Published in final edited form as:

Headache. 2010 June 1; 50(6): 1031–1040. doi:10.1111/j.1526-4610.2009.01609.x.

Migraine, Migraine Features, and Cardiovascular Disease

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Abstract

Background— Many studies support an association between migraine and cardiovascular disease (CVD). This association appears particularly in migraine with aura and is also modified by additional factors.

Objective— We sought to investigate whether the association between migraine and CVD in addition to aura status is affected by certain migraine features.

Methods— Cohort study among 27,840 women, participating in the Women's Health Study. We had detailed self-reported information on migraine and migraine features among women with active migraine (migraine during the year prior to baseline). Incident CVD events were confirmed after medical record review. We used Cox proportional hazards models to evaluate the association between migraine and incident CVD. The results have been presented in part before. We ran additional analyses according to migraine features.

Results— At baseline, 5,125 (18.4%) women reported history of migraine; 39.7% of the 3,610 women with active migraine indicated aura. During a mean of 11.9 years of follow-up, 708 CVD events occurred. Migraine with aura doubled the risk for CVD, ischemic stroke, and myocardial infarction. With regard to ischemic stroke, this association seemed stronger in the absence than in the presence of migraine features. This was most pronounced in the absence (HR=3.27; 95% CI=1.93–5.51; $p<0.0001$) than in the presence of nausea/vomiting (HR=0.91; 95% CI=0.43–1.93; $p=0.80$). In contrast, the association with myocardial infarction did not reveal a certain pattern.

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Full Disclosures

Dr. Schürks has received within the last 5 years investigator-initiated research funds from the Deutsche Forschungsgemeinschaft and the Migraine Research Foundation and honoraria from L.E.K. Consulting for telephone surveys.

Dr. Buring has received within the last 5 years investigator-initiated research funding and support as Principal Investigator from the National Institutes of Health and Dow Corning Corporation; research support for pills and/or packaging from Bayer Health Care and the Natural Source Vitamin E Association; honoraria from Bayer for speaking engagements.

Dr. Kurth has received within the last 5 years investigator-initiated research funding from Bayer AG, the National Institutes of Health, McNeil Consumer & Specialty Pharmaceuticals, Merck, Wyeth Consumer Healthcare, and the Migraine Research Foundation; he is a consultant to i3 Drug Safety and World Health Information Science Consultants, LLC, and he has received honoraria from Genzyme, Merck, and Pfizer for educational lectures.

Conclusions—These data suggest that the association between migraine with aura and ischemic stroke may differ by absence or presence of migraine features.

Keywords

migraine; migraine features; cardiovascular disease; cohort study

Introduction

Migraine is a common debilitating primary headache disorder with a complex etiology, predominantly affecting women.¹ The clinical diagnosis relies on the presence of certain migraine features. Specifically, migraine is characterized by recurrent headache attacks, which typically last 4–72 hours. The pain is located unilaterally, of pulsating quality, moderate to severe intensity, and usually aggravated by physical activity. In addition, migraine attacks are often accompanied by photophobia, phonophobia, and nausea and/or vomiting. In some patients, usually prior to headache onset, a migraine aura occurs, characterized by transient neurological symptoms, most often affecting the visual field.²

Meta-analyses of case-control and cohort studies support an association between migraine and ischemic stroke,^{3, 4} which appears to be limited to patients with migraine with aura.⁴ Recent findings further suggest an association between migraine with aura and other vascular ischemic events, including myocardial infarction (MI).^{5–7}

However, the biological mechanisms linking migraine with ischemic vascular events are not understood. These are likely to be complex.⁸ Many data seem to support the hypothesis of an underlying endothelial dysfunction,⁹ which would be in agreement with findings that the association between migraine and cardiovascular disease (CVD) is *modified* by environmental (age, smoking, oral contraceptive use)⁴ and genetic factors^{10, 11} affecting the vasculature. Further, these studies indicate that the migraine-CVD association may *differ* with regard to ischemic stroke and myocardial infarction.¹²

While the increased risk for CVD among migraineurs appears to be limited to those having aura, little is known about whether and how migraine features affect the migraine with aura-CVD association. We have previously shown in a large cohort of women participating in the Women's Health Study (WHS) that an increased risk for CVD only occurs in women with migraine with aura, but not those with migraine without aura.^{6, 13} These findings are supported by other independent reports.^{14, 15} In addition, migraine attack frequency appears to modify the risk for CVD among migraineurs with aura.^{14, 16, 17}

The aim of this study was to explore whether other migraine features in addition to aura status modify the migraine-CVD association among over 27,000 women participating in the WHS.

Subjects and Methods

Study population

The WHS was a randomized trial designed to test the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer. The design, methods, and results have been described in detail previously.^{18, 19} Briefly, a total of 39,876 U.S. female health professionals aged ≥ 45 years at study entry (1992–1995) without a history of CVD, cancer, or other major illnesses were randomly assigned to active aspirin (100 mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both placebos. All participants provided written informed consent and the Institutional Review Board of Brigham and Women's Hospital approved the WHS. Baseline information was self-reported and

collected by a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables.

Blood samples were collected in tubes containing EDTA from 28,345 participating women prior to randomization. A total of 27,939 samples could be assayed for total, high-density, and directly obtained low-density lipoprotein cholesterol. Of these we excluded 79 women with missing migraine information and 20 who reported angina prior to study entry. This left us with 27,840 women for analysis.

Assessment of migraine

Participants were asked on the baseline questionnaire: “Have you ever had migraine headaches?” and “In the past year, have you had migraine headaches?” From this information, we categorized women into “any history of migraine;” “active migraine,” which includes women with self-reported migraine during the past year; and “prior migraine,” which includes women who reported ever having had a migraine but none in the year prior to completing the questionnaire. In order to reduce potential recall-bias, only participants who reported active migraine were asked further details about their migraine attacks (“migraine features”), including attack duration of 4 to 72 hours, unilateral location of pain, pulsating pain quality, aggravation by routine physical activity, sensitivity to light, sensitivity to sound, and nausea or vomiting. In a previous study,⁶ we have shown good agreement of our classification with the 1988 International Headache Society (IHS) criteria for migraine²⁰ and we have shown excellent agreement between self-reported migraine and ICHD-II based migraine classification in the WHS.²¹ Participants who reported active migraine were further asked whether they had an “aura or any indication a migraine is coming.” Responses were used to classify women who reported active migraine into “active migraine with aura” and “active migraine without aura”.

Ascertainment of CVD

During follow-up, participants self-reported cardiovascular events. Medical records were obtained for all events and reviewed by an Endpoints Committee of physicians. Nonfatal stroke was confirmed if the participant had a new focal-neurological deficit of sudden or rapid onset that persisted for >24 hours. Major stroke subtype classification (ischemic, hemorrhagic, or unknown) was based on available clinical and diagnostic information with excellent interrater agreement.²² The occurrence of MI was confirmed if symptoms met World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes or abnormal electrocardiograms. Cardiovascular deaths were confirmed by review of autopsy reports, death certificates, medical records, or information obtained from next of kin or family members.

We evaluated major CVD, a combined endpoint defined as the first of any of these events: nonfatal ischemic stroke, nonfatal MI, or death from ischemic CVD. We also evaluated any first ischemic stroke and any first MI. There were too few CVD deaths to run meaningful analyses.

Cholesterol measurements

High-density and low-density lipoprotein cholesterol levels were measured using commercially available reagents from Roche Diagnostics (Basel, Switzerland) and Genzyme (Cambridge, Mass).

Statistics

We compared the baseline characteristics of participants, with respect to migraine categories using analysis of covariance for continuous measurements, adjusting for age. We used direct

standardization to adjust categorical variables for age in 5-year increments. We also used direct standardization to adjust migraine features among women with active migraine with aura and active migraine without aura for age in 5-year increments.

We used Cox proportional hazards models to evaluate the association between migraine categories and incident CVD. Women with no history of migraine served as the reference group. We calculated multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) adjusting for age (continuous), body mass index (continuous), history of diabetes (yes, no), exercise (rarely/never, <1/week, 1–3/week, $\geq$ 4/week), postmenopausal hormone use (never, past, current), history of oral contraceptive use (yes, no, not sure), history of hypertension (yes, no), alcohol consumption (rarely/never, 1–3 drinks/month, 1–6 drinks/week, $\geq$ 1 drinks/day), smoking (never, past, current <15 cigarettes/day, current $\geq$ 15 cigarettes/day), family history of MI prior to age 60 (yes, no), and high-density (HDL) and low-density (LDL) lipoprotein levels (quartiles).

We evaluated whether the association of migraine aura status with incident CVD is modified by migraine features, including attack duration of 4 to 72 hours (yes, no), unilateral location of pain (yes, no), pulsating pain quality (yes, no), aggravation by routine physical activity (yes, no), sensitivity to light (yes, no), sensitivity to sound (yes, no), and nausea or vomiting (yes, no), by categorizing women with migraine with aura and without aura according to each of these features in the Cox model.

We incorporated a missing value indicator if the number of women with missing information on covariates was $\geq$ 100 or imputed a value otherwise.

We tested the proportionality assumption of the Cox proportional hazards model by including an interaction term for the migraine categories with time and found no statistically significant violation.

All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC). All p-values were two-tailed and we considered $p < 0.05$ as statistically significant.

We have previously reported on the association between migraine and CVD including major CVD, ischemic stroke, and myocardial infarction.^{6, 13} For reasons of comprehensiveness we will report some important results again along with the new data.

All authors had access to all of the data.

Results

At baseline, 5,125 (18.4%) women reported any history of migraine. Of the 3,610 women who reported active migraine, 39.7% indicated migraine aura. No history of migraine was reported by 22,715 women.

Baseline characteristics of women according to migraine categories are summarized in Table 1. Body mass index, history of diabetes, smoking habits, and family history of MI prior to age 60 were equally distributed among migraine categories. Women with active migraine were slightly younger and more likely to currently use postmenopausal hormones compared to women with prior migraine and no history of migraine. Women with prior migraine were more likely to have a history of hypertension compared to women with active migraine and women without migraine. Women with no history of migraine had lower mean LDL levels and higher mean HDL levels. They were also less likely to have a history of oral contraceptive use and more likely to regularly consume alcohol and to be physically active compared to women with migraine.

Table 2 summarizes the distribution of migraine features among women with active migraine with and without aura. Unilateral pain location was present in about 60% of women, phonophobia in about 40%, and aggravation of headaches by physical activity in about one third of women. These features were equally distributed among women with and without aura. In contrast attack duration of 4–72 hours (79.8% vs. 74.6%), nausea or vomiting (66.0% vs. 61.6%), and a pulsating pain quality (55.7% vs. 49.7%) were reported more frequently by women with active migraine without aura than women with active migraine with aura. Photophobia was the only feature that was more frequent among women with active migraine with aura (74.3%) than among women with active migraine without aura (59.7%).

During a mean of 11.9 years of follow-up (330,190 person-years), 708 major CVD events (a combined endpoint defined as the first of any of these events: nonfatal ischemic stroke, nonfatal MI, or death from ischemic CVD), 312 ischemic strokes, and 305 MIs were confirmed.

In Table 3, we summarize the association between migraine and incident ischemic cardiovascular events and potential effect modification by migraine features. Compared with women without a history of migraine, women with active migraine with aura had an about 2-fold increased risk for major CVD (HR 2.01; 95% CI 1.52–2.67; $p<0.0001$). This association appeared for both ischemic stroke (HR=1.79; 95% CI=1.15–2.78; $p=0.01$) and MI (HR=2.11; 95% CI=1.39–3.21; $p=0.0004$). In contrast, women with active migraine without aura and prior migraine did not have a significantly increased risk for any of the ischemic cardiovascular events.

Further analyses among women with active migraine with aura suggested that the association with major CVD was stronger in the absence of nausea/vomiting (HR 2.66; 95% CI 1.79–3.94; $p<0.0001$) than in the presence (HR 1.64; 95% CI 1.12–2.40; $p=0.01$). However, the other effect estimates were very similar irrespective of presence or absence of the other migraine features. When we investigated the association between migraine with aura and ischemic stroke the effect estimates appeared stronger in the absence of migraine features. This was most pronounced in the absence of nausea/vomiting (HR 3.27; 95% CI 1.93–5.51; $p<0.0001$) than in the presence (HR 0.91; 95% CI 0.43–1.93; $p=0.80$). In contrast, the pattern of association between migraine with aura and MI looked more heterogeneous. While the hazard ratios appeared stronger in the presence of a typical attack duration, unilateral pain location, and photophobia, they were weaker in the presence of nausea/vomiting, pulsating pain quality, and aggravation by physical activity. Further, they were similar irrespective of the absence or presence of phonophobia. However, except for the association between migraine with aura and ischemic stroke in the presence or absence of nausea/vomiting, all confidence intervals from analyses according to migraine features overlapped.

Among women with active migraine without aura presence of pulsating pain during a migraine attack appeared to protect against major CVD (HR 0.58; 95% CI 0.32–1.02; $p=0.06$), while absence appeared to increase the risk for major CVD (HR 1.62; 95% CI 1.10–2.38; $p=0.02$). This pattern only appeared for MI, but not ischemic stroke. We did not observe a differential effect of any of the other features on any of the vascular ischemic events among women with active migraine without aura.

Discussion

Results of this large prospective cohort of women suggest that the previously shown association between migraine with aura and CVD may differ depending on the presence or absence of migraine features. The association between migraine with aura and major CVD appeared stronger in the absence than in the presence of nausea/vomiting, however, was very similar in the absence/presence of any of the other migraine features. The association with ischemic

stroke appeared stronger in the absence of all migraine features than in their presence, which again was more pronounced for nausea/vomiting. In contrast the association with MI did not reveal a certain pattern. While there was no overall association between migraine without aura and major CVD, there seemed to be a protective association in the presence of pulsating pain quality and an increased association in the absence. This pattern only occurred for MI and not for ischemic stroke.

Meta-analyses of case-control and cohort studies support an association between migraine and ischemic stroke,^{3, 4} which appears to be confined to migraine with aura.⁴ Findings from prospective cohort studies further suggest an association between migraine with aura and other vascular ischemic events, including MI.^{5–7} However, the association between migraine and CVD may be more complex due to modifying effects of certain additional factors.⁴ Among those are younger age, smoking, and oral contraceptive use, which further increase the risk of ischemic stroke among migraineurs. In addition, vascular risk factors²³ and genetic variants including the *MTHFR* 677C>T and the *ACE* D/I polymorphisms^{10, 11} appear to modify the association between migraine with aura and ischemic vascular events. Furthermore, these studies suggest that the association may differ with regard to ischemic stroke and myocardial infarction. Most of these factors are known to increase vascular risk or to affect the vasculature and are thus compatible with the hypothesis of an endothelial dysfunction in migraine.⁹ However, knowledge about the impact of migraine characteristics on the migraine-CVD association is limited.

Despite existing hypotheses regarding the biological mechanisms linking migraine with CVD,⁸ it remains unclear why the association appears only in migraine with aura. With regard to ischemic stroke altered matrix metalloproteinase activity may be involved.²⁴ Another migraine characteristic that has been reported to be associated with CVD events is migraine attack frequency.^{14, 16, 17} A possible link has been suggested by imaging studies reporting that morphological changes in the brain, like white matter hyperintensities and grey matter reduction, correlate with headache duration and lifetime headache frequency. However, this hypothesis is disputed and not consistent with the fact that migraine is often self-remitting.²⁵ In addition, hypotheses both regarding migraine aura and attack frequency do not explain the association of migraine with non-stroke CVD events.

The results of our manuscript suggest that the migraine with aura-CVD association may be even more complex when taking into consideration diagnostic migraine features according to the International Headache Society (IHS).²⁶ Specifically, we found that the absence of most of these features is more strongly associated with ischemic stroke than their presence. In contrast the association with MI is more heterogeneous, not supporting a certain pattern. We also performed sensitivity analyses by excluding all women who had both a stroke and an MI during follow-up (n=14). This did not change the pattern and magnitude of the observed associations (data not shown), arguing against a diluting effect of women with both outcomes on our observed migraine-CVD association. Our findings are in keeping with the concept that differential pathophysiological processes underlie the development of ischemic stroke and MI.

Our findings regarding the migraine with aura-CVD association, as well as the missing differential effect of migraine features (except for pulsating pain) on the lack of an association between migraine without aura and CVD suggests that indeed only the aura rather than the migraine *per se*—as defined by individual features—is a marker for incident CVD. This is in agreement with the concept, that migraine and aura may genetically be two different entities that—for reasons yet to be determined—occur more frequently together in some people.²⁷ Absence of pulsating pain was the only feature that, in addition to migraine with aura, also appeared to carry an increased risk for major CVD in migraine without aura. It may be speculated that frequent migraine attacks lead to vascular changes and ultimately rigidity

impairing pulsation and thus pulsating pain perception. However, current data do not support this concept in general, since in contrast to ischemic stroke, MI is not associated with high attack frequency,¹⁷ and altered vascular reactivity was reported in young migraineurs of recent onset, which could thus not be ascribed to frequent attacks.²⁸

Our study has several strengths, including the prospective design, the large number of participants, women with migraine, and outcome events. Further, we had collected detailed information on migraine characteristics and on a large number of potential CVD risk factors. In addition, the homogenous nature of the cohort may reduce confounding. However, several limitations should be considered. First, migraine, migraine aura, and migraine features were self-reported and women could not be classified according to strict IHS criteria. Thus, misclassification of migraine and migraine aura is possible. However, our prevalence of migraine (18.4%) and migraine aura (39.7%) is very similar to those seen in other large population-based studies in the U.S.²⁹ and the Netherlands.³⁰ Moreover, potential misclassification would likely have obscured a migraine-CVD association. Furthermore, our migraine ascertainment was in good agreement with the modified 1988 IHS criteria,⁶ and we have shown excellent agreement between self-reported migraine and ICHD-II based migraine classification in the WHS.²¹ Second, participants were white female health professionals age ≥ 45 , thus generalizability may be limited. For example, young women with migraine may be at particular risk for ischemic stroke.⁴ Finally, it should be noted that the number of outcomes in each of the migraine feature subgroups was rather low, leaving remaining uncertainties.

Due to a lack of an *a priori* biological model, that may explain our findings, our results must be regarded as hypothesis generating. Thus replication in other large cohorts with information on migraine, aura status, and migraine specific features according to the IHS criteria is warranted. In addition, further insight into the mechanisms underlying individual migraine features will also help to better understand the complex migraine pathophysiology and to discern the nature of the association between migraine with aura and CVD.

Acknowledgments

We are indebted to the participants in the Women's Health Study for their outstanding commitment and cooperation; to the entire Women's Health Study staff for their expert and unfailing assistance.

Funding and Support

The Women's Health Study is supported by grants from the National Heart, Lung, and Blood Institute (HL-43851, HL-80467), and the National Cancer Institute (CA-47988). The research for this work was supported by grants from the Donald W. Reynolds Foundation.

Abbreviations

CVD	cardiovascular disease
EDTA	ethylenediaminetetraacetic acid
HDL	high-density lipoproteins
HR	hazard ratio
ICHD-II	2 nd edition of the International Classification of Headache Disorders
IHS	International Headache Society
LDL	low-density lipoproteins
MI	myocardial infarction

WHS Women's Health Study
 95% CI 95% confidence interval

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Table 1
Baseline characteristics according to migraine categories among participants in the Women's Health Study (n=27,840)*

	No migraine history (N=22,715)	Active migraine with aura (N=1,434)	Active migraine without aura (N=2,176)	Prior migraine (N=1,515)	P value [†]
Mean age, years (SE)	54.9 (0.05)	53.2 (0.19)	52.6 (0.15)	55.5 (0.18)	<0.0001
Mean body mass index, kg/m ² (SE)	25.9 (0.03)	25.8 (0.13)	26.2 (0.11)	26.1 (0.13)	0.02
Mean low density cholesterol (LDL), mg/dL (SE)	123.9 (0.22)	124.6 (0.89)	124.7 (0.73)	127.1 (0.87)	0.003
Mean high density cholesterol (HDL), mg/dL (SE)	53.9 (0.10)	53.1 (0.40)	53.2 (0.32)	52.6 (0.39)	0.001
History of diabetes	2.5	1.8	1.6	2.6	0.21
History of hypertension	24.6	25.5	26.0	30.3	<0.0001
Smoking					
Never	51.3	52.7	56.3	50.6	
Past	37.1	37.3	34.5	35.4	
Current <15 cigarettes/day	4.4	3.9	3.5	5.2	
Current ≥15 cigarettes/day	7.3	6.2	5.8	8.8	0.05
Alcohol consumption					
Rarely/never	43.5	48.3	47.4	45.0	
1–3 drinks/month	13.1	13.1	15.4	14.2	
1–6 drinks/week	32.7	30.2	30.1	30.5	
≥1 drink/day	10.8	8.3	7.1	10.3	<0.0001
Physical activity					
Rarely/never	37.0	38.3	39.4	39.2	
<1/week	19.2	20.4	21.7	20.1	
1–3/week	32.3	30.7	29.2	29.5	
≥4/week	11.6	10.7	9.7	11.3	<0.0001
Postmenopausal hormone therapy					
Never	49.6	38.9	44.9	46.1	

	No migraine history (N=22,715)	Active migraine with aura (N=1,434)	Active migraine without aura (N=2,176)	Prior migraine (N=1,515)	P value [†]
Past	8.7	10.1	8.5	10.4	<0.0001
Current	41.7	50.9	46.6	43.6	
History of oral contraceptive use					0.0006
No	30.6	27.0	28.4	27.6	
Yes	69.0	72.2	71.4	71.7	
Not sure	0.4	0.8	0.2	0.7	
Family history of myocardial infarction prior to age 60	11.4	12.8	11.8	12.4	0.33

* Data are expressed as age-adjusted percentages unless otherwise stated. Percentages may not add up to 100 due to rounding or missing values.

[†] P values were calculated from 3 df tests of general linear models for continuous variables and Mantel-Haenszel chi-square tests for categorical variables.

Table 2

Migraine features according to migraine aura status among women with active migraine in the Women's Health Study (n=3,610)*

Feature	Active migraine with aura (N=1,434)	Active migraine without aura (N=2,176)	P value [†]
Attack duration 4–72 hours	74.6 (1,068)	79.8 (1,738)	0.0002
Unilateral pain location	61.3 (879)	58.4 (1,273)	0.08
Nausea/vomiting	61.6 (882)	66.0 (1,438)	0.007
Pulsating pain quality	49.7 (710)	55.7 (1,213)	0.0004
Photophobia	74.3 (1,062)	59.7 (1,299)	<0.0001
Phonophobia	42.2 (603)	40.5 (880)	0.30
Aggravation by physical activity	33.8 (482)	33.3 (725)	0.75

* Data are expressed as age-adjusted percentages (numbers).

[†] P values were calculated from 1 df Mantel-Haenszel chi-square tests for categorical variables.

Table 3

Multivariable-adjusted* hazard ratios (HRs) and 95% confidence intervals (CIs) for ischemic vascular events among women with active migraine according to migraine features in the Women's Health Study (N=27,840)

Major Cardiovascular Event [†]	No migraine history (N=22,715)	Active migraine with aura (N=1,434)	P value	Active migraine without aura (N=2,176)	P value	Prior migraine (N=1,515)	P value
Overall	N=567	N=54		N=39		N=48	
	1.00	2.01 (1.52–2.67)	<0.0001	1.04 (0.75–1.44)	0.81	1.13 (0.84–1.52)	0.41
Attack duration of 4–72 hours							
Yes	—	2.11 (1.53–2.89)	<0.0001	0.98 (0.67–1.44)	0.93	—	—
No		1.74 (0.98–3.09)	0.06	1.22 (0.67–2.22)	0.51	—	—
Unilateral pain location							
Yes	—	2.05 (1.43–2.96)	0.0001	0.87 (0.54–1.40)	0.57	—	—
No		1.96 (1.29–2.97)	0.002	1.24 (0.80–1.93)	0.33	—	—
Photophobia							
Yes	—	1.87 (1.33–2.61)	0.0003	1.00 (0.66–1.51)	0.99	—	—
No		2.42 (1.49–3.93)	0.0003	1.11 (0.67–1.87)	0.68	—	—
Phonophobia							
Yes	—	1.85 (1.19–2.86)	0.006	0.85 (0.50–1.46)	0.56	—	—
No		2.13 (1.50–3.04)	<0.0001	1.18 (0.79–1.77)	0.41	—	—
Nausea/vomiting							
Yes	—	1.64 (1.12–2.40)	0.01	1.00 (0.66–1.51)	0.99	—	—
No		2.66 (1.79–3.94)	<0.0001	1.11 (0.66–1.85)	0.70	—	—
Pulsating pain quality							
Yes	—	1.93 (1.30–2.86)	0.001	0.58 (0.32–1.02)	0.06	—	—
No		2.09 (1.43–3.07)	0.0002	1.62 (1.10–2.38)	0.02	—	—
Aggravation by physical activity							
Yes	—	1.73 (1.01–2.95)	0.04	0.78 (0.42–1.46)	0.43	—	—
No		2.13 (1.54–2.95)	<0.0001	1.18 (0.81–1.71)	0.40	—	—

	No migraine history (N=22,715)	Active migraine with aura (N=1,434)	P value	Active migraine without aura (N=2,176)	P value	Prior migraine (N=1,515)	P value
Ischemic stroke	N=257	N=22		N=17		N=16	
Overall	1.00	1.79 (1.15–2.78)	0.01	1.01 (0.61–1.65)	0.98	0.82 (0.50–1.36)	0.45
Attack duration of 4–72 hours							
Yes	—	1.64 (0.97–2.77)	0.06	1.17 (0.69–1.97)	0.57	—	—
No		2.22 (1.05–4.72)	0.04	0.50 (0.12–2.00)	0.33		
Unilateral pain location							
Yes	—	1.42 (0.75–2.68)	0.28	0.75 (0.35–1.59)	0.45	—	—
No		2.28 (1.28–4.08)	0.006	1.32 (0.70–2.49)	0.39		
Photophobia							
Yes	—	1.43 (0.82–2.51)	0.21	1.12 (0.62–2.00)	0.71	—	—
No		2.80 (1.44–5.46)	0.003	0.81 (0.33–1.97)	0.64		
Phonophobia							
Yes	—	1.34 (0.63–2.85)	0.44	0.55 (0.20–1.48)	0.24	—	—
No		2.12 (1.25–3.58)	0.005	1.35 (0.77–2.36)	0.30		
Nausea/vomiting							
Yes	—	0.91 (0.43–1.93)	0.80	1.20 (0.68–2.11)	0.52	—	—
No		3.27 (1.93–5.51)	<0.0001	0.66 (0.25–1.77)	0.41		
Pulsating pain quality							
Yes	—	1.66 (0.88–3.13)	0.12	0.85 (0.42–1.73)	0.66	—	—
No		1.92 (1.07–3.43)	0.03	1.20 (0.61–2.34)	0.60		
Aggravation by physical activity							
Yes	—	1.61 (0.71–3.62)	0.25	1.05 (0.46–2.36)	0.91	—	—
No		1.87 (1.13–3.11)	0.02	0.98 (0.54–1.81)	0.96		
Myocardial infarction	N=243	N=25		N=17		N=20	
Overall	1.00	2.11 (1.39–3.21)	0.0004	1.01 (0.62–1.66)	0.96	1.08 (0.68–1.70)	0.74

	No migraine history (N=22,715)	Active migraine with aura (N=1,434)	P value	Active migraine without aura (N=2,176)	P value	Prior migraine (N=1,515)	P value
Attack duration of 4–72 hours							
Yes	—	2.26 (1.42–3.59)	0.0006	0.86 (0.47–1.57)	0.62	—	—
No		1.68 (0.69–4.08)	0.25	1.51 (0.67–3.41)	0.32		
Unilateral pain location							
Yes	—	2.26 (1.34–3.83)	0.002	0.97 (0.50–1.90)	0.93	—	—
No		1.93 (1.02–3.64)	0.04	1.06 (0.53–2.16)	0.86		
Photophobia							
Yes	—	2.39 (1.52–3.76)	0.0002	1.00 (0.55–1.84)	0.99	—	—
No		1.32 (0.49–3.56)	0.58	1.03 (0.46–2.33)	0.94		
Phonophobia							
Yes	—	2.14 (1.16–3.93)	0.01	1.07 (0.52–2.16)	0.86	—	—
No		2.10 (1.22–3.61)	0.008	0.97 (0.50–1.89)	0.92		
Nausea/vomiting							
Yes	—	1.98 (1.17–3.36)	0.01	1.02 (0.55–1.87)	0.95	—	—
No		2.35 (1.24–4.43)	0.009	1.00 (0.44–2.25)	0.99		
Pulsating pain quality							
Yes	—	1.81 (0.98–3.32)	0.06	0.32 (0.10–1.00)	0.05	—	—
No		2.43 (1.41–4.18)	0.001	1.88 (1.09–3.23)	0.02		
Aggravation by physical activity							
Yes	—	1.40 (0.58–3.42)	0.46	0.51 (0.16–1.60)	0.25	—	—
No		2.42 (1.53–3.83)	0.0002	1.28 (0.74–2.20)	0.38		

* controlling for: age, body mass index, diabetes, physical activity, postmenopausal hormone use, oral contraceptive use, history of hypertension, alcohol consumption, smoking, family history of premature myocardial infarction, LDL levels, HDL levels.

† A major cardiovascular event was defined as the first of any of these events: nonfatal ischemic stroke, nonfatal myocardial infarction, or death from ischemic cardiovascular cause.