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Migraine Headache in Middle-Age and Late-Life Brain Infarcts: The Age Gene/Environment Susceptibility - Reykjavik Study

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Abstract

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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, compared to those not reporting symptoms, individuals reporting migraine symptoms in mid-life, particularly aura, are at increased risk of late-life infarct-like lesions (hereafter referred to as infarcts).

Design—A population based cohort of men and women (b 1907-35) followed since 1967, answered questions about migraine symptoms in mid-life (mean age 51, range 33–65), more than 26 years prior to a late-life exam when brain MRI was acquired. Those reporting headaches once or more per month were asked about migraine symptoms, including nausea, unilateral location, photophobia, visual disturbance, and numbness. We classified headache sufferers as having migraine without aura (MO), migraine with aura (MA), or non-migraine headache. A comprehensive cardiovascular risk assessment was performed at both examinations.

Setting—Population-based study in Reykjavik, Iceland

Participants—Men and women (n=4689, 57% women).

Main Outcome Measure—Presence of infarcts – total and specifically located in the cortical, sub-cortical, and cerebellar regions.

Results—After adjusting for age, sex, and follow-up time, compared to those not reporting headaches once or more per month (n=3243), those with mid-life MA (n=361) had an increased risk of late-life infarcts (adjusted OR, 1.4; 95% confidence interval [CI], 1.1–1.8) that specifically reflected an association with cerebellar lesions in women (Women: 23.0% vs. 14.5%, adjusted OR 1.9; 95% CI 1.4–2.6 vs. Men 19.3% vs. 21.3%, adjusted OR, 1.0; 95% CI 0.6–1.8, p<0.04 for interaction by sex). There was no increased risk associated with mid-life MO or non-migraine headache or for other brain regions.

Conclusions—Migraine with aura in mid-life was associated with late-life prevalence of cerebellar infarcts on MRI. This association was statistically significant only for women. This is consistent with the hypothesis that MA in mid-life is associated with late-life vascular disease that appears to be specific for the cerebellum and in women.

Background

Migraine, a common neurovascular disorder that affects about 11 percent of adults and five percent 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 migraine sufferers do not consult physicians and remain un-diagnosed.[3]

About one third of migraineurs experience neurological aura symptoms before headache onset (migraine with aura), usually consisting of transient visual, but 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 in a community based cohort studied as a part of the CAMERA study.[10] That study showed that, compared to controls, those with migraine had a seven times increased risk for infarcts in the cerebellum, an association that was strongest in those with aura and frequent (e.g. defined as at least monthly) attacks..

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

Methods

Study design

Detailed descriptions of the Reykjavik Study (RS)[12,14]and AGES-Reykjavik Study[13,15] have been published previously. In brief, the RS 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 1907–1935 and living in Reykjavik at baseline. In 2002, the RS 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] There were 11549 (58% women) surviving members of the Reykjavik cohort (representing 64% of the original examined cohort) of whom 8030 (68.6% of men and 70.1% of women) were randomly invited to participate in AGES-RS. Of these, 71.8% participated (74.0% of men and 70.2% of women), giving a final sample of 5764 (58% women). Responders had a slightly better cardiovascular risk profile (lower mid-life cholesterol, systolic blood pressure and fewer smokers). Recruitment details and comparisons of the AGES-Reykjavik Study to the original cohort have been described.[13]

The assessments of relevance to this study, described below, are herein referred to as “mid-life” assessments, which are from the RS, and “late-life” assessments, which are from AGES-Reykjavik Study. Mid-life 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 mid-life assessment was 1978 with most (90%) occurring between 1972 and 1986. Late-life assessments (including MRI) were conducted from 2002 through 2006.

Mid-Life 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 five features of migraine, including 1) nausea or vomiting, 2) unilateral location, 3) photophobia, 4) visual disturbance during / just before headache, and 5) unilateral numbness before headache.

Demographic and cardiovascular factors—Cardiovascular risk assessment was performed at the mid-life 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 1.5T Signa Twinspeed system (General Electric Medical Systems, Waukesha, WI). The image protocol consisted of the following pulse sequences (20): T1-weighted 1.5 mm slice thickness 3-dimensional spoiled gradient-echo sequence [time to echo (TE), 8 ms; repetition time (TR), 21 ms; flip angle (FA), 30°; field of view (FOV), 240 mm; matrix, 256×256]. In addition we acquired, with 3-mm thick interleaved slices, a proton density (PD)/T2-weighted fast spin-echo (FSE) sequence (TE1, 22 ms; TE2, 90 ms; TR, 3220 ms; echo train length, 8; FA, 90°; FOV, 220 mm; matrix, 256×256), and a fluid attenuated inversion recovery (FLAIR) sequence (TE, 100 ms; TR, 8000 ms; inversion time, 2000 ms; 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 FSE/PD images and FLAIR images.

Infarcts were defined based on radiologic characteristics as follows: 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 (CSF) on all pulse sequences (i.e. 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 subcortical infarcts. Lesions 4 mm or larger were recorded except for those in the cerebellum, for which there was no size criterion.. Infarcts that spanned two areas were assigned to the location with the largest measured (mm) diameter of the defect regardless of orientation. This protocol was comparable to that used in the CAMERA study.[10]

Image analyses were performed in a two step procedure by readers blinded to subject health status, including mid-life headache history. An experienced neuroradiologist examined the scan for clinical abnormalities that needed immediate attention. At the same time, the neuroradiologist recorded directly into a shared data base, the slice location of observed cortical and cerebellar infarcts. Trained raters with access to the shared data base identified subcortical infarcts and characterized all of the infarcts in more radiologic detail. Quality control procedures included six monthly assessments of intra-observer variability, and 3 monthly assessments for inter-observer differences. The intra-observer weighted κ statistic was 0.92 for cerebral infarcts; the inter-observer weighted κ statistic was 0.66 for cerebral infarcts. In addition, a five percent random sample was reread by a neuroradiololologist at Leiden University Medical Center (MvB) and differences discussed.

Late-life cardiovascular risk factors and disease—Late life measurements included carotid artery distensibility by ultrasonography and coronary calcification [in 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 above 7 mmol/l; systolic blood pressure was taken twice and averaged for the final measure; 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 non-participation included contraindications (n=280), refusal (n=283), or home-visit rather than clinic participant (n=198). An additional 237 participants were not included in the analysis due to either not completing all the image sequences needed for the infarct assessment or due to insufficient scan quality to assess infarcts. We excluded an additional 77 subjects who were older than 65 at the time of the mid-life examination. The final analytic sample thus consists of 4689 surviving RS subjects who had complete headache and MRI data. Those excluded were older (79 vs 76 years of age), had a higher mid-life systolic blood pressure, and a higher prevalence of CAD, stroke or TIA in late-life (all $p<0.001$). There were no differences in sex or mid-life migraine status between those included and excluded from these analyses.

Statistical Analyses—Based on the mid-life headache questions, we classified subjects into four mutually exclusive headache categories: No headache once or more per month (reference category), non-migraine headache, migraine without aura (MO), and migraine with aura (MA). The MO category included those with headache with at least two of the three non-aura symptoms (e.g. two or three of nausea, unilateral location, photophobia). The MA category included those reporting visual and/or sensory aura. Subjects with headache but no more than one non-aura symptoms (e.g. none or one of nausea, unilateral location, photophobia) were defined as suffering from non-migraine headache. Aura symptoms took precedence over other symptoms. The classification scheme represents an approximation of International Headache Society (IHS) diagnostic criteria for migraine with or without aura, which were formalized after the mid-life data were collected.[17] IHS features for migraine without aura missing from these criteria include pulsatility, exacerbation with activity, and phonophobia. IHS criteria for migraine with aura missing from these criteria include duration of aura (e.g. aura symptoms must last between five and 60 minutes) and speed of onset (aura symptoms must develop gradually over more than five minutes). Due to the screening question for headache, our case definition does not include those 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% CI) of prevalent late-life infarcts in those with mid-life migraine symptoms relative to those without mid-life migraine symptoms. Separate models were calculated for cerebellar, cortical, subcortical, and total infarcts, for the total sample and by sex. Model 1 is adjusted for age at the mid-life examination, sex (for analyses on the total sample), and duration of follow-up. In model 2 we additionally adjusted for possible confounding by mid-life cardiovascular factors. We tested for sex differences in the relationship between mid-life migraine and late-life infarcts by including an interaction term in model 1 and model 2 (e.g. migraine X 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, age >= 50), CAD, and TIA/stroke history by including interaction terms as above. All analyses were performed with Stata version 10.1 (StataCorp LP, College Station, TX).

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, who were an average age of 50.9 (range 33–65) years at the mid-life interview and 76.2 (range 66–96) years at the late-life interview. In mid-life, migraine symptoms were more common in women than men.(Tables 1a and 1b). Overall, 12.2% (5.7% men, 17.0% women) of the participants were classified as having migraine, including 4.5% MO (1.5% men, 6.6% women) and 7.7% MA (4.2% men, 10.3% women). Among those with aura the proportion with visual aura, sensory aura, and both visual and sensory aura, respectively, was 77.1%, 14.5%, 8.4% (men) and 66.2%, 17.3%, 16.5% (women). Within the MA group, 89% reported having at least one other migraine symptom.

Migraine sufferers were slightly younger at the mid-life exam compared to others (Tables 1a, 1b). Some differences were seen between those with migraine compared to others. Women with MA were more likely to report a history of CAD or TIA / stroke ($p<0.005$) 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 MA compared to women without headache (31% vs. 25%, $p<0.04$, table 2); 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 MA compared to women without headache (23% vs. 15%, $p<0.001$); 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, those with mid-life MA were at increased risk for total infarcts (adjusted 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 sub-cortical lesions (Table 3) or for those with MO or non-migraine headache. Results were similar without (model 1) or after (model 2) adjustment for mid-life measures of cardiovascular risk.

The relationship between MA 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, 1.4–2.6, $p=0.04$ 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, $p<0.18$ for interaction by age, table 4).

For cortical infarcts in the MO group, there was an interaction by sex suggesting a higher risk in men compared to women ($p=0.04$), although the individual sex-stratified OR's 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 those ≥50 years with MA (adjusted OR, 1.6 95% CI, 1.0–2.5, $p=0.07$).

Secondary Analyses

Results were similar after adjusting for late-life measures of cardiovascular risk and history of CAD or TIA / stroke The relationship between MA 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 separately for men (adjusted OR, 1.0, 95% CI, 0.5–1.7) or women (adjusted OR, 1.8, 95% CI, 1.3–2.5). The association did not differ by CAD history (no history; adjusted OR, 1.8; 95% CI, 1.2–2.5; with history, adjusted OR, 1.2; 95% CI, 0.8–1.9; $p<0.13$ for interaction by CAD history) or history of TIA or stroke (no history; adjusted OR, 1.7; 95% CI, 1.2–2.3; with history, adjusted OR, 1.6; 95% CI, 0.8–3.5, $p<0.57$ for interaction by TIA / stroke history).

Discussion

In a large cohort of Icelandic adults, we found that women who reported migraine with aura (MA) 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 sub-cortical lesions or for those with migraine without aura or non-migraine headache.

This risk was independent of cardiovascular risk factors measured in mid- or late-life. Risk was not statistically different between subjects who were less than compared to older than 50 years of age when headache was ascertained or those with or without a history of diagnosed CAD or TIA/stroke.

Our study has substantial strengths. The large well-characterized cohort was established in 1967 when, at the time of headache assessment, subjects were aged 33 to 65. At those ages, many study subjects were still experiencing migraine attacks, so recall bias is likely reduced. Subjects 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 mid-life headache status. As subjects were followed 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 effects.

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 with a higher attack frequency. Further, our assessment of migraine was based on pre-IHS diagnostic criteria although the questions touched on five symptoms included in the IHS guidelines. We note that our estimated prevalence of migraine overall (e.g., with or without aura) is highly consistent with prior studies.[1] Our assessment of the migraine aura may include frequently occurring nonspecific visual symptoms such as blurring. Our prevalence of aura (as a proportion of the total migraine population) is higher than has been reported in other population studies. However, the effect of this misclassification would be to attenuate the relationship between MA and infarcts, unless, compared to aura, non-specific symptoms are differentially more strongly related to the risk for infarcts. 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 presented herein. In particular, migraineurs with aura have been reported to be at increased risk of cardiovascular death compared to others.[7] If the mid-life migraineurs with aura were more likely to die from cardiovascular disease before the late-life exam, and if these individuals were also more likely to have infarcts in the cerebellum or overall compared to others, then our results would have been attenuated. If

however these lesions were somehow protective (e.g. migraineurs with aura and these lesions had lower all-cause mortality compared to migraineurs 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. Here we extend the findings of the CAMERA study to a longitudinal study with a long follow-up and an older cohort with a much higher background risk for brain lesions. Our results suggest that migraine with aura is a strong enough risk factor to be detected in older subjects, who typically have cardiovascular risk factors that lead to similar appearing lesions. Further, the study is based on a larger sample of men and women, so sex differences could be investigated. We found the relationship between MA and cerebellar infarcts may be specific to women. However, we cannot rule out a possible increased risk for men with MA due to the relatively small number of men with MA in our sample. The reason why migraine, particularly with aura, is a risk factor or marker for clinical and silent (presumed) ischemic stroke is uncertain and controversial; proposed mechanisms include atherosclerotic and non-atherosclerotic causes[5,6,11]including traditional cardiovascular risk factors,[11,18] endothelial dysfunction,[11,19–21] shared genetic risk factors for migraine and stroke,[11,22–24] vasoconstrictor medications taken to treat headache,[11,21] cardiac abnormalities including patent foramen ovale,[11,25] and diagnostic artifact,[11,26] among other factors. These mechanisms do not obviously explain why migraine-related infarcts would be preferentially located in the cerebellum and in women. There are clinical reports suggesting that the cerebellum is vulnerable in migraineurs[27–31] and in familial hemiplegic migraine, a rare Mendelian variant of migraine with aura.[32] In population studies, no particular location pattern was evident for clinically evident ischemic stroke among women with aura.[9,33] although, as mentioned earlier, silent infarcts (as per CAMERA) were preferentially located in the cerebellum.[10] We also note that secondary analyses suggested the possibility of increased risk of cortical infarcts in some sub-groups (e.g. men with MO or MA or men and women who were older than 50 at the time of headache assessment).

In summary, this study suggests that a remote history of migraine with aura may be a strong risk factor for brain lesions commonly found in older populations. Results were unaffected by control 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 the effects of migraine. Additional longitudinal studies with repeat measures of MRI are needed to better establish the temporality, and dose-response relationship, between the migraine aura and brain lesions. Further, the late age functional consequences of migraine on cognition and motor function require investigation.

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Reference List

1. Stovner L, Hagen K, Jensen R, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia. 2007; 27:193–210. [PubMed: 17381554]
2. Murray CJ, Lopez AD. Regional patterns of disability-free life expectancy and disability-adjusted life expectancy: global Burden of Disease Study [see comments]. Lancet. 1997; 349:1347–1352. [PubMed: 9149696]
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; 58:885–894. [PubMed: 11914403]
4. Ferrari MD. Migraine. Lancet. 1998; 351:1043–1051. [PubMed: 9546526]
5. Bousser MG, Welch KM. Relation between migraine and stroke. Lancet Neurol. 2005 Sep. 2004:533–542. [PubMed: 16109360]
6. Welch KM. Stroke and migraine--the spectrum of cause and effect. Funct Neurol. 2003; 18:121–126. [PubMed: 14703893]
7. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and Risk of Cardiovascular Disease in Women. JAMA: The Journal of the American Medical Association. 2006; 296:283–291. [PubMed: 16849661]
8. Stang PE, Carson AP, Rose KM, et al. Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. Neurology. 2005; 64:1573–1577. [PubMed: 15883318]
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; 38:2438–2445. [PubMed: 17690308]
10. Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. JAMA. 2004; 291:427–434. [PubMed: 14747499]
11. Del ZE, Pezzini A, Giossi A, Volonghi I, Padovani A. Migraine and ischemic stroke: a debated question. J Cereb Blood Flow Metab. 2008
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; 122:96–102. [PubMed: 7993002]
13. Harris TB, Launer LJ, Eiriksdottir G, et al. Age, Gene/Environment Susceptibility-Reykjavik Study: Multidisciplinary Applied Phenomics. American Journal of Epidemiology. 2007:kwk115.
14. Jonsdottir 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; 9:67–76. [PubMed: 12006913]
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; 57:1645–1650. [PubMed: 18332097]
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; 26:436–444. [PubMed: 16556245]
17. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain; Cephalalgia. 1988. p. 1-96.
18. Scher AI, Terwindt GM, Picavet HSJ, Verschuren WMM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: The GEM population-based study. Neurology. 2005; 64:614–620. [PubMed: 15728281]
19. Elkind MS. Endothelial repair capacity and migraine: the fix is in. Neurology. 2008; 70:1506–1507. [PubMed: 18427068]
20. Lee ST, Chu K, Jung KH, et al. Decreased number and function of endothelial progenitor cells in patients with migraine. Neurology. 2008; 70:1510–1517. [PubMed: 18354079]
21. Tietjen EG. Migraine and ischaemic heart disease and stroke: potential mechanisms and treatment implications. Cephalalgia. 2007; 27:981–987. [PubMed: 17661875]

22. Scher AI, Terwindt GM, Verschuren WM, et al. Migraine and MTHFR C677T genotype in a population-based sample. Ann Neurol. 2006; 59:372–375. [PubMed: 16365871]
23. 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
24. Schurks M, Zee RY, Buring JE, Kurth T. Interrelationships among the MTHFR 677C>T polymorphism, migraine, and cardiovascular disease. Neurology. 2008; 71:505–513. [PubMed: 18672474]
25. Diener HC, Kurth T, Dodick D. Patent foramen ovale, stroke, and cardiovascular disease in migraine. Curr Opin Neurol. 2007; 20:310–319. [PubMed: 17495626]
26. Hand PJ, Kwan J, Lindley RI, Dennis MS, Wardlaw JM. Distinguishing Between Stroke and Mimic at the Bedside. The Brain Attack Study. Stroke. 2006
27. Oppenheim, H. Diseases of the nervous system. A text-book for students and practitioners of medicine. J.B. Lippincott Company: Philadelphia; 1990. First American from the second revised and enlarged German edition
28. Burns RJ, Blumbergs PC, Sage MR. Brain infarction in young men. Clin Exp Neurol. 1979; 16:69–79. [PubMed: 550958]
29. Milhaud D, Bogousslavsky J, van Melle G, Liot P. Ischemic stroke and active migraine. Neurology. 2001; 57:1805–1811. [PubMed: 11723268]
30. Reid J, Riding M, Purdy A, Phillips S. Acute migraine-associated borderzone cerebellar infarction. Cephalalgia. 2006; 26:1247–1251. [PubMed: 16961796]
31. Vincent M, Hadjikhani N. The cerebellum and migraine. Headache. 2007; 47:820–833. [PubMed: 17578530]
32. Ducros A, Denier C, Joutel A, et al. The Clinical Spectrum of Familial Hemiplegic Migraine Associated with Mutations in a Neuronal Calcium Channel. The New England Journal of Medicine. 2001; 345:17–24. [PubMed: 11439943]
33. Kurth T, Slomke MA, Kase CS, et al. Migraine, headache, and the risk of stroke in women: A prospective study. Neurology. 2005; 64:1020–1026. [PubMed: 15781820]

Table 1

1a: Description of participants by mid-life migraine status: Men (n=1996) from the AGES-Reykjavik Study

Headache Status	No headache n=1589	Non-Migraine Headache n=294	Migraine Without Aura n=30	Migraine With Aura n=83
Age (years) at Mid-Life Exam	49.9 (±5.7)	49.3 (±6.1)	48.3 (±5.1)	47.6 (±5.7)
Age (years) at Late-Life Exam	76.6 (±5.3)	76.0 (±5.4)	75.0 (±3.9)	74.6 (±4.9)
Follow up time (years)	26.7 (±3.1)	26.6 (±3.1)	26.7 (±2.5)	27.0 (±2.7)
Mid-Life (Interview 1) Risk Profile				
Primary education (%)	358 (22.5%)	71 (24.2%)	5 (16.7%)	24 (28.9%)
Current smoking (%)	724 (45.6%)	131 (44.6%)	12 (40.0%)	42 (50.6%)
Fasting glucose (mg/dl)*	80.3 (±10.0)	79.2 (±9.5)	81.2 (±8.7)	81.3 (±21.9)
Cholesterol level (mmol/l)*	6.4 (±1.0)	6.3 (±1.0)	6.1 (±0.8)	6.2 (±1.0)
BMI*	25.5 (±3.1)	25.4 (±3.1)	25.5 (±3.0)	25.9 (±3.3)
Diabetes (%)	11 (0.7%)	4 (1.4%)	0 (0.0%)	1 (1.2%)
Mean systolic BP (mmHg)*	135.2 (±15.8)	134.3 (±16.6)	131.4 (±10.0)	132.4 (±13.0)
Antihypertensive medication use (%)	57 (3.6%)	13 (4.4%)	1 (3.3%)	4 (4.8%)
Late-Life (Interview 2) Risk Profile				
Coronary calcification top quartile (%)	387 (24.6%)	70 (24.1%)	9 (31.0%)	24 (29.6%)
Carotid artery distensibility (bottom quartile) (%)	385 (25.3%)	70 (24.8%)	5 (17.2%)	25 (32.1%)
Diabetes (%)	235 (14.8%)	39 (13.3%)	6 (20.0%)	16 (19.3%)
Current smoking (%)	260 (16.4%)	46 (15.7%)	6 (20.0%)	17 (20.7%)
Mean systolic BP (mmHG)*	143.0 (±20.2)	143.5 (±18.8)	142.0 (±18.3)	145.6 (±21.1)
Antihypertensive medication use (%)	979 (61.6%)	179 (60.9%)	22 (73.3%)	53 (63.9%)
History of coronary artery disease (%)	558 (39.7%)	112 (41.3%)	16 (57.1%)	38 (48.7%)
History of stroke / TIA (%)	144 (9.4%)	33 (11.5%)	6 (20.0%)	7 (9.0%)

1b: Description of participants by mid-life migraine status: Women (n=2693) from the AGES-Reykjavik Study

Headache Status	No headache n=1654	Non-Migraine Headache n=582	Migraine Without Aura n=179	Migraine With Aura n=278
Age (years) at Mid-Life Exam	52.5 (±6.1)	50.7 (±6.4)	49.2 (±6.2)	50.5 (±6.1)
Age (years) at Late-Life Exam	76.7 (±5.4)	75.3 (±5.2)	74.2 (±4.8)	75.1 (±5.3)
Follow up time (years)	24.2 (±4.1)	24.6 (±4.4)	25.0 (±4.3)	24.7 (±4.0)
Mid-Life (Interview 1) Risk Profile				
Primary education (%)	710 (42.9%)	244 (41.9%)	69 (38.6%)	122 (43.9%)
Current smoking (%)	532 (32.2%)	171 (29.4%)	40 (22.4%)	87 (31.3%)
Fasting glucose (mg/dl)*	76.9 (±9.1)	76.5 (±9.1)	78.1 (±14.7)	76.5 (±10.6)

1b: Description of participants by mid-life migraine status: Women (n=2693) from the AGES-Reykjavik Study

Headache Status	No headache n=1654	Non-Migraine Headache n=582	Migraine Without Aura n=179	Migraine With Aura n=278
Cholesterol level (mmol/l)*	6.4 (±1.1)	6.3 (±1.2)	6.1 (±1.1)	6.3 (±1.2)
BMI*	24.8 (±3.6)	25.0 (±4.1)	24.9 (±3.8)	24.7 (±3.5)
Diabetes (%)	14 (0.9%)	1 (0.2%)	3 (1.7%)	6 (2.2%)
Mean systolic BP (mmHg)*	129.2 (±17.1)	130.6(±17.5)	130.8 (±16.5)	126.4 (±14.7)
Antihypertensive medication use (%)	115 (7.0%)	57 (9.8%)	11 (6.2%)	24 (8.6%)
Late-Life (Interview 2) Risk Profile				
Coronary calcification top quartile (%)	421 (25.7%)	125 (21.6%)	26 (14.5%)	60 (21.8%)
Carotid artery distensibility (bottom quartile) (%)	398 (25.4%)	121 (21.7%)	58 (34.1%)	55 (20.8%)
Diabetes (%)	141 (8.5%)	53 (9.1%)	23 (12.9%)	25 (9.0%)
Current smoking (%)	209 (12.7%)	69 (11.9%)	19 (10.6%)	41 (14.8%)
Mean systolic BP (mmHG)*	141.8 (±20.8)	141.4 (±20.6)	144.1 (±21.7)	140.0 (±17.5)
Antihypertensive medication use (%)	1007 (60.9%)	385 (66.2%)	122 (68.2%)	190 (68.4%)
History of coronary artery disease (%)	313 (20.7%)	130 (23.9%)	37 (21.9%)	83 (31.3%)
History of stroke / TIA (%)	100 (6.2%)	37 (6.5%)	8 (4.6%)	26 (9.8%)

Migraine symptoms asked of those reporting headache once or more per month, included photophobia, nausea, unilateral location, visual disturbance during / just before headache, unilateral numbness during / just before headache

Subjects are classified according to headache symptoms into four mutually exclusive categories:

No headache	Does not have headache once or more per month
Non-migraine headache	Headaches with no more than one associated symptom
Migraine without aura (MO)	Headaches with two or three of photophobia, nausea, unilateral location
Migraine with aura (MA)	Headaches with visual and/or sensory aura

Those with aura and non-aura symptoms are included in the aura category.

*Mean ±SD; SI conversion factors; to convert glucose to mmol/l, divide by 18 (or multiply by 0.055); To convert cholesterol to mg/dl, divide by 0.02586 (or multiply by 38.67)

Table 2

Prevalence of Late-Life Infarcts by Mid-Life Migraine Status: AGES-Reykjavik Study

	Infarct Location						Total	
	Cerebellar		Cortical		Subcortical			
	N	Yes	N	Yes	N	Yes	N	Yes
MEN								
No Headache	1589	339 (21.3%)	1573	244 (15.5%)	1573	262 (16.7%)	1589	621 (39.1%)
Non-Migraine HA	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%)
Non-Migraine HA	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%)

Table 3

Adjusted Odds of Late-Life Infarcts by Mid-Life Migraine Status, Overall and Sex-Stratified: AGES-Reykjavik Study

	Cerebellar OR (95% CI)		Cortical OR (95% CI)		Subcortical OR (95% CI)		Total Infarcts OR (95% CI)	
	Model 1[1]	Model 2[2]	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
TOTAL								
No Headache	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Migraine HA	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)	*0.9 (0.5–1.6)	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)	*1.7 (1.3–2.2)	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	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Migraine HA	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	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Migraine HA	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)

*Significant ($p<0.05$) interaction by sex for cerebellar infarcts (MA) and for cortical infarcts (MO)

[1]Model 1: Adjusted for age at mid-life examination, sex, and duration of follow-up

[2]Model 2: + adjusted for mid-life systolic blood pressure, total cholesterol, fasting blood glucose, educational level, body mass index, use of medication for hypertension, smoking history, diabetes

Table 4

Adjusted Odds of Late-Life Infarcts by Mid-Life Migraine Status, Stratified by Age at Mid-Life Interview: AGES-Reykjavik Study

	Cerebellar OR (95% CI)		Cortical OR (95% CI)		Subcortical OR (95% CI)		Total Infarcts OR (95% CI)	
	Model 1[1]	**Model 2**[2]	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Age < 50								
No Headache	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Migraine HA	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								
No Headache	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Migraine HA	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)

No significant ($p<0.05$) interaction by age.

[1] Model 1: Adjusted for age at interview 1, sex, and duration of follow-up

[2] Model 2: + adjusted for mid-life systolic blood pressure, total cholesterol, fasting blood glucose, educational level, body mass index, use of medication for hypertension, smoking history, diabetes

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