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RESEARCH

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Cross-sectional associations of plasma vitamin D with cerebral β -amyloid in older adults at risk of dementia

Fati Nourhashemi^{1,2,3,4†}, Claudie Hooper^{1*†}, Christelle Cantet^{1,2,3,4}, Catherine Féart⁵, Isabelle Gennero^{6,7}, Pierre Payoux^{8,9}, Anne Sophie Salabert^{8,9}, Sophie Guyonnet^{1,2,3,4}, Philippe De Souto Barreto^{1,2,3,4}, Bruno Vellas^{1,2,3,4} and for the Multidomain Alzheimer Preventive Trial/Data sharing Alzheimer (DSA) study group

Abstract

Background: Vitamin D deficiency is associated with an increased risk of Alzheimer's disease and increased beta-amyloid (A β) in animals. Hence we sought to investigate the relationship between plasma 25-hydroxyvitamin D (25(OH)D) and cerebral A β in older adults with subjective memory complaints.

Methods: This is a secondary analysis of the Multidomain Alzheimer Preventive Trial. Participants were 178 dementia-free individuals aged 70 years or older with data on plasma 25(OH)D and cerebral A β load assessed by [¹⁸F]-florbetapir positron emission tomography. Plasma 25(OH)D was measured at study baseline using a commercially available electro-chemiluminescence competitive binding assay. Standard uptake value ratios (SUVRs) were generated using the cerebellum as a reference. Brain regions assessed included the cortex, anterior cingulate, anterior putamen, caudate, hippocampus, medial orbitofrontal cortex, occipital cortex, parietal cortex, pons, posterior cingulate, posterior putamen, precuneus, semioval centre and temporal cortex. Associations were explored using fully adjusted multiple linear regression models.

Results: Participants had a mean (SD) age of 76.2 years (4.4) and 59.6% were female. The mean (SD) plasma 25(OH)D level was 22.4 ng/ml (10.8) and the mean (SD) cortical SUVR was 1.2 (0.2). We did not find any cross-sectional associations ($p > 0.05$) between baseline 25(OH)D levels and A β in any of the brain regions studied.

Conclusions: These preliminary results suggest that circulating 25(OH)D is not associated with cerebral A β in older adults. Further longitudinal studies with the measurement of mid-life vitamin D status are required to explore the relationship between vitamin D and A β accrual over time, thereby circumventing the shortfalls of a cross-sectional study.

Keywords: Vitamin D, Beta-amyloid, Alzheimer's disease, Positron emission tomography

Background

Vitamin D is a fat-soluble steroid hormone that seems crucial for brain health in humans [1–5]. Low vitamin D status is common amongst the elderly and is considered a major health problem [6–8]. Studies have shown that vitamin D insufficiency is associated with a higher risk of Alzheimer's disease (AD) [9–16] and accelerated cognitive decline [12, 17, 18], although some conflicting

results are reported [19–21]. Randomized controlled trials (RCTs) investigating the effects of vitamin D supplementation (alone or in combination with other drugs) on cognitive decline and AD onset are limited [22–25] and have largely proven unsuccessful to date [22, 23, 25].

Despite the controversy surrounding the role of vitamin D in cognitive function and AD, animal studies suggest that vitamin D hypovitaminosis results in increased brain beta-amyloid (A β) [26] and vitamin D promotes a reduction in A β brain burden [27, 28]. In human studies, vitamin D has been shown to increase plasma A β , particularly in older adults, suggestive of decreased brain A β [29]. Furthermore, vitamin D

* Correspondence: claudie28@yahoo.com

†Equal contributors

¹Gérontopôle, Department of Geriatrics, Toulouse University Hospital, Toulouse, France

Full list of author information is available at the end of the article



status assessed through a dietary questionnaire has been associated with less A β in AD-vulnerable brain regions in subjects at risk of AD [30, 31]. However, to the best of our knowledge, studies have not addressed the relationship between circulating vitamin D (measured biochemically) and cerebral A β . Thus, we examined the cross-sectional associations between 25-hydroxyvitamin D (25(OH)D), the major circulating form of vitamin D, and cerebral A β in older adults at risk of dementia. We hypothesized that 25(OH)D would be inversely associated with A β .

Methods

The Multidomain Alzheimer Preventive Trial, ethics and approval

Data were obtained from a [¹⁸F]-florbetapir positron emission tomography (PET) study carried out as an ancillary project to the Multidomain Alzheimer Preventive Trial (MAPT) [32] (ClinicalTrials.gov, NCT00672685), a large multicentre, phase III, randomized, placebo-controlled trial. The MAPT was designed to assess the effects of omega 3 polyunsaturated fatty acid (n-3 PUFA) supplementation alone or in combination with a multidomain intervention (involving nutritional and exercise counselling and cognitive training), compared to placebo, in slowing cognitive decline in older adults with subjective memory complaints ($n = 1680$). Both the MAPT and the ancillary [¹⁸F]-florbetapir PET study were approved by the ethics committee in Toulouse (CPP SOOM II) and written consent was obtained from all participants.

Participants

At inclusion, subjects were community-dwelling men and women without dementia, aged ≥ 70 years, who met at least one of the following criteria: spontaneous memory complaints, limitation in executing ≥ 1 Instrumental Activity of Daily Living, or slow gait speed (≤ 0.8 m/s). Participants of this study were 180 individuals who had data on plasma 25(OH)D and cerebral A β load. However, two participants were excluded from the present analysis because they had CDR ≥ 1 (suggestive of dementia) at the clinical visit closest to PET-scan assessment. Thus, a total of 178 participants were included in the study described here.

[¹⁸F]-Florbetapir positron emission tomography

PET scans as a measure of cerebral A β load were performed using [¹⁸F]-florbetapir as described previously [32, 33]. PET data acquisitions commenced 50 min after injection of a mean of 4 MBq/kg weight of [¹⁸F]-Florbetapir. Radiochemical purity of [¹⁸F]-Florbetapir was superior to 99.5%. Regional standard uptake value ratios (SUVRs) were generated from semi-automated quantitative analysis with the whole cerebellum used as

the reference region. Cortical-to-cerebellar SUVRs (cortical-SUVRs) were obtained using the mean signal of the predefined cortical regions: frontal, temporal, parietal, precuneus, anterior cingulate and posterior cingulate as described previously [34]. Other brain regions independently assessed were the anterior cingulate, anterior putamen, caudate, hippocampus, medial orbitofrontal cortex, occipital cortex, parietal cortex, pons, posterior cingulate, posterior putamen, precuneus, semioval centre and temporal cortex. A Quality Control procedure was carried out using a semi-quantification-based method. PET scans were performed an average of 18.1 ± 8.8 months after baseline.

Measurement of 25(OH)D

Total plasma 25(OH)D (D3 and D2 forms) was measured using a commercially available electro-chemiluminescence competitive binding assay (Cobas, Roche) in baseline plasma samples. In brief, plasma (15 μ l) was denatured to release bound 25(OH)D from vitamin D binding protein (VDBP). The sample was then incubated with recombinant ruthenium-labelled VDBP to enable complex formation. Biotinylated 25(OH)D was subsequently added and the entire complex became bound to the electrode through an interaction of biotin with streptavidin-coated micro-particles, which are captured on the electrode surface. Unbound substance was subsequently removed and a voltage was applied to the electrode which induced a chemiluminescent emission that was quantified using a Roche Cobas 8000 e602 analyser (Roche Diagnostics, Mannheim, Germany). The concentrations of 25(OH)D (ng/ml) were determined against a standard curve.

Confounding variables

We selected the following confounding variables on the basis of data availability and the literature on AD and vitamin D [35, 36]: age at PET-scan assessment, gender, body mass index (BMI), season of blood collection (four categories: autumn, winter, spring, summer), educational level, cognitive status assessed at the clinical visit closest to the PET scan (Mini Mental State Examination (MMSE): score out of 30), time interval (months) between baseline and the PET scan, MAPT group allocation (four groups: placebo, multidomain intervention, n-3 PUFA supplementation, multidomain intervention + n-3 PUFA supplementation) and apolipoprotein E $\epsilon 4$ (ApoE $\epsilon 4$) genotype (carriers of at least one $\epsilon 4$ allele versus non-carriers).

Statistical analysis

Descriptive characteristics are presented as mean \pm standard deviation (SD) or absolute values/percentages. The relationship between plasma 25(OH)D and cerebral A β load was not an a-priori hypothesis of the MAPT. After completing the analysis of the primary hypotheses

in the MAPT, we performed additional post-hoc analyses using multiple linear regression models to evaluate the cross-sectional relationships between plasma 25(OH)D and cerebral brain A β load measured in SUVRs (both as continuous variables) adjusting for all confounders. We ran three separate sensitivity analyses in order to substantiate our main analysis exploring the relationship between 25(OH)D and cortical A β . Firstly, we classified the 25(OH)D data according to the cut-off values < 20 ng/ml, \geq 20 but \leq 30 ng/ml and > 30 ng/ml which are defined as 25(OH)D deficiency, insufficiency and sufficiency [37]. The cut-off value of < 10 ng/ml, which has been associated with worse cognitive outcomes, was not used since there were only 16 out of 178 subjects (9%) with 25(OH)D in this range. The class containing values of 25(OH)D > 30 ng/ml was used as the reference. We then ran multiple linear regression analysis adjusted for all confounders. Secondly, we dichotomized the dependent variable, cortical A β load, with a positivity threshold of mean cortical SUVR \geq 1.17 [33, 38] and then performed logistic regression adjusted for all confounders. Thirdly, we used de-seasonalized 25(OH)D values calculated according to the periodic function $y_t = B_0 + B_1 \sin(2\pi t/365) + B_2 \cos(2\pi t/365)$ [12, 39] to assess the relationship between 25(OH)D and cortical A β (both as continuous variables) using multiple linear regression analysis adjusted for all confounders (minus season categorized into four classes). To explore the role of apolipoprotein E (ApoE) ϵ 4 genotype, the major risk factor for sporadic SD [40], on the association between 25(OH)D and cortical A β (both as continuous variables) we ran a linear regression analysis with the introduction of an interaction term between ApoE ϵ 4 genotype and 25(OH)D. There was no correction for multiple comparisons: $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Sample characteristics

Clinical and demographic characteristics of the study participants are presented in Table 1. The mean age of the participants was around 76 years and approximately 60% of the subjects were female. Participants exhibited a high educational level and just less than half had a CDR score of 0.5. Approximately one-quarter of the subjects were ApoE ϵ 4 carriers. The mean (SD) plasma 25(OH)D level was 22.4 ng/ml (10.8) and the mean (SD) cortical SUVR was 1.2 (0.2).

Exploration of the relationship between 25(OH)D and cerebral A β

Neither cortical A β load nor A β levels present in the anterior cingulate, anterior putamen, caudate, hippocampus,

Table 1 Participant characteristics

Variable	Value (<i>n</i> = 178)
Age (years)	76.2 \pm 4.4
Sex, women	106 (59.6%)
Education	
No diploma or primary school certificate	47 (26.6%)
Secondary education no high-school diploma	49 (27.7%)
High school diploma	24 (13.6%)
University level	57 (32.2%)
MAPT group allocation	
Multidomain intervention	39 (21.9%)
n-3 PUFA supplementation	42 (23.6%)
Multidomain intervention and n-3 PUFA supplementation	49 (27.5%)
Placebo	48 (27.0%)
Season of vitamin D measurement	
Winter	71 (39.9%)
Spring	37 (20.8%)
Summer	15 (8.4%)
Autumn	55 (30.9%)
BMI (kg/m ²)	26.6 \pm 4.0
CDR 0.5	79 (44.4%)
MMSE score (/30)	28.3 \pm 1.6
ApoE ϵ 4 carriers ^a	42 (25.6%)
25-Hydroxyvitamin D (ng/ml)	22.4 \pm 10.8
25-Hydroxyvitamin D < 20 ng/ml	81 (45.5%)
25-Hydroxyvitamin D \geq 20 ng/ml \leq 30 ng/ml	56 (31.5%)
25-Hydroxyvitamin D > 30 ng/ml	41 (23.0%)
Cortical SUVR	1.2 \pm 0.2
Cortical SUVR positive (\geq 1.17)	75 (42.1%)

Age, CDR, BMI and MMSE score closest to the PET scan are presented
Data expressed as mean \pm standard deviation or absolute value (percentage)
BMI body mass index, CDR Clinical Dementia Rating, MAPT Multidomain
Alzheimer Preventive Trial, n-3 PUFA omega-3 polyunsaturated fatty acid,
MMSE Mini Mental State Examination, ApoE apolipoprotein E, SUVR standard
uptake ratio values

^aApoE status available for *n* = 164

medial orbitofrontal cortex, occipital cortex, parietal cortex, pons, posterior cingulate, posterior putamen, precuneus, semioval centre and temporal cortex were associated with plasma 25(OH)D after adjustment for all confounders (Table 2).

Sensitivity analysis

Categorization of the 25(OH)D data and dichotomization of the A β data showed comparable results to the main analysis using cortical A β (Table 3). Exploring the relationship between de-seasonalized vitamin D values and cortical A β load also corroborated the main analysis using cortical A β (Table 3).

Table 2 Exploration of the association of 25(OH)D with cerebral A β

Brain region	Unadjusted model			Adjusted model		
	B coefficient	SE	p	B coefficient	SE	p
Cortex	-0.001	0.001	0.587	-0.001	0.001	0.376
Anterior cingulate	-0.001	0.002	0.378	-0.002	0.002	0.325
Anterior putamen	0.000	0.001	0.972	-0.000	0.001	0.880
Caudate	-0.001	0.001	0.502	-0.000	0.001	0.872
Hippocampus	0.000	0.001	0.840	0.001	0.001	0.495
Medial orbitofrontal cortex	-0.000	0.001	0.928	-0.000	0.001	0.794
Occipital cortex	-0.001	0.001	0.351	-0.001	0.001	0.291
Parietal cortex	-0.000	0.001	0.930	-0.001	0.001	0.662
Pons	0.000	0.001	0.941	0.000	0.001	0.698
Posterior cingulate	-0.000	0.001	0.779	-0.001	0.001	0.461
Posterior putamen	0.000	0.001	0.623	0.000	0.001	0.822
Precuneus	-0.001	0.002	0.471	-0.002	0.002	0.287
Temporal cortex	-0.001	0.001	0.479	-0.001	0.001	0.240
Semioval centre	-0.001	0.001	0.646	0.000	0.001	0.803

The unadjusted linear regression model in the main analysis included all 178 participants who underwent [¹⁸F]-florbetapir positron emission tomography imaging. Cortical-to-cerebellar standard uptake value ratios were obtained using the mean signal of the following predefined cortical regions: frontal, temporal, parietal, precuneus, anterior cingulate and posterior cingulate. Other brain regions were independently assessed for A β in relation to the cerebellum as a reference region. The adjusted model contained fewer subjects ($n = 176$) due to missing data on confounders
A β beta-amyloid, 25(OH)D 25-hydroxyvitamin D, SE standard error

Exploratory analysis

Next we explored the relationship between 25(OH)D and cortical A β as a function of ApoE $\epsilon 4$ status. However, the interaction between 25(OH)D and ApoE $\epsilon 4$ genotype was not associated with cortical A β load ($p = 0.434$).

Discussion

We have shown that vitamin D measured as 25(OH)D was not associated with cerebral A β independently or as a function of ApoE $\epsilon 4$ status. To the best of our knowledge, this is the first study to explore the associations between

circulating plasma vitamin D (measured biochemically) and cerebral A β .

Our findings were against our original hypothesis based on animal experiments [27, 28] and human studies using nutritional questionnaires to assess the associations between vitamin D status and cerebral A β [30, 31]. However, the participants of these human studies were younger and cognitively normal. It might also be that dietary questionnaires do not best capture vitamin D status especially in those with memory complaints. Moreover, sun exposure is the major source of vitamin D.

Table 3 Sensitivity analyses exploring the association of 25(OH)D with cerebral A β

	Unadjusted model			Adjusted model		
	B coefficient or odds ratio*	SE or 95% CI*	p	B coefficient or odds ratio*	SE or 95% CI*	p
Sensitivity analysis A: 25(OH)D in classes ^a						
25(OH)D < 20 ng/ml	0.005	0.033	0.869	0.010	0.034	0.775
25(OH)D \geq 20 ng/ml \leq 30 ng/ml	0.061	0.036	0.089	0.039	0.035	0.273
Sensitivity analysis B: logistic regression ^b						
25(OH)D < 20 ng/ml	1.021*	0.477,2.188*	0.957	1.038*	0.421,2.557*	0.936
25(OH)D \geq 20 ng/ml \leq 30 ng/ml	1.059*	0.468,2.395*	0.891	0.769*	0.299,1.978*	0.585
Sensitivity analysis C: de-seasonalized 25(OH)D (continuous) ^c						
	-0.001	0.001	0.600	-0.001	0.001	0.421

^aMultiple linear regression was run to explore the associations between cortical A β and 25(OH)D classified according to the cut-off values < 20 ng/ml, \geq 20 but \leq 30 ng/ml and > 30 ng/ml adjusting for all confounders

^bLogistic regression was performed with A β dichotomized with a positivity threshold of mean cortical standard uptake value ratio \geq 1.17 and 25(OH)D in classes with adjustment for all confounders

^cDe-seasonalized 25(OH)D values were used to assess the relationship between cortical A β and 25(OH)D both as continuous variables using a multiple linear regression model adjusted for all confounders. The adjusted models contained fewer subjects ($n = 176$) due to missing data on confounders
A β beta-amyloid, CI confidence interval, SE standard error, 25(OH)D 25-hydroxyvitamin D

Our findings are in line with those showing that vitamin D concentrations are not associated with cognitive decline or AD [19–21], although a number of reports to the contrary are published [9–18]. Considering that RCTs investigating the effects of vitamin D supplementation on brain health are negative to date [22, 23, 25], it could be hypothesized that observational studies reporting a significant association between vitamin D status and cognitive decline or AD risk might be prone to reverse causality bias. Alternatively, the failure of vitamin D trials might be attributed to the short duration of therapy or the sub-optimal timing of vitamin D supplementation. Timing has recently been highlighted as an important criterion in the relationship between vitamin D and cognition [18, 41]. Indeed, vitamin D status mid-life has been associated with cognition 10 years later [42]. Thus, the duration and time window of vitamin D hypovitaminosis might dictate pathological changes associated with AD in older age. In the same vein, the assessment of cerebral A β in later life does not provide information on the slow pathophysiological accrual of A β [43] and the role of vitamin D. Perhaps as with cognition, mid-life vitamin D deficiency might contribute more to A β deposition than vitamin D deficiency in later life. Thus, in this study we might have failed to detect an association between vitamin D status and cerebral A β load due to the inappropriate timing of measurements; however, plasma samples in mid-life were not available in the MAPT to test further hypotheses.

It is also feasible that vitamin D hypovitaminosis is linked to cognitive decline via A β -independent processes. Indeed, 25(OH)D insufficiency is associated with an increase in white matter abnormalities indicative of cerebrovascular disease [44, 45] and decreasing 25(OH)D plasma levels are associated with an increased risk of ischaemic stroke [46]. Thus, it is plausible that vitamin D might be associated with dementia of a more vascular nature. Vitamin D has also been shown to regulate the synthesis of neurotrophins [47, 48] and therefore vitamin D hypovitaminosis could potentially promote neuronal death and cognitive decline. Moreover, vitamin D regulates the expression of a number of neurotransmitters including acetylcholine [49] and dopamine [50] and the expression of the enzyme involved in the rate-limiting step of catecholamine synthesis [51], which in turn might impact cognition. In addition, vitamin D inhibits the synthesis of inducible nitric oxide synthase [52], downregulates reactive oxygen species [53], upregulates the antioxidant glutathione [54] and inhibits the expression of pro-inflammatory cytokines [55]. Thus, vitamin D hypovitaminosis might potentiate inflammation and oxidative damage to neurons, hence promoting cognitive deterioration.

Exploratory analysis showed that there was no interaction between 25(OH)D and ApoE ϵ 4 genotype to modify

cortical A β . It has been shown previously that ApoE ϵ 4 carriers have a better vitamin D status [56], which could potentially serve to reduce cerebral A β burden according to data from animal studies [27, 28]. Moreover, a significant interaction between ApoE ϵ 4 and 25(OH)D concentrations has been reported in relation to human memory function [57]. Therefore, the links between 25(OH)D and ApoE ϵ 4 to govern A β pathology is worthy of further research.

The strengths of the current study are the relatively large sample size and the availability of PET [¹⁸F]-florbetapir imaging data and plasma 25(OH)D measurements, providing a more accurate value for vitamin D levels, as opposed to vitamin status assessed through dietary questionnaires. In addition, we considered several cofounders, including a possible interaction between vitamin D and ApoE ϵ 4 status. The limitations of our study included the cross-sectional design, which precluded the examination of the relationship between plasma 25(OH)D and change in cerebral A β load over time. PET scans were also performed throughout the 3-year period of the MAPT; therefore the study design was not truly cross-sectional. The inclusion of the time interval between baseline 25(OH)D measurements and the PET scan as a confounder in the linear regression models probably served to mitigate this bias. Furthermore, we only had data availability for vitamin D status in later life which might perhaps not be the optimal time window for studying the associations between vitamin D and cerebral A β .

Conclusions

We have shown here that circulating 25(OH)D was not associated with cerebral A β in older adults at risk of dementia cross-sectionally. However, a longitudinal observational study including mid-life vitamin D measurements is warranted to examine the relationship between plasma 25(OH)D and cerebral A β accrual over time.

Abbreviations

25(OH)D: 25-Hydroxyvitamin D; AD: Alzheimer's disease; ApoE: Apolipoprotein E; A β : Beta-amyloid; CDR: Clinical Dementia Rating; MAPT: Multidomain Alzheimer Preventive Trial; MMSE: Mini Mental State Examination; n-3 PUFA: Omega-3 polyunsaturated fatty acid; PET: Positron emission tomography; SUVR: Standard uptake value ratio

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The MAPT/DSA Group refers to the following.

MAPT Study Group

Principal investigator: Bruno Vellas (Toulouse); *Coordination:* Sophie Guyonnet; *Project leader:* Isabelle Carrié; *CRA:* Lauréane Brigitte; *Investigators:* Catherine Faisant, Françoise Lala, Julien Delrieu, Hélène Villars; *Psychologists:* Emeline Combrouze, Carole Badufle, Audrey Zueras; *Methodology, statistical analysis and data management:* Sandrine Andrieu, Christelle Cantet, Christophe Morin; *Multidomain group:* Gabor Abellan Van Kan, Charlotte Dupuy, Yves Rolland (physical and nutritional components), Céline Caillaud, Pierre-Jean Ousset (cognitive component), Françoise Lala (preventive consultation), Bertrand Fougère (Toulouse). The cognitive component was designed in collaboration with Sherry Willis from the University of Seattle, and Sylvie Belleville, Brigitte Gilbert and Francine Fontaine from the University of Montreal.

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MRI group: Carole Dufouil (Bordeaux), Stéphane Lehéricy, Marie Chupin, Jean-François Mangin, Ali Bouhaya (Paris); Michèle Allard (Bordeaux); Frédéric Ricolfi (Dijon); Dominique Dubois (Foix); Marie Paule Bonceour Martel (Limoges); François Cotton (Lyon); Alain Bonafé (Montpellier); Stéphane Chanalet (Nice); Françoise Hugon (Tarbes); Fabrice Bonneville, Christophe Cognard, François Chollet (Toulouse).

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Safety management: Pascale Olivier-Abbal.

DSA Group

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FN, CH, PDSB, CC, CF, SG and BV contributed to study concept and design. FN, CH, PDSB and CC prepared the manuscript. CC performed statistical analysis. PP and ASS performed PET analyses. IG performed vitamin D analysis. FN, CH, PDSB, CC and BV critically reviewed subsequent drafts. All authors decided on submission. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Both the MAPT and PET sub-study described in this manuscript were approved by the ethical committee in Toulouse (CPP SOOM II) and have therefore been performed in accordance with the 1964 Declaration of Helsinki and its later amendments. Written consent was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

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Author details

¹Gérotopôle, Department of Geriatrics, Toulouse University Hospital, Toulouse, France. ²INSERM UMR 1027, Toulouse, France. ³University of Toulouse III, Toulouse, France. ⁴Department of Epidemiology and Public Health, CHU Toulouse, Toulouse, France. ⁵University of Bordeaux, Inserm, Bordeaux Population Health Research Center, Team LEHA, UMR 1219, F-33000 Bordeaux, France. ⁶UMR1043 Centre de Physiopathologie Toulouse Purpan, Université de Toulouse, UPS, INSERM, Toulouse, France. ⁷Institut Federatif de Biologie, CHU Toulouse, Purpan University Hospital, Toulouse, France. ⁸UMR 1214, Toulouse Neuroimaging Center, University of Toulouse III, Toulouse, France. ⁹Department of Nuclear Medicine, Toulouse University Hospital, Toulouse, France.

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