Cerebrovascular risk-factors of prevalent and incident brain Infarcts in the general population: the AGES-Reykjavik study

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Stroke

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Cerebrovascular Risk-Factors of Prevalent and Incident Brain Infarcts in the General Population: The AGES-Reykjavik Study

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BACKGROUND: Studies on the association of cerebrovascular risk factors to magnetic resonance imaging detected brain infarcts have been inconsistent, partly reflecting limits of assessment to infarcts anywhere in the brain, as opposed to specific brain regions. We hypothesized that risk-factors may differ depending on where the infarct is located in subcortical-, cortical-, and cerebellar regions.

METHODS: Participants (n=2662, mean age 74.6±4.8) from the longitudinal population-based AGES (Age, Gene/Environment Susceptibility)-Reykjavik Study underwent brain magnetic resonance imaging at baseline and on average 5.2 years later. We assessed the number and location of brain infarcts (prevalent versus incident). We estimated the risk-ratios of prevalent (PRR) and incident (IRR) infarcts by baseline cerebrovascular risk-factors using Poisson regression.

RESULTS: Thirty-one percent of the study participants had prevalent brain infarcts and 21% developed new infarcts over 5 years. Prevalent subcortical infarcts were associated with hypertension (PRR, 2.7 [95% CI, 1.1–6.8]), systolic blood pressure (PRR, 1.2 [95% CI, 1.1–1.4]), and diabetes (PRR, 2.8 [95% CI, 1.9–4.1]); incident subcortical infarcts were associated with systolic (IRR, 1.2 [95% CI, 1.0–1.4]) and diastolic (IRR, 1.3 [95% CI, 1.0–1.6]) blood pressure. Prevalent and incident cortical infarcts were associated with carotid plaques (PRR, 1.8 [95% CI, 1.3–2.5] and IRR, 1.9 [95% CI, 1.3–2.9], respectively), and atrial fibrillation was significantly associated with prevalent cortical infarcts (PRR, 1.8 [95% CI, 1.2–2.7]). Risk-factors for prevalent cerebellar infarcts included hypertension (PRR, 2.45 [95% CI, 1.5–4.0]), carotid plaques (PRR, 1.45 [95% CI, 1.2–1.8]), and migraine with aura (PRR, 1.6 [95% CI, 1.1–2.2]). Incident cerebellar infarcts were only associated with any migraine (IRR, 1.4 [95% CI, 1.0–2.0]).

CONCLUSIONS: The risk for subcortical infarcts tends to increase with small vessel disease risk-factors such as hypertension and diabetes. Risk for cortical infarcts tends to increase with atherosclerotic/coronary processes and risk for cerebellar infarcts with a more mixed profile of factors. Assessment of risk-factors by location of asymptomatic infarcts found on magnetic resonance imaging may improve the ability to target and optimize preventive therapeutic approaches to prevent stroke.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ blood pressure ■ brain infarction ■ hypertension ■ magnetic resonance imaging ■ risk factors

Brain infarcts in older persons are common findings on magnetic resonance (MR) images and most do not cause signs or symptoms that are clinically diagnosed as stroke.[1,2] It is unclear why most infarcts tend to be asymptomatic. It has been suggested that this may be associated with size and location of infarcts.[3] Asymptomatic infarcts have been associated with higher risk of stroke, dementia, and early mortality.[4] Results on the prevalence and incidence of brain infarcts have differed across population-based studies and the association of

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AGES-Reykjavik Study	Age Gene/Environment Susceptibility-Reykjavik
Aβ	amyloid-β
HDL	high-density lipoprotein cholesterol
LDL	low-density lipoprotein cholesterol
MR	magnetic resonance
MRI	magnetic resonance imaging

brain infarcts with risk-factors have reported inconsistent and conflicting findings. As demonstrated in a systematic review,[5] results on the association of brain infarcts with risk-factors in cohort studies have varied greatly with only age and hypertension consistently shown as significant risk-factors. Significant associations between infarcts and heart failure, carotid, and coronary artery disease are likely. However, the association between infarcts and potential risk-factors including sex, tobacco consumption, dyslipidemia, atrial fibrillation, and diabetes remains unclear.[5] While clinical strokes are characterized by risk-factors and location most MR imaging (MRI)-defined asymptomatic infarcts are limited to infarcts anywhere in the brain without separate assessment for infarct subtypes.

In this study, we assessed the association of MRI identified prevalent and incident brain infarcts located in the subcortical, cortical, and cerebellar regions to vascular, atherosclerotic, and embolic risk-factors. Data are from a large well-described population-based cohort of older men and women participating in the AGES-Reykjavik Study (Age Gene/Environment Susceptibility-Reykjavik Study).

METHODS

Data Availability

Data from the AGES-Reykjavik study are available through collaboration (AGES_data_request@hjarta.is) under a data usage agreement with the IHA.

Study Population

The AGES-Reykjavik Study described previously[6] is a population-based study aimed to investigate the genetic and environmental factors contributing to clinical and subclinical disease at older age. The baseline exam (2002–2006) on 5764 men and women was followed by a second exam 5 years later from 2007 to 2011. 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 and Rating of Infarcts

Identical MRI acquisition protocols were used at both time points. Standardized criteria were established to reliably identify brain infarcts in the cortical, subcortical, and cerebellar regions and excluding subcortical lesions smaller than 4 mm to minimize misdiagnosis of dilated perivascular spaces.[7] The identification of subcortical infarcts was made in accordance with expert guidance that provided definitions and neuroimaging standards for markers and consequences of small vessel disease.[8] The MRI acquisition and semi-quantitative rating of brain infarcts have been described elsewhere[9] and are also described in detail together with the rating reliability in the Supplemental Material.

Cerebrovascular Risk-Factors

These include hypertension, systolic blood pressure, and diastolic blood pressure, diabetes, smoking, atrial fibrillation (AF), the presence of carotid plaques, migraine, total cholesterol, HDL (high-density lipoprotein) cholesterol, and Agatston coronary artery calcium, a marker of atherosclerosis. Blood pressure was assessed from the mean value of 2 measurements using a large-cuff mercury sphygmomanometer. Hypertension (current or former) was defined as measured systolic blood pressure 140 mm Hg or higher, diastolic blood pressure 90 mm Hg or higher, self-reported doctors diagnosis of hypertension, or use of antihypertensive medications. Diabetes was defined as history of diabetes, use of glucose-modifying medication, or fasting blood glucose of >7 mmol/L. Smoking status was assessed by questionnaire in categories of current and noncurrent (never/former) smokers. AF was identified by reviewing hospital records and private physicians records for all participants with the hospital discharge diagnosis codes for AF from any hospital in Reykjavik from January 1, 1987 until the day of the study examination and by reviewing a 12-lead ECG performed during the baseline study visit. The AF classification for this study included those with persistent or paroxysmal AF.[10] The assessment of carotid plaque was based on imaging with ultrasound of a predefined segment in each common carotid artery. Of the left and right carotid bifurcation and internal carotid artery the presence of a plaque was assessed semi-quantitatively. The most severe lesion per location were assessed as none, minimal, moderate and severe. In this study, only plaques at least moderate in size were included. The definition of a moderate plaque was at least one, clear, reasonable easy to be visualized plaque causing at least some diameter reduction of the vessel lumen. Migraine was defined as self-reported doctors diagnosis of migraine headache, current, or former. Positives were subclassified into those who had experienced visual aura with headaches or not. High-density lipoprotein cholesterol were measured in fasting blood samples using reagents from Roche Diagnostics (Mannheim, Germany) on a Hitachi 912 analyzer (Hitachi Ltd, Tokyo, Japan), according to the manufacturers instructions. Coronary calcium Agatston score was measured using computed tomography.

Symptomatic Infarcts

Prevalent strokes were obtained from medical records (69 of 2662 participants [3%]), 14% (11 of 69 participants) of which were adjudicated by a dementia neurologist, a stroke neurologist and a neuroradialogist. This same adjudication process was

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used to diagnose all incident strokes, which included strokes that occurred between the first and second MRI (average 5.2 years between). Based on mortality records, 49 of 520 (9%) deaths among participants with baseline data occurred because of stroke before invitation to the follow-up study.

Analytic Sample

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 were older, had more coronary calcium, were more likely to be smokers, to have hypertension, diabetes, carotid plaque, and atrial fibrillation.

Of the 4766 baseline participants, there were 3316 participants who attended the follow-up study and 2662 participants (1097 men and 1565 women) who had a second MRI and were included in the final sample. The reasons for no follow-up MRI were MRI contraindications (n=391) and claustrophobia (n=204), disability or refusals (n=59). Compared with these participants, the 654 excluded persons were more often men, more likely to be older, to have hypertension, diabetes, and atrial fibrillation (please Figure S1, Study Flow Diagram in the Supplemental Material). Of the 2662 subjects in the final sample <1% had missing values for each risk-factor except for carotid plaques where 5% had missing values. Available case analysis was performed. Sensitivity analysis using multiple imputation for missing data for the risk-factors did not change the results (data not shown).

Statistical Analysis

All analyses were performed with PROC-GENMOD and PROC-LOGISTIC in SAS/STAT®9.2 (SAS Institute Inc). The relative risks (risk-ratios) were estimated using a Poisson regression model with a robust sandwich variance estimator and presented with 95% CIs. The risk-ratios of prevalent infarcts in relation to risk-factors one at a time (univariate analysis) were estimated after adjusting for age and sex. The risk-ratios of incident infarcts in relation to risk-factors were additionally adjusted for the time interval between MR scans. The risk-ratios of infarcts in relation to total cholesterol and HDL were additionally adjusted for the use of lipid lowering medication.

To determine the association of risk-factors with infarcts independent of one another, a multivariate analysis was conducted using Poisson regression, including risk-factors that showed significant associations with infarcts in the univariate analysis. To test the robustness of the Poisson models, a sensitivity analysis was performed using logistic regression.

To test the hypothesis that risk-factor effects vary depending on the location of brain infarcts we assessed the interaction across brain regions for each risk-factor. We also assessed the interaction between the various risk-factors in a multivariable model to test for effect modification (for details, please see the Supplemental Material).

The present study used STROBE reporting guidelines[12] (Supplemental Material).

RESULTS

Compared with those with no infarcts, participants with brain infarcts were more likely to be older, to have hypertension, migraine with visual aura, diabetes, atrial fibrillation, to use lipid lowering medication (statins in 99% of cases), to use blood pressure medication, to use anticoagulation medication and to have more coronary calcium (age adjusted *P* value for all <0.05; Table 1). The average time between baseline and follow-up assessments was 5.2±0.2 (mean±SD) years. In this sample of 2662 persons, 826 (31%) had prevalent infarcts and 559 (21%) new infarcts. Of those individuals with prevalent infarcts, 441 (53%) had only one infarct and 385 (47%) had 2 or more infarcts. Of those with new infarcts, 335 (60%) had only one new infarct and 224 (40%) had 2 or more new infarcts. For more detailed number of infarcts rated per individual, overall and by subregions, please see Tables S1 and S2. Of those with prevalent infarcts on MRI, only 5% had clinically recorded events and of those with new infarcts on MRI, 7% had clinically recorded events. Among those cases, 3% of individuals with prevalent infarcts and 2% of individuals with incident infarcts had evidence of prior transient ischemic attack. For subcortical-, cortical-, and cerebellar infarcts the prevalence was 7.6%, 11.2%, and 20.9% respectively and the cumulative incidence over 5 years, 4.5%, 7.9%, and 13.0%, respectively (Table 2). The risk of infarcts in all regions increased significantly with increasing age, except for incident subcortical infarcts where the increased risk was marginally significant. The age adjusted risk of

Table 1. Baseline Characteristics of Persons Without and With Prevalent Overall Infarcts

Characteristics	Without infarcts (n=1836)	With infarcts (n=826)	*P* value
Age, y	74.3±4.7	75.6±4.9	<0.001
Men, %	37.7	49.0	<0.001
Hypertension, %	75.6	82.5	<0.001
Systolic BP, mm Hg	140.3±19.6	142.9±20.1	0.002
Diastolic BP, mm Hg	74.1±9.3	74.3±9.5	0.627
Migraine, %	12.6	12.9	0.907
Migraine with aura, %	5.4	7.0	0.118
Diabetes, %	8.0	12.6	<0.001
Use of lipid lowering medication, %	21.2	29.8	<0.001
Total cholesterol, mmol/L	5.7±1.1	5.5±1.1	<0.001
High-density lipoprotein, mmol/L	1.6±0.4	1.6±0.4	0.096
Smoking (current), %	10.8	10.8	1.000
Smoking (quit), %	44.1	48.3	0.051
Agatston coronary calcium	486.1± 799.1	768.0± 1061.0	<0.001
Atrial fibrillation, %	4.0	8.4	<0.001
Carotid plaque (≥mod plaque), %	59.5	67.6	<0.001
Use of BP lowering medication, %	57.7	66.2	<0.001
Use of antithrombotic medication, %	14.3	21.1	<0.001

Values are unadjusted means±SD or percentages. BP indicates blood pressure.

Table 2. Prevalence and Incidence of Brain Infarcts

Infarct region	Prevalence, n (%)	Incidence, n (%)
Overall	826 (31.0)	559 (21.0)
Subcortical	202 (7.6)	119 (4.5)
Cortical	298 (11.2)	209 (7.9)
Cerebellar	556 (20.9)	346 (13.0)

Values are number and percent of prevalent and incident brain infarcts by brain region in the same sample of 2662 participants from the AGES-Reykjavik study (Age Gene/Environment Susceptibility-Reykjavik Study).

both prevalent and incident infarcts was higher in men compared with women in all infarct regions, with cortical infarcts having the strongest sex difference and cerebellar the smallest (Tables 3 and 4).

Association Between Cerebrovascular Risk-Factors and Prevalent Infarcts

Of the cerebrovascular risk-factors included in this study, hypertension, elevated systolic blood pressure, diabetes, and coronary calcium all significantly associated the presence of infarcts overall and specifically subcortical infarcts. Of those same risk-factors, only coronary calcium was significantly associated with cortical infarcts whereas hypertension and coronary calcium were significantly associated with cerebellar infarcts (Table 3).

Atrial fibrillation, carotid plaques, the use of lipid lowering medication and coronary calcium were significantly associated with infarcts overall and specifically with cortical infarcts. These same risk-factors except for atrial fibrillation were significantly associated with cerebellar infarcts while none except for coronary calcium associated subcortical infarcts (Table 3).

Migraine with visual aura was significantly associated with prevalent infarcts overall and specifically cerebellar infarcts. The association of diastolic blood pressure, smoking, migraine overall, total cholesterol, and HDL with infarcts was nonsignificant for all infarct regions (Table 3).

Association Between Cerebrovascular Risk-Factors and Incident Infarcts

Elevated systolic blood pressure and diastolic blood pressure were significantly associated with new subcortical infarcts; carotid plaques and coronary calcium were associated with infarcts overall and specifically new cortical infarcts. Hypertension, overall migraine and coronary calcium were significantly associated with incident cerebellar infarcts. Diabetes, smoking, atrial fibrillation, migraine with visual aura, the use of lipid lowering medication, and cholesterol were not significantly associated with incident infarcts (Table 4). Adjusting additionally for the use of antithrombotic medication only slightly altered risk-ratios for some risk-factors without changing the significance.

Risk Factor Associations Stratified by Presence or Absence of Baseline Infarcts

Of the 1836 persons without infarcts at baseline, 258 (14.1%) had at least one new infarct detected on the

Table 3. Relationship Between Risk-Factors and Risk of Prevalent Brain Infarcts

	Risk-ratios of prevalent brain infarcts (RR, 95% CI)			
Potential risk-factor	Overall	Subcortical	Cortical	Cerebellar
Age per 5 years	1.30 (1.19–1.40)	1.43 (1.26–1.63)	1.28 (1.10–1.47)	1.26 (1.13–1.40)
Sex (men vs women)	1.75 (1.48–2.08)	2.03 (1.49–2.77)	2.55 (1.92–3.37)	1.42 (1.15–1.75)
Hypertension (yes versus no)	2.06 (1.41–3.02)	2.69 (1.06–6.84)	1.42 (0.84–2.42)	2.45 (1.49–4.03)
Systolic BP	1.11 (1.02–1.21)	1.23 (1.06–1.44)	1.05 (0.93–1.19)	1.12 (0.99–1.26)
Diastolic BP	1.03 (0.95–1.12)	1.10 (0.96–1.25)	0.94 (0.83–1.06)	1.07 (0.95–1.19)
Diabetes (yes versus no)	1.40 (1.11–1.75)	2.81 (1.92–4.11)	1.31 (0.91–1.89)	1.11 (0.80–1.52)
Smoking (current versus never)	1.26 (0.91–1.74)	1.08 (0.66–1.78)	1.20 (0.76–1.91)	1.33 (0.86–2.06)
Smoking (quit versus never)	1.03 (0.86–1.24)	1.23 (0.86–1.74)	1.01 (0.77–1.33)	1.00 (0.79–1.25)
Atrial fibrillation	1.44 (1.08–1.91)	0.97 (0.50–1.90)	1.78 (1.17–2.70)	1.39 (0.99–1.96)
Carotid plaque (≥mod plaque)	1.51 (1.26–1.82)	1.31 (0.92–1.87)	1.81 (1.32–2.49)	1.45 (1.16–1.80)
Migraine (yes versus no)	1.14 (0.90–1.43)	0.96 (0.58–1.60)	1.11 (0.71–1.74)	1.19 (0.92–1.55)
Migraine with aura (yes versus no)	1.50 (1.12–2.02)	1.17 (0.58–2.37)	1.56 (0.84–2.91)	1.56 (1.13–2.15)
Use of lipid lowering medication (yes versus no)	1.63 (1.36–1.95)	1.39 (0.99–1.96)	2.02 (1.53–2.68)	1.52 (1.21–1.91)
Total cholesterol*	0.97 (0.88–1.08)	0.90 (0.75–1.09)	0.96 (0.81–1.14)	1.04 (0.93–1.15)
High-density lipoprotein*	0.95 (0.87–1.04)	0.96 (0.80–1.14)	0.98 (0.83–1.14)	0.94 (0.84–1.06)
Agatston coronary calcium	1.31 (1.17–1.46)	1.28 (1.06–1.55)	1.40 (1.16–1.70)	1.27 (1.11–1.46)

For continuous risk factors, the unit of difference was 1 SD, except for age where it was 5 y. All risk-ratios are adjusted for age and sex. BP indicates blood pressure; and RR, risk-ratio.

*Additionally adjusted for use of lipid lowering medication.

Table 4. Relationship Between Risk-Factors and Risk of Incident Brain Infarcts

Potential risk-factor	Risk-ratios of incident brain infarcts (RR, 95% CI)			
	Overall	Subcortical	Cortical	Cerebellar
Age per 5 years	1.45 (1.25–1.70)	1.19 (0.99–1.43)	1.59 (1.28–1.97)	1.45 (1.24–1.69)
Sex (men versus women)	1.83 (1.49–2.25)	2.27 (1.54–3.33)	2.85 (2.05–3.95)	1.32 (1.03–1.70)
Presence at baseline (1+ versus 0)	3.06 (2.50–3.75)	5.76 (3.89–8.52)	4.26 (3.00–6.06)	2.96 (2.28–3.86)
Hypertension (yes versus no)	1.93 (1.21–3.07)	1.40 (0.54–3.62)	1.29 (0.61–2.76)	3.27 (1.59–6.74)
Systolic blood pressure	1.09 (0.99–1.19)	1.20 (1.03–1.40)	1.02 (0.88–1.19)	1.10 (0.99–1.23)
Diastolic blood pressure	1.02 (0.90–1.16)	1.29 (1.02–1.64)	0.89 (0.72–1.10)	1.04 (0.91–1.20)
Diabetes (yes versus no)	1.21 (0.86–1.71)	1.54 (0.92–2.60)	1.03 (0.61–1.73)	1.25 (0.85–1.82)
Smoking (current versus never)	1.00 (0.71–1.42)	1.00 (0.53–1.88)	0.84 (0.51–1.39)	1.11 (0.70–1.75)
Smoking (quit versus never)	0.96 (0.76–1.21)	0.94 (0.61–1.45)	0.90 (0.62–1.29)	1.01 (0.76–1.34)
Atrial fibrillation	1.09 (0.73–1.64)	0.64 (0.27–1.51)	1.31 (0.68–2.52)	1.07 (0.68–1.69)
Carotid plaque (≥mod plaque)	1.27 (1.01–1.59)	1.03 (0.68–1.57)	1.93 (1.29–2.89)	1.07 (0.81–1.40)
Migraine (yes versus no)	1.24 (0.94–1.63)	0.79 (0.40–1.58)	1.16 (0.72–1.88)	1.40 (1.00–1.96)
Migraine with aura (yes versus no)	1.44 (0.96–2.16)	1.19 (0.51–2.82)	1.78 (0.98–3.24)	1.33 (0.79–2.24)
Use of lipid lowering medication (yes versus no)	1.03 (0.81–1.31)	0.92 (0.61–1.40)	1.28 (0.89–1.84)	0.92 (0.69–1.22)
Total cholesterol*	0.95 (0.80–1.12)	0.89 (0.69–1.16)	1.09 (0.85–1.40)	0.89 (0.75–1.06)
High-density lipoprotein*	0.94 (0.82–1.08)	0.99 (0.79–1.23)	0.93 (0.75–1.14)	0.93 (0.80–1.09)
Agatston coronary calcium	1.19 (1.06–1.33)	1.05 (0.83–1.32)	1.29 (1.05–1.59)	1.18 (1.03–1.35)

For continuous risk-factors, the unit of difference was 1 SD, except for age where it was 5 y. All risk-ratios are adjusted for age, sex and time interval between MR scans. BP indicates blood pressure; and RR, risk-ratio.

*Additionally adjusted for use of lipid lowering medication.

second MRI, while of the 826 persons with at least one infarct at baseline, 301 (36.4%) had at least one new infarct. Having a brain infarct at baseline was strongly associated with developing new infarcts in all brain regions. The age- and sex adjusted relative-risk was strongest for subcortical infarcts, 5.76 (95% CI, 3.89–8.52) and least strong for cerebellar infarcts, 2.96 (95% CI, 2.28–3.86; Table 4). Among those with no infarct at baseline, the risk-factors of incident infarcts included age, sex, hypertension, and coronary calcium. Sex and hypertension were the strongest risk factors for new infarcts in the group with prevalent infarcts, and coronary calcium were stronger in the group without prevalent infarcts (Table S3). The risk factor related risk of incident infarcts in the specific subregions did not differ depending on presence or absence of prevalent infarcts (data not shown).

Association Between Cerebrovascular Risk-Factors and Infarcts Based on Multivariate Analysis

The multivariate analysis showed an attenuation in risk-ratios for most risk-factors due to confounding effects. Yet, most risk factors that were significantly associated with brain infarcts in the univariate analysis remained significantly associated with infarcts in the multivariate analysis. The use of lipid lowering medication becomes significantly protective for incident brain infarcts in the multivariate analysis. This can be explained by the strong confounding effect of having a prevalent infarct; considerably higher proportion of individuals with prevalent infarcts use lipid lowering medication (30%) compared with individuals without infarcts (20%; Table 1). For results from multivariate analysis, please see Tables S4 and S5.

Sensitivity analysis using logistic regression models showed similar results with respect to significant associations (Tables S6 through S9).

Tests for difference in effects size across brain regions for each of the risk factors showed that for prevalent infarcts there was a statistically significant difference in the effect size associated with diabetes (P=0.007) among the brain regions as shown in Table 3. For incident infarcts, there was a statistically significant difference in the effect size associated with prevalent infarct (P=0.04) and carotid plaque (P=0.01) among the brain regions as shown in Table 4.

None of the tests for interactions of the risk-factors were statistically significant at the significance level for interactions. Interactions with sex were not significant.

DISCUSSION

In this study, prevalent and incident infarcts in different brain regions detected with MRI were associated with different risk-factor profiles. Cerebrovascular risk-factors that have been shown consistently in other studies to be associated with small vessel disease including elevated systolic blood pressure and diastolic blood pressure, hypertension, and diabetes were associated with higher risk of subcortical infarcts than with cortical infarcts. The embolic risk factors, carotid plaques, and atrial fibrillation were more likely to be associated with cortical infarcts than with subcortical- and cerebellar infarcts. Furthermore, migraine was specifically associated with cerebellar infarcts. Otherwise, cerebellar infarcts share risk-factors with subcortical- and cortical infarcts. Although brain infarcts at baseline were strongly associated with new infarcts in all brain regions, the risk of new infarcts by cerebrovascular risk factors was similar between those with versus without prevalent infarcts.

A major strength of this study was the available information of prevalent and incident infarcts by brain region, making it possible to explore if different risk factors exist for the various infarct subtypes. There are 3 different major causes of brain infarcts. On average, ≈50% of infarcts are due to large vessel atherosclerosis and rupture of an atherosclerotic plaque, 20% are caused by cardio embolism, and ≈25% are thought to manifest as lacunar infarcts due to small vessel disease and probably occlusion of deep perforating arteries.[13] Small vessel pathologies are thought to be the most common cause of subcortical infarcts (lacunes), although the underlying mechanism is unclear.[14] Pathophysiologic processes thought to contribute to subcortical infarcts include endothelial and vascular dysfunction, arteriosclerosis, lipohyalinosis, arteriolosclerosis, glycation of proteins, and deposition of B-amyloid in the vessel wall,[15,16] leading to occlusion of the vessel.[14] Another characteristic of small vessel disease is the deposition of Aβ (amyloid-β) protein in cerebral blood vessel walls (cerebral amyloid angiopathy),[17,18] which may lead to impaired autoregulation, endothelial dysfunction, thickening of the vessel wall or even vessel occlusion, thereby inducing hypoperfusion and ischemia around the amyloid affected vessels.[19] There has been a widespread view that subcortical infarcts are mainly caused by damage to small arterioles by high blood pressure, with lipohyalinosis or fibrinoid necrosis. When these small vessels occlude the result is lacunar infarction.[20] Diabetes is another risk-factor traditionally linked with infarcts from small vessels. In diabetes, it is assumed that glycation of proteins and diffuse basement membrane thickening leads to narrowing of the vessel lumen and tortuosity, which lengthens the distance blood must travel to perfuse its targets, resulting in lacunar infarcts.[21]

Emboli becomes the most frequent cause of brain infarcts with increasing age.[22] Most emboli are fragments of blood clots that originate in the heart or major vessels. Conditions causing cardiac emboli include myocardial infarcts, atrial fibrillation, rheumatic heart disease, mitral valve prolapse, prosthetic heart valve, calcified mitral annulus, and cardiomyopathy.[23] Some emboli consist of atheromatous material that is detached from ulcerated atheromas of the aorta or carotid arteries.[24,25] Cholesterol crystals from ruptured plaques may embolize distal vessels.[26]

In this study, atrial fibrillation was only significantly associated with prevalent cortical infarcts. The presence of carotid plaque was significantly associated with cortical and cerebellar infarcts but not with subcortical infarcts A possible explanation for the association between carotid plaques and cerebellar infarcts may be emboli arising from the vertebrobasilar arteries or the aortic arch due to increased atherosclerotic burden in individuals with carotid plaques compared with those without carotid plaques. There was a significant association between coronary artery calcium and all prevalent infarct subtypes. This relationship was stronger for cortical and cerebellar infarcts than for subcortical infarcts. However, only incident cortical- and cerebellar infarcts were significantly associated with coronary artery calcium. These findings emphasize the relationship between cortical and cerebellar infarcts and underlying conditions resulting in emboli contrary to the subcortical infarcts.

A major finding in this study was the association of self-reported doctors diagnosis of migraine headache with both prevalent and incident infarcts. Migraine was first linked to MRI detected brain infarcts in the population-based CAMERA study (Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis).[27] That study showed an increased risk of cerebellar infarcts in individuals with migraine, especially migraine with aura, compared with controls. Since then, several cross-sectional population-based studies have shown similar findings,[28–30] and we reported an association of aura in mid-life to late-life prevalent cerebellar infarcts on MRI in the AGES-Reykjavik cohort.[31] Longitudinal MRI studies on the relationship between migraine and brain infarcts are scarce. A 9-year follow-up of the CAMERA study did not show significantly higher incidence of brain infarcts in migraineurs compared with nonmigraineurs based on MRIs from 2 time points.[32] The pathogenic mechanisms clarifying the migraine brain infarct association remain poorly understood, but a few theories exist including cortical spreading depression, vasoconstriction, endovascular dysfunction, shared genetic defects, and neurogenic inflammation.[33] The cerebellar predilection of infarcts in migraine has been suggested to be caused by hemodynamical changes such as altered autoregulation in the posterior circulation territory.[34] Nervous tissues of the posterior fossa may be more vulnerable to ischemic damage than other regions of the brain due to comparatively reduced capacity to adapt to a sudden hemodynamic change.[35] To the best of our knowledge this study is the first study to show association between migraine and incident infarcts based on MRIs at 2 time points.

It is well known that smoking is a leading cause of morbidity and mortality in virtual every country in the world[36] where risk-ratios of all-cause mortality in current versus never smokers has been consistently reported at 2.8 to 3.0.[37–39] The lack of significant association of smoking with brain infarcts in this study and most other studies is likely because smokers among study participants have died before the study entry so that surviving smokers in our sample may have been those least likely to develop smoking-related brain infarcts.

Most studies examining brain infarcts do not support a sex disparity in infarct risk.[5] However, the risk of prevalent and incident infarcts overall in men compared with women in this study was almost 2-fold higher and almost 3-fold higher in the cortical region. A likely explanation for this is the generally worse risk-factor profile in men as demonstrated in another study of this cohort.[40]

The multivariate analysis in this study demonstrated the protective effect of lipid lowering medication (statins in 99% of cases) on new infarcts. This finding agrees with the results from another longitudinal cohort study that observed that those treated with statins had a lower incidence of asymptomatic brain infarcts compared with those who were untreated.[41] It is of interests that the use of lipid lowering medication in this study was independently associated with lower risk of new infarcts. Cumulative evidence has suggested that statins, in addition to lowering LDL (low-density lipoprotein) cholesterol, may exhibit pleiotropic effects including plaque stabilization and endothelial homeostasis that counteract the incidence of stroke and reduce vascular event rate in general.[42]

Other strengths of the present study include the very large well-characterized longitudinal sample of older individuals, the use of a standardized MRI acquisition and brain infarct rating protocols. However, of the individuals who attended the follow-up visit with available MRI and included in the analysis compared with those without MRI and excluded were younger and healthier. Similarly, individuals that only attended the baseline study and not the follow-up were significantly older and had more cerebrovascular risk-factors than those included in the follow-up study. This may have resulted in an underestimation of infarcts and in bias if the relationships among risk-factors, presence, and location of infarcts differed between the included and excluded persons. Another limitation is that the risk-factor level may have changed between the baseline MRI and incident infarcts; therefore, subjects may have been incorrectly classified based on risk-factors that emerged during the follow-up period.

CONCLUSIONS

Infarcts in different brain regions detected with MRI have different risk-factor profiles. Majority of these infarcts are asymptomatic. Therefore, it is important to not limit the assessment of risk-factors to infarcts anywhere in the brain and include subregions. Individuals with history of migraine are more likely to sustain new infarcts, and men are at higher risk than women of having infarcts. The use of lipid lowering medication is independently associated with lower risk of new infarcts. This information may aid with targeting and optimizing preventive therapeutic approaches for clinical stroke emphasizing the importance of controlling for the risk factors in the population at large, not only those with manifest cerebral disease.

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Disclosures

None.

Supplemental Material

Supplemental Methods
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