ORIGINAL CONTRIBUTION

# Predictors of Preclinical Alzheimer Disease and Dementia

## *A Clinicopathologic Study*

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**Background:** To understand the earliest signs of cognitive decline caused by Alzheimer disease (AD) and other illnesses causing dementia, information is needed from well-characterized individuals without dementia studied longitudinally until autopsy.

**Objective:** To determine clinical and cognitive features associated with the development of AD or other dementias in older adults.

**Design:** Longitudinal study of memory and aging.

**Setting:** Alzheimer's Disease Research Center, St Louis, Mo.

**Main Outcome Measures:** Clinical Dementia Rating, its sum of boxes, and neuropathologic diagnosis of dementia.

**Participants:** Eighty control participants who eventually came to autopsy.

**Results:** Individuals who did not develop dementia showed stable cognitive performance. Entry predictors of dementia were age, deficits in problem solving as well as memory, slowed psychomotor performance, and depressive features. Minimal cognitive decline occurred prior to dementia diagnosis, after which sharp decline was noted. Even individuals who were minimally cognitively impaired (Clinical Dementia Rating = 0.5) typically had neuropathologic AD at autopsy. Histopathologic AD also was present in 34% of individuals who did not have dementia at death; these individuals without dementia showed an absence of practice effects on cognitive testing.

**Conclusions:** Increased age, depressive features, and even minimal cognitive impairment, as determined clinically by Clinical Dementia Rating sum of boxes and by slowed psychomotor performance, identify older individuals without dementia who develop dementia. Older adults who do not develop dementia have stable cognitive performance. The absence of practice effects may denote the subset of older adults without dementia with histopathologic AD, which may reflect a preclinical stage of the illness.

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ALZHEIMER DISEASE (AD) research increasingly focuses on detecting the earliest signs of cognitive decline.[1-4] Because of substantial heterogeneity in the cognitive abilities of older adults without dementia, the boundaries between age-related cognitive decline, mild cognitive impairment,[5] and very early dementia are blurred. The difficulty in distinguishing these conditions is compounded by contamination of putatively "normal aging" samples with individuals who have very mild but unrecognized dementia.[1,6-8] Cognitive function in truly healthy brain aging needs to be established to determine the threshold for abnormal function in mild cognitive impairment and early-stage AD.

Individuals without dementia, followed up longitudinally to autopsy, offer the unique opportunity to evaluate cognitive performance in those who did not have an illness causing dementia and to assess the development of dementia in those who did. We report the longitudinal clinical and cognitive course of 80 individuals without dementia who eventually came to autopsy to characterize normal aging, the development of dementia, and the pathologic bases for dementia.

## METHODS

### CLINICAL DATA

The participants represent consecutive individuals without dementia enrolled in our longitudinal studies (initiated in 1979) of healthy aging and dementia and studied post mortem (data from some individuals have been reported previously).[2-4,9-12] At entry, individuals lacked known causes of dementia and had no cognitive or functional impairment. The Wash-

ington University (St Louis, Mo) Human Studies Committee approved all procedures.

At each annual assessment, experienced dementia clinicians conducted independent semistructured interviews with the participant and a knowledgeable collateral source[4] that included a health history, neurological examination, the Mini-Mental State Examination,[13] Short Blessed Test,[14] and an aphasia battery. Depressive features were assessed in accordance with the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*[15] criteria for major affective disorders, asked independently of the participant and collateral source.

The clinical diagnostic criteria for dementia of the Alzheimer type used in this study are consistent with "probable AD" reported by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Associations.[16] Published criteria were used for the clinical diagnosis of other disorders causing dementia, including dementia with Lewy bodies (DLB)[17] and vascular dementia.[18]

The Clinical Dementia Rating (CDR) was used to determine the presence or absence of dementia and to stage its severity.[19] Using information from the clinical assessment but without reference to psychometric performance, the CDR measures cognitive function in 6 categories (memory, orientation, judgment and problem solving, and performance in community affairs, home and hobbies, and personal care). The global CDR is derived by synthesizing ratings in each of the 6 categories where a CDR of 0 indicates no dementia and a CDR of 0.5, 1, 2, or 3 corresponds to very mild, mild, moderate, or severe dementia.[19] The sum of the individual category ratings ("sum of boxes" [SB]) provides a quantitative expansion of the CDR[2] and ranges from 0 (no impairment) to 18 (maximum impairment). It is possible to have impairment in a single nonmemory domain (CDR–sum of boxes [SB] = 0.5) and have a global CDR of 0. In our sample, a CDR of 0.5 generally equated with very mild dementia[9] and was our threshold to distinguish nondemented (CDR=0) from demented (CDR≥0.5) status.

A structured interview with the collateral source was obtained a few days after death in all autopsied participants to assess any changes in the cognitive and physical status of the decedent since last assessment.[20] All available clinical data were reviewed to generate an expiration summary with final CDR and diagnosis before autopsy findings were known.[2,3]

### PSYCHOMETRICS

A 90-minute psychometric battery[2-4] was administered annually to all participants within 2 weeks of the clinical assessment to assess multiple domains as described previously.[21] The psychometrician was unaware of the participant's CDR and diagnosis. The Alzheimer's Disease Research Center Psychometric Battery tests primary memory (Wechsler Memory Scale Digits Forward), working memory (Wechsler Memory Scale Digits Backward), episodic memory (Wechsler Memory Scale Logical Memory, Wechsler Memory Scale Associate Memory, Benton Visual Retention Test: Form C-Recall), verbal memory (Word Fluency), visuospatial/constructive skills (Wechsler Adult Intelligence Scale Block Design, Benton Visual Retention Test: Form D-Copy, Wechsler Adult Intelligence Scale Digit Symbol, Trail-Making A), and language (Boston Naming Test). A composite factor score (*z* score) was created for each person using weights obtained from a previous principal components analysis of all individuals without dementia enrolled in our longitudinal study.[3]

### NEUROPATHOLOGIC EXAMINATION

All brains were examined using a standard protocol.[10,11] Following fixation in neutral buffered 10% formalin, tissue blocks were taken from 30 brain regions. Sections (6 μm) from paraffin-embedded tissue blocks were stained with hematoxylin-eosin, silver stains, and immunohistochemical methods.[10,11] Two separate histologic criteria for AD were used. Our Washington University Alzheimer's Disease Research Center criteria are based on quantification of diffuse and neuritic amyloid deposition in 5 cortical regions.[10,11] In addition, National Institute on Aging–Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease[22] neuropathologic probability estimates of AD were calculated. The 2 sets of criteria have near-complete diagnostic agreement. Braak and Braak[23] neurofibrillary scores were obtained in the majority (56/80) of cases. Ubiquitin and α-synuclein were used to identify Lewy bodies; the pathologic diagnosis for DLB was made according to published criteria.[17] Cortical and subcortical infarcts and hemorrhages were noted.

### STATISTICAL ANALYSIS

Analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC). Progression from nondemented status (global CDR=0) to dementia (global CDR≥0.5) was the primary outcome measure. The 2 groups at baseline were compared using *t* tests and analysis of covariance for quantitative variables and $\chi^2$ tests of independence for nominal variables. Because those who developed dementia were older than those who did not, all comparisons were controlled for age. The predictive value of baseline clinical and psychometric features was estimated with Kaplan-Meier survival curves for each measure using Wilcoxon tests (PROC LIFETEST in SAS). Cox proportional hazards models examined the association of covariates with dementia onset. The Cochran *Q* test assessed initial impairments in individuals with dementia with McNemar tests for pairwise comparisons. Rates of cognitive decline in the 2 groups, reflected in the longitudinally measured psychometric scores, were compared using the mixed general linear model (PROC MIXED in SAS) with a focus on the group × time interaction. The group without dementia was further divided for similar analyses to compare those who had no dementia pathologic features at autopsy with those who had pathologic AD.

## RESULTS

### BASELINE CHARACTERISTICS

At entry, the sample's mean±SD age was 80.7±9.3 years (range, 62-102 years) with 14.2±3.6 years of education; there was a slight predominance of women (1.4:1). All 80 participants did not have dementia (CDR=0) at entry and had characteristics (sex, education) similar to 2002 US Census Bureau estimates for older adults in the St Louis metropolitan area. Except for older age, they were similar demographically and in baseline cognitive performance to other participants without dementia in our study who did not come to autopsy.[24] Common comorbid disorders such as hypertension, coronary artery disease, and arthritis were present, and individuals used on average less than 3 prescription medications per month.

### CLINICAL OUTCOMES

The mean±SD age at death for the sample as a whole was 88.3±7.8 years (range, 65-106 years). The participants averaged 6 annual assessments (range, 1-17). Sample characteristics at the entry and final assessment (except age,

**Table 1. Sample Characteristics***

| | Dementia Status at Death | |
|---|---|---|
| | No Dementia (n = 41) | Dementia (n = 9) |
| Age at entry, y | 77.1 (8.4) | 84.6 (8.8)† |
| Age at death, y | 84.6 (6.8) | 92.2 (6.7) |
| Education, y | 13.5 (3.5) | 15.0 (3.7) |
| Women, % | 51 | 64 |
| *APOE*, % | | |
| ε2/3 | 18 | 12 |
| ε2/4 | 0 | 3 |
| ε3/3 | 58 | 63 |
| ε3/4 | 21 | 22 |
| ε4/4 | 3 | 0 |
| CDR-SB>0 at entry, % | 0 | 15‡ |
| CDR-SB>0 at death, % | 6 | 100 |
| No. of annual assessments | 6.2 (5) | 6.5 (4.2) |
| No. of prescription medications per subject at entry | 2.5 (2.8) | 2.6 (1.5) |
| Depressive symptoms at entry | | |
| Self-report | 0.5 (0.9) | 0.6 (0.9) |
| Collateral source report | 0.5 (1.0) | 0.8 (1.6) |
| SBT score at entry§ | 1.4 (2.0) | 2.1 (2.4) |
| SBT score at last assessment§ | 1.5 (1.6) | 10.5 (9.9) |

Abbreviations: *APOE*, apolipoprotein E; CDR-SB, Clinical Dementia Rating sum of boxes; SBT, Short Blessed Test.
*Values are expressed as mean (SD) unless otherwise indicated.
†$P<.001$.
‡$P=.02$.
§The SBT scores range from 0 (no impairment) to 28 (maximal impairment).

which is reported as age at death) are presented in **Table 1**. Clinical and pathologic diagnoses by groups are defined in **Figure 1**. Although they did not have dementia at entry, 49% (n=39) developed at least very mild dementia (global CDR≥0.5) by time of death. The expiration diagnosis was AD in 92% (n=36) of cases, either alone or combined with other disorders. In 2 cases, vascular dementia was the expiration diagnosis, and in another case, dementia was ascribed to Parkinson disease.[17]

Participants who developed dementia were older at entry ($P<.001$) than those who did not develop dementia. Of the remaining baseline features, the 2 groups differed only in CDR-SB ($P=.02$). Six participants (15% of sample) with a global CDR of 0 had a CDR-SB of 0.5; the judgment and problem-solving category most often was rated higher than 0 (n=4). All 6 developed dementia (CDR≥0.5) by time of death. Analyses performed eliminating these 6 individuals did not change the results.

## CLINICAL PREDICTORS OF DEMENTIA

Age at entry ($P<.001$) was a predictor of time to CDR of 0.5 or higher; older individuals developed dementia sooner. After controlling for age, the only other baseline clinical feature that predicted time to first CDR of 0.5 or higher in Cox models was the collateral source report of depressive features ($P=.003$). More depressive symptoms reported by the collateral source increased the risk of dementia. In participants who developed dementia, impairments in memory and judgment and problem solving were equally likely to be the first CDR domain to change, and both occurred more frequently than impairment in the other 4 domains (in all cases, $P<.05$). There was no difference in apolipoprotein E (*APOE*) genotype frequencies between groups with and without dementia or when comparing the presence of at least 1 ε4 allele.

## COGNITIVE OUTCOMES

**Table 2** presents cognitive performance at initial and final assessments comparing those who did not develop dementia with those who did. There was no difference on any of the psychometric measures at baseline between the 2 groups, after controlling for age, except for the Trail-Making A score.

There was an effect of time ($P<.001$) and a group × time interaction ($P<.001$) on the composite factor score, indicating that rates of longitudinal decline differed between groups. The group without dementia demonstrated a substantial decline (slope=−0.55; SE=0.06) on the composite factor score but only after dementia was diagnosed clinically. All individuals without dementia maintained an essentially flat course (slope=−0.03; SE=0.03).

Analyses on individual psychometric tests revealed significant group × time interactions except for the Wechsler Memory Scale Digits Backward test. Similar to the composite factor score with 2 exceptions, a flat slope was seen for participants without dementia vs declining slopes for participants with dementia after clinical diagnosis. For the Wechsler Memory Scale Associate Memory test, there was mild but significant improvement in performance over time. For the Wechsler Adult Intelligence Scale Digit Symbol test, there was a decline in performance for participants without dementia over time. Prior to diagnosis, there were no differences in the slopes of participants who developed dementia and those who did not.

## COGNITIVE PREDICTORS OF DEMENTIA

The Trail-Making A test ($P=.003$) was the only baseline cognitive measure that was a predictor of time to a global CDR of 0.5 or higher, after controlling for age. Individuals who were slower on this measure developed dementia sooner.

## NEUROPATHOLOGIC OUTCOMES

**Table 3** presents clinicopathologic relations for all 80 participants in this study. Alzheimer disease was present in 45 cases (56% of the entire sample). In the participants with dementia, AD was present in 31 cases (79%); 13 cases had AD alone, whereas 18 cases had additional pathologic features, including Lewy bodies, infarcts, and argyrophilic grains.[25] Lewy bodies were present in 12 (15%) of the 80 brains. Dementia with Lewy bodies was diagnosed pathologically in 9 cases (11%), 2 without dementia and 7 with dementia. All but 1 of the DLB cases had coexistent AD. Cerebral infarcts were identified in 31 cases (39%) in the entire sample (16 without dementia; 15 with clinical dementia). In most instances, infarcts were small in size with a predilection for the left

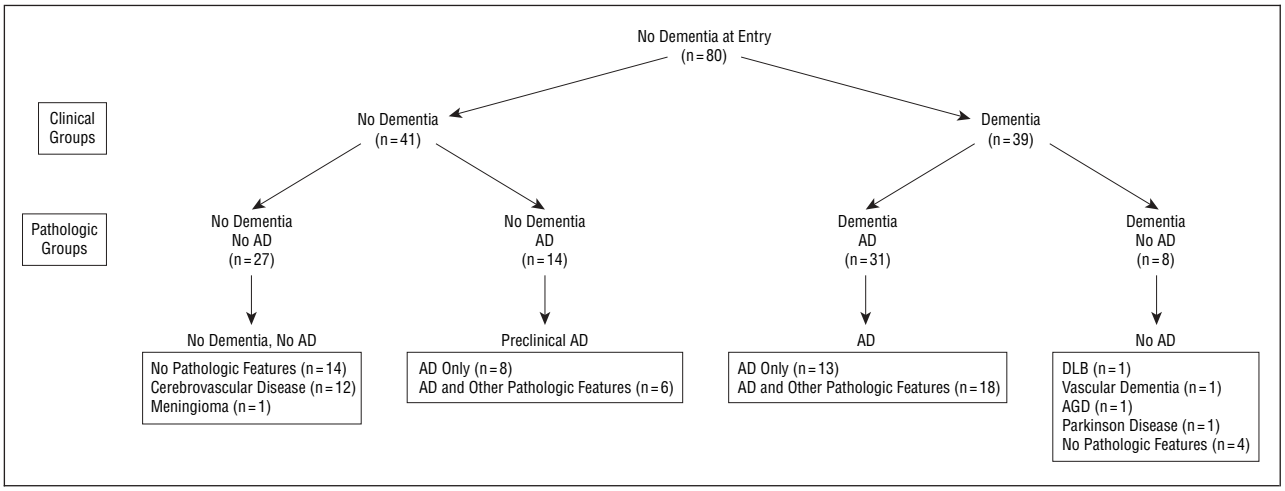


**Figure 1.** Flow chart of the longitudinal follow-up of the clinical and pathologic groups. AD indicates Alzheimer disease; AGD, argyrophilic grain disease; DLB, dementia with Lewy bodies.

**Table 2. Cognitive Outcomes***

| | Baseline Examination | | Final Examination | |
|---|---|---|---|---|
| | Diagnosis at Death | | Diagnosis at Death | |
| Test Score (Range of Values) | No Dementia | Dementia | No Dementia | Dementia† |
| Wechsler Memory Scale | | | | |
| Logical Memory (0-23) | 8.5 (3.0) | 7.7 (2.7) | 9.0 (2.8) | 5.9 (3.1) |
| Digits Forward (0-8) | 6.6 (1.2) | 6.2 (1.4) | 6.4 (1.3) | 5.8 (1.2) |
| Digits Backward (0-7) | 4.8 (1.3) | 4.3 (1.1) | 4.6 (1.1) | 3.9 (1.5) |
| Associate Memory (0-21) | 12.3 (2.9) | 11.3 (3.4) | 13.9 (3.7) | 9.2 (4.6) |
| Benton Visual Retention Test | | | | |
| Form C: Recall (0-10) | 5.2 (1.6) | 4.9 (1.8) | 5.2 (1.9) | 3.7 (2.0) |
| Form D: Copy (0-10) | 9.1 (1.3) | 9.3 (1.5) | 9.6 (0.7) | 8.4 (2.8) |
| Information (0-29) | 20.8 (4.1) | 20.6 (5.2) | 21.0 (4.1) | 17.4 (6.4) |
| Word Fluency (≥0) | 29.1 (10.1) | 26.9 (9.6) | 29.9 (10.2) | 19.4 (9.5) |
| Boston Naming (0-60) | 53.0 (6.4) | 50.1 (7.5) | 53.1 (6.8) | 41.3 (15.2) |
| Wechsler Adult Intelligence Scale | | | | |
| Digit Symbol (0-90) | 42.1 (9.8) | 36.1 (14.5) | 36.4 (11.0) | 27.3 (15.6) |
| Block Design (0-48) | 28.6 (8.2) | 27.1 (8.5) | 27.5 (9.1) | 21.7 (11.0) |
| Trail-Making A (0-180) | 49.1 (17.7) | 65.4 (34.7)‡ | 56.9 (25.8) | 84.4 (46.4) |
| Mental Control (0-9) | 7.1 (2.0) | 6.9 (1.8) | 6.8 (2.0) | 5.3 (2.9) |
| General factor score (*z* score) | –0.3 (1.1) | –0.9 (1.3) | –0.4 (1.1) | –2.2 (2.2) |

*Values are expressed as mean (SD). Low scores on Trail-Making A test indicate better performance. High scores on all other measures indicate better performance.

†After controlling for age, all scores were significantly different for the group with dementia at the $P<.05$ level compared with the group without dementia.

‡After controlling for age, there was a difference in baseline scores between the group without dementia and those who would develop dementia ($P=.003$).

frontal cortex, basal ganglia, and subcortical white matter. The infarcts were not sufficient to cause dementia, although they may have contributed to dementia onset and severity.

Eight participants with dementia (21%) did not have neuropathologic AD; 1 had Parkinson disease, 1 had vascular dementia, 1 had DLB and cerebral infarcts, 1 had argyrophilic grain disease, and 4 (all with CDR=0.5 at death) had no discernable disorder causing dementia. Neuropathologic AD was present in 14 (34%) of 41 individuals without dementia at death (CDR=0), consistent with a "preclinical" state of AD.[12,26,27]

Pathologic features of AD increased with age and were present in 40% of all individuals younger than 85 years, 67% of individuals aged 86 to 95 years, and 69% of individuals older than 95 years; this association did not reach statistical significance ($\chi^2_2=5.30$; $P=.07$) (**Figure 2**). When all dementia pathologic features were considered, however, there was a significant increase with occurrence of 44% in individuals younger than 85 years, 69% in individuals aged 86 to 95 years, and 94% in individuals older than 95 years ($\chi^2_2=11.10$; $P=.004$).

## NEUROPATHOLOGIC FEATURES AT THE CDR=0.5 STAGE

Twenty-four participants died with a global CDR of 0.5 (Table 3). Clinically, 2 of the 24 individuals met a com-

**Table 3. Clinicopathologic Relationships**

| Case | Final Diagnosis | CDR | WUSM AD | NIA-Reagan | Braak | Other |
|---|---|---|---|---|---|---|
| | | | **Cases Without Dementia** | | | |
| 1 | No dementia | 0 | No | Low | II | |
| 2 | No dementia | 0 | No | Low | I | |
| 3 | No dementia | 0 | No | Low | I | |
| 4 | No dementia | 0 | No | Low | II | Meningioma |
| 5 | No dementia | 0 | No | Low | | |
| 6 | No dementia | 0 | No | Low | II | |
| 7 | No dementia | 0 | No | Low | II | |
| 8 | No dementia | 0 | No | Low | II | |
| 9 | No dementia | 0 | No | Low | III | |
| 10 | No dementia | 0 | No | Low | III | |
| 11 | No dementia | 0 | No | Low | | |
| 12 | No dementia | 0 | No | Low | II | |
| 13 | No dementia | 0 | No | Low | III | |
| 14 | No dementia | 0 | No | Low | III | |
| 15 | No dementia | 0 | No | Low | II | |
| 16 | No dementia | 0 | No | Low | | CVD |
| 17 | No dementia | 0 | No | Low | III | CVD |
| 18 | No dementia | 0 | No | Low | | CVD |
| 19 | No dementia | 0 | No | Low | I | CVD |
| 20 | No dementia | 0 | No | Low | II | CVD |
| 21 | No dementia | 0 | No | Low | | CVD |
| 22 | No dementia | 0 | No | Low | II | CVD |
| 23 | No dementia | 0 | No | Low | II | CVD |
| 24 | No dementia | 0 | No | Low | I | CVD |
| 25 | No dementia | 0 | No | Low | II | CVD |
| 26 | No dementia | 0 | No | Low | | CVD |
| 27 | No dementia | 0 | No | Intermediate | II | CVD |
| | | | **Preclinical Cases** | | | |
| 28 | No dementia | 0 | Yes | High | V | DLB, CVD |
| 29 | No dementia | 0 | Yes | High | IV | |
| 30 | No dementia | 0 | Yes | High | VI | |
| 31 | No dementia | 0 | Yes | High | | CVD |
| 32 | No dementia | 0 | Yes | High | | |
| 33 | No dementia | 0 | Yes | High | | |
| 34 | No dementia | 0 | Yes | High | IV | |
| 35 | No dementia | 0 | Yes | Intermediate | | |
| 36 | No dementia | 0 | Yes | High | | PD |
| 37 | No dementia | 0 | Yes | High | V | |
| 38 | No dementia | 0 | Yes | High | II | |
| 39 | No dementia | 0 | Yes | Intermediate | II | DLB, AGD |
| 40 | No dementia | 0 | Yes | Low | I | CVD |
| 41 | No dementia | 0 | Yes | Low | IV | CVD |

*(continued)*

mon definition of mild cognitive impairment[5] with episodic memory performance at their last assessment more than 1.5 SDs lower than age- and education-matched normative values (ie, <5.3 score on Wechsler Memory Scale Logical Memory test) but otherwise generally preserved cognitive abilities (Mini-Mental State Examination scores ≥24). Both individuals had AD at autopsy. The remaining 22 individuals with a CDR of 0.5 were less impaired than the operational definition of mild cognitive impairment.[5] Of these 22 cases, 16 had AD, 1 had nigral Lewy bodies, and 1 had argyrophilic grain disease. Four individuals with a CDR of 0.5 did not have pathologic features sufficient to diagnose AD or other illnesses causing dementia. Of the 7 individuals who died with a CDR of 0.5 in memory only, all had dementia pathologic features at autopsy (6 had AD, 1 had argyrophilic grain disease).

## PREDICTORS OF PRECLINICAL AD

Participants with preclinical AD were identical clinically and cognitively at baseline to those individuals with a CDR of 0 and without neuropathologic AD except that the preclinical group scored higher in word fluency ($P=.03$). Longitudinally, the 2 groups were alike with 3 exceptions: (1) the individuals with preclinical AD performed more poorly over time on the Short Blessed Test (slope=0.14; SE=0.06; interaction $P=.01$); (2) although both groups improved over time on the Wechsler Memory Scale Associate Memory test, the group without AD improved (slope=0.38; SE=0.06) to a greater degree (interaction $P=.05$) than the preclinical group (slope=0.20; SE 0.06); and (3) the group without AD improved longitudinally on the Boston Naming Test (slope=0.15; SE=0.05), but the preclinical group

**Table 3. Clinicopathologic Relationships (cont)**

| Case | Final Diagnosis | CDR | WUSM AD | NIA-Reagan | Braak | Other |
|---|---|---|---|---|---|---|
| | | | **Cases With Dementia** | | | |
| 42 | DAT | 0.5 | Yes | High | IV | CVD |
| 43 | DAT | 0.5 | No | Low | | |
| 44 | DAT | 0.5 | Yes | Intermediate | | CVD |
| 45 | DAT | 0.5 | Yes | High | IV | |
| 46 | DAT | 0.5 | Yes | Intermediate | III | DLB, CVD |
| 47 | DAT | 0.5 | Yes | High | VI | CVD |
| 48 | DAT | 0.5 | Yes | High | | |
| 49 | DAT | 0.5 | Yes | High | II | |
| 50 | DAT | 0.5 | Yes | High | IV | |
| 51 | DAT | 0.5 | Yes | High | | CVD |
| 52 | DAT | 0.5 | Yes | High | V | DLB, CVD |
| 53 | DAT | 0.5 | Yes | High | V | DLB |
| 54 | DAT | 0.5 | Yes | High | | |
| 55 | DAT | 0.5 | No | Low | II | |
| 56 | DAT | 0.5 | Yes | High | V | |
| 57 | DAT | 0.5 | No | Low | III | |
| 58 | DAT | 0.5 | Yes | High | | |
| 59 | VaD | 0.5 | Yes | High | | CVD |
| 60 | VaD | 0.5 | Yes | Intermediate | III | CVD |
| 61 | DAT | 0.5 | No | Low | I | |
| 62 | DAT | 0.5 | No | Low | III | PD |
| 63 | DAT | 0.5 | Yes | Intermediate | IV | DLB, CVD, AGD |
| 64 | DAT | 0.5 | Yes | High | | PD |
| 65 | DAT | 0.5 | No | Low | IV | AGD |
| 66 | DAT | 1 | Yes | High | | |
| 67 | DAT | 1 | Yes | High | V | HS |
| 68 | DAT | 1 | No | Low | | CVD |
| 69 | DAT | 2 | Yes | High | VI | |
| 70 | DAT | 2 | Yes | High | | CVD |
| 71 | DAT | 2 | Yes | High | VI | CVD |
| 72 | DAT | 3 | Yes | High | VI | DLB |
| 73 | DAT, PD | 3 | No | Low | | DLB, CVD, HS |
| 74 | MSA, PD | 3 | Yes | High | VI | DLB |
| 75 | DAT | 3 | Yes | Intermediate | II | HS |
| 76 | DAT | 3 | Yes | High | VI | |
| 77 | DAT | 3 | Yes | High | | |
| 78 | DAT | 3 | Yes | High | VI | CVD |
| 79 | DAT | 3 | Yes | High | VI | CVD |
| 80 | DAT | 3 | Yes | High | VI | |

Abbreviations: AGD, argyrophilic grain disease; Braak, Braak and Braak[23] neurofibrillary score; CDR, Clinical Dementia Rating; CVD, cerebrovascular disease; DAT, dementia of the Alzheimer type; DLB, dementia with Lewy bodies; HS, hippocampal sclerosis; MSA, multiple systems atrophy; NIA-Reagan, National Institute on Aging–Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease neuropathologic probability estimate; PD, Parkinson disease; VaD, vascular dementia; WUSM AD, Washington University Alzheimer's Disease Research Center criteria.

did not (slope=0.00; SE=0.06; interaction $P=.01$). These observations suggest that individuals without dementia without AD pathologic features demonstrate practice effects on certain cognitive measures and that the attenuation or absence of this learning may characterize individuals without dementia who have AD neuropathologic characteristics (preclinical AD). There was no difference between the 2 groups on the factor score, suggesting that preclinical AD is not accompanied by general cognitive deficits or decline, at least as measured by the tests used in this study.

## COMMENT

We report 3 important findings. The first is that almost half of our sample developed dementia by time of death (mean age, 88 years) consistent with reports that dementia prevalence approaches 50% in older adults at this age.[28] Neuropathologic AD was responsible for dementia in most cases. The second is that because truly nondemented older adults are characterized by relatively stable cognitive performance, the clinical detection of any impairment (ie, CDR-SB of 0.5 in any domain), slower performance on a speeded psychomotor task, and depressive features reported by a collateral source are predictive of future dementia. Lastly, we report on 14 cases of preclinical AD and provide novel data to suggest that the absence of practice effects on certain cognitive measures may indicate those individuals without dementia who have underlying neuropathologic AD.

The onset of dementia was marked by a sharp inflection point in longitudinal psychometric performance, sub-

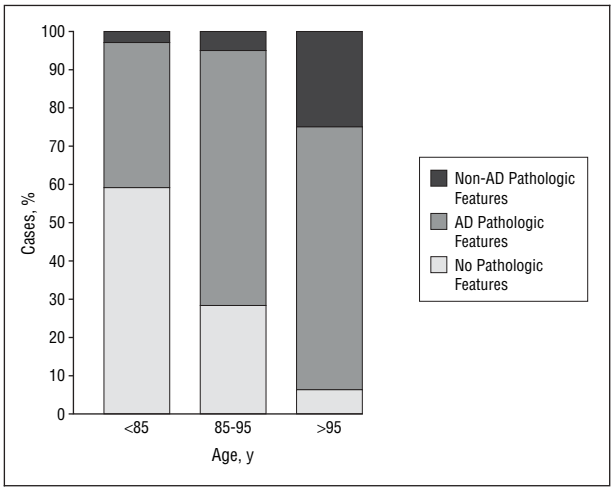


**Figure 2.** The relationship of brain pathologic features and age in a longitudinal sample of older adults. AD indicates Alzheimer disease.

sequent substantial cognitive decline, and dementia-related pathologic features on autopsy. Longitudinal assessment may be preferable to cross-sectional comparison with normative criteria to identify subtle changes that indicate the onset of dementia, particularly for high-functioning individuals who, in the beginning stages of decline, still perform higher than traditional "cutoff" scores. Emphasis on detecting change also may prevent inappropriate diagnosis of dementia in individuals with poorer lifelong abilities.

The finding that the collateral source report of depressive features was related to the development of dementia is consistent with reports suggesting depression may be a prodromal symptom of dementia.[29,30] Traditional depression screening tools based only on participants' responses may underestimate the presence of depression.[31] Although poorer baseline speeded performance was also a harbinger of the onset of dementia, it was uncorrelated with depressive features.

The prevalence of dementia pathologic features in the oldest old (>85 years) is not well established. Our data suggest that the frequency of autopsy-proven AD tends to stabilize after age 85 years, although it remains very high (69%). Other potentially dementing pathologic features continue to increase so that by age 95 years, 94% of individuals have some dementia pathologic features. Neuropathologic AD was also found in about a third of individuals without dementia. This preclinical AD precedes any cognitive impairment and is clinically indistinguishable from individuals without dementia with the possible exception of reduced practice effects on tests amenable to such carry over.

Of the 24 individuals with the very mildest detectable impairments (CDR=0.5), neuropathologic AD was present in 18 cases, suggesting that even very minimal clinical deficits distinguish these individuals from aging individuals without dementia. Four cases had scattered senile plaques and neurofibrillary tangles that were insufficient for a neuropathologic diagnosis of AD. It remains a clinical challenge to distinguish the small number of individuals with very subtle clinical deficits who do not have neuropathologic evidence of AD or other dementias from the large majority of similarly minimally impaired individuals who do.

Our study has limitations. The sample was not population-based, and thus we cannot determine incidence rates. Its limited size precludes detection of small effects (ie, *APOE* alleles). As with any volunteer sample, there may be selection biases, limiting generalization of the results. On the other hand, our sample was not recruited from memory disorder clinics but rather from the community, and the participants' demographic attributes reflect those of the similarly aged population in the metropolitan area. Other unique aspects include the large number of aged individuals without dementia evaluated longitudinally over a long surveillance period (mean, 6 years); a short period between last assessment and death (median, 9.9 months); and the extensive clinical, cognitive, and pathologic data.

The finding that even the mildest of cognitive change as detected by clinical interview correlates highly with dementia pathologic features has important implications. As the population continues to age, the prevalence of dementing illnesses such as AD will increase. If some individuals currently labeled as having mild cognitive impairment are considered as having early-stage AD,[9] then the true prevalence of AD may be much greater than is generally appreciated. Carefully applied clinical criteria for dementia, even in its very mildest stages, can be highly accurate as confirmed by autopsy.[2] Early appreciation of dementia may alleviate uncertainty concerning the diagnosis, permit patients to participate in future planning while only minimally impaired, and allow for early intervention with potential disease-modifying therapies.

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