Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study

Victor L Villemagne, Samantha Burnham, Pierrick Bourgeat, Belinda Brown, Kathryn A Ellis, Olivier Salvado, Cassandra Szoeke, S Lance Macaulay, Ralph Martins, Paul Maruff, David Ames, Christopher C Rowe, Colin L Masters, for the Australian Imaging Biomarkers and Lifestyle (AIBL) Research Group

Summary

Background Similar to most chronic diseases, Alzheimer's disease (AD) develops slowly from a preclinical phase into a fully expressed clinical syndrome. We aimed to use longitudinal data to calculate the rates of amyloid β (Aβ) deposition, cerebral atrophy, and cognitive decline.

Methods In this prospective cohort study, healthy controls, patients with mild cognitive impairment (MCI), and patients with AD were assessed at enrolment and every 18 months. At every visit, participants underwent neuropsychological examination, MRI, and a carbon-11-labelled Pittsburgh compound B (^{11}C-PiB) PET scan. We included participants with three or more ^{11}C-PiB PET follow-up assessments. Aβ burden was expressed as ^{11}C-PiB standardised uptake value ratio (SUVR) with the cerebellar cortex as reference region. An SUVR of 1·5 was used to discriminate high from low Aβ burdens. The slope of the regression plots over 3–5 years was used to estimate rates of change for Aβ deposition, MRI volumetrics, and cognition. We included those participants with a positive rate of Aβ deposition to calculate the trajectory of each variable over time.

Findings 200 participants (145 healthy controls, 36 participants with MCI, and 19 participants with AD) were assessed at enrolment and every 18 months for a mean follow-up of 3·8 (95% CI CI 3·6–3·9) years. At baseline, significantly higher Aβ burdens were noted in patients with AD (2·27, SD 0·43) and those with MCI (1·94, 0·64) than in healthy controls (1·38, 0·39). At follow-up, 163 (82%) of the 200 participants showed positive rates of Aβ accumulation. Aβ deposition was estimated to take 19·2 (95% CI 16·8–22·5) years in an almost linear fashion—with a mean increase of 0·043 (95% CI 0·037–0·049) SUVR per year—to go from the threshold of ^{11}C-PiB positivity (1·5 SUVR) to the levels observed in AD. It was estimated to take 12·0 (95% CI 10·1–14·9) years from the levels observed in healthy controls with low Aβ deposition (1·2 [SD 0·1] SUVR) to the threshold of ^{11}C-PiB positivity. As AD progressed, the rate of Aβ deposition slowed towards a plateau. Our projections suggest a prolonged preclinical phase of AD in which Aβ deposition reaches our threshold of positivity at 17·0 (95% CI 14·9–19·9) years, hippocampal atrophy at 4·2 (3·6–5·1) years, and memory impairment at 3·3 (2·5–4·5) years before the onset of dementia (clinical dementia rating score 1).

Interpretation Aβ deposition is slow and protracted, likely to extend for more than two decades. Such predictions of the rate of preclinical changes and the onset of the clinical phase of AD will facilitate the design and timing of therapeutic interventions aimed at modifying the course of this illness.

Funding Science and Industry Endowment Fund (Australia), The Commonwealth Scientific and Industrial Research Organisation (Australia), The National Health and Medical Research Council of Australia Program and Project Grants, the Austin Hospital Medical Research Foundation, Victorian State Government, The Alzheimer's Drug Discovery Foundation, and the Alzheimer's Association.

Introduction

The increasing age of the population is leading to an increased prevalence of Alzheimer's disease (AD). Identification of individuals at risk for developing sporadic AD and estimation of the timing of dementia onset is a fundamental prerequisite for testing therapeutic interventions. The increased awareness of the difficulty in altering the rates of cognitive decline in fully established AD[1,2] has fostered the growing consensus that intervention at the earliest possible phase, perhaps even at the asymptomatic stage, is desirable.[3]

It is widely assumed that amyloid β (Aβ) deposition precedes cerebral atrophy and cognitive decline[4–6] since results from both post-mortem[7,8] and Aβ PET studies[9–11] show that about 20–40% of cognitively normal individuals aged 60–90 years have high levels of Aβ deposition in the brain. Furthermore, cognitively normal elderly individuals with high Aβ deposition show significantly faster rates of grey matter atrophy and memory decline than those with low Aβ deposition.[12,13]

On the basis of preliminary evidence from prospective Aβ imaging studies,[14,15] the rate of Aβ accumulation has been estimated to be very slow. Cross-sectional data from

Department of Nuclear Medicine and Centre for PET, Austin Health, Melbourne, VIC, Australia (V L Villemagne MD, Prof C C Rowe MD); **Mental Health Research Institute** (V L Villemagne, C Szoeke MBBS, Prof C L Masters MD), **Department of Medicine** (V L Villemagne, Prof C C Rowe), **Department of Psychiatry** (K A Ellis PhD), **The University of Melbourne, Melbourne, VIC, Australia; Commonwealth Scientific and Industrial Research Organization (CSIRO) Preventative Health Flagship: Mathematics, Informatics and Statistics, Floreat, WA, Australia** (S Burnham PhD); **CSIRO Preventative Health Flagship: The Australian e-Health Research Centre, Brisbane, QLD, Australia** (P Bourgeat PhD, O Salvado PhD); **Edith Cowan University, School of Exercise, Biomedical and Health Sciences, Perth, WA, Australia** (B Brown PhD, Prof R Martins PhD); **National Ageing Research Institute, Melbourne, VIC, Australia** (C Szoeke, Prof D Ames MD); **CSIRO Preventative Health Flagship: Materials Science and Engineering, Melbourne, VIC, Australia** (L Macaulay PhD); **and CogState Ltd, Melbourne, VIC, Australia** (P Maruff PhD)

Correspondence to:
Dr Victor L Villemagne,
Department of Nuclear Medicine and Centre for PET, Austin Health, 145 Studley Road, Heidelberg, VIC 3084, Australia
villemagne@petnm.unimelb. edu.au

For the **AIBL Research Group** see http://www.aibl.csiro.au/about/aibl-research-team

studies of dominantly inherited AD have provided the first quantitative insights into rates of biomarker change in preclinical AD, showing that changes start decades before onset of clinical symptoms.[16]

To understand how Aβ accumulation is related to cerebral atrophy and the clinical manifestations of AD, it is necessary to prospectively estimate how each of these aspects of the disease change over time. Here we report rates of Aβ deposition, cerebral atrophy, and cognitive impairment in people aged 55–89 years classified as being healthy or who met clinical criteria for mild cognitive impairment (MCI)[17] or AD.[18]

Methods

Study design and participants

This prospective cohort study started in Sept 17, 2004, and was designed to assess all participants every 18 months.

Healthy controls were recruited by advertisement in the community or were spouses of the participants with MCI or AD recruited from tertiary Memory Disorders Clinics or from primary care physicians who specialise in dementia care in Melbourne, VIC, and Perth, WA, Australia. Irrespective of their classification at baseline, the clinical and neuropsychological performance of all participants was assessed at every visit; classification on the basis of these results was by consensus of a panel of clinicians and neuropsychologists masked to carbon-11-labelled Pittsburgh compound B (^{11}C-PiB) PET status.[11,19] Individuals classified as healthy controls performed within normal limits on the Australian Imaging, Biomarkers, and Lifestyle (AIBL) neuro-psychological test battery,[19] individuals classified as having MCI group met criteria for subjective and objective cognitive difficulties in the absence of significant functional loss,[17] and all patients with AD met National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[18] criteria for probable AD. For the current study, we included only participants with three or more ^{11}C-PiB-PET follow-up assessments.

Written informed consent was obtained from all participants. Approval for the study was obtained from the human research ethics committees of Austin Health, St Vincent's Hospital, Edith Cowan University, and Hollywood Private Hospital. The study commenced in 2004, and in 2006 these and further participants were enrolled into the longitudinal AIBL study of ageing being conducted in Melbourne and Perth, which has been described in detail elsewhere.[11,19]

Procedures

The primary cognitive performance measures were the composite memory and non-memory scores that were calculated as previously described.[20] Briefly, we calculated a composite episodic memory score by taking the average

of the z scores (generated with results from 65 healthy controls with both low ^{11}C-PiB PET retention and normal MRI as the reference) for Rey complex figure test (RCFT, 30 min) long delay and California verbal learning test second edition (CVLT-II) long delay, and logical memory II. We calculated a composite non-memory score by taking the average of the z scores for the Boston naming test, letter fluency, category fluency, digit span forwards and backwards, digit symbol-coding, and RCFT copy.[20]

Participants received an MRI scan using a 3D magnetisation prepared rapid gradient echo (MPRAGE; appendix). The primary MRI performance measures were the cortical grey matter and hippocampal volumes normalised for total intracranial volume.

PET studies consisted of a 30 min acquisition starting 40 min after injection of 370 MBq ^{11}C-PiB (appendix). We processed PET images using a semi-automatic region-of-interest method as previously described.[14] Standardised uptake values (SUV) for ^{11}C-PiB were calculated for all brain regions examined. The primary performance measure used for all the PET assessments was the SUV ratio (SUVR), generated by dividing all regional SUV by the cerebellar cortex SUV. *APOE* genotype was determined by direct sequencing.

Statistical analysis

To calculate the rate of change, we fitted a least-square linear regression to the three or more available points for each participant. We used the slope of the regression to compute every participant's yearly rate of change for each variable.

For the composite cognitive scores, we used –1·5 SD to establish a threshold between normality and abnormality. In view of the normal distributions of MRI volumetrics in the groups of healthy controls and participants with AD, we applied a two-graph receiver operator curve approach to establish the optimum cutoff for hippocampal volume (4·0 cm³) between them).[21] In view of the bimodal distribution of ^{11}C-PiB SUVR, we did a hierarchical cluster analysis on all research participants aged 59–89 years of the healthy control group, yielding a cutoff for high or low ^{11}C-PiB neocortical SUVR of 1·5, consistent with cutoff values used in previous ^{11}C-PiB-PET studies.[14,22] This threshold of 1·5 SUVR provides the highest sensitivity (0·99) and accuracy (0·78) and the largest effect size ($d=2·4$) for the comparison of healthy controls and patients with AD, helping identify those individuals with substantial Aβ deposition in the brain.[9,11,14,15] In our previous report, we identified individuals who, irrespective of their ^{11}C-PiB status, accumulated Aβ over time (accumulators) compared with those who did not (non-accumulators).[23] In the present study, we used a rate threshold of 0 SUVR per year or lower to differentiate between these two groups.[23] For comparison across variables, we used median values for every variable, whereas we identified minimum and maximum values using their respective 25th and 75th percentiles.[24]

To establish the trajectory of Aβ accumulation and associated variables over time, we included only those participants who had high ^{11}C-PiB retention and those who had low ^{11}C-PiB retention but showed Aβ accumulation over time (accumulators) in the generation of the trajectory curves. We did not include the non-accumulators (those individuals who presented with low ^{11}C-PiB retention and showed no Aβ accumulation over time) in the generation of the trajectory curves for any of the variables assessed.

We plotted every individual's rate of change for every variable of the accumulators against the respective variable mean. We used three different curve-fitting models: linear, quadratic, and cubic. We used the Akaike information criterion (AIC)[25] to compare which curve-fitting approach conformed best to the data. We then computed integrals along the predicted values from the best curve fit to generate a model of the average trajectory of the different variables over time.

We tested normality of distribution using the Shapiro-Wilk test and visual inspection of variable histograms. We performed statistical assessments between groups using a Tukey-Kramer honestly significant difference (HSD) test to establish differences between clinical groups, and using a Dunnet's test to compare every group with controls. We assessed categorical differences using Fisher's exact test. We adjusted regression analysis of the data for age, sex, years of education, and *APOE* status.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (VLV) and co-senior authors (CCR and CLM) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 366 participants who were initially assessed, 200 (145 healthy controls, 36 participants with MCI, and 19 patients with AD) were assessed at enrolment and 1·5 and 3 years later. Up to Nov 15, 2012, 72 participants were also assessed at 4·5 years, and 12 participants at 6 years. The mean follow-up for the cohort was 3·8 (95% CI 3·6–3·9) years.

Table 1 shows the characteristics of the participants included in the analyses. While the group of healthy controls not included in the study had a higher Aβ burden, lower mini-mental state examination (MMSE), less years of education, and a higher proportion of participants with high ^{11}C-PiB retention than did the healthy controls group included in the study, participants with MCI not included in the study had a lower MMSE and non-memory composite score than did those with MCI included in the study (appendix). The appendix contains a detailed list of factors affecting completion of the assessments.

As expected, at baseline the MCI and AD groups significantly differed from healthy controls in MMSE, clinical dementia rating (CDR), episodic memory and non-memory composite scores, MRI volumetrics, and ^{11}C-PiB retention. The participants with MCI were slightly older than the healthy controls and those with AD. The prevalence of *APOE ε4* carriers was higher in patients with MCI and AD than in healthy controls. Groups did not differ significantly in education level or sex. Irrespective of clinical classification, 163 (82%) of 200 participants (83 [69%] of 120 with low Aβ burden and 77 (96%) of 80 with high Aβ burden at baseline) showed Aβ accumulation over time (figure 1). Comparing the accumulators with non-accumulators (33 healthy controls and four participants with MCI; table 2), we noted a significantly higher proportion of *APOE ε4* carriers in the healthy control accumulators than in healthy controls

	Healthy controls (n=145)	Mild cognitive impairment (n=36)	p value*	Alzheimer's disease (n=19)	p value*
Age, years	71·3 (7·1)	74·6 (6·5)	0·012	69·8 (9·4)	0·49
Male sex	74 (51%)	20 (56%)	0·71	10 (53%)	1·00
MMSE	28·9 (1·1)	27·3 (2·1)	<0·0001	22·0 (2·9)	<0·0001
CDR-SOB	0·06 (0·3)	1·03 (0·7)	<0·0001	3·84 (1·1)	<0·0001
Positive for *APOE ε4*	58 (40%)	20 (58%)	0·037	12 (63%)	0·047
Years of education	13·6 (3·7)	13·0 (3·8)	0·36	12·6 (3·8)	0·28
Episodic memory composite score	−0·23 (0·88)	−2·10 (0·91)	<0·0001	−3·21 (0·6)	<0·0001
Non-memory composite score	−0·15 (0·65)	−0·77 (0·80)	<0·0001	−2·46 (1·19)	<0·0001
Grey matter volume (cm³)†	349 (15)	339 (16)	0·0012	326 (23)	0·0008
Hippocampal volume (cm³)†	4·18 (0·30)	3·76 (0·60)	0·005	3·92 (0·37)	0·014
Amyloid β burden (SUVR)	1·38 (0·39)	1·94 (0·64)	<0·0001	2·27 (0·43)	<0·0001
High ^{11}C-PiB retention	38 (26)%	24 (67%)	<0·0001	18 (95%)	<0·0001

Data are mean (SD) or number (%) unless otherwise stated. MMSE=mini-mental state examination. CDR-SOB=clinical dementia rating scale sum of boxes. *APOE*=apolipoprotein E. SUVR=standard uptake value ratio.[11]C-PiB=Carbon-11-labelled Pittsburgh compound B. *Compared with healthy controls. †Grey matter and hippocampal volumes normalised to intracranial volume.

Table 1: **Characteristics of the study cohort**

non-accumulators group. Of the 82 accumulators with low Aβ burden at baseline who were healthy controls or had MCI, eight (10%; six healthy controls and two participants with MCI) reached or passed the 1·5 SUVR threshold within 3 years of follow-up (figure 1). All non-accumulators had SUVR values lower than the 1·5 cutoff, and the four non-accumulator participants with MCI are presumed to have diagnoses other than prodromal AD.[26]
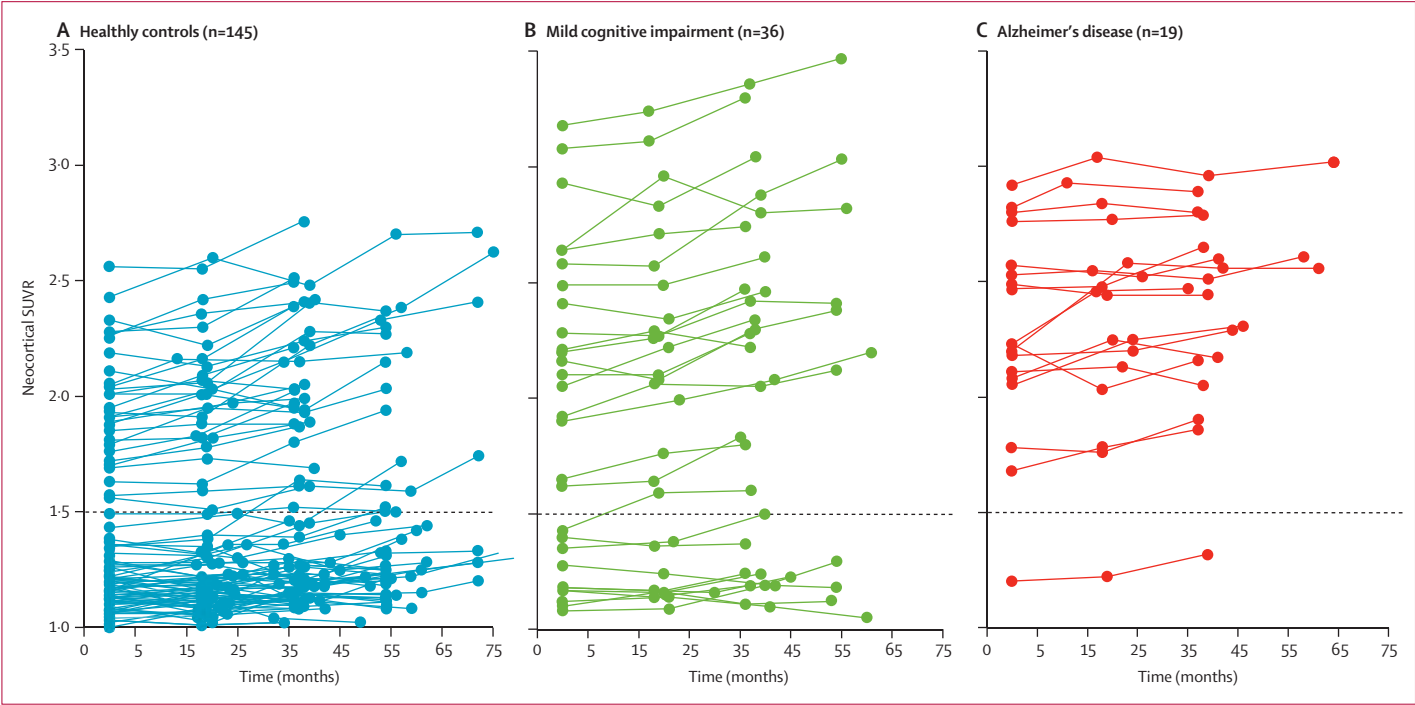

Figure 1: Individual longitudinal ¹¹C-PiB SUVR by clinical group
Most participants (82%) showed a slow and steady increase in Aβ deposition over time. Dotted lines indicate the SUVR threshold of 1·5 separating low from high Aβ burdens.
¹¹C-PiB=carbon-11-labelled Pittsburgh compound B. SUVR=standardised uptake value ratio. Aβ=amyloid β.

	Non-accumulators			Accumulators						
	Healthy controls (n=33)	Mild cognitive impairment (n=4)	p value	Healthy controls (n=112)	p value	Mild cognitive impairment (n=32)	p value	Alzheimer's disease (n=19)†	p value
Age, years	72·0 (6·7)	77·3 (6·3)	0·19	71·2 (7·2)	0·57	74·2 (6·6)	0·03‡	69·7 (9·4)	0·54
Male sex	16 (48%)	2 (50%)	1·00	58 (52%)	0·84	18 (56%)	0·69	10 (53%)	1·00
MMSE	29·0 (1·2)	28·8 (1·5)	0·63	28·9 (1·1)	0·54	27·1 (2·1)‡	<0·0001‡	22·0 (2·9)‡	<0·0001‡
CDR-SOB	0·02 (0·1)	0·88 (0·8)	0·11	0·08 (0·3)	0·07	1·05 (0·7)‡	<0·0001‡	3·84 (1·1)‡	<0·0001‡
Positive for *APOE ε4*	6 (18%)	0	1·00	52 (46%)§	0·0021§	20 (65%)§‡	0·045‡; 0·023§	12 (63%)	0·15
Years of education	14·0 (3·5)	13·3 (3·6)	0·36	13·6 (3·8)	0·55	13·0 (3·8)	0·45	12·6 (3·8)	0·33
Episodic memory composite score	−0·32 (0·8)	−1·58 (1·5)	0·12	−0·20 (0·9)	0·45	−2·16 (0·8)‡	<0·0001‡	−3·21 (0·6)‡	<0·0001‡
Non-memory composite score	−0·23 (0·7)	−0·53 (0·3)	0·19	−0·13 (0·6)	0·42	−0·81 (0·9)‡	<0·0001‡	−2·46 (1·2)‡	<0·0001‡
Grey matter volume (cm³)¶	350 (13)	342 (9)	0·16	349 (15)	0·64	338 (17)‡	0·0013‡	326 (23)‡	<0·0001‡
Hippocampal volume (cm³)¶	4·17 (0·25)	3·85 (0·90)	0·52	4·18 (0·31)	0·98	3·75 (0·56)‡	0·005‡	3·92 (0·37)‡	0·0029‡
Aβ burden (SUVR)	1·17 (0·07)	1·22 (0·17)	0·57	1·44 (0·42)§	0·0002§	2·03 (0·62)‡§	<0·0001‡; 0·014§	2·27 (0·43)‡	<0·0001‡
High ¹¹C-PiB retention	0	0	··	38 (34%)§	<0·0001§	24 (75%)‡§	<0·0001‡; 0·0084§	18 (95%)‡	<0·0001‡

Dara are mean (SD) or number (%) unless otherwise stated. MMSE=mini mental state examination. CDR-SOB=clinical dementia rating scale sum of boxes. *APOE*=apolipoprotein E. Aβ=amyloid β. SUVR=standard uptake value ratio. ¹¹C-PiB=Carbon-11-labelled Pittsburgh Compound B. *Accumulators were participants with an already high Aβ burden (SUVR >1·5) in the brain or those who, despite having a low Aβ burden (SUVR<1·5) in the brain presented with rates of Aβ deposition higher than 0; non-accumulators were participants who presented with a low Aβ burden in the brain (SUVR <1·5) and had a rate of Aβ deposition equal or lower than 0. †None of the 19 patients in the Alzheimer's disease group was a non-accumulator. ‡Significantly different from their respective healthy controls. §Significantly different from non-accumulators in the same clinical group. ¶Grey matter and hippocampal volumes normalised to intracranial volume (cm³).

Table 2: Characteristics of accumulators and non-accumulators*

Of the healthy control accumulators, those with high ^{11}C-PiB retention presented significantly faster rates of Aβ deposition, episodic memory decline and non-memory decline, cortical grey matter loss, and hippocampal atrophy than those with low ^{11}C-PiB retention (table 3). By contrast, of the accumulators with MCI, those with high ^{11}C-PiB retention showed significantly faster rates of Aβ deposition and hippocampal atrophy than did those with low ^{11}C-PiB retention, but not significantly faster rates of cortical grey matter atrophy, episodic memory decline, and non-memory decline (table 3). In the 18 patients with AD and high ^{11}C-PiB retention, the rates of non-memory decline, grey matter atrophy, and hippocampal atrophy were
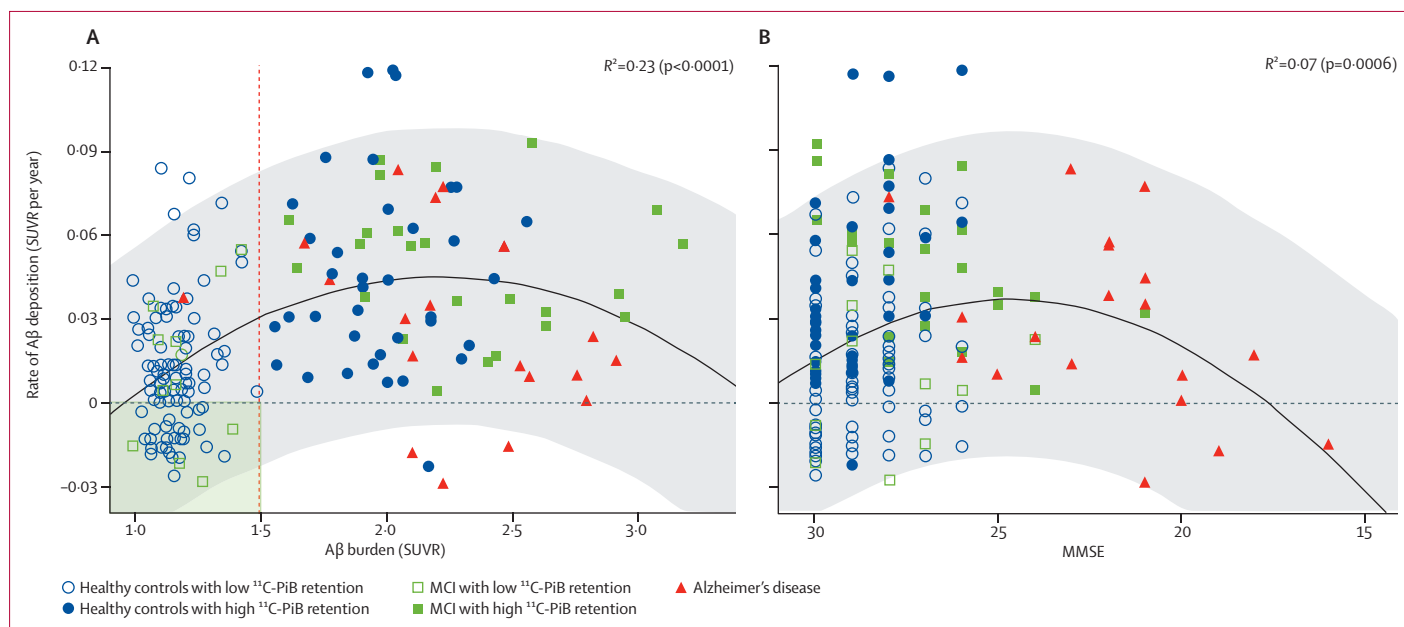
significantly faster than in healthy controls with high ^{11}C-PiB retention, but the rate of episodic memory decline was not (table 3). By comparison with healthy controls with high ^{11}C-PiB retention, the rate of Aβ deposition in patients with AD and high ^{11}C-PiB retention was slower than that in healthy controls with high ^{11}C-PiB retention, but the difference was not significant (table 3).

In accumulators, after adjusting for age, sex, and years of education, *APOE ε4* genotype was associated with faster episodic memory decline in patients with AD (R^2=0·45, p=0·049) and to a much lesser degree in healthy controls (R^2=0·09, p=0·009), and with faster hippocampal atrophy in MCI (R^2=0·37, p=0·006). Whereas healthy controls and participants with MCI presented slightly faster Aβ

	Healthy controls with low ^{11}C-PiB retention (n=74)	Healthy controls with high ^{11}C-PiB retention (n=38)	p value*	MCI with low ^{11}C-PiB retention (n=8)	MCI with high ^{11}C-PiB retention (n=24)	p value*	p value†	AD with high ^{11}C-PiB retention (n=18)	p value†
Aβ deposition (SUVR per year)	0·022 (0·02)	0·046 (0·03)	<0·0001	0·025 (0·02)	0·049 (0·02)	0·017	0·64	0·026 (0·03)	0·054
Episodic memory decline (SD per year)	−0·03 (0·28)	−0·19 (0·26)	0·0037	−0·09 (0·15)	−0·22 (0·21)	0·10	0·59	−0·15 (0·16)	0·059
Non-memory decline (SD per year)	−0·06 (0·13)	−0·16 (0·22)	0·0034	−0·11 (0·15)	−0·26 (0·24)	0·13	0·09	−0·52 (0·32)	<0·0001
Grey matter atrophy (cm³ per year)	−1·6 (2·2)	−2·9 (2·2)	0·0093	−0·6 (1·9)	−2·6 (2·9)	0·13	0·71	−4·7 (3·3)	0·028
Hippocampal atrophy (cm³ per year)	−0·031 (0·04)	−0·052 (0·06)	0·019	−0·043 (0·03)	−0·093 (0·05)	0·039	0·0098	−0·098 (0·09)	0·049

^{11}C-PiB=Carbon-11-labelled Pittsburgh compound B. MCI=mild cognitive impairment. AD=Alzheimer's disease. Aβ=amyloid β. SUVR=standard uptake value ratio. *Compared with participants in the same clinical group with low Aβ burden (low ^{11}C-PiB). †Compared with healthy controls with high Aβ burden (healthy controls with high ^{11}C-PiB retention).

Table 3: Rates of amyloid β deposition, grey matter and hippocampal atrophy, and cognitive decline in participants who had amyloid β accumulation during the study

Figure 2: Relation between amyloid β burden, MMSE, and rates of amyloid β deposition
(A) Rates of Aβ deposition, independent of clinical classification, reached a peak around a SUVR of 2·2–2·3, followed by a gradual slowing in individuals with the highest Aβ burdens. (B) Similarly, the rates of Aβ deposition reached a peak around a MMSE of 24–25, followed by a progressive slowing as the severity of dementia advanced. The green shade highlights those participants who presented with a low Aβ burden in the brain (SUVR <1·5) and a rate of Aβ deposition of 0 or less (non-accumulators). The rest of the participants are deemed accumulators because they either already present with a high Aβ burden (SUVR ≥1·5) in the brain or, despite having a low Aβ burden (SUVR <1·5) in the brain present with rates of Aβ deposition >0. Shaded area represents confidence intervals of the fit. The blue dashed line represents the threshold for the rate of Aβ deposition (>0 or <0), discriminating accumulators from non-accumulators. The vertical red dashed line represents the SUVR threshold (>1·5 or < 1·5) discriminating between high or low ^{11}C-PiB retention. Aβ=amyloid β. MMSE=mini-mental state examination. SUVR=standardised uptake value ratio. ^{11}C-PiB=Carbon-11-labelled Pittsburgh compound B. MCI=mild cognitive impairment. AD=Alzheimer's disease.

deposition in *APOE ε4* carriers than in non-*APOE ε4* carriers, the differences were not significant ($R^2=0.08$, p=0.08; and $R^2=0.27$, p=0.07, respectively). No associations between the rates of change of ¹¹C-PiB, MRI volumetrics, and cognition with *APOE* genotype were noted in the AD group.

The rates of Aβ deposition reached a peak around an SUVR of 2·2–2·3, followed by a gradual slowing of accumulation in individuals with increased Aβ burdens, independent of clinical classification (figure 2A). A similar effect was noted for disease severity, as the rates of Aβ deposition reached a peak around an MMSE of 24–25, followed by a progressive slowing as the severity of dementia advanced (figure 2B).

Whereas the mean SUVRs of participants with MCI and AD with high ¹¹C-PiB retention were similar (2·31 [SD 0·43] for MCI and 2·33 [0·36] for AD), the mean SUVR for healthy controls with high ¹¹C-PiB retention was significantly lower (1·98 [0·24], p=0·0002; figure 3A).

The AIC showed that linear regression was possibly the best model for fitting the rates of change in MRI volumetrics and cognitive variables. However, a robust quadratic was a better fitting model for the rates of change in ¹¹C-PiB retention SUVR. The integration of the rate of Aβ deposition curve of the accumulators showed a tendency towards a sigmoidal shape (figure 3B). The curves derived from partial volume corrected data

showed this tendency much clearer (appendix). Longitudinal assessment of Aβ burden in patients with AD showed that as AD progresses, Aβ deposition slows towards a plateau (appendix). The integrated curve also portrays the slowing in the rate of Aβ deposition in the fully developed AD syndrome (appendix).

Anchoring of the curve at the 1·5 threshold showed that it may take 19·2 years (95% CI 16·8–22·5) for an individual to go from a SUVR of 1·5 to a SUVR of 2·33, the mean SUVR observed in patients with established AD who had high ¹¹C-PiB retention at baseline, equivalent to a 0·043 SUVR (95% CI 0·037–0·049) increase per year. Likewise, it would take on average 12·0 years (95% CI 10·1–14·9), for an individual to go from a SUVR of 1·17, the mean SUVR of healthy controls with Aβ accumulation and low ¹¹C-PiB retention at baseline, to an SUVR of 1·5.

The whole span of the natural history of Aβ deposition within the mean values of healthy controls with low ¹¹C-PiB retention and patients with mild AD was therefore estimated to be 31 years. We obtained a similar time span (26·0 years, 95% CI 22·1–31·1) when we used the 25th (SUVR 1·17) and 75th (SUVR 2·08) percentiles of the distribution of the SUVR of the cohort as lower and upper limits, instead of the mean values of healthy controls with low ¹¹C-PiB retention and patients with AD with high ¹¹C-PiB retention.

The integration of the rate of MRI volumetrics and cognition yielded different time spans for each variable. Whereas for hippocampal volume the mean time to decrease from the 75th to the 25th percentile was 13·0 years (95% CI 10·9–16·1), for cortical grey matter volume, the average time was 11·5 years (9·1–14·3). The average time to decline from the 75th to the 25th percentile was 22·2 years (13·8–28·0) for episodic memory scores and 10·4 years (8·5–14·4) for non-memory scores.

When we scaled every variable trajectory to a maximum value using the median for each variable associated with a CDR of 1, and aligned it along the ordinate axis using its respective thresholds between "normal" and "abnormal" levels, we noted a clear progression where Aβ deposition, hippocampal atrophy, and memory impairment became sequentially abnormal at 17·0 (95% CI 14·9–19·9), 4·2 (3·6–5·1), and 3·3 (2·5–4·5) years before the onset of dementia, respectively (figure 4), suggesting a protracted preclinical phase of AD.

When we compared these trajectories with the estimated trajectories derived from the cross-sectional data in mutation carriers from the Dominantly Inherited Alzheimer Network (DIAN),[16] we noted similar slopes and time spans for Aβ deposition in the posterior cingulate and memory decline, whereas the rate of hippocampal atrophy in our accumulator group was markedly faster than that reported for mutation carriers in DIAN (appendix).

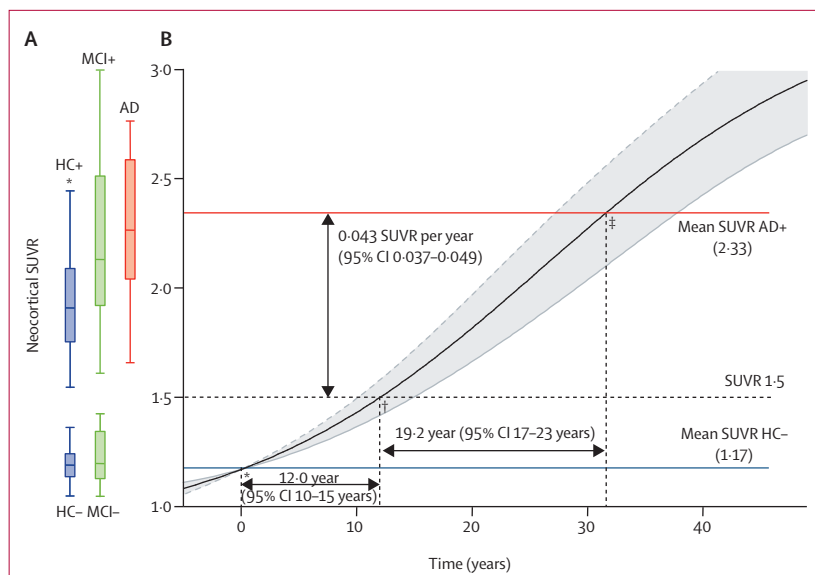By contrast with the reported relation between age and Aβ burden in healthy controls and individuals with

***Figure 3*: The natural history of Aβ deposition in sporadic Alzheimer's disease**
AD=Alzheimer's disease. MCI=mild cognitive impairment. ¹¹C-PiB=Carbon-11-labelled Pittsburgh compound B. SUVR=standardised uptake value ratio. Aβ=amyloid β. (A) While there were no significant differences in SUVR between participants with MCI and AD with high Aβ burden (2·31 [SD 0·43] for MCI+ and 2·33 [0·36] for AD+), the mean values for healthy controls with high ¹¹C-PiB retention (HC+) were significantly lower (1·98 [SD 0·24], *p=0·0002). (B) Aβ deposition follows sigmoidal kinetics over time, where it takes 12 years to go from a mean SUVR of 1·17 (SD 0·09) noted in healthy controls with low ¹¹C-PiB retention (HC–) to reach the 1·5 PiB SUVR threshold. It then takes another 19 years to go from the 1·5 SUVR to the mean SUVR of 2·33 (0·36) observed in established AD. As disease progresses, the rates of Aβ deposition start to slow, trending towards a plateau. The shaded area represents 95% CIs. The horizontal dashed line represents the SUVR threshold (>1·5 or < 1·5) discriminating between high or low ¹¹C-PiB retention. *Aβ accumulation begins. †Aβ positivity threshold is crossed. ‡Mean SUVR of established AD.

MCI,[11] we noted no age effects on the rate of Aβ deposition, or on the rates of hippocampal atrophy or memory decline in healthy controls and participants with MCI. Although in the AD group there was also no age effect on the rates of hippocampal atrophy or memory decline, we noted a positive association between age and the rates of Aβ deposition ($R^2=0.24$, p=0.034), an effect that persisted even after adjusting for sex, years of education, and *APOE* status ($R^2=0.31$, p=0.021).

The rates of change in episodic memory were inversely associated with the rates of Aβ deposition in healthy controls ($R^2=0.12$, p=0.005), individuals with MCI ($R^2=0.19$, p=0.03), and individuals with AD ($R^2=0.67$, p=0.01, figure 5A, C and D). When we examined the healthy controls on the basis of their Aβ accumulation status, we noted a significant association between rates of change of Aβ deposition and rates of episodic memory decline in healthy control accumulators ($R^2=0.12$, p=0.03), but the association was not present in non-accumulator healthy controls (data not shown).

Since both healthy controls and individuals with MCI who have high Aβ deposition are significantly more likely to progress to AD than those who have low Aβ deposition,[14] we examined whether the associations persisted when the groups were examined separately. Although the correlation between Aβ deposition and rates of episodic memory decline persisted when we examined the 38 healthy controls with high ^{11}C-PiB retention ($R^2=0.27$, p=0.011; figure 5B) and 18 patients with AD with high ^{11}C-PiB retention ($R^2=0.60$, p=0.016) separately, it did not persist in the 24 participants with MCI and high ^{11}C-PiB retention ($R^2=0.34$, p=0.55). We noted no associations of Aβ deposition and rates of episodic memory decline in either healthy controls with low ^{11}C-PiB retention or participants with MCI with low ^{11}C-PiB retention. When adjusting for baseline SUVR, correlations with rates of memory decline became non-significant in the healthy controls ($R^2=0.12$, p=0.07) and MCI groups ($R^2=0.27$, p=0.06). When adjusting for baseline hippocampal volume, the correlations with rates of memory decline disappeared in the AD group, but persisted in healthy controls ($R^2=0.12$, p=0.007) and MCI group ($R^2=0.25$, p=0.04). We did not find associations between the rates of Aβ deposition and the rates of non-memory cognitive decline in any group.

Only in the healthy control group was there a significant correlation between rates of episodic memory decline and rates of hippocampal atrophy ($R^2=0.09$, p=0.029), and a much stronger association was noted between rates of Aβ deposition and rates of hippocampal atrophy ($R^2=0.13$, p=0.0008). When accounting for rates of Aβ deposition, the association between hippocampal atrophy and memory decline in healthy controls disappeared ($R^2=0.12$, p=0.14). We did not note an association between rates of Aβ deposition and rates of cortical grey matter atrophy in any of the groups.
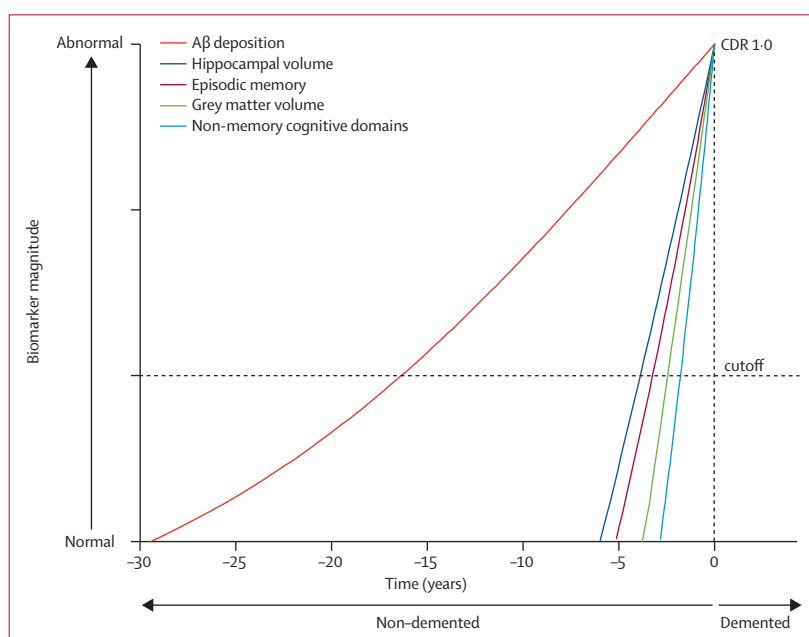

Figure 4: Sequence of parameter changes in accumulators
IQR (25th–75th percentile) curves were anchored using the median value of each variable corresponding to a CDR of 1 and using their respective cutoffs to establish the threshold between normal and abnormal values. The resulting graph shows that Aβ deposition (cutoff 1.5 SUVR)[8,10,13,14] is followed by hippocampal atrophy (cutoff 4.0 cm³) and then by episodic memory impairment (cutoff –1.5 SD), grey matter atrophy (cutoff 339 cm³), and finally non-memory cognitive domains (cutoff –1.5 SD). Whereas Aβ deposition was estimated to become abnormal around 17 years before the onset of dementia, memory impairment and hippocampal atrophy were estimated to become abnormal about 3–6 years before the onset of dementia. Aβ=amyloid β. CDR=clinical dementia rating. SUVR=standardised uptake value ratio.

Discussion

New proposed diagnostic criteria for AD incorporate the use of biomarkers,[27–30] which show either the underlying pathogenesis by assessing Aβ in the brain or CSF, or synaptic and neuronal damage as indicated in reduced glucose metabolism, grey matter atrophy, or tau in CSF. Intra-individual changes in Aβ deposition, brain atrophy, and cognitive decline provide a more accurate estimation of disease progression than inter-individual comparisons of groups. This approach is crucial in the assessment of cognitively unimpaired individuals (panel).[31]

According to our estimates, Aβ deposition increases slowly and continuously from levels found in healthy controls to those in patients with AD, and that these changes can be measured non-invasively with PET. Moreover, we confirmed that the rates of Aβ deposition seem to be slower at higher Aβ burdens[23] and at lower MMSE scores,[14] suggesting that Aβ deposition slows in the later stages of AD. For the construction of the curves of Aβ deposition over time, we excluded 37 of the 200 participants (33 healthy controls and four participants with MCI) who, during the observation period of 3 or more years, showed neither Aβ in the brain nor Aβ accumulation over time. Although inclusion of these participants would have prolonged the phase extending from the mean SUVR of healthy controls with low Aβ
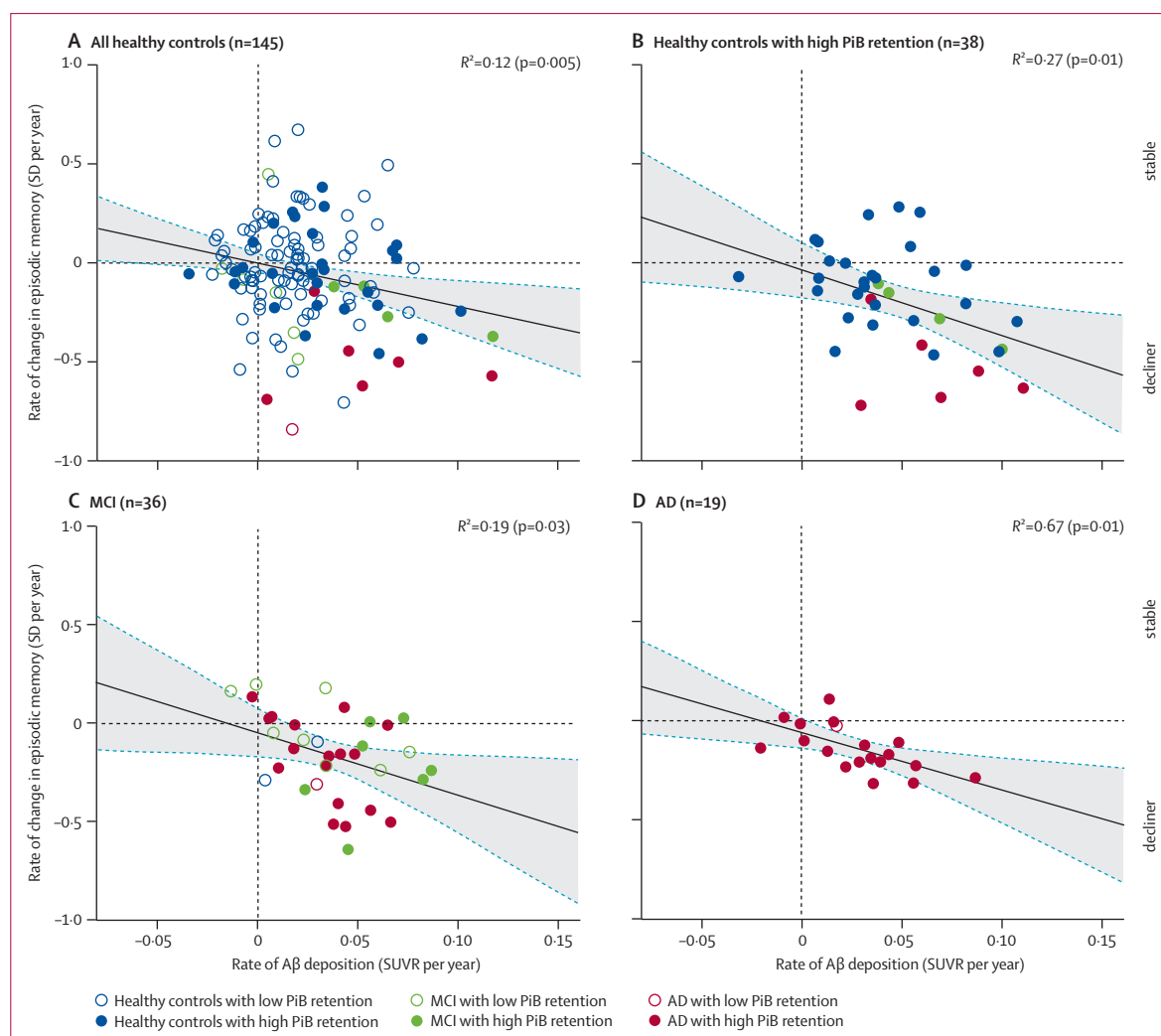
Figure 5: **Relation between rates of Aβ deposition and memory decline in healthy controls, participants with MCI, and participants with Alzheimer's disease**
(A) All healthy controls. (B) Healthy controls with ^{11}C-PiB retention. (C) Patients with MCI. (D) Patients with AD. There was a significant association between the rates of Aβ deposition and the rates of memory decline in all groups examined, including participants with low (open symbols) and high (solid symbols) Aβ burden. When examined separately in 38 healthy controls with high Aβ burden, faster Aβ deposition was significantly associated with a faster rate of memory decline. Faster Aβ deposition accumulation was also associated with disease progression with healthy controls progressing to either MCI (indicated in green) or to AD (indicated in red), or MCI subjects progressing to AD (indicated in red). Regression to classification as a healthy control by two participants in the MCI group are indicated in blue. Shaded area represents 95% CIs. The vertical dashed line represents the threshold for the rate of Aβ deposition (>0 or <0), discriminating accumulators from non-accumulators. The horizontal dashed line represents the threshold (>0 or <0) discriminating between "stable" from "decliners". AD=Alzheimer's disease. ^{11}C-PiB=carbon-11-labelled Pittsburgh Compound B. MCI=mild cognitive impairment. Aβ=amyloid β.

burden to the threshold of ^{11}C-PiB positivity, it would have had no effect on the part of the curve extending from the threshold of ^{11}C-PiB positivity to the ^{11}C-PiB retention degree observed in AD. Although the prevalence of accumulators in our sample population was higher than in our previous report,[23] the estimated trajectory of Aβ accumulation over time was slower. The rates reported here were derived not only from a longer follow-up of some of the same participants (18 months *vs* 36–45 months), but also from a minimum of three assessments per individual instead of only two. Longitudinal assessment of Aβ deposition is susceptible to both intra-individual and inter-individual variability.[14]

Therefore a single follow-up assessment might not be able to accurately determine the trajectory of Aβ deposition over time. Given the estimated slow rate of Aβ deposition, 3 or 5 years is still a short period, but multiple assessments allow a much better characterisation of the intra-individual change in Aβ burden over time.

Methodologically, we recognise that the evaluation of longitudinal PET data, especially in patients with AD, would benefit from partial volume corrected data to account for the progressive brain atrophy. That said, the merits and optimum partial volume corrected techniques, usually associated with the introduction of noise and an increased variance of the PET

measurements, are still being actively discussed. In this study, because we noted a smaller variance in the rates of Aβ deposition and a similar interval between the 11C-PiB positivity threshold and the levels in AD using partial volume corrected and non-partial volume corrected data (17·7 [95% CI 13·7–24·9] years for partial volume corrected and 19·2 [16·8–22·5] years for non-partial volume corrected; appendix), we used the more robust non-partial volume corrected SUVR data for all the assessments.

The increases in Aβ between the 1·5 SUVR threshold and the SUVR noted in AD behave in an almost linear way, with increases averaging 0·043 SUVR per year (roughly 3% per year), in agreement with previous reports.[14,23,34] Participants from the AIBL study are generally well educated, with more than half of them reporting 13 or more years of education.[19] Although in the present report groups did not significantly differ from one another in education, nor did APOE genotype significantly affect the rates of Aβ accumulation, further elucidation of the role that Aβ burden, genotype, and cognitive or brain reserve have in relation to the manifestation of AD phenotype is needed.

This study supports the idea that Aβ accumulation precedes by many years the substantial changes in brain volumetrics and cognition, which, added to the slow rate of Aβ accumulation, potentially affords a wide time window for intervention with anti-Aβ therapy. One of the benefits of establishing the rate of Aβ accumulation is that it might eventually provide a potential prognostic timeframe based on individual current Aβ burden. Furthermore, knowledge of the timeframes associated with Aβ deposition of the sequence of events leading to AD dementia is also relevant for the design of therapeutic trials, allowing investigators to establish critical periods suitable for intervention along the disease pathway, estimate the duration of a specific trial, or select biomarkers that are sensitive for specific outcomes.

There was an association between the rates of Aβ deposition and memory decline in the healthy control and MCI groups, and this association was even stronger in the healthy controls with high 11C-PiB retention, supporting the idea that Aβ deposition is neither part of normal ageing nor a benign process. Results from this study show, for what is to our knowledge the first time, an association between the rates of Aβ deposition and memory decline in patients with AD, in whom faster deposition was significantly associated with faster memory decline. Correlation does not imply causality, and this association might reflect two ongoing parallel independent processes that, as Aβ deposition slows and memory impairment reaches a so-called floor value, is likely to disappear. Whereas we did not note associations between rates of Aβ deposition and rates of cortical grey matter atrophy in any of the groups, we noted significant correlations between the rates of hippocampal atrophy,

memory decline, and Aβ deposition in the healthy control group. However, the association between hippocampal atrophy and memory decline disappeared when accounting for rates of Aβ deposition, suggesting that Aβ probably has a role in cognitive impairment at the very early stages of the disease.

A limitation of the present study is that we estimate a time response that is likely to extend decades on the basis of a relatively short longitudinal observation. As data from longer follow-up becomes available, they will need to be incorporated to reassess, revise, and refine the present estimates. The number of participants included in the assessments is larger than in previous reports, but is somewhat small, especially in the AD group, warranting validation in an independent large cohort such as from Alzheimer's Disease Neuroimaging Initiative (ADNI)[35] and by use of other Aβ radiotracers. Some criticism might also be raised with regard to bias

---

Panel: Research in context

Systematic review

We searched Medline via PubMed for "amyloid imaging" AND "Alzheimer", for "amyloid imaging" AND "dementia", and for "amyloid imaging" AND "Aβ cascade", and for "amyloid imaging" AND "Aβ deposition", and for "Aβ deposition" AND "Alzheimer", up to Dec 6, 2012. Systematic review of the scientific literature showed that in vivo amyloid β (Aβ) imaging has transformed the assessment of Aβ pathology and its changes over time. It has extended our insight into Aβ deposition in the brain by providing highly accurate, reliable, and reproducible quantitative statements of regional or global Aβ burden in the brain, essential for therapeutic trial recruitment and for the assessment of anti-Aβ treatments.[32] A rational approach to clinical and therapeutic strategies aimed at Aβ requires an in-depth knowledge of the underlying pathological process.[33] Even before the introduction of Aβ imaging, several hypothetical models had been postulated about the natural history of Aβ deposition and the sequence of events leading to Alzheimer's dementia in relation to other variables such as neurodegeneration and cognition.[5,6] However, no model has been constructed on the basis of longitudinal assessments of Aβ deposition in the brain for 3 or more years in a large cohort.

Interpretation

Predicting the rate of evolution of preclinical changes and the onset of the clinical phase of AD might prove essential for the design and timing of disease-modifying therapeutic interventions.[33] Applying a multidisciplinary approach including Aβ and structural imaging, as well as cognitive assessment and APOE genotyping, we have constructed a model of the natural history of Aβ deposition and the sequence of changes in brain structure and cognition leading to Alzheimer's dementia. According to our estimates, Aβ deposition is a slow process that extends for more than two decades. These results are in agreement with the postulated protracted changes in Aβ deposition.[14] We also found that faster Aβ deposition was significantly associated with faster memory decline and disease progression but the rate of Aβ deposition did not differ between APOE ε4 carriers and non-carriers. These results are in accord with the presumed lack of effect of APOE on the rates of Aβ deposition.[33] Whereas Aβ levels in the brain reached an SUVR of 1·5, a level we classed as abnormal, more than 15 years before the onset of dementia, hippocampal and cortical volumes and cognitive performance sequentially decline and rapidly progress about 5–7 years before the onset of dementia, indicating that the preclinical phase of AD is roughly 10–15 years, suggesting a wide window for altering Aβ accumulation. These findings are concordant with the postulated sequence of dynamic changes in biomarkers.[6]

because analyses were restricted to individuals with three or more assessments; however, individuals with fewer than three assessments were not more severely affected than those with more assessments (appendix). There is also a chance of spurious correlations derived from analysing subgroups. These correlations were undertaken to dissect the relation between the different aspects of Aβ deposition in the presence or absence of Aβ accumulation, and how a high or low Aβ burden is related to other variables. The time between Aβ deposition and neurodegenerative or cognitive variables also requires caution: cognitive reserve, cardiovacular or cerebrovascular factors, and concurrent diseases might contribute to inter-individual variations in these intervals (figure 4).

When we compared the projected data from DIAN[16] with our longitudinal sporadic AD results, the rates of Aβ deposition showed a striking similarity, suggesting that similar basic mechanisms are at play irrespective of putative dissimilar pathogenic pathways (overproduction of Aβ in autosomal dominant AD compared with a failure of clearance of Aβ in sporadic AD). The rates of hippocampal atrophy seemed to be greatly slower in the projections from the DIAN study.[16] Whether technical differences in data acquisition or analysis account for some of the discrepancy is yet to be explored.

Early detection of the AD process is crucial for early therapeutic interventions to delay the onset of the clinical symptoms or slow the cognitive decline. Combining our approach with data emerging from those of other investigators, we might soon be able to predict the time it will take for an individual with a given Aβ burden to reach the levels usually noted in AD. Understanding the natural history and rates of change of clinical phenotypes and biomarkers will facilitate appropriate specific interventions. The slow rate of Aβ deposition indicates a wide time window for altering Aβ accumulation and supports the growing consensus that, to be effective, anti-Aβ therapy might need to be given early in the disease course, most likely at the presymptomatic stages, to successfully prevent the development of AD.[3,33]

References
1   Blennow K, Zetterberg H, Rinne JO, et al, and the AAB-001201/202 Investigators. Effect of immunotherapy with bapineuzumab on cerebrospinal fluid biomarker levels in patients with mild to moderate Alzheimer disease. *Arch Neurol* 2012; **69:** 1002–10.
2   Uenaka K, Nakano M, Willis BA, et al. Comparison of pharmacokinetics, pharmacodynamics, safety, and tolerability of the amyloid β monoclonal antibody solanezumab in Japanese and white patients with mild to moderate alzheimer disease. *Clin Neuropharmacol* 2012; **35:** 25–29.
3   Sperling RA, Jack CR Jr, Aisen PS. Testing the right target and right drug at the right stage. *Sci Transl Med* 2011; **3** (111): 111cm33.
4   Jack CR Jr, Knopman DS, Weigand SD, et al. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Ann Neurol* 2012; **71:** 765–75.
5   Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010; **9:** 119–28.
6   Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013; **12:** 207–16.
7   Price JL, McKeel DW Jr, Buckles VD, et al. Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. *Neurobiol Aging* 2009; **30:** 1026–36.
8   Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol* 1999; **45:** 358–68.
9   Aizenstein HJ, Nebes RD, Saxton JA, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch Neurol* 2008; **65:** 1509–17.
10   Mintun MA, Larossa GN, Sheline YI, et al. [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology* 2006; **67:** 446–52.
11   Rowe CC, Ellis KA, Rimajova M, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging* 2010; **31:** 1275–83.
12   Chételat G, Villemagne VL, Villain N, et al, and the AIBL Research Group. Accelerated cortical atrophy in cognitively normal elderly with high β-amyloid deposition. *Neurology* 2012; **78:** 477–84.
13   Lim YY, Pietrzak RH, Ellis KA, et al. Rapid Decline in Episodic Memory in Healthy Older Adults with High Amyloid-beta. *J Alzheimers Dis* 2012; DOI:10.3233/JAD-2012-121516.
14   Villemagne VL, Pike KE, Chételat G, et al. Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease. *Ann Neurol* 2011; **69:** 181–92.
15   Vlassenko AG, Mintun MA, Xiong C, et al. Amyloid-beta plaque growth in cognitively normal adults: longitudinal [11C]Pittsburgh compound B data. *Ann Neurol* 2011; **70:** 857–61.
16   Bateman RJ, Xiong C, Benzinger TL, et al, and the Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 2012; **367:** 795–804.
17   Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999; **56:** 303–08.
18   McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; **34:** 939–44.
19   Ellis KA, Bush AI, Darby D, et al, and the AIBL Research Group. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. *Int Psychogeriatr* 2009; **21:** 672–87.
20   Pike KE, Savage G, Villemagne VL, et al. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain* 2007; **130:** 2837–44.
21   Greiner M, Sohr D, Göbel P. A modified ROC analysis for the selection of cut-off values and the definition of intermediate results of serodiagnostic tests. *J Immunol Methods* 1995; **185:** 123–32.

22   Bourgeat P, Chételat G, Villemagne VL, et al, and the AIBL Research Group. Beta-amyloid burden in the temporal neocortex is related to hippocampal atrophy in elderly subjects without dementia. *Neurology* 2010; **74:** 121–27.

23   Villain N, Chételat G, Grassiot B, et al, and the AIBL Research Group. Regional dynamics of amyloid-β deposition in healthy elderly, mild cognitive impairment and Alzheimer's disease: a voxelwise PiB-PET longitudinal study. *Brain* 2012; **135:** 2126–39.

24   Jack CR Jr, Wiste HJ, Vemuri P, et al, and the Alzheimer's Disease Neuroimaging Initiative. Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. *Brain* 2010; **133:** 3336–48.

25   Akaike H. Information theory and an extension of the maximum likelihood principle. In: Petrov BN, Csaki F, editors. Second International Symposium on Information Theory; 1973; Budapest: Akademiai Kiado; 1973: 267–81.

26   Jicha GA, Parisi JE, Dickson DW, et al. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol* 2006; **63:** 674–81.

27   Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 2010; **9:** 1118–27.

28   Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7:** 270–79.

29   McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7:** 263–69.

30   Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7:** 280–92.

31   Tractenberg RE, Pietrzak RH. Intra-individual variability in Alzheimer's disease and cognitive aging: definitions, context, and effect sizes. *PLoS ONE* 2011; **6:** e16973.

32   Rowe CC, Villemagne VL. Brain amyloid imaging. *J Nucl Med* 2011; **52:** 1733–40.

33   Karran E, Mercken M, De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov* 2011; **10:** 698–712.

34   Rinne JO, Brooks DJ, Rossor MN, et al. 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. *Lancet Neurol* 2010; **9:** 363–72.

35   Mueller SG, Weiner MW, Thal LJ, et al. The Alzheimer's disease neuroimaging initiative. *Neuroimaging Clin N Am* 2005, **15:** 869–77, xi-xii.