Cognitive and neuroimaging features and brain β-amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study

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Summary

Background Improved understanding is needed of risk factors and markers of disease progression in preclinical Alzheimer's disease. We assessed associations between brain β-amyloidosis and various cognitive and neuroimaging parameters with progression of cognitive decline in individuals with preclinical Alzheimer's disease.

Methods The INSIGHT-preAD is an ongoing single-centre observational study at the Salpêtrière Hospital, Paris, France. Eligible participants were age 70–85 years with subjective memory complaints but unimpaired cognition and memory (Mini-Mental State Examination [MMSE] score ≥27, Clinical Dementia Rating score 0, and Free and Cued Selective Reminding Test [FCSRT] total recall score ≥41). We stratified participants by brain amyloid β deposition on ^{18}F-florbetapir PET (positive or negative) at baseline. All patients underwent baseline assessments of demographic, cognitive, and psychobehavioural, characteristics, *APOE* ε4 allele carrier status, brain structure and function on MRI, brain glucose-metabolism on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET, and event-related potentials on electroencephalograms (EEGs). Actigraphy and CSF investigations were optional. Participants were followed up with clinical, cognitive, and psychobehavioural assessments every 6 months, neuropsychological assessments, EEG, and actigraphy every 12 months, and MRI, and ^{18}F-FDG and ^{18}F-florbetapir PET every 24 months. We assessed associations of amyloid β deposition status with test outcomes at baseline and 24 months, and with clinical status at 30 months. Progression to prodromal Alzheimer's disease was defined as an amnestic syndrome of the hippocampal type.

Findings From May 25, 2013, to Jan 20, 2015, we enrolled 318 participants with a mean age of 76·0 years (SD 3·5). The mean baseline MMSE score was 28·67 (SD 0·96), and the mean level of education was high (score >6 [SD 2] on a scale of 1–8, where 1=infant school and 8=higher education). 88 (28%) of 318 participants showed amyloid β deposition and the remainder did not. The amyloid β subgroups did not differ for any psychobehavioural, cognitive, actigraphy, and structural and functional neuroimaging results after adjustment for age, sex, and level of education More participants positive for amyloid β deposition had the *APOE* ε4 allele (33 [38%] *vs* 29 [13%], p<0·0001). Amyloid β_{1-42} concentration in CSF significantly correlated with mean ^{18}F-florbetapir uptake at baseline (r=–0·62, p<0·0001) and the ratio of amyloid β_{1-42} to amyloid β_{1-40} (r=–0·61, p<0·0001), and identified amyloid β deposition status with high accuracy (mean area under the curve values 0·89, 95% CI 0·80–0·98 and 0·84, 0·72–0·96, respectively). No difference was seen in MMSE (28·3 [SD 2·0] *vs* 28·9 [1·2], p=0·16) and Clinical Dementia Rating scores (0·06 [0·2] *vs* 0·05 [0·3]; p=0·79) at 30 months (n=274) between participants positive or negative for amyloid β. Four participants (all positive for amyloid β deposition at baseline) progressed to prodromal Alzheimer's disease. They were older than other participants positive for amyloid β deposition at baseline (mean 80·2 years [SD 4·1] *vs* 76·8 years [SD 3·4]) and had greater ^{18}F-florbetapir uptake at baseline (mean standard uptake value ratio 1·46 [SD 0·16] *vs* 1·02 [SD 0·20]), and more were carriers of the *APOE* ε4 allele (three [75%] of four *vs* 33 [39%] of 83). They also had mild executive dysfunction at baseline (mean FCSRT free recall score 21·25 [SD 2·75] *vs* 29·08 [5·44] and Frontal Assessment Battery total score 13·25 [1·50] *vs* 16·05 [1·68]).

Interpretation Brain β-amyloidosis alone did not predict progression to prodromal Alzheimer's disease within 30 months. Longer follow-up is needed to establish whether this finding remains consistent.

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Introduction

In the past decade, substantial progress has been achieved in the field of Alzheimer's disease. The International Working Group[1,2] and the US National Institute on Aging/Alzheimer's Association[3–5] have conceptualised the disease as a continuum, with dementia representing the end stage of a long period of cumulative pathological insults in the brain. With this approach, a preclinical stage of the disease, in which individuals are free from cognitive and behavioural symptoms, has been identified by in-vivo evidence of Alzheimer's pathology.[6] With a preclinical stage, interventions might be able to prevent

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Research in context

Evidence before this study

We searched PubMed and ClinicalTrials.gov with the terms "preclinical Alzheimer('s) disease", "presymptomatic Alzheimer('s) disease", and "asymptomatic Alzheimer('s) disease" for articles published up to July 31, 2017, without any language restrictions. A 2015 meta-analysis including more than 3000 cognitively healthy individuals showed that positive amyloid β PET results are frequent in middle-aged people, which is in line with post-mortem studies. However, long-term outcomes in cognitively healthy individuals who had markers of brain β-amyloidosis only (ie, negative for raised tau protein concentrations in CSF or neurodegeneration markers) suggest that the risk of rapid progression to overt clinical disease is not high. The natural history of at-risk asymptomatic people has not been completely elucidated, and understanding the evolution of the processes associated with Alzheimer's disease is essential for the design of adequate clinical trials.

Added value of the study

Among cognitively healthy elderly participants with subjective memory complaints, those with brain β-amyloidosis did not differ in terms of cognition as measured with the Mini-Mental State Examination and Clinical Dementia Rating scores (global cognitive efficiency) from those without β-amyloidosis at baseline and at 24 months of follow-up, after adjustment for age, sex, and level of education. Progression from preclinical to prodromal Alzheimer's disease, defined as amnestic syndrome of the hippocampal type, was diagnosed in four participants. This number was low, possibly due in part to the high level of education in our study cohort, but it might increase with time.

Implications of all the available evidence

When strict inclusion criteria are used to ensure participants with no measurable cognitive impairment are included in studies of preclinical Alzheimer's disease, no association is seen between brain β-amyloidosis alone and even slight cognitive changes. We saw a low annual rate of progression to clinically confirmed prodromal Alzheimer's disease that has not been clearly described in previous studies. Future clinical trials of preclinical Alzheimer's disease should be designed with large numbers of participants and for longer than 30 months to assess the clinical efficacy of interventions.

progression to clinical disease and biomarkers might enable early treatment decisions. Amyloid β brain lesions are necessary for the development of clinical Alzheimer's disease, but might not be the only cause. Specific interactions between factors that favour or decrease the risk of progression might also contribute, which could yield possible predictors of progression.

The Investigation of Alzheimer's Predictors in Subjective Memory Complainers (INSIGHT-preAD) study was designed to identify risk factors for and markers of progression to clinical Alzheimer's disease in asymptomatic at-risk individuals. The use of cognitive composite scores to define preclinical Alzheimer's disease, progression, and clinical expression has varied across studies,[7–12] which raises the issue of the relevance of these scores in practice. The INSIGHT-preAD study aimed to tackle this issue by using evidence-based and clinically meaningful criteria for inclusion and outcomes. In this Article, we present our assessment of the associations between amyloid β deposition and several domains, including subjective cognitive complaints, neuropsychological performance, fluid biomarkers, specific brain structures on volumetric MRI, and regional brain metabolism, at baseline and 24 months, and clinical status at 30 months.

Methods

Study design and participants

The INSIGHT-preAD study is an ongoing single-centre observational cohort study being done at the Institute of Memory and Alzheimer's disease, Pitié-Salpêtrière University Hospital, Paris, France. Participants were recruited from people referred to the university's memory clinic and by announcements of the study in the media (press releases and television coverage). Eligible participants were aged 70–85 years, had subjective memory complaints, unimpaired cognition (Mini-Mental State Examination [MMSE][13] score ≥27 and Clinical Dementia Rating[14] score 0), no evidence of episodic memory deficit (Free and Cued Selective Reminding Test score [FCSRT][15] total recall score ≥41), visual and auditory acuity adequate for testing, and no systemic or chronic disease that might interfere with follow-up. We excluded people who were under guardianship, were residents in nursing facilities, had presymptomatic monogeneic Alzheimer's disease, who could not undergo or refused MRI, had undergone radiopharmaceutical imaging or treatment unrelated to this trial within 2 days before the study imaging session, had neurological diseases (eg, treated epilepsy, extrapyramidal signs, visual hallucinations, brain tumour, subdural haematoma, and history of head trauma followed by persistent neurological effects), stroke in the previous 3 months, or illiteracy (reading or counting).

The ethics committee of the Pitié-Salpêtrière University Hospital approved the study protocol. All participants signed an informed consent form, given and explained to them 2 weeks before enrolment.

Procedures All testing was done by the same neuropsychologists and physicians. All patients underwent all tests at baseline, except for actigraphy and CSF biomarker measurement, which were optional. We followed up participants with surveys of subjective feelings about memory and cognition and with clinical, cognitive, and psychobehavioural testing every 6 months, neuropsychological assessments, electroencephalograms (EEGs), and

actigraphy every 12 months, and blood tests for biomarkers (results for which will be reported elsewhere), brain structural and functional MRI, brain glucose-metabolism by use of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET, and brain amyloid β by use of ^{18}F-florbetapir PET every 24 months (panel).

We did brain PET scans 50 min after injection of 370 MBq (10 mCi) ^{18}F-florbetapir[35] and 30 min after injection of 2 MBq/kg ^{18}F-FDG. Reconstructed images were analysed with a pipeline developed by the Centre d'Acquisition et Traitement des Images (appendix). For amyloid β ^{18}F-florbetapir PET images, we calculated standard uptake value ratios (SUVRs) by averaging the mean activity of cortical regions of interest: left and right precuneus, cingulum posterior, cingulum anterior, and parietal, temporal, and orbitofrontal cortices (appendix). The reference region was a combination of whole cerebellum and pons regions. The SUVR threshold to determine abnormal uptake was extracted by linear correlation of results obtained by our method[18] and that used by Besson and colleagues[36] for 53 PET scans (26 elderly healthy controls, 11 patients with mild cognitive impairment, and 16 patients with clinical probable Alzheimer's disease) obtained from the Multimodal Imaging of Early-Stage Alzheimer's Disease cohort.[37] This strategy smooths differences between different tracers and methods.[38] The threshold set for positive versus negative amyloid β deposition was 0·7918 (appendix). Neither the participants nor the investigators were aware of participants' amyloid β status.

The same image-assessment pipeline was applied to measure brain glucose metabolism on ^{18}F-FDG PET scans. Cortical metabolic indices were calculated in four bilateral regions (posterior cingulate cortex, inferior parietal lobule, precuneus, and inferior temporal gyrus) that are specifically affected by Alzheimer's disease,[39] and the pons was used as the reference region.

We obtained MRI scans over a 1 h period on a 3T Magnetom VERIO system (Siemens Medical Solutions, Erlangen, Germany). Scanning sessions were as follows: three-dimensional T1-weighted magnetisation-prepared rapid gradient echo; two-dimensional fluid-attenuated inversion recovery; two-dimensional T2* diffusion tensor imaging acquisition and a T2*-weighted gradient-echo echo-planar series for use in the resting-state connectivity analysis; and a pulsed arterial spin labelling scan for measurement of cerebral blood flow at rest. Hippocampal volume was measured on three-dimensional T1 sequences with our in-house SACHA software,[40] normalised to the mean total intracranial volume. Cortical thickness was measured in 68 regions of interest in the Desikan-Killiany cortical atlas with Freesurfer software (version 5.3).

EEG data were acquired with a 256-channel whole-head Geodesic 300 EEG System (Electrical Geodesics, Eugene, OR, USA). High-density EEG was recorded while participants were at rest (each eye was closed for 30 s then opened for 30 s after an audio cue, then closed and opened twice more) and during a cognitive task (in which words memorised 1 h earlier from the FCSRT were recalled to measure event-related potentials).[15]

We measured concentrations of total tau protein, phosphorylated tau at threonine 181, and amyloid β_{1-42} ($A\beta_{1-42}$) as biomarkers in CSF with the double antibody sandwich ELISA method (Innotest, Fujirebio, Courtaboeuf, France).[41] Our laboratory participates in the Alzheimer's Association external quality control programme for CSF testing.[42] We also calculated the ratio of $A\beta_{1-42}$ to amyloid β_{1-40} ($A\beta_{1-40}$).

Genomic DNA was prepared from frozen blood samples with the ArchivePure DNA purification system (5 PRIME, Gaithersburg, MD, USA) according to the manufacturer's instructions. *APOE* ε4 allele genotyping was done for each individual by PCR-based Sanger sequencing. The amplified fragments were purified and sequenced with the same primers (appendix).

MMSE and FCSRT scores that fell to below the threshold for inclusion during the study were indicative of possible clinical progression to prodromal Alzheimer's disease, which was defined as positive amyloid β deposition on ^{18}F-florbetapir PET and a persistent amnestic syndrome of the hippocampal type.[43] A low score in one visit was not deemed to be sufficient to establish progression. If cognitive decline was seen on two consecutive neuropsychological assessments, an independent committee of two neurologists (BD and SE), a neuropsychologist (GG), and a neuroimaging expert (AB), who were unaware of the participant's amyloid β status, reviewed the medical file. All participants with incident prodromal Alzheimer's disease were included in a separate clinical cohort in this study and assessed in parallel with the same cognitive and neuroimaging investigations as those used in the main INSIGHT-preAD cohort.

Statistical analysis

We calculated a study sample size aimed at achieving sufficient confidence around a positive and a negative likelihood ratio.[44] These likelihood ratios incorporate the sensitivity and specificity of the predictive model, providing a direct estimate of how much the combination of predictors would change the odds of a progression to prodromal Alzheimer's disease. Based on Rowe and colleagues' reported progression of 14% over 3 years[45] and the use of 95% CIs, we calculated that we would need to include a minimum of 82 participants positive for amyloid β deposition. We assumed an attrition rate of 8% of participants during the study and, therefore, aimed to continue enrolment until 88 participants positive for amyloid β deposition had been included.

We compared cognitive and behavioural tests scores, hippocampal volume, ^{18}F-FDG PET indices, and cortical thickness in participants positive and negative for amyloid β deposition, with the *t* test for continuous data,

For more on the **Alzheimer's Association** see http://neurophys.gu.se/sektioner/psykiatri_och_neurokemi/neurokem/theAlzAssQCprogram

For more on **Neuroimaging** see http://cati-neuroimaging.com/

See **Online** for appendix

***Panel*: Assessments used in INSIGHT-preAD**

Subjective feelings about memory and cognition*
- Modified 15-item version of the McNair Frequency of Forgetting Questionnaire[16]†
- Healthy Age Brain Care Monitor[17]†
- INSIGHT-preAD questionnaire of cognitive decline[18]
- Self-Evaluation of Complaints[18]
- Visual analogue scale for complaints[18]
- Alzheimer's disease-related anxiety questionnaire[18]

Behaviour, mood, autonomy, and quality of life
- Neuropsychiatric Inventory[19]
- State-Trait-Anxiety Inventory Form Y[20]
- Geriatric Depression Scale[21]
- Starkstein Apathy Scale[22]
- Bristol Activities of Daily Living Scale[23]
- Amsterdam Instrumental Activity of Daily Living Questionnaire[24]†
- EuroQol EQ-5D[25]

Cognitive functions

Global assessment of cognitive functioning
- Mini-Mental State Examination[13]
- Clinical Dementia Rating[14]

Episodic memory
- Free and Cued Selective Reminding Test[15]
- Delayed Matching to Sample Task 48 (immediate and delayed)[26]
- Rey-Osterrieth Complex Figure (3 min and 30 min recall)[27]
- Memory Binding Test[28]

Working memory and executive functions
- Forward and Backward Digit Span and Visuospatial Span[29]
- Frontal Assessment Battery[30]
- Trail Making Test (B–A time)[31]
- Lexical fluency (p-words in 2 min)[32]

Instrumental functions
- Semantic fluency (animals in 2 min)[32]
- DO80 image naming test[33]
- Praxis assessment[34]
- Rey-Osterrieth Complex Figure (copy)[27]

Brain imaging
- ^{18}F-florbetapir PET (amyloid β deposition)[35]
- ^{18}F-fluorodeoxyglucose PET (glucose metabolism)
- Three-dimensional T1-weighted magnetisation-prepared rapid gradient echo MRI
- Two-dimensional fluid-attenuated inversion recovery MRI
- Two-dimensional T2-star, diffusion tensor imaging acquisition and T2-star-weighted gradient-echo echo-planar MRI series
- Pulsed arterial spin labelling MRI
- Hippocampal volume, measured on three-dimensional T1 MRI sequences‡
- Cortical thickness

Neural dynamics
- High-density EEG at rest
- High-density EEG during cognitive task (memory recall of words) to measure event-related potentials

Biomarkers
- Total tau protein concentration in CSF
- Concentration of tau protein phosphorylated at threonine 181 in CSF
- $A\beta_{1-42}$ concentration in CSF
- Ratio of $A\beta_{1-42}$ to $A\beta_{1-40}$ in CSF
- Blood biomarkers

***APOE* ε4 allele genotyping**
- PCR-based Sanger sequencing

All assessments listed here were done at baseline; clinical, cognitive, and psychobehavioural tests were done every 6 months, neuropsychological, EEG, and actigraphy assessments every 12 months, and blood sampling, MRI, ^{18}F-FDG PET, and ^{18}F-florbetapir PET every 24 months. Results for the Amsterdam Instrumental Activity of Daily Living Questionnaire, blood biomarkers, praxis assessments, and some brain imaging tests will be reported elsewhere because they are being assessed by a different research group. EEG=electroencephalogram. Aβ=amyloid β. *More information is available in the appendix. †Also measured in independent informants suspecting cognitive decline. ‡Measured with in-house SACHA software.

the χ^2 test for categorical variables, and a paired *t* test for right and left hippocampal volumes. For other comparisons between amyloid β subgroups, we used linear models for continuous variables, Poisson models for discrete variables, and logistic models for dichotomous variables. We adjusted all p values for age, sex, and level of education, except those in the exploratory analysis of CSF biomarkers. ^{18}F-FDG PET indices were also adjusted for blood glucose concentrations. In tests in which large numbers of participants scored 0, we dichotomised the results into 0 versus non-0 categories. Group differences were tested with log-likelihood tests. We also corrected all non-exploratory p values for multiple testing with the Benjamini-Hochberg correction. Missing data were not imputed. We used generalised linear models to assess the relation between outcomes and ^{18}F-florbetapir uptake. All statistical analyses were done with R software (version 3.3.2). We took p values less than 0·05 to be significant.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled participants between May 25, 2013, and Jan 20, 2015. Of 363 people screened, 318 met the inclusion

criteria (figure 1). The mean age of participants was 76·0 years (SD 3·5), more participants were women than men, the education level was high, mean MMSE and FCSRT scores were high, and no participant showed naming difficulties (table 1). 62 (20%) participants were *APOE* ε4 carriers. The right hippocampal volume was significantly higher than the mean normalised total (left+right) hippocampal volume (table 1). Cortical metabolic activity on ^{18}F-FDG PET was greatest in the right precuneus and parietal inferior regions. 51 participants consented to CSF baseline biomarker assessments (table 1) and 88 underwent actigraphy at baseline.

All 318 participants underwent ^{18}F-florbetapir PET investigation, which revealed amyloid β deposition in 88 (28%) and no deposition in 230 (72%). Participants positive for amyloid β deposition were older and more were *APOE* ε4 allele carriers than those negative for deposition (table 1), but no differences were found for sex or education. The two groups did not significantly differ for any questionnaires assessing subjective feelings, behaviour, mood, autonomy, or quality of life. The numbers of participants who underwent each cognitive, behavioural, and neuroimaging investigation at baseline are shown in the appendix. Before adjustment, those positive for amyloid β deposition had significantly lower scores on the MMSE and Frontal Assessment Battery and a longer Trail Making Test B–A time (table 1), but these differences disappeared when the results were adjusted for age, sex, and education. There was no difference for the other cognitive tests, including the FCSRT total recall and the Memory Binding Test, or in regional metabolic imaging values (table 1, appendix). We found a significant correlation between SUVR and ^{18}F-FDG PET values in the left and right cingulate posterior, precuneus, and left parietal and temporal inferior regions, which disappeared after adjustment for age, sex, and education (appendix).

Among the 51 participants assessed for CSF biomarkers, 16 (31%) were positive for amyloid β deposition and 35 (69%) were not. As expected, $A\beta_{1-42}$ concentrations were significantly lower and those of total tau and tau phosphorylated at threonine 181 were higher in participants positive for than in those negative for amyloid β deposition (table 1). The mean SUVR for ^{18}F-florbetapir was significantly correlated with CSF $A\beta_{1-42}$ concentration (r=–0·62, p<0·0001), and with the ratio of $A\beta_{1-42}$ to $A\beta_{1-40}$ (r=0·61; p<0·0001), and both could discriminate participants positive for amyloid β deposition from those negative for amyloid β deposition with high accuracy (area under the curve values 0·89, 95% CI 0·80–0·98 for CSF $A\beta_{1-42}$ concentration and 0·84, 0·72–0·96 for the ratio of $A\beta_{1-42}$ to $A\beta_{1-40}$).

On structural MRI, before statistical adjustment, participants positive for amyloid β deposition at baseline had lower total, left, and right hippocampal volumes than those negative for amyloid β deposition; after adjustment for age, sex, and multiple comparisons, the difference remained only for the right hippocampus (table 1).

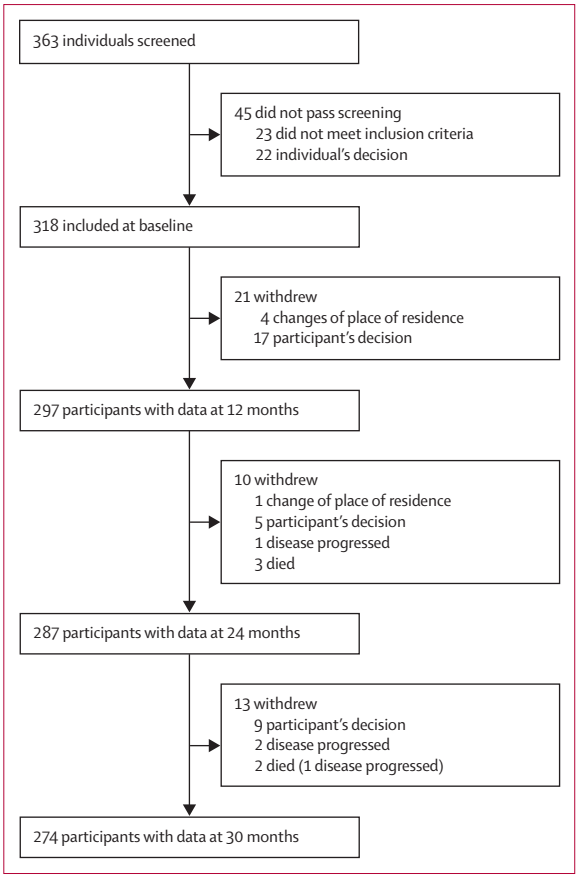

Figure 1: **Study profile**

Significant differences were observed in cortical thickness of the left temporal pole with and without adjustment for age, sex, and education, but not after correction for multiple comparisons (appendix). The left anterior cingulate (rostral) and right pars orbitalis differed significantly between amyloid β groups after adjustment, but not before (appendix). None of these values remained significant after correction for multiple comparisons (appendix).

We saw no differences between participants positive and negative for amyloid β deposition in any of the most commonly used cognitive tests (MMSE, FCSRT, Frontal Assessment Battery, and Trail Making Time) at 12 months or 24 months (table 2; more detailed results for these tests and all results for some tests will be reported separately). Resting-state EEG showed significant longitudinal changes in cortical oscillatory activity in participants positive for amyloid β deposition, as indicated by the θ:α power ratio (figure 2).

After 30 months of follow-up, 274 participants remained in the study (figure 1), among whom cognitive performance was stable up to 24 months (table 2, appendix). Scores for global cognitive efficiency were similar in participants positive and negative for amyloid β deposition on the MMSE (mean score 28·3 [SD 2·0] *vs*

	All participants (n=318)	Participants with amyloid β deposition (n=88)	Participants without amyloid β deposition (n=230)	p value*	Adjusted p value†	Corrected p value‡
Characteristics						
Age (years)	76·0 (3·5)	76·8 (3·4)	75·7 (3·5)	0·0111	..	0·0332
Men	117 (37%)	32 (36%)	85 (37%)	1·0	..	1·0
Women	201 (63%)	56 (63%)	145 (63%)	..	..	..
High education level§	215 (68%)	53 (60%)	162 (70%)	0·11	..	0·16
APOE ε4 allele	62 (20%)	33 (38%)	29 (13%)	<0·0001	<0·0001	0·0001
Subjective feelings about memory and cognition						
Modified McNair Frequency of Forgetting Questionnaire	12·91 (6·16)	12·24 (5·39)	13·16 (6·41)	0·20	0·19	0·68
Healthy Aging Brain Care Monitor	11·60 (9·13)	11·28 (8·19)	11·72 (9·48)	0·70	0·55	0·97
INSIGHT-preAD questionnaire of cognitive decline	5·07 (3·22)	5·39 (3·14)	4·95 (3·25)	0·28	0·29	0·91
Self-Evaluation of Complaints	20·51 (11·92)	21·01 (12·73)	20·32 (11·62)	0·66	0·94	0·97
Visual analogue scale for complaints	140 (44%)	40 (46%)	100 (44%)	0·85	0·63	0·97
Alzheimer's disease-related anxiety questionnaire	24·82 (9·20)	25·99 (9·02)	24·37 (9·24)	0·17	0·19	0·68
Behaviour, mood, autonomy, and quality of life						
Neuropsychiatric Inventory	243 (76%)	61 (69%)	182 (79%)	0·09	0·09	0·59
State-Trait Anxiety Inventory	40·82 (9·18)	41·27 (9·66)	40·69 (9·09)	0·80	0·83	0·97
Geriatric Depression Scale	2·34 (2·68)	2·41 (2·72)	2·32 (2·69)	0·84	0·76	0·97
Starkstein Apathy Scale	9·85 (4·04)	9·32 (3·28)	10·05 (4·28)	0·11	0·09	0·59
Bristol Activities of Daily Living Scale	254 (85%)	64 (81%)	190 (87%)	0·29	0·32	0·92
EuroQol EQ-5D	6·31 (0·97)	6·22 (0·99)	6·35 (0·96)	0·36	0·60	0·97
Cognitive functions¶						
Mini-Mental State Examination	28·67 (0·96)	28·48 (0·90)	28·74 (0·97)	0·0302	0·82	0·97
Free and Cued Selective Reminding Test						
Immediate Free Recall	30·03 (5·42)	29·08 (5·44)	30·39 (5·39)	0·06	0·14	0·65
Delayed Free Recall	11·85 (2·26)	11·44 (2·43)	12·00 (2·18)	0·06	0·11	0·59
Total score	46·09 (1·98)	46·06 (1·90)	46·10 (2·01)	0·60	0·99	0·99
Delayed Matching to Sample Task 48						
Immediate	46·05 (2·60)	46·05 (3·35)	46·05 (2·25)	0·29	0·91	0·97
Delayed	45·62 (3·23)	45·95 (1·98)	45·49 (3·59)	0·40	0·50	0·97
Memory Binding Test	81·11 (16·39)	81·10 (16·25)	81·11 (16·48)	0·10	0·88	0·97
Rey-Osterrieth Complex Figure						
Copy	33·40 (3·13)	32·96 (3·56)	33·57 (2·94)	0·08	0·62	0·97
Recall						
3 min	17·34 (6·44)	17·08 (5·62)	17·43 (6·72)	0·65	0·82	0·97
30 min	17·00 (6·50)	16·62 (5·69)	17·14 (6·78)	0·50	0·91	0·97
Digit Span						
Forwards	5·63 (1·09)	5·53 (1·00)	5·67 (1·12)	0·40	0·88	0·97
Backwards	4·32 (1·00)	4·38 (0·93)	4·30 (1·02)	0·45	0·53	0·97
Visuospatial Span						
Forwards	5·29 (0·99)	5·30 (1·02)	5·29 (0·98)	0·53	0·78	0·97
Backwards	4·68 (0·97)	4·58 (1·00)	4·72 (0·96)	0·29	0·80	0·97
Frontal Assessment Battery	16·41 (1·68)	16·05 (1·68)	16·54 (1·66)	0·0064	0·52	0·97
Trail Making Test (B–A time [s])	48·91 (36·28)	57·06 (38·67)	45·83 (34·93)	0·0200	0·06	0·59
Lexical fluency	22·42 (5·91)	22·98 (5·97)	22·21 (5·88)	0·31	0·10	0·59
Semantic fluency	31·32 (7·10)	30·60 (6·10)	31·60 (7·44)	0·23	0·61	0·97
DO80 image naming test	79·21 (1·11)	79·22 (1·08)	79·20 (1·12)	0·95	0·94	0·97
^{18}F-florbetapir PET imaging						
Standardised uptake value ratios	0·78 (0·19)	1·02 (0·20)	0·69 (0·05)	..	..	..

(Table 1 continues on next page)

	All participants (n=318)	Participants with amyloid β deposition (n=88)	Participants without amyloid β deposition (n=230)	p value*	Adjusted p value†	Corrected p value‡
(Continued from previous page)						
^{18}F-fluorodeoxyglucose PET imaging						
Left cingulum posterior	2·44 (0·28)	2·40 (0·27)	2·46 (0·29)	0·11	0·11	0·22
Right cingulum posterior	2·53 (0·29)	2·49 (0·31)	2·54 (0·29)	0·16	0·14	0·22
Left parietal inferior	2·45 (0·26)	2·41 (0·25)	2·47 (0·26)	0·08	0·12	0·22
Right parietal inferior	2·58 (0·27)	2·54 (0·28)	2·60 (0·27)	0·09	0·11	0·22
Left precuneus	2·52 (0·29)	2·49 (0·28)	2·54 (0·29)	0·17	0·22	0·29
Right precuneus	2·58 (0·29)	2·54 (0·28)	2·60 (0·29)	0·12	0·14	0·21
Left temporal inferior	2·15 (0·20)	2·13 (0·21)	2·16 (0·20)	0·28	0·38	0·41
Right temporal inferior	2·36 (0·24)	2·33 (0·24)	2·36 (0·24)	0·29	0·31	0·37
Volumetric MRI (cm^3)						
Total hippocampal volume‖	2·71 (0·31)	2·63 (0·32)	2·74 (0·31)	0·0052	0·0175	0·11
Left hippocampal volume‖	2·65 (0·32)	2·59 (0·33)	2·68 (0·31)	0·0250	0·06	0·22
Right hippocampal volume‖	2·77 (0·33)	2·67 (0·35)	2·81 (0·32)	0·0010	0·0027	0·0325
CSF biomarkers						
Number of participants assessed	51 (16%)	16 (18%)	35 (15%)	..	..	..
Men	27 (53%)	4 (25%)	23 (66%)	0·65	..	..
Women	24 (47%)	12 (75%)	12 (34%)	..	..	..
Age (years)	76·01 (3·40)	76·34 (3·27)	75·86 (3·50)	0·0164	..	..
$A\beta_{1-42}$ concentration (pg/mL)	918·75 (365·64)	612·50 (201·29)	1058·74 (338·26)	<0·0001	..	..
Ratio of $A\beta_{1-42}$ to $A\beta_{1-40}$	20·17 (10·16)	28·52 (12·02)	16·35 (6·33)	0·0001	..	..
Total tau concentration (pg/mL)	295·2 (122·0)	382·3 (114·6)	255·4 (104·3)	0·0009	..	..
Phosphorylated tau concentration in threonin 181 (pg/mL)	50·49 (15·97)	62·25 (12·30)	45·11 (14·62)	0·0003	..	..

Data are mean (SD) or number (%). Aβ=amyloid β. *Comparison of participants positive *vs* negative for amyloid β deposition; *t* test used for continuous variables and χ^2 test for qualitative variables. †Adjusted with generalised linear models for age, sex, and level of education, plus for blood glucose concentration for ^{18}F-fluorodeoxyglucose PET indices, except in exploratory analyses of CSF biomarkers. ‡Corrected for multiple testing by Benjamini-Hochberg correction except in exploratory analyses of CSF biomarkers. §On a scale of 1–8, where 1=primary education and 8=higher education, high was defined as scores >6. ¶Clinical Dementia Rating is not shown because all participants score 0. ‖Normalised to the mean total intracranial volume.

Table 1: **Baseline characteristics and test results**

28·8 [1·2]; mean difference 0·53, 95% CI 0·14–1·20, p=0·16) and Clinical Dementia Rating (0·06 [0·2] *vs* 0·05 [0·3]; –0·01, –0·08 to 0·06, p=0·79). Four (2%) patients progressed to prodromal Alzheimer's disease, all of whom were positive for amyloid β deposition at baseline (table 2). Compared with other participants positive for amyloid β deposition, at baseline these patients seemed to be older and to have higher *APOE* ε4 allele carrier frequency, greater ^{18}F-florbetapir SUVRs, lower normalised hippocampal volumes, and lower FCSRT free recall and Frontal Assessment Battery scores, indicating mild executive dysfunction (table 2). By contrast, they did not differ for baseline MMSE or FCSRT total recall scores. In each of the four cases, episodic memory scores dropped sharply within the 12 months preceding the diagnosis of prodromal Alzheimer's disease. When looking at the FCSRT total recall score, we saw striking decreases in scores (mean decrease 10·75 points) in these four participants at 24 months of follow-up, whereas the remaining 84 participants positive for amyloid β deposition had a mean increase of 0·5 points in the same test (table 2). As all four participants were positive for amyloid β deposition, the annual conversion rate was 1·8% in this subgroup (four of 88 over 30 months), compared with zero in the subgroup negative for amyloid β deposition. Being an *APOE* ε4 allele carrier was a strong predictor for progression to prodromal Alzheimer's disease in participants positive for amyloid β deposition (3·24% per year [three of 37 over 30 months] *vs* 0·78% per year [one of 51 over 30 months]). At 30 months, three participants who progressed to prodromal Alzheimer's disease were alive and one had died.

Discussion

In individuals without measurable cognitive impairment but with subjective memory complaints, β-amyloidosis status at baseline and after 24 months of follow-up was not sufficient to predict progression to Alzheimer's disease. The cognitive status of each participant was confirmed at baseline, and none had any evidence of an amnestic mild cognitive impairment when assessed with the FCSRT. Use of this test as a screening tool is novel in a cohort of people at risk of Alzheimer's disease. Being an observational study, no interventions were used that

	Participants with amyloid β deposition but without disease progression (n=83)	Participants without amyloid β deposition (n=230)	Participants with prodromal Alzheimer's disease by 30 months (n=4)				
			Participant 1	Participant 2	Participant 3	Participant 4	All
Characteristics							
Age at baseline (years)	76·8 (3·4)	75·7 (3·4)	85	80	75	81	80·2 (4·1)
APOE ε4 allele	33 (39%)	29 (13%)	Yes	No	Yes	Yes	3 (75%)
Imaging measures							
SUVR	1·02 (0·20)	0·69 (0·05)	1·23	1·52	1·58	1·51	1·46 (0·16)
Hippocampal volume (cm^3)	2·63 (0·32)	2·71 (0·31)	2·30	2·38	2·25	2·18	2·28 (0·08)
Mini-Mental State Examination score							
Baseline	28·48 (0·90)	28·73 (0·96)	28	29	28	28	28·25 (0·50)
12 months	28·67 (1·27)	28·80 (1·21)	29	27	30	27	28·25 (1·50)
24 months	28·66 (1·52)	28·79 (1·26)†	Not available	27	28	28	27·67 (0·58)
Free and Cued Selective Reminding Test score							
Free recall							
Baseline	29·08 (5·44)	30·39 (5·38)	20	18	24	23	21·25 (2·75)
12 months	30·05 (5·64)	30·94 (5·73)	21	13	29	24	21·75 (6·70)
24 months	31·95 (6·17)	33·15 (5·39)	Not available	10	17	16	14·33 (3·78)
Total recall							
Baseline	46·06 (1·90)	46·10 (2·01)	44	44	45	45	44·50 (0·58)
12 months	46·23 (2·82)	45·97 (2·71)	32†	34†	47	40	38·25 (6·75)
24 months	46·78 (1·31)	46·62 (1·71)	Not available	39	31†	35†	35·00 (4·00)
Frontal Assessment Battery score							
Baseline	16·05 (1·68)	16·54 (1·66)	12	14	12	15	13·25 (1·50)
12 months	16·14 (1·77)	16·76 (1·43)	16	9	14	15	13·50 (3·11)
24 months	16·18 (1·82)	16·84 (1·37)	Not available	14	12	14	13·33 (1·15)
Trail Making Test (B–A time [s])							
Baseline	57·06 (38·67)	45·56 (34·22)	112	74	49	47	70·50 (30·27)
12 months	51·04 (41·19)	45·03 (36·41)	87	Data missing	39	47	57·67 (25·72)
24 months	52·48 (43·24)	40·30 (29·16)	Not available	71	36	49	52·00 (17·69)

Data are mean (SD) or number (%) unless given for individuals participants. SUVR=standardised uptake value ratio. *Results for the full set of tests at all timepoints will be reported elsewhere. †Score dropped in the 12 months preceding progression.

Table 2: **Comparison of selected results* over time, by amyloid β deposition status and progression to prodromal Alzheimer's disease**

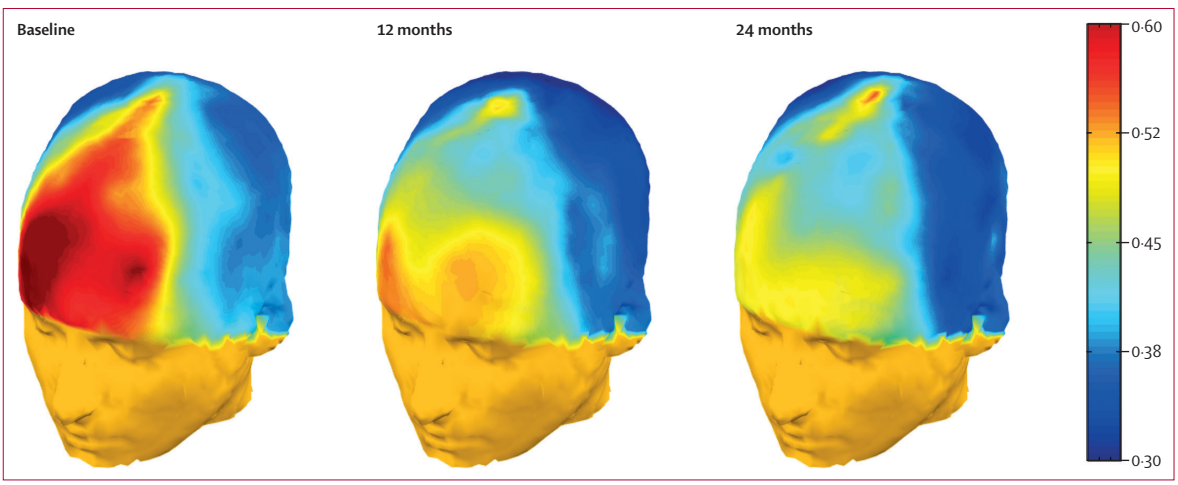

Figure 2: **Mean longitudinal changes in θ:α power ratio on electroencephalograms at rest in 88 participants positive for amyloid β deposition**
Decrease in α:θ ratio was mainly driven by a substantial increase in α oscillations over time in prefrontal areas in participants who were positive for amyloid β deposition at baseline, including those who progressed to prodromal Alzheimer's disease.

might modify the follow-up and affect statistical power. We investigated many domains, including objective measures of cognition and behaviour, different MRI and PET investigations, and EEG at rest and during a cognitive task. An additional strength is that the INSIGHT-preAD study is based in only one centre, meaning that all participants are assessed by the same team and with the same neuroimaging scanners, which keeps variance of data and results to a minimum. Among various psychometric methods, the high number of scales investigating the subjective feelings of the participants and their carers might provide a unique opportunity to evaluate the impact of cortical amyloid β deposition on subtle cognitive or behavioural changes.

At baseline, only 28% of all participants, who had a mean age of 76·0 years, had amyloid β deposition, which is slightly less than the proportions in the other ongoing multicentre studies.[46–50] In previously published cross-sectional studies of individuals with preclinical Alzheimer's disease, around 27% of participants have been classified as positive for β-amyloidosis on PET,[51–53] but the proportion increases to 30% when the mean age is older than 70 years (mean 74·4 years).[45] In our study, participants who were positive and negative for amyloid β deposition differed at baseline for some results, such as MMSE score, tests for executive functions, and hippocampal volume, although not after adjustment for age, sex, and level of education and correction for multiple analyses. This finding underscores the necessity to control for age, which is a known confounder for executive functioning[54] and hippocampal volume.[55] Of note, in studies of individuals without cognitive impairment at baseline, participants positive for β-amyloidosis are consistently significantly older than those negative for β-amyloidosis,[7–11] and decline occurs after at least 18 months of follow-up.[8] In sum, our results suggest that cortical amyloid β deposition has no effect on cognitive and behavioural domains.

The severity of cognitive complaints was similar in our groups positive and negative for amyloid β deposition. All participants must have had some memory complaints to be included, but those with amyloid β deposition did not complain more, which suggests that the intensity of subjective memory complaints is not a strong candidate marker of preclinical Alzheimer's disease. This result is in line with the findings of the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL), in which the intensity of subjective memory complaints was not a strong marker of preclinical Alzheimer's disease.[56,57] Moreover, we have found previously in the INSIGHT-preAD participants that the presence of amyloid β brain lesions is associated with low awareness of cognitive decline.[18] Although this finding might seem to contradict some data,[53] it should be noted that our participants only had complaints and did not fully correspond to the definition of subjective cognitive decline.[58] However, we investigated their subjective feelings extensively and, to our knowledge, INSIGHT-preAD is the first study to assess so many different aspects of cognitive complaints, with use of 88 items in six questionnaires.

Overall cognitive performance on all tests did not decline over time in our whole cohort (table 2) or, after exclusion of the four people who progressed to prodromal Alzheimer's disease, among participants positive for amyloid β deposition at baseline. This result was surprising, and suggests that age-related changes in individuals negative for amyloid β deposition at baseline and cortical amyloid β deposition in those positive at baseline are not severe enough to affect cognitive functioning or are compensated by brain changes, reserve, or both. The significant increase over 24 months of at-rest α oscillations on EEG, suggestive of frontal compensatory activation, in participants positive for amyloid β deposition supports compensation in cognitive control.[59] These changes indicate that EEG captures neuronal dynamics associated with onset of brain amyloidosis β deposition and over time. To conclude, the stability of cognitive performance in the participants positive for amyloid β deposition (table 2) favours the hypothesis of a compensated state in asymptomatic at-risk individuals through decoupling of structural lesions from maintenance of cerebral functioning. We suggest that this phase precedes the decompensation in clinical disease rather than there being a slow progressive decline with no clear distinctions between the asymptomatic and symptomatic states (figure 3).[7,9] Strict inclusion criteria, short period of follow-up, exclusion of individuals who progressed to prodromal Alzheimer's disease from analyses, and adjustment for the age difference between β-amyloidosis subgroups might explain the absence of decline in people with amyloid β deposition but no diagnosis of prodromal Alzheimer's disease in this study. Besides the short follow-up so far, another limitation of our study is the censoring effect due to the inclusion criterion of age older than 70 years.

The number of participants who progressed to prodromal Alzheimer's disease was surprisingly low, especially given the mean age for participants with amyloid β deposition. Follow-up is continuing, and the number who progress might increase, as is suggested by estimated prevalence.[60] The low number, however, might be due to selection bias. This study involved several hours of cognitive and behavioural investigations and several PET and MRI scans and, therefore, the participants are likely to have had some degree of social interest in supporting research, which might be related to their high mean level of education. Cognitive reserve might have compensated for the effect of brain amyloid β lesions and delayed progression to clinical disease. The analysis of four people who did progress raises the question of which factors might have facilitated progression. In these participants, increased age and amyloid β deposition and evidence of mild executive dysfunction at baseline, along

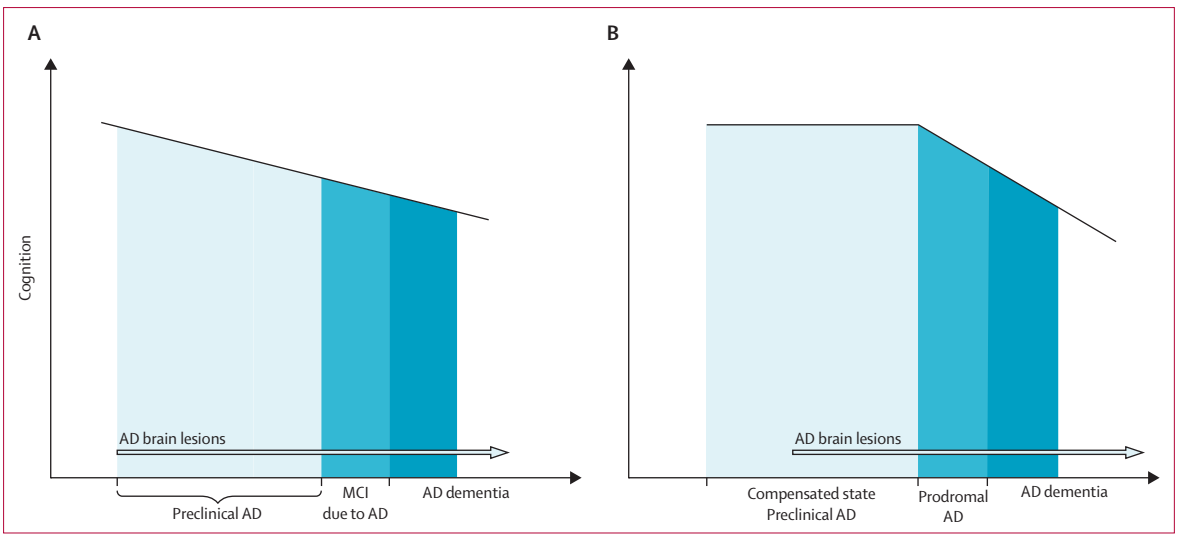

Figure 3: **Two hypothetical models of the natural history of Alzheimer's disease**
(A) Model 1 illustrates the dominant view of progressive deterioration: in Alzheimer's disease, cognition is progressively impaired from the preclinical phase (characterised by amyloid β deposition followed by tau pathology), to the prodromal clinical stage (with subtle cognitive changes), then the clinical stages of MCI and dementia. (B) Model 2 represents an alternative view of preclinical compensation that we have based on our data for brain β-amyloidosis. Cognition remains stable in the preclinical phase of the disease despite underlying brain lesions, until brain compensatory mechanisms are overwhelmed, leading to clinical disease. MCI=mild cognitive impairment. AD=Alzheimer's disease.

with a high frequency of the *APOE* ε4 allele compared with the rest of the cohort, suggest saturation of functional mechanisms. By contrast, they did not differ from the rest of the participants for baseline MMSE and FCSRT total recall scores. In all four participants, severe decline in total recall performance was a marker of progression in the 12 months before prodromal Alzheimer's disease was diagnosed. Being a carrier of the *APOE* ε4 allele was also a strong predictor of progression to prodromal Alzheimer's disease in participants positive for amyloid β deposition.

Our findings are important for ongoing and future clinical trials involving people with preclinical Alzheimer's disease. The demographic characteristics of the randomised participants will probably be similar to those in INSIGHT-preAD, with the same potential selection bias. Therefore, the numbers of participants, duration of trials, or both, need to be increased in future trials aimed at assessing preclinical Alzheimer's disease.Associated factors that affect decline, such as age, *APOE* ε4 allele carrier status, and initial amyloid β burden, also need to be determined. Another related issue is the definition of new markers of disease progression. If the onset of prodromal Alzheimer's disease is an outcome for trials of efficacy of disease modifiers, it would be interesting to identify surrogate markers that predict events to help to distinguish people with amyloid β deposition who are likely to progress from those who are likely to remain stable over time. Large and persistent decline in FCSRT total recall score seemed to identify the participants who converted to prodromal Alzheimer's disease. Decrease in cued recall, therefore, might be a useful marker of disease progression. Our follow-up will continue long term and should help to confirm whether this pattern is consistent.

In the study of disease-modifying therapies, a shift is being made from the dementia stages to the prodromal stages of Alzheimer's disease. Definition of the dynamic processes that precede progression to clinical disease is crucial. The INSIGHT-preAD study is designed to identify the best multimodal biomarker combinations for predicting the secondary occurrence of prodromal Alzheimer's disease and is likely to constitute a valuable repository of clinical, cognitive, neuroimaging, neurophysiological, and biological data for the scientific community. Our data so far suggest that brain β-amyloidosis had not affected behaviour and cognition when measured at 30 months, which suggests that compensatory mechanisms maintain brain structure and functioning and that β-amyloidosis alone is insufficient to identify patients at high risk of rapid progression to prodromal Alzheimer's disease.

Contributors

BD, FN, HBa, and HBe designed the study. SE, HBa, GG, AB, J-FM, and M-OH collected the data and BD, SE, FN, HBa, GG, MH, SL, FC, M-OH, M-CP, FL, OC, RG, and HH Analysed the data. All authors contributed to the writing and revisions of the paper and approved the final version.

Declaration of interests

BD has received consultancy fees from Biogen, Boehringer Ingelheim, Eli Lilly, and MedAvante and grants for his institution from Merck, Pfizer, and Roche. SE has received grants from Eli Lilly and consul tant fees from Astellas Pharma. HBa has received speaker fees from Roche. GG has received grants from France Alzheimer. OU is an employee of IQVIA

(formerly QuintilesIMS). SL has received speaker fees from Roche. M-CP has received grants from Fondation Vaincre Alzheimer, Laboratoires Servier, Pfizer, and Roche. OC has received speaker fees from Roche and grants to his institution from Air Liquide Medical Systems, myBrainTechnologies, and Qynapse. RG is a former employee of and owns stock options in Sanofi. M-OH has received consultant fees from Eli Lilly and speaker fees from Piramal. HH has received grants for his institution from Avid and Pfizer, personal fees from Anavex and Jung Diagnostics, personal fees and non-financial support from Axovant Sciences, Cytox, Eli Lilly, GE Healthcare, Oryzon Genomics, Roche, Takeda, and Zinfandel Pharmaceuticals, and holds patents for in-vitro determination methods (8916388; 20100062463, 7547553, and 20080199966) and in-vitro procedures (8298784, 20100035286, and 20090263822), for diagnosis and early diagnosis of neurodegenerative disorders, for neurodegenerative markers for psychiatric conditions (20120196300 and 20080131921), and for a CSF diagnostic in-vitro method for diagnosis of dementias and neuroinflammatory diseases (20080206797). The other authors declare no competing interests.

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