

Decision Rules Guiding the Clinical Diagnosis of Alzheimer's Disease in Two Community-Based Cohort Studies Compared to Standard Practice in a Clinic-Based Cohort Study

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Key Words

Alzheimer's disease · Alzheimer's disease, diagnosis · Decision rules · Alzheimer's disease, pathology

Abstract

We developed prediction rules to guide the clinical diagnosis of Alzheimer's disease (AD) in two community-based cohort studies (the Religious Orders Study and the Rush Memory and Aging Project). The rules were implemented without informant interviews, neuroimaging, blood work or routine case conferencing. Autopsies were performed at death and the pathologic diagnosis of AD made with a modified version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria. We compared the positive predictive value of the clinical diagnosis in the two community-based studies to the positive predictive value of the clinical diagnosis of AD made by standard clinical practice in a clinic-based cohort study using AD pathology as the gold standard. Of 306 clinic cases with probable AD, 286 (93.5%) met CERAD neuropathologic criteria for AD; the results were comparable for those with possible AD (51 of 54, 94.4%). Of 141 study subjects with probable AD, 130 (92.2%) met CERAD

neuropathologic criteria for AD; the results were lower but acceptable for those with possible AD (26 of 37, 70.3%). The results were similar in secondary analyses using alternate neuropathologic criteria for AD. The clinical diagnosis of AD can be made in community-based studies without the use of informant interviews, neuroimaging, blood work or routine case conferencing. This approach holds promise for reducing the operational costs of epidemiologic studies of aging and AD.

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Introduction

Epidemiologic studies of risk factors for incident Alzheimer's disease (AD) depend on correct diagnostic classification of disease status. However, the clinical diagnosis of AD in community-based studies can be difficult, time-consuming and expensive. We are conducting two community-based studies of risk factors for incident AD that include organ donation at death: the Religious Orders Study [1] and the Rush Memory and Aging Project [1, 2]. Evaluations take place across the country and

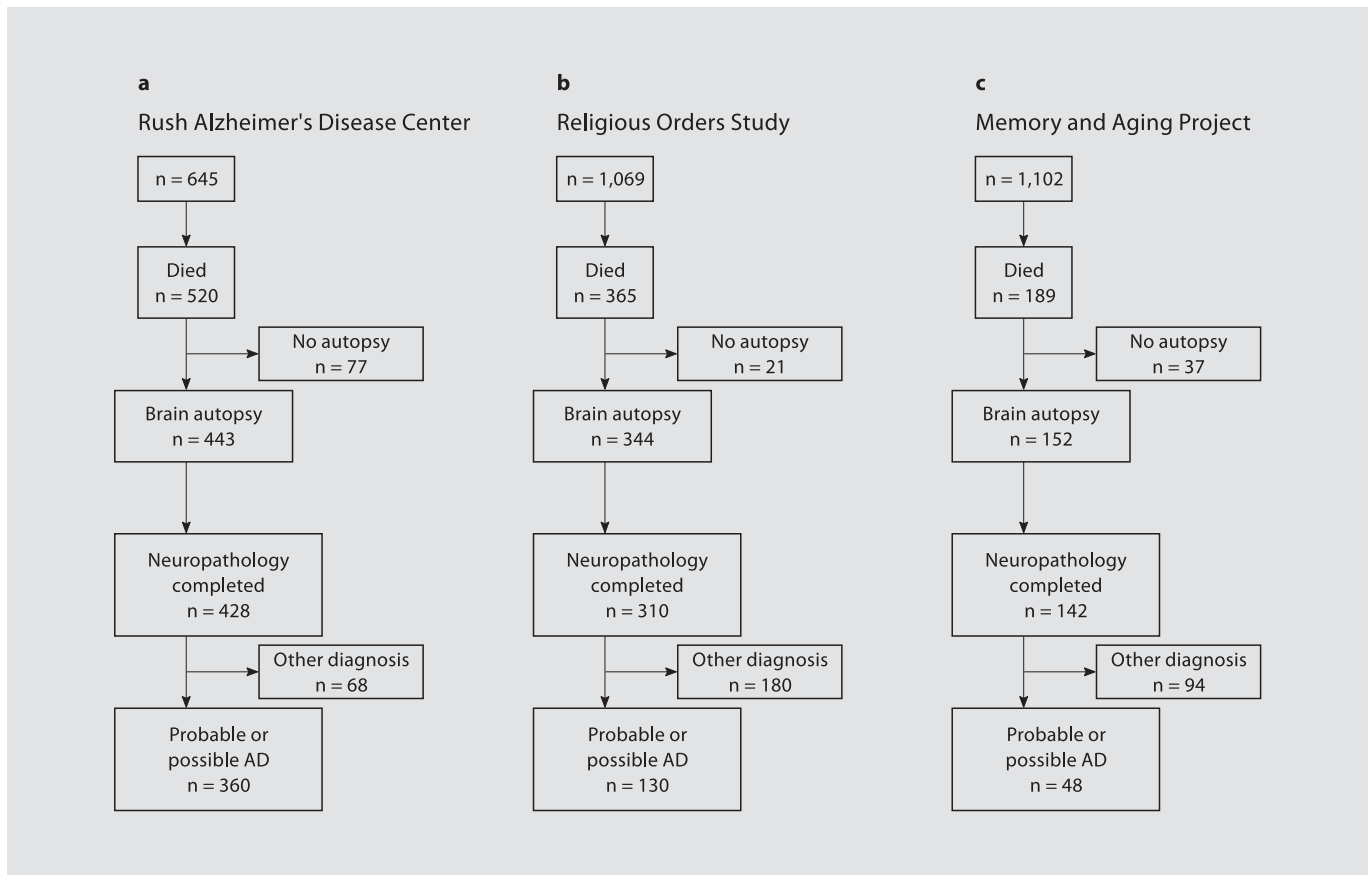


Fig. 1. Flow of subjects, deaths, autopsies and completed neuropathologic evaluations for the clinic-based cohort study (a) and each of the two community studies (b, c).

Northeastern Illinois. We conduct a complete clinical evaluation on all study participants each year to ensure that postmortem indices can be related to clinical data and diagnoses proximate to death. To maintain diagnostic consistency across time, space and examiners, we developed a computer-based system of prediction rules to guide clinical judgment for the diagnosis of AD. It was not operationally feasible or cost-efficient to interview informants, obtain neuroimaging and blood work or perform case conferences for all evaluations. Because in-person evaluations were not always possible, the system permits diagnoses to be made by clinicians based on review of clinical data obtained by trained nurses, neuropsychological test technicians and research assistants. In this report, we examine the relation of the clinical diagnosis of AD to the pathologic diagnosis of AD for more than 175 study subjects. The results are compared to the clinical diagnosis of AD made by standard clinical practice to the pathologic diagnosis of AD for more than 350 persons

evaluated at the Rush Alzheimer's Disease Center. We present the positive predictive value (true positives divided by true and false positives) rather than sensitivity, specificity and diagnostic accuracy because AD pathology is common in persons without dementia [3–7].

Methods

Study Populations

Rush Alzheimer's Disease Center Clinic

Participants were persons evaluated for possible dementia at the Rush Alzheimer's Disease Center clinic who agreed to brain autopsy as part of the clinical core of the Rush Alzheimer's Disease Core Center. The study was approved by the Institutional Review Board of the Rush University Medical Center. Following death, next of kin provided consent for autopsy. Of more than 650 persons who underwent clinical evaluation between March 1992 and June 2006, the autopsy rate exceeds 85% with 443 autopsies of 520 deaths (fig. 1a).

Religious Orders Study

The participants were older Catholic nuns, priests and brothers without known dementia who agreed to annual clinical evaluations and signed an informed consent and an Anatomical Gift Act donating his/her brain to Rush investigators at the time of death [1]. The study was approved by the Institutional Review Board of the Rush University Medical Center. The subjects come from about 40 groups in 12 states across the country. The study has a rolling admission, and more than 1,000 persons completed a uniform structured baseline clinical evaluation between January 1994 and June 2006. Follow-up evaluations, identical in all essential details, were performed annually by examiners blinded to previously collected data. Participation in the annual follow-up evaluations exceeds 95% of survivors. The autopsy exceeds 90% with 344 autopsies of 365 deaths (fig. 1b).

Rush Memory and Aging Project

The participants were older community-dwelling persons without known dementia who agreed to annual clinical evaluations and signed an informed consent and an Anatomical Gift Act donating his/her brain, spinal cord, and selected nerve and muscle to Rush investigators at the time of death [1, 2]. The study was approved by the Institutional Review Board of the Rush University Medical Center. The subjects come from about 40 retirement communities and senior housing buildings across Cook and the collar counties in northeastern Illinois. Subjects also are recruited from local churches. The study has a rolling admission, and more than 1,100 persons completed a uniform structured baseline clinical evaluation between October 1997 and June 2006. Follow-up evaluations, identical in all essential details, were performed annually by examiners blinded to previously collected data. Participation in the annual follow-up evaluations exceeds 95% of survivors. The autopsy rate exceeds 80% with 152 autopsies of 189 deaths (fig. 1c).

Clinical Procedures

Rush Alzheimer's Disease Center Clinic

All subjects underwent a uniform, structured, clinical evaluation. Details of the evaluation have been previously reported [8–10]. Briefly, the evaluation included a detailed medical history with the patient and a knowledgeable informant, neurologic examination, and brief psychiatric evaluation conducted by skilled neurologists, geriatricians and geriatric nurse practitioners. Laboratory testing and structural neuroimaging were performed, and ancillary tests (e.g. examination of cerebrospinal fluid, positron emission tomography) were obtained when clinically indicated. The procedures were compatible with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [11], similar to those conducted by clinical cores of other federally funded AD centers, and consistent with the current practice parameters for the diagnostic evaluation for dementia [12]. Cognitive function was assessed with a battery of 19 neuropsychological tests administered by neuropsychological test technicians. The battery included measures of orientation, attention, memory, language and visual perception widely used in clinical evaluation of older persons with suspected dementia. Detailed psychometric information on the test battery used from 1992 to 1999 is published elsewhere [8]. In 1999, the core battery was changed to be compatible with the cognitive testing being performed in the Religious Orders Study and the Memory and Aging Project (below). Five tests were administered across all 14 years.

The diagnosis of AD required a history of cognitive decline and evidence of impairment in memory and other cognitive abilities according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINDCS/ADRDA) criteria [13]. Cognitive impairment related to stroke was made according to the National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS/AIREN) criteria for vascular dementia [14], parkinsonism and Parkinson's disease according to the clinical criteria recommended by the Core Assessment Program for Intracerebral Transplantation (CAPIT) [15], and major depression based on DSM-III-R criteria supported by the Hamilton rating scale for depression [16].

Religious Orders Study and Memory and Aging Project

All subjects underwent a uniform, structured, clinical evaluation that included a self-report medical history obtained by trained nurses and research technicians, a neurologic examination by trained nurses and cognitive function testing by trained neuropsychological test technicians. Years of formal education, lifetime and current occupation, and history of change in memory and other cognitive abilities were documented. History of stroke, Parkinson's disease, depression, head trauma and other conditions with the potential to cause cognitive impairment were obtained by structured questionnaire. Depression was assessed with items from the Diagnostic Interview Schedule [17]. All medications used in the prior two weeks were directly inspected and recorded. A complete neurologic examination documented evidence of stroke and Parkinson's disease [18]. A battery of 21 neuropsychological tests was administered and scored by a computer as previously described [2, 19]. Because participants reside throughout the United States, the battery included a subset of tests that could be administered by telephone [20].

We developed a set of prediction rules to guide clinical classification of AD, incorporating selected clinical judgments at several key decision points. Such rules have been used in many areas of medicine [21–23]. Because the Catholic clergy are without spouses and children, and because of the need to maintain confidentiality in settings in which participants live communally, we did not identify and interview informants. To ensure uniformity of procedures and reduce costs, we did not include neuroimaging and blood laboratory work. Because of the number of clinical evaluations, we did not case conference all evaluations. The decision rules were implemented in a multi-step process [24, 25]:

(1) History of cognitive decline was based on a structured interview with the participant as done by others [26]. We previously reported that self-report cognitive decline identified by this interview is related to AD pathology [27].

(2) We developed cutoff scores for 11 commonly used tests, adjusted them for 4 educational strata and used an algorithm to convert the impairment ratings for the 11 tests into impairment ratings in 5 areas of cognition (orientation, attention, memory, language and visuospatial ability) as previously described (see table 1, p. 199, in Bennett et al. [24]).

(3) A neuropsychologist, without access to subject age, gender and race, reviewed the impairment ratings, the remaining cognitive test results, education, occupation, sensory and motor deficits, effort and comments from the neuropsychological test technician regarding protocol deviation (e.g. participant blind and

test not administered) and rendered a clinical judgment (i.e. agreed or disagreed with the computer-generated impairment rating) regarding the presence of impairment in each area of cognition. Impairment in 1 or 2 areas was consistent with single- or multiple-domain mild cognitive impairment [28], and impairment in 3–5 areas was consistent with dementia. When 2 areas of impairment were present, the neuropsychologist rendered an opinion regarding the presence of dementia.

(4) A clinician (neurologist, geriatrician or geriatric nurse practitioner) reviewed all available data and examined the participant and entered selected data into a computer, including (a) history of cognitive decline, (b) the neuropsychologist's judgment of the number of impaired domains and the presence of memory impairment and (c) a clinical judgment regarding meaningful cognitive decline. An actuarial decision tree generated a clinical diagnosis of dementia and AD based on NINCDS/ADRDA criteria [13]. The clinician was then offered an opportunity to override the actuarial decision. Similar procedures were used for dementia related to stroke, Parkinson's and Lewy body disease, and depression [14–16]. Other conditions (e.g. frontotemporal dementia) were made by strict clinical judgment.

For all 3 studies, all available clinical data were reviewed at the time of death by a neurologist, and a summary diagnostic opinion was rendered regarding the most likely clinical diagnosis at the time of death. In most cases, the clinical diagnosis was straightforward. Case conferencing with a second neurologist and a neuropsychologist occurred when the diagnosis was not obvious, typically in the presence of a coexisting condition (e.g. stroke, parkinsonism, delirium).

Brain Autopsy Procedures

Brain autopsies were performed at Rush and 11 predetermined sites across the United States for nearly all cases as described previously [1,29]. Following drainage of cerebrospinal fluid, the brains were removed and weighed. The brainstem and cerebellum were removed, and the brain was hemisected. Each hemisphere was placed in a Plexiglas jig and cut coronally into 1-cm slabs. Slabs from one hemisphere were fixed for 3–21 days in 4% paraformaldehyde, at which time they underwent complete macroscopic evaluation and dissection of diagnostic blocks, including midfrontal, superior temporal, inferior parietal and entorhinal cortex, hippocampus, basal ganglia, thalamus and substantia nigra. These were embedded in paraffin, cut into 6- μ m sections and mounted on glass slides.

Pathologic Diagnosis of AD

Bielschowsky silver stain was used to visualize neuritic plaques, diffuse plaques and neurofibrillary tangles in the frontal, temporal, parietal and entorhinal cortex, and the hippocampus. Neuropathologic diagnoses were made by a board-certified neuropathologist without access to any clinical information. 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 CERAD [30]. To examine the rate of agreement between clinical and pathologic diagnoses, the CERAD neuropathologic diagnosis of AD was modified to be implemented without clinical information (i.e. without adjustment for age and clinical diagnosis), as previously reported [1, 29]. Braak stages I–VI were based upon the distribution and severity of neurofibrillary tangle pathology [31]. All cases also received a

neuropathologic diagnosis of 'no AD,' 'low likelihood AD,' 'intermediate likelihood AD' or 'high likelihood AD' by the National Institute on Aging (NIA)-Reagan criteria [32].

Pathologic Diagnoses of Cerebral Infarcts and Lewy Body Disease

For each brain the age, volume (in mm³), side and location of all macroscopic cerebral infarctions were recorded, and microscopic infarcts were also recorded on sections stained with hematoxylin and eosin as previously described [33]. Lewy bodies were identified with antibodies to α -synuclein and recorded as nigral predominant, limbic or neocortical type as recommended by the report of the consortium on dementia with Lewy bodies international workshop as previously described [34, 35].

Data Analysis

Probable AD refers to persons with clinical AD who did not have any other condition contributing to dementia, and possible AD refers to persons with clinical AD and another coexisting condition contributing to dementia (e.g. stroke). We computed the positive predictive value, true positives divided by true plus false positives [TP/(TP+FP)], of the clinical diagnoses of AD with the pathologic diagnoses separately for the clinic cases and study subjects. The primary analyses were performed with CERAD neuropathologic diagnosis. NIA-Reagan pathologic diagnosis was provided as another way to examine the postmortem data.

Results

Of 428 completed clinic autopsies, 306 persons had clinically probable AD and 54 clinically possible AD (fig. 1a). Of 452 completed Religious Orders Study and Memory and Aging Project autopsies, 141 persons had clinically probable AD and 37 clinically possible AD (fig. 1b, c). The study subjects with probable AD were about 10 years older at death, had about 4 years more education and scored more than 10 points higher on the Mini-Mental State Examination (MMSE) [36]; the study subjects with possible AD were about 7 years older at death, had about 3 years more education and scored about 8 points higher on the MMSE (table 1).

Relation of Clinical Diagnoses of AD to Pathologic Diagnoses in Clinic Cases

Of 306 clinic cases with clinically probable AD, 286 (93.5%) met CERAD pathologic criteria for definite or probable AD (table 2). Similarly, more than 90% met NIA-Reagan criteria for intermediate or high likelihood of pathologic AD. In addition, nearly 15% had 1 or more chronic macroscopic cerebral infarctions, and nearly a quarter had nigral, limbic or neocortical Lewy bodies. Of 54 clinic cases with clinically possible AD, 51 (94.4%) met CERAD pathologic criteria for definite or probable AD

Table 1. Demographic characteristics of autopsied patients with probable AD and possible AD from the Rush Alzheimer's Disease Center clinic (clinic cases), and the Religious Orders Study and the Rush Memory and Aging Project (ROS/MAP study subjects)

	Probable AD	Possible AD
<i>Clinic cases</i>		
Number	306 (85.0)	54 (15.0)
Mean age at death \pm SD, years	79.2 \pm 9.6	80.7 \pm 6.6
Male	107 (35.0)	25 (46.3)
Non-hispanic white	279 (91.2)	49 (90.7)
Mean education \pm SD, years	12.7 \pm 3.3	13.8 \pm 3.7
Mean MMSE proximate to death \pm SD	4.6 \pm 7.0	5.7 \pm 7.3
<i>ROS/MAP study subjects</i>		
Number	141 (79.2)	37 (20.8)
Mean age at death \pm SD, years	89.5 \pm 5.4	87.3 \pm 6.5
Male	57 (40.4)	17 (46.0)
Non-hispanic white	136 (96.5)	34 (91.9)
Mean education \pm SD, years	16.7 \pm 3.7	16.6 \pm 3.2
Mean MMSE proximate to death \pm SD	14.4 \pm 8.7	13.4 \pm 8.8

The figures in parentheses represent the percentage.

(table 2). Nearly 90% also met NIA-Reagan criteria for intermediate or high likelihood of pathologic AD. Persons with clinically probable AD were more likely to have a co-existing condition. One or more cerebral infarcts were present in nearly 30%, and almost half had Lewy bodies.

Relation of Clinical Diagnoses of AD to Pathologic Diagnoses in Study Subjects

Of 141 study subjects with clinically probable AD, 130 (92.2%) met CERAD pathologic criteria for definite or probable AD (table 3). Similarly, more than 90% met intermediate or high likelihood of AD by NIA-Reagan pathologic criteria. In addition, more than a third had 1 or more chronic macroscopic cerebral infarctions, and nearly a quarter had nigral, limbic or neocortical Lewy bodies. Of 37 study subjects with clinically possible AD, 26 (70.3%) met CERAD pathologic criteria for definite or probable AD (table 3). More than 70% met intermediate or high likelihood of AD by NIA-Reagan pathologic criteria. Persons with clinically possible AD were more likely to have a coexisting condition. One or more cerebral infarcts were present in more than 60%, and more than a quarter had Lewy bodies.

Table 2. Relation between the clinical diagnosis of probable AD and possible AD with pathologic diagnoses of AD (by CERAD and NIA-Reagan criteria), chronic macroscopic cerebral infarctions and Lewy body disease for autopsied participants from the Rush Alzheimer's Disease Center clinic (clinic cases)

Pathologic diagnoses	Probable AD	Possible AD
CERAD		
Definite AD	244 (79.7)	41 (75.9)
Probable AD	42 (13.7)	10 (18.5)
Possible AD	4 (1.3)	1 (1.9)
No AD	16 (5.2)	2 (3.7)
NIA-Reagan		
High likelihood	221 (72.2)	32 (59.3)
Intermediate likelihood	65 (21.2)	16 (29.6)
Low likelihood	13 (4.4)	5 (9.3)
No AD	7 (2.3)	1 (1.9)
Cerebral infarctions		
Not present	262 (85.6)	38 (70.4)
Present	44 (14.4)	6 (29.6)
Lewy body disease ¹		
Not present	205 (76.2)	26 (54.2)
Present	64 (23.8)	22 (45.8)

The figures in parentheses represent the percentage.

¹ 37 probable AD and 6 possible AD cases missing Lewy body disease diagnoses.

Table 3. Relation between the clinical diagnosis of probable AD and possible AD with pathologic diagnoses of AD (by CERAD and NIA-Reagan criteria), chronic macroscopic cerebral infarctions and Lewy body disease for autopsied participants from the Religious Orders Study and Rush Memory and Aging Project (ROS/MAP study subjects)

Pathologic diagnoses	Probable AD	Possible AD
CERAD		
Definite AD	78 (55.3)	10 (27.0)
Probable AD	52 (36.9)	16 (43.2)
Possible AD	5 (3.6)	5 (13.5)
No AD	6 (4.3)	6 (16.2)
NIA-Reagan		
High likelihood	59 (41.8)	7 (18.9)
Intermediate likelihood	69 (48.9)	16 (43.2)
Low likelihood	13 (9.3)	14 (37.8)
No AD	0 (0)	0 (0)
Cerebral infarctions		
Not present	87 (61.7)	14 (37.8)
Present	54 (38.3)	22 (62.2)
Lewy body disease		
Not present	106 (75.2)	27 (73.0)
Present	35 (24.8)	10 (27.0)

The figures in parentheses represent the percentage.

Discussion

Most studies of the relation between the clinical and pathologic diagnosis of AD are from specialty dementia clinics following an evaluation that includes an interview with a knowledgeable informant, neuroimaging and blood work, and multi-disciplinary case conferencing. In these settings, pathologic confirmation of the diagnosis of clinically probable AD typically exceeds 80% and can approach 100% when restricted to typical AD [37–41]. In general, pathologic confirmation of the diagnosis of possible AD is somewhat lower, ranging from about 65 to 85% in clinic settings. Of the more than 300 patients with clinically probable AD in this study, the diagnosis was confirmed by neuropathology in more than 90%. Likewise, about 90% of the more than 50 patients with clinically possible AD also met neuropathologic criteria for AD. These data suggest that the procedures used in the Rush Alzheimer's Disease Center clinic are comparable to those used at other tertiary-care dementia specialty centers.

There have been fewer reports of the relation between the clinical and pathologic diagnosis of AD in community-based studies. In general, the rates have been lower, ranging from 65 to 85% for clinically probable AD and 35 to 70% for clinically possible AD [42–46]. The lower rates in these studies likely result from several factors. First, in contrast to clinic-based samples [47], persons in community-based studies are often not recognized by family members [48] or community physicians [49] as having cognitive difficulties. Second, in longitudinal, community-based studies, the diagnosis of AD is often made at a time when cognitive impairment is mild and the presence of dementia unclear. In other words, in the community, the differential diagnosis is about both the presence of dementia and its cause, compared to the clinic, where dementia is typically obvious and the differential only about its cause. Third, many clinical-pathologic studies in clinic-based settings are restricted to more typical cases of AD, which may inflate correlations in such studies. By contrast, the study subjects are often considerably older, which likely increases the prior probability of AD in such studies.

We developed a system of decision rules to guide the clinical diagnosis of AD in two large community-based studies. The procedures were implemented in a time-efficient manner by neurologists, geriatricians and geriatric nurse practitioners. It did not require an interview with an informant, neuroimaging or blood work. Of more than 140 study subjects with clinically probable AD, the diagnosis was confirmed by neuropathology in more

than 90%. For the 37 study subjects with clinically possible AD, 60–70% met neuropathologic criteria for AD. Consistent with other community-based studies [42], more than a third of the study subjects with probable AD and more than 60% of those with possible AD had cerebral infarctions at autopsy. This suggests that MRI would likely have increased the detection of cerebrovascular disease and potentially increased the number of cases of vascular dementia [50]. Further, studies that focus on causes of dementia other than AD (e.g. vascular cognitive impairment, frontotemporal dementia) would likely benefit from ancillary tests such as structural or functional neuroimaging.

The pathologic diagnosis of AD was based only on the degree of AD pathology, even if other pathologic changes were present. The most common coexisting pathology was cerebral infarctions. These were much more common in study subjects than in clinic patients and more common in possible AD than probable AD for both groups. Although there are no accepted criteria for the pathologic diagnosis of vascular dementia [51–53], it is now accepted that these 2 lesions commonly coexist and add to or interact with one another to cause dementia [42, 54–56]. These data suggest that the presence of infarctions reduces the amount of AD pathology needed to cause cognitive impairment and may account in part for a greater number of persons with possible AD having intermediate amounts of AD pathology.

AD is a complex function of numerous genetic and environmental risk factors that cause or interact with a variety of pathologic, biochemical and molecular changes in the brain. Understanding this complex disease will increasingly require large, longitudinal, multidisciplinary studies that can simultaneously address the myriad factors involved in its occurrence. These studies will be time-consuming and expensive. The present data provide support for the use of clinical prediction rules to guide clinical judgment in these studies.

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