

Ecology of the Aging Human Brain

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Background: Alzheimer disease, cerebral vascular brain injury, and isocortical Lewy body disease (LBD) are the major contributors to dementia in community- and population-based studies.

Objective: To estimate the prevalence of clinically silent forms of these diseases in cognitively normal (CN) adults.

Design: Autopsy study.

Setting: Community- and population based.

Participants: A total of 1672 brain autopsies from the Adult Changes in Thought study, Honolulu-Asia Aging Study, Nun Study, and Oregon Brain Aging Study, of which 424 met the criteria for CN.

Main Outcome Measures: Of these, 336 cases had a comprehensive neuropathologic examination of neuritic plaque density, Braak stage for neurofibrillary

tangles, LB distribution, and number of cerebral microinfarcts.

Results: Forty-seven percent of CN cases had moderate or frequent neuritic plaque density; of these, 6% also had Braak stage V or VI for neurofibrillary tangles. Fifteen percent of CN cases had medullary LBD; 8% also had nigral and 4% isocortical LBD. The presence of any cerebral microinfarcts was identified in 33% and of high-level cerebral microinfarcts in 10% of CN individuals. Overall, the burden of lesions in each individual and their comorbidity varied widely within each study but were similar across studies.

Conclusions: These data show an individually varying complex convergence of subclinical diseases in the brain of older CN adults. Appreciating this ecology should help guide future biomarker and neuroimaging studies and clinical trials that focus on community- and population-based cohorts.

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RESULTS OF RECENT NEUROIMAGING and cerebrospinal fluid biomarker studies^{1,2} have indicated that fibrillar β amyloid ($A\beta$) accumulation in the cerebrum occurs in approximately one-quarter to one-half of cognitively normal (CN) older adults and likely represents latent Alzheimer disease (AD). These findings are consonant with a large body of literature from neuropathologic studies³⁻¹³ that have characterized features of AD, including neuritic plaque (NP) formation, in CN older adults.

Most of the previously cited studies have investigated research clinic cohorts that commonly use clinical criteria to enrich for individuals with probable AD and often exclude individuals with a history of cerebrovascular disease or its risk factors, thereby limiting the representation of other common diseases that can contribute to dementia.^{14,15} Indeed, investigations^{16,17} of community- or population-based cohorts for brain aging and dementia

repeatedly have observed 3 common contributors to dementia: AD, vascular brain injury (VBI), and Lewy body disease (LBD). Although there are accepted histopathologic criteria for assessing the lesions of AD or LBD, there are no widely used criteria for VBI; however, 2 of the population-based studies included herein (the Honolulu-Asia Aging Study [HAAS]¹⁸ and the Adult Changes in Thought [ACT] study¹⁹) have independently shown that microvascular brain injury (μ VBI) as assessed by systematic screening for cerebral microinfarcts (CMIs) carries a relative risk of dementia similar to that of AD. Although changes in AD, μ VBI, and LBD are the most prevalent structural correlates of dementia in community- and population-based cohorts, we hasten to add that there are other diseases that cause dementia and produce distinctive lesions in brain. However, these diseases are relatively uncommon and are not captured efficiently in community- and population-based studies of elderly individuals.^{15,19}

Table 1. Characteristics of the 1672 Participants by Study

Characteristic	ACT	HAAS	NS	OBAS	Total
Total autopsies, No.	344	446	548	334	1672
Last evaluation within 2 y of death, No.	299	262	475	280	1316
"Not dementia" by <i>DSM</i> at last evaluation, No. ^a	182	126	182	166	656
Eligible cases					
Upper 4 quintiles of cognition function for the entire cohort, No. ^b	116	59	162	87	424
Complete neuropathologic examination, No.	116	59	106 ^c	55 ^d	336
Age at death, mean (SD), y	84 (6)	83 (5)	89 (5)	91 (5)	87 (4)
Sex, M/F, No.	52/64	59/0	0/106	23/32	134/202
Last MMSE score, median (range)	28 (25-30)	27 (23-29)	28 (24-30)	29 (28-30)	NA
Last CASI score, mean (SD)	95 (3)	89 (4)	NA	NA	NA
Brain weight, mean (SD), g	1178 (143)	1292 (101)	1143 (122)	1222 (125)	1209 (64)

Abbreviations: ACT, Adult Changes in Thought study; CASI, Cognitive Assessment Screening Instrument; *DSM*, *Diagnostic and Statistical Manual of Mental Disorders*; HAAS, Honolulu-Asia Aging Study; MMSE, Mini-Mental State Examination; NA, not applicable; NS, Nun Study; OBAS, Oregon Brain Aging Study.

^aThe *DSM-III-Revised* for HAAS and the *DSM-IV* for the NS and ACT.

^bUsing the MMSE for the NS (score ≥ 24), the OBAS (score ≥ 28), the CASI for HAAS (score ≥ 83), and ACT (score ≥ 91).

^cOnly NS cases without missing Braak or cerebral microinfarct scores were included (n=106).

^dNeuropathologic examination for the OBAS switched to a protocol identical to that of ACT in 2004; all eligible cases accrued past this date had comparable neuropathologic examinations and were included.

Because there are as yet no validated neuroimaging or biomarker protocols for μ VBI or LBD, current information about clinically silent forms of these diseases is available only from autopsy-based studies. Some community- or population-based studies of brain aging and dementia with autopsy have investigated clinically silent disease^{3,4,14,15,20-22}; however, all but 1 study¹⁵ have focused on a single cohort, resulting in a relatively low number of cases and potentially restricted generalization. Moreover, differences in the methods for histologic assessment or the definition of CN have varied among these studies and might account for some of the apparently discrepant outcomes. Herein we address these limitations with a harmonized histologic assessment of AD, μ VBI, and LBD in participants with uniformly defined cognitive function from ACT, HAAS, the Nun Study (NS), and the Oregon Brain Aging Study (OBAS).

METHODS

ACT, HAAS, NS, and OBAS were approved by their respective institutional review boards. All cases were drawn from the existing databases for brain autopsies from these 4 studies as of January 2010.

All the cohorts shared the same general characteristics. Each individual was recruited as a participant for a longitudinal study of brain aging from a defined community or population. Individuals did not present for the study because of concerns about memory or cognitive function. The NS cohort is composed of American sisters of the School Sisters of Notre Dame religious congregation born before 1917 who volunteered to join a longitudinal study of aging and Alzheimer disease²³; the HAAS cohort is a subset of the Honolulu Heart Program observed for cognitive and aging function²⁴; the ACT cohort is composed of individuals 65 years or older who were members of Group Health Cooperative, a managed care organization in the Seattle area²⁵; and the OBAS study cohort is composed of initially healthy seniors recruited from the community via advertising and senior congregate site canvassing for studies focused on the oldest old.²⁶

CLINICAL ASSESSMENTS

Only individuals whose last clinical evaluation was within 2 years of death were included in this study. At the time of last evaluation, study participants were diagnosed as having dementia or as not having dementia based on *Diagnostic and Statistical Manual of Mental Disorders (DSM)* criteria: *DSM-III-Revised* for the HAAS and *DSM-IV* for the ACT, NS, and OBAS. Individuals who were diagnosed as not having dementia were further stratified based on performance on a cognitive screening test: the Mini-Mental State Examination for the NS and the OBAS and the Cognitive Assessment Screening Instrument for ACT and HAAS. To minimize misclassification, we further restricted analysis to individuals whose scores on their respective cognitive screening test at last evaluation were in the upper 4 quintiles for the entire cohort; this cutoff value was a Mini-Mental State Examination score of at least 24 for the NS and of at least 28 for the OBAS and a Cognitive Assessment Screening Instrument score of at least 83 for the HAAS and of at least 91 for ACT (**Table 1**).

HISTOPATHOLOGIC SCORING

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score for NPs was determined as described previously and was recorded as part of the primary data for ACT, OBAS, and NS using modified Bielschowsky staining.²⁷ HAAS used the same method but recorded data as density of NP in different regions of the cerebral cortex from which the CERAD NP score was derived. Braak staging for neurofibrillary tangles (NFTs) was determined by the same method in all 4 studies.²⁸ The CMIs were determined in all 4 studies by the same method of screening hematoxylin-eosin-stained sections of the cerebrum for infarcts that were not observed grossly.¹⁹ HAAS screened more regions of the cerebrum for microinfarcts than did the other studies; however, all the data presented herein are limited to the same 12 sections from the same 6 bilateral cerebral regions as previously described.¹⁹ Immunohistochemical analysis for α -synuclein was used to highlight LBs in all the studies.²⁹ The regions evaluated for LBs overlapped in all the studies only for the frontal and temporal cortices. ACT and the NS also evaluated LBs in the medulla, and ACT, HAAS, and OBAS assessed LBs in the substantia nigra.

Table 2. Alzheimer Disease Pathologic Changes in 336 Cognitively Normal Adults^a

CERAD NP Score	Braak NFT Stage			Total
	None to II/None ^b	III or IV	V or VI	
None	23 (6)/5 (1)	6 (4)	0 (1)	29 (8)
Sparse	15 (5)/3 (2)	7 (4)	1 (1)	23 (8)
Moderate	13 (4)/1 (1)	8 (3)	3 (2)	24 (6)
Frequent	12 (4)/0 (1)	9 (3)	3 (1)	24 (7)
Total	63 (6)/9 (3)	30 (5)	7 (8)	100

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NFT, neurofibrillary tangle; NP, neuritic plaque.

^aStratification of the 336 eligible participants with complete neuropathologic examination from the 4 studies into CERAD NP score and Braak stage for NFT groups. Percentage of individuals from each study was calculated separately; data are mean (SD) percentages for the 4 studies.

^bBraak stage for NFTs was stratified as "None to II" to correspond with later analyses but also as "None" to highlight individuals without NFTs.

We previously used a summary neuropathology score as a convenient metric to capture the magnitude of AD, μ VBI, and LBD in each individual in the ACT cohort.³⁰ As previously published, this summary neuropathology score derives from the sum of subscores for each of the main axes: (1) AD subscore (Braak stage for NFTs expressed as a number divided by 2, thus ranging from 0 [lowest] to 3 [highest]), (2) CMI subscore (number of CMIs with ≥ 3 by screening protocol assigned a value of 3, thus ranging from 0 [lowest] to 3 [highest]), and (3) LBD subscore (0 indicating none; 1, medullary LBD; 2, substantia nigra LBD; and 3, isocortical LBD in the frontal or temporal cortex). Statistical analyses were performed using GraphPad Prism (GraphPad Software Inc, La Jolla, California).

RESULTS

We pursued a uniform analysis of cases from ACT, HAAS, NS, and OBAS with the goal of obtaining comparable data sets from these community- and population-based studies of brain aging and dementia. Table 1 lists the selection criteria and the eligible cases from each cohort. Overall, this study derived from 1672 individuals who participated in 1 of these 4 studies and who consented to brain autopsy as part of a research study. Of these, 424 people were CN as defined by the following: (1) their last clinical evaluation being within 2 years of death (average=369 days), (2) at that time they were diagnosed as not having dementia, and (3) at that time their cognitive testing battery results were in the upper 4 quintiles for the entire cohort in which they participated. Of these 424 CN cases, complete neuropathologic evaluation was performed on 336; missing CMI data was the most frequent cause of an incomplete evaluation. These 336 autopsies with complete neuropathologic examination from CN older adults who participated in population- and community-based studies form the basis of the present study (Table 1).

We chose to reference all other lesions to NP score because this was the most prevalent lesion in eligible cases. However, CERAD NP score has potential challenges as a measure of fibrillar A β . For this reason, we performed 2 experiments to assess the limits of this measure. First, because ACT also collects rapidly frozen tissue, we compared mean (SD) tissue burden of detergent-insoluble A β ₄₂

Table 3. Lewy Body Disease (LBD) in 336 Cognitively Normal Adults^a

CERAD NP Score	Region of Lewy Body Disease ^b		
	Medulla (ACT and NS)	SN (ACT, HAAS, and OBAS)	Isocortical (All 4 Studies)
None	6 (1)	1 (1)	0 (0)
Sparse	4 (3)	3 (2)	2 (2)
Moderate	3 (3)	3 (1)	1 (1)
Frequent	2 (2)	1 (2)	1 (1)
Total	15 (2)	8 (3)	4 (2)

Abbreviations: ACT, Adult Changes in Thought study; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; HAAS, Honolulu-Asia Aging Study; NP, neuritic plaque; NS, Nun Study; OBAS, Oregon Brain Aging Study; SN, substantia nigra.

^aStratification of the 336 eligible participants with complete neuropathologic examination by CERAD NP score and LBD. Percentage of individuals from each study was calculated separately; data are mean (SD) percentages for the 4 studies.

^bRegional LBD was assessed differently in the 4 studies. ACT and NS screened for medullary LBDs using α -synuclein; HAAS and OBAS did not have data on medullary LBDs. ACT, HAAS, and OBAS screened for LBDs in the SN using hematoxylin-eosin-stained slides. All the studies used surface nonspecific cross-reacting antigen immunohistochemical analysis in the frontal or temporal cortex.

with CERAD NP score in the cortex from the middle frontal gyrus and the superior and middle temporal gyri, respectively: CERAD NP "none" (n=5), 0.3 (0.1) and 0.2 (0.1); "sparse" (n=10), 2.0 (0.1) and 1.5 (0.5); and "moderate" (n=4), 13 (4.1) and 9.6 (4.6) ng/g detergent-soluble A β ₄₂ (Spearman rank correlation $P < .001$ in both cerebral cortical regions). Second, analogous to a method commonly used in transgenic mice that express mutant human APP,³¹ we measured the percentage of gray matter area occupied by A β immunoreactive peptide in temporal cortices from randomly selected ACT cases and correlated these results with CERAD NP scores from the contralateral temporal cortex; again, these 2 measures were highly significantly correlated (n=86; Spearman rank correlation $r = 0.50$, $P < .001$). These results indicate that CERAD NP score, a measure that was applied across all 4 studies, is highly significantly correlated with cerebral cortical burden of plaque-associated A β peptides as determined by immunohistochemical analysis with antibody 6E10 and with cerebral cortical detergent-insoluble A β ₄₂.

Table 2 stratifies CERAD NP score by Braak stage for NFTs in CN adults in the 4 studies. Approximately 47% of CN older individuals had moderate or frequent NP scores across all Braak stages. However, only 6% of these individuals also had Braak stage V or VI for NFTs. Thus, the substantial cerebral cortical accumulation of NPs that was observed in approximately one-half of CN older adults was not usually accompanied by high Braak stage for NFTs. Interpretation of these necessarily cross-sectional data is limited but suggests that although accumulation of cerebral cortical A β is common, the full spectrum of pathologic changes of AD is relatively uncommon in CN older adults.

Table 3 lists a similar stratification for LBD in the 4 studies. Because data for LBD were not collected in the same manner across all the studies, data from only 2 stud-

Table 4. Cerebral Microinfarcts in 336 Cognitively Normal Adults^a

CERAD NP Score	CMIs			Total
	0	1 or 2	≥3	
None	22 (12)	6 (2)	3 (1)	31 (11)
Sparse	13 (5)	6 (1)	3 (1)	22 (6)
Moderate	14 (7)	5 (2)	1 (1)	20 (6)
Frequent	18 (4)	6 (4)	3 (3)	27 (8)
Total	67 (8)	23 (6)	10 (3)	100

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CMIs, cerebral microinfarcts; NP, neuritic plaque.

^aStratification of the 336 eligible participants with complete neuropathologic examination by number of CMIs and CERAD NP score. Percentage of individuals from each study was calculated separately; data are mean (SD) percentages for the 4 studies.

ies could be combined for the medulla and from 3 studies for the substantia nigra; all 4 studies collected comparable data for LBD in the isocortex. Lewy body disease in CN older adults followed an apparent anatomical progression, with 15% showing medullary LBD; a subset of these (8%) also had LBD in the substantia nigra, and a further subset (4%) also had isocortical LBD, similar to observations made by other researchers.³²

Although several groups have reported results about subclinical NPs, NFTs, and LBs in CN individuals from research cohorts, there have been relatively few data on μ VBI in CN older adults. **Table 4** gives CMI data from CN individuals in the 4 studies stratified by CERAD NP score. No significant correlation was noted between CERAD NP score and the categories for CMI as listed in Table 4. Overall, approximately one-third of CN older adults had CMIs captured by the screening protocol; of these, 10% had 3 or more CMIs, a level of disease that is associated with increased risk of clinically evident dementia.¹⁹

No instances were reported of other less common diseases that can cause dementia in this cohort of CN individuals (eg, frontotemporal lobar degeneration or prion disease). Three cases of hippocampal sclerosis were observed (1 each in ACT, HAAS, the NS); each was comorbid with AD or μ VBI. Two of 116 CN cases from the ACT cohort had amygdala-only LBD; this was not evaluated in the other cohorts.

Figure 1 shows each CN individual's summary neuropathology score as a bar divided into its corresponding subscores for AD, μ VBI, and LBD; these data have been arranged by summary neuropathology score (lowest to highest), then ranked by AD subscore, and then ranked by μ VBI subscore, with the individual bars opposed so that they appear (appropriately) as a continuum. Results from ACT (Figure 1A), NS (Figure 1B), HAAS (Figure 1C), and OBAS (Figure 1D) are similar and show that it is uncommon for CN older individuals to have no neuropathologic evidence of disease(s) that can cause dementia (**Table 5**). Moreover, the burden of diseases ranged widely within each study and showed substantial individually varying comorbidity. Although we can only speculate on the extent of diseases that existed at the time of cognitive testing, on average, approximately 1 year before neuropathologic evaluation, the cross-validating results strongly suggest that CN older individuals have widely varying burdens of disease(s)

that can cause dementia and that there is highly individually varying comorbidity among these 3 common diseases.

Figure 2 shows the cumulative relative frequency of the summary neuropathology score for individuals in each study. In addition to CN older adults, who have been the focus of the preceding analyses, we included for comparison data on individuals from each study who were last seen by study investigators within 2 years of death and were diagnosed as not having dementia but performed in the lowest quintile on the cognitive screening test (lower cognitive function) and those who were diagnosed as having dementia; to be eligible, all individuals were required to have undergone complete neuropathologic examination. These data support the conclusion that individuals with lower cognitive function or dementia carry a progressively greater average burden of lesions from AD, μ VBI, and LBD. Indeed, when we applied nonparametric analysis of variance to the data presented in Figure 2, the overall result of the Kruskal-Wallis test was significant ($P < .001$) for the 3 groups, as was that of the Dunn corrected paired post test ($P < .001$) for each of the 3 paired comparisons. These results suggest a high degree of correlation between structure and function when a broad perspective is brought to evaluating the 3 diseases that commonly cause dementia in older individuals.

In the final analysis, we correlated summary neuropathology score with age at death. Results from this analysis were mixed. When all 4 cohorts were combined, there was a weak correlation between summary neuropathology score and age (Spearman rank correlation $P < .02$); however, this was driven by the relatively younger ACT cohort of men and women (Spearman rank correlation $P < .01$) but by none of the other 3 cohorts (Spearman rank correlation $P > .05$), which may be due, in part, to their smaller sample size (HAAS and OBAS), average older age (OBAS), or inclusion of women only (NS). Correlation of the AD or μ VBI subscores with age yielded somewhat clearer results; AD score, which is simply Braak stage divided by 2, was significantly associated with increasing age in both of the larger cohorts ($P < .01$ for ACT and NS), whereas μ VBI score was weakly associated with age only in the ACT cohort ($P < .04$).

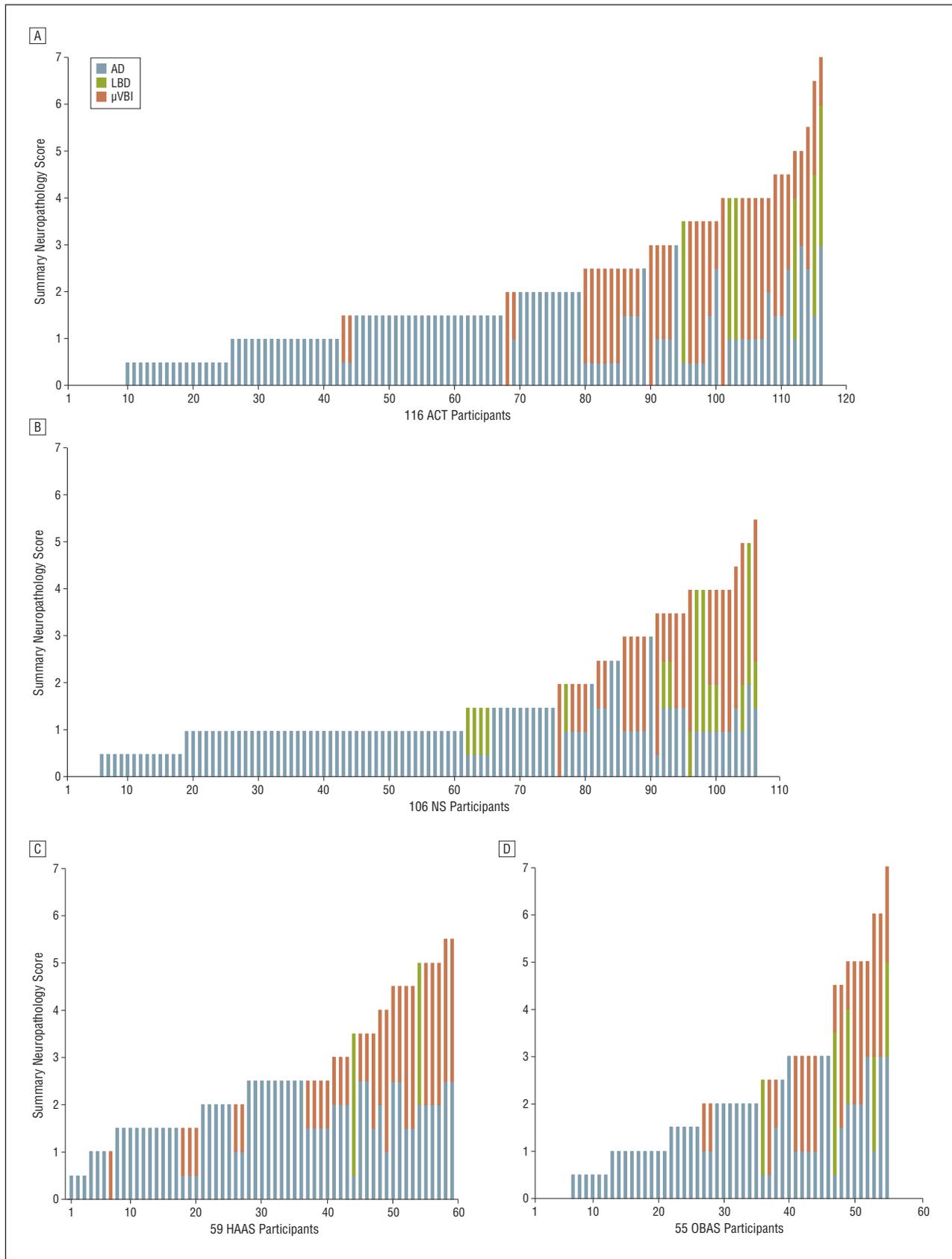


Figure 1. Brain autopsy results from 336 cognitively normal individuals expressed as summary neuropathology scores (range, 0-9) ranked from lowest to highest. Each stacked bar shows an individual's burden of Alzheimer disease (AD) (blue), Lewy body disease (LBD) (green), and microvascular brain injury (μ VBI) (red). A, One hundred sixteen Adult Changes in Thought study (ACT) participants. B, One hundred six Nun Study (NS) participants. C, Fifty-nine Honolulu-Asia Aging Study (HAAS) participants. D, Fifty-five Oregon Brain Aging Study (OBAS) participants.

Table 5. Comorbidity in 336 Cognitively Normal Adults^a

Comorbidity	Participants, %				Mean (SD)
	ACT	HAAS	NS	OBAS	
No pathologic changes	8	0	3	6	4 (3)
AD only	58	54	67	56	59 (6)
AD plus μ VBI or LBD	34	46	30	36	37 (7)
μ VBI only	0	0	0	2	1 (1)
LBD only	0	0	0	0	0

Abbreviations: ACT, Adult Changes in Thought study; AD, Alzheimer disease; HAAS, Honolulu-Asia Aging Study; LBD, Lewy body disease; μ VBI, microvascular brain injury; NS, Nun Study; OBAS, Oregon Brain Aging Study.

^aPercentage of the 336 eligible participants with complete neuropathologic examination from the 4 studies who had no pathologic changes in AD, μ VBI, or LBD or who had different combinations of these 3 diseases. "No pathologic changes" indicates no neuritic plaques, neurofibrillary tangles, LBs, or cerebral microinfarcts. The mean (SD) percentage of the results from all 4 studies is shown.

COMMENT

Building on the efforts of the late William Markesbery, MD, we have applied similar protocols in ACT, HAAS, NS, and OBAS for evaluation of NPs, NFTs, LBs, and CMI; however, to date, databasing and analyses have been done independently in these studies. Because these lesions are the standard means to assess the most common diseases that contribute to dementia in community- or population-based cohorts, we undertook an evaluation in CN individuals to estimate the occurrence and interaction of clinically silent diseases in cohorts drawn from multiple regions of the United States.

The resource for this analysis was 1672 brain autopsies from participants in ACT, HAAS, NS, and OBAS, from which we selected 424 CN individuals whose last clinical examination was performed, on average, approximately 1 year before death; average age at death was in the mid-80s. Because not all studies used comprehensive neuropathologic examinations from their inception, only 336 brain autopsies from among these 424 CN cases were eligible to be included. The major conclusions are that (1) AD, μ VBI, and LBD were prevalent in CN older adults; (2) the burden of these 3 diseases varied widely; and (3) comorbidity among these 3 diseases is variable across individuals. Many other researchers have reported on neuropathologic evidence of usually 1 or 2 of these diseases, mostly in research clinic cohorts and less commonly in community- and population-based cohorts. Any interval between the last clinical evaluation and autopsy creates a potential for misclassification, especially because progression to dementia typically seems to be preceded by a prodrome.³³ We made an effort to minimize inclusion of people with prodromal dementia by selecting only those performing within the upper 4 quintiles on a cognitive screening test at last evaluation rather than simply including all the individuals without a diagnosis of dementia. To our knowledge, the present study is the first to report evidence of clinically silent dementia-associated neuropathologic changes in CN individuals from multiple independent community- and popu-

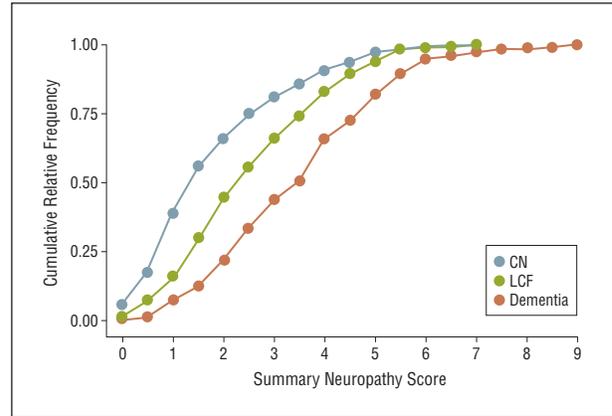


Figure 2. Cumulative relative frequency of the summary neuropathology score for autopsied individuals with complete neuropathologic examination from the 4 studies who were cognitively normal (CN) as defined in Table 1 (n=336); those with lower cognitive function (LCF), defined as individuals last evaluated within 2 years of death at which time they were diagnosed as not having dementia but scored in the lowest quintile on the cognitive screening test (n=189); and those who were diagnosed as having dementia (n=522). Nonparametric analysis of variance comparing summary neuropathology scores among the 3 groups had $P < .001$ and the Dunn corrected multiple paired comparisons had $P < .001$ for CN vs LCF, LCF vs dementia, and CN vs dementia.

lation-based cohorts. The present results show an intricate complexity among clinically silent diseases. We hope that these data on the ecology of the aging brain will be useful in guiding expectations of future neuroimaging and biomarker studies and clinical trials with CN older individuals in the community setting.

Using similar but not directly comparable methods of histopathologic assessment, other researchers have reported findings about clinically silent lesions of AD, μ VBI, and LBD in older individuals without dementia in the Religious Orders Study and the Memory and Aging Project (n=202, mean age=84 years) and observed a prevalence of these lesions similar to that of the present cohorts, although with somewhat less comorbidity.¹⁵ Indeed, the concordance among the 4 cohorts analyzed in this study and in the Religious Orders Study and the Memory and Aging Project mitigates the serious concern about generalizability among cohorts that focused on specific populations, such as men or women in religious orders or ethnic Japanese on Oahu; indeed, the neuropathologic outcomes from all these diverse studies are remarkably similar. Nevertheless, we should be cautious in extrapolating these validated findings in nondemented or CN individuals to other ethnic or racial groups or other societies.

Cerebral NP accumulation was the most common disease process in CN older adults. The proportion of CN older adults with a moderate or frequent CERAD NP score, a metric significantly correlated with A β peptide immunoreactive plaque area and detergent-insoluble A β ₄₂ accumulation, matches well with studies using fibrillar A β positron emission tomography in CN individuals. Indeed, these neuroimaging studies from CN older individuals observe a prevalence of positron emission tomography-positive fibrillar A β ranging from approximately one-fifth to approximately one-half, the variance related, at least in part, to age, apolipoprotein

E level, and socioeconomic status, with socioeconomic status perhaps related to educational level or cognitive reserve.^{34,35}

The CMIs were the next most prevalent clinically silent lesion in the present cohorts, present in approximately one-third of CN older adults. A high burden of CMIs, meaning lesions at the magnitude significantly associated with dementia,¹⁹ was present in approximately 1 in 10 CN older adults. This screening protocol for CMIs has been shown independently in HAAS and ACT to be correlated with other forms of VBI, such as lacunes and territorial infarcts. However, among these forms of VBI, increased CMIs are most strongly and independently associated with increased risk of dementia.^{18,19} These results are consistent with neuroimaging estimates of white matter hyperintensities, imaging abnormalities that seem to derive, at least in part, from pathogenic mechanisms overlapping with those that produce CMIs (reviewed by Gouw et al³⁶).

Lewy body disease was the least prevalent clinically silent disease in the present cohorts. These data suggest that future imaging modalities for LBD should expect to detect medullary LBD in approximately 1 in 6 CN individuals; approximately one-half of these also will have nigral LBD, and approximately one-half of those with mid-brain LBD will have isocortical LBD. Amygdala-only LBD seems to be uncommon in CN individuals, as is hippocampal sclerosis. Finally, it is important to stress that although we are evaluating lesions that are diagnostic for specific underlying diseases, the neuropathologic protocols likely have varying sensitivities, and this should be remembered when considering the estimates of disease burden. Nevertheless, evaluating these histologic lesions remains the only means of which we are aware to assess simultaneously the presence and extent of AD, μ VBI, and LBD.

Many studies referenced previously herein have noted extensive comorbidity among AD, μ VBI, and LBD, especially with advancing age, but with somewhat different protocols for histologic assessment. The present results validate this important point in multiple population- and community-based cohorts from different regions of the United States. We add to this body of work by showing that the extent of comorbidity was remarkably similar in CN older adults among the 4 studies. In further accord with the work of other researchers, including from the present individual cohorts, we observed that approximately 10% to 15% of CN individuals across the 4 studies harbored clinically silent AD, μ VBI, or LBD at levels that equaled or exceeded the average burden of lesions in individuals diagnosed as having dementia, a finding that may be interpreted as suggesting some form of compensation or reserve capacity. Although not a focus of this analysis, it is at least interesting to note that a similarly sized subset of individuals with dementia have a burden of lesions in the cerebrum that is less than the average burden in CN individuals. Because this is an autopsy study and is not limited by technologies focused on a particular disease process, we demonstrated that these individuals with dementia and low burden of AD, μ VBI, and LBD do not instead have less common diseases that also can cause demen-

tia, such as frontotemporal lobar degeneration or prion disease. These are the opposite of the “cognitive reserve” group and raise questions about heightened susceptibility or additional contributing disease mechanisms not captured by neuropathologic examination in a small subset of patients who meet the clinical criteria for dementia.

The present results from 4 independent community- and population-based studies of brain aging and dementia demonstrate that clinically silent AD, μ VBI, and LBD are prevalent and commonly comorbid but with extensive individual variation. Although it is a challenge to generalize from any research study to the primary medical setting, these results at least should guide expectations for neuroimaging and biomarker studies and for clinical trials focused on disease prevention that will be populated with community-dwelling CN individuals. Moreover, the present results suggest that the aging brain is experiencing multiple simultaneous stressors, injuries, and responses to injury that likely interact with each other to generate a complex convergent environment. These results also suggest that there are yet-to-be identified factors that in some individuals may suppress and in others may promote clinical expression of disease. Although autopsy-based studies provide important insight, further studies of the ecology of the aging brain will require intravital disease- and mechanism-specific markers that will be critical to the efficient conduct of research focused on disease prevention or neuroprotection.

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