Incidence of Brain Infarcts, Cognitive Change, and Risk of Dementia in the General Population

The AGES-Reykjavik Study (Age Gene/Environment Susceptibility-Reykjavik Study)

Sigurdur Sigurdsson, MSc; Thor Aspelund, PhD; Olafur Kjartansson, MD; Elias F. Gudmundsson, MSc; Maria K. Jonsdottir, PhD; Gudny Eiriksdottir, MSc; Palmi V. Jonsson, MD, PhD; Mark A. van Buchem, MD, PhD; Vilmundur Gudnason, MD, PhD*; Lenore J. Launer, PhD*

Background and Purpose—The differentiation of brain infarcts by region is important because their cause and clinical implications may differ. Information on the incidence of these lesions and association with cognition and dementia from longitudinal population studies is scarce. We investigated the incidence of infarcts in cortical, subcortical, cerebellar, and overall brain regions and how prevalent and incident infarcts associate with cognitive change and incident dementia.

Methods—Participants (n=2612, 41% men, mean age 74.6±4.8) underwent brain magnetic resonance imaging for the assessment of infarcts and cognitive testing at baseline and on average 5.2 years later. Incident dementia was assessed according to the international guidelines.

Results—Twenty-one percent of the study participants developed new infarcts. The risk of incident infarcts in men was higher than the risk in women (1.8; 95% confidence interval, 1.5–2.3). Persons with both incident and prevalent infarcts showed steeper cognitive decline and had almost double relative risk of incident dementia (1.7; 95% confidence interval, 1.3–2.2) compared with those without infarcts. Persons with new subcortical infarcts had the highest risk of incident dementia compared with those without infarcts (2.6; 95% confidence interval, 1.9–3.4).

Conclusions—Men are at greater risk of developing incident brain infarcts than women. Persons with incident brain infarcts decline faster in cognition and have an increased risk of dementia compared with those free of infarcts. Incident subcortical infarcts contribute more than cortical and cerebellar infarcts to incident dementia which may indicate that infarcts of small vessel disease origin contribute more to the development of dementia than infarcts of embolic origin in larger vessels. **(*Stroke*. 2017;48:2353-2360. DOI: 10.1161/STROKEAHA.117.017357.)**

Key Words: cognition ■ cohort studies ■ dementia ■ incidence ■ risk

Brain infarcts are common findings on magnetic resonance (MR) images in older adults and have been associated with cognitive decline and dementia. Their prevalence has been well documented in several population-based studies.[1–4] Imaging studies generally agree that the prevalence of brain infarcts increases steeply with increasing age, and it is >20% in the 70 to 79 age group and 35% in those older than 85.[4,5] Most studies with data on prevalence of brain infarcts show no sex disparity in infarct risk.[5] Information on the incidence of brain infarcts from population-based longitudinal studies is, however, scarce.

Previous studies suggest that cerebrovascular abnormalities contribute to cognitive decline and the development of vascular dementia and Alzheimer's disease.[6,7] There is, however, limited information from imaging studies on whether this differs by brain region. The assessment of brain infarcts by region or type is important because the cause and clinical implications of cerebellar, cortical, and subcortical infarcts may differ. A distal branch middle cerebral artery occlusion resulting in a cortical stroke usually results from an embolus from either the heart, aortic arch, or carotid artery, whereas a small infarct in the subcortical white matter is usually because of a blockage of small penetrating artery (lacunar infarct). The most common causes of cerebellar infarcts are, however, thought to be atherosclerosis, cardiac embolism, and migraine.[8,9]

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From the Icelandic Heart Association, Kopavogur, Iceland (S.S., T.A., O.K., E.F.G., G.E., V.G.); The University of Iceland, Reykjavik (T.A., P.V.J., V.G.); Department of Radiology, Leiden University Medical Center, the Netherlands (M.A.v.B.); Laboratory of Epidemiology and Population Science, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, MD (L.J.L.); and Department of Psychology, Reykjavik University, Iceland (M.K.J.).

*Drs Gudnason and Launer share senior authorship.

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Correspondence to Sigurdur Sigurdsson, MSc, The Icelandic Heart Association, 201 Kopavogur, Iceland. E-mail sigurdur@hjarta.is

At least 3 longitudinal population studies have shown an association of prevalent brain infarcts with increased risk of incident dementia.[10–12] These studies had a relatively small number of incident dementia events, and only one of them had MR imaging (MRI) observations at 2 time points and none evaluated the association of infarcts with dementia by infarct location.

The objectives of this study were to investigate the incidence and risk of incident infarcts in cortical, subcortical, cerebellar, and overall brain regions by sex. Further, to investigate cognitive change and the risk of incident overall dementia in relation to prevalent and incident infarcts in those brain regions.

Materials and Methods

Study Population

The longitudinal data in the present study are from a population-based cohort of men and women, who participated in the AGES-Reykjavik Study (Age Gene/Environment Susceptibility-Reykjavik Study). In brief, from 2002 to 2006, 5764 surviving participants of the Reykjavik Study were examined. From 2007 to 2011, a follow-up visit was conducted comprising 3316 surviving participants who agreed to participate. Reasons for not attending the follow-up examination included: death (n=1039), refusal (n=1198), and could not be contacted (n=211). The AGES-Reykjavik Study has been approved by the Icelandic National Bioethics Committee and by the Institutional Review Board for the Intramural Research Program of the National Institute on Aging, National Institutes of Health. Written informed consent was obtained from all participants.

MRI Acquisition

MR images were acquired on a single research-dedicated 1.5-T Signa system (General Electric Medical Systems, Waukesha, WI). The image protocol used for the analysis of brain infarcts and described in detail elsewhere[13] included a proton density/T2-weighted fast spin echo sequence, a fluid-attenuated inversion recovery (FLAIR) sequence, and a T2*-weighted gradient echo planar imaging sequence. Imaging at both time points used identical acquisition parameters.

MRI Semiquantitative Rating

Brain infarcts from both time points were rated semiquantitatively by 2 trained radiographers who recorded the presence, number, and location of the lesions. An infarct was defined as a defect of the brain parenchyma with a signal intensity isointense to that of cerebrospinal fluid on all sequences used for the rating (FLAIR, proton density/T2/T2* weighted).[14] All infarcts were included regardless of whether they were clinically apparent or not. Cortical infarcts were defined as defects involving or limited to the cortical ribbon and surrounded by an area of high signal intensity on FLAIR images (Figure 1A). Subcortical infarcts were defined as parenchymal defects not extending into the cortex, surrounded by an area of high signal intensity on FLAIR with a minimal size diameter of 4 mm (Figure 1B). This minimal size was used because for smaller parenchymal defects, it is harder to assess reliably whether they are based on perivascular spaces or lacunar infarcts. Defects surrounded by a rim of hemosiderin were excluded because it is not possible to distinguish parenchymal hematomas from hemorrhagic infarcts. The presence of hemosiderin was defined as an area of signal loss on T2*-weighted scans that was invisible or smaller on T2- and proton density-weighted images. Cerebellar infarcts were defined as parenchymal defects in the cerebellum. They were not required to have a surrounding rim of high signal intensity on FLAIR or T2-weighted images because cerebellar infarcts often lack such rims (Figure 1C and 1D). There were no size criteria for cortical nor cerebellar infarcts. Infarcts that spanned 2 different anatomic areas were assigned to the location with the largest diameter of the defect. Defects in the subcortical area without a rim or area of high signal intensity on FLAIR, with a minimal size diameter of 4 mm, and without evidence of hemosiderin were regarded as enlarged perivascular spaces and excluded.

Intra- and interobserver reliability was assessed for the 2 observers every 6 months and shown to be good. The intraobserver reliability (κ statistics) was 0.90 and 0.85 for cortical; 0.85 and 0.87 for cerebellar, and 0.89 and 0.93 for subcortical infarcts. The interobserver reliability for cortical, cerebellar, and subcortical infarcts was 0.82, 0.70, and 0.76, respectively.

Cognition and Dementia

The assessments of cognition and dementia have been described in detail elsewhere.[15] In brief, a battery of cognitive tests was administered to all participants and 3 cognitive domain scores calculated: memory, processing speed, and executive function. We computed sex-specific composite measures by averaging the standardized *Z* scores across the tests in each domain. A change in cognition was calculated separately by domain by subtracting the follow-up from baseline scores.

Participants with dementia were identified in a 3-step procedure described previously.[14] In brief, the Mini-Mental State Examination and the Digit Symbol Substitution Test were administered to all participants. Screen positives were administered a diagnostic battery of neuropsychological tests, and among them, screen positives were examined by a neurologist, and a proxy interview was administered. A consensus diagnosis, according to the international guidelines, was made by a panel of experts. In addition to case identification at the baseline and follow-up exams, all participants who attended the baseline examination were tracked for dementia diagnosis through vital statistics and hospital records, and the nursing and home-based Resident Assessment Instrument,[16] allowing for a more complete follow-up and less misclassification of cases as controls.

Analytic Sample

Of the 3316 participants who attended the follow-up study, 2612 participants (1070 men and 1542 women) were included in the final sample. Compared with these participants, the 704 excluded persons were more often men, more likely to be older, to have hypertension, diabetes mellitus, and atrial fibrillation. The reasons for exclusions were MRI contraindications and claustrophobia (n=595), disability or refusals preventing a visit to the MRI facility (n=59). Additional 50 persons were excluded because of the diagnosis of dementia at baseline (n=31) or missing dementia assessment (n=19). Of the 5764 participants in the baseline study, 4766 had baseline MRI. Participants with MRI at baseline and not included in the final sample with follow-up MRI had higher prevalence of brain infarcts, more white matter hyperintensity (WMH), volume, and lower relative brain volume relative to intracranial volume.

Symptomatic Infarcts

Prevalent strokes were obtained from medical records (69 of 2612 participants [3%]), 14% (11 of 69 participants) of which were adjudicated by a dementia neurologist, a stroke neurologist, and a neuroradiologist. This same adjudication process was used to diagnose all incident strokes, which included strokes that occurred between the first and second MRI (average 5.2 years between).

Statistical Analysis

All analyses were performed with SAS/STAT9.2 (SAS Institute Inc). For each infarct region (cortical, cerebellar, subcortical, and infarcts overall), subjects in the study sample were divided into 4 groups based on the absence/presence of infarcts: (1) no prevalent and no incident; (2) ≥1 prevalent and no incident; (3) no prevalent and ≥1 incident; and (4) ≥1 prevalent and ≥1 incident. Baseline characteristics of the study sample between infarct groups were compared using a general linear model after adjusting for age.

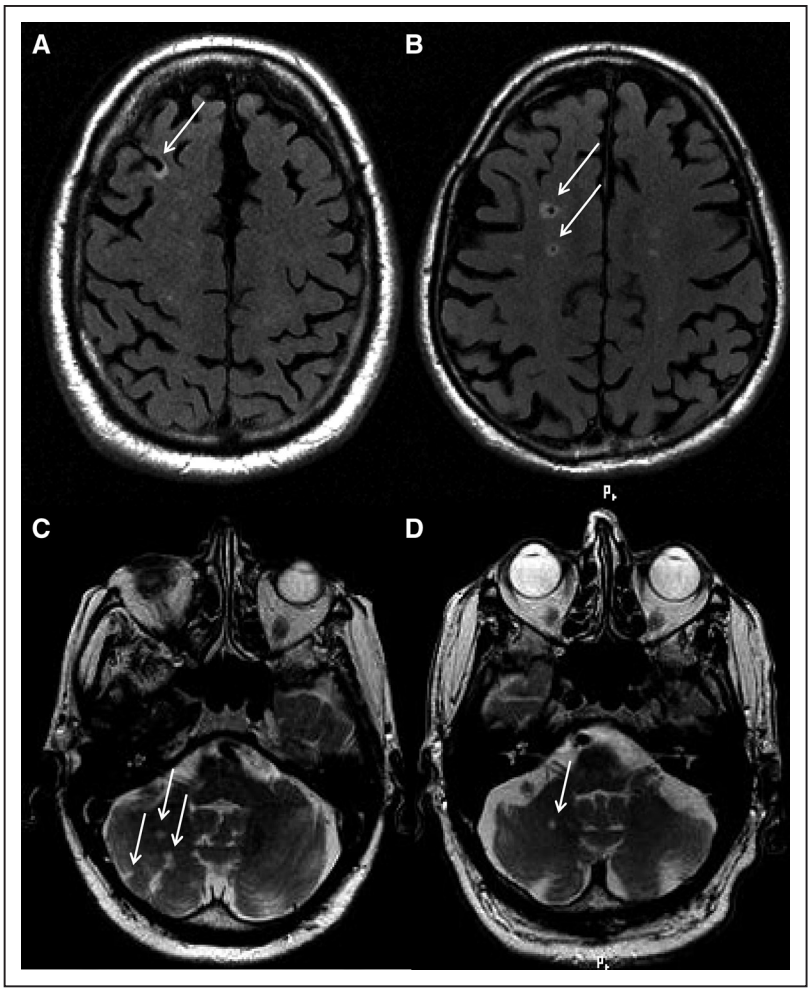

Figure 1. Example images of infarcts in subregions. **A**, Cortical infarct in the right frontal lobe on a fluid-attenuated inversion recovery (FLAIR) image. **B**, Subcortical infarcts on a FLAIR image in the right frontal lobe. **C** and **D**, Cerebellar infarcts on a T2-weighted image.

Modeling the association between infarct groups with longitudinal change in the different cognitive domains was performed using a random effects model (PROC-MIXED) for men and women separately. The longitudinal change in cognition was presented in *Z* scores with 95% confidence interval using time between MR scans as the time variable and adjusting for age at baseline. Multiplicative terms between time and infarct group and time and baseline age were tested, to allow for the different estimates of change over time among the 4 brain infarct groups and to test whether the change between brain infarct groups was statistically significant or not.

The relative risks (risk ratios) were estimated using a Poisson regression model with a robust variance estimator within PROC-GENMOD. The risk ratios of incident infarcts in relation to sex were estimated after adjusting for age and the time interval between MR scans. The analysis of the effect of sex was repeated after additionally adjusting for brain volume and vascular risk factors, including smoking (current and former), total serum cholesterol, high-density lipoprotein cholesterol, use of cholesterol-lowering medication, hypertension (use of antihypertensive medication, systolic blood pressure>140 mm Hg and diastolic blood pressure>90 mm Hg), C-reactive protein, and coronary artery calcium score.

Finally, the risk ratios of incident dementia were estimated in relation to the 4 groups of infarcts after adjusting for age, sex, and time interval between MR scans where the reference group was the group of persons without infarcts (model 1). These analyses were repeated after additionally adjusting for potential confounders: first, by adding baseline vascular risk factors and level of education (model 2), second, by additionally adding history of symptomatic brain infarcts (model 3), and third, by additionally adding baseline presence of brain microbleeds and baseline WMH volume (model 4), both MRI markers of manifest cerebral small vessel disease[17] Definitions of microbleeds and WMH are provided in the online-only Data Supplement).

Results

Overall, 803 of the 2612 participants (31%) had prevalent infarcts on MRI of whom 43 (5.4%) had clinical stroke events. Both men and women with ≥1 prevalent or incident infarct compared with men and women without infarcts were more likely to be older and to have higher coronary calcium (Table 1). For the same groups, men but not women were significantly more likely to have diabetes mellitus, atrial fibrillation, lower relative brain volumes, and cognitive scores for all domains (age-adjusted *P* value for all <0.05). The average time between baseline and follow-up assessments was 5.2±0.2 (mean±SD) years.

Incidence and Risk Estimates of Brain Infarcts

Overall, 545 of 2612 individuals had 1240 new brain infarcts in total with an average size of 8.5±6.0 mm and n=87 (7%) being larger than 15 mm. The cumulative incidence of new MRI detected infarcts over a mean period of 5.2 years was 20.9% (26.4% in men versus 17.0% in women). Of those with a new infarct on MRI, 37 (6.8%) had clinically recorded events. For cortical, cerebellar, and subcortical infarcts detected with MRI, the incidence was 7.8%, 13.0%, and 4.4%, respectively. The incidence in all regions was higher in men compared with

Table 1. Baseline Characteristics of Participants by Infarcts Overall and Sex

Characteristics	No Prevalent and No Incident		One or More Prevalent and No Incident		No Prevalent and One or More Incident		One or More Prevalent and One or More Incident	
	Men (n=567)	Women, (n=990)	Men, (n=220)	Women, (n=290)	Men, (n=113)	Women, (n=139)	Men, (n=170)	Women, (n=123)
Age, mean±SD	74.1±4.4	74.0±4.7	74.8±4.6	75.3±5.0	75.0±4.4	75.5±5.4	76.4±4.9	76.1±4.7
BMI, mean±SD	26.8±3.6	27.6±4.6	27.2±3.5	27.3±4.2	26.6±3.3	27.5±4.3	26.8±3.5	27.7±4.3
Hypertension (%)	74.4	75.6	80.5	83.5	75.2	80.6	81.8	82.9
Diabetes mellitus (%)	9.7	6.7	16.9	8.3	9.7	8.6	15.9	8.9
Smoking status (%)								
Never	28.9	52.6	25.5	51.7	32.7	53.6	32.4	57.7
Former	60.9	32.5	61.8	38.3	59.3	32.6	58.2	32.5
Current	10.2	15.0	12.7	10.0	8.0	13.8	9.4	9.8
Total cholesterol, mmol/L, mean±SD	5.3±1.1	6.0±1.1	5.0±1.0	5.9±1.1	5.4±1.1	5.9±1.2	5.1±1.0	6.0±1.0
Atrial fibrillation (%)	6.6	2.4	12.3	4.2	7.2	2.9	13.6	1.6
Coronary calcium, mean±SD	735±919	294±568	1061±1291	442±758	877±1112	416±607	1057±1168	521±743
Education level (%)								
Primary	14.1	25.0	12.8	23.8	10.8	23.2	11.2	29.5
Secondary	51.1	51.6	58.0	51.0	67.6	50.0	51.2	43.4
College	14.3	17.3	12.3	19.7	10.8	15.2	12.9	21.3
University	20.4	6.2	16.9	5.5	10.8	11.6	24.7	5.7
Cognition *Z* score, mean±SD								
Memory	–0.12±0.82	0.28±0.89	–0.21±0.86	0.26±0.84	–0.29±0.77	0.18±1.0	–0.44±0.76	0.03±0.82
Executive function	0.08±0.80	0.09±0.75	0.01±0.75	0.05±0.78	0.06±0.75	0.03±0.70	–0.25±0.78	–0.04±0.79
Processing speed	0.03±0.70	0.16±0.77	–0.02±0.74	0.16±0.73	–0.09±0.73	0.08±0.70	–0.20±0.79	–0.07±0.75
Relative brain volume (%)	72.2±3.4	74.3±3.6	71.1±3.2	73.3±3.4	71.7±3.3	73.8±3.5	70.9±3.6	73.1±3.2
Relative WMH volume (%)	0.94±0.84	0.97±1.04	1.34±1.26	1.27±1.17	1.11±1.10	1.43±1.51	1.65±1.33	1.70±1.65
Cerebral microbleeds (%)	25.2	13.1	44.7	23.4	22.8	14.9	31.8	19.4

BMI indicates body mass index; and WMH, white matter hyperintensity.

women, and the age-adjusted risk was significantly higher in men compared with women in all regions ($P<0.05$) with cortical infarcts having the strongest sex difference. After adjusting additionally for vascular risk factors and brain volume, the increased risk in men compared with women remained significant for all infarct regions except cerebellar (Table 2).

Prevalence and Incidence of Brain Infarcts and Cognitive Change

Individuals, especially men, with both prevalent and incident infarcts overall showed steeper cognitive decline in all domains compared with persons without infarcts (Figure 2). In men, this association was significant for all infarct regions

Table 2. Incidence and Risk of Brain Infarcts by Sex

Infarct Region	Overall (n=2612)	Men (n=1070)	Women (n=1542)	Men vs Women	
	Incidence, n (%)	Incidence, n (%)	Incidence, n (%)	Model 1; Risk Ratio (95% CI)	Model 2; Risk Ratio (95% CI)
Overall	545 (20.9)	283 (26.4)	262 (17.0)	1.8 (1.5–2.3)	1.5 (1.1–1.9)
Cortical	203 (7.8)	126 (11.8)	77 (5.0)	2.9 (2.1–4.0)	2.4 (1.6–3.7)
Cerebellar	340 (13.0)	162 (15.1)	178 (11.5)	1.3 (1.0–1.7)	1.0 (0.7–1.5)
Subcortical	116 (4.4)	68 (6.4)	48 (3.1)	2.3 (1.6–3.4)	1.9 (1.0–3.4)

Values in first 3 columns are number and percent of incident brain infarcts, overall and by sex. Values in last 2 columns are risk ratios with 95% confidence intervals (95% CIs). Model 1: adjusted for age and time interval between magnetic resonance scans. Model 2: additionally adjusted for brain volume and vascular risk factors. CI indicates confidence interval.

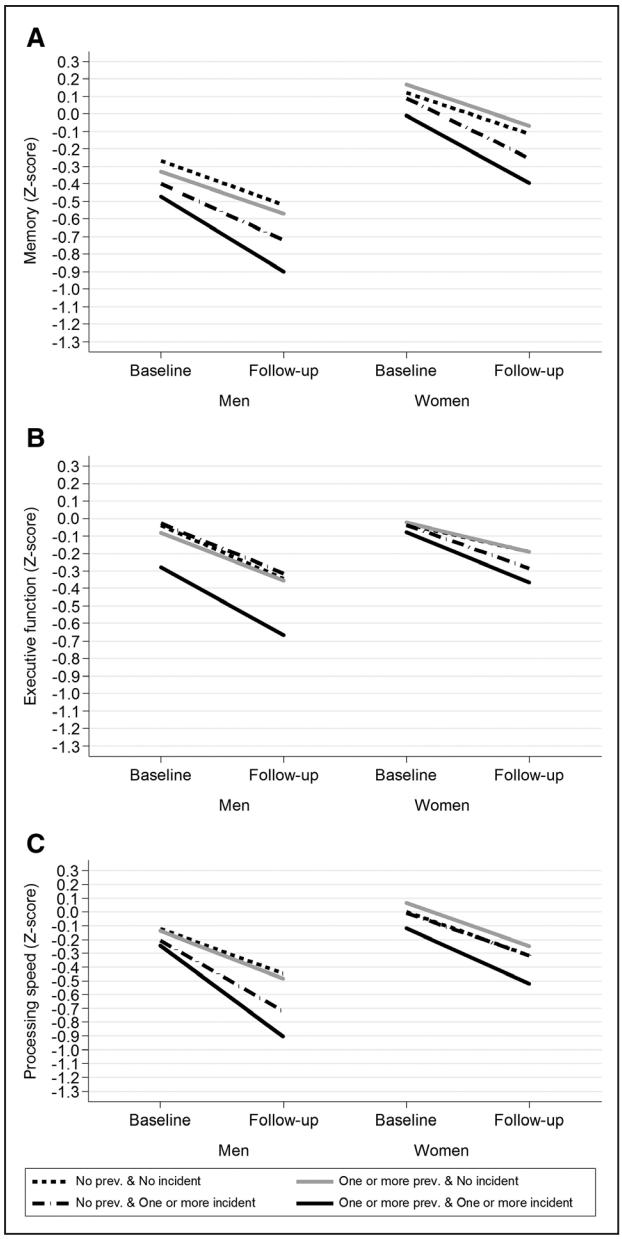

Figure 2. Infarcts overall: Mean change in cognition by prevalence and incidence of infarcts and sex. The graphs show mean change in (**A**) memory, (**B**) executive function, and (**C**) speed, respectively, for men and women by groups of prevalent and incident infarcts overall after adjusting for age and time interval between magnetic resonance imaging scans.

and domains except overall and cerebellar infarcts which were not significantly associated with performance in executive function (Tables I through IV in the online-only Data Supplement; Figures I through III in the online-only Data Supplement). In women, this association was significant for infarcts overall and performance in memory and executive function but not speed (Figure 1;Table I in the online-only Data Supplement). Further, in women, this association was only significant for cortical infarcts and performance in executive function (Tables II through IV in the online-only Data Supplement; Figures I through III in the online-only Data Supplement).

The Risk of Incident Dementia

Dementia was diagnosed in 120 (4.6%) at the study consensus meeting (including 86 with Alzheimer's disease, 21 with ascular dementia, 9 with other subtype, and 4 with mixed dementia), and 238 were identified later through vital statistics, hospital records, and the Resident Assessment Instrument. Therefore, a total of 358 (13.7%) became demented during 9-year average follow-up.

Persons with new brain infarcts showed an increased risk of incident dementia compared with persons without infarcts or persons with prevalent infarcts. The risk of incident dementia after adjusting for age, sex, and time interval between MRI scans was almost double for persons with both prevalent and incident infarcts (Table 3, model 1). This relationship was independent of vascular risk factors and level of education (model 2). This estimate remained statistically strong (P=0.009) after additionally adjusting for history of symptomatic infarcts (model 3), which attenuated risk estimate by 6% and by 18% after additionally adjusting for brain microbleeds and WMH volume (model 4). There was no significant interaction with sex in the relationship between overall infarcts and incident dementia (P=0.42).

Compared with those without infarcts or with prevalent infarcts only, the risk of dementia was higher in persons with incident infarcts only or both prevalent and incident infarcts in all subregions (Table 4). Of the 3 subregions, the risk for persons with new cortical infarcts was similar to the risk of having new infarcts in any brain region; 1.7 (95% confidence interval, 1.3–2.2). The risk of developing a new infarct was lowest for persons with cerebellar infarcts, 1.5 (95% confidence interval, 1.1–2.1), and highest for persons with subcortical infarcts, 2.6 (95% confidence interval, 1.9–3.4; Table 4). The relationship of dementia with infarcts by subregion was independent of vascular risk factors and level of education, but similar to the results on all infarcts, estimates were attenuated by 5% to 15% after additionally adjusting for symptomatic infarcts, brain microbleeds, and WMH volume. There were no significant interactions with sex in the relationship between infarcts in the subregions and dementia (data not shown).

Discussion

We found the incidence of brain infarcts to be almost double in men compared with women. Persons, especially, men with both incident and prevalent infarcts showed steeper cognitive decline than people without infarcts. The risk of incident dementia was 1.7-fold in those with both prevalent and incident infarcts compared with those without infarcts and was not significantly different in men compared with women. Of the brain subregions, incident subcortical infarcts contributed most to the development of dementia with 2.6-fold risk of incident dementia compared with persons without infarcts.

Three population-based imaging studies determined brain infarct incidence.[18–20] The overall incidence in these studies ranged from 9.5% to 18.5% in a 5-year follow-up period, which is consistent with the incidence in this study (20.9%) when considering age differences between these studies and an estimated 40% increase in relative risk of new infarcts for every 5 years of increasing age.[20]

Table 3. Relationship Between the Presence of Infarcts Overall and Incident Dementia

Overall Infarcts	Infarcts vs No Infarcts (n)		Model 1	Model 2	Model 3	Model 4
	Incident Dementia (n=358)	Without Dementia (n=2254)	Risk Ratio (95% CI)	Risk Ratio (95% CI)	Risk Ratio (95% CI)	Risk Ratio (95% CI)
No prevalent and no incident	169	1388	Reference	Reference	Reference	Reference
≥1 prevalent and no incident	65	445	1.0 (0.8–1.3)	1.1 (0.8–1.4)	1.0 (0.8–1.4)	1.0 (0.7–1.3)
≥1 incident and no prevalent	52	200	1.5 (1.2–2.00)	1.6 (1.2–2.1)	1.6 (1.2–2.1)	1.6 (1.2–2.1)
≥1 prevalent and ≥1 incident	72	221	1.7 (1.3–2.2)	1.7 (1.3–2.2)	1.6 (1.2–2.1)	1.4 (1.1–1.9)

Values show number of persons with infarcts overall vs those without infarcts in groups of persons with and without incident dementia together with the risk ratios of incident dementia by infarct group. Risk ratios are with 95% confidence intervals (95% CIs). Model 1: adjusted for baseline age, sex, and time interval between magnetic resonance imaging scans. Model 2: additionally adjusted for vascular risk factors and education. Model 3: additionally adjusted for symptomatic infarcts. Model 4: additionally adjusted for brain microbleeds and white matter hyperintensity volume. CI indicates confidence interval.

The age-adjusted risk of incident infarcts overall in men compared with women was 1.8-fold higher and 2.9-fold higher in the cortical region. Conversely, 2 other studies of the older general population found no significant difference in brain infarct incidence between men and women,[19,20] and most studies examining brain infarct prevalence do not support a sex disparity in infarct risk.[5] In our study, men were at greater risk than women of developing new brain infarcts in all subregions. However, after adjusting additionally for vascular risk factors and brain volume, the risk remained significant for cortical and subcortical infarcts only, suggesting that the sex difference is driven by disease in both large and small vessels.

Table 4. Relationship Between the Presence of Cortical, Cerebellar, and Subcortical Infarcts and Incident Dementia

Infarct Region/Infarct Groups	Infarcts vs No Infarcts		Risk Ratio (95% CI)
	Incident Dementia (n=358)	Without Dementia (n=2254)	
Cortical			
No prevalent and no incident	267	1928	Reference
≥1 prevalent and no incident	39	175	1.3 (1.0–1.7)
No prevalent and ≥1 incident	32	97	1.7 (1.3–2.2)
≥1 prevalent and ≥1 incident	20	54	1.5 (1.00–2.2)
Cerebellar			
No prevalent and no incident	234	1643	Reference
≥1 prevalent and no incident	50	345	0.9 (0.7–1.2)
No prevalent and ≥1 incident	39	155	1.2 (0.9–1.6)
≥1 prevalent and ≥1 incident	35	111	1.5 (1.1–2.1)
Subcortical			
No prevalent and no incident	290	2050	Reference
≥1 prevalent and no incident	27	129	1.2 (0.8–1.6)
No prevalent and ≥1 incident	32	48	2.6 (1.9–3.4)
≥1 prevalent and ≥1 incident	9	27	1.9 (1.1–3.3)

Values show number of subjects with infarcts in the various regions vs those with no infarcts in corresponding regions in the groups of subjects with and without incident dementia together with the risk ratios of incident dementia by infarct group. Risk ratios are with 95% confidence intervals (95% CIs) adjusted for baseline age, sex, and time interval between magnetic resonance imaging scans. CI indicates confidence interval.

We found a trend of greater decline in cognitive function with increased overall infarct load. Persons with both prevalent and incident infarcts showed a steeper decline in cognition compared with persons without infarcts or persons with only prevalent or only incident infarcts. This relationship was stronger and more often significant in men than in women for all infarct regions and cognitive domains. Men with prevalent and incident cortical and subcortical infarcts showed significantly more cognitive decline than men without infarcts in all cognitive domains.

This study showed a significant increase in the risk of dementia in persons with new brain infarcts. Several clinical MRI studies have revealed increased odds of dementia in subjects with brain infarcts[21–23] but others not.[24] Four population-based studies assessed this relationship, 1 using a cross-sectional design[25] and 3 using a longitudinal design.[10–12] Results from the Chicago Health and Aging Project[25] showed no significant relationship between overall infarcts and dementia but did find that persons with cortical infarcts were 4-fold more likely to have dementia. Our results are similar to the 3 longitudinal cohort studies where the presence of overall brain infarcts was shown to increase the risk of dementia. However, two of these studies did not have information on incident infarcts from a follow-up MRI[10,12] so there was no information on how those new infarcts may contribute to developing dementia. As we have shown, additional new infarcts are associated with more cognitive decline and an even higher risk for dementia than just having prevalent infarcts. Together our findings may well indicate a pattern of stepwise decline after the first infarct and that new infarcts trigger steeper cognitive decline and increase the risk of dementia. There was also no assessment of the specific subregions we investigated[10–12] which provides information about the location of the vascular damage, which has clinical implications.

Although evidence has accumulated that vascular abnormalities and brain infarcts contribute to the development of dementia, limited information exists on whether this contribution differs by brain regions. Alzheimer's disease and small vessel disease share risk factors that lead to cognitive decline and dementia.[26] In clinical pathological studies, it has been demonstrated that individuals with subcortical infarcts are more likely to have dementia or require fewer plaques and tangles for a clinical diagnosis of Alzheimer's disease.[27,28] Subcortical infarcts found by MRI are a measure of small

vessel disease.[17] Our results showed that persons with new subcortical infarcts on MRI were >2-fold more likely to have incident dementia, even after adjusting for microbleeds and WMH volume that are other MRI markers of manifest small vessel disease. The association of cortical and cerebellar infarcts with incident dementia was not as strong as for subcortical infarcts. This may indicate that infarcts of small vessel disease origin contribute more to the development of dementia than infarcts of embolic origin in larger vessels.

Strengths of this study include the very large well-characterized longitudinal cohort of older persons from the general population with a high number of incident dementia events. To the best of our knowledge, this is the first imaging study of a population-based cohort to report the incidence of infarcts and their associations with dementia in the subregions included in this study. However, persons with higher prevalence and incidence of brain infarcts may have been underrepresented as those not included in the sample were more often men, more likely to be older, to have hypertension, to have diabetes mellitus, and to have atrial fibrillation.

Conclusions

The cumulated 5.2-year incidence of brain infarcts in the elderly general population is >20%. Men are at greater risk of developing incident brain infarcts than women, particularly in the cortical region. Persons with incident brain infarcts decline faster in cognition and have an increased risk of dementia compared with those free of such lesions. The risk is higher in those with both prevalent and incident infarcts compared with those with either alone, suggesting a cascade where additional infarcts dispose people toward clinical dementia. Incident subcortical infarcts contribute more than cortical and cerebellar infarcts to incident dementia which may indicate that infarcts of small vessel disease origin contribute more to the development of dementia than infarcts of embolic origin in larger vessels.

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Disclosures

None.

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