Amyloid, neurodegeneration, and small vessel disease as predictors of dementia in the oldest-old

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ABSTRACT

Objective: To examine the association between brain structural changes and β -amyloid deposition, and incident dementia in 183 elderly subjects without dementia (mean age 85.5 years) 2 years later.

Methods: Subjects had a brain structural MRI scan and a PET scan with ^{11}C -labeled Pittsburgh compound B (PiB) in 2009, and were evaluated clinically in 2011.

Results: At baseline evaluation, of the 183 participants (146 cognitively normal [CN]); 37 mild cognitive impairment [MCI]), 139 (76%) were PiB+, had small hippocampal volume (<25th percentile), or had high white matter lesion (WML) volume (>75th percentile). Two years later, 111 (61%) were classified as CN, 51 (28%) as MCI, and 21 (11%) as dementia. At baseline, 51% of the CN participants and 67.5% of the MCI cases were PiB+. Thirty percent of the CN and 51% of the MCI cases had small hippocampi, and 24% of the CN and 40.5% of the MCI cases had abnormal WMLs. Of the 21 participants who progressed to dementia, 20 (95%) had at least one imaging abnormality. Only 3 (14%) were only PiB+, 1 (5%) had only small hippocampi, 1 (5%) had only WMLs, 1 (5%) was biomarker negative, and the other 16 had various pairs of imaging abnormalities. Continuous variables of PiB retention, left and right hippocampal volume, and WML volume were independent predictors of dementia in a logistic regression analysis controlling for age, sex, education level, and Mini-Mental State Examination scores.

Conclusions: The prevalence of β -amyloid deposition, neurodegeneration (i.e., hippocampal atrophy), and small vessel disease (WMLs) is high in CN older individuals and in MCI. A combination of 2 or 3 of these factors is a powerful predictor of short-term incidence of dementia. *Neurology*® 2014;83:1804-1811

GLOSSARY

A β = β -amyloid; **AD** = Alzheimer disease; **CI** = confidence interval; **CN** = cognitively normal; **FMRIB** = Oxford Centre for Functional Magnetic Resonance Imaging of the Brain; **GEM** = Ginkgo Evaluation of Memory; **ICV** = intracranial volume; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **PiB** = Pittsburgh compound B; **ROI** = region of interest; **RR** = relative risk; **SUVr** = standardized uptake value ratio; **WML** = white matter lesion.

Studies of cognition and neurodegeneration in the oldest-old are important because these individuals are at the highest risk of developing dementia, especially Alzheimer disease (AD).¹ Furthermore, the neurodegenerative process that causes AD begins years before the clinical expression of the syndrome.²⁻⁴ The proportion of subjects without dementia who have amyloid deposition detected in vivo is approximately 20% to 30%,⁴ with rates up to 65% in those aged 80 years or older.^{4,5}

Amyloid deposition detected with Pittsburgh compound B (PiB) is associated with the development of AD from mild cognitive impairment (MCI),^{6,7} and to MCI or AD from normal cognition.⁸ Similarly, low hippocampal volume, as a marker of neurodegeneration, is associated with progression to AD in cognitively normal (CN) subjects and in those with MCI.⁹ It has been hypothesized that AD pathology starts with amyloid deposition, followed by neuronal loss closer

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to the onset of the clinical symptoms.¹⁰ However, CN subjects can have neurodegeneration without amyloid deposition,^{11,12} and 48% of normal subjects who progressed from normal to MCI or dementia had low PiB retention levels.¹³ Furthermore, white matter lesions (WMLs), as markers of small vessel disease, are also risk factors for MCI¹⁴ and incident dementia.¹⁵ WMLs, but not smaller hippocampal volume, may predict incident AD,¹⁶ and cross-sectional studies found that neurodegeneration is associated with WMLs^{12,17} but not amyloid deposition.¹² Thus, the sequence of pathologic events in the transition from normal cognition to dementia is complex; some individuals may progress to AD with asynchronous patterns of amyloidosis and neurodegeneration, with or without small vessel disease. The present study examined the relationship between PiB retention, hippocampal volume, and WMLs and progression to MCI or dementia in a group of individuals without dementia aged 85 years or older who participated in the Ginkgo Evaluation of Memory (GEM) Study.

METHODS Population. The GEM Study was a multisite, placebo-controlled, double-blind, randomized clinical trial of daily use of *Ginkgo biloba* in 3,069 community-dwelling participants aged 72 to 96 years.¹⁸ In 2009, approximately 10 (± 3) months after the GEM Study drug closeout visit, 194 participants without dementia from the Pittsburgh site underwent MRI and PiB-PET imaging.⁵ In 2011, the participants were invited to return for a second neuroimaging study and clinical evaluation. The present analysis was conducted in 183 subjects who provided both PiB and MRI data. Eleven participants were excluded because of technical limitations with the PiB ($n = 3$) or MRI ($n = 8$) scans.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the institutional review board, and all participants completed the informed consent process before any study procedures.

PET imaging of brain β -amyloid deposition. PiB-PET data acquisition has been described previously,⁵ but involved 20 minutes' acquisition (4×5 minute frames) beginning 50 minutes after injection of 15 ± 1.5 mCi of PiB on a Siemens/CTI ECAT HR+ scanner in 3-dimensional imaging mode equipped with a Neuro-Insert. The data were reconstructed using filtered back projection (Fourier rebinning and 2-dimensional back-projection with Hann filter kernel full width at half maximum = 3 mm). Emission data were corrected for dead-timer photon attenuation, scatter, and radioactive decay. The final reconstructed PET image resolution was approximately 6 mm (transverse and axial). An iterative mild outlier cutoff method defined subjects as β -amyloid (A β)-positive if the atrophy-corrected composite standardized uptake value ratio (SUVR) of 5 regions was >1.57 .¹⁹ A continuous variable was the mean PiB value in these 5 regions bilaterally.⁵

MRI. MRI scanning was performed using a GE Signa 1.5 T scanner (GE Healthcare, Waukesha, WI) and a standard head coil,²⁰ including fluid-attenuated inversion recovery (echo time = 172 milliseconds (ms), repetition time = 9,004 ms) and spoiled echo gradient (echo time = 5 ms, repetition time = 25 ms) images. Brain tissue volumes (gray matter, white matter, and CSF) were calculated by segmenting the skull-stripped T1-weighted image in native anatomical space using the FMRIB's Automated Segmentation Tool. Total intracranial volume (ICV) was computed as the volume contained within the "inner skull" using the Brain Extraction Tool with an advanced option (–A). Hippocampal volumes were calculated using the automated labeling pathway, an atlas-based segmentation technique using a fully deformable registration approach to measure predefined regions of interest (ROIs),²¹ and anatomical ROIs were from the automated anatomical labeling atlas.²² Hippocampal ROIs were defined on the reference brain (Montreal Neurological Institute colin27) and transformed to fit each individual's anatomical image. Here, we present the hippocampal volumes as the proportion of the ICV. A participant was considered to have small hippocampi when either the right or left hippocampus was ≤ 25 th percentile of that of the normal participants. A fuzzy-connectedness algorithm was used to segment the WMLs from each individual's T2-weighted fluid-attenuated inversion recovery images.²³ The volume of WMLs is presented as the proportion of the ICV, and those volumes ≥ 75 th percentile of the normal participants were considered abnormal. These classifications were done before the data analysis.

Clinical assessments. All participants underwent a neuropsychological evaluation in 2009 that included Mini-Mental State Examination (MMSE)²⁴ and a detailed neuropsychological battery.²⁵ Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale,²⁶ and we obtained an inventory of the participant's prescription and over-the-counter medications before imaging of the brain.

Cognitive status. In 2011, the cognitive diagnosis was determined by consensus among a neurologist, a psychiatrist, and a neuropsychologist, who were blinded to the 2009 neuroimaging results, but who had available all clinical information from 2000 to 2011. The diagnosis of dementia was based on a deficit in test performance in 2 or more cognitive domains of sufficient severity to affect activities of daily living, with normal intellectual function before the onset of cognitive abnormalities.²⁷ After the clinicians agreed that the participant met criteria for dementia, they used a set of multiple diagnostic criteria (e.g., National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for AD) to determine the etiology of the syndrome. Criteria for MCI included 1 to 3 tests impaired at cutoffs of 1.5 SDs below age- and education-adjusted means. Participants with MCI were classified according to 4 MCI cognitive subtypes,²⁸ although we grouped them as a single group for the present study.

Although there were participants who did not return for follow-up evaluation, we made significant efforts to obtain information in all cases. Of the 183 participants, 159 had complete neurologic and cognitive evaluations in 2011, and 24 could not be evaluated at the clinic: 5 died, 10 were interviewed by phone using the Telephone Interview for Cognitive Status,²⁹ and 9 did not want to have repeat cognitive testing (see table e-1 on the *Neurology*[®] Web site at Neurology.org). The clinicians obtained a narrative of the participants' cognitive status, activities of daily living, and medical conditions (including diagnoses of AD from family physicians) from the proxies in all study participants. Of

the 8 subjects we excluded because of technical problems with the MRI, 2 were classified as dementia, one with AD, and the other with Parkinson disease with dementia/Lewy body dementia.

Statistical analysis. Contingency tables were analyzed with χ^2 , t test, and analysis of variance methods. A nonparametric version of analysis of variance was used for all comparisons involving continuous outcomes. We used exact methods to compute the significance levels of all tests when the sample size in a group fell below 20, and for the contingency tables based on the likelihood ratio test. Dichotomous variables were used to examine the co-occurrence of the 3 pathologic markers. A logistic regression analysis controlling for age, MMSE, sex, and education level was used to examine the association between incident dementia and the 3 pathologic markers as continuous variables. All models were assessed for potential outliers/influential observations. When modeling the composite mean of the hippocampal volume, we multiplied the hippocampal volume measures by 100 when reporting the odds ratios in the table. Note that this has no impact on the significance level; however, the odds ratios are larger as a result.

RESULTS The participants who progressed to dementia were older and had lower MMSE scores compared with those who remained CN or MCI (table 1). The changes in diagnosis from 2009 to 2011 are presented in table 2. There were 21 incident dementia cases from 2009 to 2011, and more MCI ($n = 12$ [32%]) than CN ($n = 9$ [6%]) participants progressed to dementia ($\chi^2 = 50.6$, $df 1$, $p < 0.001$; relative risk [RR] 5.70, 95% confidence interval [CI] 2.16–145.2). Sixteen subjects developed probable or possible AD, and 5 were classified simply as dementia because they did not have a full clinical evaluation at the clinic. However, the medical information provided by the family indicated a progressive AD-dementia syndrome; 2 were classified as PiB+ with hippocampal atrophy (one of them had WMLs), 2 were PiB+ with hippocampal atrophy, and 1 had hippocampal atrophy with WMLs.

Fifty-six percent of participants (100/183) had A β deposition in the brain, and over the follow-up period, half of those individuals remained CN; 6

PiB– subjects progressed to AD. Of the 100 participants who were PiB+ in 2009, 15% developed dementia, and 30% were classified as MCI and 55% as CN (see table 3). Of the 83 PiB– participants, 7% developed dementia, and 25% were classified as MCI and 67.5% as CN. The percent converting to dementia did not differ significantly ($\chi^2 = 3.90$, $df 2$, $p = 0.14$; RR 2.26, 95% CI 0.83–6.10) as a function of PiB positivity. More participants with hippocampal atrophy progressed to dementia than those with normal volumes (21% vs 7%) ($\chi^2 = 12.9$, $df 2$, $p = 0.002$; RR 3.64, 95% CI 1.46–9.33). There were more participants with WMLs ≥ 75 th percentile volume progressing to dementia ($\chi^2 = 11.7$, $df 2$, $p = 0.004$; RR 3.41, 95% CI 1.26–9.18) than those with low WMLs volume.

We examined the co-occurrence of abnormal biomarkers in 2009 as a function of clinical outcome in 2011 (table 4). Seventy-six percent of all 183 participants, and 95% of those who converted to dementia had some pathology relative to the preestablished cut-offs. Of the 21 participants who converted to dementia, 4 had 3 abnormal biomarkers, 9 had 2, 7 had 2, and 1 had no abnormal biomarkers. Among the participants who were CN in 2009 and developed dementia in 2011 ($n = 9$), 3 had all 3 biomarkers. Among those who had MCI and developed dementia, only 1 had the 3 biomarkers, 6 had 2, and 5 had only 1.

We examined the relationship between these dichotomous indicators of the biomarkers and incident dementia among the 107 CN participants who remain normal, and the 21 who developed dementia. We found that after adjusting for age, sex, education, and MMSE score, low hippocampal volume increased risk more than 5-fold, and abnormal WMLs increased risk almost 3 times (see models 1 and 2 in table 5). The dichotomous measure of amyloid deposition was not significantly associated with incident dementia over this 2-year period. The analysis of the factors associated with conversion to dementia separately in CN and MCI subjects was precluded because of the small number of cases in each group.

We then used the continuous measures of each of the 3 biomarkers in order to examine the relationship and extent of abnormality and incident cognitive impairment (table 3). The amount of PiB retention (mean SUVR) was greater in those participants who developed dementia than in those who remained CN ($F_{2,182} = 4.08$, $p = 0.01$) (see figure e-1 and table e-2). The mean right and left hippocampal volume was different among CN, MCI, and dementia subjects ($F_{2,183} = 10.1$, $p < 0.001$) (see figure e-2). The mean WML volume was greater among those who progressed to dementia and MCI compared with those who remained normal ($F_{2,183} = 7.47$, $p = 0.001$) (see figure e-3).

Table 1 Characteristics of the participants in 2009 by clinical diagnosis in 2011

	CN	MCI	Dementia	p Value
No. of participants	111	51	21	
Age, y	85.0 $\pm$ 2.6	86.1 $\pm$ 3.1	86.8 $\pm$ 3.0	0.009
Sex, women	62 (56)	34 (67)	11 (52)	0.36
Education level, y	14.9 $\pm$ 2.7	14.0 $\pm$ 2.4	15.0 $\pm$ 2.4	0.09
Race, white	109 (98)	47 (92)	21 (100)	0.09
MMSE score	28.3 $\pm$ 1.6	26.6 $\pm$ 2.2	26.2 $\pm$ 2.2	<0.001
APOE ϵ 4 ($n = 168$)	20 (19)	9 (19)	5 (28)	0.75

Abbreviations: CN = cognitively normal; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination.
Data are n (%) or mean $\pm$ SD.

Table 2 Diagnosis change from 2009 to 2011

	Diagnoses in 2009 ^a	Diagnoses in 2011 ^b		
	Total	CN	MCI	Dementia
Normal	146 (80)	107 (73)	30 (21)	9 (6)
MCI	37 (20)	4 (11)	21 (57)	12 (32) ^c
Total	183	111 (60)	51 (28)	21 (12)

Abbreviations: CN = cognitively normal; MCI = mild cognitive impairment.

Data are n (%).

^aPercent of columns.

^bPercent of rows.

^c $p < 0.001$.

Amyloid deposition did not correlate with hippocampal volume ($\rho = -1.25$, $p = 0.09$) or WMLs ($\rho = -0.06$, $p = 0.93$). There was no correlation between hippocampal volume and WMLs ($\rho = -0.003$, $p = 0.97$).

We examined factors associated with progression to dementia in 107 CN participants who remained normal through to 2011 and in 21 incident dementia cases using these continuous measures (see model 3 in table 5). We found that a greater extent of amyloid deposition, low hippocampi volumes, and of WML volumes increased risk of incident dementia approximately 3-fold. Of note, these findings were not driven by the MCI group. Of the 21 participants (9 CN and 12 with MCI) who progressed to dementia in 2011, 67% of the CN (6/9) and 75% of those with MCI (9/12) were PiB+; 78% of the CN (7/9) and 50% of those with MCI (6/12) had atrophic hippocampi; and 44% of the CN (4/9) and 42% of those with MCI (5/12) had abnormal WMLs. None of these differences were statistically significant.

DISCUSSION A β deposition (amyloidosis), hippocampal atrophy (neurodegeneration), and WMLs (small vessel disease) are common in this age group. Measures of hippocampal volume, extent of A β deposition, and WMLs alone or in combination were all necessary for prediction of dementia or AD. The risk of dementia was a function of a combination of the variables because only 1 (5%) of the 21 participants with incident dementia did not have abnormal A β deposition, hippocampal volume, or WMLs compared with 4 (33%) with all 3 abnormalities. However, only 3 participants (6.5%) with PiB positivity alone developed dementia.

A β deposition and brain atrophy are common in CN subjects and subjects with MCI in this age group.^{4,30} Approximately 55% of this group of subjects without dementia were PiB+ at baseline, including 40% of those who remained CN, which may explain the weaker prediction of dementia when a dichotomized measure of amyloid deposition was used. Furthermore, there was a wide range of A β deposition in individuals who remained CN at

follow-up (SUVr range 0.80–2.85) and in those who progressed to dementia (SUVr range 1.24–2.82). Thus, some of the CN subjects who remained normal had SUVrs as high as those of participants who developed dementia. Similar variability was observed in the participants with MCI (SUVr range 1.16–2.90). Therefore, PiB retention as a continuous variable across ROIs in the brain is probably a better measure than categorical cutpoints for predicting dementia.

Hippocampal volume, as a marker of neurodegeneration, is a well-known predictor of conversion to dementia in elderly subjects,⁹ and we also found that hippocampal atrophy was associated with conversion to dementia. However, there are individuals with small hippocampi who remained CN and subjects with relatively normal hippocampal volumes who progressed to dementia. Other studies also support this mismatch in the timing of detection of amyloid deposition and measures of neurodegeneration. Twenty-nine percent of the MCI cases from the Mayo Clinic Aging Study and 17% from the Alzheimer's Disease Neuroimaging Initiative had neurodegeneration (by MRI or [¹⁸F]-fluorodeoxyglucose-PET) without amyloid deposition,³¹ and 42% of the Mayo Clinic Aging Study subjects who became amyloid-positive at follow-up had evidence of neurodegeneration before showing amyloid positivity.³²

WMLs, as markers of small vessel disease, are independent predictors of dementia.¹⁵ Some studies found that WMLs were better predictors of dementia than hippocampal volume,¹⁶ and others showed that WMLs were associated with increased A β deposition in subjects with AD.³³ Cross-sectional studies have shown WMLs were associated with markers of neurodegeneration, but not with A β deposition,^{12,34} while other studies reported an association between severity of WMLs and low CSF A β -42 levels only in *APOE* ϵ 4 carriers.³⁵ We found that WMLs are predictors of incident AD, but (as with PiB retention and neurodegeneration) there were individuals without WMLs who progressed to dementia, and others with severe WMLs who remained CN.

We do not have follow-up neuroimaging studies in the incident AD subjects that would allow us to examine the CNS structural changes over time. It is possible that those subjects who progressed to AD with low baseline levels of amyloid deposition or with hippocampal volume above the established cutpoint had increased amyloid accumulation or decreased hippocampal volume over the 2 years of follow-up. The amyloid deposition process appears to continue after the clinical dementia syndrome is manifested,³⁶ even up to moderate stages of AD. A study conducted in mainly *APOE* ϵ 4 allele carriers showed that there was no change over time in A β deposition in converters and nonconverters to AD. However, hippocampal atrophy was worse in converters than in nonconverters, and increased significantly in

Table 3 Clinical diagnoses in 2011 by PiB status and hippocampal volume in 2009

Diagnoses in 2009		Diagnoses in 2011			p Value
	Total cases (n = 183)	CN (n = 111)	MCI (n = 51)	Dementia (n= 21)	
PiB status					
All cases					0.14
PiB+	100	55 (55)	30 (30)	15 (15)	
PiB–	83	56 (67.5)	21 (25)	6 (7)	
SUVR of 5 regions		1.71 ± 0.46	1.81 ± 0.49	2.02 ± 0.51	0.01 ^a
Normal subjects					
PiB+	75	52 (69)	17 (23)	6 (8)	
PiB–	71	55 (77.5)	13 (18)	3 (4)	
SUVR of 5 regions		1.70 ± 0.46	1.80 ± 0.48	1.90 ± 0.48	0.35
MCI					
PiB+	25	3 (12)	13 (52)	9 (36)	
PiB–	12	1 (8)	8 (67)	3 (25)	
SUVR of 5 regions		1.83 ± 0.36	1.83 ± 0.49	2.12 ± 0.53	0.33
Hippocampal volume ^b					
All cases					0.002 ^c
Abnormal	63	28 (44)	22 (35)	13 (21)	
Normal	120	83 (69)	29 (24)	8 (7)	
Hippocampal volume ^d		0.26 ± 0.32	0.25 ± 0.03	0.23 ± 0.02	<0.001 ^e
Normal subjects					
Abnormal	44	26 (59)	11 (25)	7 (16)	
Normal	102	81 (79)	19 (19)	2 (2)	
Hippocampal volume ^d		0.26 ± 0.03	0.25 ± 0.03	0.23 ± 0.02	0.006 ^a
MCI					
Abnormal	19	2 (11)	11 (58)	6 (32)	
Normal	18	2 (11)	10 (56)	6 (33)	
Hippocampal volume ^d		0.23 ± 0.33	0.24 ± 0.02	0.23 ± 0.03	0.70
White matter lesions ^f					
All cases					0.004 ^g
Abnormal	49	20 (41)	20 (41)	9 (18)	
Normal	134	91 (68)	31 (23)	12 (9)	
Mean white matter lesions		0.00786	0.01039	0.01241	0.001 ^a
Normal subjects					
Abnormal	34	19 (56)	11 (32)	4 (12)	
Normal	112	88 (78.5)	19 (17)	5 (4.5)	
Mean white matter lesions		0.00786	0.00998	0.01125	0.04 ^g
MCI					
Abnormal	22	1 (7)	9 (60)	5 (33)	
Normal	15	3 (14)	12 (54.5)	7 (32)	
Mean white matter lesions		0.00789	0.01097	0.01328	0.39

Abbreviations: CN = cognitively normal; MCI = mild cognitive impairment; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio. Data are n (%) or mean ± SD. PiB+: mean SUVR of 5 regions ≥1.57.

^aCN different from dementia.

^bAbnormal hippocampus: right or left hippocampal volume ≤25th percentile.

^cMore dementia cases with hippocampal volume ≤25th percentile.

^dAnalysis of variance: mean right and left hippocampal volume and white matter volume adjusted for intracranial volume.

^eMCI and dementia different from CN.

^fAbnormal white matter lesions: lesion volume ≥75th percentile.

^gDementia different from the other 2 groups.

Table 4 Clinical diagnoses in 2011 by combination of biomarkers (PiB status, hippocampal volume, and WMLs) in 2009

Diagnoses and PiB and MRI in 2009		Diagnoses in 2011 ^a			p Value
	Total cases	CN	MCI	Dementia	
All cases					0.001
No abnormalities	44	32 (73)	11 (25)	1 (2)	
Only PiB+	46	38 (83)	5 (11)	3 (6.5)	
Only abnormal HIP	19	12 (63)	4 (21)	3 (18)	
Only WMLs	13	8 (61.5)	4 (31)	1 (8)	
PiB+ and abnormal HIP	26	10 (38.5)	11 (42)	5 (19)	
Abnormal HIP and WMLs	6	3 (50)	2 (33)	1 (18)	
PiB+ and WMLs	17	6 (35)	8 (47)	3 (16)	
PiB+, abnormal HIP, and WMLs	12	2 (17)	6 (50)	4 (33)	
Normal subjects					<0.01
No abnormalities	41	32 (78)	8 (19.5)	1 (2)	
Only PiB+	40	36 (90)	3 (7.5)	1 (2.5)	
Only abnormal HIP	16	12 (75)	3 (19)	1 (6)	
Only WMLs	9	8 (89)	1 (11)	0 (0)	
Abnormal HIP and WMLs	4	2 (50)	1 (25)	1 (25)	
PiB+ and abnormal HIP	16	9 (56)	5 (31)	2 (12.5)	
PiB+ and WMLs	13	6 (46)	7 (54)	0 (0)	
PiB+, abnormal HIP, and WMLs	7	2 (29)	2 (29)	3 (43)	
MCI					0.29
No abnormalities	3	0 (0)	3 (100)	0 (0)	
Only PiB+	6	2 (33)	2 (33)	2 (33)	
Only abnormal HIP	3	0 (0)	1 (33)	2 (67)	
Only WMLs	4	0 (0)	3 (75)	1 (25)	
Abnormal HIP and WMLs	2	1 (50)	1 (50)	0 (0)	
PiB+ and abnormal HIP	10	1 (10)	6 (60)	3 (30)	
PiB+ and WMLs	4	0 (0)	1 (25)	3 (75)	
PiB+, abnormal HIP, and WMLs	5	0 (0)	4 (80)	1 (20)	

Abbreviations: CN = cognitively normal; HIP = hippocampal volume; MCI = mild cognitive impairment; PiB = Pittsburgh compound B; WML = white matter lesion.

Data are n (%). PiB+: mean standardized uptake value ratio of 5 regions ≥ 1.57 . HIP: mean right and left hippocampal volume (abnormal ≤ 25 th percentile). WMLs: WML volume ≥ 75 th percentile.

^a Row percentages.

both groups,³⁷ suggesting that a dissociation between neurodegeneration and amyloidosis can occur.

Some study participants had levels of the biomarkers within our range of normal values; this means that in some cases in this age group, progression to AD does not need significant amounts of pathology. Neuropathologic studies also found that although dementia was associated with neurofibrillary tangles and neuritic plaques in individuals older than 90 years,³⁸ some of these patients had less severe pathology than those aged 75 years,³⁹ and no clear thresholds of AD or vascular pathology were associated with clinical dementia.⁴⁰

The prevalence of these 3 pathologies is high in the oldest-old and contributes to the high incidence of

dementia and disability. Indeed, 76% were “positive” for at least one of these biomarkers, and 66% of the CN participants were either PiB+ or had hippocampal atrophy. However, there is a wide range of pathology severity, and subjects considered to be “negative” for a specific biomarker can still carry pathology, which could be of sufficient severity to cause a clinical syndrome. However, there are many subjects “positive” for AD pathology that can remain CN. Therefore, these findings suggest that the events leading to clinical dementia may be more complex and heterogeneous than previously thought.

The critical question that can only be answered by longitudinal studies or clinical trials is whether the extent of hippocampal atrophy, A β deposition,

Table 5 Predictors of incident dementia (logistic regression analysis)

	Model 1		Model 2		Model 3	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.18 (1.00-1.39)	0.05 ^a	1.04 (0.85-1.27)	0.74	1.01 (0.81-1.25)	0.95
Sex	0.77 (0.29-2.08)	0.61	0.67 (0.20-2.21)	0.51	0.61 (0.18-2.09)	0.43
Education	1.16 (0.95-1.41)	0.15	1.21 (0.97-1.51)	0.10	1.21 (0.96-1.53)	0.11
MMSE scores	0.72 (0.58-0.89)	0.002 ^a	0.75 (0.59-0.95)	0.02 ^a	0.81 (0.64-1.04)	0.09
PiB+ status			2.17 (0.64-7.34)	0.21		
Right or left abnormal HIP ^b			5.61 (1.59-19.78)	0.01 ^a		
WMLs ≥75th percentile			2.80 (1.25-6.30)	0.01 ^a		
WML volume					3.23 (1.34-7.79)	0.01 ^a
Composite right and left HIP ^b					0.71 (0.57-0.90)	0.004 ^a
Composite SUVR of 5 PiB regions of interest					2.94 (0.90-9.63)	0.08 ^a

Abbreviations: CI = confidence interval; HIP = hippocampal volume; MMSE = Mini-Mental State Examination; OR = odds ratio; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio; WML = white matter lesion.

Model 1: adjusted for age, sex, education level, and MMSE scores. Model 2: adjusted for dichotomized measures of amyloid deposition and HIP. Model 3: adjusted for continuous measures of amyloid deposition and HIP.

^a Significant values.

^b Hippocampal atrophy: ≤25th percentile.

and small vessel disease in these older individuals are independent predictors of dementia, and whether factors other than A β deposition that affect brain structure can modulate the rate of progression over time. The fact that we did not find a correlation among the 3 variables suggests that a multifactorial approach will be necessary for the treatment of AD pathology.

AUTHOR CONTRIBUTIONS

O.L. Lopez, MD, participated in the conceptualization of the study, analysis and interpretation of the data, and drafted and revised the manuscript. W.E. Klunk, MD, PhD, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript. C. Mathis, PhD, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript. R.L. Coleman, BS, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript. J. Price, PhD, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript. J.T. Becker, PhD, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript. H.J. Aizenstein, MD, PhD, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript. B. Snitz, PhD, participated in the conceptualization of the study and interpretation of the data, and has drafted and revised the manuscript. A. Cohen, PhD, participated in the conceptualization of the study and interpretation of the data, and has drafted and revised the manuscript. M. Ikonomic, MD, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript. E. McDade, DO, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript. S.T. DeKosky, MD, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript. L. Weissfeld, PhD, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript. L.H. Kuller, MD, DrPH, participated in the conceptualization of the study and interpretation of the data, and drafted and revised the manuscript.

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DISCLOSURE

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