Brain Volume and Survival from Age 78 to 85: The Contribution of Alzheimer-Type Magnetic Resonance Imaging Findings

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OBJECTIVES: To test the prediction of survival using magnetic resonance imaging (MRI)–derived global and regional brain volumes in subjects aged 78 to 79 without dementia.

DESIGN: Observational follow-up study.

SETTING: University teaching hospital.

PARTICIPANTS: Participants born in 1921, recruited in 1997/98 to a longitudinal study, who underwent brain MRI in 1999/2000.

MEASUREMENTS: Vital status on May 12, 2006, global and regional brain volumes.

RESULTS: Thirty-seven of 98 (34.9%) participants died during follow-up. After adjustment for cognitive ability at time of MRI examination, childhood intelligence, sex, hypertension, smoking history, obesity, hyperlipidemia, and age at MRI, proportion of intracranial volume occupied by the brain (brain fraction) predicted death before age 85 ($P = .04$). Participants with brain fraction less than 0.726 had more than twice the relative risk (2.8, 95% confidence interval = 1.1–7.3) of death than participants with brain fraction greater 0.726. Lower survival was significantly associated with lower gray matter volumes in bilateral parietal and left frontoparietal areas and with lower white matter volumes in left parietal and right posterior temporal regions. Cox regression analysis showed that parietal white matter volume ($P = .003$), a subsequent diagnosis of dementia ($P < .001$), and sex ($P = .004$) were independent predictors of survival.

CONCLUSION: In participants aged 78 to 79, a lower global brain fraction predicted survival to approximately age 85. Smaller regional volumetric brain reductions, seen in Alzheimer's disease (AD), also predicted survival independent of dementia. The presence of prodromal AD probably explain the main findings. **J Am Geriatr Soc 58:688–695, 2010.**

Key words: survival; structural MRI; dementia; risk factors

There is a much greater contribution of dementia to mortality than is evident in conventional mortality statistics. At age 65, the lifetime risk in both sexes of stroke or dementia is more than one in three,[1] yet the exact contribution of Alzheimer-type neuropathology to overall mortality in older people remains uncertain. It is well established that death certificates underreport dementia as the underlying cause of death.[2] Subclinical Alzheimer's disease (AD) makes an unknown contribution to mortality. Such subclinical disease might be indicated by volume loss of those brain regions typically affected by AD,[3] but brain volume is also likely to reflect long-standing cognitive traits,[4] so adjustment for prior cognitive ability is desirable to aid the interpretation of any mortality associations with brain volume measures, because such long-standing cognitive traits themselves predict mortality.[5] In addition, there are numerous factors that can influence survival in an aged sample that need to be taken into account when estimating the possible contribution of magnetic resonance imaging (MRI) volumetric measures to time to death. Major influences include diminished lung function[6,7] and failing cognition.[7] It is hypothesized that there is an association between smaller relative volumes of those brain regions typically affected by AD and greater mortality.

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METHOD

Participants

With the approval of the regional ethics committee and the help of family doctors, 382 local residents born in 1921 who had taken part in the Scottish Mental Survey, 1932,[8] were identified. Research methods and study background are detailed elsewhere.[9] Those in poor health or who were recently bereaved were excluded, and between 1998 and 1999, 235 (292 of whom were eligible) were recruited into a follow-up study of brain aging and health. Written informed consent was obtained for clinical examination, cognitive testing, brain imaging, and follow-up, with access to all relevant clinical records. In 1999, a subsample of 144 of these 235 participants was randomly selected for brain MRI examination. Individuals with a history of epilepsy (n = 1), severe depression (n = 2), schizophrenia (n = 1), or major stroke (n = 1) were excluded. Medical contraindications prevented 17 from participating, and 21 refused; 106 (65 men and 41 women) were imaged. Excess movement during acquisition of volumetric MRI data removed eight subjects from the study (6 men and 2 women). Satisfactory MRI data were obtained from 98 participants in relatively good health, aged 78 to 79 (56 men and 42 women).

MRI Acquisition

Subjects were imaged using a 1 Tesla Magnetom Impact MR scanner (Siemens AG, Erlangen, Germany) and a conventional circularly polarized radio frequency head coil. The MRI protocol included a T1-weighted sequence. The T1 sequence was a three-dimensional magnetization-prepared rapid-acquisition gradient echo sequence. This sequence produced 128 sagittal slices of the head with an effective thickness of 1.41 mm. The in-plane pixel size was 0.98 mm, and the data were acquired into 256-by-256 arrays. The repetition time was 11.4 ms, the echo time was 4.4 ms, the radio frequency flip angle was 15°, the field of view was 250 mm, the slab thickness was 180 mm, and the acquisition time was 6 minutes and 7 seconds. In addition, a T2-weighted fast spin-echo MR sequence was acquired in the commissural plane with repetition time/echo time of 4,000 ms/96 ms, a total acquisition time of 1 minute and 53 seconds, a section thickness of 5 mm, and an intersection gap of 1.5 mm.

Image Processing

The T1 imaging data were processed using the Statistical Parametric Mapping (SPM2) image processing package (Wellcome Department of Cognitive Neurology, University College, London). Each data set was automatically segmented into images representing the probability that any voxel contained gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), or other tissue. The segmentation algorithm was described previously[10] and uses an a priori estimate of the distribution of GM, WM, and CSF and cluster analysis to estimate the distribution within individuals. As part of the segmentation algorithm, the data were corrected for the effect of heterogeneity attributable to magnetic field nonuniformity.[11] The resultant images were inspected for adequate segmentation into the different tissue types. Using GM and WM probability maps, bit map masks representing the parenchymal brain (PB) were created for each participant using the software feature available within SPM2. Mutually exclusive bit maps for GM and WM were then classified using the tissue type with greatest probability within the PB. After manual editing, a CSF bit map was created by including those voxels that had a probability greater than 0.5 of containing CSF. The three bit maps obtained were then adjusted by classifying any conflicting voxels as CSF so that these constituted mutually exclusive data sets. Axial slices inferior to the cerebellum were not included in the calculations. The results were expressed as fractions of the total intracranial volume (TICV) calculated as the sum of GM, WM, and CSF. Parenchymal brain fraction (BF) was calculated as the ratio of PB to TICV. This ratio has previously been used to estimate whole brain shrinkage[12] and thus may offer an index of brain aging or atrophy. In addition, GM and WM fractions, expressed as the ratio of GM and WM to TICV, respectively, were calculated. Regional brain volumes were examined using an optimized voxel-based morphometry (VBM) approach.[13] This technique "modulated" gray and white segmented image data described above so that the value in each voxel represented a regional volume. The images were then smoothed using a 14-mm Gaussian kernel. Differences between those who had survived for 6 years after imaging and those who had died were then tested for. Regional volumetric differences linked to sex or head size (TICV) were accounted for by introducing sex and TICV as nuisance variables into the model. T2-weighted MR images were scored for WM hyperintensities (WMHs) and periventricular hyperintensities (PVHs) according to a semiquantitative rating scale devised previously.[14]

Cognitive Testing and Clinical Examination

Moray House Test (MHT) scores of general mental ability from age 10.5 to 11.5 were available for all subjects from the records of the Scottish Mental Survey, 1932.[8] An entry criterion for this study was a Mini-Mental State Examination Score (MMSE) of 25 or greater. A trained psychologist administered Raven's Progressive Matrices,[15] a nonverbal reasoning measure of fluid-type intelligence, and the Auditory Verbal Learning Test,[16] which assesses short-term and longer-term memory, to obtain mental test scores from old age. Lifelong cognitive change was measured by calculating the change in Z score between MHT and RPM scores. Participants were reassessed in a structured clinical interview up to five times at intervals of 14 to 16 months to age 85. Ability to balance on one leg; time (seconds) to walk 6 m; and history of heart disease, diabetes mellitus, cerebrovascular disease, smoking, and treated hypertension were obtained at clinical assessment. A more-detailed description of the vascular characteristics of this group can be found elsewhere.[17] Fasting blood lipids were estimated in the Central Biochemistry Department, Aberdeen Royal Infirmary, and apolipoprotein E (APOE) genotype was determined as described previously.[18] Systolic and diastolic blood pressures (mmHg) were measured using an Omron digital sphygmomanometer (Omron Healthcare UK Ltd., Milton Keynes, United Kingdom) after 5 minutes of rest. Lung function was measured by spirometry using the highest value recorded during three attempts after one practice session with a spirometer (Microlab 3000, Micro Medical, Rochester, UK). Forced expiratory volume in 1 second was measured in liters per minute and adjusted for subject's height in meters. Means of three blood pressure measurements and maximal respiratory values were used in the analyses. A diagnosis of hypertension was based on mean systolic pressure greater than 139 mmHg, diastolic pressure greater than 94 mmHg, or use of an antihypertensive drug. The presence of cerebrovascular disease was determined according to clinical history of stroke confirmed by a physician or the presence of cortical or lacunar infarct on MRI, as assessed by a neuroradiologist (ADM). Physical and cognitive testing took place on average 16 ± 17 weeks before MRI.

Contact with participants was maintained by telephone throughout the follow-up period supplemented by postal recall for review. A trained research nurse interviewed (at 12- to 18-month intervals) all participants at the Research Unit or, more often in later years, at home or in residential care. Failure to agree to follow-up clinical examinations was associated with lower childhood mental ability, cognitive decline, and transfer to residential care. In addition, contacts with medical services were followed up, and possible progression to dementia was investigated in advance of planned review appointments. Vital status was recorded from public records (General Registrar Office for Scotland) and from local health records. By these means, all the original sample (N = 235) was traced up to May 12, 2006. An experienced clinical psychiatrist (DM or LW) reviewed the records of participants referred to old age psychiatry services, whose cognitive performance declined, or whose relatives were concerned about possible dementia. A research diagnosis of dementia was made by consensus between the research nurse and psychiatrists, with supporting evidence of decline in cognitive performance on repeat testing, clinical examination, and case note review, and these sources were sufficient to meet International Classification of Diseases, Tenth Revision, (ICD10) criteria for dementia.[19] Distinction was made using ICD10 criteria (www.who.int/classifications/apps/icd/icd10online/) between AD (F00), vascular dementia (01), and other dementias, including dementia with Lewy bodies (G31.8), and was based on all available clinical data with results of brain imaging.

Demographic Measures

Sex, years of education, and occupation of participants (usual occupational status, United Kingdom's Office of Population Statistics Classification 1990) were recorded at interview. Occupations were distributed between managerial (n = 9), professional (n = 10), administrative or managerial (n = 3), secretarial (n = 24), skilled manual (n = 21), semiskilled (n = 13), and unskilled (n = 15).

Statistical Methods

Associations between vital status at age 85 and global and regional brain MRI volumes were tested in two stages. First, exploratory general linear models (GLMs) or chi-square tests were used to identify variables predictive of death before the age of 86. Second, Cox regression analyses tested the study hypotheses by modelling time to death. Variables shown using GLM to be associated with death by age 85 were included as predictor variables in the Cox regression analyses, allowing the contributions of several covariables to be evaluated in a single model. Seventeen nonimaging measurements (continuous parameters in Table 1) were missing from the data set (1.3% of all data). The missing data imputation estimation available within the SPSS statistical package (SPSS, Inc., Chicago, IL) was applied to estimate missing values.

Table 1. Sample Characteristics at Recruitment Age 78

Characteristic	Alive at 85 n = 63	Dead at 85 (n = 35)
Male/female	34/29	22/13
Proportion of intracranial volume occupied by the brain	0.753 ± 0.030	0.739 ± 0.033[+]
Proportion of intracranial volume occupied by the gray matter	0.445 ± 0.022	0.441 ± 0.036
Proportion of intracranial volume occupied by the white matter	0.303 ± 0.018	0.298 ± 0.024
White matter hyperintensity score	1.24 ± 0.71	1.31 ± 0.83
Periventricular hyperintensity score	1.43 ± 0.64	1.54 ± 0.81
MHT at age 11	42.2 ± 11.2	40.5 ± 10.9
Mini-Mental State Examination score	28.2 ± 1.7	27.9 ± 1.6
RPM at age 78	29.6 ± 8.7	27.2 ± 8.6
Auditory Verbal Learning Test at age 78	50.7 ± 13.6	47.2 ± 14.1
Lifelong cognitive change (delta Z scores MHT and RPM)	0.04 ± 1.20	− 0.07 ± 1.16
Education, years	9.8 ± 1.6	9.7 ± 1.5
Body mass index, kg/m^2	26.5 ± 3.7	25.54.5
Diastolic blood pressure, mmHg[*]	77.2 ± 10.0	74.5 ± 11.4
Systolic blood pressure, mmHg[*]	147.6 ± 18.4	147.7 ± 22.2
Balance for 5 seconds, yes/no	55/8	24/11[+]
6-m walk time, seconds	6.62 ± 2.17	7.01 ± 2.10
Smoking history		
Never	22	10
Former	38	19
Current	2	6
Cerebrovascular disease, yes/no	17/45	11/24
Coronary heart disease, yes/no	16/48	10/25
Hypertension, yes/no	32/30	14/21
FEV in 1 second, L, adjusted for sex and height[†]	1.90 ± 0.38	1.98 ± 0.32
Diabetes mellitus, yes/no	4/58	2/33
Cholesterol, mmol/L	5.43 ± 1.38	5.34 ± 1.04
Triglycerides, mmol/L	1.96 ± 1.03	2.16 ± 1.20
Low-density lipoproteins, mmol/L	1.33 ± 0.43	1.29 ± 0.41
High-density lipoproteins, mmol/L	3.20 ± 1.00	3.08 ± 0.91
APOE ε4, yes/no	12/37	8/26
Incident dementia not otherwise specified, present/absent	10/53	21/14[+]

In some cases, data collection was not complete, and the total number of subjects is less than 98. Apolipoprotein E (APOE) genotyping was done for 83 (85%) of the participants.

[*] Average of three sitting measurements.

[†] Forced expiratory volume (FEV) (best of three) was adjusted for height and sex using a method previously suggested.[31]

[+] $P<.05$.

MHT = Moray House Test; RPM = Ravens Progressive Matrices.

RESULTS

Participants

By May 2006, 58 of the original study sample (N = 235; 25% of the whole cohort) had developed cognitive impairment, of whom 30 (13% of the whole cohort) met ICD10 criteria for probable AD. Over the same period, 31 of the subsample (n = 98) entered into the MRI study (32% of the imaged subsample) met ICD10 criteria for dementia of the Alzheimer type (F00), vascular dementia (F01), or atypical or mixed Alzheimer–vascular type (F00.2). Twenty-two of 56 men and 13 of 42 women had died (35% total deaths in the imaged subsample). Sample characteristics are presented according to vital status in Table 1. The results show that brain fraction, dementia, and the ability to balance on one leg at age 78 differed significantly according to vital status at age 85 years. These differences were maintained after adjustment for age when imaged. For survivors (n = 63, 65% of the imaged subsample) at age 85, dementia was absent in 53 and present in 10 (16% of the surviving imaged subsample). Of survivors without dementia, 22 were living independently in the community without mental or physical disability (35% of the surviving imaged subsample). Of 35 who had died, 21 were diagnosed with dementia before death (60% of the deceased imaged subsample), and 14 had died without evidence of dementia less than 6 months before death. Of the 31 subjects who met criteria for dementia, 15 met criteria for probable AD; other dementia diagnoses were vascular dementia or had imaging data to support mixed dementia pathologies (Alzheimer's and vascular). Table 1 shows that examination of differences between survivors with and without demential found no differences between any of the continuous variables measured (*t*-test $P<.05$) or any categorical measure (chi-square = 188 $P<.05$). More women than men had dementia, although not significantly so ($P=.10$). Those with dementia were less likely to be able to balance for 5 seconds on one leg ($P=.10$).

MRI and Survival

All MR images were acquired in 1999/2000. The influence of BF (the percentage of total intracranial volume occupied by the brain) on subsequent survival was tested using Cox proportional hazards regression using age at scanning as a covariable. This showed that BF was a significant predictor of survival ($P=.03$). BF was stratified into quartiles, and the lowest quartile was compared with the three higher quartiles and a Kaplan-Meier graph plotted (Figure 1). The lowest BF quartile comprised participants with BF values less than 0.726. The relative risk of death associated with BF less than 0.726 was 2.765 (95% confidence interval (CI) 1.047–7.305) (Figure 1). The relative risks of death associated with dementia and balance were 7.96 (95% CI = 3.06–20.68) and 3.03 (95% CI = 1.11–8.23), respectively. Comparing the lowest two quartiles with the highest two and the highest against the other three did not yield significant results.

Survival was examined using a multivariate Cox regression, forward conditional ($P<.05$) approach by first using dementia and sex as categorical variables and BF and age at imaging as continuous covariables. This showed that dementia and BF were independent predictors of survival (dementia $P<.001$, BF $P=.04$), and that sex and age at imaging did not significantly contribute to the prediction of death. Next, in addition to dementia and BF, balance was introduced (as a categorical yes or no variable), and it was found that balance was not an independent predictor of survival (dementia $P<.001$, BF $P=.03$, balance $P=.16$).

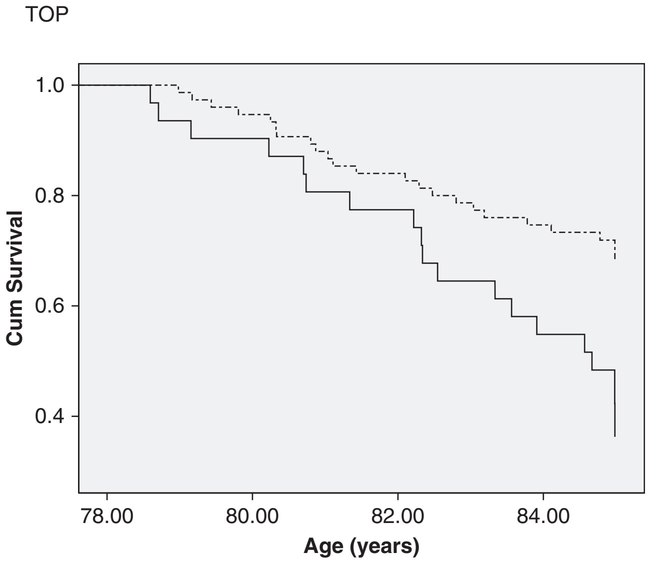

Figure 1. Kaplan-Meier graph for individuals with a brain fraction of 0.726 or greater (dotted line/upper three quartiles) and less than 0.726 (solid line/lowest quartile).

MRI-Derived Regional Brain Volumes and Survival

The GM and WM regional differences between survivors and those who died were explored using statistical parametric mapping VBM. Using GLM and adjusting for sex, age at imaging, and TICV, the survivors were compared with those who died (Figure 2). Findings in gray matter identified significant voxels ($P<.05$ after correction for multiple comparisons using a false detection rate (FDR) approach) bilaterally in the parietal lobes, in the left medial temporal lobe, and in the left frontoparietal region. The WM results also showed two significant brain regions: bilaterally in the parietal lobes and the right posterior temporal region and unilaterally in the left anterior temporal lobe ($P<.05$ FDR corrected). In each case, the uncorrected threshold was $P<.001$. The introduction of age at imaging had no influence on the pattern of significant associations. In addition to the whole-group VBM analysis, a comparison was performed between the subgroups with and without dementia. No significant differences were found between those who survived and those who died in either of the subgroups. This is possibly due, at least in part, to the reduced statistical power because of the small number of subjects.

The whole-sample VBM analysis identified areas associated with survival. What is unclear is whether the subsequent diagnosis of dementia could explain these associations. To analyze further the significance of these regions, estimates of the GM and WM volumes in each significant cluster were extracted for each participant from the segmented imaging data. The extracted values for each cluster were first entered separately into a Cox regression along with sex for the whole group and the subgroups with

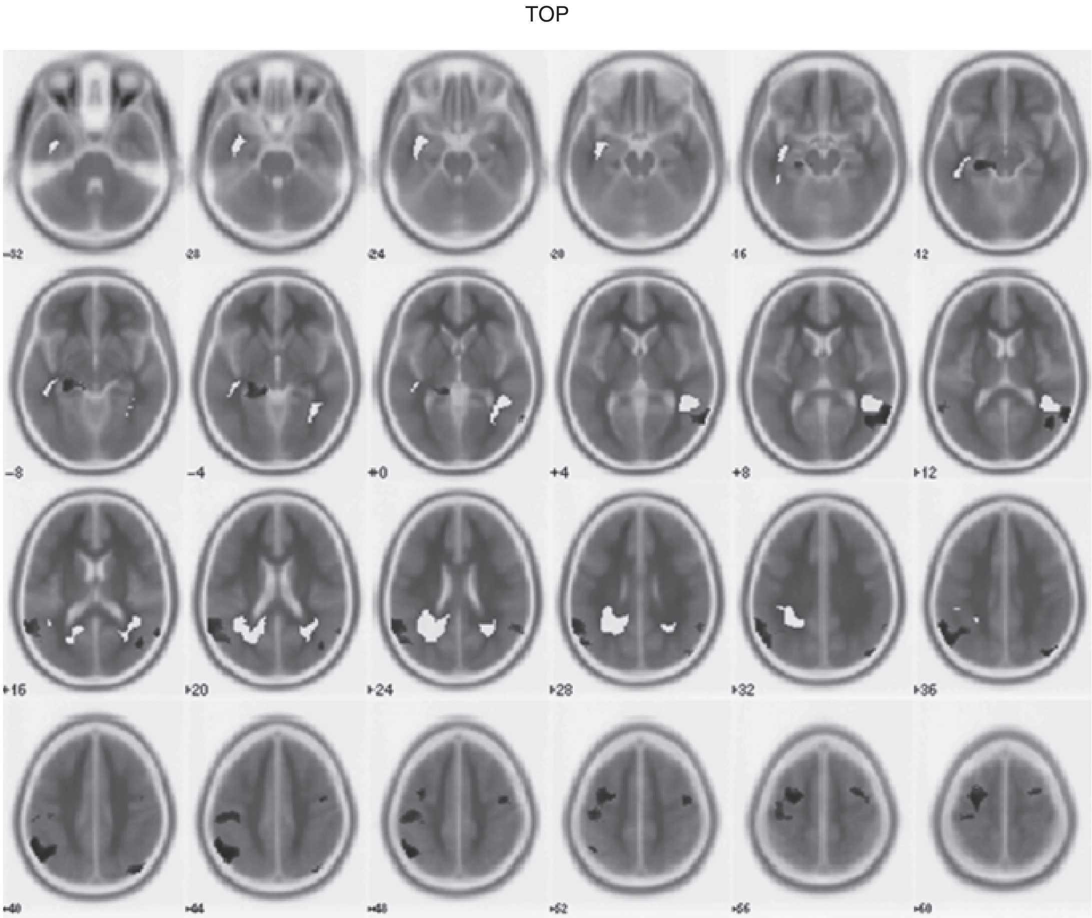

Figure 2. Voxel-based morphometry findings for comparisons of subjects who survive and those who died. Black regions within the brain represent gray matter differences. White regions within the brain represent white matter differences. Uncorrected threshold: $P<.001$. Cluster level significance: $P<.05$. Nuisance variable: sex, age at imaging, and total intracranial volume.

and without dementia. After sex was adjusted for, the hazard ratios were then calculated for each cluster for two groups (one above and one below the median standardized cluster volume).

Table 2 shows that the VBM-extracted values for each cluster predict survival in the whole sample. This was to be expected because the voxels in clusters were shown to predict survival in the mapping analysis. The hazard ratio calculated using subjects above and below the median indicate a two to three times greater risk if the volume in the cluster was below the median.

The subsample without dementia produced results similar to the whole sample. In the subsample without dementia, the white parietal and temporal clusters indicated a greater risk of death, as did the gray frontoparietal cluster. The extracted value obtained from the other cluster did not reach statistical significance, although when tested in a similar manner, the trend was consistent. The reduced power could explain the lack of significance.

A Cox regression model was constructed, using the whole sample, first with dementia and sex as categorical variables and left parietal GM volume as a continuous variable. Dementia, GM volume, and sex were found to be significant independent predictors of death (dementia $P<.001$, left parietal GM volume $P=.008$, sex $P=.02$). The left parietal region was chosen because it contained the most significant location in the statistical parametric mapping analysis. Next, in addition to these, balance was added as a categorical variable, and this showed that balance was not an independent predictor of survival (dementia $P<.001$, GM volume $P=.002$, sex $P=.005$, balance $P=.21$). When TICV (a proxy for premorbid brain volume) was introduced into this model, all significant predictors of death were retained. Balance and TICV were not predictors of death. When balance and BF are modeled together without dementia, each independently predicts survival (balance $P=.03$; BF $P=.04$). A model that included dementia and balance found that balance was not independent of dementia for the prediction of survival.

Similarly, WM right parietal lobe adjusted cluster volume (the most significant location) and dementia in a Cox regression were found to predict death (dementia $P<.001$, WM volume $P<.001$, sex $P=.004$). As before, adding balance to the model showed that it was not independently significant (dementia $P<.001$, WM volume $P<.001$, sex $P=.002$, balance $P=.61$). Adding TICV to the model made no difference to the pattern of significance.

The following variables were then introduced separately into the dementia, parietal WM, and sex model: preexisting heart disease, hypertension, history of cerebrovascular disease, lung function, obesity, walk time, current cognitive function, childhood cognitive ability, APOE ε4 status (83 of

Table 2. Hazard Ratios (HRs) for Survival According to Clusters Identified Using VBM

	HR (95% Confidence Interval)		
Region	**Whole Sample**	**Without Dementia**	**With Dementia**
Gray			
Left parietal	0.36 (0.18–0.75)***	0.28 (0.09–0.90)**	0.50 (0.20–1.26)
Right parietal	0.43 (0.21–0.87)***	0.56 (0.19–1.64)*	0.77 (0.28–2.10)
Right frontal parietal	0.37 (0.18–0.76)***	0.34 (0.11–1.02)*	0.66 (0.26–1.73)*
Right temporal	0.56 (0.29–1.14)**	0.57 (0.19–1.69)*	0.61 (0.25–1.48)
Left frontal	0.44 (0.22–0.88)**	0.50 (0.17–1.46)*	0.57 (0.22–1.49)
White			
Left parietal	0.40 (0.20–0.82)***	0.38 (0.12–1.19)**	0.36 (0.14–0.92)**
Right parietal	0.33 (0.16–0.68)***	0.41 (0.14–1.24)*	0.36 (0.13–0.98)*
Right temporal	0.33 (0.16–0.68)***	0.58 (0.38–3.21)*	0.49 (0.19–1.27)**

Values shown above indicate where, using a Cox regression, the extracted VBM cluster value (a continuous variable) had a significant association with survival. Sixty-three participants survived (53 without dementia, 10 with dementia), and 35 died (14 without dementia, 21 with dementia).

P < * .05, ** .01, *** .001; the HR for the clusters found using voxel-based morphometry (VBM). Each HR represents the relative risk for death of two groups (one above and one below the median extracted VBM volume within the cluster, for the whole sample).

the 98 participants (85%) had their APOE genotype determined), education (years), smoking history, WMH, PVH, cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and diabetic status. No additional significant relationships were found. Including both of the parietal volume estimates (GM and WM), it was found that parietal WM significance was retained, and parietal GM was lost (dementia $P<.001$, parietal WM volume $P=.003$, parietal GM volume $P=.98$, sex $P=.004$). From the sample and data set, a combination of dementia status, sex, and parietal WM volume were together the best predictors of survival.

DISCUSSION

The main result is that smaller global and regional brain volumes are more associated than intracranial volume with shorter survival from age 78 to 85. This association is independent of sex or subsequent dementia. MRI brain regional volume differences between those who survived and those who died, characteristic of Alzheimer's pathology, were found in the absence of clinical dementia. Regional findings were therefore independent of the presence of dementia.

Possible relationships between brain volumes and survival have not been widely examined. No studies on MRI-derived regional brain differences and mortality were found in a review of the relevant literature. The Cardiovascular Health Study examined the density of WMHs and ventricular volumes (as a proxy for cortical atrophy) and found that greater ventricular size and more WMHs are associated with greater risk of death during follow-up.[20] These results were consistent with this volumetric finding, but the current study did not find an association with WMHs.

The strengths of the study are the analysis of regional brain GM and WM volumes with adjustment for risk factors for mortality. In addition, the subgroups of survivors and those who died were matched at baseline for an extensive list of functional, cognitive, and vascular measures. Recruitment to a brain imaging study of participants who were in good general health and from a narrow age range facilitated interpretation of survival data. There are, however, certain limitations. Those who participated in imaging were a self-selected subsample of those invited at random to take part and may not have been representative of the population from which they were drawn, being healthier and less likely to be cognitively impaired. The baseline comparison (Table 1) reported here may be limited, and it is possible that some cognitive or functional difference existed that the baseline measures could not identify. In addition, some dementia cases were probably missed because not all incident dementias could be ascertained, and participants might therefore have been misidentified as dying without dementia. This would have increased the likelihood of the erroneous conclusion that BF and dementia are independent predictors of death when they may not be. The relatively short intervals between last review and death (always <6 months) probably reduced the number of missed dementia cases.

The primary hypotheses concerned regional brain BM and WM volumetric measures and the prediction of survival. These differences were partly explained when dementia was introduced into the model and concerned those regions of GM typically affected early in AD. From this, it was concluded that the presence of prodromal AD in participants who were without a clinical diagnosis of dementia largely explained the main findings. The association between smaller WM volume in the white posterior parietal lobe and greater mortality without dementia could suggest that this brain area might contribute to greater susceptibility to age-related disease and through this to greater mortality. Alternatively, it may be that mortality and WM volume loss share a common cause, namely age-related disease. It would not be possible to identify the causal direction in this sample. A younger sample imaged in early midlife and tracked longer may answer this question.

These findings are relevant to brain imaging studies of cortical atrophy in prodromal (preclinical) AD. The neuropathological changes of AD are detectable many years before clinical dementia is apparent. Histological lesions (amyloid plaques and neurofibrillary tangles) precede neuronal and brain volume losses.[21] A large body of evidence[22] shows that structural MRI studies contribute to the early detection of AD and to prediction of progression to dementia, but problems remain in the structural evaluation of mixed pathologies (most often when vascular changes and AD coexist). In early AD, the focus of interest is in progressive changes in the entorhinal cortex and hippocampus, whereas in this study, loss of volume was associated with poorer survival. It is therefore reasonable to argue in the face of lack of evidence of dementia that prodromal AD accounts for differences in survival between subjects. Consistent with this view are the many reports that brain imaging changes arise earlier in the course of AD than the occurrence of the first clinical evidence of dementia in those at high risk of dementia[23,24] and in the general population.[25]

Survival to death after dementia diagnosis varies widely between individuals but is consistently shorter than survival of comparable members of the general population without dementia.[26–29] If it is assumed that survival from the preclinical phase is consistently greater than survival from the clinical (postdiagnostic) phase, then it is reasonable to suggest that median survival times in this sample (when aged 78) would be greater than median estimates of between 4 and 6 years in a general U.S. population sample of dementia sufferers.[28] Therefore, more than half of the study sample who developed dementia should have survived up to the final census point, although such comparisons are not straightforward because younger dementia sufferers typically survive longer than the older patients reported here, and survival from diagnosis may be shorter than accepted estimates.[30] In this study, it is possible that some subjects remained free of clinical dementia up to the time of death and that their shorter survival was related to the presence of prodromal AD brain pathology.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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Author Contributions: Whalley (principal investigator), Staff, Murray, and Deary designed the study, applied for funding, and analyzed and interpreted the results. Whalley and Staff wrote the first drafts of the manuscript. Starr was involved in study design, analysis, and data interpretation. Deary revised the manuscript before submission. Ahearn and Salariad were involved in analysis of MRI data, supervised by Murray and Staff. Lemmon recruited the participants, obtained written informed consent, and with Herbert, obtained follow-up data. Whalley, Mowat, and Lemmon obtained follow-up data and, with Murray and Staff, provided consensus diagnoses of outcome and approved the final version of the manuscript.

All authors participated in the study as described above, have no conflicts of interest, and have seen and approved the final version of the manuscript.

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REFERENCES

1. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: Current concepts, and estimates from the Framingham study. Lancet Neurol 2007;6:1106–1114.
2. Goldacre MJ, Duncan ME, Griffith M et al. Psychiatric disorders certified on death certificates in an English population. Soc Psychiatry Psychiatr Epidemiol 2006;41:409–414.
3. Ridha BH, Barnes J, Bartlett JW et al. Tracking atrophy progression in familial Alzheimer's Disease: A serial MRI study. Lancet Neurol 2006;5:828–834.
4. MacLullich AMJ, Ferguson KJ, Deary IJ et al. Intracranial capacity and brain volumes are associated with cognition in healthy elderly men. Neurology 2002;59:169–174.
5. Whalley LJ, Deary IJ. Longitudinal cohort study of childhood IQ and survival up to age 76. Br Med J 2001;322:819–822.
6. Ebikryston KL. Respiratory symptoms and pulmonary-function as predictors of 10-year mortality from respiratory-disease, cardiovascular-disease, and all causes in the Whitehall Study. J Clin Epidemiol 1988;41:251–260.
7. Ostbye T, Krause KM, Norton MC et al. Ten dimensions of health and their relationships with overall self-reported health and survival in a predominately religiously active elderly population: The Cache County Memory Study. J Am Geriatr Soc 2006;54:199–209.
8. Scottish Council for Research in Education. The Intelligence of Scottish School Children: A National Survey of an Age Group. London, UK: University of London Press, 1933.
9. Deary IJ, Whiteman MC, Starr JM et al. The impact of childhood intelligence on later life: Following up the Scottish Mental Surveys of 1932 and 1947. J Pers Soc Psychol 2004;86:130–147.
10. Ashburner J, Friston KJ. Voxel-based morphometry—the methods. Neuroimage 2000;11:805–821.
11. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imag 1998;17:87–97.
12. Rudick RA, Fisher E, Lee JC et al. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Neurology 1999;53:1698–1704.
13. Good CD, Johnsrude IS, Ashburner J et al. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14:21–36.
14. Fazekas F, Kleinert R, Offenbacher H et al. Pathological correlates of incidental MRI white-matter signal hyperintensities. Neurology 1993;43:1683–1689.
15. Raven JC. Guide to the Progressive Matrices. London, UK: Lewis, 1960.
16. Query WT, Megran J. Age-related norms for AVLT in a male patient population. J Clin Psychol 1983;39:136–138.
17. Murray AD, Staff RT, Shenkin SD et al. Brain white matter hyperintensities: Relative importance of vascular risk factors in nondemented elderly people. Radiology 2005;237:251–257.
18. MacLeod MJ, De Lange RP, Breen G et al. Lack of association between apolipoprotein E genotype and ischaemic stroke in a Scottish population. Eur J Clin Invest 2001;31:570–573.
19. World Health Organization. International Classification of Disease (ICD) 311. 1992.
20. Kuller LH, Arnold AM, Longstreth WT Jr. et al. White matter grade and ventricular volume on brain MRI as markers of longevity in the Cardiovascular Health Study. Neurobiol Aging 2007;28:1307–1315.
21. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 1991;82:239–259.
22. Scheltens P. Neuroimaging in dementia: Beyond exclusion. Neurobiol Aging 2002;23:2059.
23. Convit A, DeLeon MJ, Tarshish C et al. Specific hippocampal volume reductions in individuals at risk for Alzheimer's disease. Neurobiol Aging 1997;18:131–138.
24. Reiman EM, Uecker A, Caselli RJ et al. Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. Ann Neurol 1998;44:288–291.
25. Morris JC. Mild cognitive impairment and preclinical Alzheimer's disease. Geriatrics 2005;Suppl:9–14.
26. Brookmeyer R, Corrada MM, Curriero FC et al. Survival following a diagnosis of Alzheimer disease. Arch Neurol 2002;59:1764–1767.
27. Hui JS, Wilson RS, Bennett DA et al. Rate of cognitive decline and mortality in Alzheimer's disease. Neurology 2003;61:1356–1361.

28. Larson EB, Shadlen MF, Wang L et al. Survival after initial diagnosis of Alzheimer disease. Ann Intern Med 2004;140:501–509.
29. Ganguli M, Dodge HH, Shen CY et al. Alzheimer disease and mortality—a 15-year epidemiological study. Arch Neurol 2005;62:779–784.
30. Wolfson C, Wolfson DB, Asgharian M et al. A reevaluation of the duration of survival after the onset of dementia. N Engl J Med 2001;344:1111–1116.
31. Hole DJ, Watt GCM, DaveySmith G et al. Impaired lung function and mortality risk in men and women: Findings from the Renfrew and Paisley Prospective Population Study. BMJ 1996;313:711–715.