Amyloid deposition and brain structure as long-term predictors of MCI, dementia, and mortality

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Abstract

Objectives

To test the hypothesis that brain structural integrity (i.e., hippocampal [HIP] volume), white matter lesions (WMLs), and β -amyloid deposition are associated with long-term increased risk of incident dementia and mortality in 183 cognitively normal individuals and patients with mild cognitive impairment (MCI) aged 80 years and older.

Methods

All participants had a brain structural MRI scan and PET scan with ^{11}C -labeled Pittsburgh compound B in 2009 and were reexamined yearly through 2015 (mean follow-up time 5.2 ± 1.3 years).

Results

In the last evaluation through 2010–2015, 56 (31%) participants were cognitively normal, 67 (37%) had MCI, and 60 (33%) had dementia. Fifty-seven (31%) died during follow-up, and 20 (35%) developed dementia before their death. All 3 biomarkers were independent predictors of incident dementia in all participants. After adjusting for the risk of dying, amyloid deposition and WMLs remained strong predictors. Of the 60 participants with incident dementia, 54 (90%) had at least one imaging abnormality. Participants with no biomarker positivity had a very low risk of dementia (16%), while 75% of the participants with the 3 biomarkers progressed to dementia. HIP volume and β -amyloid deposition were associated with death only in participants with MCI.

Conclusions

This study showed the presence of more than one biomarker was a stronger long-term predictor of incident dementia than any biomarker alone. After adjusting for the risk of dying, amyloid deposition and WMLs were stronger predictors of dementia than HIP volume. The risk of dying during follow-up was associated with both neurodegeneration and amyloid deposition, especially in individuals with MCI.

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Glossary

A β = β -amyloid; AD = Alzheimer disease; CI = confidence interval; CN = cognitively normal; HIP = hippocampal; HR = hazard ratio; ICV = intracranial volume; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; Pys = person-years; ROI = region of interest; SUVR = standardized uptake value ratio; WML = white matter lesion.

The brain pathology of Alzheimer disease (AD) is present long before the clinical symptoms of dementia manifest. Neuroimaging biomarkers that signal imminent progression from mild cognitive impairment (MCI) to dementia of the Alzheimer type include amyloid deposition and neurodegeneration.^{1–3} Similarly, white matter lesions (WMLs), which are markers of cerebral small vessel disease, are also risk factors for developing dementia in the elderly.^{4,5}

The study of clinical outcomes of the combination of biomarkers is particularly important because it has been shown that the risk of incident dementia is increased in dementia-free individuals when 2 or more of the biomarkers are present.⁶ A recent report showed that by ages 70 to 89, 35% of the normal population had both β -amyloid (A β) deposition and neurodegeneration, and only 25% had neither biomarker.⁷ In addition, dementia-free individuals with the combination of A β deposition and a marker of neurodegeneration (i.e., hippocampal [HIP] volume) had a steeper rate of decline in cognitive testing during a 12-year follow-up.⁸

We have previously reported that A β deposition, HIP volume, and WMLs were independent predictors of progression to dementia after 2 years in individuals without dementia.⁶ Ninety-five percent of the individuals who developed dementia in that study had at least one imaging abnormality, 43% expressed the phenotype of combined A β deposition with small HIP volume, but only 19% expressed all 3 biomarkers (i.e., amyloid, HIP volume, WMLs). Other studies have found heterogeneity among the biomarkers predicting dementia—some individuals have predominantly HIP atrophy, others have a predominant A β pattern,⁹ and others a vascular pattern.¹⁰ In this report, we describe the relationship between these 3 biomarkers and outcome after more than 5 years of follow-up in this same study sample.⁶

This group has an average age of 85 years and thus has a high risk of death during follow-up. Consequently, to understand the biomarkers/risk of dementia, we must also understand their relationship to death. For example, HIP volume¹¹ and WMLs^{12,13} are predictors of mortality in individuals younger than 80 years, and those with CSF markers of A β deposition and neuronal injury had increased risk of death.¹⁴ Thus, we examined the relationships between the biomarkers and clinical disease accounting for the competing risk of death.

Methods

Study sample

The present analyses were conducted in 183 participants without dementia who participated in the *Ginkgo biloba* memory study (GEM [Ginkgo Evaluation of Memory] Study) from 2000 to 2008.^{15,16} In 2009, 194 dementia-free participants from the Pittsburgh site underwent MRI and Pittsburgh compound B (PiB)-PET imaging. Eleven participants were excluded because of technical limitations.¹⁷ In 2010–2011, the participants were invited to continue with biannual neuroimaging studies and clinical and cardiovascular evaluations; the clinical examinations were done annually until 2014 and every 6 months thereafter.⁶ The mean follow-up time was 5.7 ± 1.7 years (range 0.14–6.9 years). Deaths were reported by the proxies when contacted for the annual visits and corroborated by death certificates.

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 A β deposition

PiB-PET data acquisition has been described previously.¹⁷ It involved 20-minute acquisition (4×5 minute frames) beginning 50 minutes after injection of 15 ± 1.5 mCi of PiB on a Siemens/CTI ECAT HR+ scanner (Knoxville, TN) 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 Hanning 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 participants as A β -positive if the atrophy-corrected composite of 5 regions' standardized uptake value ratio (SUVR) was >1.57 ,¹⁸ or PiB(+). Because A β deposition follows a regional pattern such that very early deposits may be missed by the dichotomous classification systems, we also treated A β deposition as a continuous variable composed of the mean PiB SUVR in these 5 regions bilaterally.¹⁷

Magnetic resonance imaging

MRI scanning was performed on a GE Signa 1.5T scanner with a standard head coil,¹⁹ including fluid-attenuated

inversion recovery (echo time = 172, repetition time = 9,004, inversion time = 2,200, flip angle = 90, number of slices = 27, field of view = 200 × 150, in-plane resolution = 0.78 × 0.78) and spoiled echo gradient (sagittal, repetition time = 25, echo time = 5, flip angle = 40, field of view = 240 × 180 mm, slice thickness = 1.5 mm, number of slices = 124, in-plane resolution = 0.94 × 0.94 mm) 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 (FAST, FSL 4.1.4). Total intracranial volume (ICV) was computed as the volume contained within the "inner skull" using the Brain Extraction Tool with an advanced option (−A). HIP 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),²⁰ and anatomical ROIs were from the automated anatomical labeling atlas.²¹ HIP ROIs were defined on the reference brain (Montreal Neurological Institute colin27) and transformed to fit each individual's anatomical image; trilinear interpolation was used. Volumes were calculated as the number of cubic millimeter voxels. Here, we use the HIP volumes as the proportion of the ICV. A participant was considered to have small hippocampi (HIP[+]) when *either* the right or left hippocampus was <25th percentile of that in individuals who remained cognitively normal (CN) throughout follow-up. A fuzzy-connectedness algorithm was used to segment the WMLs from each individual's T2-weighted, fluid-attenuated inversion recovery images.²² The volume of WMLs is presented as the proportion of the ICV, and volumes >75th percentile of those in normal participants were considered abnormal, or WML(+). These classifications were done before the data analysis.

Clinical assessments

All participants underwent a neuropsychological evaluation in 2009 that included the Mini-Mental State Examination (MMSE)²³ and a detailed neuropsychological battery.²⁴ Symptoms of depression were measured with the Center for Epidemiologic Studies Depression Scale,²⁵ and we obtained an inventory of the participant's prescription and over-the-counter medications.

Cognitive status

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 2015. 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.²⁶ Participants with MCI were classified according to 4 MCI cognitive subtypes,²⁷ although for the present study, they were considered as a single group.

Statistical analysis

Contingency tables were analyzed with χ^2 test; *t* tests and nonparametric analysis of variance methods were used for continuous variables. 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. Cox proportional hazard models controlling for age, MMSE, and sex were used to examine the association between the baseline pathologic markers and time to clinical dementia. These analyses were conducted with and without death as competing risk. All models were assessed for potential outliers/influential observations. When modeling the composite mean of the HIP and PiB values, we reported the hazard ratios (HRs) as per SD increment, and this has no effect on the significance level.

Data availability

Procedure for requesting shared resources

Any qualified investigator may contact the corresponding author with a specific request that includes details of the resources requested, how they will be used in the proposed research, and the qualifications of the investigator requesting the resources. Investigators may be asked to provide further details if necessary.

Review process

Requests for resources are reviewed at the next available monthly Pittsburgh Resource Sharing Committee meeting. Criteria discussed include (1) availability of the requested resource, (2) potential for duplication of ongoing studies, (3) scientific merit of the proposed research use, and (4) qualifications of the investigator/institution to conduct the research. Although the initial review process is typically completed within 60 days, the process often then becomes an iterative one between the committee and the requesting investigator to modify the amount of resource requested or, in the case of duplication, to modify the specific focus of the study or to facilitate collaborations between investigators interested in similar areas of research. In many cases, the investigator is urged to partner with a specific Pittsburgh investigator to better understand the availability and organization of data or resources and sometimes encouraged to formally include that person as an academic consultant or collaborator if that expertise does not already exist in the requesting investigator's research group. If the request is approved, data requests are sent to our database manager. The requesting investigator is asked to sign a "Data Use Agreement" that ensures the investigator will not share the resource(s) with a third party, will cite P01-AG025204 in any presentation or publication, and will comply with the general policies described above.

Results

Of the 183 participants, 30% were CN, 37% had MCI, and 33% were diagnosed with dementia at their last clinic visit.

There were more conversions to dementia in the 2009-MCI group (65.7%) compared to those classified as CN (25%) in 2009 (χ^2 : 21.4, $p < 0.0001$). There were no age-adjusted correlations between PiB and HIP (r_p : -0.11, $p = 0.14$) and WML (r_p : -0.02, $p = 0.75$) volumes. Similarly, no significant partial correlations were noted between HIP and WML volumes (r_p : 0.08, $p = 0.29$). The incidence of dementia increased from 56.07/1,000 person-years (Pys) among individuals younger than 84 years to 96.5/1,000 Pys among those older than 86 years (table e-1, [links.lww.com/WNL/A460](https://www.lww.com/WNL/A460)).

Of the 60 participants who developed dementia during follow-up, 22% went directly from CN to dementia, 40% went through MCI to dementia, and 38% went directly from MCI to dementia. Participants with incident dementia had lower baseline MMSE scores than participants who remained CN. Participants with dementia or MCI at follow-up were more likely to be PiB(+) and had a higher mean PiB SUVR at baseline (table 1). Participants with incident dementia were more likely to be HIP(+) than those who remained CN (odds ratio 2.39, 95% confidence interval [CI] 1.10–5.21, $p = 0.035$), and no differences were noted between CN and MCI groups. The mean HIP volume was not different among the 3

diagnostic groups with a small effect size ($\eta^2 = 0.03$). Participants with incident dementia were more likely to be WML (+) compared to those who remained CN (odds ratio 2.44, 95% CI 1.07–5.56, $p = 0.04$), and the WML volume was greater for participants with MCI and dementia than for CN participants.

We examined the co-occurrence of dichotomized biomarkers in 2009 as a function of clinical outcome (table e-2, [links.lww.com/WNL/A460](https://www.lww.com/WNL/A460)); 77% of all 183 participants, 90% of those who converted to dementia, had at least one abnormal biomarker at baseline, and 11 (6%) had all 3 biomarkers. Conversion to dementia occurred in participants with none ($n = 6$), 1 ($n = 22$), or 2 or 3 ($n = 32$) biomarkers. The incidence of dementia varied from 37/1,000 Pys among the individuals with no abnormalities to 215/1,000 Pys for those with 3 biomarker abnormalities (table e-2A). Among the participants with no biomarker positivity ($n = 43$), 7 (16%) developed dementia, while 9/11 (75%) of those with the 3 biomarkers did. The participants who were CN in 2009 and had no biomarker positivity were relatively unlikely to develop dementia (6/39 [15%]) (table e-2B), whereas 71% ($n = 5/7$) of those with the 3 biomarkers developed dementia during

Table 1 Demographic and clinical characteristics in 2009 by clinical diagnoses from baseline to 2015

	Diagnoses 2010–2015			χ^2 /ANOVA	p Value	Effect size ^a
	Normal	MCI	Dementia			
No. of participants	56	67	60			
Characteristics in 2009						
Age, y	84.2 ± 2.5	85.6 ± 2.9	86.0 ± 2.9	2.69	0.07	0.03
Education, y	15.2 ± 2.7	14.2 ± 2.4	14.6 ± 2.6	2.45	0.08	0.03
Female, n (%)	25 (45)	41 (39)	25 (42)	0.42	0.80	0.05
MMSE score	28.4 ± 1.5	27.4 ± 2.2	26.9 ± 2.0	9.05 ^b	<0.001 ^c	0.10
APO ε4 (n = 179), n (%)	8 (15)	17 (27)	9 (17)	3.00	0.22	0.13
Amyloid deposition						
PiB(+), n (%)	20 (36)	38 (57)	42 (70)	14.1 ^b	0.001 ^c	0.28
Mean SUVR of 5 regions	1.59 ± 0.42	1.76 ± 0.47	1.95 ± 0.47	8.60 ^d	<0.001 ^c	0.09
Hippocampal volume^e						
Abnormal, n (%)	15 (27)	20 (30)	28 (47)	6.05 ^b	0.04 ^c	0.18
Mean hippocampal volume	0.25 ± 0.030	0.26 ± 0.034	0.24 ± 0.031	2.71	0.06	0.03
WMLs^e						
Abnormal, n (%)	12 (21)	13 (19)	24 (40)	8.01 ^b	0.01 ^c	0.21
Mean WML volume	0.007 ± 0.005	0.089 ± 0.008	0.010 ± 0.006	6.15 ^b	0.003 ^c	0.06

Abbreviations: ANOVA = analysis of variance; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio; WML = white matter lesion.

^a η^2 for continuous variables and Cramér V for categorical variables.

^b Dementia different from MCI and cognitively normal.

^c Statistically significant.

^d The 3 groups were different from each other.

^e Proportion of intracranial volume.

follow-up. There were few participants with MCI in 2009 ($n = 35$), and only 4 (10.5%) were biomarker negative and had no conversion to dementia. By contrast, 3/4 (75%) with the 3 biomarkers progressed to dementia (table e-2C). We examined the mean PiB SUVR in relationship to co-occurrence of dichotomized biomarkers in 2009 and clinical outcome (table e-3). Twenty-three percent of all participants were biomarker negative, and 6% had all 3 biomarkers.

There was a linear relationship between incident dementia and PiB from 32.1/1,000 Pys in the lowest quartile to 97.1/1,000 Pys in the highest quartile ($p = 0.02$ for linear trend) in CN participants in 2009 (table 2). The association between dementia and HIP volume was mainly in the lowest quartile (91.2/1,000 Pys, $p = 0.08$ for linear trend) and with WML volume in the highest quartile (94.4/1,000 Pys, $p = 0.18$ for linear trend). Results were similar when both CN and MCI participants were included in the analysis.

We used Cox proportional hazard models with and without death as competing risk to examine the relationship between presence of the 3 biomarker abnormalities and incident dementia among all study participants (table 3). Among all participants, the risk of developing dementia was associated with low MMSE scores. Continuous and dichotomized variables of the 3 biomarkers were associated with incident dementia in all participants in the analysis without death as competing risk. When death was a competing risk, amyloid deposition and WMLs remained as significant predictors of incident dementia. HIP volume remained related to risk of dementia but not significant. Continuous variables of the 3 biomarkers were associated with incident MCI in CN participants (tables e-3 and e-4, links.lww.com/WNL/A460). Similarly, amyloid deposition and WMLs were predictors of dementia in CN participants (table 4). The Kaplan-Meier survival curves showing incidence of dementia in the CN and all other participants are shown in figures e-1 and e-2 (links.lww.com/WNL/A459).

Thirty-one percent of the original 183 study participants died during follow-up. Those who died were significantly older at baseline than those who remained alive to the end of observation. There were no significant differences between those who survived through follow-up in education, sex, MMSE score, or APOE genotypes (table e-5, links.lww.com/WNL/A460). Twenty of these 57 individuals (i.e., 35%) developed dementia before their death.

All-cause mortality increased from 33.0/1,000 Pys in individuals younger than 84 years to 99.8/1,000 Pys in those older than 87 years (table 5). Among individuals in whom all 3 biomarkers were present, 63.6% died during follow-up, with age-adjusted rate of 144.2/1,000 Pys, as compared to 12 (28%) deaths and an age-adjusted death rate of 60.2/1,000 Pys for participants with no biomarker positivity (table 5).

Table 2 Biomarker quartiles in 2009 in relation to incident dementia from 2010 to 2015 in cognitively normal participants and all groups

	No. of participants	Incident dementia, n (%)	Age-adjusted rate per 1,000 person-years
Cognitively normal			
PiB			
<1.34	39	6 (14)	32.9 (10.3–108.7)
1.35–1.63	40	8 (20)	41.4 (13.6–135.7)
1.64–2.16	35	10 (28.5)	57.9 (20.2–196.5)
>2.16	34	13 (38)	97.1 (38.5–247.3)
HIP^a			
<0.23	32	14 (44)	91.2 (37.6–242.9)
0.231–0.25	39	8 (20.5)	44.6 (13.3–151.0)
0.251–0.27	32	4 (12.5)	21.9 (5.9–94.1)
>0.27	45	11 (24)	50.1 (18.1–145.0)
WMLs^a			
<0.005	38	8 (21)	50.6 (14.8–175.9)
0.006–0.008	39	10 (26)	54.5 (18.4–166.7)
0.009–0.011	39	6 (15)	32.0 (7.9–144.8)
>0.011	32	13 (40)	94.3 (36.9–255.2)
All participants			
PiB			
<1.34	44	9 (20)	45.2 (19.5–138.8)
1.35–1.63	48	10 (21)	42.1 (14.9–123.6)
1.64–2.16	45	18 (40)	95.8 (42.6–216.2)
>2.16	46	23 (50)	130.1 (65.0–265.2)
HIP^a			
<0.23	46	24 (52)	130.2 (64.7–264.2)
0.231–0.25	46	12 (26)	60.8 (22.9–162.0)
0.251–0.27	45	12 (27)	55.6 (22.8–155.1)
>0.27	46	12 (26)	54.2 (20.8–149.9)
WMLs^a			
<0.005	46	14 (30)	77.8 (32.6–186.9)
0.006–0.008	45	13 (29)	52.2 (22.5–160.9)
0.009–0.011	46	9 (19.5)	46.0 (14.4–151.3)
>0.011	46	24 (52)	129.3 (63.8–275.6)

Abbreviations: HIP = hippocampal; PiB = Pittsburgh compound B; WML = white matter lesion.

PiB: mean standardized uptake value ratio of 5 regions. HIP: mean right and left hippocampal volume. WMLs: white matter lesion volume.

^a Proportion of intracranial volume.

Table 3 Predictors of incident dementia (n = 60) in all participants with and without death as competing risk

	Without death as competing risk ^a		With death as competing risk ^a	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Continuous biomarker measures				
Age	1.02 (0.93–1.11)	0.67	0.97 (0.87–1.07)	0.52
MMSE	0.84 (0.75–0.94)	0.003 ^b	0.86 (0.75–0.99)	0.03 ^b
Education	0.98 (0.88–1.09)	0.69	1.01 (0.90–1.13)	0.83
Composite right or left hippocampal volume ^c	0.73 (0.54–0.97)	0.03 ^b	0.81 (0.62–1.06)	0.12
logWML volume	3.14 (1.12–8.78)	0.02 ^b	4.56 (1.39–14.9)	0.01 ^b
Composite SUVR of 5 PiB regions of interest ^d	1.69 (1.31–2.20)	<0.0001 ^b	1.58 (1.22–2.03)	<0.0001 ^b
Dichotomized biomarker measures				
Age	1.03 (0.94–1.12)	0.54	0.99 (0.91–1.08)	0.87
MMSE	0.78 (0.69–0.88)	<0.0001 ^b	0.81 (0.71–0.92)	0.001 ^b
Education	1.02 (0.92–1.14)	0.67	1.04 (0.93–1.17)	0.47
Hippocampal atrophy ^e	1.79 (1.06–3.04)	0.03 ^b	1.62 (0.97–2.71)	0.06
WMLs >75th percentile	2.30 (1.31–4.06)	0.004 ^b	2.65 (1.53–4.59)	0.001 ^b
PiB(+) status	2.75 (1.51–5.00)	0.001 ^b	2.46 (1.35–4.51)	0.003 ^b

Abbreviations: CI = confidence interval; HR = hazard ratio; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio; WML = white matter lesion.

^a Cox proportional hazard model.

^b Statistically significant.

^c HR was for 1-SD (0.032) increment.

^d HR was for 1-SD (0.48) increment.

^e Hippocampal atrophy: <25th percentile.

However, because of the small number of deaths in each category, confidence limits around the point estimates were large. A Cox regression model including HIP, WMLs, PiB, age, MMSE score, and education level showed that age was a significant predictor of death in all study participants, as was PiB positivity (HR 1.84, 95% CI 1.02–3.35) (table 6). Among individuals who were CN at baseline, only age and education level predicted time until death, while continuous measures of HIP volume (HR 0.40, 95% CI 0.17–0.98) and amyloid deposition predicted death (HR 3.97, 95% CI 1.49–10.6) in the MCI group.

Discussion

This study showed that the presence of more than one biomarker was a stronger long-term predictor of incident dementia than any biomarker alone, and the absence of all 3 biomarkers was associated with a very low risk of dementia. The risk of dementia among the CN in 2009 was linearly related to the extent of amyloid deposition, with almost a 3-fold increased difference in risk between the lowest and highest quartiles. The risk of dementia was inversely related to HIP volume, with much of the association limited to the lowest quartile, and to higher amounts of WMLs. After adjusting for demographic characteristics, incident dementia

was associated with the baseline presence of the 3 biomarkers. However, after adjusting for the risk of dying during follow-up, amyloid deposition and WMLs were stronger predictors than HIP volume. The risk of dementia, as expected, was strongly related to MCI status at baseline. Finally, the risk of dying during follow-up was associated with older age, HIP volume, and the presence of amyloid deposition in the brain, especially in individuals with MCI.

Our findings are consistent with previous observations that more advanced AD cerebral pathology and clinical disease are associated with mortality.¹⁴ Our failure to observe an association between WMLs and death may be attributable to selective survival in the sample. We originally recruited in 2000, and the participants had to be free of dementia and willing and able to have MRI and PET imaging in 2009. WMLs are a marker of cerebral small vessel disease, and those individuals with significant cardio/cerebrovascular disease may have died before study enrollment or may have been unable to enroll in the project. This would mean we would be following healthier participants.

The finding that 81% of the CN participants who converted to dementia had at least one biomarker present confirms the notion that some pathology leading to AD is likely present years before the clinical symptoms develop. However, *which* biomarker was abnormal did not seem to matter. Among the

Table 4 Predictors of incident dementia in cognitively normal participants with and without death as competing risk

	Without death as competing risk ^a		With death as competing risk ^a	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Continuous biomarker measures				
Age	1.02 (0.89–1.15)	0.80	0.97 (0.85–1.11)	0.65
MMSE	0.75 (0.62–0.91)	0.003 ^b	0.74 (0.63–0.88)	0.001 ^b
Education	1.02 (0.90–1.17)	0.71	1.06 (0.93–1.20)	0.41
Composite right or left hippocampal volume^c	0.73 (0.52–1.03)	0.07	0.82 (0.59–1.15)	0.25
logWML volume	3.82 (0.83–17.69)	0.08	5.80 (0.99–33.9)	0.05 ^b
Composite SUVR of 5 PiB regions of interest^d	2.62 (1.27–5.39)	0.009 ^b	1.58 (1.17–2.14)	0.003 ^b
Dichotomized biomarker measures				
Age	1.01 (0.89–1.14)	0.88	1.01 (0.90–1.29)	0.93
MMSE	0.75 (0.65–0.86)	0.003 ^b	0.74 (0.62–0.89)	0.001 ^b
Education	1.01 (0.89–1.15)	0.86	1.09 (0.95–1.26)	0.21
Hippocampal atrophy^e	1.96 (0.95–4.03)	0.06	1.53 (0.80–2.94)	0.19
WMLs >75th percentile	4.47 (0.95–21.02)	0.05 ^b	2.65 (1.25–5.61)	0.01 ^b
PiB(+) status	1.60 (1.16–2.22)	0.005 ^b	2.25 (1.10–4.60)	0.02 ^b

Abbreviations: CI = confidence interval; HR = hazard ratio; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio; WML = white matter lesion.

^a Cox proportional hazard model.

^b Statistically significant.

^c HR was for 1-SD (0.032) increment.

^d HR was for 1-SD (0.48) increment.

^e Hippocampal atrophy: <25th percentile.

CN individuals, those who had evidence of amyloid deposition, either alone or in combination with the other 2 biomarkers, had a 32% conversion rate to dementia. Similar rates were found for HIP(+) (33%) and WML(+) (37%) alone or in combination.

These findings reinforce the point that multiple pathologies—amyloidosis, neurodegeneration, and vascular disease—each contribute to the expression of clinical dementia in the elderly.^{28,29} We show here that there is an additive effect—75% of the participants with all 3 abnormal biomarkers progressed to dementia compared with 43% with 2 abnormal biomarkers and 27% with only one abnormal biomarker present.

WMLs, as a marker of small vessel disease in the brain, are common in old age and are a risk factor for both MCI³⁰ and dementia.⁴ Incident dementia in all participants with WMLs alone was relatively low (21%) but was more than 50% when WMLs occurred in combination with other biomarkers. These findings suggest that vascular pathology augments the effect of AD pathology and accelerates the transition to dementia.^{31,32}

MCI is a risk factor for conversion to dementia. We divided the incident dementia cases into those that had occurred within the first 2.5 years and those from 2.5 to 5 years. Of the

60 incident dementia cases, 18 occurred in the first 2.5 years and 42 after 2.5 years. Among the 38 participants with MCI in 2009, 11 (29%) developed incident dementia within the first 2.5 years and 12 (31.5%) after 2.5 years. By contrast, among the CN, 7 (5%) participants developed dementia within the first 2.5 years and 30 (21%) after 2.5 years. Of the 18 individuals who developed dementia within the first 2.5 years, 11 (61%) were MCI at baseline. By contrast, 12 (28.5%) of the 42 individuals who developed dementia after 2.5 years were MCI at baseline. The risk of dementia was very high for participants with MCI as compared to CN individuals, whether the dementia occurred rapidly or more slowly.

The determination of biomarker abnormality was made as long as 5+ years from the development of a dementia syndrome. While this addresses the question of long-term prediction of clinical change, it does not tell us whether there are additional changes to biomarker status in the time immediately prior to expression of dementia or the sequence of events that lead to dementia. The attenuated effect of HIP atrophy as a risk factor for incident dementia should be interpreted with caution, since the point estimates of dementia risk were similar in the models with and without death as competing risk, and the confidence limits substantially overlapped.

Table 5 All-cause mortality by PiB status, HIP volume, and WMLs

Baseline biomarker			No. of participants (%)	Deceased, n (%)	Age-adjusted rate per 1,000 person-years (95% CI)
PiB(+)	HIP(+)	WML(+)			
No	No	No	43 (23)	12 (28)	60.2 (24.2–154.9)
No	No	Yes	14 (8)	1 (7)	15.8 (2.23–112.4)
No	Yes	No	20 (11)	5 (25)	45.8 (11.0–225.5)
No	Yes	Yes	6 (3)	2 (33)	80.1 (20.0–320.2)
Yes	No	No	47 (26)	14 (30)	71.8 (29.7–177.6)
Yes	No	Yes	18 (18)	7 (39)	77.0 (26.8–222.98)
Yes	Yes	No	26 (14)	9 (35)	79.5 (25.0–308.3)
Yes	Yes	Yes	11 (6)	7 (64)	144.2 (68.7–302.4)

Abbreviations: CI = confidence interval; HIP = hippocampal; PiB = Pittsburgh compound B; WML = white matter lesion.

PiB(+): mean standardized uptake value ratio of 5 regions >1.57. HIP: mean right or left hippocampal volume; abnormal <25th percentile. WMLs: WML volume >75th percentile.

This is one of the first long-term studies to evaluate neuroimaging risks of dementia. The strengths of the study include careful annual clinical evaluations of dementia, almost complete ascertainment, relatively long follow-up (5+ years), and further evaluation of death as a competing risk of dementia. Of

note, a small number of individuals aged 85 and older remained free of amyloid deposition, HIP atrophy, and WMLs, and had very low risk of dementia even into age 90 and older. One limitation of this study was that the hypothesis tested primarily relates to MRI and PET imaging, and no

Table 6 Predictors of death^a

	All participants		Cognitively normal		MCI	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Continuous biomarker measures						
Age	1.13 (1.03–1.25)	0.009 ^b	1.18 (1.06–1.32)	0.003 ^b	0.81 (0.61–1.08)	0.15
MMSE	0.94 (0.82–1.08)	0.39	0.98 (0.79–1.20)	0.81	1.03 (0.83–1.27)	0.81
Education	0.89 (0.80–1.00)	0.04 ^b	0.87 (0.77–1.00)	0.04 ^b	0.89 (0.65–1.22)	0.47
Composite right and left hippocampal volume ^c	0.80 (0.60–1.06)	0.12	0.86 (0.63–1.17)	0.33	0.40 (0.17–0.98)	0.04 ^b
logWML volume	0.74 (0.23–2.33)	0.60	0.40 (0.09–1.82)	0.23	3.26 (0.28–38.3)	0.34
Composite SVUR of 5 PiB regions of interest ^d	1.25 (0.95–1.64)	0.10	1.06 (0.77–1.45)	0.73	3.97 (1.49–10.60)	0.006 ^b
Dichotomized biomarker measures						
Age	1.12 (1.02–1.22)	0.01 ^b	1.15 (1.04–1.27)	0.008 ^b	0.98 (0.77–1.24)	0.86
MMSE	0.92 (0.80–1.06)	0.24	0.99 (0.80–1.22)	0.89	0.85 (0.67–1.07)	0.15
Education	0.93 (0.83–1.04)	0.18	0.90 (0.79–1.02)	0.10	1.03 (0.79–1.36)	0.81
Hippocampal atrophy ^e	1.18 (0.67–2.07)	0.57	1.07 (0.55–2.11)	0.84	1.50 (0.44–5.09)	0.51
WMLs >75th percentile	1.13 (0.60–2.11)	0.70	0.91 (0.41–2.02)	0.81	1.92 (0.59–6.30)	0.28
PiB(+) status	1.84 (1.02–3.35)	0.04 ^b	1.70 (0.88–3.29)	0.11	4.04 (0.61–26.70)	0.14

Abbreviations: CI = confidence interval; HR = hazard ratio; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; WML = white matter lesion.

^a Cox proportional hazard model.

^b Statistically significant.

^c HR was for 1-SD (0.032) increment.

^d Standardized uptake value ratio of 5 PiB regions of interest; HR was for 1-SD (0.48) increment.

^e Hippocampal atrophy: <25th percentile.

other risk factors were included in the analyses (e.g., hypertension).¹³ In addition, while we focused on well-established summary MRI measures, other areas of the brain associated with incident dementia were not examined^{33,34}; whole-brain, voxel-wise analysis would also be informative to more fully understand the regional variation in these changes.^{33,34}

Author contributions

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Disclosure

O. Lopez served as a consultant for Lundbeck, Grifols, and Raman Technologies. J. Becker and Y. Chang report no disclosures relevant to the manuscript. W. Klunk served as a consultant for GE Healthcare. GE Healthcare holds a license agreement with the University of Pittsburgh based on the technology described in this manuscript. Dr. Klunk is a co-inventor of PiB and, as such, has a financial interest in this license agreement. C. Mathis served as a consultant for GE Healthcare. GE Healthcare holds a license agreement with the University of Pittsburgh based on the technology described in this manuscript. Dr. Mathis is a coinventor of PiB and, as such, has a financial interest in this license agreement. J. Price, H. Aizenstein, B. Snitz, and A.D. Cohen report no disclosures relevant to the manuscript. S. DeKosky serves on the advisory boards of Acumen Pharmaceuticals, Amgen, Inc., and Cognition Therapeutics, and chairs a drug monitoring committee for Biogen Idec. M. Ikonovic, M. Kamboh, and L. Kuller report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Amyloid deposition and brain structure as long-term predictors of MCI, dementia, and mortality

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Study question

Are hippocampal volume, white matter lesions (WMLs), and β -amyloid (A β) deposition associated with the risk of incident dementia in the elderly?

Summary answer

All 3 biomarkers are predictors of incident dementia in the elderly, with the presence of multiple biomarkers being a stronger predictor than that of a single biomarker.

What is known and what this paper adds

The study authors have previously reported that hippocampal volume, WMLs, and A β deposition independently predicted conversion to dementia over a 2-year period. This study analyzes 5-year follow-up data from the same cohort to further elucidate the long-term prediction of dementia among these biomarkers.

Participants and setting

This study analyzed 183 Pittsburgh site participants (50% women, and 145 were cognitively normal and 38 mild cognitive impairment in 2009) from the *Ginkgo biloba* Memory Study (2000–2008) who were older than 80 years and initially free of dementia. The participants were examined between 2009 and 2015.

Design, size, and duration

In 2009, the participants underwent baseline magnetic resonance imaging (MRI), which was performed to determine hippocampal volumes and WML volumes, and Pittsburgh compound B (PiB) positron emission tomography, which was performed to quantify A β deposition. Follow-up neuroimaging assessments were conducted biannually beginning in 2010 or 2011. The participants also underwent baseline neuropsychologic evaluation in 2009 and annual follow-up clinical assessments beginning in 2010 or 2011. Diagnoses of dementia were based on the consensus opinions of a neurologist, a psychiatrist, and a neuropsychologist who were blinded to the baseline neuroimaging results.

Main results and the role of chance

Incident dementia was detected in 60 (33%) participants. Cox proportional hazards models showed that hippocampal

Table Development of dementia as a function of positivity for variable numbers of biomarkers

No. of positive biomarkers at baseline	No. of participants	Percentage who developed dementia
0	43	14
1	79	28
2	50	48
3	11	73

volume, WML volume, and A β deposition each independently predicted incident dementia. Positivity for multiple biomarkers outperformed positivity for any single biomarker as a predictor of incident dementia. Ninety percent of the incident dementia participants had at least one imaging abnormality. Those with no biomarker positivity had a low risk of dementia (14%), while 73% of the participants with the 3 biomarkers progressed to dementia. Only 27% of the cognitively normal individuals at baseline had no biomarker positivity and remained normal after 5 years follow up.

Bias, confounding, and other reasons for caution

This study lacked data on potential dementia risk factors, such as hypertension, and did not examine MRI findings for certain brain areas relevant to the development of dementia.

Generalizability to other populations

This study's relatively long follow-up period favors the generalizability of the results to other populations of very advanced ages.

Study funding/potential competing interests

This study was funded by the NIH. Some authors report serving as consultants for various companies. Dr. Mathis and Dr. Klunk coinvented PiB. Dr. DeKosky reports serving on advisory boards for various companies. Go to Neurology.org/N for full disclosures.

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