International Journal of Cerebrovascular Disease and Stroke
Sin MK et al. Int J Cerebrovasc Dis Stroke 7: 171.
www.doi.org/10.29011/2688-8734.000071
www.gavinpublishers.com

Research Article

Relationship between Cerebral Microinfarcts and Dementia by Sex: Findings from a community-based Autopsy Study

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Citation: Sin MK, Cheng Y, Roseman J, Zamrini E, Ahmed A (2024) Relationship between Cerebral Microinfarcts and Dementia by Sex among a Community-based Autopsy Cohort. Int J Cerebrovasc Dis Stroke 7: 171. DOI: https://doi.org/10.29011/2688-8734.100171

Received Date: 11 January, 2024**; Accepted Date:** 14 January, 2024**; Published Date:** 17 January, 2024

Abstract

Cerebral microinfarcts are common in older adults and are associated with cognitive impairment. Less is known about sex-related variation in the relationship between cerebral microinfarcts and dementia in older adults, the examination of which was the objective of this study. This case-control study was based on the 727 participants (419 women) in the Adult Changes in Thought (ACT) autopsy data. Microinfarcts were ascertained by blinded board-certified neuropathologists, and dementia diagnoses were made by the ACT Consensus Diagnosis Conference per DSM-IV. Multivariable logistic regression models were used to estimate adjusted odds ratio (aOR) and 95% confidence interval (CI). Microinfarcts were present in 49% (356/727) of the participants, which was numerically higher in women: 51% (213/419) vs 46% (143/308). aOR (95% CI) for dementia associated with any microinfarct for female and male participants were 1.45 (0.91-2.30) and 1.24 (0.75-2.06), respectively (p for interaction, 0.34). Respective aORs (95%CIs) associated with ≥2 microinfarcts were 1.37 (0.79-2.36) and 1.53 (0.84-2.78), with interaction p, 0.84. Subcortical microinfarcts were present in 36% (138/381) and 23% (78/346) of patients with and without dementia (aOR, 1.65; 95% CI, 1.14-2.38). Respective aOR (95% CI) in female and male participants were 1.70 (1.03-2.82) and 1.59 (0.90-2.80), (p for interaction, 0.55). There was no association with cortical microinfarcts (aOR, 1.19; 95% CI, 0.83-1.69). These findings suggest that association between microinfarcts and dementia is primarily mediated by subcortical microinfarcts, but we found no evidence of sex-related variation. Future studies with greater power are needed to determine if the associations we found are replicable.

Keywords: Cortical, Dementia, Microinfarcts, Subcortical, Sex

Introduction

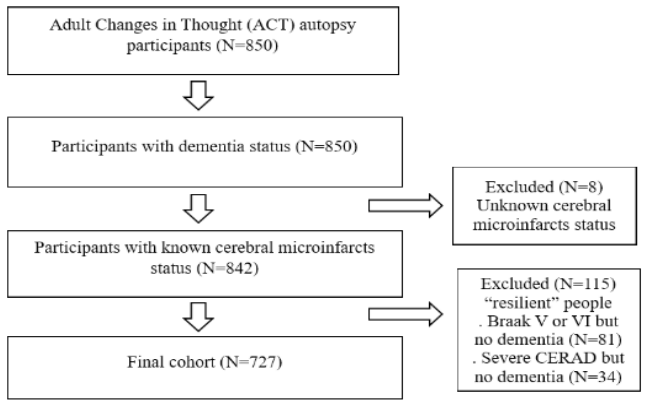
Cerebral microinfarcts are highly prevalent in older adults [1-5] and are associated with a higher risk of cognitive impairment and dementia [6-8]. Several studies reported a strong association between cerebral microinfarcts and poorer cognitive function and faster progression of dementia [9-12]. For example, a study based on the Religious Orders Study showed increased odds of dementia (OR=1.77; 95%: 1.07, 2.92) in persons with microinfarcts, especially those with multiple microinfarcts [12]. However, that study was conducted in a small older cohort of Catholic clergy (n=425) who have demographic and life-style features unique from other community-based lay populations. Studies are needed to validate the findings in a more representative cohort of the general population with a larger sample size. Dementia is more common in women probably because women live longer than men [13], but less is known about the sex-related variation in the relationship between cerebral microinfarcts and dementia. The purpose of this autopsy-based study is to examine the relationship of cerebral microinfarcts with dementia, overall, and stratified by sex.

Methods

Data and participants

We used data from the ACT study, an ongoing population-based cohort study of incident dementia, the details of which have been previously described [14,15]. Briefly, a random sample of 2,581 adults 65 years and older free of dementia who were members of Kaiser Permanente Washington (previously Group Health) in the Seattle region were enrolled during 1994-1996 and followed biennially to screen for dementia. A cohort of 811 adults were subsequently enrolled during 2000-2003 with the same methods, and ACT continued enrolling participants from 2004-present to replace attrition from dementia, dropout, and death, ensuring a consistent cohort of ≥2,000 at risk for dementia. Some participants consented to autopsy. The ACT participants underwent biennial follow-up visits for cognitive screening and those who screened "positive" (Cognitive Abilities Screening Instrument score < 86) underwent a full neuropsychological evaluation [15]. Total enrollment over the course of the study is >5,000 with 850 autopsies available at time of this analysis; the current study is based on the 727 autopsied participants who had complete data on presence, count and locations of microinfarcts and dementia (see Figure 1). We excluded 115 people who were "resilient" [16] (no cognitive impairment despite severe neuropathology). The study protocols were approved by Kaiser Permanente Washington Institutional Review Boards.

Figure 1. Flow Chart for Inclusion and Exclusion



Identification of cases and controls

Dementia status was categorized into two groups: present and without. The ACT subjects were re-screened every two years using the Cognitive Abilities Screening Instrument (CASI). All subjects showing a significant cognitive deficit on the CASI (< 86, score range 0 - 100) [17] underwent a dementia diagnostic work-up, including neuropsychological testing and physical and neurological examination by a geriatrician and neurologist. The neuropsychological test battery included the CERAD Neuropsychological battery, Wechsler Memory Scale (Paired Associates/Recall and Logical Memory/Recall), Mattis Dementia Rating Scale, Boston Naming Test and selected questions from WAIS-R. Relevant laboratory results and brain CT or MRI results were obtained from Kaiser Permanente records. Clinical dementia diagnoses were made by the ACT Consensus Diagnosis Conference per DSM-IV criteria (procedures are described in detail elsewhere) [18]. Subjects who did not meet criteria for dementia were re-screened at subsequent biennial follow-up visits. Subjects who met criteria for new onset dementia entered annual follow-up for verification of dementia diagnosis and monitoring of cognitive decline. Cases were defined by the presence of dementia, and those without dementia were considered control.

Ascertainment of exposure

Neuropathological examinations were performed by board-certified neuropathologists blinded to the clinical diagnosis and status of risk factors. We limited our evaluation of microinfarcts to chronic [19] as acute and subacute infarcts would be expected to be rare shortly before death and would be unlikely to contribute to dementia [8]. Chronic microinfarcts were defined as "a focal lesion attributed to ischemia, found only on microscopic examination, and judged to be temporally remote" [8]. Microinfarcts were measured in cortical gray matter and its underlying white matter, and in deep ganglionic masses that included deep white matter [8]. Based on the judgements of the neuropathologists, microinfarcts were categorized as none, 1, and ≥ 2. Chronic microinfarcts in cortical

gray matter regions (frontal, temporal, occipital, and parietal) were classified as cortical, and those with caudate nucleus, putamen, internal capsule, and thalamus were classified as subcortical.

Other variables

AD pathology (CERAD, Braak)**.** Neuritic plaques and neurofibrillary tangles were evaluated by established methods [20-25]. CERAD staging for neuritic amyloid β plaque was categorized as 0=none, 1=sparse, 2=intermediate, 3=frequent [21]. Braak stage for neurofibrillary tangles was categorized as 0=none (normal), 1=I (very mild), 2=II (mild), 3=III (moderate), 4=IV (moderately severe), 5=V (severe), 6=VI (very severe) [22].

The variables, age at death, sex, APOE e4 genotype, arteriolosclerosis, and cerebral amyloid angiopathy, were included as adjustments in all models. APOE genotyping has been completed using previously established methods [19,20]. APOE e4 status was rated as 0 = absence of the e4 allele, 1 = 1 or 2 e4 alleles. Arteriolosclerosis was evaluated by histologic examination on existing Hematoxylin-Eosin stained sections from each region of interest. Severity of this pathology was graded based on concentric hyaline thickening of vessel walls. Smaller arterioles, less than approximately 50 microns, were used for evaluation. The severity was categorized into four levels: none, mild, moderate, and severe. The presence of cerebral amyloid angiopathy (CAA) was determined by immunohistochemistry to assess degree of compacted amyloid β deposits in the brain leptomeninges and occipital cortex [25], and its severity was ranked on a four-point scale (none, mild, moderate, or severe).

Statistical analyses

The analyses were conducted in 727 participants with both microinfarcts and dementia data available among 850 autopsy participants. The process of creating the cohort is shown in Figure 1. We excluded 8 participants without known microinfarct status and 115 participants who were resilient to Alzheimer's disease (81 with BRAAK stage of V or VI but no dementia and 34 with severe CERAD but no dementia). We compared participant characteristics in the overall cohort and sub-cohorts stratified by sex, respectively. Due to the sample size of the study, we reported absolute standardized difference (ASD) instead of p-value to estimate the magnitude of difference between groups. It is commonly accepted that ASD >10% indicates imbalanced characteristics between comparison groups [23].

Then we fit five multivariable logistic regression models to estimate adjusted odds ratio (aOR) and 95% confidence interval (CI) for dementia associated with each of five microinfarct measures, respectively, adjusting for the other covariates. Microinfarcts were used in four different ways: categorical variable indicating presence (present vs. not), continuous variable measuring number of microinfarcts, categorical variable categorizing number of microinfarcts (one vs. none, two or more vs. none), and categorical variable by location of microinfarcts: cortical (present vs. not) and subcortical microinfarcts (present vs. not). The regression models were adjusted for age, sex, APOE e4 carrier, CAA, and arteriolosclerosis. Because the objective of the study was to examine whether the association between microinfarct and dementia varied by sex, we ran the regression models separately in males and females. Finally, we checked for interaction between microinfarct and sex in the overall cohort. To understand the association between dementia and other covariates, we also report ORs with 95% CI in the model with the main exposure of presence of microinfarcts. Similarly, we also estimated the interaction between sex and each of the covariates and conducted the subgroup analysis stratified by sex. All analyses were conducted using SAS 9.4.

Results

Participant characteristics

Among 727 participants with available microinfarct data in the autopsy cohort, 381 (52.4%) had dementia. Among 308 males and 419 females dementia was present in 150 (48.7%) and 231 (55.1%) individuals, respectively. Compared to participants with no dementia, a higher proportion of those with dementia were older, were APOE e4 carriers, and had higher severity of Braak (V-VI), CERAD (moderate and severe), CAA (moderate and severe) and arteriolosclerosis (moderate and severe) (Table 1). Distribution of these characteristics was generally similar among males and females (Table 1).

Table 1. Characteristics of the Participants

Variables, n (%)	Overall (n=727)			Male (n=308)			Female (n=419)		
	No dementia (n=346)	Dementia (n=381)	ASD (%)	No dementia (n=158)	Dementia (n=150)	ASD (%)	No dementia (n=188)	Dementia (n=231)	ASD (%)
Age categories									
<80 years	77 (22.3)	15 (3.9)	56	36 (22.8)	11 (7.4)	44	41 (21.8)	4 (1.7)	66
80-89 years	148 (42.8)	140 (36.8)	12	72 (45.6)	59 (39.3)	13	76 (40.4)	81 (35.1)	11
≥90 years	121 (34.9)	226 (59.3)	50	50 (31.6)	80 (53.3)	45	71 (37.8)	146 (63.2)	53
APOE e4									
No	260 (75.2)	250 (65.6)	21	124 (78.5)	97 (64.7)	31	136 (72.3)	153 (66.2)	13
Yes	70 (20.2)	121 (31.8)	27	29 (18.3)	49 (32.7)	33	41 (21.8)	72 (31.2)	21
Unknown	16 (4.6)	10 (2.6)	11	5 (3.2)	4 (2.6)	3	11 (5.9)	6 (2.6)	16
Braak									
Stage 0-II	168 (48.6)	44 (11.5)	88	87 (55.1)	23 (15.3)	91	81 (43.1)	21 (9.1)	84
Stage III-IV	176 (50.9)	107 (28.1)	48	70 (44.3)	47 (31.4)	27	106 (56.4)	60 (26)	65
Stage V-VI	0 (0)	229 (60.1)	174	0 (0)	80 (53.3)	151	0 (0)	149 (64.5)	191
Unknown	2 (0.5)	1 (0.3)	5	1 (0.6)	0 (0)	11	1 (0.5)	1 (0.4)	1
CERAD									
Absent	140 (40.5)	47 (12.3)	67	62 (39.2)	24 (16.0)	54	78 (41.5)	23 (10.0)	77
Sparse	128 (37.0)	67 (17.6)	45	56 (35.5)	31 (30.7)	33	72 (38.3)	36 (15.6)	53
Moderate	78 (22.5)	102 (26.8)	10	40 (25.3)	36 (24.0)	3	38 (20.2)	66 (28.5)	20
Severe	0 (0)	165 (43.3)	124	0 (0)	59 (39.3)	114	0 (0)	106 (45.9)	130
CAA									
Absent	257 (74.3)	209 (54.8)	41	120 (75.9)	89 (59.3)	36	137 (72.9)	120 (51.9)	44
Mild	53 (15.3)	78 (20.5)	13	21 (13.3)	24 (16.0)	8	32 (17.0)	54 (23.4)	16
Moderate	30 (8.7)	80 (21.0)	35	14 (8.9)	33 (22.0)	37	16 (8.5)	47 (20.4)	34
Severe	6 (1.7)	14 (3.7)	12	3 (1.9)	4 (2.7)	5	3 (1.6)	10 (4.3)	16
Arteriolosclerosis									
Absent	6 (1.7)	2 (0.5)	11	3 (1.9)	1 (0.7)	11	3 (1.6)	1 (0.4)	12
Mild	103 (29.8)	56 (14.7)	37	44 (27.8)	29 (19.3)	20	59 (31.4)	27 (11.7)	49
Moderate	118 (34.1)	167 (43.8)	20	58 (36.7)	63 (42.0)	11	60 (31.9)	104 (45.0)	27
Severe	43 (12.4)	117 (30.7)	46	21 (13.3)	39 (26.0)	32	22 (11.7)	78 (33.8)	55
Unknown	76 (22.0)	39 (10.2)	32	32 (20.3)	18 (12.0)	23	44 (23.4)	21 (9.1)	40
Microinfarcts									
None	205 (59.3)	166 (43.6)	32	93 (58.9)	72 (48.0)	22	112 (59.6)	94 (40.7)	38
One	62 (17.9)	82 (21.5)	9	30 (19.0)	26 (17.3)	4	32 (17.0)	56 (24.2)	18
Multiple	79 (22.8)	133 (34.9)	27	35 (22.1)	52 (34.7)	28	44 (23.4)	81 (35.1)	26
Microinfarcts (cortical)									
Not present	247 (71.4)	223 (58.5)	27	114 (72.2)	91 (60.7)	24	133 (70.7)	132 (57.1)	29
Present	99 (28.6)	158 (41.5)	27	44 (27.8)	59 (39.3)	24	5	99 (42.9)	29
Microinfarcts (subcortical)									
Not present	268 (77.5)	243 (63.8)	30	122 (77.2)	100 (66.7)	24	146 (77.7)	143 (61.9)	35
Present	78 (22.5)	138 (36.2)	30	36 (22.8)	50 (33.3)	24	42 (22.3)	88 (38.1)	35

Microinfarcts and dementia

Microinfarcts were present in 356 (49%) participants; 144 (40.4%) had one microinfarct; 211 (59.3%), two or more; 257 (72.2%), cortical; and 216 (60.7%), subcortical microinfarcts. Compared with participants without dementia, more of those with dementia had two or more microinfarcts, although there were no differences in the distribution of a single microinfarct (Table 1). The aOR (95% CI) for dementia associated with the presence of any microinfarct was 1.36 (0.97-1.91; Table 2). aORs (95% CIs) for males and females were 1.24 (0.75-2.06) and 1.45 (0.91-2.30), respectively. There was no interaction by sex in this association (p for interaction, 0.34; Table 2).

When microinfarcts were used as a continuous variable, the aOR estimate indicated that increasing number of microinfarcts by one, the odds of developing dementia would increase 7% (Table 2); however, the association was not statistically significant. The association was significant in males only with having one more microinfarct increasing the odds of dementia by 16%, although the interaction with sex was not significant with p-value at 0.32 (Table 2), when microinfarcts were used as a categorical variable, aORs (95% CIs) for dementia associated with one microinfarct and two or more microinfarcts were 1.24 (0.80-1.92) and 1.46 (0.98-2.18), respectively (Table 2). A similar numeric dose-response or graded association was also observed in males but not in females (Table 2). When microinfarcts were used as a continuous variable, aORs (95% CIs) for dementia associated with increase in the number of microinfarcts by one in the overall cohort and among males and females were 1.07 (0.98-1.16), 1.16 (1.01-1.33), and 1.01 (0.91-1.13), with no evidence of sex interaction in the relationship (p for sex interaction, 0.32; Table 2).

In the overall cohort, aOR (95% CI) for dementia associated with cortical microinfarcts was 1.19 (0.83-1.69), which was higher in males (OR, 1.29; 95% CI, 0.76-2.19) than in females (aOR, 1.11; 95% CI, 0.69-1.80), but the between-sex difference was not statistically significant (p for sex interaction, 0.96; Table 2). In contrast, subcortical microinfarcts had a significant association with dementia in the overall cohort (OR, 1.65; 95% CI, 1.14-2.38), which also had no interaction by sex (p for sex interaction, 0.55; Table 2).

Table 2. Association of microinfarcts presence, number, location with dementia adjusting for age, sex, APOE e4, arteriolosclerosis, cerebral amyloid angiopathy

Microinfarcts	Adjusted odds ratio (95% CI)			P for interaction
	Overall (n=727)	Male (n=308)	Female (n=419)	(microinfarcts*sex)
Presence	1.36 (0.97-1.91)	1.24 (0.75-2.06)	1.45 (0.91-2.30)	0.34
Number (continuous)	1.07 (0.98-1.16)	1.16* (1.01-1.33)	1.01 (0.91-1.13)	0.32
Number				
1	1.24 (0.80-1.92)	0.93 (0.48-1.81)	1.56 (0.86-2.83)	0.14
≥ 2	1.46 (0.98-2.18)	1.53 (0.84-2.78)	1.37 (0.79-2.36)	0.84
Location				
Cortical	1.19 (0.83-1.69)	1.29 (0.76-2.19)	1.11 (0.69-1.80)	0.96
Subcortical	1.65* (1.14-2.38)	1.59 (0.90-2.80)	1.70* (1.03-2.82)	0.55

Note: * p <0.05

Other predictors of dementia

When compared with participants younger than 80 years, aOR (95% CI) for dementia associated with age 80-89 years was 3.66 (1.95-6.86), which was significantly higher in females (aOR, 8.38; 95% CI, 2.74-25.62) than in males (aOR, 2.18; 95% CI, 0.96-4.92; p for interaction, 0.03; Table 3). Respective aOR (95% CI) associated with ≥90 years was 6.67 (3.55-12.55), which was also significantly stronger for females (p for interaction, 0.03; Table 3). APOE e4 carrier (vs. non-carrier) state was associated with higher odds of dementia (aOR, 1.76; 95% CI, 1.19-2.61), without any evidence of interaction by sex (p for interaction, 0.53; Table 3). Moderate to severe CAA was associated with dementia (aOR, 2.62; 95% CI, 1.63-4.22), which was similar for both males and females (p for interaction, 0.7; Table 3). Moderate and severe arteriolosclerosis were also significantly associated with dementia (aOR, 2.62; 95% CI, 1.63-4.22), which was stronger in females (p for interaction, 0.06 and 0.11 for moderate and severe arteriolosclerosis; Table 3).

Table 3. Other predictors of dementia

Other predictors	Adjusted odds ratio (95% CI)			P for interaction
	Overall	Male (n=308)	Female (n=419)	
Age 80-89 vs <80 years	3.66 (1.95-6.86)	2.18 (0.96-4.92)	8.38 (2.74-25.62)	0.03
Age ≥ 90 vs <80 years	6.67 (3.55-12.55)	4.12 (1.81-9.38)	14.49 (4.75-44.25)	0.03
Female vs Male	1.11 (0.80-1.55)	-	-	-
APOE e4 carrier vs non-carrier	1.76 (1.19-2.61)	2.07 (1.16-3.68)	1.67 (0.95-2.92)	0.53
CAA mild vs absent	1.52 (0.99-2.33)	1.37 (0.68-2.76)	1.53 (0.87-2.67)	0.85
CAA moderate or severe vs absent	2.62 (1.63-4.22)	2.35 (1.19-4.62)	2.92 (1.47-5.77)	0.75
Arteriolosclerosis moderate vs absent or mild	2.12 (1.38-3.25)	1.37 (0.73-2.57)	2.99 (1.64-5.44)	0.06
Arteriolosclerosis severe vs absent or mild	3.40 (2.02-5.73)	2.24 (1.03-4.84)	4.74 (2.30-9.74)	0.11

Note: The estimates of covariates were derived from the model with the main exposure of presence of microinfarcts.

Discussion

The findings from the current study demonstrate that cerebral microinfarcts were more common in older adults with dementia. When adjusted for age, sex, APOE e4 carrier, CAA, and arteriolosclerosis, microinfarcts were associated with higher odds of dementia, and the odds were higher in those with more than one microinfarct. Although these associations were not statistically significant, lack of sufficient power might have contributed to the non-significant association. However, the direction of the point estimates of the association and the graded or "dose-response" nature of the association, taken together with the plausible mechanistic explanations in the literature [8,24], suggest a contribution of microinfarcts, even in small numbers, to cognitive impairment. Furthermore, the association between microinfarcts and dementia was higher in females than males. Finally, this association was higher with microinfarcts in the subcortical regions than cortical regions, which also appeared to be more pronounced in females. To the best of knowledge, this is a first autopsy-based study describing potential sex-related variation in the relationship between microinfarcts and dementia. Findings from this study are hypothesis generating and may provide insights into understanding potential needs for developing sex-specific interventions in lowering the risk of microinfarct-associated dementia.

The association between cerebral microinfarcts and dementia was not significant in our study, likely due to lack of adequate power, patient characteristics, and study methodology. However, taken together with prior evidence of association with cognitive impairment and graded association with higher risk of dementia associated with a higher number of microinfarcts and a significant association with subcortical microinfarcts suggests a potential association. Precise mechanisms by which microinfarcts are related with cognitive impairment and ultimately dementia are not well known. Plausible explanations include: widespread and diffuse hypoperfusion, hypoxia, oxidative stress and inflammation resulting in cumulative, brain-wide disruptions to neural

connectivity, glial dysfunction, and neuroinflammation. It has been suggested these effects of hypoperfusion extend well beyond the core of the microinfarct lesions thereby explaining many of the vascular contributions to the cognitive and behavioral disturbances of Alzheimer's disease [25-27]. It has also been suggested these effects occur in both cortical [28] and subcortical regions [29]. Findings from our study suggest that the microinfarct-dementia association may have a predilection for subcortical brain regions, especially for females. It is not clear why a higher number of microinfarcts and the presence of cortical microinfarcts did not have a graded association with dementia in females. The findings of a graded association overall for the presence of any microinfarct, specifically the presence of one microinfarct, may be an artifact of the proportional age difference (for example, women <90 are fewer than men, and women ≥90 are greater than men in Table 1) or a higher threshold for risk of dementia in females, which needs to be examined in future studies.

Prior studies have reported variable associations between microinfarcts and dementia [3,7,12,30-32]. For example, a study using 7T MRI reported a significant relationship between a higher number of microinfarcts and decreased cognitive functioning although microinfarcts were measured on MRI [4]. In that study, people with Alzheimer's disease had a high prevalence of microinfarcts in the frontal, parietal, and occipital lobes [4]. In the Honolulu Asia-Aging Study (HAAS) both cortical and subcortical microinfarcts were independently associated with impairment of cognitive function [32]. In other studies, only microinfarcts in cortical regions were related to dementia, whereas microinfarcts in the occipital or subcortical regions (basal ganglia, thalamus) were more frequent but not related to dementia [3,7]. A 2007 ACT autopsy study of a smaller sample size of 221 participants demonstrated that the presence of >2 microinfarcts was associated with dementia, like the Religious Orders Study [8,12]. However, the current ACT autopsy study is based on a slightly larger sample size and a more representative population sample. It is also distinguished by its focus on sex differences as well as regional differences.

The findings of the current study need to be replicated in larger contemporary populations. They provide important insights into sex-related variations in the pathophysiology of microinfarct-associated dementia. Taken together with the findings from other similar studies, our findings support the possible contribution of subcortical microinfarcts in dementia. Microinfarcts, along with other vascular pathologies such as cerebral amyloid angiopathy and arteriolosclerosis, were highly prevalent among our participants. Cerebral amyloid angiopathy and arteriolosclerosis are common vascular pathologies in older adults and have been found to accelerate cognitive decline and development of clinical dementia in older adults, even when the burden of AD pathology is low [33,34].

Despite this study being based on one of the largest autopsy datasets from a longitudinal community-based cohort, several limitations of our study need to be acknowledged. As in any observational study, findings of our study may be biased by residual or unmeasured confounders. Although the approach of microscopic detection of microinfarcts used in the current study is the standard [4], an estimation of the total number of microinfarcts based on delineated regions may underestimate the total microinfarct burden in all regions of the brain. The ascertainment of microinfarcts, the primary exposure of the current study, from autopsy-based data limits our ability to infer causality as the temporal relationship between microinfarct and dementia could not be determined, and it is possible that dementia preceded microinfarcts. In addition, the participants being over 90% non-Hispanic white urban-dwelling individuals enrolled in one of the largest managed care systems may limit generalizability to other population settings. People who consent to autopsy are not representative of the entire ACT sample. In particular dementia is over-represented, and this suggests the distribution of dementia-related pathology is more common in the autopsy group than in the overall ACT cohort.

Conclusions

Although the associations with the cerebral microinfarcts in general and in those with two or more microinfarcts were not statistically significant, likely due to lack of adequate statistical power, the higher odds of dementia in the cohort as a whole and in both males and females is intriguing and deserves further exploration. The findings of the current study demonstrate that cerebral microinfarcts in the subcortical region of the brain have a significant association with higher odds of dementia, which is higher than microinfarcts in the cortical region of the brain, and that there is no evidence of a sex-related variation in either association. Finally, the higher odds of dementia in females with a single microinfarct is intriguing and suggest that females may be more sensitive to microinfarcts. These findings support the importance of early control of vascular risk factors to minimize the risk of microinfarcts and cognitive impairment. Future studies need to examine strategies to delay and manage vascular risk factors contributing to microinfarcts formation.

Disclosure: Study concept and design, data acquisition, data interpretation, manuscript writing: Mo-Kyung Sin; Data analysis and interpretation: Yan Cheng; Data interpretation and critical review of the manuscript for important intellectual content: Ali Ahmed, Edward Zamrini, Jeffrey Roseman.

Funding: Research reported in this publication was supported by the National Institute on Aging of the National Institutes of Health under Award Number R03AG070579 and R03AG072110. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Institutional Review Board Statement: The Seattle University IRB has determined the study to be exempt from IRB review in accordance with federal regulation criteria.

Informed consent statement: Not applicable.

Acknowledgement: The ACT study was funded by the National Institute on Aging (U19AG066567). Data collection for this work was additionally supported, in part, by prior funding from the National Institute on Aging (U01AG006781). We thank the participants of the Adult Changes in Thought (ACT) study for the data they have provided and the many ACT investigators and staff who steward that data.

Data availability statement: Data supporting the study results can be provided followed by request sent to the ACT at: https://actagingstudy.org/

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