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Authors
Corrada, María M
Sonnen, Joshua A
Kim, Ronald C
et al.

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Microinfarcts are common and strongly related to dementia in the oldest-old: The 90+ Study

María M. Corrada, ScM, ScD[a,b], **Joshua A. Sonnen, MD**[c], **Ronald C. Kim, MD**[d], and **Claudia H. Kawas, MD**[a,e]

[a] Department of Neurology, University of California, Irvine, CA, USA 92697

[b] Department of Epidemiology, University of California, Irvine, CA, USA 92697

[c] Department of Pathology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA 84103

[d] Department of Pathology, University of California, Irvine, CA, USA 92697

[e] Department of Neurobiology & Behavior, University of California, Irvine, CA, USA 92697

Abstract

INTRODUCTION—We estimated the prevalence of microinfarcts and their association with dementia in a cohort of oldest-old participants.

METHODS—Participants were from The 90+ Study, a population-based study of people 90 and older. Dementia diagnoses were assigned post-mortem during a consensus conference. Microinfarcts were evaluated in six brain regions.

RESULTS—At death, the 213 participants were on average 97 years old, 69% were women, and 52% had dementia. 51% of participants had microinfarcts and 17% had 3+ microinfarcts. The odds ratio (OR) for dementia was similar for 3+ microinfarcts (OR=4.75, $p<0.01$) and tangle stage V-VI (OR=4.70, $p<0.001$). Only microinfarcts in cortical regions (other than occipital) were associated to dementia.

DISCUSSION—In this oldest-old cohort, microinfarcts are common and contribute independently and similarly in magnitude to dementia as tangles. As risk factors for microinfarcts and other dementing pathologies are likely to differ, identifying these factors is crucial to developing prevention strategies for dementia in the oldest-old.

Corresponding Author: María M. Corrada, 1513 Hewitt Hall, University of California, Irvine, Irvine, CA 92697-1400, Phone : 949-824-9109 Fax : 949-824-4165, mcorrada@uci.edu.

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Conflicts of Interest

The authors do not have any conflicts of interest.

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Keywords

oldest-old; cohort studies; epidemiology; dementia; Alzheimer's disease; neuropathology; microinfarctions; brain infarctions

1. Background

Large vessel vascular pathologies have long been considered an important contributor to dementia[1]. Microvascular pathologies, such as microinfarcts, are typically given less attention but some have found microinfarcts to be a contributor to dementia as important as AD pathology[2, 3]. Studies suggest that the prevalence of microinfarcts increases with age[4]. Given that rates of dementia also increase with age, it would be natural to hypothesize that microinfarcts may be related to dementia at very advanced ages. The average age of death of participants in most studies to date that evaluate microinfarcts, is below 90 but the one study with an average of 90.7 years reported that microinfarcts were very prevalent, detected in almost half of the participants (48%)[5], and was strongly related to dementia. With the fast growing numbers of oldest-old people (those 90 and older) in the US and many other countries and with their very high rates of dementia[6], identifying factors related to the development of dementia in the oldest-old are crucial. Our work has two main objectives: 1) to estimate the prevalence of microinfarcts and 2) to study the association between the presence of microinfarcts and the likelihood of dementia after adjusting for the presence of other dementing pathologies in a cohort of oldest-old participants.

2. Methods

2.1 Participants

Participants were members of The 90+ Study, a longitudinal study of aging and dementia in people aged 90 and older. Participants in The 90+ Study are survivors from the Leisure World Cohort Study (LWCS), an epidemiological investigation in a Southern California retirement community. In the early 1980s, all residents of the community were mailed a health survey and those who returned it constitute the LWC. All LWCS participants, with or without dementia, who were alive and 90 years or older in January 1, 2003 were invited to participate in The 90+ Study. A similar invitation was extended to participants who turned 90 on January 1, 2008 and every year thereafter. All 90+ Study participants who agreed to in-person examination (N=978) were invited to be part of the autopsy program[7]. A small number of people who were not part of the original LWCS but lived in the same region (N=25) were also recruited. As of December 31, 2013, 354 participants had enrolled in the autopsy program, representing 36% of those invited to the program. Of the 354 participants enrolled, 239 died and of those, 219 came to autopsy (92% autopsy rate). All participants or their designated informants provided consent to participate in the study. All procedures were reviewed and approved by the University of California, Irvine (UCI) Institutional Review Board.

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2.2 Pathological Evaluations

All procedures for procuring and preparing tissues were performed by the UCI Alzheimer's Disease Center Pathology Core in harmony with uniform datasets and forms of the National Alzheimer Coordinating Center (NACC). If the examiner performing the neurological evaluation found clinical signs of stroke, the affected hemisphere was pre-specified for pathological evaluation. If there were no clinical signs, the left hemisphere was selected for evaluation. Brain cutting was performed after approximately two weeks of fixation and regions of interest (middle frontal, superior temporal, inferior parietal, occipital, entorhinal, and cingulate gyri, as well as basal ganglia, thalamus, hippocampus, amygdala, midbrain, pons, medulla, and cerebellum) were paraffin-embedded and sectioned. Two board certified neuropathologists performed all pathological evaluations blinded to clinical diagnosis. Joshua Sonnen performed all evaluations for microinfarcts with the same methodology he applied in other population-based cohorts[2, 3] and Ronald Kim performed evaluations for other pathologies.

The presence of *microinfarcts* were assessed as suggested by the NIA-AA guidelines[8] using one hematoxylin & eosin stained brain tissue section for each of six predefined regions: middle frontal, inferior parietal, superior temporal, occipital, basal ganglia, and thalamus. Microinfarcts were defined as foci of pallor, loss of vulnerable cells, gliosis, and macrophage presence[2]. These measures pioneered in the Honolulu Asia Aging Study (HAAS)[2] have been validated in other population- and community-based autopsy studies[9]. The adjacent white matter in the sections of the middle frontal, inferior parietal, superior temporal, occipital, and basal ganglia, was available. Thus, microinfarcts were evaluated in both gray and white matter for these regions, although white was not as heavily sampled as gray matter. *Macroinfarcts* were defined as ischemic and hemorrhagic infarcts identified grossly at the time of dissection. These infarcts were evaluated for size, location, and number. Infarcts coded by the pathologist as either large infarcts or lacunes, are included in this category. Acute and subacute macroinfarcts proximal to death were excluded. *Neurofibrillary tangle* pathology was graded with Braak & Braak staging[10] and *neuritic plaque* pathology categorized according to CERAD score[11]. *Subcortical arteriolosclerotic leukoencephalopathy* was assessed within periventricular white matter immediately adjoining the rostral cingulate gyrus and caudal cingulate gyrus and was defined by lipohyalinosis/arteriolar sclerosis, widening of perivascular spaces, white matter gliosis, and pallor of myelin staining[12]. *Cerebral amyloid angiopathy* (CAA) was assessed with β-amyloid immunostaining of cerebral blood vessels and classified as absent, mild, moderate, or severe. Details about the pathological evaluations have been published previously [13].

2.3 Evaluations and Dementia Determination

Participants were examined every 6 months and evaluations included a neurological examination, physical exam, neuropsychological battery, review of medical history, and interviews with knowledgeable informants. After a participant's death, we performed additional interviews with informants to inquire about cognition and function since last evaluation. We assigned dementia diagnoses (DSM-IV)[14] during a consensus conference using all available clinical information including longitudinal evaluations, brain imaging when clinically available, informant questionnaires and medical records. One of the authors

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(CK), a geriatric neurologist, led the consensus conferences, with conferees blinded to pathological evaluations. As we wanted to examine the association between dementia (a clinical diagnosis) and pathologic findings, the two assessments were performed independently of each other.

2.4 Additional Variables

Demographic and medical history information was reported by participants or their surrogates if cognitively impaired. Relevant medical histories include cardio- and cerebrovascular histories, which consist of stroke, transient ischemic attack (TIA), diabetes, and heart disease. We considered history of heart disease present if any of the following were reported: coronary artery disease, myocardial infarction, atrial fibrillation or other arrhythmias, heart valve disease, congestive heart failure, coronary artery bypass, or pacemaker placement. APOE genotyping was done from DNA extracted from blood or check swabs for most participants and from frozen brain tissue when DNA was not collected during life.

2.5 Statistical Analyses

We used Fisher's exact tests to compare characteristics between people with different number of microinfarcts and to compare characteristics of people included and not included in the analyses. Our first goal was to report the prevalence of microinfarcts as the proportion of people with one or more microinfarcts in any of the six brain regions and in each individual region. Our next goal was to explore the association between microinfarcts and dementia and to explore the independent contribution of microinfarcts to dementia after adjustment for other dementing pathologies. We selected pathologies known to be important to dementia in this cohort (neuritic plaques and tangles)[13, 15] and pathologies previously identified as being related to microinfarcts (macroinfarcts and leukoencephalopathy)[4, 16]. Although CAA has been related to microinfarcts in other studies[17, 18] we did not include it in our dementia analyses because it is not related to dementia in our cohort[13]. Pathologies were categorized to allow comparisons with other publications[2, 3] as follows: microinfarcts (0, 1 or 2, 3+), larger infarcts (0, 1, 2+), neuritic plaque (none-sparse, moderate, frequent), tangle stage (0-II, III-IV, V-VI), and leukoencephalopathy (absent vs. present). We used logistic regression to estimate the odds of dementia in relation to microinfarcts and other pathologies. We first estimated the odds of dementia in relation to each individual pathology then performed analyses that included multiple pathologies. Finally, we quantified the association between dementia and the presence of one or more microinfarct in each brain region. All analyses adjusted for age at death, sex, and education and analyses of brain regions further adjusted for tangle stage and leukoencephalopathy. Analyses were performed with SAS 9.4 for Windows.

3. Results

Of the 219 participants available for study, we included 213 in our analyses. We excluded one participant without enough information to assign a cognitive diagnosis and excluded four without a full pathological evaluation. Most participants were Caucasian (99%), women (69%), about half had dementia (52%), and at least a college degree (50%). Participants

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median age was 97 years (range: 90-108) at the time of death (Table 1). When the 213 included participants were compared to the 570 deceased participants of The 90+ Study who were not included in this study, they were found to be slightly older and better educated (see supplemental material).

In terms of pathologic findings (Table 1), tangles were present in all but one participant with 36% having Braak stages V-VI. We found moderate/frequent plaques in 54% of participants, moderate/severe CAA in 12%, and leukoencephalopathy in 8% of participants. Macroinfarcts were identified in a quarter of participants (24%). Single macroinfarcts were more common than multiple macroinfarcts with one macroinfarct found in 17% of people and two or more in only 7% of people. Microinfarcts were more prevalent and were found in half the participants (51%). Multiple microinfarcts were as frequent as single microinfarcts: 25% of participants had one microinfarct, 26% had two or more, and 17% had three or more.

3.1 Factors Associated with Microinfarcts

Table 2 shows associations between microinfarcts and a variety of factors. The presence of microinfarcts was significantly associated with lower education ($p=0.03$) and history of TIAs ($p=0.05$), and trended towards a significant association with history of strokes ($p=0.08$). Macro- and microinfarcts were found frequently in the same people ($p<0.001$) where of the 52 people who had macroinfarcts 40 (77%) also had microinfarcts. There were no associations with sex, APOE genotype, Braak tangle stage, CERAD plaque score, CAA, leukoencephalopathy, or history of other cardiovascular diseases.

3.2 Microinfarcts and Dementia

Table 3 shows the results of analyses relating pathologies to dementia. When analyzed separately, microinfarcts, tangle stage, plaque score, and leukoencephalopathy were significantly associated with dementia with odds ratios [OR] above 4.0 for all four pathologies (Table 3, Model 1). Conversely, the presence of macroinfarcts was not significantly related to dementia. When the four significant pathologies were analyzed together, microinfarcts, tangle stage, and leukoencephalopathy but not plaque score, were associated with dementia (Table 3, Model 2). In a final model that included only microinfarcts, tangle stage, and leukoencephalopathy (Table 3, Model 3), all three pathologies remained independently and significantly associated with dementia with ORs that were similar in magnitude (3+ microinfarcts OR=4.75; tangle stages V-VI OR=4.70; leukoencephalopathy OR=5.48).

3.3 Microinfarcts in Different Brain Regions

A total of 270 microinfarcts were found among the 213 participants. Table 4 shows the frequency of these microinfarcts within the different brain regions. The occipital lobe had the highest number of microinfarcts (43%), followed by basal ganglia (31%). Microinfarcts were less common in the remaining regions (middle frontal, inferior parietal, superior temporal, and thalamus) with each of these regions having between 3% and 11% of the microinfarcts identified. Most microinfarcts were found in the gray matter (80%) and a smaller percentage (11%) in white matter, although white matter was not sampled as heavily.

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We then analyzed the association between dementia and microinfarcts in the different regions after adjusting for age, sex, education, tangle stage, and leukoencephalopathy (Table 4). The OR for dementia in people with 1+ microinfarcts in the middle frontal or superior temporal regions where both above 4.5 but only statistically significant for middle frontal (OR=4.52, p=0.01) but not superior temporal (OR=5.85, p=0.12). We could not estimate an OR for the inferior parietal region because the seven people with microinfarcts in this region all had dementia. Because the odds of dementia were high in people with microinfarcts in these cortical regions (middle frontal, superior temporal, and inferior parietal), we performed an additional analysis combining the three regions. 27 people (13%) had 1+ microinfarcts in at least one of these regions and the odds of dementia was significantly higher than in people with no microinfarcts (OR=4.71, p=0.003). Microinfarcts in the occipital region, basal ganglia, or thalamus were not significantly related to dementia with ORs between 1.20 and 1.43.

Finally, we related the location of microinfarcts to other brain pathologies (Table 5). Microinfarcts in all regions evaluated were more common in people with one or more macroinfarcts, compared to people with none, reaching significance in occipital, basal ganglia, and thalamus (all $p<0.01$) and trending towards significance in inferior parietal and superior temporal ($p<0.1$) regions. Microinfarcts in the occipital cortex were also more common in people with moderate or severe CAA (46%) compared to people with none or mild CAA (24%, p=0.02). There were no other significant associations between the location of microinfarcts and brain pathologies.

4. Discussion

In this cohort of 90+ participants, microinfarcts are common, occurring in about half of participants, and frequently coexist with larger infarcts. We also found that microinfarcts and neurofibrillary tangles contribute independently and similarly in magnitude to the presence of dementia. Although most microinfarcts were in the occipital lobe and basal ganglia, only microinfarcts in other cortical regions (middle frontal, inferior parietal, and superior temporal) were related to the presence of dementia.

Microinfarcts have been underappreciated as a correlate of dementia considered too small to be clinically significant. Increasingly, however, it is being recognized that these lesions reflect significant microvascular disease and are associated with a higher likelihood of dementia[19]. Our results extend to the oldest-old the findings of several community-based studies that have reported on the association between microinfarcts and dementia. A review article summarizing findings from 7 community-based studies estimated the pooled odds of dementia in relation to the presence of microinfarcts as 2.15 (95%CI=1.38-3.37)[19]. The Honolulu Asia Aging Study (HAAS), one of the first studies to report on microinfarcts, found a high burden of microinfarcts to be significantly (OR=4.6) and independently associated with dementia in Japanese American men[2]. The Adult Changes in Thought (ACT) study, extended these results to men and women and found that 3+ microinfarcts were significantly related to dementia (OR=4.8) independently from AD and other pathologies[3]. Other studies including the Baltimore Longitudinal Study of Aging (BLSA) [16], the Religious Orders Study (ROS)[20], and the Cambridge City over-75 Cohort

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(CC75C) Study[5] have reported similar associations with dementia in a variety of populations, although the magnitude of the association with microinfarcts was smaller than for AD. Not all community-based studies have found an association, including the Bronx Aging Study[21] and the Rush Memory Aging Study[22], although the latter study only reported on subcortical microinfarcts. The differences in results between studies may be due to differences in the definition of pathologies, size of the cohorts, or their age distribution. The only other study to report on the association between dementia and microinfarcts in the oldest-old, a hospital-based autopsy series of 93 people aged 90 and older, found Braak tangle stage and cortical microinfarcts as the two key independent determinants of dementia[23].

Microinfarcts were prevalent in our oldest-old cohort with about half of participants (51%) having 1+microinfarcts. In the community-based studies, the prevalence of microinfarcts varied considerably from 16% to 48%[19], and increased with age. Indeed, the highest prevalence (48%) was observed in the CC75C cohort, which had the oldest average age at death (90.7 years)[5] and had results similar to ours. Another likely contributor to the variability in prevalence is the sampling of tissue examined[19] with some studies examining as many as 38 regions[2]. In our study, assessment of microinfarcts was done in only six regions, and yet we have among the highest prevalence reported. Given the small volume of brain tissue sampled in relation to the overall brain volume, the lesions detected are likely a gross underestimate. Elegant research has estimated that detection of one microinfarct may represent a total brain burden of 552 microinfarcts, while the identification of three microinfarcts on routine examination would represent more than 1,600 microinfarcts[24].

Microinfarcts were more frequently found in occipital cortex and basal ganglia possibly because these brain regions have intersecting vascular territories. These regions are recognized as areas of potentially compromised perfusion (“vascular watersheds”)[25]. For example, the section of occipital cortex sampled includes the “triple watershed” where the vascular territories of the anterior, middle, and posterior cerebral arteries intersect.

We found a strong relation between the location of microinfarcts and dementia. Only microinfarcts in cortical regions (other than occipital) were related to dementia, whereas microinfarcts in the occipital or subcortical regions (basal ganglia, thalamus) were more frequent but not related to dementia. There are only a handful of reports on the association between microinfarcts in different brain regions and dementia. Our findings are consistent with others that have a stronger association with dementia for hemispheric microinfarcts (cortical gray matter or underlying white matter above the basal ganglia) compared to subcortical infarcts[16, 26]. These results suggest that microvascular disease in the frontal, temporal, and parietal lobes may be most relevant to cognition.

Microinfarcts have been reported to coexist with other pathologies, particularly vascular pathologies. For example, microinfarcts have been related to macroinfarcts[4, 16], leukoencephalopathy[4], and CAA[17, 18, 27, 28]. In our study, the only other pathological finding related to microinfarcts was larger infarcts. We did not find an association between microinfarcts and leukoencephalopathy although both pathologies were independently and

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strongly related to dementia suggesting two distinct underlying pathomechanisms leading to dementia. CAA was also not related to microinfarcts in our study, when considering all brain regions. Microinfarcts in the occipital region, however, were significantly related to the presence of moderate/severe CAA, perhaps because CAA is especially common in the occipital lobe[29].

We know little about risk factors or underlying mechanisms of microinfarcts as few studies have attempted to describe these. In our study, the only risk factors related to microinfarcts were history of TIA and to a lesser extent a history of stroke. Some studies[16, 26], but not all[30], have found hypertension to be a risk factor for microinfarcts. In the BLSA, severe hypertension (lasting 10 years, requiring two or more medications, and systolic blood pressure >160mm Hg) was related to the presence of microinfarcts[16]. In the ACT study[26], where blood pressure was measured 7 years earlier, microinfarcts were related to increasing blood pressure in *younger elderly* (aged 65 to 80) but not in *older elderly* (aged >80). The lack of association at older ages may be due to a modest number of participants at very old ages (N=91) or because risk factors for microinfarcts may be different at older ages.

Our study has several limitations. The number of regions sampled in our study was small, especially when compared to other studies, and was limited to one hemisphere. This limited sampling is almost certain to result in an underestimate of the number of microinfarcts. The sampled regions, however, are those recommended by current NIA-AA guidelines[8]. Despite limited sampling, we report numbers of microinfarcts higher than most studies, suggesting that our high prevalence may be due to characteristics of our cohort, such as advanced age. We chose to study all-cause dementia, rather than dementia subtypes because diagnostic criteria for dementia subtypes are not validated in the oldest-old and because multiple concurrent dementing pathologies are common in this cohort [13]. This approach limits our ability to understand the association between microinfarcts and dementia subtypes, but reflects the reality of a mix of pathologies at very advanced ages. Another potential limitation is the generalizability of our results to other populations. The 90+ Study participants are mostly women, Caucasian, and highly educated. Although our participants do not reflect the elderly population in general, they are similar to current 90+ year olds in the US particularly with regards to sex and race[31]. Moreover, the relationship between microinfarcts and dementia has now been shown to be relevant in a variety of cohorts, ranging from Asian American men to mostly Caucasian cohorts of men and women in the US and Europe.

Our study also has strengths we would like to highlight. The 90+ Study includes one of the largest samples of oldest-old participants ever assembled allowing us to extend current research on microinfarcts and dementia to the oldest-old. The 90+ Study includes participants with a wide spectrum of cognitive and physical abilities, who reside in the community as well as in institutions. In addition, the thorough pathological evaluation was performed blinded to any clinical information. Furthermore, evaluation of microinfarcts was done by a Board-certified neuropathologist with experience in their detection using a similar definition and methodology as other epidemiological studies, facilitating comparison of results. Finally, we report on the association in specific brain regions and after taking into consideration a variety of important dementing pathologies.

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In this cohort of oldest-old participants, microinfarcts, but not large infarcts, are related to dementia independently from neurofibrillary tangle pathology. Thus, microinfarct pathologies in this age group appear to be as important for dementia as AD pathology. The high prevalence and morbidity of microinfarcts in the oldest-old warrants greater attention. As risk factors for microinfarcts, other vascular pathologies, and AD pathology are likely to differ, identifying factors specific to each pathology will be crucial to developing prevention strategies for dementia in the oldest-old.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

1) Microinfarct pathology is common in the oldest-old.

2) Microinfarcts are strongly associated with dementia.

3) Microinfarcts contribute independently and similarly in magnitude to dementia as tangle pathology.

4) Only microinfarcts in cortical regions (other than occipital) are associated with dementia.

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RESEARCH IN CONTEXT

Systematic review: We reviewed the literature using PubMed and reference lists from relevant manuscripts. The association of microinfarcts and dementia has not been studied in the oldest-old but we identified a few publications on younger elderly.

Interpretation: Microinfarcts have typically been underappreciated as a correlate of dementia and are generally considered too small to be clinically significant. Here we extend current research of microinfarcts and dementia to the oldest-old. We found microinfarcts to be highly prevalent and strongly related to dementia. Furthermore, microinfarcts were an independent predictor of dementia and as strongly related as neurofibrillary tangle pathology.

Future directions: Identifying risk factors for microinfarcts is important, as they are likely to differ from risk factors for other vascular pathologies and Alzheimer's pathology. As the oldest-old represent the fastest growing segment of the population and have the highest rates of microinfarcts and dementia, identifying factors that contribute to microinfarcts will be essential for developing strategies to prevent dementia in the oldest-old.

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TABLE 1

Characteristics of Autopsied Participants with and without Dementia in *The 90+ Study*

Characteristic*	All Participants (N=213)	No Dementia (N=103)	Dementia (N=110)
	Median (Range)		
Age at death (y)	97.5 (90 - 108)	97.7 (90 - 108)	97.5 (90 - 106)
Months between last evaluation and death	4.0 (0.2 - 45.1)	4.0 (0.2 - 45.1)	4.1 (0.2 - 43.3)
No. of microinfarcts	1 (0 - 13)	0 (0 - 9)	1 (0 - 13)
No. of macroinfarcts	0 (0 - 3)	0 (0 - 2)	0 (0 - 3)
	Number (%)		
Sex			
Men	67 (31.5)	38 (36.9)	29 (26.4)
Women	146 (68.5)	65 (63.1)	81 (73.6)
Education			
Less than college grad	106 (50.0)	46 (44.7)	60 (55.1)
College grad or higher	106 (50.0)	57 (55.3)	49 (45.0)
Race			
Caucasian	211 (99.1)	103 (100)	108 (98.2)
Other	2 (0.9)	0 (0)	2 (1.8)
Microinfarcts			
0	104 (48.8)	54 (52.4)	50 (45.5)
1	54 (25.4)	30 (29.1)	24 (21.8)
2	19 (8.9)	12 (11.7)	7 (6.4)
3 or more	36 (16.9)	7 (6.8)	29 (26.4)
Macroinfarcts†			
0	161 (75.6)	77 (74.8)	84 (76.4)
1	37 (17.4)	21 (20.4)	16 (14.6)
2 or more	15 (7.1)	5 (4.9)	10 (9.1)
Braak tangle stage			
0 - II	51 (23.9)	33 (32.0)	18 (16.4)
III - IV	85 (39.9)	49 (47.6)	36 (32.7)
V - VI	77 (36)	21 (20)	56 (51)
CERAD plaque score			
None - sparse	98 (46.0)	58 (56.3)	40 (36.4)
Moderate	70 (32.9)	34 (33.0)	36 (32.7)
Frequent	45 (21.1)	11 (10.7)	34 (30.9)
Cerebral amyloid angiopathy			

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Characteristic*	All Participants (N=213)	No Dementia (N=103)	Dementia (N=110)
None/mild	187 (87.8)	94 (91.3)	93 (84.6)
Moderate/severe	26 (12.2)	9 (8.7)	17 (15.5)
Subcortical arteriolosclerotic leukoencephalopathy			
No	196 (92.5)	100 (98.0)	96 (87.3)
Yes	16 (7.6)	2(2.0)	14 (12.7)

Abbreviations: CERAD= Consortium to Establish a Registry for Alzheimer's Disease

*Missing data: education (n=1), leukoencephalopathy (n=1)

†Macroinfarcts include large infarcts or lacunes

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TABLE 2

Characteristics of Autopsied Participants By Numbers of Microinfarcts in *The 90+ Study*

Characteristic*	No Microinfarcts (N=104)	1 or 2 Microinfarcts (N=73)	3 or more Microinfarcts (N=36)	p-value§
		Number (%)		
Demographics and genetics				
Women	73 (70.2)	47 (64.4)	26 (72.2)	0.64
Colle graduate or more	48 (46.6)	45 (61.6)	13 (36.1)	0.03
Caucasian	103 (99.0)	73 (100.0)	35 (97.2)	0.43
APOE e4 allele present	19 (18.5)	20 (29.0)	8 (22.2)	0.27
APOE e2 allele present	20 (19.4)	12 (17.4)	4 (11.1)	0.59
Pathology				
1 or more macroinfarcts†	12 (11.5)	19 (26.0)	21 (58.3)	<0.001
Braak tangle stage V - VI	39 (37.5)	22 (30.1)	16 (44.4)	0.32
CERAD plaque moderate/frequent	58 (55.8)	40 (54.8)	17 (47.2)	0.68
Moderate/severe CAA	8 (7.7)	12 (16.4)	6 (16.7)	0.13
Leukoencephalopathy	5 (4.9)	6 (8.2)	5 (13.9)	0.21
Medical History				
Hypertension	58 (56.3)	43 (59.7)	19 (52.8)	0.78
High cholesterol	29 (29.3)	15 (21.4)	11 (31.4)	0.42
Diabetes	6 (5.8)	3 (4.2)	1 (2.8)	0.83
Heart disease‡	56 (54.4)	43 (59.7)	19 (52.8)	0.72
CAD	22 (21.8)	15 (20.8)	3 (8.3)	0.20
MI	12 (11.9)	11 (15.3)	4 (11.1)	0.82
HVD	9 (8.9)	6 (8.3)	3 (8.3)	0.99
CHF	19 (18.8)	17 (23.6)	6 (16.7)	0.66
Arrhythmia	33 (33.0)	26 (36.1)	15 (41.7)	0.65
CAB	6 (5.9)	3 (4.2)	2 (5.6)	0.92
Pacemaker	12 (11.9)	11 (15.5)	6 (17.1)	0.64
Stroke	16 (16.0)	8 (11.3)	10 (28.6)	0.08
TIA	24 (25.3)	27 (38.6)	15 (45.5)	0.05

Abbreviations: APOE=apolipoprotein, CERAD= Consortium to Establish a Registry for Alzheimer's Disease, CAA=cerebral amyloid angiopathy, CAD=coronary artery disease, MI=myocardial infarction, HVD=heart valve disease, CHF=congestive heart failure, CAB= coronary artery bypass, TIA=transient ischemic attack

*Missing data: education (n=1), APOE (n=5), leukoencephalopathy (n=1), hypertension (n=2), cholesterol (n=9), diabetes (n=2), heart disease (n=2), CAD (n=4), MI (n=4), HVD (n=4), CHF (n=4), arrhythmia (n=5), CAB (n=4), pacemaker (n=6), stroke (n=7), TIA (n=15)

†Macroinfarcts include large infarcts or lacunes

‡Heart disease includes a history of any of the following: coronary artery disease, myocardial infarction, heart valve disease, congestive heart failure, arrhythmia, coronary artery bypass, or pacemaker

§p-values are from Fisher's exact tests comparing the frequency of the characteristics among people in the different microinfarct categories.

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TABLE 3

Results From Logistic Regression Models of Neuropathology in Relation to the Odds of Dementia in *The 90+ Study*

	Model 1† Individual Pathologies		Model 2† Combined Pathologies		Model 3† Combined Pathologies	
Neuropathology	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
No. of microinfarcts						
0	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
1 or 2	0.86 (0.47 - 1.60)	0.64	0.81 (0.42 - 1.58)	0.54	0.81 (0.42 - 1.57)	0.54
3 or more	4.53 (1.81 - 11.36)	0.001	5.08 (1.88 - 13.72)	<0.001	4.75 (1.78 - 12.70)	0.002
No. of macroinfarcts*						
0	1.00 (reference)	--	--	--	--	--
1	0.71 (0.35 - 1.48)	0.36	--	--	--	--
2 or more	1.72 (0.55 - 5.33)	0.35	--	--	--	--
Braak tangle stage						
0 - II	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
III - IV	1.34 (0.65 - 2.76)	0.43	1.37 (0.62 - 3.01)	0.44	1.50 (0.69 - 3.26)	0.30
V - VI	4.48 (2.06 - 9.72)	<0.001	3.05 (1.15 - 8.09)	0.02	4.70 (2.06 - 10.73)	<0.001
CERAD plaque score						
None - Sparse	1.00 (reference)	--	1.00 (reference)	--	--	--
Moderate	1.49 (0.79 - 2.79)	0.22	1.32 (0.64 - 2.73)	0.45	--	--
Frequent	4.18 (1.87 - 9.35)	<0.001	2.35 (0.83 - 6.63)	0.11	--	--
Subcortical arteriolosclerotic leukoencephalopathy						
No	1.00 (reference)	--	1.00 (reference)	--	1.00 (reference)	--
Yes	6.86 (1.49 - 31.61)	0.02	5.42 (1.05 - 27.94)	0.04	5.48 (1.06 - 28.23)	0.04

Abbreviations: OR = odds ratio, CI = Confidence Interval, CERAD= Consortium to Establish a Registry for Alzheimer's Disease

Model 1: Separate logistic regression models were done for each pathology. Model 2: One logistic regression model with microinfarcts, tangle stage, plaque score, and leukoencephalopathy as covariates. Model 3: One logistic regression model with microinfarcts, tangle stage and leukoencephalopathy as covariates.

*Macroinfarcts include large infarcts or lacunes

†All models are adjusted for age at death, sex, and education (<college vs ≥ college).

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TABLE 4

Prevalence, Percentage of Total, and Association with Dementia for Microinfarcts in Various Brain Regions

Brain Region	Prevalence* N (%)	% of 270 microinfarcts†	OR (95%CI)‡	p-value‡
Occipital	56 (26.3)	43.0	1.43 (0.73 - 2.80)	0.30
Basal ganglia	54 (25.4)	31.1	1.31 (0.67 - 2.57)	0.43
Thalamus	22 (10.3)	8.9	1.20 (0.46 - 3.12)	0.71
Middle frontal	20 (9.4)	11.1	4.52 (1.42 - 14.44)	0.01
Inferior parietal	7 (3.3)	3.3	unable§	--
Superior temporal	7 (3.3)	2.6	5.85 (0.64 - 53.60)	0.12
Middle frontal, inferior parietal, and superior temporal	27 (12.7)	17.0	4.71 (1.70 - 13.09)	0.003

Abbreviations: OR = odds ratio; CI = Confidence Interval.

*Prevalence refers to the number of people (and percentage) with one or more microinfarcts in the specified region.

†Percentage of the total 270 microinfarcts identified in all regions combined.

‡Results of logistic regression model for odds of dementia, adjusted for age at death (continuous), sex, education (<college vs college degree or higher), tangle stage (0-IV vs V-VI), and leukoencephalotpathy (absent vs present). Separate models were done for each brain region.

§All 7 people w microinfarcts in inferior parietal region had dementia.

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TABLE 5

ber (%) of People with One or more Microinfarcts in Various Brain Regions in Relation to Other Brain Pathologies in *The 90+ Study*

n Region	Braak Tangle Stage		CERAD Plaque Score		Macroinfarcts		Cerebral Amyloid Angiopathy		Subcortical Arteriolosclerotic Leukoencephalopathy	
	0 - IV (N=136)	V - VI (N=77)	None/Sparse (N=98)	Moderate Frequent (N=115)	None (N=161)	1 or more (N=52)	None/Mild (N=187)	Moderate/Severe (N=26)	No (N=196)	Yes (N=16)
pital	34 (25)	22 (28.6)	28 (28.6)	28 (24.3)	33 (20.5)	23 (44.2) **	44 (23.5)	12 (46.2) *	49 (25)	7 (43.8)
l ganglia	33 (24.3)	21 (27.3)	25 (25.5)	29 (25.2)	31 (19.3)	23 (44.2) **	46 (24.6)	8 (30.8)	50 (25.5)	4 (25)
amus	16 (11.8)	6 (7.8)	13 (13.3)	9 (7.8)	10 (6.2)	12 (23.1) **	20 (10.7)	2 (7.7)	19 (9.7)	3 (18.8)
dle frontal	14 (10.3)	6 (7.8)	13 (13.3)	7 (6.1) †	12 (7.5)	8 (15.4)	17 (9.1)	3 (11.5)	18 (9.2)	2 (12.5)
ior parietal	2 (1.5)	5 (6.5)	1 (1.0)	6 (5.2)	3 (1.9)	4 (7.7) †	7 (3.7)	0 (0.0)	7 (3.6)	0 (0.0)
rior temporal	4 (2.9)	3 (3.9)	3 (3.1)	4 (3.5)	3 (1.9)	4 (7.7) †	6 (3.2)	1 (3.8)	6 (3.1)	1 (6.3)
dle frontal + ior parietal + rior temporal	17 (12.5)	10 (13)	14 (14.3)	13 (11.3)	17 (10.6)	10 (19.2)	23 (12.3)	4 (15.4)	25 (12.8)	2 (12.5)

viations: CERAD= Consortium to Establish a Registry for Alzheimer's Disease

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.; p-values are from Fisher's exact tests and compare the percentage of people with one or more microinfarcts in each brain region between dichotomized pathology groups

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