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Ventricular volume and dementia progression in the Cardiovascular Health Study

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Abstract

Elevated cerebral ventricular volume may be associated with dementia risk and progression. A fully-automated technique that agreed highly with radiological readings was used to estimate lateral ventricle volume on MR scans done at baseline in 1997-99 of 377 subjects in the Cardiovascular Health Study (CHS) from the Pittsburgh center. 327 subjects were normal or diagnosed with mild cognitive impairment (MCI) at baseline and were evaluated 4 years later. Baseline ventricular volume was analyzed in multivariate models with age, gender, education level, presence and incidence of cerebral infarcts, and dementia category (normal, MCI, or dementia) at baseline and follow-up as fixed effects. Ventricular volume at baseline was significantly higher among subjects normal at baseline and demented 4 years later. Age, gender, education level, and dementia progression were significant factors affecting ventricular volume. Ventricular volume was higher in dementia compared to MCI, higher in MCI compared to controls, and higher in Possible-Alzheimer's-Disease (AD) dementia compared to Probable-AD. Larger ventricles in healthy subjects may indicate susceptibility to, or progression of, dementia-related pathology.

1 Introduction

A robust body of cross-sectional studies have shown that structural brain changes in Alzheimer's Disease (AD), other dementias, and mild cognitive impairment (MCI) are detectable through measures derived from magnetic resonance (MR) images [20] [8]. Additionally, a growing number of prospective studies have given preliminary evidence that MR-derived measures of region-of-interest (ROI) atrophy, white matter lesions, and infarcts have the potential to be useful predictors of cognitive decline. In particular, baseline volumes of temporal lobe structures, estimated by manually or semi-manually tracing structures on MR images, have shown initial promise for predicting cognitive decline in small groups of elderly normal or MCI subjects at

follow-up evaluations one to three years later [13] [42] [25] [9] [45]. Semi-quantitative MR image ratings, evaluated by trained radiologists, have also shown potential for assessing risk of future cognitive decline in much larger, community-based subject pools [37] [44] [27] [31].

This study provides a prospective analysis of MR-based lateral ventricle volume as a risk factor for cognitive decline in a group of subjects from a large, community-based cohort of elderly individuals. We aim to combine three important characteristics that were found to varying degrees in prior studies. First, we use a fully-automated method for estimating lateral ventricle volume that requires no human intervention, thus removing trained human operators as sources of variability that may limit the reproducibility of results. Second, we assess a large, well-characterized community-based cohort in order to alleviate issues of selection bias and small sample sizes. Third, we relate baseline measurements of ventricular volume to future transitions between normal cognitive function, MCI, and dementia. Prior work employed automated MRI processing techniques for prospective analysis of AD in a smaller sample with different selection criteria than those of the CHS [16]. Other studies used automated techniques for cross-sectional analysis of healthy aging, in some cases over a large subject pool [21][46]. However, we feel this study is unique in combining prospective analysis of AD, automated techniques, and a large community-based sample. Specifically, we estimate ventricular volume for all subjects who received an MRI between 1997 and 1999 as part of the CHS Cognition Study. We provide a cross-sectional analysis of these volumes, as well as a prospective study relating 1997-99 ventricular volume to 1997-99 and 2002-03 clinical characteristics for those subjects who completed a follow-up examination four years later.

We focus on lateral ventricle volumetry due to previously-reported associations between dementia risk and ventricle-related MRI findings at baseline [27] [37]. Furthermore, abnormally fast ventricular dilation over time has been linked to antemortem levels of AD-related pathological features [39], rates of cognitive decline in AD patients and controls [1] [10], and pre-mortem AD diagnosis [12] [33] [43]. Additionally, cross-sectional studies have suggested associations between ventricular size and cognitive test scores [35] [3] [28], vascular risk factors [23], and presence of AD, MCI, and vascular dementia [14] [15]. These studies complement the growing body of studies demonstrating that MR-based measures of hippocampal volume progression may provide useful indicators of dementia progression [18] [24].

1998 Diagnosis	2002 Diagnosis	N
Normal	Normal	147
MCI	MCI	21
Normal	MCI	59
MCI	Dementia (possible-AD)	19
	Dementia (probable-AD)	20
Normal	Dementia (possible-AD)	21
	Dementia (probable-AD)	28
MCI	Normal	12

Table 1: Categorization of subjects in the prospective pool by dementia diagnoses at baseline (1998) and follow-up (2002).

2 Methods

2.1 Subjects

There were 388 subjects who received clinical evaluations and high-resolution MR scans in 1997-99 as part of the CHS Cognition Study at the Pittsburgh center. Details of the diagnostic criteria and clinical evaluation have been reported previously [32] [30]. A prospective pool of 333 subjects who were non-demented at baseline returned for follow-up clinical examination in 2002-03 at which time they were classified into normal, MCI, or dementia groups. As part of the 1997-99 and 2002-03 evaluations, dementia cases were diagnosed as Non-Alzheimer's-Disease (AD), Possible-AD, or Probable-AD dementia based on established NINCDS-ADRDA criteria [34]. Briefly, a Probable-AD diagnosis required progressive memory loss and deficits in two or more areas of cognition as measured by standardized neuropsychological testing. Additionally, findings of impaired daily activities, specific cognitive deficits in areas such as language and motor skills, and a family history of AD support a Probable-AD diagnosis. A Possible-AD diagnosis is supported by findings of an additional brain disease or systemic disorder that could account for clinical symptoms, such as stroke or major depression, or by variations in dementia onset, presentation, or clinical course. Subjects diagnosed with Non-AD dementias at baseline (N=6) and follow-up (N=5) were excluded from analysis due to their rarity and high variability in clinical features, leaving a cross-sectional pool of 377 subjects and prospective pool of 327 subjects for all subsequent analysis. Inclusion of Non-AD subjects did not significantly affect any of the findings reported below. Subjects in the prospective pool were assigned to dementia

	1997-99 Normal	1997-99 MCI	1997-99 Dementia
Age in 1997-99 (Mean, S. D.)	72.7, 3.56	74.4, 4.45	77.9, 5.51
Gender (Female, Male)	161, 103	46, 34	21, 12
Race (Caucasian, African-American, Other)	217, 47, 0	56, 23, 1	27, 6, 0
Education Level (Up to, beyond high school)	93, 171	38, 42	17, 16
Hachinski Ischemic Scale (Mean, S. D., N/A)	.99, 1.32, 36	1.64, 1.21, 21	1.63, 1.62, 6
Unified Parkinson Disease Rating Scale (UPDRS; Mean, S.D.)	3.87, 3.62, 36	7.73, 5.89, 21	12.15, 9.42, 6
Modified Mini Mental State Exam (3MSE; Mean, S.D.)	96.17, 3.93	90.3, 6.73	77, 14.3
Digit-Symbol Substitution Test (DSST; Mean, S.D.)	47.25, 12.33	37.76, 12.42	27.3, 12.93

Table 2: Demographic data for subjects in the cross-sectional pool, broken out by 1997-99 dementia diagnosis.

progression groups according to dementia diagnoses at both baseline and follow-up (see Table 1). Note that 16.4% of subjects diagnosed with MCI at baseline were re-classified as normal on follow-up, and previous community-based studies have reported similar re-classification rates [19]. Demographic information for the cross-sectional subject pool is shown in Table 2.

2.2 MRI Acquisition and Processing

High-resolution MR images were collected in 1997-99 using a 1.5T Signa scanner (GE Medical Systems) with high performance gradients (4 G/cm and 150 T/m-s). The subjects were positioned in a standard head coil and a volumetric Spoiled Gradient Recalled Acquisition (SPGR) sequence with parameters optimized for maximal contrast among gray matter, white matter, and cerebrospinal fluid was acquired in the coronal plane (TE/TR = 5/25, flip angle = 40 deg., NEX = 1, slice thickness = 1.5mm/0mm interslice).

Lateral ventricular volumes were estimated fully automatically on all high-resolution scans using a technique described in a previous study and validated on a set of dilated ventricles [5] [6]. In short, images were resampled to obtain 1x1x1 mm^3 voxels, anisotropically smoothed [41], skull-stripped [40], cropped to remove all-zero planes, and nonlinearly aligned [7] to a reference image on which the lateral ventricles had been traced by an trained rater. The reference image was a randomly-selected MR image of a control subject from a previous study [6]. The lateral ventricles were delineated on the reference image to include the frontal horn and body, as well as the temporal and posterior horns, using a tracing protocol described previously [36]. The alignment between subject and reference images allowed the ventricle tracing to be transferred from the reference image to the subject image. The ventricle-to-brain ratio (VBR) was calculated by measuring ventricular volume in the native space of each subject image and normalizing by the volume of a whole-brain mask calculated by the skull-stripping software. The whole-brain mask included parenchyma and ventricular and sulcal CSF spaces. VBR was used as the measure of ventricular volume in

all subsequent analysis. However, we note that we achieved results very similar to those below by using the raw ventricular volume– not normalized by whole-brain volume– in the statistical analysis.

In addition, lower-resolution MR scans were acquired in 1997-99 among the cross-sectional pool, and in both 1997-99 and 2002-03 among the prospective pool, for adjudication purposes. The scanning protocol included standard sagittal T1-weighted and axial T1-weighted, spin-density, and T2-weighted images– all with 5-mm thickness and no inter-slice gaps. The lower-resolution MR images were evaluated by neuroradiologists using procedures described previously [26] [4] [29]. A cerebral infarct was defined as an area of abnormal signal in a vascular distribution that lacked of mass effect. Infarcts in the cortical gray and deep nuclear regions had to be brighter on spin density and T2-weighted images than normal grey matter. Infarcts in the white matter were similarly defined except that they had to be hypodense in T1-weighted images to distinguish them from diffuse white matter disease. We emphasize that the analyses below relate ventricular volume measured on 1997-99 high-resolution MR scans to clinical variables gathered in 1997-99 and 2002-03. Infarcts on low-resolution 2002-03 scans were the only source of imaging data from 2002-03 included in statistical models of the prospective group.

2.3 Statistical Analysis

Fixed-effects linear statistical models evaluated the impact of clinical and demographic factors on VBR at time of study enrollment. Subject age, gender, education, and presence of infarcts on 1997-99 and/or 2002-03 low-resolution MR scans were entered as fixed effects of each model. Education was dichotomized into two levels: up to, *vs.* beyond high school level. Presence of infarcts was dichotomized into two levels for the prospective group: zero infarcts in both 1997-99 and 2002-03, *vs.* one or more infarcts in 1997-99 and/or 2002-03. Presence of infarcts was also dichotomized into two levels for the cross-sectional group: zero infarcts in 1997-99, *vs.* one or more infarct in 1997-99. An additional factor corresponding to dementia status was entered into each model. For the cross-sectional pool, this factor corresponded to dementia diagnosis at time of study enrollment (normal, MCI, or dementia), while in the prospective pool, the factor corresponded to dementia progression group as described in Table 1. In both the cross-sectional and prospective analyses, two models were estimated: one grouped all demented subjects into the same category, and the other specified dementia type by NINCDS-ADRDA criteria (Probable-AD and Possible-AD, respectively). The significance of each model factor was evaluated by omnibus F tests, and significant differences between pairs of factor levels (*e.g.*, between control and MCI groups) was evaluated by focused

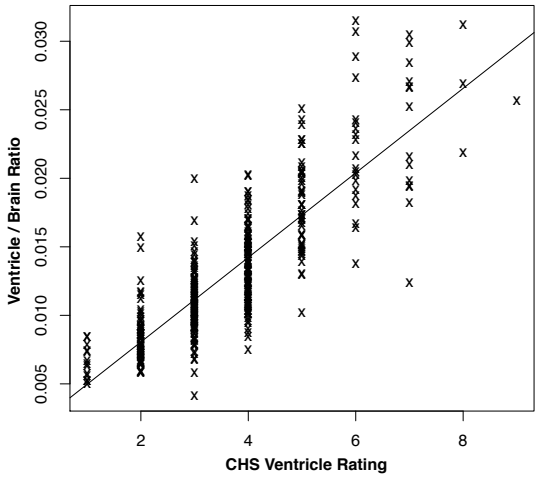

Figure 1: Agreement between visual assessment of ventricular dilation (x axis) and ventricular volume computed by the fully-automated technique (y axis) in the cross-sectional pool (N=377). The best-fit line for the data is also shown. The fraction of variance explained, R^2, is .698.

F tests between the model coefficients for those factor levels. To reduce the number of comparisons between prospective groups, we only tested differences between pairs of groups with the same 1997-99 diagnosis. Effect size was measured by the contrast coefficient $r_{contrast}$ [38].

3 Results

3.1 Agreement Between Manual and Automated Ventricular Assessments

Figure 1 compares VBR computed by the automated method on the cross-sectional pool to the visual ratings of ventricular dilation that were part of the CHS clinical evaluation. Details of the visual rating scale have been described previously [47]. In short, trained neuroradiologists assigned each MR scan an integer score between 1 and 9, with lower scores corresponding to relatively small ventricles and higher scores corresponding to relatively large ones. Agreement between the visual ratings and VBR was high in the cross-sectional pool ($R^2 = .698$), suggesting that the automated method was able to robustly and accurately estimate ventricular size in concordance with radiological readings.

3.2 Cross-Sectional Analysis

Table 3 summarizes a linear model of the cross-sectional data with all dementia cases pooled into a single factor level. VBR significantly increased with age, was higher in men, and was significantly affected by dementia category. Significant differences between pairs of dementia categories in this model are summarized

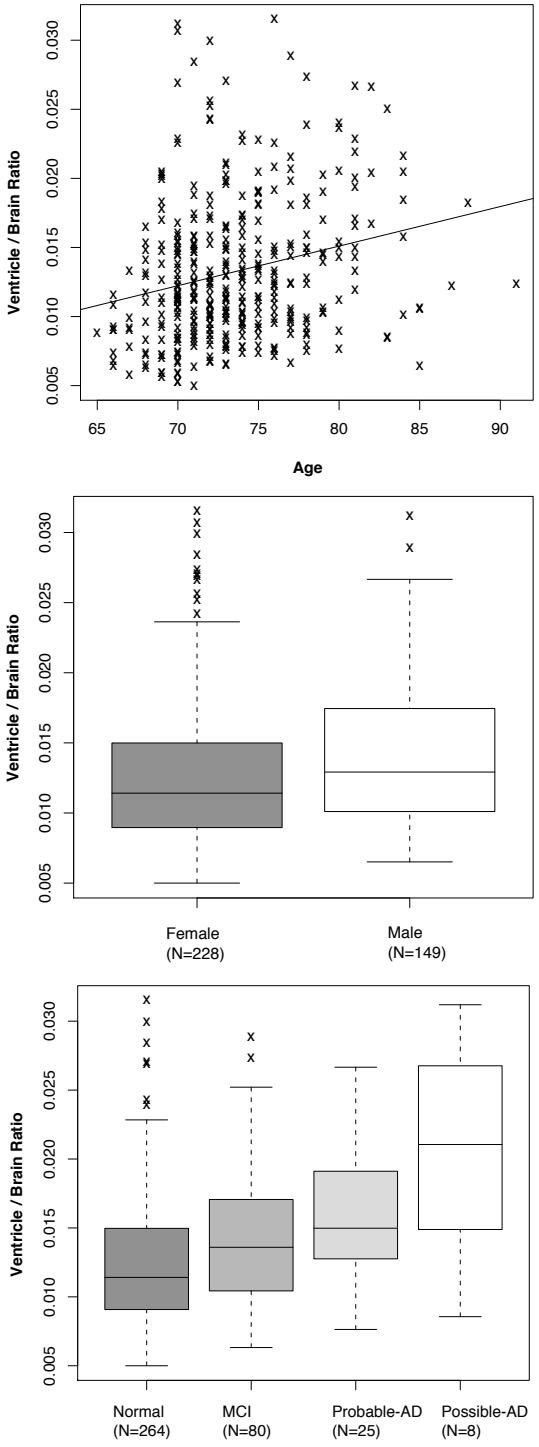

Figure 2: Ventricle-to-brain ratio as a function of age, dementia category, and gender in the cross-sectional analysis.

Factor	F	df	p	$r_{contrast}$
Age	**5.7544**	**1**	**0.0169**	**0.1239**
Gender	**4.0731**	**1**	**0.0443**	**0.1045**
Education	3.2203	1	0.0736	0.0930
Infarcts	0.6071	1	0.4364	0.0405
Dementia Status	**10.1027**	**3**	**¡ .0001**	**0.1632**

Table 3: Summary of cross-sectional model relating clinical factors to ventricular volume. The F value, degrees of freedom, p value, and effect size of each factor is shown. Factors with $p < .05$ are shown in bold.

Contrast	F	p	$r_{contrast}$
MCI *vs.* Dementia	**6.8097**	**0.0094**	**0.1344**
Normal *vs.* Dementia	**21.2190**	**<0.0001**	**0.2329**
MCI *vs.* Normal	**7.5889**	**0.0062**	**0.1418**
Possible-AD Dementia *vs.* Probable-AD Dementia	**5.5482**	**0.0190**	**0.1217**

Table 4: Summary of differences between dementia categories in the cross-sectional model. Differences with $p < .05$ are shown in bold.

in Table 4. VBR was significantly higher in MCI subjects compared to controls, and significantly higher in demented subjects compared to MCI subjects. Among dementia subjects, VBR was significantly higher in Possible-AD cases compared to Probable-AD cases. Figure 2 plots VBR as a function of age, gender, and dementia category in the cross-sectional analysis.

3.3 Prospective Analysis

Table 5 summarizes a linear model of the prospective data. As in the cross-sectional models, VBR at enrollment time was affected significantly by age, gender, and dementia progression category. Additionally, VBR was significantly higher among subjects with educational level beyond high school. Table 6 summarizes differences between dementia progression categories that had the same enrollment-time diagnoses. VBR was significantly higher among initally-normal subjects who declined to dementia compared to those that remained stable or declined to MCI. Differences in VBR between normals that remained stable and those

Factor	F	df	p	$r_{contrast}$
Age	**7.8421**	**1**	**0.0054**	**0.1573**
Gender	**6.9792**	**1**	**0.0087**	**0.1486**
Education	**4.6336**	**1**	**0.0321**	**0.1215**
Infarct1	0.4455	1	0.5050	0.0379
Infarct2	0.4302	1	0.5124	0.0373
Conversion	**4.4228**	**5**	**0.0007**	**0.1188**

Table 5: Summary of prospective model relating clinical factors to baseline ventricular volume. The F value, degrees of freedom, p value, and effect size of each factor are shown. Factors with $p < .05$ are shown in bold.

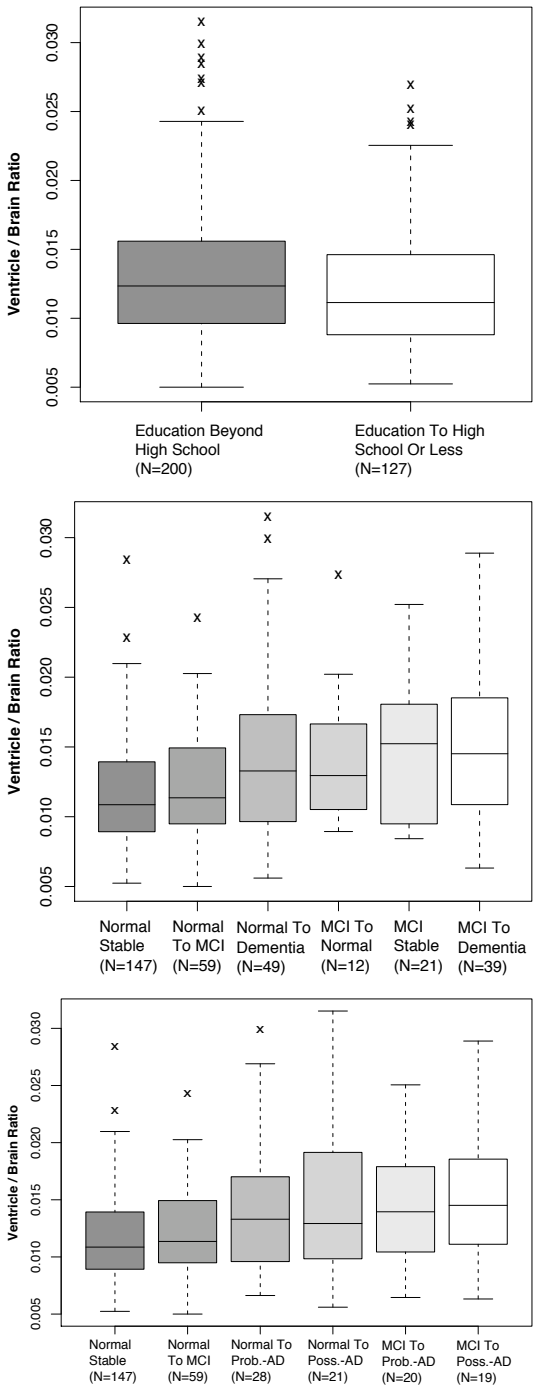

Figure 3: Plots of significant factors in the prospective model of baseline ventricular volume.

Contrast	F	p	$r_{contrast}$
Normal Stable *vs.* Normal To MCI	0.5710	0.4504	0.0429
Normal To MCI *vs.* Normal To Dementia	**6.2064**	**0.0133**	**0.1403**
Normal Stable *vs.* Normal To Dementia	**12.8439**	**0.0004**	**0.1998**
MCI Stable *vs.* MCI To Dementia	0.0258	0.8725	0.0091
MCI Stable *vs.* MCI To Normal	0.1531	0.6959	0.0223
MCI To Normal *vs.* MCI To Dementia	0.0880	0.7669	0.0169

Table 6: Summary of differences between dementia categories in the prospective model of baseline ventricular volume. Differences with $p < .05$ are shown in bold.

Contrast	F	p	$r_{contrast}$
Normal *vs.* Normal To Possible-AD	**6.6000**	**0.0107**	**0.1451**
Normal *vs.* Normal To Probable-AD	**8.0439**	**0.0049**	**0.1598**
Normal To MCI *vs.* Normal To Possible-AD	3.6261	0.0578	0.1080
Normal To MCI *vs.* Normal To Probable-AD	**4.3357**	**0.0381**	**0.1180**
Normal To Possible-AD *vs.* Normal To Probable-AD	0.0006	0.9803	0.0014
MCI Stable *vs.* MCI To Possible-AD	0.0715	0.7893	0.0153
MCI Stable *vs.* MCI To Probable-AD	0.2749	0.6005	0.0299
MCI To Possible-AD *vs.* MCI To Probable-AD	0.5803	0.4468	0.0434

Table 7: Summary of differences between Possible-AD and Probable-AD cases in the prospective model of baseline ventricular volume.

that declined to MCI were not significant. Differences in VBR between groups of initially-MCI subjects were not significant. Table 6 summarizes differences between subjects who declined to Possible-AD as opposed to Probable-AD dementia. Normals who declined to either dementia type had higher VBR than normals who remained stable or normals who declined to MCI, although the difference between normals who declined to MCI and normals who declined to Possible-AD was not statistically significant. Differences between subjects who declined to Possible-AD and Probable-AD were not significant. Figure 3 plots VBR by dementia progression group, education level, and dementia progression group broken out by Possible-AD and Probable-AD dementia types.

4 Discussion

The first key finding of this study is that at baseline, the lateral ventricles of normal subjects who decline rapidly to dementia are larger than those of normals who remain stable or decline gradually. This finding suggests that normal subjects who rapidly decline to dementia may have a distinct course of brain structure changes compared to those who decline gradually. Future study should determine whether larger ventricular size represents a susceptibility factor for AD or a marker of AD-related pathology in rapidly-declining

subjects. That is, it is possible that AD-related pathological processes had already reached a relatively advanced stage at baseline in the rapid decliners, causing their ventricles to dilate, and that compensatory mechanisms in these subjects were uniquely poised to dramatically postpone symptom progression until they suddenly collapsed between baseline and follow-up. However, it is also possible that large ventricles indicate a pre-existing structural vulnerability that hampers the ability of the brain to delay AD-related pathology progression. For example, earlier studies have suggested that larger ventricles are highly correlated with lower white matter integrity, which may in turn indicate the presence of small vessel disease [28]. This issue may be clarified in the future by relating ventricular size to MRI markers related to AD pathology or white matter integrity, such as volumes of medial temporal lobe structures or radiological assessments of white matter grade. The finding of larger ventricular size among rapid decliners also suggests that fully-automated ventricular assessments may be useful in a clinical setting for assessing risk of rapid cognitive decline among healthy elderly subjects, regardless of age, gender, or education level, in concordance with previous CHS findings [26].

The second key finding is that Possible-AD subjects had significantly larger ventricles than Probable-AD subjects. This result highlights the importance of treating the two diagnoses as distinct, rather than grouping all Possible-AD and Probable-AD subjects into the same category [13] [1] [33]. Larger ventricles could reflect the damaging effects of a variety of co-morbidities, for example stroke, that contributed to the Possible-AD diagnosis. However, future study is needed to determine the structural effects of these factors in conjunction with AD-related pathology.

The third key finding is that the ventricular volume of MCI subjects lie in an intermediary range between those of normal and demented subjects. This result supports earlier evidence that MCI represents a transitional state between health and dementia in terms of clinical symptoms as well as volumetric brain changes [2] [8]. The result also agrees with a study by Fischl *et al.* that used an automated MRI processing technique to demonstrate that subjects in a transitional cognitive state under different clinical criteria (”questionable AD”) had ventricular volumes that were between normals and demented subjects [16]. Our use of a large, community-based subject pool together with fully-automated ventricular assessment strengthens earlier findings in this area by reducing concerns related to small sample sizes, inter-rater reliability of the ventricular assessment, and selection bias that limited earlier studies of brain volumetrics in MCI to varying degrees.

The cross-sectional findings agree strongly with previous cross-sectional studies that were based on

manual tracings, visual grading, or automated analysis of the ventricles on MR images. In particular, previous studies reported that ventricular volume increases with age [17] [28] [46], is higher in males [47], is higher in AD subjects compared to MCI subjects, and is higher in MCI subjects compared to controls [14].

The fact that rapid decliners formed a relatively distinct, yet relatively small sub-group of the overall population highlights the importance of large sample sizes in MR-based studies of dementia progression. In previous prospective studies, the presence of rapid decliners was reported, but they did not appear in sufficient numbers to be analyzed statistically as a distinct group [9] [42] [11]. The large sample size was made possible by a reliable, fully-automated MR-based ventricular assessment technique that obviated the need for relatively expensive and time-consuming human interaction with each image. The fully-automated technique also removed the need for careful training of individual human operators to insure that their ventricular gradings or tracings coincide with each other.

We normalized lateral ventricle volume by total brain volume– the sum of ventricular CSF, sulcal CSF, and parenchyma volumes– in order to account for gross differences in overall brain size between subjects. This normalization is a well-established technique, especially in studies of schizophrenia and other disorders [22]. However, methods for normalization of regional volumes vary widely [2]. In particular, other authors have normalized ventricular volume by total intracranial volume (ICV), which, unlike total brain volume, includes the volume of CSF between the cortical surface and the skull [17]. Since total brain volume is reduced by age-associated global brain atrophy, normalization by ICV may be an appropriate way to account for total brain size and global atrophy simultaneously. Future investigation should compare the sensitivity and specificity of normalization by total brain volume and ICV for detecting differences between dementia progression groups.

Our study was limited by a lack of information on the size, location, and number of apparent infarcts on MR. Infarcts were represented in our statistical models as a binary variable which took a value of 1 if and only if one or more infarcts were seen on MR. Stronger associations between 1997-99 VBR and infarcts could possibly be observed if a more detailed accounting of the volume and spatial distribution of infarcts were included in the analysis.

In 1997-99, 8 subjects were diagnosed with Possible-AD dementia and 25 were diagnosed with Probable-AD dementia; in 2002-03, 40 subjects who were normal or MCI in 1997-99 were diagnosed with Possible-AD dementia and 48 were diagnosed with Probable-AD dementia. We suggest that the higher relative prevalence of Possible-AD in the 2002-03 group reflects increased mortality associated with the comorbidi-

ties that support a Possible-AD diagnosis. Specifically, the 1997-99 Possible-AD group consists of subjects whose AD and comorbid conditions were at a broad range of stages, including subjects who have had a long history of serious conditions such as cerebrovascular disease. The 2002-03 Possible-AD group, meanwhile, consists of subjects who were normal or MCI in 1997-99, and therefore are possibly earlier in the course of AD and comorbid conditions. Thus, we suggest that the decreased relative prevalence of Possible-AD in the 1997-99 dementia group is associated with higher risk of mortality at their possibly later disease stages.

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