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RESEARCH ARTICLE

Study of neuropathological changes and dementia in 100 centenarians in The 90+ Study

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Abstract

INTRODUCTION: The association between neuropathological changes and dementia among centenarians and nonagenarians remains unclear.

METHODS: We examined brain tissue from 100 centenarians and 297 nonagenarians from *The 90+ Study*, a community-based longitudinal study of aging. We determined the prevalence of 10 neuropathological changes and compared their associations with dementia and cognitive performance between centenarians and nonagenarians.

RESULTS: A total of 59% of centenarians and 47% of nonagenarians had at least four neuropathological changes. In centenarians, neuropathological changes were associated with higher odds of dementia and, compared to nonagenarians, the odds were not attenuated. For each additional neuropathological change, the Mini-Mental State Examination score was lower by 2 points for both groups.

DISCUSSION: Neuropathological changes continue to be strongly related to dementia in centenarians, highlighting the importance of slowing or preventing the development of multiple neuropathological changes in the aging brain to maintain cognitive health.

KEYWORDS
centenarians, cognition, dementia, neuropathological changes, nonagenarians

Highlights

- Individual and multiple neuropathological changes are frequent in centenarians.
- These neuropathological changes are strongly associated with dementia.
- There is no attenuation of this association with age.

1 | BACKGROUND

Increased life expectancy has resulted in more persons reaching their 100th birthday. In the United States, the centenarian population is growing at a faster rate than the total population,[1] increasing 44% between 2000 and 2014.[2]

Among centenarians, the prevalence of dementia is about 60%.[3,4] Recent studies on the clinical neuropathological characteristics of

centenarians have investigated the prevalence of pathological brain changes and relationships to cognitive decline.[5–7] These studies found that the high prevalence of neuropathological changes in centenarians is strongly related to poorer cognitive performance. However, some studies suggest the relationship between neuropathological changes, particularly Alzheimer's disease neuropathological change (ADNC), and dementia attenuates with increasing age, although data in centenarians are limited.[8]

Our objectives were to determine (1) the prevalence of individual and multiple neuropathological changes in centenarians and nonagenarians, (2) the association of individual and multiple neuropathological changes with dementia in centenarians and nonagenarians, and (3) the impact of the multiple neuropathological changes, that is, the total burden of neuropathological changes affecting cognition. For all objectives, we compared centenarians and nonagenarians from the same cohort to determine whether the relationship changed with age.

RESEARCH IN CONTEXT

1. **Systematic review**: We searched PubMed for articles on the prevalence of neuropathological changes and the associated risks of dementia in centenarians and nonagenarians. Previous studies were limited by the small sample size of centenarians, the variety of neuropathological changes examined, and the lack of comparison with nonagenarians.
2. **Interpretation**: We report a high prevalence of individual and multiple co-existing neuropathological changes in centenarians and their strong association with cognition and dementia that does not attenuate with increasing age.
3. **Future directions**: Our study suggests that the prevalence of neuropathological changes continues to increase in centenarians and remains associated with dementia. Future studies with larger sample sizes should further investigate the continued associations of individual and multiple co-existing pathologies with dementia in very advanced ages.

2 | METHODS

2.1 | Study population

Figure 1 displays the participant flowchart for our study. Participants were from *The 90+ Study*, a southern California community-based longitudinal study of aging and dementia in individuals aged 90 years and older.[9,10] Initial *The 90+ Study* participants were survivors of the Leisure World Cohort study (LWCS),[11] an epidemiologic study of a retirement community in California conducted from 1981 to 1984. On January 1, 2003, LWCS participants aged 90 or older were invited to join *The 90+ Study*. A similar invitation was extended thereafter to those turning 90 years old. Although all participants lived in Leisure World during the early 1980s, most were no longer living there during our study, necessitating enrollment, evaluation, and brain procurement in 37 states. Regardless of location, ~80% of eligible candidates were successfully recruited. Since 2017, volunteers aged 90 years and older who lived within a 2-h drive were also enrolled.[12] While LWCS participants were recruited regardless of cognitive diagnosis, volunteers had no or mild dementia and were willing to consider autopsy participation.

All *The 90+ Study* participants seen in person are invited to join the autopsy study. The present investigation includes data on 397 participants (100 centenarians and 297 nonagenarians at the time of death) with completed brain autopsies as of February 18, 2022. Of the 397 participants, 260 were LWC survivors, and the rest were volunteers.

2.2 | Standard protocol approvals, registrations, and patient consents

The study was approved by the University of California, Irvine (UCI) Institutional Review Board, and all participants or their designated informants provided informed consent to participate.

2.3 | Pathological evaluation

Donated brains were procured and fixed in formalin by the UCI Alzheimer's Disease Research Center Neuropathology Core and sent to the Department of Pathology at Stanford University, where immunohistopathological evaluations were performed with current consensus criteria, blinded to clinical diagnosis and other participant information. We considered 10 different neuropathological changes. The National Institute on Aging-Alzheimer's Association "ABC" score, which incorporates Thal Phase for beta amyloid (Aβ) plaques, Braak staging for neurofibrillary tangles, and Consortium to Establish a Registry for AD (CERAD) score for neuritic plaques, was used to assess ADNC, which was categorized as not, low, intermediate, or high severity.[13,14] We considered five vascular neuropathological changes: cerebral amyloid angiopathy (CAA), atherosclerosis, arteriolosclerosis, large (territorial and lacunar) infarcts, and microinfarcts characterized as follows: CAA—none, mild, moderate, and severe[15]; atherosclerosis—none, mild when present at branch points in the circle of Willis, moderate when present at branch points and elsewhere in the circle of Willis, severe when present on the cerebral convexity; arteriolosclerosis—none, mild for partial replacement of vascular smooth muscle cells, moderate for full replacement of vascular smooth muscle cells, severe for concentric thickening of the sclerotic vessel wall. Other categorizations were large infarcts—none or ≥ 1; microinfarcts—1 to 2, or ≥ 3[13,14]; hippocampal sclerosis (HS) absent or present.[13,14] Limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC)[16] was categorized based on anatomical location: none, amygdala, hippocampus, or frontal

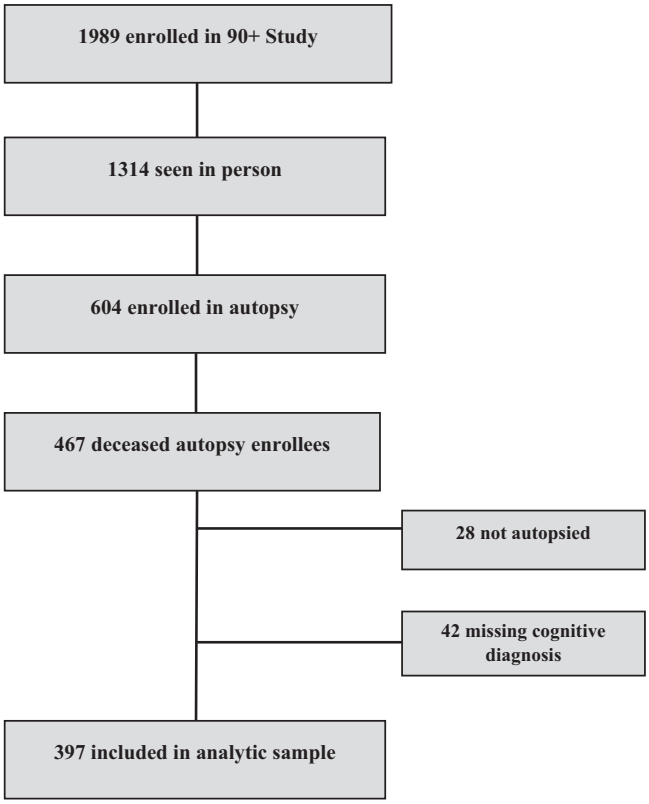


FIGURE 1 Participant flowchart.

cortex. Age-related tau astrogliopathy (ARTAG) was categorized as none, occasional, or numerous.[17] Lewy body disease (LBD) was categorized based on anatomical location as none, olfactory bulb, brainstem predominant, limbic transitional, or neocortical diffuse.[18]

2.4 | Dementia determination

Participants were evaluated every 6 months. In-person assessments included physical and neurological examination, a neuropsychological test battery[19] that included the Mini-Mental State Examination (MMSE),[20] medical history, and medication review. Participants were given a MMSE score of zero if they were unable to correctly answer any questions because of severe cognitive deficits. Dementia diagnosis (DSM-IV)[21] was assigned during a postmortem consensus conference using all available clinical information, including longitudinal evaluations, brain imaging when clinically available, medical records, and informant questionnaires. Cognitive status was classified as normal, cognitive impairment no dementia (CIND), or dementia.[9] Physical illnesses and sensory deficits can make the evaluation of cognitive decline in this age group challenging. Our assessments were modified to incorporate the examiners' impression of the role of sensory, physical, and other functional limitations. Dementia diagnosis was limited to those who had functional loss specifically related to cognitive impairment. For all analyses, the cognitive diagnosis was dichotomized as dementia versus no dementia (normal and CIND).

2.5 | Statistical analysis

Statistical analyses were done in R (version 4.0.0) software. Participant characteristics are reported as numbers and proportions for categorical variables and mean and range for continuous variables. To compare the means of continuous variables between centenarians and nonagenarians, we used the Welch's two sample *t* test. To compare the proportions of categorical variables between groups (age group or cognitive status), we used Fisher's exact test.

We dichotomized each of the 10 neuropathological changes as follows: ADNC (intermediate/high), CAA (mild/moderate/severe), atherosclerosis (severe), arteriolosclerosis (mild/moderate/severe), large infarcts (≥1), microinfarcts (≥3), HS (present), LATE-NC (amygdala/hippocampus/frontal cortex), ARTAG (occasional/numerous), and LBD (brainstem/amygdala/limbic/neocortical). For most neuropathological changes, dichotomies were selected to agree with standard criteria or previous similar studies. CAA, LBD, atherosclerosis, and arteriolosclerosis were dichotomized to reflect the strong associations with dementia in our oldest old cohort. For each dichotomized neuropathological change, prevalence was calculated separately for nonagenarians, centenarians, and the entire study cohort.

For each of the 10 neuropathological changes, a logistic regression model, adjusting for age at death (continuous), sex, education (college graduate or less than college graduate), and participation type (LWC or volunteer), was used to estimate the odds ratio (OR) for dementia for that neuropathological change. Analyses were done separately for centenarians and nonagenarians. To determine whether the association between each neuropathological change and dementia was different for the two age groups, we included in the logistic regression model an interaction term for age group (100+ vs. 90 to 99) and the neuropathological change. To estimate the odds of dementia in relation to multiple co-existing neuropathological changes, we created a variable "number of neuropathological changes," which was the sum of positive dichotomies for the 10 individual neuropathological changes. We included different vascular neuropathological changes separately because they were not associated with each other (all chi-square $p > 0.1$) and contributed independently to dementia. The number of neuropathological changes was categorized as follows: 0 to 3 (reference group), 4, 5, and 6+ neuropathological changes to ensure adequate number of participants in each category, particularly the centenarian reference group.

We examined the association between MMSE score closest to death and the number of neuropathological changes for all participants. We used a linear regression model with MMSE score (continuous variable) as the outcome and the number of neuropathological changes (continuous variable) as the independent variable, adjusting for age at death category (100+ vs 90 to 99), sex, participant type (LWC or volunteer), education (college graduate or less than college graduate), interval in months between last MMSE and death (continuous), and an interaction

TABLE 1 Characteristics of autopsied centenarians and nonagenarian participants of The 90+ Study.

	All participants (*N* = 397)	Nonagenarians (*N* = 297)	Centenarians (*N* = 100)	
	Mean (Range)			*P* value*
Age at death (years)	97.2 (90 to 110)	95.6 (90 to 99)	102.0 (100 to 110)	**<0.001**
Last MMSE score[a]	21 (0 to 30)	21 (0 to 30)	19 (0 to 30)	**0.04**
Months between last MMSE and death[a]	6.6 (0.2 to 84.5)	6.4 (0.2 to 83.0)	7.1 (0.2 to 84.5)	0.28
Brain weight (g)[b]	1129 (728 to 1670)	1144 (865 to 1670)	1084 (728 to 1403)	**<0.001**
For women	1094 (865 to 1412)	1106 (865 to 1412)	1064 (880 to 1337)	**0.004**
For men	1211 (728 to 1670)	1222 (910 to 1670)	1162 (728 to 1403)	**0.06**
		N (%)		*P* value*
Sex				**0.01**
Men	121 (30)	100 (34)	21 (21)	
Women	276 (70)	197 (66)	79 (79)	
Education				0.35
Less than college graduate	194 (49)	143 (48)	51 (51)	
College graduate	203 (51)	154 (52)	49 (49)	
Cognitive diagnosis				0.50
Normal	113 (29)	89 (30)	24 (24)	
CIND	112 (28)	83 (28)	29 (29)	
Dementia	172 (43)	125 (42)	47 (47)	
APOE allele[c]				0.50
APOE ε2 present	55 (15)	38 (14)	17 (18)	
APOE ε4 present	65 (18)	51 (19)	14 (15)	
Participant type				0.11
Leisure World Cohort	260 (65)	189 (64)	71 (71)	
Volunteers	137 (35)	108 (36)	29 (29)	

Abbreviations: CIND, cognitive impairment no dementia; MMSE, Mini-Mental State Examination.
[a]Excludes nine nonagenarians and three centenarians with missing MMSE scores.
[b]Excludes 20 nonagenarians and four centenarians with missing values for brain weight.
[c]*APOE ε3* allele frequencies were not included in the analysis.
*Bolded *p* values represent significant (<0.05) comparisons of no dementia and dementia groups within the specific age group.

term between age at death category and number of neuropathological changes.

3 | RESULTS

Participant characteristics are displayed in Table 1. The mean age at death was 102.0 years for centenarians and 95.6 years for nonagenarians. Centenarians had a higher proportion of females than nonagenarians (79% vs 66%, $p = .01$). About half of the participants (51%) were college graduates, and almost all (99%) were White. A higher proportion of centenarians had a dementia diagnosis (47%) compared to nonagenarians (42%), but the difference was not statistically significant ($p = .50$). Centenarians had lower mean MMSE score than nonagenarians (19 vs 21, $p = .04$). Mean brain weight was lower in centenarians compared to nonagenarians (1144 g vs 1084 g, $p < .001$). Centenarian women had a lower mean brain weight than nonagenarian women (1064 g vs 1106 g, $p = .004$), but no difference was observed between the age groups in men.

Centenarian and nonagenarian characteristics classified by dementia versus no dementia are displayed in Table 2. With the exception of the MMSE score, characteristics were similar between the no-dementia and dementia centenarian groups.

3.1 | Prevalence of individual neuropathological changes in centenarians and comparison with nonagenarians

Figure 2B shows the prevalence of the 10 neuropathological changes in centenarians and nonagenarians. Among centenarians, the most common neuropathological change was arteriolosclerosis (88%), followed by ADNC (75%) and ARTAG (66%). Among other vascular neuropathological changes, CAA was most common (54%), with atherosclerosis

TABLE 2 Characteristics of autopsied centenarians and nonagenarians participants of The 90+ Study by dementia status.

	Nonagenarians (*N* = 297)			Centenarians (*N* = 100)		
	No Dementia (*N* = 172)	Dementia (*N* = 125)		No Dementia (*N* = 53)	Dementia (*N* = 47)	
	Mean (range)		*P* value*	Mean (range)		*P* value*
Age at death (years)	95.6 (90 to 99)	95.6 (90 to 99)	0.97	101.9 (100 to 108)	102.0 (100 to 110)	0.82
Last MMSE score[a]	26 (0 to 30)	14 (0 to 28)	**<0.001**	24 (0 to 30)	13 (0 to 28)	**<0.001**
Brain weight (g)[b]	1159 (866 to 1670)	1124 (865 to 1434)	0.02	1107 (897 to 1347)	1058 (728 to 1403)	0.38
Months between last MMSE and death[a]	5.2 (0.23 to 27.5)	8.3 (0.16 to 83)	**0.005**	5.3 (0.36 to 45.2)	9.2 (0.20 to 84.5)	0.11
	N (%)		*P* value*	*N* (%)		*P* value*
Sex			0.08			0.79
Men	64 (37)	36 (29)		14 (26)	7 (15)	
Women	108 (63)	89 (71)		39 (74)	40 (85)	
Education			**0.007**			0.27
Less than college graduate	72 (42)	71 (57)		25 (47)	26 (55)	
College graduate	100 (58)	54 (43)		28 (53)	21 (45)	
APOE allele[c]			0.44			0.06
APOE ε2 present	20 (13)	18 (16)		12 (24)	5 (12)	
APOE ε4 present	26 (17)	25 (22)		4 (8)	10 (23)	
Participant type			**<0.001**			0.17
Leisure World Cohort	94 (55)	95 (76)		35 (66)	36 (77)	
Volunteers	78 (45)	30 (24)		18 (34)	11 (23)	

Abbreviations: MMSE, Mini-Mental State Examination; SD, standard deviation.
[a]Excludes nine nonagenarians and three centenarians with missing MMSE scores.
[b]Excludes 20 nonagenarians and four centenarians with missing values for brain weight.
[c]*APOE ε3* allele frequencies were not included in the analysis.
*Bolded *p* values represent significant (<0.05) comparisons of no dementia and dementia groups within the specific age group.

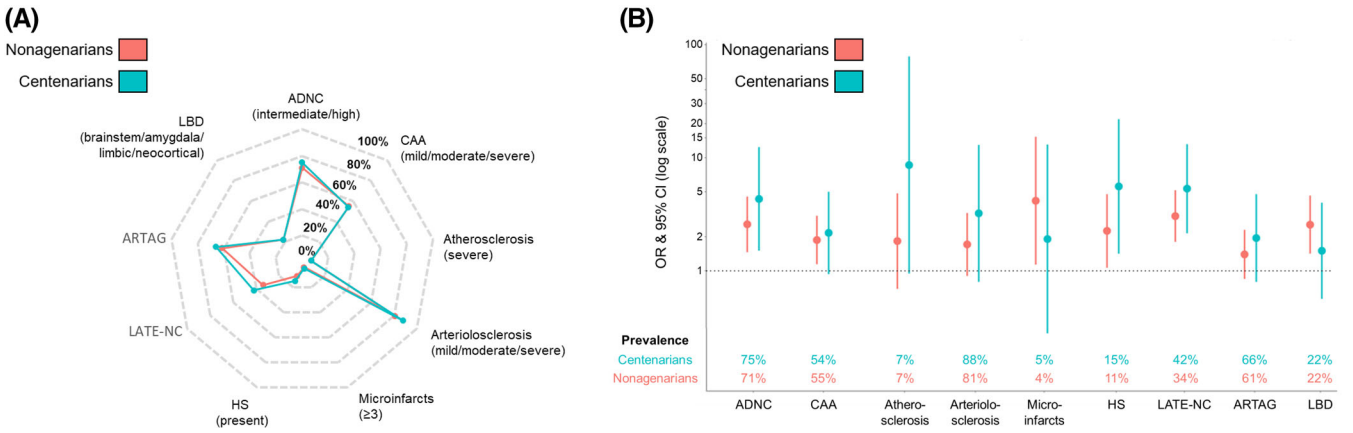


FIGURE 2 (A) Prevalence of individual neuropathological changes for nonagenarians and centenarians. (B) Prevalence of each neuropathological change and odds of dementia for individual neuropathological change for nonagenarians (red) and centenarians (blue). ADNC, Alzheimer's disease neuropathological change; ARTAG, age-related tau astrogliopathy; CAA, cerebral amyloid angiopathy; HS, hippocampal sclerosis; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathological change; LBD, Lewy body disease.

present in 7%, microinfarcts in 5%, and large infarcts in 1%. LATE-NC was present in 42%, LBD in 22%, and HS in 15%. Among nonagenarians, the ordering of prevalence of neuropathological change was the same as centenarians: arteriolosclerosis (81%), followed by ADNC (71%), ARTAG (61%), CAA (55%), LATE-NC (34%), LBD (22%), and HS (11%).

Figure 2A graphically represents the prevalence of the individual dichotomized neuropathological changes in nonagenarians and centenarians (large infarcts are not shown due to their low prevalence [4%] in the entire cohort). Compared with nonagenarians, centenarians had equal or slightly higher (non-significant) prevalence of all 10 individual

neuropathological changes except large infarcts. Table S1 shows the prevalence for all severity levels of individual neuropathological changes for both age groups, including Thal phase, Braak stage, and CERAD score.

3.2 | Odds of dementia associated with individual neuropathological changes in centenarians and comparison with nonagenarians

Figure 2B shows the ORs of dementia for the individual neuropathological changes. In centenarians, degenerative neuropathological changes associated with higher odds of dementia were ADNC (OR = 4.3, 95% confidence interval (CI): 1.5 to 12.4), HS (OR = 5.6, 95% CI: 1.4 to 21.9), and LATE-NC (OR = 5.3, 95% CI: 2.2 to 13.2). Among vascular neuropathological changes, severe atherosclerosis (OR = 8.6, 95% CI: 0.9 to 78.7), CAA (OR = 2.2; 95% CI: 0.9 to 5.0), arteriolosclerosis (OR = 3.2; 95% CI: 0.8 to 13.0), and microinfarcts (OR = 1.9; 95% CI: 0.3 to 13.1) showed nonsignificantly higher odds of dementia. Likewise, ARTAG (OR = 1.9; 95% CI: 0.8 to 4.8) and LBD (OR = 1.5; 95% CI: 0.6 to 4.0) had nonsignificantly higher odds of dementia.

The odds of dementia associated with individual neuropathological changes did not differ significantly between centenarians and nonagenarians (Figure 2B). However, centenarians had a pattern of higher odds of dementia for all neuropathological changes except microinfarcts and LBD compared with nonagenarians. Table S2 reports the ORs for individual neuropathological changes for nonagenarians and centenarians.

3.3 | Prevalence of multiple neuropathological changes in centenarians and comparison with nonagenarians

We evaluated the prevalence of multiple co-existing neuropathological changes (Figure 3A). Figure 3A illustrates the prevalence of the number of neuropathological changes in nonagenarians and centenarians. All centenarians had at least one neuropathological change, with 59% of centenarians having four or more neuropathological changes compared to 47% of nonagenarians. Centenarians had more multiple co-existing neuropathological changes compared with nonagenarians, but the difference was not significant ($p = .15$). Table S1 reports the prevalence for the entire range of severity for each neuropathological change for nonagenarians and centenarians, including Thal phase, Braak stage, and CERAD score.

3.4 | Odds of dementia associated with multiple neuropathological changes in centenarians and comparison with nonagenarians

Evaluation of the association between multiple co-existing neuropathological changes and odds of dementia demonstrated that centenarians had significantly higher odds of dementia with four (OR = 5.8; 95% CI: 1.8 to 18.0), five (OR = 10.1; 95% CI: 2.4 to 43.2), and six or more neuropathological changes (OR = 56.6; 95% CI: 5.7 to 560.6), compared with having zero to three neuropathological changes. For both centenarians and nonagenarians, the odds of dementia increased with increasing number of neuropathological changes, with centenarians having a steeper increasing pattern. However, centenarians and nonagenarians with the same number of neuropathological changes did not differ in odds of dementia (Figure 3B). Table S2 gives details of the ORs for multiple neuropathological changes for nonagenarians and centenarians.

3.5 | Relationship of increasing number of neuropathological changes to worsening cognitive performance in centenarians and nonagenarians

The relationship between cognitive performance and neuropathological changes was evaluated using a linear regression model of MMSE score and number of neuropathological changes. MMSE scores were lower by about 2 points for each additional neuropathological change in both centenarians and nonagenarians (estimate = −2.21; standard error = 1.55; $p < .001$). With the inclusion of an interaction term between number of neuropathological changes and age group, there was a further (non-significant) 0.2 points decrease in MMSE score for centenarians with each additional neuropathological change (estimate = −0.23; standard error = 0.67; $p = .74$) (Figure 4).

4 | DISCUSSION

In this clinico-pathological study of *The 90+ Study* participants, the three most common neuropathological changes found in centenarians were arteriolosclerosis (88%), ADNC (75%), and ARTAG (66%). All centenarians had at least one neuropathological change, and more than half (59%) had at least four. Nonagenarians had a prevalence of individual and multiple neuropathological changes similar to that of centenarians. In centenarians, ADNC, LATE-NC, and HS were associated with increased odds of dementia. In centenarians, there was a striking increase in the odds of dementia with accumulating number of neuropathological changes. No attenuation in odds of dementia was observed for individual neuropathological changes or number of neuropathological changes in centenarians compared with nonagenarians.

Neuropathological changes in centenarians were previously studied in smaller cohorts (ranging from 40 to 77 participants).[5–7] These studies reported lower prevalence than we observed for LATE-NC (31% to 37% vs. 42%)[5–7] and for ADNC (50% to 54% vs. 75%)[6,7] but a higher prevalence for CAA (59% to 77% vs. 54%).[6,7] Between-study differences contributing to the disparity in neuropathological prevalence are difficult to determine but likely include sample sizes and differences in the dichotomization of neuropathological changes. Given that our study includes the largest number of centenarians to date ($N = 100$) and used standardized, consensus pathological evaluation protocols,

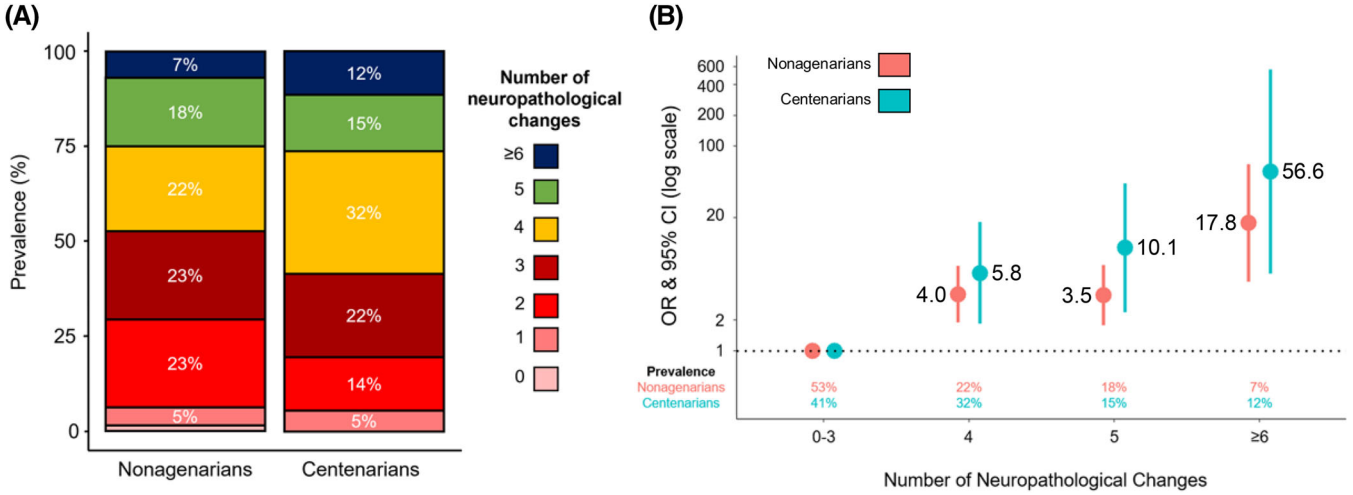
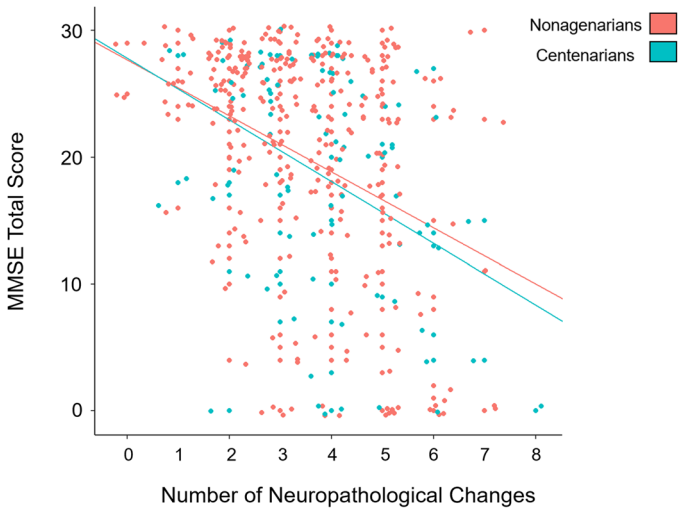


FIGURE 3 (A) Prevalence of number of neuropathological changes (including ADNC, CAA, atherosclerosis, arteriolosclerosis, microinfarcts, HS, LATE-NC, ARTAG, and LBD, ranging from zero to eight) in centenarians and nonagenarians. 1% of nonagenarians and 0% of centenarians had 0 neuropathological changes. (B) Odds of dementia for having four, five, and six or more neuropathological changes compared with having zero to three (reference group) in nonagenarians (red) and centenarians (blue). ADNC, Alzheimer's disease neuropathological change; ARTAG, age-related tau astrogliopathy; CAA, cerebral amyloid angiopathy; HS, hippocampal sclerosis; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathological change; LBD, Lewy body disease.

FIGURE 4 Relationship between Mini-Mental State Examination (MMSE) total score and the number of neuropathological changes for nonagenarians (red) and centenarians (blue) using a linear regression model adjusted for age at death, sex, participant type (Leisure World Cohort [LWC] participants vs. volunteers), education level, interval (in months) between the last MMSE and death, and an interaction term between number of neuropathological changes and age at death. Each point is an individual participant. The lines represent a typical nonagenarian (red) and centenarian (blue). To plot the line, for nonagenarians, mean value of age used was 95.6 years and for centenarians 102.0 years. For other variables, values corresponding to the mean of the entire cohort were used: months between the last MMSE and death (6.6), sex (female), participant type (LWC), and education level (college graduate). Twenty-three participants were excluded from this analysis for lack of MMSE data near death.



our study provides strong evidence for the centenarian prevalence of dementia and neuropathological change. Future studies with larger, more diverse samples of centenarians are needed to further elucidate the prevalence of these neuropathological changes.

In centenarians, we observed higher dementia odds associated with ADNC, HS, and LATE-NC than with other neuropathological changes. The association of dementia odds with neuropathological changes in centenarians has, to our knowledge, not been previously reported. However, our findings are consistent with previous studies among the middle-aged (55+ years old) and the oldest-old (80+ years old) that have found increased dementia odds associated with these neuropathological changes.[22–25] Our study further demonstrates that neuropathological changes, particularly ADNC, HS, and LATE-NC, continue to increase the odds of dementia in those living past a century.

We observed that centenarians had a similar ordering of prevalence of neuropathological changes compared with nonagenarians, but with a pattern of increasing prevalence. Previous studies reported varying results in neuropathological changes with increasing age. One study reported an increased prevalence of HS and microinfarcts and a similar prevalence of ADNC, LATE-NC, and LBD in centenarians compared with nonagenarians.[26] Another study looking at the effect of age on AD-related neuropathological changes found an increased prevalence of hippocampal tangles in centenarians but little or no change in the prevalence of hippocampal and neocortical neuritic plaques compared with younger ages.[8] Our results suggest that the prevalence of neuropathological changes may increase in individuals over 100 years old. More studies are needed to investigate further this age-related pattern.

We also found increased odds of dementia in relation to multiple neuropathological changes in centenarians, consistent with earlier research.[24,27,28] In a study including 301 participants with average age of 94 years from the Religious Orders Study and Rush Memory and Aging Project, the prevalence ratio of dementia was higher in those with ADNC plus infarcts and/or LBD (prevalence ratio = 8.98) than in those with ADNC alone (prevalence ratio = 7.12).[27] A previous report from *The 90+ Study* with a smaller sample ($N = 183$) reported that dementia odds in the presence of three to eight neuropathological changes was almost 60-fold greater than that in those with no neuropathological change.[28] Our study adds to the growing body of evidence that the presence of multiple co-existing neuropathological changes increases dementia odds in centenarians, as it does in younger cohorts.

Our study showed no attenuation of the association of dementia with neuropathological changes in centenarians compared with nonagenarians. Previous studies on how the association between dementia and neuropathological severity varies with age found inconsistent results. A population-based study on individuals aged 69 to 103 years old compared a model 75-year-old with a 95-year-old and found that the association of AD-type changes (neurofibrillary tangles and neuritic plaques) with estimated odds of dementia attenuates with increasing age.[8] Similarly, although not significant, the relationship of vascular neuropathological changes and dementia also attenuated with increasing age.[8] In contrast, we showed that above 90 years old, the relationship between dementia and neuropathological changes does not attenuate and continues to be relevant, not only for ADNC, but for other dementia-related neuropathological changes. A larger Brazilian autopsy study investigating two age groups categorized as less than 80 years old (mean 67 years, range 50 to 79 years) and greater than 80 years old (mean 86 years, range 80 to 105 years) reported that the associations of dementia and ADNC (neurofibrillary tangles and neuritic plaques), CAA, arteriolosclerosis, HS, and LBD were not different between older and younger age groups.[24] Although both groups in that study were younger, their results were similar to ours, showing that the relationship did not change with age.

For the association between dementia and multiple neuropathological changes, we similarly found no attenuation with age. Studies on this relationship with advanced age are limited. Contrasting findings were found in the Brazilian autopsy study,[24] where the association of dementia with multiple neuropathological changes decreased with age. The lack of attenuation with age in the relationship between dementia and neuropathological change in our study may be related to several factors. First, neuropathological changes are more common and frequently co-occur in extreme old age. With more neuropathological changes contributing to dementia in centenarians, the relationship with individual neuropathological changes may be diminished compared to younger elderly. Moreover, the attenuation observed in younger cohorts may level out in nonagenarians and centenarians.

We also observed that increasing number of neuropathological changes corresponded to worse scores on the MMSE similarly in centenarians and nonagenarians. Previous centenarian studies reported AD-type changes, like neurofibrillary tangles and neuritic plaques, to be associated with poorer cognitive performance.[5–7] Our findings in centenarians align with earlier results from The 90+ Study that found increasing number of neuropathological changes associated with poorer MMSE performance.[28] Our new data also build on current literature by showing that in centenarians, multiple, co-existing neuropathological changes continue to impact cognition.

Our study had several strengths, including a sample size of 100 centenarians, a uniquely large sample for this age group. Sample sizes for previous neuropathological studies on centenarians ranged from 40 to 77.[5–7,25] Moreover, some of the previous centenarian studies included individuals aged 98 and 99 years.[5,7] Our study included only "true" centenarians, that is, participants who were at least 100 years of age at the time of death. Another advantage of *The 90+ Study* data is that the cohort is well characterized and the participants are followed and evaluated every 6 months allowing for accurate and timely detection of cognitive changes and short interval between the last cognitive assessment and brain autopsy. This is particularly useful and a necessary condition in centenarians given their high mortality and high odds of dementia.[28–30] Finally, our clinical and neuropathology teams conducted the postmortem analyses under standardized consensus protocols and each team was blinded to the other's assessments.

Our findings are subject to some limitations. First, although this study has the largest sample of centenarians, for several individual and multiple neuropathological changes the ORs had wide confidence intervals, particularly in the centenarians. Second, the majority of the participants in *The 90+ Study* are White and well educated, which may limit the generalizability of the findings to ethnically and racially diverse groups with varying socioeconomic statuses. Third, our study only included participants 90 years and older, which prevented us from comparing centenarians with individuals younger than 90 years of age. Fourth, in our study, the prevalence of dementia in centenarians was 43%, which was lower than what was reported in a previous publication from *The 90+ Study* that included all participants, even those never seen in person.[3] Only *The 90+ Study* participants seen in person were invited to join the autopsy study, and therefore, many cognitively impaired individuals were not included. Furthermore, volunteers were required to have no or mild cognitive impairment at recruitment, and a greater proportion consented to autopsy compared to LWCS participants (Table S3). Thus, the prevalence in this study might be less reflective of the general population.

Our results from the largest study on centenarian brain autopsies to date demonstrated that the prevalence of individual and multiple neuropathological changes is exceptionally high, and both individual and multiple neuropathological changes are strongly associated with dementia in this age group. Contrary to earlier reports, we observed that the prevalence of neuropathological changes and association with dementia does not attenuate in centenarians but may in fact increase compared with younger age groups. With the rapid growth of the oldest-old, these results emphasize the need to address prevention and treatment for multiple dementia-related pathological changes at all ages to impact the enormous, growing public health burden of dementia.

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CONFLICT OF INTEREST STATEMENT

All authors report no conflicts of interest. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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