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Original Research

Associations between frailty, biomarkers of cerebral pathology, cognitive and neuropsychiatric symptoms: a memory clinic study

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ABSTRACT

Background: Frailty is a prevalent condition among older adults with neurocognitive disorders.
Objectives: To ascertain whether frailty contributes to the severity of cognitive impairment and neuropsychiatric symptoms, and its association with cerebral pathology measured *in vivo* by fluid and imaging biomarkers.
Design: We conducted cross-sectional and longitudinal analyses based on CLEM Study, a multicentre memory-clinic cohort that recruited participants between 2014 and 2018.
Setting: CLEM Study occurred in eight memory centres in France (Lyon, Paris, Strasbourg, Poitiers, Tours, Grenoble) and Monaco.

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Participants: A total of 168 participants (mean age 80.5 ± 4.8 years) with mild to moderate dementia due to at least one aetiological diagnosis between Alzheimer's disease, dementia with Lewy bodies or vascular dementia were included in the study.
Measurements: The participants were evaluated at baseline and followed up for two years. The concept of frailty was operationalised using a 45-item Frailty Index. Cognition was assessed using the ADAS-cog scale, while neuropsychiatric symptoms were evaluated with the Neuropsychiatric Inventory. The cerebral pathological score, a proxy for brain pathologies, was a composite score based on the presence of several *in vivo* biomarkers: presynaptic dopaminergic denervation on ^{123}I-FP-CIT SPECT (DaTscan®), vascular lesions on MRI, elevated blood-based pTau181, neurofilaments light-chain or glial fibrillary acid protein. Linear and mixed regression analyses were conducted to model the relationships between cognitive or neuropsychiatric symptoms, frailty and cerebral pathologic score, adjusted for age, sex and education.
Results: The findings indicate an impact of both frailty ($\beta = 0.28$, 95 % CI [0.14–0.43], $p < 0.001$) and cerebral pathological score ($\beta = 0.30$, 95 % CI [0.13–0.47], $p = 0.002$) on cognitive impairment. However, only frailty was associated with neuropsychiatric symptoms ($\beta = 0.28$, 95 % CI [0.14–0.43], $p < 0.001$), particularly with apathy ($\beta = 0.40$, 95 % CI [0.26–0.53], $p < 0.001$). We found an association between cerebral pathological score and longitudinal cognitive decline ($\beta = 0.36$, 95 % CI [0.19–0.53], $p < 0.001$) in exploratory analyses with available longitudinal data at 24 months ($n = 74$).
Conclusions: Neurocognitive disorders are complex entities, where cognitive and neuropsychiatric symptoms are not fully influenced by the same factors. When cognitive symptoms seem more driven by cerebral pathology than frailty, neuropsychiatric symptoms appear to be more influenced by general state of frailty. Measuring and treating frailty might be a key factor in dealing with neuropsychiatric symptoms and their consequences.

1. Introduction

Frailty is defined as a state of increased vulnerability to stressful events, leading to a higher risk of poor health outcomes and reduced resilience [1,2]. This concept helps us to better understand the heterogeneity observed during the ageing process, rather than based on chronological age [3,4].

Several approaches have been described to conceptualize and measure frailty. Two common approaches were proposed in 2001, with the physical phenotype model on the one hand [5], and the health deficit accumulation model on the other hand [2,6]. In the latter, health deficits could relate to medical history, clinical examination, blood abnormalities or functional dependency and are measured during a comprehensive geriatric assessment [7,8]. Frailty Index (FI) may be a proxy of frailty according to this deficit accumulation model. FI is defined in an individual, as the proportion of health deficits present out of the total number of health variables considered. FI has been the subject of extensive study for more than twenty years and has several advantages, notably that it can be constructed using existing clinical data and is replicable across different databases [7].

FI has been linked to cognitive decline and neurodegenerative diseases (for review, see [9]). This association extends from the early to late stages of the disease, including the risk of institutionalisation and death [10–14]. More specific studies have investigated the respective impact of frailty, as estimated by the FI, and brain pathologies on cognition in older adults [15–19]. Brain pathologies refer to all the basic neuropathological lesions found in the brain, such as neurofibrillary tangles, Lewy bodies and/or arteriolosclerosis. These studies suggest that frailty and neuropathology are both predictors of cognitive impairment in older adults, in an independent way but also with potential interactive effects. Indeed, individuals with a high burden of Alzheimer's pathology are at less risk of exhibiting clinical symptoms of dementia if they have low frailty scores, compared to those with higher frailty scores [2,16,18]. A limitation of these observations is that the assessment of neuropathology is based on autopsy data. Post-mortem analysis allows for an accurate assessment of the neuropathological burden (gold standard), however clinicopathological correlations may be difficult to interpret due to the time between clinical and pathological assessments, and the potential occurrence of health events between clinical assessments and death. Furthermore, while the relationship between cognition and frailty has been the subject of prior research, there is a paucity of studies that have examined the association between frailty and neuropsychiatric symptoms, another prevalent manifestation of dementia [20,21].

The aim of this study is to examine the association between frailty (measured using a 45-item FI) and brain pathologies (measured using blood-based and neuroimaging biomarkers) with cognition and neuropsychiatric symptoms. This study is based on a prospective multicentre memory clinic cohort including cognitively impaired patients. We hypothesise that higher frailty index and impaired brain biomarkers are associated with worse cognitive scores and more severe neuropsychiatric symptoms at baseline, and with faster cognitive or behavioural decline during the follow-up.

2. Methods

2.1. Study setting, design and participants

The present work is based on the CLEM (Co-Lésions dans la Maladie d'Alzheimer et les maladies apparentées) Study, a prospective multicentre French cohort [22]. This cohort recruited 178 outpatients followed up in eight memory centres, enrolled between February 3, 2014 and June 26, 2020. The primary objective of the CLEM study was to ascertain imaging markers illustrating colesions of Alzheimer's, cerebrovascular and Lewy body types of dementia the most predictive of functional disability progression. The main outcome paper is not yet published; this study is an ancillary study. The study was approved by an ethical research committee, and written informed consent was obtained from the patient and/or their next of kin. This trial was registered with ClinicalTrials.gov (NCT02052947).

Participants had primary clinical diagnosis of Alzheimer's disease (AD), vascular dementia (VD) or dementia with Lewy bodies (DLB) or combinations of these three diagnoses. Clinical diagnosis was established for patients meeting diagnostic criterion for dementia due to AD [23], VD [24], or DLB [25]. No biomarker was mandatory to reinforce the clinical diagnosis at baseline, made by experimented memory clinic physicians. Due to the study's objectives, population included was recruited for exhibiting a high prevalence of brain pathologies, due to advanced age and the possibility for physicians to include patients with a pure diagnosis of one neurodegenerative disease but also with possible combinations of AD, DLB and/or VD.

Patients had to meet specific criteria to be included in the study. Firstly, they had to be over 70 years old, and secondly, they had to have a Mini-Mental State Evaluation (MMSE) score greater than 15/30. The cut-off of 70 years old was selected to get higher prevalence of brain copathologies [26,27]. Patients were not taking any antipsychotic medication and did not have symptoms of any other neurodegenerative or

neurological diseases at the beginning of the study. Participants were observed over a period of 24 months, with assessments conducted at the outset of the study and then every six months for a total of five assessments. Patients underwent a range of assessments at the outset, including a clinical examination (medical history, clinical exam, functional independence assessment, medication assessment), a comprehensive neuropsychological assessment, blood sample analyses and sampling, structural MRI and ^{123}I-FP-CIT SPECT (DaTscan®). Functional independence, medical events and neuropsychiatric symptoms were recorded on a six-month basis. Neurocognitive tests were performed on an annual basis.

Seven participants were excluded because they did not meet the inclusion and non-exclusion criteria after recruitment.

2.2. Frailty index

A FI can be regarded as a measure of frailty, defined as an increased vulnerability to stressful events. The FI is calculated using a number of health deficits. It is the number of health deficits presented by a single patient compared to the total list of deficits. Therefore, a participant with 20 deficits out of 45 has an FI of 0.44. A higher FI is indicative of poorer health.

We calculated a 45-item FI (Functional Independence Measure) as outlined by Mitnitski, Mogilner and Rockwood [6]. The selection of variables from the initial visit to construct the FI was based on existing standardised procedures [7,28]. It was determined that the variables in question were non-ubiquitous health deficits. Consequently, variables related to cognitive status or cognitive assessment were excluded from the study. The variables included may be related to functional independence, medical history, clinical examination or medication, as well as to biological conditions. All of these were measured at baseline according to the study's procedures. Variables were coded binarily, with 0 points if the variable was absent, and 1 point if it was present. Refer to Supplementary Table 1 for a comprehensive list of the variables. For continuous variables, we used our laboratory standards or commonly accepted thresholds. For activities of daily living, data is captured from the Lawton Instrumental Activities of Daily Living (IADL) scale or the French Disability Assessment for Dementia – 6 (DAD6) scale [29,30], we divided the variables into different subcategories, scoring them from 0 to 1 point.

As certain variables included in the 45-item FI appear to be associated with the stage of cognitive impairment and more severe dementia (*e.g.*, functional and autonomy variables) or with specific causes or symptoms of dementia (*e.g.*, traumatic brain injury or depression), we decided, for sensitivity analyses, to compute a 30-item FI, excluding all variables that have been shown to have a strong and consistent link with cognitive impairment or cognitive decline. We have not excluded any variables that have been identified as risk factors for dementia, such as diabetes, hypertension and hearing loss. Excluded items are indicated by an asterisk in Supplementary Table 1.

Participants were excluded from the study if they presented at least 25 % of missing data points in the 45-item FI, *i.e.* strictly over than 10 items out of 45. The FI was then calculated based on the total number of known variables, with a participant having 10 positives items in the FI and 5 missing data having a FI of $10/40 = 0.25$.

2.3. Cerebral pathological score

We constructed a 5-item cerebral pathological score (CPS) by combining multiple neuroimaging and biological data into one global score. This included nigrostriatal denervation on ^{123}I-FP-CIT SPECT, vascular lesions on structural MRI, Alzheimer's biomarker with phosphorylated tau-181, neurodegeneration biomarker with neurofilaments lights and markers of astrogliosis with GFAP.

- **^{123}I-FP-CIT SPECT (DaTscan®)** was performed for each participant at baseline, as previously described [22]. For the CPS, we considered visual read (performed by a senior nuclear medicine physician) as a binary variable, where 0 means no significant nigrostriatal denervation, and 1 means nigrostriatal denervation. Beyond the CPS, the quantitative variable was considered on an individual basis. For this analysis, the CATI was responsible for the quality control and post-processing of SPECT data (centre alignment, homogenisation, attenuation correction, scatter corrections when exams were acquired with both scatter windows, and correction of the limited spatial resolution, automatic positioning of region of interest). We then computed the specific binding ratio (SBR), calculated as the striatal target-to-background ratio [31].
- **Structural 3T MRI** was conducted on each participant at the initial stage of the study, as previously outlined [22]. Several sequences were performed, including 3DT1 without contrast, 3DFlair, axial T2, T2 SE, gradient echo, diffusion B1000 with ADC cartography. Following a thorough review of the relevant sequences, vascular lesions were subjected to a visual inspection. This inspection included white matter hyperintensities (WMH) on T2/FLAIR sequences, lacunes, macroinfarcts and microbleeds, as defined by the STRIVE criteria [32]. The visual assessment was conducted by three experts (AGC, AT and PKS), and any necessary discussions were held following the completion of the scans. An MRI score was calculated based on the number of each type of vascular lesion, drawing inspiration from previous studies [33,34]. This score was ranged from 0 to 4, considering positive lesions when there was at least one lacune (one point), one microbleed (one point), one stroke sequelae (one point), or WMH according to the Fazekas scale 2 or 3 (one point) [35]. The MRI score was then analysed as a binary variable in the CPS, considering the presence (from 1 to 4) or absence (0) of vascular lesions.
- Levels of **blood-based biomarkers** were determined for each participant at baseline. These biomarkers include **phosphorylated tau-181 (pTau181), neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP).** These biomarkers are indicative of Alzheimer's pathology, neurodegeneration and astrocytic activation. Quantification was performed by means of Simoa technology [36] using the commercial Neurology 4-Plex E (GFAP, NfL) and pTau181v2 ultrasensitive immunoassay kit (Quanterix, USA) on the Simoa HD-X machine. The cut-off value for pTau181 positivity was 2.43 pg/mL. This threshold was estimated with a subsample of 41 patients who also had an amyloid-florbetapir PET scan. The area under the curve to detect amyloid positivity on PET with this threshold was 0.81. In order to binarise the biological variables GFAP and NfL, the median was used.

The CPS was then calculated by aggregating the binary values for MRI score, ^{123}I-FP-CIT SPECT, blood-based pTau181, GFAP and NfL. The CPS ranged from 0 to 5, with higher scores indicating greater pathological burden. For instance, a patient with a positive MRI score (*e.g.* due to extensive WMH), positive ^{123}I-FP-CIT SPECT scan (nigrostriatal denervation), negative Alzheimer's pathology (pTau181 $<$ 2.43 pg/mL), elevated neurofilament light (level $>$ median) and normal GFAP (level $<$ median) has a CPS of 3/5.

2.4. Cognitive and neuropsychiatric symptoms, socio-demographic variates

Cognitive performance was evaluated by the Alzheimer's Disease Assessment Scale – Cognition (ADAS-cog) [37], a composite cognitive evaluation of 11 cognitive tasks in memory, executive functions, praxis and language. ADAS-cog is expressed by a score, ranging from 0 to 70. A higher score indicates lower cognitive performance.

Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI) [38], a clinical score, completed with the patient's

caregiver that evaluates 12 neuropsychiatric disturbances commonly associated with cognitive neurodegenerative disorders (delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and appetite and eating abnormalities). The rating measures the frequency and severity of each disturbance, resulting in a numerical score ranging from 0 (no disturbance) to 12 (severe and frequent disturbance). The total NPI score ranges from 0 to 144, with higher scores indicating more severe neuropsychiatric symptoms.

At the initial visit, the subjects' age, sex and years of study were documented. At the initial visit, as well as at each follow-up visit, a clinical examination was carried out and medication was reviewed. The MMSE score was recorded at the beginning of the study and then checked each year during follow-up by a trained nurse or neuropsychologist. Functional independence was measured using the Instrumental Activities of Daily Living (IADL) scale [29] and the French Disability Assessment for Dementia – 6 (DAD6) scale [30]. These measurements were recorded at the beginning of the study and at each follow-up visit.

2.5. Statistical analyses

The population was described using mean values and standard deviation (SD) or percentages, as appropriate. The relationship between CPS (independent variable) and FI (dependent variable) was assessed by a linear regression model adjusted for age and sex. The relationships between the ADAS-cog or NPI total score and subscores as dependent variables, and the FI and CPS as the independent variables were assessed using multivariate linear regression or logistic regression models. We tested interaction between FI and CPS (independent variables) on ADAS-COG and NPI (dependent variable). Longitudinal analyses were performed to examine the association between changes in ADAS-cog or NPI scores during the follow-up period (dependent variables) and the baseline values of FI and CPS (independent variable) at a participant-level. Linear mixed models with random intercept and slope with estimations of the slopes of ADAS-cog and NPI scores over the follow-up period were used in the subsample with available longitudinal ADAS-COG values in the database. We used FI was analysed as a continuous numerical variable and CPS was used as a categorical variable in ANOVA models with ADAS-cog and NPI total scores or subscores. CPS was also transformed into a continuous variable in order to analyse its interaction with FI in linear regressions and mixed models. The relationships between ADAS-cog or NPI (total score or subscores) as dependent variables and each CPS component as an independent variable (MRI linear score, SBR on ^{123}I-FP-CIT SPECT, pTau 181 levels, binarized pTau 181 levels, NfL levels and GFAP levels) were also assessed separately in linear regression with multivariate models. CPS was also analysed as a 3-level categorical variable (Low (CPS = 0, 1 or 2), moderate (CPS = 3) and high (CPS = 4 or 5) cerebral pathology). The relationships between FI as a dependent variable and cerebral pathological variables (MRI, ^{123}I-FP-CIT SPECT, pTau181 levels, NfL and GFAP) and CPS as independent variables were also assessed.

All models were adjusted for age, sex, and level of education. Associations were estimated using standardised β coefficients with 95 % confidence intervals. The significance level was set at uncorrected $p < 0.05$. The statistical analyses were performed using R Studio version 2024.04.2 + 764 (Copyright © 2024 Posit Software, PBC).

3. Results

3.1. Demographics and characteristics of the population

A total of 168 participants were analysed in our study after excluding 7 participants that finally did not meet inclusion and non-exclusion criteria (see Methods), and 3 participants for having more than 10 items of FI missing (Supplementary Table 1). The demographic data are shown in Table 1. For the analysis of CPS, participants were excluded if there was at least one missing data, analyses were conducted on a total of 122 participants. Indeed, DaTscan® was missing for 26 participants, MRI was missing for 25 participants, pTau 181 was missing for 10 participants, NfL and GFAP were missing for 11 participants. Supplementary Table 2 describes the characteristics at baseline of 46 patients that did not meet the criterion to calculate the CPS.

GFAP and NfL were binarized to create the CPS using median value (IQR); respectively 197.71 (139.6) pg/mL for GFAP and 31.69 (16.6) pg/mL for NfL.

45-item FI ranged from 0.05 to 0.59, with a mean (SD) value of 0.26 (0.1). 30-item FI ranged from 0.04 to 0.52, with a mean (SD) value of 0.25 (0.1). The Supplementary Figure 2 shows the graphical distribution of the 45-item FI across the population.

3.2. Cross-sectional relationships between cognition, CPS and 45-item FI

There was no statistical association between 45-item FI and CPS ($\beta = 0.12$, $p = 0.21$). Across components of CPS, 45-item FI was not associated with any cerebral pathological variable analysed linearly or binarily (SBR on ^{123}I-FP-CIT SPECT, MRI linear score, plasmatic levels of pTau181, GFAP, NfL).

Cerebral pathological items, combined in CPS, analysed as a categorical ($F(0,5) = 2.51$, $p = 0.03$, see Fig. 1.A) or a linear ($\beta = 0.30$, $p = 0.002$) variable was significantly associated with lower cognition (ADAS-cog measured at baseline). When each biomarker was analysed individually GFAP, NfL, and abnormally elevated pTau181 were associated with higher ADAS-cog, *i.e.* lower cognition.

45-item FI was associated with ADAS-cog ($\beta = 0.28$, $p < 0.001$, see

Table 1
Characteristics of the population.

Characteristics of the population		Overall ($n = 168$)
Age, mean (SD)		80.48 (4.8)
Women, *n* (%)		76 (45.2)
Years of education (mean (SD)) [$n = 163$]		10.05 (4.3)
MMSE (mean (SD)) [$n = 166$]		22.35 (3.8)
NPI (mean (SD)) [$n = 167$]		15.51 (15.6)
ADAS-cog (mean (SD)) [$n = 159$]		25.96 (7.8)
45-items FI (mean (SD))		0.26 (0.10)
30-items FI (mean (SD))		0.25 (0.10)
GFAP (mean (SD) / median (IQR)) [$n = 157$]		219.56 (113.4) / 197.71 (139.6)
NfL (mean (SD) / median(IQR)) [$n = 157$]		37.67 (23.6) / 31.69 (16.7)
pTau181 (mean (SD)) [$n = 158$]		4.28 (2.8)
Abnormal (elevated) pTau181 (*n*(%)) [$n = 158$]		129 (76.8)
Linear MRI score (mean (SD)) [$n = 143$]		1.37 (1)
^{123}I-FP-CIT SPECT, negative (*n*(%))[$n = 142$]		120 (71.4)
Cerebral pathologic score (mean (SD)) [$n = 122$]		2.76 (1.2)
Cerebral pathologic score (score, effectives (%)) [$n = 122$]*	0	4 (3.3)
	1	15(12.3)
	2	31(25.4)
	3	36 (29.5)
	4	28 (23)
	5	8 (6.5)
Clinical Diagnosis at baseline [$n = 167$]	AD	35 (20.8)
	DLB	27 (16.0)
	VD	19 (11.3)
	Mixed†	86 (51.1)

AD: Alzheimer's disease; DLB: Dementia with Lewy bodies; VD: Vascular dementia.
The number of data points for each variable is indicated in brackets.
† Mixed category considers patients with a baseline clinical diagnosis of AD + DLB (5 patients), AD + VD (59 patients), AD + VD + DLB (7 patients) and DLB + VD (15 patients). The clinical diagnosis at baseline was missing for one patient.
* Cerebral pathological score could only be calculated for 122 participants.

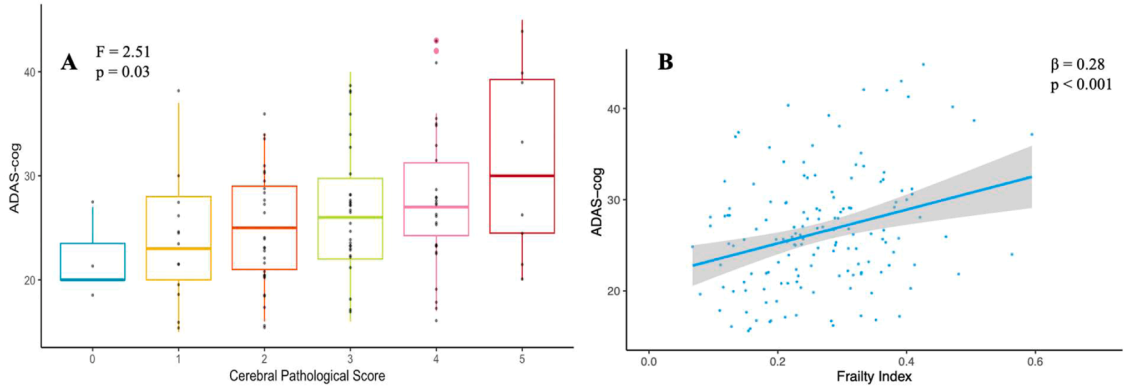

Fig. 1. Relationships between ADAS-cog and CPS or 45-item FI.
A. Relationship between ADAS-cog (*y*-axis) and different categories of CPS (*x*-axis).
B. Relationship between ADAS-cog (*y*-axis) and 45-item FI (*x*-axis).
F test for ANOVA and Beta (β) standardized for linear regressions are indicated with p-value, from models adjusted for age, sex and level of education.

Fig. 1.B). When both CPS and FI were added in the model with ADAS-COG as the dependent variable, CPS remained associated with ADAS-COG ($\beta = 0.27$, $p = 0.004$) whereas FI did not ($\beta = 0.15$, $p = 0.10$). There was no statistical interaction between CPS and 45-item FI on ADAS-cog (Supplementary Figure 3). The associations between 45-items FI, CPS and ADAS-cog are shown in Fig. 1 and summarized in Table 2. When clinical diagnosis was used as a covariate to adjust the association between CPS or FI and ADAS-cog, the association remained unchanged.

3.3. Cross-sectional relationships between neuropsychiatric symptoms, CPS and 45-item FI

NPI total score is associated with the 45-item FI ($\beta = 0.28$, $p < 0.001$ (see Table 2, Fig. 2), even after adjustment for CPS ($\beta = 0.31$, $p = 0.001$). When interested in subscores of NPI (see Fig. 3), we found a significant association between 45-item FI and apathy ($\beta = 0.40$, $p < 0.001$), anxiety ($\beta = 0.18$, $p = 0.03$) and aberrant motor behaviour ($\beta = 0.22$, $p = 0.006$) remaining after the adjustment for CPS. There was no association between CPS and NPI (Fig. 2), nor interaction between 45-item FI and CPS on NPI.

There was a significant association between CPS and hallucinations ($\beta = 0.26$, $p = 0.005$), probably driven by the nigrostriatal denervation associated with Lewy Body pathology (association lost significance when adjusted for ^{123}I-FP-CIT SPECT visual reading). There were no association between CPS and other NPI subscores.

3.4. Longitudinal relationships between cognition, neuropsychiatric symptoms and FI/CPS

Linear mixed models were run based on longitudinal NPI and ADAS-cog measures at 12 and 24 months. Unfortunately, a high rate of missing data for ADAS-cog at 12 months ($n = 60$) and at 24 months ($n = 49$) lead us the consider these analyses as exploratory. A subsample of 74 participants with available CPS at baseline and ADAS-COG at baseline, 12 months and 24 months was included in this analyse.

ADAS-cog seemed to increase with time ($\beta = 0.13$, $p < 0.001$) and this increase seemed to be associated with baseline CPS considered as quantitative ($\beta = 0.31$, $p < 0.001$, see Supplementary Figure 4) but not by baseline 45-item FI ($\beta = 0.14$, $p = 0.07$). There was no evolution of NPI over the follow-up period, and no association was found between baseline CPS or 45-item FI and NPI variation.

3.5. Sensitivity analyses with the 30-item FI

Same analyses were carried out with the 30-item FI. There was still no association between 30-item FI and cerebral pathological variables, including CPS. There was no longer association between 30-item FI and ADAS-cog ($\beta = 0.13$, $p = 0.13$), or NPI ($\beta = 0.09$, $p = 0.29$). Association between 30-item FI and apathy remained significant ($\beta = 0.17$, $p = 0.04$).

Table 2
Cross-sectional relationship between the cerebral pathological score, 45-items frailty index, ADAS-cog and NPI.

A					
	Independent variable	β coefficient	95 % CI	*p* value	Multiple R-squared
ADAS-cog	Cerebral pathological Score	0.30	0.13 to 0.47	**0.002**	**0.15**
ADAS-cog	45-items Frailty Index	0.28	0.13 to 0.43	**< 0.001**	**0.13**
ADAS-cog	Cerebral pathological Score	0.27	0.10 to 0.45	**0.004**	**0.18**
	+ 45-item Frailty Index	0.15	−0.02 to 0.32	0.10	
ADAS-cog	Cerebral pathological Score * 45-item Frailty Index	0.05	−0.72 to 0.82	0.89	0.17
B					
NPI	Cerebral pathological Score	0.06	−0.13 to 0.25	0.57	0.01
NPI	45-items Frailty Index	0.28	0.14 to 0.43	**< 0.001**	**0.09**
NPI	Cerebral pathological Score	0.02	−0.16 to 0.20	0.82	**0.10**
	+ 45-item Frailty Index	0.31	0.14 to 0.48	**0.001**	
NPI	Cerebral pathological Score * 45-item Frailty Index	0.49	−0.27 to 1.25	0.22	0.11

A. Representation of the results of the linear regression with ADAS-cog as dependent variable and 45-item FI and linear CPS as independent variables.
B. Representation of the results of the linear regression with NPI as dependent variable and 45-item FI and CPS as independent variables.
Multivariate regression with 45-item FI and CPS in the same analyse is represented by the sign "+". Interaction between the terms 45-item FI and CPS is represented by the sign "*". All the models were adjusted for age, sex and level of education.

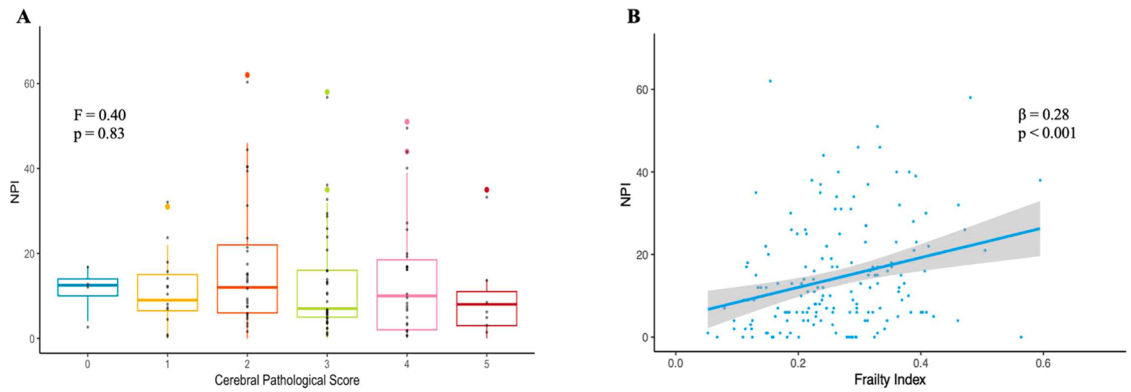

Fig. 2. Relationship between NPI and CPS or 45-item FI.
A. Relationship between CPS (*x*-axis) and NPI (*y*-axis).
B. Linear relationship between 45-item FI (*x*-axis) and NPI (*y*-axis).
F test for ANOVA and Beta (β) standardized for linear regressions are indicated with p-value, from models adjusted for age, sex and level of education.

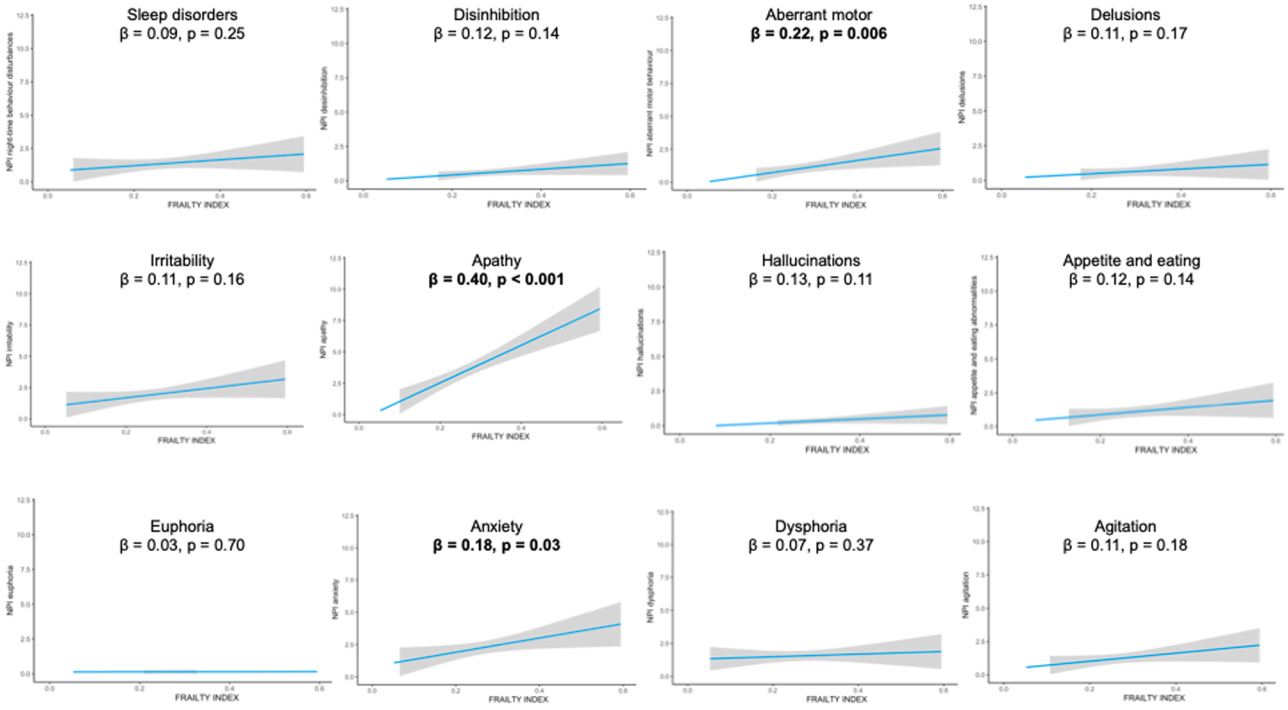

Fig. 3. Relationship between 45-item FI and NPI sub-categories.
Scatter plot showing the association between the 45-item FI (*x*-axis) and the 12 sub-scores of NPI.
From left to right and from top to the bottom, associations between 45-item FI and night-time behaviour disturbances, disinhibition, aberrant motor behaviour, delusions, irritability, apathy, hallucinations, appetite and eating abnormalities, euphoria, anxiety, dysphoria and agitation. 45-item FI was significantly associated with apathy ($\beta = 0.40$, $p < 0.001$), anxiety ($\beta = 0.18$, $p = 0.03$) and aberrant motor behaviour ($\beta = 0.22$, $p = 0.006$).
All the models were adjusted for age, sex and level of education.

4. Discussion

This study highlighted the dissociated and probably complementary role of cerebral pathologies and frailty on the explanation of cognitive and neuropsychiatric symptoms in patients with dementia, based on a unique and innovative multimodal *in vivo* approach. Indeed, higher frailty was associated with poorer cognition and more severe neuropsychiatric symptoms. Brain lesions, as measured by a cerebral pathology score (the sum of lesions detected using blood-based and neuroimaging biomarkers), were not associated with frailty or neuropsychiatric symptoms. However, they were associated with lower cognitive function at baseline and cognitive decline throughout the follow-up period. There was no evidence of an interaction between frailty and brain lesions on cognitive or neuropsychiatric outcomes, which suggests that the contributions of brain lesions and frailty to clinical phenotypes are independent and potentially additive.

Frailty and brain lesions were significantly associated with lower cognition, confirming previous results in neuropathological studies [16,18,19] while using a new *in vivo* multimodal approach. The relationships between frailty and cognitive impairment at various stages, from early to late dementia, has been demonstrated previously [12,39]. There is a statistical association between CPS or 45-item FI and cognitive impairment in our study. However, when both CPS and FI were included in the same model, the association between CPS and ADAS-cog remained

significant, while the association with FI became insignificant. It can be hypothesised that the accumulation of cerebral pathologies is a key factor in explaining cognitive impairment, rather than frailty. Nevertheless, we found out an improvement in the fit of the models when FI and CPS were analysed together, suggesting that both frailty and cerebral pathology contribute to cognitive impairment.

In this study, we found no evidence of an interaction between frailty and brain lesions on cognitive outcomes. Previous studies have produced contrasting results [16–18]. Wallace and colleagues previously demonstrated an interaction between frailty and neuropathological burden on the risk of dementia [17,18], suggesting that people with a low neuropathological burden are at an increased risk for dementia if they are highly frail and *vice versa*. However, these results were not found in all previous studies [16], and in the present study, this could be explained by the smaller sample size, particularly with regard to patients with extreme brain lesions (the number of patients with CPS = 0 or CPS = 5 was low), the differences in population (from population-based *versus* memory clinic studies with probable different aetiological diagnoses) and the younger age in our study compared to previous clinico-pathological studies.

We developed a cerebral pathological score — a composite score combining imaging and blood-based biomarkers of cerebral pathology — to measure the clinical impact of multiple brain "pathologies" ascertained *in vivo*. Biomarkers were selected *a posteriori*, trying to investigate multiple pathways involved in neurodegenerative and cerebrovascular diseases pathophysiology. By this way, neurodegeneration, vascular disease, neuroinflammation, AD pathology and nigrostriatal degeneration could be approached by the available biomarkers. This approach enables us to compare clinical, radiological, and biological data collected over a short period of time. This avoids the inherent bias of *ex vivo* neuropathology, which is always performed after the neuropsychological assessment with some delay and may be affected by the cause of death. Although this score has not been validated by previous studies, we decided to calculate it as several previous studies emphasised that the sum of pathologies is a significant factor in cognitive impairment [18,19]. Ageing is strongly associated with multiple neuropathological lesions, and our aim was to capture *in vivo* these co-pathologies for each participant [40,41]. The lack of ponderation for each biomarker was chosen to highlight the accumulation of different pathophysiological pathways, without giving priority only to neurodegeneration, vascular disease or neuroinflammation. Moreover, this approach is closely related to the construction of a FI, where every health deficit is rated the same. This kind of composite score was already used in neuropathological studies focusing of the association between frailty and neuropathological burden [16,18,19]. However, the absence of an external validation and weighting of different included biomarkers in the CPS is a limitation of this study. CPS has other limitations. We do not measure brain lesions directly, but *in vivo* biomarkers of downstream brain damage. For example, we do not measure the accumulation of Lewy bodies, but rather the downstream consequence of dopaminergic nigrostriatal denervation. Similarly, we do not measure arteriolosclerosis or cerebral amyloid angiopathy, but rather the downstream neuroimaging consequences of vascular dysfunction, such as lacunes or white matter hyperintensities. Furthermore, there is overlap between the measures of the pathophysiological pathways, *e.g.* GFAP and NFL are also associated with Alzheimer's pathology and are correlated with pTau181 [42,43]. Individual lesions were not weighted to create the CPS. For instance, a patient with pure Alzheimer's disease, without other lesions (*e.g.*, dopaminergic nigrostriatal denervation or cerebral small vessel disease) could have a low CPS yet still exhibit a severe cognitive impairment. However, the degree of cognitive impairment was associated with the CPS, with a dose-response relationship in the present analyses, suggesting that the sum of these individual markers is relevant to measure and analyse. Moreover, the median CPS was 3/5, reinforcing the idea that older adults suffer from multiple neuropathological lesions. Analysing them as a single composite score might help us to get more information on the relationship between cerebral pathology and cognitive impairment.

Our study found out a stronger association between blood-based biomarkers and ADAS-COG than with neuroimaging biomarkers (MRI and DaTscan®). It is possible to suggest different explanations to this result, beginning by the high proportion of participants with negative DaTscan® (120/142) and the high proportion of participants with positive MRI score (114/143). These proportions might explain a part of the lack of association between imaging biomarkers and cognitive performance. Moreover, blood-based biomarkers are reflection of neurodegeneration and neuroinflammation, but GFAP is also a biomarker for AD pathology [43–45]. Nigrostriatal denervation (as measured by DaTscan©) and small vessel disease (as measured by structural MRI) may be less associated with cognition than blood markers, because AD pathology may be the main driver of cognitive decline in this population. Another clinico-pathological study showed that Alzheimer's pathology is more associated with cognitive decline than Lewy body or cerebrovascular pathologies in a population with mixed pathologies, and consistent with our results [46].

In our study, neuropsychiatric symptoms, as measured by the NPI score, were associated with the 45-item FI, but not with the CPS. This association has rarely been studied [20,47,48], and this original result needs to be highlighted. It provides further support for the hypothesis that neuropsychiatric symptoms are complex and multifactorial manifestations of the diseases and need to be understood "beyond the brain". We can hypothesise that frailty is involved in the presence or severity of neuropsychiatric symptoms by minimising resilience and ability to respond appropriately to a stressful state as cognitive impairment. Only a few studies examined the association between mental health, chronical psychiatric diseases and incident frailty [49,50]. Neuropsychiatric symptoms, as measured in the NPI score, are not only associated with cognitive impairment but may be also related to history of psychiatric disorders or personality disorders that may induce long-term frailty [50,51]. In this study, apathy is particularly associated with frailty, as in previous works [20,47,52]. This seems intuitive from a clinical point of view, with a possible overlap between apathy and the frailty syndrome, particularly in the sedentary and slowing-down component. The potential causal link and the mechanisms underlying this association will have to be clarified in the future. In our study, the only sub-score associated with CPS was hallucinations, and this association was no longer significant after adjustment for nigrostriatal dopaminergic denervation, which can be easily explained as nigrostriatal dopaminergic denervation and hallucinations are core features of DLB.

In terms of longitudinal analyses, we found an association between baseline CPS and ADAS-cog evolution, *i.e.* higher burden of brain lesions was associated with higher cognitive decline. However, despite a tendency, baseline higher FI was not associated with cognitive decline. We can hypothesize that our analyses suffer from a lack of statistical power due to the sample size and a high rate of missing data concerning ADAS-cog. Thus, these longitudinal analyses should be interpreted cautiously. Moreover, longitudinal measures of frailty might be necessary to clarify the link between frailty and cognitive decline in patients with cognitive impairment.

In this study, we created a 45-item FI based on standardised procedures [7,28], with various health deficits. As in previous works, we found a mean FI of around 0.25, and a maximum frailty score of less than 0.7 [7,9,19,53]. 45-item FI was correlated with age; variables were not highly correlated with each other. We found no association between 45-item FI and cerebral pathological variables, either individually or combined in the CPS. The lack of association is consistent with previous studies where neuropathological indexes were not correlated with FI, even though some variables could have been associated, such as neurofibrillary pathology (Braak stages) [17–19,54]. Frailty index was computed according to the health deficit accumulation model of frailty. One criticism of this model in dementia studies is that FI could include variables that are also associated with the risk of dementia. Thus, there

is a risk of overestimating the association between frailty and dementia due to the presence of these variables. To test this hypothesis, we decided to carry out sensitivity analyses, by excluding variables of the 45-item FI that were potentially associated with dementia stage, *i.e.* variates which have a strong and consistent link with cognitive and functional decline. These analyses showed that the associations between the 30-item FI and ADAS-cog or NPI were no longer significant. We can hypothesise that the correlation between frailty, cognitive impairment and neuropsychiatric symptoms can be driven by functional independence which is captured by the 45-items FI. This limitation comes from the nature of the FI, which is an accumulation of health deficits model, which captures "frailty" (*i.e.* the state of increased vulnerability) but also, by nature, the evolution of cognitive disorders. However, similar sensitivity analyses have been performed by other studies [14,17] and no such results were found. Our hypothesis is that our memory clinic population is moderately frail, and that the documented presence of mild to moderate cognitive impairment suggests that a large part of this frailty is due to functional dependence caused by cognitive disorders. In future studies, other proxies of frailty, such as the physical frailty phenotype could be analysed in relation with brain lesions, cognitive decline and neuropsychiatric symptoms. Furthermore, the concept of intrinsic capacity (the sum total of an individual's physical and mental capacities), developed by the World Health Organization, and its association with biomarkers, cognitive decline, and neuropsychiatric symptoms, may be investigated further [55,56].

Our study has several strengths. This study is based on a real-life prospective cohort, with patients recruited from standard care at eight specialised memory clinics in France and Monaco. The ADAS-cog and NPI are validated scales for assessing cognition and neuropsychiatric symptoms, respectively. According to the standardised procedures for creating an FI, our 45-item FI appears valid. Blood-based and neuroimaging biomarkers were used as proxies for neuropathology, enabling dynamic *in vivo* measurements that can be easily reproduced, unlike neuropathological studies.

Our findings should be interpreted with caution as this study has some limitations. Our study sample was reduced when using the CPS because data were missing for a part of the population as well as for longitudinal analyses. According to study design and exclusion criteria from the CLEM study, patients treated by antipsychotics at baseline were not included, even if the use of these treatments was accepted during follow-up. Excluding patients with more severe neuropsychiatric symptoms could decrease our ability to capture a stronger association between CPS, FI and NPI. Moreover, the fact that mean NPI did not significantly differ across follow-up can indicate that only a few patients get a worsening of their neuropsychiatric symptoms. We used cut-offs that were not previously validated for the binary variables in the CPS, especially for blood-based biomarkers. Blood-based pTau181 was used to assess the presence of Alzheimer's pathology, however other biomarkers have recently been described as presenting better sensitivity and specificity, as pTau217 [57]. The limitations of the CPS were previously discussed (see infra). Longitudinal follow-up was only assessed for two years and with missing data, and future research should focus on establishing an association between FI, CPS and cognition over several years, perhaps by recruiting patients from earlier stages of cognitive impairment or healthy participants at risk. Using sensitivity analyses, we attempted to remove variables associated with dementia and cognitive decline from the FI, but the complex and multifactorial aetiology of dementia rendered this impossible. Other variables could have been considered for removal, such as vascular risk factors or hearing loss.

5. Conclusion

A 45-item FI and a composite score of 5 biomarkers of brain lesions were associated with cognitive impairment in memory clinic outpatients. Neuropsychiatric symptoms, and notably apathy, were associated with FI but not with brain lesions. This study highlights the complex relationship between cerebral pathology, frailty and clinical phenotypes of neurocognitive disorders including cognitive decline and neuropsychiatric symptoms. This opens up a new avenue for the convergence of geroscience and neuroscience, with the aim of improving our understanding of neurodegenerative diseases. This approach considers not only brain lesions, but also systemic factors 'beyond the brain', with the ultimate goal of improving our understanding of the clinical phenotype at the level of each patient. Further studies should enhance our understanding of the mechanisms linking frailty, cognitive symptoms and neuropsychiatric symptoms. They should also investigate whether interventions aimed at mitigating the risk of frailty could help to decrease the burden of neurocognitive disorders.

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Conflicts of interest statements

Independent of this work, Garnier-Crussard A is an unpaid sub-investigator or local principal investigator in NCT04867616 (UCB Pharma), NCT04241068 (Biogen), NCT05310071 (Biogen), NCT03446001 (TauRx Therapeutics), NCT03444870 (Roche), NCT04374253 (Roche), NCT04777396 (Novo Nordisk), NCT04777409 (Novo Nordisk), NCT04770220 (Alzheon), NCT05423522 (Medesis Pharma), NCT06079190 (GlaxoSmithKline).

Independent of this work, Dautricourt S is an unpaid sub-investigator or local principal investigator in NCT04867616 (UCB Pharma), NCT04241068 (Biogen), NCT05310071 (Biogen), NCT03446001 (TauRx Therapeutics), NCT03444870 (Roche), NCT04374253 (Roche), NCT04777396 (Novo Nordisk), NCT04777409 (Novo Nordisk), NCT04770220 (Alzheon), NCT05423522 (Medesis Pharma), NCT06079190 (GlaxoSmithKline).

Verny M has received personal fees for lectures or advice from: Eisai and Lilly.

Gilles V, Krolak-Salmon P, Novais T, Cotton F, Teillac A, Sauvée M and Desestret V have no conflict to declare regarding this paper.

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Blanc F was the national coordinator for France for the Eisai Delphia (E2027), Axovant Headway-DLB and Roche Graduate therapeutic trials; he had received honoraria from Roche, Eisai and Biogen for oral presentations and from Eisai and Novo Nordisk for boards.

Independent of this work, Louchart de la Chapelle S is an unpaid sub-investigator or local principal investigator in NCT06785948 (AREBISN), NCT05267028 (AREBISN), NCT05254873 (AREBISN), NCT05211752 (AREBISN), NCT04731246 (AREBISN), NCT04730167 (AREBISN), NCT04702763 (AREBISN), NCT04705610 (AREBISN), NCT04748263 (CHPG), NCT03924258 (VIFOR Pharma), NCT03924271 (VIFOR Pharma), NCT01962753 (CHRU Tours), NCT00672685 (CHU Toulouse),

Data statement

The datasets used and/or analysed during the current study are not publicly available and may be available from the corresponding author on reasonable request and according to regulatory and ethical restrictions.

Declaration of generative AI and AI-assisted technologies in the writing process

AI-assisted technology (DeepL Write) was used to enhance the quality of the English writing; no Generative AI technology was used for this manuscript. Authors assume the entire responsibility of the

manuscript content.

CRediT authorship contribution statement

Victor Gilles: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Anthime Flaus:** Writing – review & editing, Formal analysis. **Achille Teillac:** Writing – review & editing, Formal analysis. **Marc Verny:** Writing – review & editing, Investigation, Data curation. **Frédéric Blanc:** Writing – review & editing, Investigation, Data curation. **Marc Paccalin:** Writing – review & editing, Investigation, Data curation. **Thomas Desmidt:** Writing – review & editing, Investigation, Data curation. **Sandrine Louchart de la Chapelle:** Writing – review & editing, Investigation, Data curation. **Constance Dumay:** Writing – review & editing. **Mathilde Sauvée:** Writing – review & editing, Investigation, Data curation. **Sylvain Lehmann:** Writing – review & editing, Formal analysis. **Christophe Hirtz:** Writing – review & editing, Formal analysis. **François Cotton:** Writing – review & editing, Formal analysis. **Anthony Bathsavanis:** Writing – review & editing, Investigation, Data curation. **Frédéric Gervais:** Writing – review & editing, Formal analysis. **Teddy Novais:** Writing – review & editing, Formal analysis. **Virginie Desestret:** Writing – review & editing. **Nawele Boublay:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Pierre Krolak-Salmon:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Sophie Dautricourt:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Antoine Garnier-Crussard:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Pierre Krolak-Salmon reports financial support was provided by Direction générale de l'offre de soins. Marc Verny reports a relationship with Eisai Inc that includes: consulting or advisory. Marc Verny reports a relationship with Eli Lilly and Company that includes: consulting or advisory. Anthime Flaus reports a relationship with GE Healthcare that includes: travel reimbursement. Frederic Blanc reports a relationship with Eisai Inc that includes: board membership and speaking and lecture fees. Frederic Blanc reports a relationship with Roche SAS that includes: non-financial support and speaking and lecture fees. Frederic Blanc reports a relationship with Axovant Sciences Ltd that includes: consulting or advisory and non-financial support. Frederic Blanc reports a relationship with Biogen that includes: speaking and lecture fees. Frederic Blanc reports a relationship with Novo Nordisk Inc that includes: board membership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2026.100148.

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