

Migraine Headache in Middle Age and Late-Life Brain Infarcts

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MIGRAINE, A COMMON NEUROVASCULAR disorder that affects approximately 11% of adults and 5% of children worldwide, is more common in women than men and is most prevalent in the third and fourth decades of life.¹ Although a severe migraine attack is among the most disabling of neurological disorders,² many individuals with migraine do not consult physicians.³

Approximately one-third of individuals with migraine experience neurological aura symptoms before headache onset (migraine with aura), usually consisting of transient visual, and also sensory, aphasic, or motor disturbances.⁴ Recent evidence suggests that migraine with aura is associated with an increased risk of clinically evident stroke or coronary artery disease.⁵⁻⁹

Migraine has also been linked to silent infarct-like lesions (identified on magnetic resonance imaging [MRI] regardless of clinical manifestations) in a community-based cohort evaluated as a part of the CAMERA study,¹⁰ which showed that individuals with migraine had a 7-fold increased risk for

Context Migraine is considered to be an episodic condition with no long-term consequences. However, recent studies suggest that migraine attacks may be associated with pathologic changes in the brain, particularly in the cerebellum.

Objective To determine whether individuals not reporting headache compared with individuals reporting migraine symptoms, particularly aura, in midlife are at increased risk of late-life infarct-like lesions found on magnetic resonance imaging (MRI) without consideration of clinical symptoms.

Design, Setting, and Participants A population-based study of men and women in Reykjavik, Iceland (cohort born 1907-1935; n=4689; 57% women) were followed up since 1967, examined, and interviewed about migraine symptoms in midlife (mean age, 51 years; range, 33-65 years). Between 2002 and 2006, more than 26 years later, brain MRIs were performed. Participants reporting headaches once or more per month were asked about migraine symptoms including nausea, unilateral location, photophobia, visual disturbance, and numbness. These individuals with headache were classified as having migraine without aura, migraine with aura, or nonmigraine headache. A comprehensive cardiovascular risk assessment was performed at both examinations.

Main Outcome Measure Presence of infarct-like lesions (total) and specifically located in the cortical, subcortical, and cerebellar regions.

Results Infarct-like lesions were present in 39.3% of men and 24.6% of women. After adjusting for age, sex, and follow-up time, compared with those not reporting headaches once or more per month (n=3243), those with midlife migraine with aura (n=361) had an increased risk of late-life infarct-like lesions (adjusted odds ratio [OR], 1.4; 95% confidence interval [CI], 1.1-1.8) that specifically reflected an association with cerebellar lesions in women (prevalence of infarcts 23.0% for women with migraine with aura vs 14.5% for women not reporting headaches; adjusted OR, 1.9; 95% CI, 1.4-2.6 vs a 19.3% prevalence of infarcts for men with migraine with aura vs 21.3% for men not reporting headaches; adjusted OR, 1.0; 95% CI, 0.6-1.8; *P*<.04 for interaction by sex). Migraine without aura and nonmigraine headache were not associated with an increased risk.

Conclusions Migraine with aura in midlife was associated with late-life prevalence of cerebellar infarct-like lesions on MRI. This association was statistically significant only for women. This is consistent with the hypothesis that migraine with aura in midlife is associated with late-life vascular disease in the cerebellum and in women.

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infarcts in the cerebellum compared with controls, an association that was strongest in those with aura and frequent attacks (at least monthly).

Although the precise etiology linking migraine with aura and vascular disease is uncertain,^{5,6,11} the degree to which migraine is a marker or risk factor for brain changes that may have

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functional consequences in old age is a question of public health importance. We had the opportunity to study the relationship of midlife migraine symptoms and late-life infarct-like lesions (hereafter called infarcts) evident on MRI. The study is based on a large population-based cohort of men and women who have been followed up first as part of the Reykjavik Study and later as part of the Age Gene/Environment Susceptibility-Reykjavik Study (AGES-RS).^{12,13} We examined risk in men and women for infarcts in specific regions of the brain, and secondarily considered whether the risk varied by age at headache assessment and other established risk factors for vascular disease.

METHODS

Study Design

Detailed descriptions of the Reykjavik Study^{12,14} and AGES-Reykjavik Study^{13,15} have been published previously. In brief, the Reykjavik Study is a population-based cohort study established in 1967 by the Icelandic Heart Association to prospectively study cardiovascular disease in Iceland.¹² The cohort included a random sample of men and women born between 1907 and 1935 and living in Reykjavik at baseline. In 2002, the Reykjavik Study continued as the AGES-Reykjavik Study to examine risk factors, genetic susceptibility, and gene-environment interactions in relation to disease and disability in old age.¹³ Of the 11 549 (58% women) surviving members of the Reykjavik cohort (representing 64% of the original examined cohort), 8030 (68.6% of men and 70.1% of women) were randomly selected and invited to participate in the AGES-Reykjavik Study. Of these individuals, 71.8% participated (74.0% of men and 70.2% of women), deriving a final sample of 5764 (58% women). Participants had a slightly better cardiovascular risk profile (lower midlife cholesterol, systolic blood pressure, and fewer smokers). Recruitment details and comparisons of the AGES-Reykjavik Study with the original cohort have been described.¹³

We refer to the assessments of relevance to this study from the Reykjavik Study as midlife assessments, and to those from the AGES-Reykjavik Study as late-life assessments. Midlife assessments included questions about headache, measurement of cardiovascular risk factors, and demographic characteristics. Late-life assessments included MRI of the brain, measurement of cardiovascular risk factors, and history of cardiovascular disease. The average year of the midlife assessment was 1978 with 90% occurring between 1972 and 1986. Late-life assessments (including MRI) were conducted from 2002 through 2006.

Midlife Assessments

Headache. Participants were asked about current headache symptoms as part of the Reykjavik Study.¹⁶ Those reporting headache once or more per month were asked whether the headaches were accompanied by any of the following 5 features of migraine: nausea or vomiting, unilateral location, photophobia, visual disturbance during or preceding headache, and unilateral numbness preceding headache.

Demographic and Cardiovascular Factors. Cardiovascular risk assessment was performed at the midlife examination concurrently with the migraine assessment. The following variables were considered putative confounders or mediators: educational level (primary, secondary, college, university), self-reported current use of medication for hypertension, smoking history (never, former, current smoker), and history of diabetes, as well as measured body mass index, systolic blood pressure, total cholesterol, and fasting blood glucose.

Late-Life Assessments

Brain MRI Protocol. All eligible participants were offered a high-resolution brain MRI acquired on a study-dedicated 1.5-T Signa Twin-speed system (General Electric Medical Systems, Waukesha, Wisconsin). The image protocol consisted of the following pulse sequences: T1-weighted

1.5-mm slice thickness 3-dimensional spoiled gradient-echo sequence (echo time [TE], 8 milliseconds; repetition time [TR], 21 milliseconds; flip angle [FA], 30°; field of view [FOV], 240 mm; matrix, 256 × 256) and in addition, with 3-mm thick interleaved slices, a proton density (PD)/T2-weighted fast spin-echo (SE) sequence (TE1, 22 milliseconds; TE2, 90 milliseconds; TR, 3220 milliseconds; echo train length, 8; FA, 90°; FOV, 220 mm; matrix, 256 × 256), and a fluid-attenuated inversion recovery (FLAIR) sequence (TE, 100 milliseconds; TR, 8000 milliseconds; inversion time, 2000 milliseconds; FA, 90°; FOV, 220 mm; matrix, 256 × 256). All images were acquired to give full brain coverage and slices were angled parallel to the anterior-posterior commissure line to give reproducible image views in the oblique axial plane.

Image Analysis. Infarcts were evaluated based on the T2-weighted fast SE/PD images and FLAIR images.

Infarcts were defined based on radiologic characteristics as described. A parenchymal defect (infarct) was defined as a defect of the brain parenchyma with a signal intensity that is isointense to that of cerebrospinal fluid on all pulse sequences (ie, FLAIR, T2-weighted, PD-weighted). Cortical infarct-like lesions were defined as parenchymal defects involving or limited to the cortical ribbon and surrounded by an area of high signal intensity on FLAIR images. Subcortical infarcts were defined as parenchymal defects not extending into the cortex that are surrounded by an area of high signal intensity on FLAIR images. Defects in the subcortical area without a rim or area of high signal intensity on FLAIR, and without evidence of hemosiderin on the T2*-weighted GRE-EPI scan were labeled as large Virchow-Robin Spaces (VRS); these were excluded from the definition of subcortical infarcts. Defects in the subcortical area with evidence of hemosiderin on the T2*-weighted GRE-EPI scan were labeled as resorbed hematomas and were also excluded from the definition of subcor-

tical infarcts. Lesions 4 mm or larger were recorded except for those in the cerebellum, for which there was no size criterion. Infarcts that spanned 2 areas were assigned to the location with the largest measured (mm) diameter of the defect regardless of orientation. This protocol was comparable with the protocol used in the CAMERA study.¹⁰

Image analyses were performed in a 2-step procedure by readers blinded to participant health status, including midlife headache history. An experienced neuroradiologist examined the scan for clinical abnormalities that needed immediate attention. At the same time, the neuroradiologist recorded the slice location of observed cortical and cerebellar infarcts directly into a shared database. Trained raters with access to the shared database identified subcortical infarcts and characterized all of the infarcts in more radiologic detail. Quality control procedures included 6 monthly assessments of intraobserver variability, and 3 monthly assessments for interobserver differences. The intraobserver weighted κ statistic was 0.92 for cerebral infarcts; the interobserver weighted κ statistic was 0.66 for cerebral infarcts. In addition, a 5% random sample was reread by a trained neuroradiologist at Leiden University Medical Center, Leiden, the Netherlands, and differences discussed.

Late-Life Cardiovascular Risk Factors and Disease. Late-life measurements included carotid artery distensibility by ultrasonography and coronary calcification (Agatston units) measured by computed tomography; both these measures were categorized into sex-specific quartiles. Diabetes was defined based on self-reported history of diabetes, use of medication, or fasting glucose levels greater than 126 mg/dL; systolic blood pressure was taken twice and averaged for the final measure; and standard questions were administered to assess smoking history (never, former, current) and history of physician diagnosis of stroke and transient ischemic attack (TIA). History of coronary artery disease (CAD)

was defined as a self-reported physician diagnosis of myocardial infarction or angina, or a history of coronary angioplasty or coronary artery bypass graft with supporting evidence from electrocardiography or nitrate use.

Analytic Sample. Of the 5764 AGES-Reykjavik participants, 5003 underwent MRI. Reasons for nonparticipation included contraindications ($n=280$), refusal ($n=283$), or being examined via home visit rather than clinic ($n=198$). An additional 237 participants were not included in the analysis because of either not completing all image sequences needed for infarct assessment or insufficient scan quality for infarct assessment. We excluded an additional 77 individuals who were older than 65 years at the time of the midlife examination. The final analytic sample thus consists of 4689 surviving Reykjavik Study participants who had complete headache and MRI data. Those excluded were older (79 vs 76 years of age), had a higher midlife systolic blood pressure, and a higher prevalence of CAD, stroke, or TIA in late life ($P<.001$ for all). Sex or midlife migraine status did not differ between individuals who were included and excluded from these analyses.

Statistical Analyses. Based on the midlife headache questions, we classified participants into 4 mutually exclusive headache categories: No headache once or more per month (reference category), nonmigraine headache, migraine without aura, and migraine with aura. The migraine without aura category included individuals with headache with at least 2 of the 3 nonaura symptoms (nausea, unilateral location, photophobia). The migraine with aura category included those reporting visual aura, sensory aura, or both. Individuals with headache but no nonaura symptoms or 1 nonaura symptom (nausea, unilateral location, or photophobia) were defined as having nonmigraine headache. Aura symptoms took precedence over other symptoms.

The classification scheme represents an approximation of Interna-

tional Headache Society diagnostic criteria for migraine with or without aura, which were formalized after the midlife data were collected.¹⁷ International Headache Society features for migraine without aura that are missing from these criteria include pulsatility, exacerbation with activity, and photophobia. International Headache Society criteria for migraine with aura missing from these criteria include duration of aura (aura symptoms must last between 5 and 60 minutes) and speed of onset (aura symptoms must develop gradually over more than 5 minutes). Due to the screening question for headache, our case definition does not include individuals who experience aura exclusively without headache.

A priori analyses were conducted for the total sample and stratified by sex. We used logistic regression to estimate the odds (95% confidence interval [CI]) of prevalent late-life infarcts in those with midlife migraine symptoms relative to individuals without midlife migraine symptoms. Separate models were calculated for cerebellar, cortical, subcortical, and total infarcts for the total sample and by sex. In model 1, we adjusted for age at the midlife examination, sex (for analyses on the total sample), and duration of follow-up. In model 2 we additionally adjusted for possible confounding by midlife cardiovascular factors. We tested for sex differences in the relationship between midlife migraine and late-life infarcts by including an interaction term in model 1 and model 2 (eg, migraine \times sex).

In secondary analyses, we adjusted for late-life cardiovascular risk factors and stratified by a history of CAD or TIA/stroke, to examine whether the associations of migraine to infarcts were changed by these factors. We tested for interaction by the age at which migraine symptoms were assessed (age <50 years, age ≥ 50 years), CAD, and TIA/stroke history by including interaction terms as previously shown. All analyses were performed with Stata version 10.1 (StataCorp LP, College Station, Texas).

The AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee (VSN-00-063), which acts as the institutional review board for the Icelandic Heart Association and by the institutional review board for the US National Institute on Aging, National Institutes of Health. Written informed consent was obtained from all participants.

RESULTS

Participants were 2693 women and 1996 men with an average age of 50.9 years (range, 33-65) at the midlife interview and 76.2 years (range, 66-96) at the late-life interview (TABLE 1). Overall, 12.2% of the participants (5.7% of men; 17.0% of women) were classified as having migraine, including 4.5%

migraine without aura (1.5% of men; 6.6% of women) and 7.7% migraine with aura (4.2% of men; 10.3% of women). Among participants with aura, the proportion with visual aura, sensory aura, and both visual and sensory aura, respectively, was 77.1%, 14.5%, and 8.4% for men and 66.2%, 17.3%, and 16.5% for women. Within the mi-

Table 1. Characteristics of Participants by Midlife Migraine Status^a

Headache Status	No. of Men (n = 1996) ^b				No. of Women (n = 2693) ^b			
	No Headache (n = 1589) ^c	Non-migraine Headache (n = 294) ^d	Migraine Without Aura (n = 30) ^e	Migraine With Aura (n = 83) ^f	No Headache (n = 1654) ^c	Non-migraine Headache (n = 582) ^d	Migraine Without Aura (n = 179) ^e	Migraine With Aura (n = 278) ^f
Age at midlife examination, mean (SD), y	49.9 (5.7)	49.3 (6.1)	48.3 (5.1)	47.6 (5.7)	52.5 (6.1)	50.7 (6.4)	49.2 (6.2)	50.5 (6.1)
Age at late-life examination, mean (SD), y	76.6 (5.3)	76.0 (5.4)	75.0 (3.9)	74.6 (4.9)	76.7 (5.4)	75.3 (5.2)	74.2 (4.8)	75.1 (5.3)
Follow-up time, mean (SD), y	26.7 (3.1)	26.6 (3.1)	26.7 (2.5)	27.0 (2.7)	24.2 (4.1)	24.6 (4.4)	25.0 (4.3)	24.7 (4.0)
Midlife interview 1, risk profile								
Primary education, No. (%)	358 (22.5)	71 (24.2)	5 (16.7)	24 (28.9)	710 (42.9)	244 (41.9)	69 (38.6)	122 (43.9)
Current smoking, No. (%)	724 (45.6)	131 (44.6)	12 (40.0)	42 (50.6)	532 (32.2)	171 (29.4)	40 (22.4)	87 (31.3)
Body mass index, mean (SD) ^g	25.5 (3.1)	25.4 (3.1)	25.5 (3.0)	25.9 (3.3)	24.8 (3.6)	25.0 (4.1)	24.9 (3.8)	24.7 (3.5)
Diabetes, No. (%)	11 (0.7)	4 (1.4)	0	1 (1.2)	14 (0.9)	1 (0.2)	3 (1.7)	6 (2.2)
Fasting glucose level, mean (SD), mg/dL	80.3 (10.0)	79.2 (9.5)	81.2 (8.7)	81.3 (21.9)	76.9 (9.1)	76.5 (9.1)	78.1 (14.7)	76.5 (10.6)
Antihypertensive medication use, No. (%)	57 (3.6)	13 (4.4)	1 (3.3)	4 (4.8)	115 (7.0)	57 (9.8)	11 (6.2)	24 (8.6)
Systolic blood pressure, mean (SD), mm Hg	135.2 (15.8)	134.3 (16.6)	131.4 (10.0)	132.4 (13.0)	129.2 (17.1)	130.6 (17.5)	130.8 (16.5)	126.4 (14.7)
Total cholesterol level, mean (SD), mg/dL	247.5 (38.7)	243.6 (38.7)	235.9 (31.0)	239.8 (38.7)	247.5 (42.5)	243.6 (46.4)	235.9 (42.5)	243.6 (46.4)
Late-life interview 2, risk profile								
Coronary calcification top quartile, No. (%)	387 (24.6)	70 (24.1)	9 (31.0)	24 (29.6)	421 (25.7)	125 (21.6)	26 (14.5)	60 (21.8)
Carotid artery distensibility (bottom quartile), No. (%)	385 (25.3)	70 (24.8)	5 (17.2)	25 (32.1)	398 (25.4)	121 (21.7)	58 (34.1)	55 (20.8)
Diabetes, No. (%)	235 (14.8)	39 (13.3)	6 (20.0)	16 (19.3)	141 (8.5)	53 (9.1)	23 (12.9)	25 (9.0)
Current smoking, No. (%)	260 (16.4)	46 (15.7)	6 (20.0)	17 (20.7)	209 (12.7)	69 (11.9)	19 (10.6)	41 (14.8)
Antihypertensive medication use, No. (%)	979 (61.6)	179 (60.9)	22 (73.3)	53 (63.9)	1007 (60.9)	385 (66.2)	122 (68.2)	190 (68.4)
Systolic blood pressure, mean (SD), mm Hg	143.0 (20.2)	143.5 (18.8)	142.0 (18.3)	145.6 (21.1)	141.8 (20.8)	141.4 (20.6)	144.1 (21.7)	140.0 (17.5)
History of coronary artery disease, No. (%)	558 (39.7)	112 (41.3)	16 (57.1)	38 (48.7)	313 (20.7)	130 (23.9)	37 (21.9)	83 (31.3)
History of stroke or transient ischemic attack, No. (%)	144 (9.4)	33 (11.5)	6 (20.0)	7 (9.0)	100 (6.2)	37 (6.5)	8 (4.6)	26 (9.8)

SI conversions; To convert glucose to mmol/L, multiply by 0.0555; cholesterol to mmol/L, divide by 0.02586.

^aFrom the AGES-Reykjavik study.

^bMigraine symptoms asked of individuals reporting headache once or more per month included photophobia, nausea, unilateral location, visual disturbance during or just before headache, and unilateral numbness during or just before headache. Four categories of headache symptoms are mutually exclusive.

^cNo headache: does not have headache once or more per month.

^dNonmigraine headache: headache with no more than 1 associated symptom.

^eMigraine without aura: headache with 2 or 3 associated symptoms of photophobia, nausea, or unilateral location. Individuals with aura and nonaura symptoms are included in the aura category.

^fMigraine with aura: headache with visual aura, sensory aura, or both. Individuals with aura and nonaura symptoms are included in the aura category.

^gBody mass index calculated as weight in kilograms divided by height in meters squared.

graine with aura group, 89% reported having at least 1 other migraine symptom.

Individuals with migraine were slightly younger at the midlife examination compared with others (Table 1). Other differences were that women with migraine with aura were more likely to report a history of CAD or TIA/stroke than those without ($P < .005$), although most other measures of cardiovascular risk were not obviously different.

Infarcts were present on MRI in 39.3% of men and 24.6% of women. The most common lesion location was the cerebellum (21.0% in men and 14.7% in women; TABLE 2).

Primary Results

In unadjusted comparisons, infarcts overall were more prevalent in women with migraine with aura compared with women without headache (31% vs 25%; $P = .04$; Table 2) but there was no difference in prevalence for men (41% vs 39%). Infarcts in the cerebellum, but not in other locations, were more prevalent in women with migraine with aura compared with women without headache (23% vs 15%; $P < .001$); there was no difference in prevalence for men (19% vs 21%).

After adjusting for age, sex, and follow-up time in a pooled model for men and women, participants with midlife migraine with aura were at increased risk for total infarcts (adjusted odds ratio [OR], 1.4; 95% CI, 1.1-1.8; TABLE 3). This mainly reflects the risk associated with lesions located in the cerebellum (adjusted OR, 1.6; 95% CI, 1.3-2.2; Table 3). There was no increased risk for cortical or subcortical lesions (Table 3) for participants with midlife migraine with aura, migraine without aura, or nonmigraine headache. Results were similar without (model 1) or after (model 2) adjustment for midlife measures of cardiovascular risk.

The relationship between migraine with aura and cerebellar infarcts was only significant in women (men, adjusted OR, 1.0; 95% CI, 0.6-1.8 vs women, adjusted OR, 1.9; 95% CI, 1.4-

Table 2. Prevalence of Late-Life Infarct-Like Lesion by Midlife Migraine Status: AGES-Reykjavik Study

	No. With Status/No. With Infarct (%)			
	Cerebellar	Cortical	Subcortical	Total
Men				
No headache	1589/339 (21.3)	1573/244 (15.5)	1573/262 (16.7)	1589/621 (39.1)
Nonmigraine headache	294/61 (20.8)	291/52 (17.9)	291/42 (14.4)	294/118 (40.1)
Migraine without aura	30/3 (10.0)	30/7 (23.3)	30/5 (16.7)	30/12 (40.0)
Migraine with aura	83/16 (19.3)	83/15 (18.1)	83/11 (13.3)	83/34 (41.0)
Total	1996/419 (21.0)	1977/318 (16.1)	1977/320 (16.2)	1996/785 (39.3)
Women				
No headache	1654/240 (14.5)	1642/131 (8.0)	1642/138 (8.4)	1654/415 (25.1)
Nonmigraine headache	582/66 (11.3)	578/35 (6.1)	578/43 (7.4)	582/125 (21.5)
Migraine without aura	179/26 (14.5)	178/7 (3.9)	178/10 (5.6)	179/36 (20.1)
Migraine with aura	278/64 (23.0)	278/23 (8.3)	278/20 (7.2)	278/86 (30.9)
Total	2693/396 (14.7)	2675/196 (7.3)	2675/211 (7.9)	2693/662 (24.6)

2.6; $P = .04$ for interaction by sex; Table 3), but was not statistically different by the age at which headache symptoms were assessed (age < 50 years, adjusted OR, 2.0; 95% CI, 1.4-3.0 vs age ≥ 50 years, adjusted OR, 1.4; 95% CI, 0.9-2.0; $P = .18$ for interaction by age, TABLE 4).

For cortical infarcts in the migraine without aura group, there was an interaction by sex, suggesting a higher risk in men compared with women ($P = .04$), although the individual sex-stratified ORs were not significant (Table 4). Results were generally similar when stratified by age (Table 4), although there was also a marginally increased risk for cortical infarcts in participants aged ≥ 50 years with migraine with aura (adjusted OR, 1.6; 95% CI, 1.0-2.5; $P = .07$).

Secondary Analyses

Results were similar after adjusting for late-life measures of cardiovascular risk and history of CAD or TIA/stroke. The relationship between migraine with aura and cerebellar infarcts was not changed by adjustment for late-life measures of cardiovascular risk and history of CAD or TIA/stroke in the total sample (adjusted OR, 1.5; 95% CI, 1.2-2.0) or when analyzed separately for men (adjusted OR, 1.0; 95% CI, 0.5-1.7) and women (adjusted OR, 1.8; 95% CI, 1.3-2.5). The association did not differ by CAD history (interaction, $P < .13$) with no CAD history having an ad-

justed OR of 1.8 (95% CI, 1.2-2.5) and with CAD history having an adjusted OR of 1.2 (95% CI, 0.8-1.9). The relationship did not differ by history of TIA or stroke (no history, adjusted OR, 1.7; 95% CI, 1.2-2.3; vs with history, adjusted OR, 1.6; 95% CI, 0.8-3.5; $P = .57$ for interaction by TIA/stroke history).

The separate analyses of visual and sensory aura symptoms suggested that the association of cerebellar infarcts with migraine with aura in women was stronger in those (8.6% of all women) with visual aura (adjusted OR, 2.2; 95% CI, 1.5-3.1) compared with those (1.7% of all women) with only sensory aura symptoms (adjusted OR, 1.3; 95% CI, 0.6-2.8).

COMMENT

In a large cohort of Icelandic adults, we found that women who reported migraine with aura in middle age were at increased risk of late-life infarcts relative to those without migraine symptoms. The risk was primarily for cerebellar lesions; there was no increased risk for cortical or subcortical lesions in these women or for those with migraine without aura or nonmigraine headache.

This risk was independent of cardiovascular risk factors measured in midlife or late life. Risk was not statistically different between individuals who were aged 50 years or younger vs those who were older when headache was ascer-

tained or between those with a history of diagnosed CAD or TIA/stroke vs those without.

Our study has substantial strengths. The large well-characterized cohort was established in 1967 when, at the time of headache assessment, participants were aged 33 to 65 years. At those ages, many participants were still experiencing migraines, therefore recall bias is likely reduced. Participants were also at low risk for TIA or stroke, making the identification of migraine visual aura

symptoms more robust. Measurement of late-life infarcts on MRI was performed by raters blinded to midlife headache status. Because participants were followed up as part of a cardiovascular disease study, we were also able to rigorously adjust for plausible confounding cardiovascular risk factors. Other strengths include the size of our cohort and broad age range, which gave us statistical power to consider sex, age, and cardiovascular disease in our analyses.

Some limitations of this study should be taken into account when interpreting the findings. Because migraine symptom questions were not asked of those reporting headache less than once per month, we are likely capturing only those with severe migraine occurring with a higher frequency. Participants with aura only and no headache would be classified as having no migraine. Further, our assessment of migraine was based on pre-IHS diagnostic criteria, although the questions addressed 5 symp-

Table 3. Adjusted Odds of Late-Life Infarct-Like Lesions by Midlife Migraine Status, Overall and Sex-Stratified: AGES-Reykjavik Study

	Odds Ratio (95% Confidence Interval)							
	Cerebellar		Cortical		Subcortical		Total Infarcts	
	Model 1 ^a	Model 2 ^b	Model 1 ^a	Model 2 ^b	Model 1 ^a	Model 2 ^b	Model 1 ^a	Model 2 ^b
Total								
No headache	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Nonmigraine headache	0.9 (0.7-1.1)	0.9 (0.7-1.1)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
Migraine without aura	1.0 (0.7-1.5)	1.0 (0.7-1.5)	0.9 (0.5-1.5) ^c	0.9 (0.5-1.6) ^c	0.8 (0.5-1.4)	0.9 (0.5-1.5)	0.9 (0.7-1.3)	1.0 (0.7-1.4)
Migraine with aura	1.6 (1.3-2.2) ^c	1.7 (1.3-2.2) ^c	1.3 (0.9-1.8)	1.3 (0.9-1.9)	0.9 (0.6-1.3)	0.9 (0.6-1.4)	1.4 (1.1-1.8)	1.5 (1.2-1.9)
Men								
No headache	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Nonmigraine headache	1.0 (0.7-1.4)	1.0 (0.7-1.4)	1.2 (0.9-1.7)	1.3 (0.9-1.8)	0.9 (0.6-1.2)	0.9 (0.6-1.2)	1.1 (0.8-1.4)	1.1 (0.9-1.4)
Migraine without aura	0.5 (0.1-1.5)	0.5 (0.2-1.7)	1.8 (0.8-4.3)	2.0 (0.8-4.8)	1.1 (0.4-2.9)	1.1 (0.4-3.0)	1.2 (0.6-2.5)	1.3 (0.6-2.7)
Migraine with aura	1.0 (0.6-1.8)	1.0 (0.6-1.8)	1.3 (0.7-2.4)	1.4 (0.8-2.6)	0.9 (0.4-1.6)	0.8 (0.4-1.6)	1.3 (0.8-2.0)	1.3 (0.8-2.0)
Women								
No headache	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Nonmigraine headache	0.8 (0.6-1.1)	0.8 (0.6-1.1)	0.8 (0.6-1.2)	0.8 (0.6-1.2)	1.0 (0.7-1.4)	1.0 (0.7-1.4)	0.9 (0.7-1.1)	0.9 (0.7-1.1)
Migraine without aura	1.1 (0.7-1.8)	1.1 (0.7-1.8)	0.6 (0.3-1.3)	0.6 (0.3-1.3)	0.8 (0.4-1.5)	0.9 (0.4-1.7)	0.9 (0.6-1.3)	0.9 (0.6-1.3)
Migraine with aura	1.9 (1.4-2.6)	2.0 (1.4-2.7)	1.2 (0.7-1.9)	1.2 (0.7-1.9)	0.9 (0.6-1.5)	1.0 (0.6-1.7)	1.5 (1.1-2.0)	1.5 (1.2-2.1)

^aModel 1: adjusted for age at midlife examination, sex, and duration of follow-up.

^bModel 2 (includes model 1 adjustments): adjusted for midlife systolic blood pressure, total cholesterol, fasting blood glucose, educational level, body mass index (calculated as weight in kilograms divided by height in meters squared), use of medication for hypertension, smoking history, and diabetes.

^cSignificant ($P < .05$) interaction by sex for cerebellar and cortical infarcts.

Table 4. Adjusted Odds of Late-Life Infarct-Like Lesions by Midlife Migraine Status, Stratified by Age at Midlife Interview: AGES-Reykjavik Study^a

	Odds Ratio (95% Confidence Interval)							
	Cerebellar		Cortical		Subcortical		Total Infarcts	
	Model 1 ^b	Model 2 ^c	Model 1 ^b	Model 2 ^c	Model 1 ^b	Model 2 ^c	Model 1 ^b	Model 2 ^c
Age <50 y								
No headache	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Nonmigraine headache	1.1 (0.8-1.5)	1.1 (0.8-1.5)	1.0 (0.7-1.5)	1.0 (0.7-1.5)	0.9 (0.6-1.3)	0.9 (0.6-1.3)	1.1 (0.8-1.4)	1.1 (0.8-1.4)
Migraine without aura	1.4 (0.9-2.4)	1.4 (0.8-2.5)	0.9 (0.4-2.0)	0.9 (0.4-2.1)	0.7 (0.3-1.6)	0.7 (0.3-1.6)	1.2 (0.8-1.9)	1.2 (0.8-1.9)
Migraine with aura	2.0 (1.4-3.0)	2.1 (1.4-3.1)	1.0 (0.6-1.8)	1.1 (0.6-2.0)	0.7 (0.4-1.3)	0.7 (0.4-1.3)	1.5 (1.1-2.1)	1.5 (1.1-2.2)
Age ≥50 y								
No headache	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Nonmigraine headache	0.8 (0.6-1.0)	0.8 (0.6-1.0)	1.1 (0.8-1.5)	1.1 (0.8-1.5)	0.9 (0.7-1.3)	1.0 (0.7-1.3)	0.9 (0.7-1.1)	0.9 (0.7-1.2)
Migraine without aura	0.6 (0.3-1.3)	0.6 (0.3-1.3)	0.9 (0.4-2.0)	0.9 (0.4-2.1)	0.9 (0.4-2.0)	1.1 (0.5-2.4)	0.7 (0.4-1.2)	0.8 (0.4-1.3)
Migraine with aura	1.4 (0.9-2.0)	1.4 (0.9-2.1)	1.6 (1.0-2.5)	1.6 (1.0-2.6)	1.1 (0.7-1.9)	1.2 (0.7-2.0)	1.4 (1.0-2.0)	1.5 (1.1-2.1)

^aNo significant ($P < .05$) interaction by age.

^bModel 1: adjusted for age at midlife examination, sex, and duration of follow-up.

^cModel 2 (includes model 1 adjustments): adjusted for midlife systolic blood pressure, total cholesterol, fasting blood glucose, educational level, body mass index (calculated as weight in kilograms divided by height in meters squared), use of medication for hypertension, smoking history, and diabetes.

toms included in the IHS guidelines. We note that our estimated prevalence of migraine overall (eg, with or without aura) is highly consistent with prior studies.¹ Our prevalence of aura (as a proportion of the total migraine population) is higher than has been reported in other population studies and may include frequently occurring non-specific visual symptoms such as blurring. However, the likely effect of this misclassification would be to attenuate the relationship between migraine with aura and infarcts, unless, compared with aura, nonspecific symptoms are differentially more strongly related to the risk for infarcts, a hypothesis we believe is unlikely.

Given the age of our study population, it is worth considering the extent to which overall or cardiovascular-related mortality may have affected our results. In particular, those with migraine with aura have been reported to be at increased risk of cardiovascular death compared with others.⁷ If individuals with midlife migraine with aura were more likely to die of cardiovascular disease before the late-life examination, and if these individuals were also more likely to have infarcts in the cerebellum or overall compared with others, then our results would have been attenuated. However, if these cerebellar or overall lesions were somehow protective (eg, individuals with migraine with aura and these lesions had lower all-cause mortality compared with those with migraine with aura without these lesions), then our results would have been exaggerated. The second scenario seems unlikely.

Our results are consistent with the cross-sectional CAMERA study,¹⁰ the only other study that measured infarcts on MRI, which also found the migraine-associated infarcts to be preferentially located in the cerebellum. This prospective longitudinal study had a long follow-up and an older cohort with a much higher background risk for brain lesions. Our results suggest that the association of infarcts with migraine with aura is detectable in older individuals who typically have cardio-

vascular risk factors that lead to similar-appearing lesions.¹⁸ Further, the study is based on a larger sample of men and women, therefore, sex differences could be investigated. We found that the relationship between migraine with aura and cerebellar infarcts may be specific to women. However, we cannot rule out a possible increased risk for men with migraine with aura due to the relatively small number of men with migraine with aura in our sample.

Why migraine, particularly with aura, is associated with clinical and silent (presumed) ischemic stroke is uncertain. Proposed mechanisms include atherosclerotic and nonatherosclerotic causes,^{5,6,11} including traditional cardiovascular risk factors,^{11,19} endothelial dysfunction,^{11,20-22} shared genetic risk factors for migraine and stroke,^{11,23-25} vasoconstrictor medications taken to treat headache,^{11,22} cardiac abnormalities including patent foramen ovale,^{11,26} and diagnostic artifact,^{11,27} among other factors. These mechanisms do not obviously explain why infarcts associated with migraine with aura would be preferentially located in the cerebellum and in women. There are clinical reports suggesting that the cerebellum is vulnerable in individuals with migraine²⁸⁻³² and in familial hemiplegic migraine—a rare Mendelian variant of migraine with aura.³³ In population studies, no particular location pattern was evident for clinically evident ischemic stroke among women with aura,^{9,34} although as mentioned earlier, silent infarcts (as per the CAMERA study) were preferentially located in the cerebellum.¹⁰ We also note that secondary analyses suggested an association of migraine with aura to cortical infarcts in some subgroups was stronger (eg, men with migraine with or without aura or men and women who were older than aged 50 years at the time of headache assessment).

In summary, this study suggests that a remote history of migraine with aura is associated with brain lesions commonly found in older populations. Results persisted after controlling for cardiovascular risk factors and history of

cardiovascular disease, thus suggesting that the mechanism linking the migraine aura with these lesions is independent of the usual risk factors for ischemic vascular disease and may be specifically related to migraine with aura. Additional longitudinal studies with repeated MRIs are needed to better establish the temporality and dose-response relationship between migraine with aura and brain infarcts. Finally, the clinical implications of the infarct-like lesions identified have not been established and will require investigation.

Author Contributions: Dr Scher had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Sigurdsson, Eiriksdottir, Gudnason. **Analysis and interpretation of data:** Scher, Gudmundsson, Sigurdsson, Ghambaryan, Aspelund, van Buchem, Gudnason.

Drafting of the manuscript: Scher.

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REFERENCES

1. Stovner L, Hagen K, Jensen R, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia*. 2007; 27(3):193-210.
2. Murray CJ, Lopez AD. Regional patterns of disability-free life expectancy and disability-adjusted life expectancy: global Burden of Disease Study. *Lancet*. 1997; 349(9062):1347-1352.
3. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. *Neurology*. 2002;58(6):885-894.

4. Ferrari MD. Migraine. *Lancet*. 1998;351(9108):1043-1051.
5. Bousser MG, Welch KMA. Relation between migraine and stroke. *Lancet Neurol*. 2005;4(9):533-542.
6. Welch KM. Stroke and migraine—the spectrum of cause and effect. *Funct Neurol*. 2003;18(3):121-126.
7. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. *JAMA*. 2006;296(3):283-291.
8. Stang PE, Carson AP, Rose KM, et al. Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. *Neurology*. 2005;64(9):1573-1577.
9. MacClellan LR, Giles W, Cole J, et al. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. *Stroke*. 2007;38(9):2438-2445.
10. Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. *JAMA*. 2004;291(4):427-434.
11. Del Zotto E, Pezzini A, Giossi A, Volonghi I, Padovani A. Migraine and ischemic stroke: a debated question [published online ahead of print May 7, 2008]. *J Cereb Blood Flow Metab*. 2008;28(8):1399-1421.
12. Sigurdsson E, Thorgeirsson G, Sigvaldason H, Sigfusson N. Unrecognized myocardial infarction: epidemiology, clinical characteristics, and the prognostic role of angina pectoris: the Reykjavik Study. *Ann Intern Med*. 1995;122(2):96-102.
13. Harris TB, Launer LJ, Eiriksdottir G, et al. Age, gene/environment susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am J Epidemiol*. 2007;165(9):1076-1087.
14. Jónsdóttir LS, Sigfusson N, Gudnason V, Sigvaldason H, Thorgeirsson G. Do lipids, blood pressure, diabetes, and smoking confer equal risk of myocardial infarction in women as in men? the Reykjavik Study. *J Cardiovasc Risk*. 2002;9(2):67-76.
15. Qiu C, Cotch MF, Sigurdsson S, et al. Retinal and cerebral microvascular signs and diabetes: the age, gene/environment susceptibility-Reykjavik study. *Diabetes*. 2008;57(6):1645-1650.
16. Gudmundsson LS, Thorgeirsson G, Sigfusson N, Sigvaldason H, Johannsson M. Migraine patients have lower systolic but higher diastolic blood pressure compared with controls in a population-based study of 21 537 subjects: the Reykjavik Study. *Cephalalgia*. 2006;26(4):436-444.
17. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain: Headache Classification Committee of the International Headache Society. *Cephalalgia*. 1988;8(suppl 7):1-96.
18. Launer LJ. Epidemiology of white-matter lesions. *Int Psychogeriatr*. 2003;15(suppl 1):99-103.
19. Scher AI, Terwindt GM, Picavet HSJ, Verschuren WMM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: The GEM population-based study. *Neurology*. 2005;64(4):614-620.
20. Elkind MS. Endothelial repair capacity and migraine: the fix is in. *Neurology*. 2008;70(17):1506-1507.
21. Lee ST, Chu K, Jung KH, et al. Decreased number and function of endothelial progenitor cells in patients with migraine. *Neurology*. 2008;70(17):1510-1517.
22. Tietjen EG. Migraine and ischaemic heart disease and stroke: potential mechanisms and treatment implications. *Cephalalgia*. 2007;27(8):981-987.
23. Scher AI, Terwindt GM, Verschuren WM, et al. Migraine and MTHFR C677T genotype in a population-based sample. *Ann Neurol*. 2006;59(2):372-375.
24. Pezzini A, Grassi M, Del ZE, et al. Migraine mediates the influence of C677T MTHFR genotypes on ischemic stroke risk with a stroke-subtype effect. *Stroke*. 2007;38(12):3145-3151.
25. Schürks M, Zee RY, Buring JE, Kurth T. Interrelationships among the MTHFR 677C>T polymorphism, migraine, and cardiovascular disease. *Neurology*. 2008;71(7):505-513.
26. Diener HC, Kurth T, Dodick D. Patent foramen ovale, stroke, and cardiovascular disease in migraine. *Curr Opin Neurol*. 2007;20(3):310-319.
27. Hand PJ, Kwan J, Lindley RI, Dennis MS, Wardlaw JM. Distinguishing Between Stroke and Mimic at the Bedside. The Brain Attack Study [published online ahead of print February 16, 2006]. *Stroke*. 2006;37(3):769-775.
28. Oppenheim H. *Diseases of the Nervous System: A Text-Book for Students and Practitioners of Medicine*. Mayer EA, trans-ed. American ed from the 2nd German ed. Philadelphia, PA: JB Lippincott Co; 1900.
29. Burns RJ, Blumbergs PC, Sage MR. Brain infarction in young men. *Clin Exp Neurol*. 1979;16:69-79.
30. Milhaud D, Bogousslavsky J, van Melle G, Liot P. Ischemic stroke and active migraine. *Neurology*. 2001;57(10):1805-1811.
31. Reid J, Riding M, Purdy A, Phillips S. Acute migraine-associated borderzone cerebellar infarction. *Cephalalgia*. 2006;26(10):1247-1251.
32. Vincent M, Hadjikhani N. The cerebellum and migraine. *Headache*. 2007;47(6):820-833.
33. Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. *N Engl J Med*. 2001;345(1):17-24.
34. Kurth T, Slomke MA, Kase CS, et al. Migraine, headache, and the risk of stroke in women: a prospective study. *Neurology*. 2005;64(6):1020-1026.