Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions

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Abstract—*Objectives:* To examine the extent to which persons with mild cognitive impairment have intermediate levels of Alzheimer disease (AD) pathology, cerebral infarcts, and Lewy body disease. *Methods:* A total of 180 Catholic clergy participating in the Religious Orders Study underwent annual detailed evaluation and brain autopsy. Blocks of midfrontal, superior temporal, medial temporal lobe, inferior parietal, entorhinal cortex, hippocampus, and substantia nigra were paraffin embedded, and sectioned at 6 μm. Cortical neuritic plaques, diffuse plaques, and neurofibrillary tangles were visualized with Bielschowsky silver stain, and counted and summarized to yield a Braak stage, Consortium to Establish a Registry for Alzheimer's Disease (CERAD) diagnosis, National Institute on Aging (NIA)–Reagan diagnosis, and composite measure of AD pathology. The authors recorded the number and location of all gross chronic cerebral infarctions. Lewy bodies were identified with antibodies to alpha-synuclein. Multiple regression analyses were used to examine the relation of AD pathology and cerebral infarctions to clinical diagnosis proximate to death, controlling for age, sex, and education. *Results:* A total of 37 had mild cognitive impairment, 60 did not have cognitive impairment, and 83 had dementia proximate to death. Nearly all persons had at least some AD pathology. Cerebral infarctions were present in 35.2%, and 15.6% had Lewy body disease. Persons with mild cognitive impairment were intermediate in terms of Braak stage and CERAD and NIA–Reagan neuropathologic criteria for AD compared to the other two groups. In multiple regression analyses, persons with mild cognitive impairment had intermediate levels of AD pathology from those without cognitive impairment and those with dementia (test for trend, $F = 45.2$, $p < 0.001$). Further, the relation between cognition and AD pathology in persons with mild cognitive impairment did not differ significantly from the relation between cognition and AD pathology in persons with dementia or those without cognitive impairment. Persons with mild cognitive impairment also had intermediate levels of cerebral infarctions (test for trend, $p = 0.04$). Only 3 (8.1%) persons with mild cognitive impairment had Lewy body disease. *Conclusion:* These data suggest that mild cognitive impairment may be the earliest clinical manifestation of common age-related neurologic diseases.

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Older persons display a spectrum of cognitive abilities that range from cognition little different from that of younger persons to mild impairment to clinical dementia. Interest in the border zone between normal cognition and dementia has increased markedly in recent years, and the term mild cognitive impairment is now being used with increasing frequency to refer to these persons.[1] Although there is no consensus regarding the precise definition of mild cognitive impairment, there is widespread conceptual agreement that the condition represents older persons whose memory or other cognitive abilities are not normal, but who do not meet accepted criteria for dementia. Mild cognitive impairment is a public health problem because it is common and associated with significant morbidity and mortality. The occurrence of the condition increases with age and affects up to a quarter of older persons.[2] Persons with mild cognitive impairment are more impaired in measures of activities of daily living[3] and managing financial affairs,[4] and are about twice as likely to develop dementia,[5] be institutionalized,[6] and die[7] compared to persons without cognitive impairment.

Despite the intense recent interest in mild cognitive impairment, there are little data available regarding the extent to which age-related neurologic diseases are responsible for the condition. Recent data reporting that the neuropathologic indices of common dementing illnesses are also found in the brains of persons without dementia[8,9] raise the possibility that mild cognitive impairment is the earliest clinical manifestation of the pathology of Alzheimer disease (AD), or other common age-related pathologies. We used data from the Religious Orders Study,

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a longitudinal clinical-pathologic study of aging and dementia, to test the hypothesis that persons with mild cognitive impairment have intermediate levels of the neuropathology of the three most common age-related neurologic diseases that cause dementia: AD, stroke, and Lewy body disease.

Methods. *Study population.* The Religious Orders Study is a longitudinal clinical-pathologic study of aging and dementia funded by the National Institute on Aging since July 1993. All participants are older Catholic nuns, priests, or brothers. Subjects come from about 40 groups from 12 states and the District of Columbia (see Acknowledgment). Eligibility requires that the person agree to annual clinical evaluation and be competent to sign an Anatomic Gift Act. Each subject signs an informed consent and an anatomic gift act donating his or her brain to Rush investigators at the time of death. The study was approved by the Institutional Review Board of Rush University Medical Center. Through September 30, 2003, 996 persons (32.0% men, 88.6% non-Hispanic white, mean age of 75.8 years, and mean education of 18.1 years) enrolled in the study and recruitment is ongoing. Clinical evaluations began in January 1994. The follow-up rate exceeds 95% of survivors and the autopsy rate exceeds 90%. Baseline demographic characteristics of the cohort, follow-up, and autopsy rates have been described elsewhere.[5]

Subjects. The current study was based on the first 184 persons in the study who died and had a brain autopsy. Because we were interested in the role of AD pathology, cerebral infarctions, and Lewy bodies on the development of mild cognitive impairment, we included all persons without cognitive impairment, with mild cognitive impairment, and with clinical dementia due to AD, cerebral infarctions, Parkinson disease (PD), Lewy body disease, or a combination of these conditions. Four persons were excluded from all analyses, including three with delirium due to a comorbid condition that made it difficult to assign the cause of dementia, and one with a brain tumor, leaving 180 persons for analyses.

Clinical evaluation. Details of the clinical evaluation have been reported previously.[5] Briefly, each subject underwent a uniform structured baseline clinical evaluation. The evaluation included a medical history, neurologic examination, neuropsychological performance testing, review of a brain scan when available, and diagnostic classification by an examining physician. History of stroke was assessed with items adapted from the Consortium to Establish a Registry for AD (CERAD).[10] History of parkinsonism and PD were assessed with items adapted from the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) Study.[11] The neurologic examination included items adapted from the NIH Stroke Scale and also included a modified version of the complete motor section of the United PD Rating Scale (UPDRS).[12] All participants underwent detailed neuropsychological performance tests (see below) which were reviewed by a board-certified neuropsychologist. Participants were evaluated in person by a neurologist or geriatrician with expertise in the evaluation of older persons with dementia at which time they were classified with respect to AD, mild cognitive impairment, and other common neurologic disorders (see below). Uniform, structured follow-up evaluations performed by examiners blinded to previously collected data were performed annually. Follow-up data collection was essentially the same as baseline except that medical history was interval rather than lifetime.

Neuropsychological performance testing. The neuropsychologic performance tests were selected to assess a broad range of cognitive abilities commonly affected by aging and AD. Details of the cognitive function testing are published elsewhere.[13] The Mini-Mental State Examination (MMSE)[14] was used to describe the cohort but was not used in analyses. Nineteen cognitive function tests representing five different cognitive domains were administered at each annual evaluation. There were seven tests of episodic memory: Word List Memory, Recall, and Recognition,[15] and immediate and delayed recall of two brief stories[16,17]; four tests of semantic memory: Verbal Fluency[15] and short forms of the Boston Naming Test,[18] National Adult Reading Test,[19] and Extended Range Vocabulary[20]; four tests of working memory: Digit Span Forward and Backward,[17] Digit Ordering,[21] and Alpha Span[22]; two tests of perceptual speed: Symbol Digit Modalities Test[23] and Number Comparison[20]; and two tests of visuospatial ability: short forms of Judgment of Line Orientation[24] and Standard Progressive Matrices.[25] A previously established composite measure of global cognition was used to describe the sample rather than individual test scores. The composite measure was computed by converting raw scores on each component test to z scores, using the baseline mean and SD for all participants in the Religious Orders Study, and averaging the z scores to yield the composite measure. Further information about the individual tests and the derivation of the composite measure, and its use, has been previously reported.[13]

Clinical diagnoses. Diagnostic classification was performed at each annual clinical evaluation by an examining physician blinded to previously assigned diagnoses. The diagnosis of dementia, AD, and mild cognitive impairment followed a three stage process as previously described.[5] Briefly, the diagnosis of dementia and AD followed the recommendations of the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA).[26] It required evidence of meaningful decline in cognitive function from a previous level of performance and impairment on tests of memory and at least one other cognitive domain. Mild cognitive impairment referred to those individuals rated as cognitively impaired by the neuropsychologist but not demented by the examining physician. These criteria have been used in previous clinical[5] and clinical-pathologic[27] studies. The diagnosis of cognitive impairment related to stroke was consistent with the National Institute of Neurologic Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement in Neurosciences (NINDS-AIREN) criteria for vascular dementia except that brain scans were only available on a subset of participants.[28] The diagnosis of Lewy body disease required evidence of cognitive impairment that was atypical for AD and spontaneous parkinsonian signs, similar to those recommended by the Report of the Consortium on DLB International Workshop.[29]

At the time of death, all available clinical data from all years were reviewed by a neurologist, blinded to all postmortem data, and a summary diagnostic opinion was rendered regarding the most likely clinical diagnoses at the time of death as previously described.[30]

Brain autopsy procedures. Brain autopsies were performed at 11 predetermined sites across the United States for nearly all cases. Brains of the deceased participants at each site were removed using standard techniques as described previously.[31] Brains were weighed, placed in a Plexiglas jig, and the hemispheres were cut coronally into 1 cm slabs. Slabs not designated for freezing were fixed for 3 to 21 days in 4% paraformaldehyde. Uniform examination for cerebral infarctions was conducted on these fixed slabs (see below). After complete macroscopic evaluation, blocks, including midfrontal, superior temporal, medial temporal lobe (including entorhinal cortex), hippocampus, inferior parietal cortex, basal ganglia, thalamus, and substantia nigra, were paraffin embedded and cut into 6 μm sections. Sections were mounted on glass slides.

Measures of AD pathology. Bielschowsky silver stain was used to visualize neuritic plaques, diffuse plaques, and neurofibrillary tangles as previously described.[31] All neuropathologic diagnoses were made by a board-certified neuropathologist blinded to all clinical data. For each case, Braak scores were based upon the staging of neurofibrillary tangle pathology.[32] For descriptive purposes, Braak scores of I and II were combined, as were III and IV, and V and VI. A neuropathologic diagnosis was made of no AD, possible AD, probable AD, or definite AD based on semiquantitative estimates of neuritic plaque density as recommended by the Consortium to Establish a Registry for AD (CERAD).[33] The CERAD criteria were modified such that the neuropathologist made the diagnosis blinded to age and all clinical data. All cases also received an NIA–Reagan neuropathologic diagnosis based on the Braak score for neurofibrillary pathology and the CERAD estimate of neuritic plaques.[34]

We used a graticule to count the total number of neuritic plaques, diffuse plaques, and neurofibrillary tangles in one square mm area (× 100 magnification) in midfrontal cortex, superior temporal cortex, superior temporal cortex, entorhinal cortex, and inferior parietal cortex. Counts were performed by a board-certified neuropathologist or trained technician blinded to all clinical data. Inter-rater reliability on 40 cases ranged from $r = 0.89$ to $r = 0.93$ for the three neuropathologic indices. Because the

three neuropathologic markers of AD were strongly related, we created a summary measure of AD pathology for analyses. Because the distribution of plaques and tangles was not normally distributed and to maintain a true "0," we first created standardized scores for each plaque and tangle count by converting the raw counts from each area to standard scores by dividing by the SD of the mean raw count of that marker from that region from the entire deceased cohort. The scaled score for neuritic plaques, diffuse plaques, and neurofibrillary tangles for each region was then averaged across the four regions (midfrontal, superior temporal, inferior parietal, and entorhinal cortex) to develop a summary score for diffuse plaques, neuritic plaques, and neurofibrillary tangles for each subject. We then averaged the summary scores of the three AD markers to yield the global measure of AD pathology for each subject. Cronbach's coefficient alpha, a measure of internal consistency, was 0.90 for the 12 postmortem indices, supporting the formation of the global measure of AD pathology. The development of the summary measure of AD pathology has been described in detail elsewhere and has been used in previous clinical-pathologic studies.[31]

Measures of cerebral infarcts. For each brain we identified the age, volume (in mm^3), side, and location of all cerebral infarctions visible to the naked eye as previously reported.[35] For these analyses, we included all old cortical and subcortical gray and white matter cerebral infarctions. Infarction age was estimated by size and degree of excavation. Acute and subacute infarctions, which are typically less than 3 to 6 months of age, were not included in the analyses. Ischemic lesions with small amounts of hemorrhage were included in analyses. Though infarctions in the brainstem or cerebellum were recorded they were not included in these analyses. We dichotomized the number of infarctions as present or absent.

Measures of Lewy bodies. Lewy bodies were identified with antibodies to alpha-synuclein using alkaline phosphatase as the chromogen as previously described.[36] Lewy bodies were recorded as nigral predominant (Lewy bodies limited to the substantia nigra), limbic type (Lewy bodies in the entorhinal cortex or cingulate gyrus), or neocortical type (Lewy bodies in the frontal, temporal, or parietal neocortex) as recommended by the Report of the Consortium on DLB International Workshop.[29]

Statistical analysis. Analyses were performed to examine the relation of clinical diagnosis (no cognitive impairment, mild cognitive impairment, or dementia) proximate to death to AD pathology, cerebral infarcts, and Lewy bodies. Because we hypothesized that the level of pathology in mild cognitive impairment would be intermediate between the levels in those without cognitive impairment and those with dementia, we first examined the relation between clinical diagnosis and the global measure of AD pathology using multiple linear regression, regressing pathology on diagnosis, controlling for age, sex, and education. We treated diagnostic group as a linear trend variable rather than a class variable, with no cognitive impairment equal to 1, mild cognitive impairment equal to 2, and dementia equal to 3. Additional analyses were performed that also controlled for cerebral infarctions and Lewy bodies.

An assumption of the linear trend analyses is that the mathematical distance from 1 (no cognitive impairment) to 2 (mild cognitive impairment) is exactly the same interval distance as 2 (mild cognitive impairment) to 3 (dementia). Because there is no agreed-upon characterization of mild cognitive impairment, it is unclear whether this assumption is justified. Therefore, additional analyses were performed to examine the relation between global cognition and AD pathology in each of the diagnostic groups. We again used multiple linear regression analyses that controlled for age, sex, and education. In these models, persons without cognitive impairment were the reference group, and the models included terms for mild cognitive impairment and dementia, and their interaction with global cognition. These models explicitly addressed the question of whether the relation between cognitive function and AD pathology differed for persons with mild cognitive impairment compared to those without cognitive impairment, and those with dementia.

Multiple logistic regression was used to examine the relation between the presence of cerebral infarcts (a binary outcome) and clinical diagnosis, controlling for age, sex, and education. Again, we treated diagnostic group as a linear trend variable rather than a class variable. Subsequent models controlled for the global measure of AD pathology and Lewy bodies. There were too few persons with mild cognitive impairment and Lewy bodies for meaningful analyses. Thus, data on Lewy bodies are provided for descriptive purposes. Models were validated both graphically and analytically. Analyses were carried out using SAS/STAT software version 8 (SAS Institute, Inc., Cary, NC)[37] on a SunUltraSparc workstation.

Results. A total of 180 persons were included in these analyses. Of these, 37 had mild cognitive impairment, 60 did not have cognitive impairment, and 83 had dementia, of whom 63 had probable AD, 15 had mixed AD and a coexisting condition (9 with stroke, 4 with PD, and 2 with Lewy body variant), and 5 had vascular dementia. Persons with mild cognitive impairment were intermediate in terms of age and education (table 1). The interval from last clinical evaluation to autopsy averaged 6 to 7 months in each diagnostic group (see table 1). The global cognitive score was about a half unit lower in persons with mild cognitive impairment compared to persons without cognitive impairment and about a unit higher than those with dementia (see table 1). The box plot shows that there is no overlap in the middle half of the distributions among the three diagnostic groups suggesting that the persons with mild cognitive impairment are clinically separable from those without cognitive impairment and those with dementia (figure 1). By contrast, although the global AD pathology score in persons with mild cognitive impairment was about 50% higher than those without cognitive impairment and about 60% of that of persons with dementia (see table 1), there was marked overlap of AD pathology among groups (see figure 1).

More than half of persons with mild cognitive impairment had a Braak stage of III/IV, and more than half met CERAD neuropathologic criteria for probable or definite AD (table 2). By contrast, fewer than half of persons with mild cognitive impairment had intermediate likelihood of AD by NIA–Reagan criteria, with only four persons having high likelihood (see table 2). Twelve (32.4%) persons with mild cognitive impairment had one or more cerebral infarctions, five of whom had low, and seven of whom had intermediate likelihood of AD (see table 2). Only three had concomitant Lewy bodies (see table 2).

Relation of pathologic diagnoses of AD to clinical diagnosis proximate to death. We first examined the relation of clinical diagnosis proximate to death to Braak stage and the pathologic diagnoses of AD. About two thirds of those with mild cognitive impairment were Braak stage III/IV with the remainder split between I/II and V/VI (table 3, figure 2). By contrast, almost half of those with dementia were Braak stage V/VI with most of the rest III/IV, and half of those without cognitive impairment were Braak stage III/IV with most of the rest I/II.

The results for the modified CERAD criteria for AD showed a bit more heterogeneity, with persons with mild cognitive impairment practically equally divided among those with no AD, with probable AD, and with definite AD (see table 3, figure 2). By contrast, nearly all of those with dementia met the modified CERAD criteria for probable AD or definite AD. The results for those without cognitive impairment were intriguing. Although the most common modified CERAD diagnosis was no AD, nearly half had sufficient density of neuritic plaques to meet criteria for probable AD or definite AD.

The NIA–Reagan neuropathologic criteria, which incor-

Table 1 *Selected characteristics of participants with no cognitive impairment (NCI), mild cognitive impairment (MCI), and dementia*

Characteristics	NCI	MCI	Dementia	Total
Demographic				
n	60	37	83	180
Men, %	50.0	40.5	44.6	45.6
Mean age at death, y (SD)	81.8 (6.6)	85.0 (5.6)	87.2 (6.2)	84.9 (6.6)
Mean education, y (SD)	18.7 (3.4)	18.5 (4.1)	17.4 (3.2)	18.1 (3.5)
Mean MMSE (SD)	28.2 (1.4)	26.8 (2.1)	16.8 (7.8)	22.6 (7.7)
Global cognitive score (SD)	0.08 (0.42)	−0.52 (0.41)	−1.79 (0.97)	−0.91 (1.11)
Interval, mo (SD)	5.9 (3.5)	7.2 (3.7)	6.7 (3.6)	6.5 (3.6)
Pathologic				
AD pathology measure (SD)	0.45 (0.40)	0.67 (0.54)	1.15 (0.72)	0.82 (0.67)
Neuritic plaques (SD)	0.44 (0.57)	0.59 (0.60)	1.28 (0.99)	0.86 (0.88)
Diffuse plaques (SD)	0.64 (0.69)	0.91 (0.74)	1.24 (0.90)	0.97 (0.85)
Neurofibrillary tangles (SD)	0.26 (0.27)	0.50 (0.58)	0.94 (0.99)	0.62 (0.80)
Macroscopic infarctions, %	22.0	32.4	45.8	35.2
Lewy body disease, %	11.7	8.1	21.7	15.6

MMSE = Mini-Mental State Examination; AD = Alzheimer disease.

porate elements of both Braak stage and the estimates of the density of neuritic plaques as recommended by CERAD and do not age adjust or incorporate the clinical diagnosis, were the best discriminator among the diagnostic groups. More than half of those with mild cognitive impairment met criteria for intermediate likelihood of AD with most of the remainder having low likelihood (see table 3, figure 2). By contrast, less than half of those with dementia met criteria for intermediate likelihood with most of the remainder with high likelihood, and more than half of those without cognitive impairment met criteria for low likelihood with most of the remainder with intermediate likelihood.

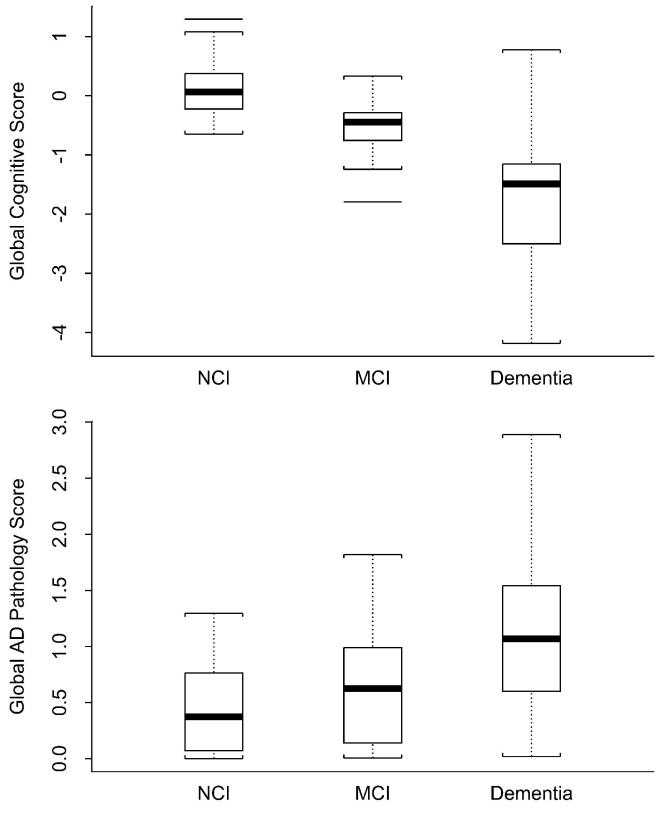

Figure 1. The global cognitive score and the global Alzheimer disease (AD) pathology score by diagnostic group in persons with no cognitive impairment (NCI), mild cognitive impairment (MCI), and dementia.

Relation of AD pathology to clinical diagnosis proximate to death. We next examined the relation between the amount of AD pathology and clinical diagnosis proximate to death. As would be suspected from the categorical data from Braak stage and the neuropathologic diagnoses, both clinically and pathologically, persons with mild cognitive impairment overlap with the other two groups suggesting that they lie on a continuum between normality and dementia (see figure 1). We used multiple linear regression to test for a linear trend between level of AD pathology and clinical diagnosis proximate to death (no cognitive impairment, mild cognitive impairment, and dementia), controlling for the potential confounding effects of age, sex, and education. Persons with mild cognitive impairment had intermediate levels of AD pathology from those without cognitive impairment and those with dementia (test for trend, $F = 45.2$, $p < 0.001$). Similar results were obtained in analyses that controlled for the presence of cerebral infarctions and Lewy bodies ($F = 45.8$, $p < 0.001$).

Because the mathematical distance from 1 (no cognitive impairment) to 2 (mild cognitive impairment) may not be exactly the same interval distance as 2 (mild cognitive impairment) to 3 (dementia), we conducted an additional analysis to further examine whether persons with mild cognitive impairment represented an intermediate stage of AD pathology between normality and dementia. In this analysis we asked whether the relation between AD pathology and global cognition differs among the three diagnostic groups. In this model, which controlled for age, sex, and education, persons with no cognitive impairment

Table 2 *Neuropathologic diagnoses of 37 persons with MCI proximate to death*

Age, y	Braak	CERAD	NIA–Reagan	Infarct	Lewy body disease
81	I	No AD	Low likelihood	Yes	Not present
88	II	No AD	Low likelihood	Yes	Not present
90+	I	No AD	Low likelihood	Yes	Nigra predominant
88	V	Definite	High likelihood	No	Not present
82	III	Possible	Low likelihood	Yes	Not present
86	III	Probable	Intermediate likelihood	Yes	Not present
81	V	Probable	Intermediate likelihood	No	Not present
84	IV	Definite	Intermediate likelihood	No	Not present
73	II	No AD	Low likelihood	No	Not present
77	II	No AD	Low likelihood	No	Not present
81	V	Definite	High likelihood	No	Not present
89	III	Probable	Intermediate likelihood	No	Not present
83	IV	Probable	Intermediate likelihood	Yes	Not present
84	III	No AD	Low likelihood	No	Not present
89	IV	Definite	Intermediate likelihood	Yes	Not present
87	IV	Definite	Intermediate likelihood	Yes	Not present
86	IV	No AD	Low likelihood	No	Not present
78	IV	Definite	Intermediate likelihood	No	Not present
90+	III	No AD	Low likelihood	No	Not present
81	IV	Possible	Low likelihood	No	Not present
89	IV	Probable	Intermediate likelihood	No	Not present
90+	III	No AD	Low likelihood	Yes	Not present
82	IV	No AD	Low likelihood	No	Not present
84	V	Definite	High likelihood	No	Not present
90+	V	Definite	High likelihood	No	Not present
85	IV	Probable	Intermediate likelihood	No	Neocortical type
90+	IV	Definite	Intermediate likelihood	Yes	Not present
89	III	Probable	Intermediate likelihood	Yes	Not present
80	IV	Probable	Intermediate likelihood	No	Not present
82	I	No AD	Low likelihood	No	Not present
90+	V	Probable	Intermediate likelihood	No	Not present
80	IV	Probable	Intermediate likelihood	No	Not present
75	IV	Definite	Intermediate likelihood	No	Nigra predominant
90+	IV	Probable	Intermediate likelihood	No	Not present
83	IV	No AD	Low likelihood	No	Not present
81	IV	Definite	Intermediate likelihood	Yes	Not present
82	IV	Definite	Intermediate likelihood	No	Not present

MCI = mild cognitive impairment; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; NIA = National Institute on Aging; AD = Alzheimer disease.

served as the reference group, and persons with mild cognitive impairment and persons with dementia were allowed to have intercepts and the slopes that differed from the persons without cognitive impairment. In this model, the relation between cognition and AD pathology in persons with mild cognitive impairment was not significantly different than the relation between cognition and AD pathology in persons with dementia or those without cognitive impairment (likelihood ratio test, $F = 0.33$, $p = 0.72$). Figure E-1 (on the *Neurology* Web site at www.neurology.org) plots the raw data for each person by diagnostic group, and also shows the predicted regression line for each diagnostic group. Note the similar regression line for persons with mild cognitive impairment is intermediate to, but similar in slope, to the other two groups. These data provide additional evidence that the relation of cognition to AD pathology lies on a continuum from normality to mild cognitive impairment to dementia.

Relation of cerebral infarctions to clinical diagnosis proximate to death. About a third of persons with mild cognitive impairment had one or more cerebral infarctions

Table 3 *Neuropathologic diagnoses for persons with no cognitive impairment (NCI), mild cognitive impairment (MCI), and dementia*

Characteristics	NCI	MCI	Dementia
Braak stage			
0	3 (5.0)	0	0
I/II	24 (40.0)	6 (16.2)	11 (13.3)
III/IV	30 (50.0)	25 (67.6)	34 (41.0)
V/VI	3 (5.0)	6 (16.2)	38 (45.8)
CERAD			
No AD	25 (41.7)	12 (32.4)	6 (7.2)
Possible	7 (11.7)	2 (5.4)	5 (6.0)
Probable	21 (35.0)	11 (29.7)	32 (38.6)
Definite	7 (11.7)	12 (32.4)	40 (48.2)
NIA–Reagan			
No AD	3 (5.0)	0	0
Low likelihood	35 (58.3)	14 (37.8)	15 (18.1)
Intermediate likelihood	20 (33.3)	19 (51.4)	38 (45.8)
High likelihood	2 (3.3)	4 (10.8)	30 (36.1)
Lewy body disease			
Nigra predominant	5 (8.3)	2 (5.4)	1 (1.2)
Limbic type	2 (3.3)	0	3 (3.6)
Neocortical type	0	1 (2.7)	14 (16.9)

Values are n (%).

CERAD = Consortium to Establish a Registry for Alzheimer's Disease; AD = Alzheimer disease; NIA = National Institute on Aging.

compared to nearly half of those with dementia and less than a quarter of those without cognitive impairment (see table 1, figure 3). We performed a series of multiple logistic regression analyses to examine the relation between the log-odds of having a cerebral infarction and clinical diagnosis, controlling for the potential confounding effects of age, sex, and education. In the first analysis, the percent of persons with mild cognitive impairment who had cerebral infarctions was intermediate between those without cognitive impairment and those with dementia (test for trend, $p = 0.04$). Similar results were obtained in analyses that controlled for the presence of AD pathology and Lewy bodies ($p = 0.02$).

Relation of Lewy body disease to clinical diagnosis proximate to death. Lewy bodies were present in about 15% of persons; those with dementia were more likely to have Lewy bodies than those with mild cognitive impairment or those without cognitive impairment (see table 1). Only 3 (8.1%) persons with mild cognitive impairment met criteria for Lewy body disease, two of whom were nigral predominant and one was neocortical type (figure E-2). By contrast, 7 (11.7%) persons without cognitive impairment met criteria for Lewy body disease, 5 (71.4%) of which were nigral predominant, and 18 (21.7%) persons with dementia met criteria for Lewy body disease, 17 (94.4%) of which were limbic or neocortical type. There were too few persons with mild cognitive impairment who had Lewy body disease (3) for meaningful analysis. Thus, these data are provided for descriptive purposes.

Discussion. In a prior study from this cohort, we showed that persons with mild cognitive impairment were at greater risk of cognitive decline, dementia, and mortality compared to those without cognitive impairment, suggesting that this group is on a continuum from normality to disease.[5] In this study, we found persons with mild cognitive impairment had intermediate levels of AD pathology using a variety of different approaches, compared to those with dementia and those without cognitive impairment. In fact, not only was the relation between cognition and AD pathology in persons with mild cognitive impairment similar to those with dementia, but a similar relation between cognition and AD pathology was also seen in persons without cognitive impairment. Persons with mild cognitive impairment were also intermediate in terms of the number of cerebral infarctions. By contrast, the number of persons with Lewy body disease was similar to that of those without cognitive impairment, and markedly lower than the number with dementia. However, in view of the small number of cases, these results must be viewed with caution. Together, these data suggest that mild cognitive impairment represents the earliest clinical manifestations of two common conditions responsible for age-related dementia.

It has long been known that the pathologic indices of AD, cerebral infarctions, and Lewy bodies can be found in the brains of older persons without overt dementia,[8,9] raising the possibility that their presence may be related to the earliest clinical manifestations of dementia. However, little data are available regarding the pathologic basis of mild cognitive impairment because of the difficulty of obtaining brain tissue from persons known to have the condition proximate to death. A few prior studies have related measures of AD pathology to clinical diagnosis proximate to death. However, only one study reported cerebral infarcts and Lewy bodies in addition to measures of AD pathology, and that study was limited to three persons with mild cognitive impairment.[9] Other studies restricted their analyses to measures of AD pathology, and these too have been small, ranging from only 3[38] to 18[39] persons with mild cognitive impairment proximate to death, and between 8[38] and 58[39] total subjects.

In view of the lack of robust pharmacotherapy for the symptomatic treatment of AD and other dementias, it is fair to question the wisdom of suggesting that people with mild cognitive impairment actually have an early dementia. However, the findings have several important implications. First, depending on the criteria employed and the demographic characteristics of the population, up to a third of older persons have mild cognitive impairment.[2] If a large proportion of mild cognitive impairment is due to the pathology that causes dementia, the public health problem posed by these diseases is much greater

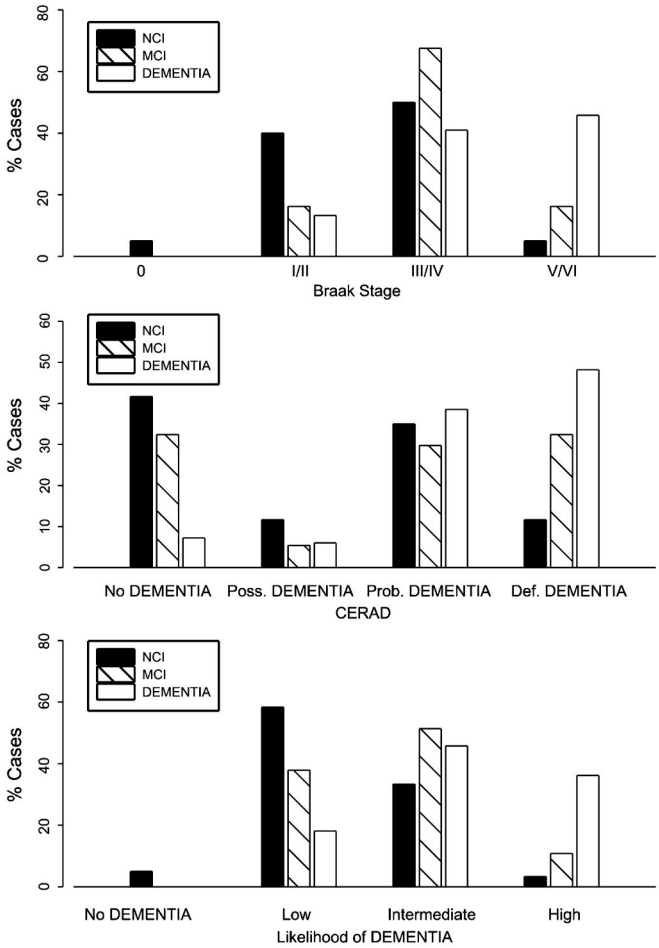

Figure 2. Percentages of persons with no cognitive impairment (NCI), mild cognitive impairment (MCI), and dementia by Braak Stage, modified Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria, and National Institute on Aging–Reagan neuropathologic criteria.

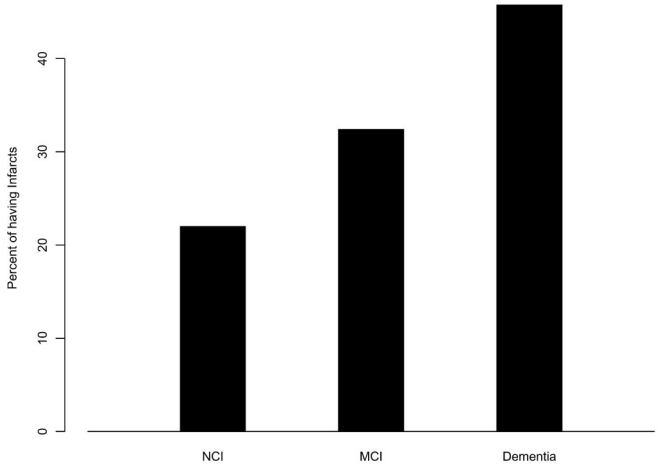

Figure 3. Percent of persons with cerebral infarctions in persons with no cognitive impairment (NCI), mild cognitive impairment (MCI), and dementia.

than currently recognized. Second, it suggests caution in using mild cognitive impairment as an enrichment strategy in clinical trials to increase power for studies of incident dementia since many of these individuals already have disease pathology. Thus, such studies should be considered secondary prevention. Finally, analytic epidemiologic studies that include persons with mild cognitive impairment in the unaffected group may inadvertently limit power to detect risk factors of small to moderate effect sizes by including relatively large numbers of persons with AD pathology in the unaffected group.

To highlight a more positive finding from this study, a third of the cohort, with a mean age greater than 80 years, did not have evidence of cognitive impairment, suggesting that many persons can live to advanced old age without experiencing a significant decrement in cognitive function. This is consistent with recent longitudinal studies demonstrating that older persons can maintain cognition over several years of follow-up.[13] This implies that loss of memory is not an inevitable consequence of aging, but rather is usually the consequence of age-related diseases. This suggests that evidence of memory loss among persons of any age should be taken seriously by individuals, family members, and health-care professionals alike.

A second positive finding is that depending on the neuropathologic criteria used, between a third and a half of persons without cognitive impairment had a significant amount of AD pathology, and almost a quarter had cerebral infarcts. While it is possible that had they lived longer they would have experienced cognitive decline, the fact remains that they had remarkably good cognition at a time when they also had a significant burden of pathology. This suggests that other factors must contribute to the extent to which these lesions manifest as cognitive impairment, or that some of these subjects had a greater amount of neural reserve, allowing them to tolerate a greater burden of pathology without expressing cognitive loss.[30]

There are several strengths that lend confidence to the study results. Measures of AD pathology and cerebral infarctions were both linked to clinical diagnosis proximate to death. All analyses were performed on comparable persons from a single cohort who came to autopsy following high rates of follow-up participation and brain autopsy. This cohort minimizes the potential influence of other confounding variables such as occupation and lifestyle, and the sample size was sufficiently large to control for other important and potentially confounding variables such as age, sex, and education. Finally, uniform structured procedures were followed, examiners were blinded to previously collected data, and all postmortem data were collected by personnel blinded to clinical data, further reducing the potential for bias.

The study also has several limitations. Clinical-pathologic analyses are inherently cross-sectional and causal inferences must be made with caution. The present study used standard neuropathologic

density measurements widely employed in postmortem diagnostic studies of AD rather than antibody-specific staining methods. Finally, participants are not representative of the United States population as a whole in terms of education and lifestyle. It is possible that these factors could alter the relation of amyloid and tau to clinical disease. Therefore, the findings will need to be replicated in similar studies of lay persons.

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