tau181 level, by comparing tertiles or through a linear regression method, we first identified age and BMI as cofounding factors. These two factors have previously been associated with P-tau181, as well as with other blood biomarkers like neurofilaments.<sup>28</sup> Age increases both plasma and CSF values of neurodegenerative biomarkers like total tau<sup>29</sup> yet to be determined reasons. For BMI, a likely

**Table 4** Performance of plasma P-tau181 for A $\beta$ + detection with regard to renal function (creatinine and eGFR)

Population with CSF biomarkers available	Total	Creatinine <68 First tertile	Creatinine 69–82 Second tertile	Creatinine $\geq$ 82 Third tertile
Creatinine ( $\mu$ mol/L)	74 (71–77)	61 (57–64)	73 (71–80)	95 (84–111)
Plasma P-tau 181 (pg/mL)	3.0 (2.8–3.4)	2.3 (1.8–3.3)	2.9 (2.5–3.9)	3.7 (2.7–5.2)
Plasma P-tau 181 in A $\beta$ –	2.2 (1.9–2.4)	1.9 (1.5–2.4)	2.3 (1.6–2.7)	2.9 (1.9–4.0)
Plasma P-tau 181 in A $\beta$ +	3.7 (2.8–4.5)	3.1 (2.2–4.3)	3.6 (2.9–4.0)	4.2 (3.6–5.4)
AUC Plasma P-tau 181 A $\beta$ +	0.783	0.763	0.872	0.733
Plasma P-tau 181 cutpoints (pg/mL)	2.77	2.31	2.77	3.52
Sensitivity (%)	80.9	75.0	89.5	80.0
Specificity (%)	69.6	73.0	80.0	70.0
Population with CSF biomarkers available	Total	eGFR <74 first tertile	eGFR 74–86 second tertile	eGFR >86 third tertile
eGFR (mL/min/1.73 m <sup>2</sup> )	79 (68–89)	64 (54–69)	79 (76–84)	91 (89–93)
Plasma P-tau 181 (pg/mL)	3.0 (2.1–3.9)	3.5 (2.4–4.2)	3.1 (2.1–3.9)	2.7 (1.8–3.9)
Plasma P-tau 181 in A $\beta$ –	2.2 (1.7–3.0)	2.7 (1.7–3.4)	2.0 (1.7–2.6)	2.0 (1.6–2.9)
Plasma P-tau 181 in A $\beta$ +	3.7 (2.8–4.5)	3.8 (3.1–5.4)	3.8 (2.8–4.5)	3.3 (2.7–4.2)
AUC Plasma P-tau 181 A $\beta$ +	0.783	0.763	0.872	0.733
Plasma P-tau 181 cutpoints (pg/mL)	2.77	2.81	2.71	2.44
Sensitivity (%)	80.9	86.4	84.2	78.8
Specificity (%)	69.6	60.0	77.8	68.6

Values of creatinine and plasma P-tau181 are express as median (25–75th percentile). Cutpoints correspond to the best Youden index on the ROC curves. AUC, area under the curve; A $\beta$ +, amyloid positive; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate; ROC, receiving operator characteristic.

relevant factor is the dilution of neuronal biomarkers in the blood volume.

Among the comorbidities that were associated with P-tau181, CKD was the most differential. This association with CKD has already been reported in recent studies.<sup>30 31</sup> However, in the BALTAZAR cohort, we have access to the clinical chemistry profile realised on the same plasma sample used for P-tau181 measurement. We thus noted that P-tau181 correlates with markers of kidney function: creatinine and eGFR. Adding these parameters improved the ability of P-tau181 to detect A $\beta$ + patients, whereas adding age and BMI did not. Strikingly P-tau181 and creatinine stratify together irrespective of other variables. Namely, in situations with increased creatinine ( $\geq$ 82  $\mu$ mol/L) or low eGFR (<74 mL/min/1.73 m<sup>2</sup>), indicating a moderate impaired kidney function, levels of P-tau181 were increased in both A $\beta$ + and A $\beta$ – patients, as well as in MCI patients converting or not to dementia.

A major suggestion of our study is tailoring the clinical cutpoints of P-tau181 to renal function. We advocate minimising the false detection of a pathological situation in patients by always combining plasma P-tau181 with an assessment of renal function, for example, through creatinine measurement and GFR estimation. This recommendation should be confirmed for other P-tau isoforms (P-tau217, P-tau231) measured by immunoassay<sup>25</sup> or mass spectrometry.<sup>32</sup> We cannot exclude at this stage that altered renal function may also contribute in some way to the progression of AD.<sup>33</sup> Indeed, this hypothesis is supported by the difference in creatine level between naMCI and aMCI population. To understand the relationship between renal function and P-tau levels, its clearance by the kidney will therefore have to be studied in more detail. Of note, only very small amounts of this biomarker were detected in the free form or associated with exosome in urine.<sup>34 35</sup>

The present study has some limitations. To increase the likelihood of conversion to AD we excluded participants with Lewy body, Parkinson, frontotemporal or vascular MCI disorders. Therefore, 77% of subjects had aMCI and 30% of participants

developed dementia which in 95% of cases was represented by probable AD. Amyloid status was available in only a part of the population, since the BALTAZAR study focused on conversion, and it was defined using CSF biomarkers rather than with PET amyloid.

The main strengths of the study lie in the large sample size of MCI participants that are well described, the controlled preanalytical conditions, the centralised plasma P-tau181 analyses and the availability of clinical chemistry analyte measurement realised in the same sample tube.

## CONCLUSION

This study of our well-characterised population confirms the clinical relevance of plasma P-tau181 for the detection of amyloid status, which is important for risk assessment, patient management and inclusion in clinical trials. We also demonstrate the strong predictive value of this blood biomarker for the prognosis of MCI patients, thus addressing an important medical need in memory centres. The question remains as to the use of blood biomarkers as a screening tool in patients without cognitive impairment who have risk factors and may benefit most from preventive strategies, and/or as triage tests in patients with early symptoms for whom future investigations, including imaging and spinal tap, are being considered. Finally, we identified and quantified the impact of renal function, assessed by creatinine levels and GFR estimation, on P-tau181 blood levels. These measures are an easy and standardisable way to provide essential information about kidney function and thus to optimise interpretation of results in routine clinical practice.

## Author affiliations

<sup>1</sup>LBPC-PPC, Université de Montpellier, INM INSERM, IRMB CHU de Montpellier, Montpellier, France

<sup>2</sup>Université de Lille, Inserm UMRS1172, CHU Lille, Lille, France

<sup>3</sup>Université Paris Cité, EA 4468, Hôpital Broca, Geriatric department, Memory Resource and Research Centre of Paris-Broca-Ile de France, APHP, Paris, France

<sup>4</sup>Hospital de la Santa Creu i Sant Pau - Biomedical Research Institute Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>5</sup>Neuropsychology Unit and Geriatric Day Hospital, University Hospital of Strasbourg, Strasbourg, France

<sup>6</sup>Université Paris Cité, GHU APHP Nord Lariboisière Fernand Widal, Centre de Neurologie Cognitive, Paris, France

<sup>7</sup>UMR-S 1266, Université Paris Cité, Institute of Psychiatry and Neurosciences, Inserm, Paris, France

<sup>8</sup>Assistance Publique-Hôpitaux de Paris (AP-HP), Département de Neurologie, Centre des Maladies Cognitives et Comportementales, GH Pitié-Salpêtrière, Paris, France

<sup>9</sup>Université de Montpellier, CHRU Montpellier, Memory Research and Resources center, department of Neurology, Inserm INM, Montpellier, France

**Twitter** Sylvain Lehmann @sylvain\_lehmann

**Collaborators** BALTAZAR study group Olivier Hanon [1], Frédéric Blanc [2], Yasmina Boudali [1], Audrey Gabelle [3], Jacques Touchon [3], Marie-Laure Seux [1], Hermine Lenoir [1], Catherine Bayle [1], Stéphanie Bombois [4], Christine Delmaire [4], Xavier Delbeuck [5], Florence Moulin [1], Emmanuelle Duron [6], Florence Latour [7], Matthieu Plichart [1], Sophie Pichierri [8], Galdric Orvoën [1], Evelyne Galbrun [9], Giovanni Castelnuovo [10], Lisette Volpe-Gillot [11], Florian Labourée [1], Pascaline Cassagnaud [12], Claire Paquet [13], Françoise Lala [14], Bruno Vellas [14], Julien Dumurgier [13], Anne-Sophie Rigaud [1], Christine Perret-Guillaume [15], Eliana Alonso [16], Foucaud du Boisgueheneuc [17], Laurence Hugonot-Diener [1], Adeline Rollin-Sillaire [12], Olivier Martinaud [18], Clémence Bouilly [1], Yann Spivac [19], Agnès Devendeville [20], Joël Belmin [21], Philippe-Henri Robert [22], Thierry Dantoine [23], Laure Caillard [1], David Wallon [24], Didier Hannequin [18], Nathalie Sastre [14], Sophie Haffen [25], Anna Kearney-Schwartz [15], Jean-Luc Novella [26], Vincent Deramecourt [12], Valérie Chauvire [27], Gabel Abitbol [1], Nathalie Schwald [19], Caroline Hommet [28], François Sellal [29], Marie-Ange Cariot [16], Mohamed Abdellaoui [30], Sarah Benisty [31], Salim Gherabli [1], Pierre Anthony [29], Frédéric Bloch [32], Nathalie Charasz [1], Sophie Chauvelier [1], Jean-Yves Gaubert [1], Guillaume Sacco [22], Olivier Guerin [22], Jacques Boddaert [33], Marc Paccalin [17], Marie-Anne Mackowiak [12], Marie-Thérèse Rabus [9], Valérie Gissot [34], Athanase Benetos [15], Candice Picard [20], Céline Guillemaud [35], Gilles Berrut [8], Claire Gervais [22], Jacques Hugon [13], Jean-Marc Michel [29], Jean-Philippe David [19], Marion Paulin [12], Pierre-Jean Ousset [14], Pierre Vandell [36], Sylvie Pariel [21], Vincent Camus [37], Anne Chawakilian [1], Léna Kermanach [1], Anne-Cécile Troussiere [12], Cécile Adam [23], Diane Dupuy [20], Elena Paillaud [16], Héléne Briault [9], Isabelle Saulnier [38], Karl Mondon [37], Marie-Agnès Picat [23], Marie Laurent [16], Olivier Godefroy [20], Rezki Daheb [16], Stéphanie Libercier [29], Djamilia Krabchi [1], Marie Chupin [39], Luc Buée [42], Jean-Sébastien Vidal [1], Edouard Chaussade [1], Sylvain Lehmann [40], Bernadette Allinquant [41], Susanna Schraen-Maschke [42]. Affiliations of the BALTAZAR group [1] Université de Paris, EA 4468, APHP, Hôpital Broca, Memory Resource and Research Centre of de Paris-Broca-Ile de France, F-75013 Paris, France. [2] Université de Strasbourg, CHRU de Strasbourg, Memory Resource and Research Centre of Strasbourg/Colmar, French National Centre for Scientific Research (CNRS), iCube Laboratory and Fédération de Médecine Translationnelle de Strasbourg (FMTS), Team Imagerie Multimodale Intégrative en Santé (MIS)/Neurocrypt, F-67000 Strasbourg, France. [3] Université de Montpellier, CHRU Montpellier, Memory Research and Resources center, department of Neurology, Inserm INM NeuroPEPs team, excellence center of neurodegenerative disorders, F-34000 Montpellier, France. [4] Univ. Lille, CHU Lille, Memory Resource and Research Centre of Lille, Department of Neurology, Inserm U1171, Degenerative and Vascular Cognitive Disorders, F-59000 Lille, France. [5] Univ. Lille, Inserm U1171 Degenerative and Vascular Cognitive Disorders, F-59000 Lille, France. [6] Université Paris-Saclay, APHP, Hôpital Paul Brousse, département de gériatrie, UVSQ, Inserm, CESP, Team MOODS, F-94800 Villejuif, France. [7] Centre Hospitalier de la Côte Basque, Department of Gerontology, F-64100 Bayonne, France. [8] Université de Nantes, EA 4334 Movement-Interactions-Performance, CHU Nantes, Memory Research Resource Center of Nantes, F-44000 Nantes, France. [9] Sorbonne Universités, AP-HP, Centre Hospitalier Émile-Roux, Department of Gérontologie 2, F-94450 Limeil-Brévannes, France. [10] CHU de Nîmes, Neurology Department, F-30000 Nîmes, France. [11] Hôpital Léopold Bellan, Memory Clinic, F-75014 Paris, France. [12] Univ. Lille, CHU de Lille, Memory Resource and Research Centre of Lille, Department of Neurology, F-59000 Lille, France. [13] Université de Paris, APHP, Groupe Hospitalier Saint-Louis-Lariboisière-Fernand Widal, Memory Resource and Research Centre of Paris Nord-Ile de France, F-75010 Paris, France. [14] Université de Toulouse III, CHU La Grave-Casselardit, Memory Resource and Research Centre of Midi-Pyrénées, F-31300 Toulouse, France. [15] Université de Lorraine, CHRU de Nancy, Memory Resource and Research Centre of Lorraine, F-54000 Nancy, France. [16] AP-HP, HEGP, Service de Gériatrie, F-75015, Paris, France. [17] CHU de Poitiers, Memory Resource and Research Centre of Poitiers, F-86000 Poitiers, France. [18] CHU Charles Nicolle, Memory Resource and Research Centre of Haute-Normandie, F-76000 Rouen, France. [19] APHP, Centre Hospitalier Émile-Roux, Department of Gérontologie 1, F-94450 Limeil-Brévannes, France. [20] CHU d'Amiens-Picardie, Memory Resource and Research Centre of Amiens Picardie, F-80000 Amiens, France. [21] APHP, Hôpitaux Universitaires Pitié-Salpêtrière-Charles Foix, Service de Gériatrie Ambulatoire, F-75013 Paris, France. [22] CHU de Nice, Memory Research Resource Center of PACA Est, F-06100 Nice, France.

[23] CHU de Limoges, Memory Research Resource Center of Limoges, F-87000 Limoges, France. [24] Université de Rouen Normandie, CHU Charles Nicolle, Memory Resource and Research Centre of Haute-Normandie, Inserm U1079, IRIB, F-76000 Rouen, France. [25] CHU de Besançon, Memory Resource and Research Centre of Besançon-Franche-Comté, F-25000 Besançon, France. [26] Université de Reims Champagne Ardenne, EA 3797, CHU de Reims, Memory Resource and Research Centre of Champagne Ardenne, F-51100 Reims, France. [27] CHU d'Angers, Memory Resource and Research Centre of Angers, F-49000 Angers, France. [28] CHRU de Tours, Memory Resource and Research Centre of Tours, F-37000 Tours, France. [29] Université de Strasbourg, CHRU de Strasbourg, Memory Resource and Research Centre of Strasbourg/Colmar, Inserm U-118, F-67000 Strasbourg, France. [30] Univ Paris Est Creteil, EA 4391 Excitabilité Nerveuse et Thérapeutique, CHU Henri Mondor, Department of Neurology, F-94000 Créteil, France. [31] Fondation ophtalmologique Adolphe de Rothschild, Department of Neurology, F-75019 Paris, France. [32] CHU d'Amiens-Picardie, Department of Gerontology, F-80000 Amiens, France. [33] Sorbonne Universités, APHP, Hôpitaux Universitaires Pitié-Salpêtrière-Charles Foix, Memory Resource and Research Centre, Centre des Maladies Cognitives et Comportementales IM2A, Inserm UMR 8256, F-75013 Paris, France. [34] Université François-Rabelais de Tours, CHRU de Tours, Memory Resource and Research Centre of Tours, Inserm CIC 1415, F-37000 Tours, France. [35] Sorbonne Universités, APHP, Hôpitaux Universitaires Pitié-Salpêtrière-Charles Foix, Memory Resource and Research Centre, Centre des Maladies Cognitives et Comportementales IM2A, F-75013 Paris, France. [36] Université Bourgogne Franche-Comté, EA 481 Neuroscience, IFR 133, CHU de Besançon, Memory Resource and Research Centre of Besançon-Franche-Comté, F-25000 Besançon, France. [37] Université François-Rabelais de Tours, CHRU de Tours, Memory Resource and Research Centre of Tours, Inserm U930 Imagerie et Cerveau, F-37000 Tours, France. [38] Université de Limoges, EA 6310 HAVAE, CHU de Limoges, Memory Research Resource Center of Limoges, F-87000 Limoges, France. [39] Université Paris-Saclay, Neurospin, CEA, cati-neuroimaging.com, CATI Multicenter Neuroimaging Platform, F-91190 Gif-sur-Yvette, France. [40] LBPC-PPC, Université de Montpellier, INM INSERM, IRMB CHU de Montpellier, Montpellier, France. [41] Université de Paris, Inserm UMR-S 894, F-75014 Paris, France. [42] Univ. Lille, Inserm, CHU Lille, U1172-LiInCog, LiCEND, LabEx DISTALZ, F-59000 Lille, France.

**Contributors** SL, J-SV and OH take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: OH, SB, AG, SS-M and SL. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: SL. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: SL and J-SV. Obtained funding: OH, SB, AG, SS-M and SL. All authors had full access to the data and contributed to revision and editing of the manuscript. SL is responsible for the overall content as the guarantor.

**Funding** The French ministry of Health (Programme Hospitalier de Recherche Clinique), Grant/Award Numbers:PHRC2009/01-04,PHRC-13-0404; The Foundation Plan Alzheimer; Fondation pour la Recherche Médicale (FRM); The Gerontopôle d'Ile de France (GEROND'IF). None of the funding bodies had any role in study design, in the collection, analysis, and interpretation of data, in the writing of the report or in the decision to submit the paper for publication.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by The study was approved by the Paris Ethics Committee (CPP Ile de France IV Saint Louis Hospital). ClinicalTrials.gov Identifier#NCT01315639 Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Data and informed consent form are available upon request after publication (APHP, Paris). Requests will be considered by each study investigator based on the information provided by the requester regarding the study and analysis plan. If the use is appropriate, a data sharing agreement will be put in place before distributing a fully de-identified version of the dataset, including the data dictionary used for analysis with individual participant data.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is



properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Sylvain Lehmann <http://orcid.org/0000-0001-6117-562X>  
 Jean-Sébastien Vidal <http://orcid.org/0000-0001-6770-0720>  
 Constance Delaby <http://orcid.org/0000-0002-8606-6814>  
 Olivier Hanon <http://orcid.org/0000-0002-4697-122X>

#### REFERENCES

- Lee M, Whitsel E, Avery C, et al. Variation in population attributable fraction of dementia associated with potentially modifiable risk factors by race and ethnicity in the US. *JAMA Netw Open* 2022;5:e2219672.
- Piton M, Hirtz C, Desmetz C, et al. Alzheimer's disease: advances in drug development. *J Alzheimers Dis* 2018;65:3–13.
- Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia* 2018;14:535–62.
- Dumurgier J, Schraen S, Gabelle A, et al. Cerebrospinal fluid amyloid- $\beta$  42/40 ratio in clinical setting of memory centers: a multicentric study. *Alzheimers Res Ther* 2015;7:30.
- Gabelle A, Dumurgier J, Vercrucy O, et al. Impact of the 2008-2012 French Alzheimer plan on the use of cerebrospinal fluid biomarkers in research memory center: the PLM study. *J Alzheimers Dis* 2013;34:297–305.
- Hanon O, Vidal Jean-Sébastien, Lehmann S, et al. Plasma amyloid beta predicts conversion to dementia in subjects with mild cognitive impairment: the BALTAZAR study. *Alzheimer's & Dementia* 2022 (published Online First: 2022/02/22).
- Zetterberg H, Wilson D, Andreasson U, et al. Plasma tau levels in Alzheimer's disease. *Alzheimers Res Ther* 2013;5:9.
- Mielke MM, Hagen CE, Xu J, et al. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. *Alzheimer's & Dementia* 2018;14:989–97.
- Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *The Lancet Neurology* 2020;19:422–33.
- McGrath ER, Beiser AS, O'Donnell A, et al. Blood phosphorylated tau 181 as a biomarker for amyloid burden on brain PET in cognitively healthy adults. *J Alzheimers Dis* 2022;87:1517–26.
- Karikari TK, Benedet AL, Ashton NJ, et al. Diagnostic performance and prediction of clinical progression of plasma phospho-tau181 in the Alzheimer's Disease Neuroimaging Initiative. *Mol Psychiatry* 2021;26:429–42.
- Clark C, Lewczuk P, Kornhuber J, et al. Plasma neurofilament light and phosphorylated tau 181 as biomarkers of Alzheimer's disease pathology and clinical disease progression. *Alzheimers Res Ther* 2021;13:65.
- Chen S-D, Huang Y-Y, Shen X-N, et al. Longitudinal plasma phosphorylated tau 181 tracks disease progression in Alzheimer's disease. *Transl Psychiatry* 2021;11:356.
- Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's Association Appropriate Use Recommendations for Blood Biomarkers in Alzheimer's Disease. *Alzheimer's & Dementia* 2022;18.
- Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *The Lancet Neurology* 2022;21:66–77.
- Hanon O, Vidal Jean-Sébastien, Lehmann S, et al. Plasma amyloid levels within the Alzheimer's process and correlations with central biomarkers. *Alzheimer's & Dementia* 2018;14:858–68.
- Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
- Lehmann S, Delaby C, Boursier G, et al. Relevance of A $\beta$ 42/40 ratio for detection of Alzheimer disease pathology in clinical routine: the PLMR scale. *Front Aging Neurosci* 2018;10:138.
- Rissin DM, Walt DR. Digital concentration readout of single enzyme molecules using femtomolar arrays and Poisson statistics. *Nano Lett* 2006;6:520–3.
- Pencina MJ, D'Agostino RB, D'Agostino RB, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157–72.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.
- Delaby C, Alcolea D, Hirtz C, et al. Blood amyloid and tau biomarkers as predictors of cerebrospinal fluid profiles. *J Neural Transm* 2022;129:231–7.
- Thijssen EH, La Joie R, Strom A, et al. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. *The Lancet Neurology* 2021;20:739–52.
- Bayoumy S, Verberk IMW, den Dulk B, et al. Clinical and analytical comparison of six Simoa assays for plasma p-tau isoforms p-Tau181, P-tau217, and P-tau231. *Alzheimers Res Ther* 2021;13:198.
- Thijssen EH, La Joie R, Wolf A, et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. *Nat Med* 2020;26:387–97.
- Benussi A, Karikari TK, Ashton N, et al. Diagnostic and prognostic value of serum NfL and p-Tau<sub>181</sub> in frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry* 2020;91:960–7.
- Benkert P, Meier S, Schaedelin S, et al. Serum neurofilament light chain for individual prognostication of disease activity in people with multiple sclerosis: a retrospective modelling and validation study. *The Lancet Neurology* 2022;21:246–57.
- Blomberg M, Jensen M, Basun H, et al. Cerebrospinal fluid tau levels increase with age in healthy individuals. *Dement Geriatr Cogn Disord* 2001;12:127–32.
- Syrjanen JA, Campbell MR, Algeciras-Schimmich A, et al. Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. *Alzheimer's & Dementia* 2022;18:1128–40.
- Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med* 2022;28:1398–405.
- Janelidze S, Bali D, Ashton NJ, et al. Head-To-Head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. *Brain* 2022. doi:10.1093/brain/awac333. [Epub ahead of print: 10 Sep 2022].
- Singh-Manoux A, Oumarou-Ibrahim A, Machado-Fragua MD, et al. Association between kidney function and incidence of dementia: 10-year follow-up of the Whitehall II cohort study. *Age Ageing* 2022;51.
- Chan H-N, Xu D, Ho S-L, et al. Ultra-Sensitive detection of protein biomarkers for diagnosis of Alzheimer's disease. *Chem Sci* 2017;8:4012–8.
- Sun R, Wang H, Shi Y, et al. A Pilot Study of Urinary Exosomes in Alzheimer's Disease. *Neurodegener Dis* 2020;19:184–91.

**Suppl Table 1: Characteristics of participants and plasma biomarkers at baseline according to the cognitive status**

Patient characteristics	All MCI N=476	aMCI N=365	naMCI N=111	P
Age (years)	77.7 (5.5)	77.6 (5.5)	78.1 (5.4)	.40
Women (%)	292 (61.4)	210 (57.4)	82 (73.9)	<b>·0019</b>
BMI (kg/m <sup>2</sup> )	25 (3.8)	25.1 (3.8)	24.6 (3.7)	.21
1 or 2 APOE4 alleles (%)	185 (39.8)	158 (43.3)	27 (24.3)	<b>·0003</b>
MMSE (/30)	26.4 (2.5)	26.1 (2.6)	27.4 (2.1)	<b>&lt;·0001</b>
Hippocampal volume (R+L) (cm <sup>3</sup> )	4.55 (1.12)	4.43 (1.16)	4.96 (0.86)	<b>&lt;·0001</b>
CSF biomarkers	All MCI	aMCI	naMCI	P
Aβ1-40 (pg/mL)	7434 (2241)	7525 (2258)	7103 (2167)	.25
Aβ1-42 (pg/mL)	766 (384)	744 (394)	848 (335)	.07
Aβ1-42/Aβ1-40	0.104 (0.045)	0.1 (0.046)	0.12 (0.038)	<b>·0026</b>
Tau (pg/mL)	578 (254)	486 (247)	322 (152)	<b>&lt;·0001</b>
p-Tau181 (pg/mL)	76.7 (30.2)	74.3 (33.9)	56.1 (19.0)	<b>&lt;·0001</b>
Blood biomarkers	All MCI	aMCI	naMCI	P
Fasting glycemia (mmol/L)	5.37 (1.19)	5.43 (1.3)	5.19 (0.7)	<b>·018</b>
Triglycerides (mmol/L)	1,21 (0.59)	1,24 (0.6)	1,14 (0.53)	0,1409
Cholesterol (mmol/L)	5,5 (1,16)	5,45 (1,15)	5,65 (1,18)	0,1434
Cholesterol HDL (mmol/L)	1,74 (0,52)	1,7 (0,52)	1,87 (0,49)	0,0030
Cholesterol LDL (mmol/L)	3,2 (1)	3,18 (1)	3,27 (1,01)	0,4754
Creatinine (μmol/L)	78.2 (21.3)	79.3 (22.3)	74.5 (17.2)	<b>·022</b>
Prealbumin (mg/dL)	27.6 (5.4)	28.2 (6.4)	27.2 (5.9)	.14
Albumin (g/L)	40.3 (3.9)	40.5 (4.1)	39.8 (3.1)	.10
eGFR (mL/min/1.73m <sup>2</sup> )	76.9 (14.7)	76.7 (15.2)	77.4 (13.1)	.68
Plasma P-tau181(pg/mL)	3.19 (1.49)	3.29 (1.5)	2.87 (1.42)	<b>·0083</b>

Abbreviations: MCI: mild cognitive impairment; aMCI, amnesic MCI; naMCI, nonamnesic MCI; APOE: apolipoprotein E; BMI, body mass index; eGFR, estimated glomerular filtration rate; MMSE, Mini-Mental State Examination; R+L, right+left;

P: Comparison between the aMCI and naMCI, with Student t test or  $\chi^2$ ;

% (number) were used to describe categorical variables, mean  $\pm$  standard deviation for continuous variables.

CSF biomarkers were available only in 179 and 49 patients with aMCI and naMCI, respectively.

**Suppl Table 2: Correlation between plasma P-tau181 and covariates in the A $\beta$ - and A $\beta$ + populations**

Amyloid status	Plasma P-tau181 vs.	Age	BMI	eGFR	Creatinine
A $\beta$ -	Correlation coefficient	0.065	-0.079	-0.256	0.337
	Significance Level P	0.5301	0.4429	<b>0.0139</b>	<b>0.001</b>
A $\beta$ +	Correlation coefficient	0.075	-0.009	-0.341	0.41
	Significance Level P	0.4203	0.9254	<b>0.0002</b>	<b>&lt;0.0001</b>

**Suppl Table 3: Added value of plasma or CSF P-tau181 in combination with age, sex, APOE4 and MMSE for MCI conversion and A $\beta$ + detection**

Population / comparison	Logistic regression with	AUC	95% CI	AUCs comparison	NRI
All study population MCI non-converters vs MCI converters	Age, sex, APOE4 and MMSE	0.691	0.655 to 0.741	Delong test <b>&lt; .0001</b>	12.8%
	+ Plasma P-tau181	0.744	0.702 to 0.784		
Patients with CSF biomarkers MCI non-converters vs MCI converters	Age, sex, APOE4 and MMSE	0.694	0.629 to 0.753	Delong test <b>&lt; .0001</b>	17.5%
	+ Plasma P-tau181	0.750	0.687 to 0.805		
	+ CSF P-tau181	0.752	0.690 to 0.807		
Patients with CSF biomarkers A $\beta$ - vs A $\beta$ +	Age, sex, APOE4 and MMSE	0.786	0.723 to 0.840	Delong test .0075	13.7%
	+ Plasma P-tau181	0.849	0.792 to 0.895		
	+ CSF P-tau181	0.857	0.801 to 0.902		

Abbreviations: CSF: cerebrospinal fluid; MCI: mild cognitive impairment; APOE: apolipoprotein E; MMSE, Mini-Mental State Examination; AUC: area under the ROC curve; CI: confidence interval; NRI: net reclassification improvement. The AUCs of the combination Age+Sex+APOE4+MMSE+Plasma P-tau181 and Age+Sex+APOE4+MMSE+CSF P-tau181 were not significantly different for amyloid or conversion detection, as tested using Delong test (P=.81).

### BALTAZAR study group

Olivier Hanon [1], Frédéric Blanc [2], Yasmina Boudali [1], Audrey Gabelle [3], Jacques Touchon [3], Marie-Laure Seux [1], Hermine Lenoir [1], Catherine Bayle [1], Stéphanie Bombois [4], Christine Delmaire [4], Xavier Delbeuck [5], Florence Moulin [1], Emmanuelle Duron [6], Florence Latour [7], Matthieu Plichart [1], Sophie Pichierri [8], Galdric Orvoën [1], Evelyne Galbrun [9], Giovanni Castelnovo [10], Lisette Volpe-Gillot [11], Florian Labourée [1], Pascaline Cassagnaud [12], Claire Paquet [13], Françoise Lala [14], Bruno Vellas [14], Julien Dumurgier [13], Anne-Sophie Rigaud [1], Christine Perret-Guillaume [15], Eliana Alonso [16], Foucaud du Boisgucheneuc [17], Laurence Hugonot-Diener [1], Adeline Rollin-Sillaire [12], Olivier Martinaud [18], Clémence Bouilly [1], Yann Spivac [19], Agnès Devendeville [20], Joël Belmin [21], Philippe-Henri Robert [22], Thierry Dantoine [23], Laure Caillard [1], David Wallon [24], Didier Hannequin [18], Nathalie Sastre [14], Sophie Haffen [25], Anna Kearney-Schwartz [15], Jean-Luc Novella [26], Vincent Deramecourt [12], Valérie Chauvire [27], Gabiel Abitbol [1], Nathalie Schwald [19], Caroline Hommet [28], François Sellal [29], Marie-Ange Cariot [16], Mohamed Abdellaoui [30], Sarah Benisty [31], Salim Gherabli [1], Pierre Anthony [29], Frédéric Bloch [32], Nathalie Charasz [1], Sophie Chauvelier [1], Jean-Yves Gaubert [1], Guillaume Sacco [22], Olivier Guerin [22], Jacques Boddaert [33], Marc Paccalin [17], Marie-Anne Mackowiak [12], Marie-Thérèse Rabus [9], Valérie Gissot [34], Athanase Benetos [15], Candice Picard [20], Céline Guillemaud [35], Gilles Berrut [8], Claire Gervais [22], Jaques Hugon [13], Jean-Marc Michel [29], JeanPhilippe David [19], Marion Paulin [12], Pierre-Jean Ousset [14], Pierre Vandell [36], Sylvie Pariel [21], Vincent Camus [37], Anne Chawakilian [1], Léna Kermanac'h [1], Anne-Cécile Troussiere [12], Cécile Adam [23], Diane Dupuy [20], Elena Paillaud [16], Hélène Briault [9], Isabelle Saulnier [38], Karl Mondon [37], Marie-Agnès Picat [23], Marie Laurent [16], Olivier Godefroy [20], Rezki Daheb [16], Stéphanie Libercier [29], Djamila Krabchi [1], Marie Chupin [39], Luc Buée [42], JeanSébastien Vidal [1], Edouard Chaussade [1], Sylvain Lehmann [40], Bernadette Allinquant [41], Susanna Schraen-Maschke [42].

### Affiliations of the BALATAZAR group

[1] Université de Paris, EA 4468, APHP, Hopital Broca, Memory Resource and Research Centre of de Paris-Broca-Ile de France, F-75013 Paris, France.

[2] Université de Strasbourg, CHRU de Strasbourg, Memory Resource and Research Centre of Strasbourg/Colmar, French National Centre for Scientific Research (CNRS), ICube Laboratory and Fédération de Médecine Translationnelle de Strasbourg (FMTS), Team Imagerie Multimodale Intégrative en Santé (IMIS)/Neurocrypto, F-67000 Strasbourg, France.

[3] Université de Montpellier, CHRU Montpellier, Memory Research and Resources center, department of Neurology, Inserm INM NeuroPEPs team, excellence center of neurodegenerative disorders, F-34000 Montpellier, France.

[4] Univ. Lille, CHU Lille, Memory Resource and Research Centre of Lille, Department of Neurology, Inserm U1171, Degenerative and Vascular Cognitive Disorders, F-59000 Lille, France.

[5] Univ. Lille, Inserm U1171 Degenerative and Vascular Cognitive Disorders, F-59000 Lille, France.

[6] Université Paris-Saclay, APHP, Hôpital Paul Brousse, département de gériatrie, UVSQ, Inserm, CESP, Team MOODS, F-94800 Villejuif, France.

- [7] Centre Hospitalier de la Côte Basque, Department of Gerontology, F-64100 Bayonne, France.
- [8] Université de Nantes, EA 4334 Movement-Interactions-Performance, CHU Nantes, Memory Research Resource Center of Nantes, F-44000 Nantes, France.
- [9] Sorbonne Universités, AP-HP, Centre Hospitalier Émile-Roux, Department of Gérontology 2, F-94450 Limeil-Brévannes, France.
- [10] CHU de Nîmes, Neurology Department, F-30000 Nîmes, France.
- [11] Hôpital Léopold Bellan, Memory Clinic, F-75014 Paris, France.
- [12] Univ. Lille, CHU de Lille, Memory Resource and Research Centre of Lille, Department of Neurology, F-59000 Lille, France.
- [13] Université de Paris, APHP, Groupe Hospitalier Saint Louis-Lariboisière-Fernand Widal, Memory Resource and Research Centre of Paris Nord-Ile de France, F-75010 Paris, France.
- [14] Université de Toulouse III, CHU La Grave-Casselardit, Memory Resource and Research Centre of Midi-Pyrénées, F-31300 Toulouse, France.
- [15] Université de Lorraine, CHRU de Nancy, Memory Resource and Research Centre of Lorraine, F-54000 Nancy, France.
- [16] AP-HP, HEGP, Service de Gériatrie, F-75015, Paris, France.
- [17] CHU de Poitiers, Memory Resource and Research Centre of Poitiers, F-86000 Poitiers, France.
- [18] CHU Charles Nicolle, Memory Resource and Research Centre of Haute-Normandie, F-76000 Rouen, France.
- [19] APHP, Centre Hospitalier Émile-Roux, Department of Gérontology 1, F-94450 Limeil-Brévannes, France.
- [20] CHU d'Amiens-Picardie, Memory Resource and Research Centre of Amiens Picardie, F-80000 Amiens, France.
- [21] APHP, Hôpitaux Universitaires Pitie-Salpêtrière-Charles Foix, Service de Gériatrie Ambulatoire, F-75013 Paris, France.
- [22] CHU de Nice, Memory Research Resource Center of PACA Est, F-06100 Nice, France.
- [23] CHU de Limoges, Memory Research Resource Center of Limoges, F-87000 Limoges, France.
- [24] Université de Rouen Normandie, CHU Charles Nicolle, Memory Resource and Research Centre of Haute-Normandie, Inserm U1079, IRIB, F-76000 Rouen, France.
- [25] CHU de Besançon, Memory Resource and Research Centre of Besançon-Franche-Comté, F-25000 Besançon, France.
- [26] Université de Reims Champagne Ardenne, EA 3797, CHU de Reims, Memory Resource and Research Centre of Champagne Ardenne, F-51100 Reims, France.
- [27] CHU d'Angers, Memory Resource and Research Centre of Angers, F-49000 Angers, France.
- [28] CHRU de Tours, Memory Resource and Research Centre of Tours, F-37000 Tours, France.
- [29] Université de Strasbourg, CHRU de Strasbourg, Memory Resource and Research Centre of Strasbourg/Colmar, Inserm U-118, F-67000 Strasbourg, France.
- [30] Univ Paris Est Creteil, EA 4391 Excitabilité Nerveuse et Thérapeutique, CHU Henri Mondor, Department of Neurology, F-94000 Créteil, France.
- [31] Fondation ophtalmologique Adolphe de Rothschild, Department of Neurology, F-75019 Paris, France.
- [32] CHU d'Amiens-Picardie, Department of Gerontology, F-80000 Amiens, France.

- [33] Sorbonne Universités, APHP, Hôpitaux Universitaires Pitie-Salpêtrière-Charles Foix, Memory Resource and Research Centre, Centre des Maladies Cognitives et Comportementales IM2A, Inserm UMR 8256, F-75013 Paris, France.
- [34] Université François-Rabelais de Tours, CHRU de Tours, Memory Resource and Research Centre of Tours, Inserm CIC 1415, F-37000 Tours, France.
- [35] Sorbonne Universités, APHP, Hôpitaux Universitaires Pitie-Salpêtrière-Charles Foix, Memory Resource and Research Centre, Centre des Maladies Cognitives et Comportementales IM2A, F-75013 Paris, France.
- [36] Université Bourgogne Franche-Comté, EA 481 Neurosciences, IFR 133, CHU de Besançon, Memory Resource and Research Centre of Besançon Franche-Comté, F-25000 Besançon, France.
- [37] Université François-Rabelais de Tours, CHRU de Tours, Memory Resource and Research Centre of Tours, Inserm U930 Imagerie et Cerveau, F-37000 Tours, France.
- [38] Université de Limoges, EA 6310 HAVAE, CHU de Limoges, Memory Research Resource Center of Limoges, F-87000 Limoges, France.
- [39] Université Paris-Saclay, Neurospin, CEA, cati-neuroimaging.com, CATI Multicenter Neuroimaging Platform, F-91190 Gif-sur-Yvette, France.
- [40] LBPC-PPC, Université de Montpellier, INM INSERM, IRMB CHU de Montpellier, Montpellier, France.
- [41] Université de Paris, Inserm UMR-S 894, F-75014 Paris, France.
- [42] Univ. Lille, Inserm, CHU Lille, U1172-LilNCog, LiCEND, LabEx DISTALZ, F-59000 Lille, France.