# Migraine and Risk of Cardiovascular Disease in Men

*Tobias Kurth, MD, ScD; J. Michael Gaziano, MD, MPH; Nancy R. Cook, ScD; Vadim Bubes, PhD; Giancarlo Logroscino, MD, PhD; Hans-Christoph Diener, MD, PhD; Julie E. Buring, ScD*

**Background:** The vascular component of the migraine-specific physiologic profile and the observed adverse cardiovascular risk profile in migraineurs suggest an association between migraine and cardiovascular disease (CVD). In women, migraine has been associated with increased risk of CVD, including coronary events. Compatible data in men are lacking.

**Methods:** Prospective cohort study of 20 084 men aged 40 to 84 years participating in the Physicians' Health Study. In yearly questionnaires, men were asked for information on migraine, risk factors, and the occurrence of study end points. We classified men as having migraine if they indicated migraine during the first 5 years, after which time follow-up began. Information on aura was not available. All the men were free of CVD at the start of follow-up. During a mean of 15.7 years, we followed up participants for the occurrence of a first major CVD event (nonfatal ischemic stroke, nonfatal myocardial infarction, or death from ischemic CVD). We also evaluated the individual end points, coronary revascularization, and angina.

**Results:** A total of 1449 men (7.2%) reported migraine, and during follow-up, 2236 major CVD events occurred. Compared with nonmigraineurs, men who reported migraine had multivariable-adjusted hazard ratios (95% confidence intervals) of 1.24 (1.06-1.46; $P=.008$) for major CVD, 1.12 (0.84-1.50; $P=.43$) for ischemic stroke, 1.42 (1.15-1.77; $P<.001$) for myocardial infarction, 1.05 (0.89-1.24; $P=.54$) for coronary revascularization, 1.15 (0.99-1.33; $P=.068$) for angina, and 1.07 (0.80-1.43; $P=.65$) for ischemic cardiovascular death.

**Conclusion:** In this large prospective cohort of apparently healthy men, migraine was associated with increased risk of major CVD, which was driven by increased risk of myocardial infarction.

*Arch Intern Med. 2007;167:795-801*

**Author Affiliations:** Divisions of Preventive Medicine (Drs Kurth, Gaziano, Cook, Bubes, and Buring) and Aging (Drs Kurth, Gaziano, Logroscino, and Buring), Department of Medicine, Brigham and Women's Hospital, and Department of Ambulatory Care and Prevention (Dr Buring), Harvard Medical School, Boston, Mass; Department of Epidemiology, Harvard School of Public Health, Boston (Drs Kurth, Cook, Logroscino, and Buring); Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, Boston (Dr Gaziano); and Department of Neurology, University of Duisburg-Essen, Essen, Germany (Dr Diener).

MIGRAINE IS A PRIMARY chronic intermittent headache disorder characterized by pulsating unilateral severe pain attacks with associated autonomic and gastrointestinal symptoms.[1,2] In some patients, transient neurologic symptoms—mostly visual disturbances—can occur that are known as "migraine aura." The prevalence of migraine peaks in midlife, and in the United States alone, more than 28 million people, approximately 18% and 6% of the female and male populations, respectively, have migraines.[3]

The physiologic profile of migraine involves the neurovascular system,[4,5] and population-based studies have linked migraine with a higher prevalence of cardiovascular risk factors, such as elevated blood pressure, an unfavorable cholesterol profile, and an elevated Framingham risk score for coronary heart disease (CHD),[6] as well as a higher prevalence of prothrombotic factors, including von Willebrand factor,[7] factor V Leiden,[8] prothrombin factor 1.2,[9] serotonin,[10] and endothelin.[11] Moreover, the genetic polymorphism C677T methylenetetrahydrofolate reductase has been associated with migraine,[12] which also is associated with increased levels of homocysteine, a risk factor for cardiovascular disease (CVD). Thus, it seems plausible that migraine may be associated with increased risk of ischemic vascular events. Several epidemiologic studies[13-18] have linked migraine with increased risk of ischemic stroke, but a firm association between migraine and coronary events has not been established.[19-21] Recently, however, data from the Women's Health Study (WHS) indicated an association between migraine, specifically migraine with aura, and major ischemic CVD, including CHD, after a mean of 10 years of follow-up[22] that was not apparent with shorter follow-up.[21]

In a previous report from the Physicians' Health Study (PHS), no association between migraine and CHD was observed after a mean of 12 years of follow-up.[21] Because the prevalence of migraine is lower

in men than in women,[3] it is plausible that long-term follow-up is needed to associate migraine with subsequent risk of CVD, specifically, CHD. We aim to evaluate the association between migraine and risks of overall and specific ischemic vascular events in the PHS, a large prospective cohort of apparently healthy men, during a mean of almost 16 years of follow-up.

## METHODS

### STUDY POPULATION

This prospective cohort study consisted of participants from the PHS, a completed randomized placebo-controlled trial designed to test the benefits and risks of low-dose aspirin and beta carotene in the primary prevention of CVD and cancer in apparently healthy men. The design, methods, and results have been described in detail previously.[23,24] Briefly, 22 071 US male physicians aged 40 to 84 years at study entry (1981-1984) and without a history of CVD, cancer, or other major illnesses were randomly assigned to receive active aspirin (325 mg on alternate days), active beta carotene (50 mg every other day), both active agents, or both placebos. All the participants provided written informed consent, and the institutional review board of Brigham and Women's Hospital approved the PHS. Baseline information was self-reported and was collected by means of a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes and other information during the study period. Posttrial follow-up is ongoing.[25] For this analysis, we included information through February 28, 2005. As of this date, follow-up was more than 97% complete.

### ASSESSMENT OF MIGRAINE

On the 6-month and subsequent annual questionnaires, participants were asked whether they had experienced a migraine since they last filled out the questionnaire. Because we did not ask participants about any history of migraine and to make the migraine ascertainment more comparable with other studies,[17,22] we classified men as having migraine if they indicated migraine during the first 5 years of follow-up. We furthermore classified participants as having "frequent migraine" if they reported migraine 4 or more times during this exposure window. We also ascertained reports of nonmigraine headache (indication of headache but not migraine) in a similar manner. We had no further details about the migraine headache that would have allowed us to classify migraine according to the 1988 International Headache Society criteria.[26] However, results from the WHS, a prospective cohort study similar in design and data ascertainment as the PHS, showed good agreement with these criteria, indicating that 83.5% fulfilled all but 1 modified International Headache Society criteria (code 1.7, migrainous disorder) and 46.6% fulfilled all modified International Headache Society criteria for migraine (code 1.1).[22] Information on migraine aura was not recorded in the PHS.

### OUTCOME ASCERTAINMENT

All the participants were followed up after the 60-month questionnaire for the first occurrence of major CVD—a combined end point composed of nonfatal ischemic stroke, nonfatal myocardial infarction (MI), or death from ischemic CVD. Coronary revascularization (bypass surgery and percutaneous coronary angioplasty) and angina were also recorded. Medical records were obtained for all cardiovascular events, but not for coronary revascularization and angina, and were reviewed by an end points committee of physicians. The occurrence of MI was confirmed if symptoms met the World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiograms. Nonfatal stroke was confirmed if the participant had a new focal neurologic deficit of sudden onset and vascular origin that persisted for more than 24 hours. Stroke was classified into its major subtypes based on available clinical and diagnostic test information, including brain scans with excellent interrater agreement.[27] Cardiovascular deaths were confirmed by review of autopsy reports, death certificates, medical records, and information obtained from next of kin or other family members. For this analysis, we included only ischemic events.

### STATISTICAL ANALYSES

Of the 22 071 participants, we excluded 462 who died, 57 with missing migraine information, 958 who reported CVD or coronary revascularization, and 510 who reported angina during the 60-month exposure window, leaving 20 084 men free of CVD or angina at 5-year follow-up for this analyses. We compared the characteristics of participants with respect to their migraine status at 60 months using analyses of covariance for continuous measurements, adjusting for age. We used direct standardization to adjust categorical variables and incidence rates for CVD for age in 5-year increments.

We used Cox proportional hazards models to evaluate the association between migraine and the various outcomes. We calculated age- and multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs). In the multivariable models, we adjusted for age (continuous), history of hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive drug treatment), history of diabetes mellitus, smoking status (never, past, or current), exercise (rarely or never, <1 time per week, 1-4 times per week, or ≥5 times per week), body mass index (continuous) (calculated as weight in kilograms divided by height in meters squared), alcohol consumption (rarely or never, 1-3 times per month, 1-6 times per week, or ≥1 time per day), history of a cholesterol level of 240 mg/dL or greater (≥6.21 mmol/L), parental history of MI before age 60 years, and randomized treatment assignments. In further analysis, we also evaluated the association between frequent migraine and nonmigraine headaches and the various outcome events.

We tested the proportionality assumption by including an interaction term for migraine status with the logarithm of time to the proportional hazards models and found no significant violation. We evaluated effect modification by age (<55, 55-64, or ≥65 years), smoking status (never, past, or current), history of hypertension (yes or no), and randomized aspirin assignment. We assessed statistically significant effect modification by contrasting models with and without an interaction term indicator variable(s) using the likelihood ratio test. We performed all analyses using statistical software (SAS version 9.1; SAS Institute Inc, Cary, NC). All tests were 2-tailed, and $P<.05$ was considered statistically significant.

## RESULTS

Of the 20 084 participants, 1449 (7.2%) reported migraine until the 60-month questionnaire, and 434 reported migraine 4 or more times ("frequent migraine") during this period. **Table 1** summarizes the age-adjusted characteristics of the participants according to

**Table 1. Age-Adjusted Characteristics According to Migraine Status in 20 084 Participants From the Physicians' Health Study**

| Characteristic | No Migraine (n = 18 635) | Migraine* (n = 1449) | Frequent Migraine† (n = 434) |
|---|---|---|---|
| Age, mean (SE), y | 58.2 (0.07) | 56.5 (0.22) | 56.0 (0.39) |
| Body mass index, mean (SE)‡ | 24.8 (0.02) | 24.6 (0.07) | 24.5 (0.13) |
| Systolic blood pressure, mean (SE), mm Hg | 125.9 (0.09) | 125.7 (0.31) | 124.9 (0.56) |
| Diastolic blood pressure, mean (SE), mm Hg | 78.7 (0.06) | 78.9 (0.20) | 78.8 (0.36) |
| History of hypertension, % | 31.4 | 34.2 | 34.0 |
| Smoking, %§ | | | |
| Never | 49.0 | 51.2 | 53.5 |
| Past | 43.8 | 43.0 | 40.1 |
| Current | 7.3 | 5.8 | 6.0 |
| Alcohol consumption, %§ | | | |
| Rarely/never | 14.5 | 16.3 | 18.3 |
| 1-3/mo | 10.8 | 13.4 | 13.5 |
| 1-6/wk | 49.8 | 48.1 | 46.0 |
| ≥1/d | 24.9 | 22.3 | 21.9 |
| Exercise, %§ | | | |
| Rarely/never | 38.2 | 39.0 | 38.1 |
| <1/wk | 4.4 | 4.6 | 3.9 |
| 1-4/wk | 44.6 | 44.6 | 45.6 |
| 5-7/wk | 12.9 | 11.8 | 12.1 |
| History of cholesterol ≥240 mg/dL, %§ | 9.8 | 10.9 | 7.3 |
| Family history of premature myocardial infarction, %§ | 9.1 | 8.3 | 9.1 |
| History of diabetes mellitus, %§ | 3.7 | 3.0 | 0.8 |

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.
*Any indication of migraine during a 5-year exposure window.
†Four or more migraine reports during a 5-year exposure window.
‡Calculated as weight in kilograms divided by height in meters squared.
§Because of rounding and missing values, percentages may not total 100.

migraine status. Compared with men who did not report migraine, migraineurs were younger, more often reported hypertension, were less likely to currently smoke cigarettes and consume alcohol regularly, and were more likely to report a history of an elevated cholesterol level of 240 mg/dL or greater (≥6.21 mmol/L).

During a mean of 15.7 years of follow-up (316 076 person-years), 2236 major ischemic CVD events, 750 ischemic strokes, 1046 MIs, and 866 ischemic CVD deaths were confirmed. In addition, 2257 coronary revascularizations and 2625 cases of angina were reported.

**Table 2** summarizes the age- and multivariable-adjusted associations between migraine and frequent migraine and the various outcome events. Compared with men who did not report migraine, those who reported migraine were at significantly increased risk of major CVD and MI. The multivariable-adjusted HRs (95% CIs) were 1.24 (1.06-1.46; $P=.008$) for major cardiovascular events, 1.12 (0.84-1.50; $P=.43$) for ischemic stroke, 1.42 (1.15-1.77; $P<.001$) for MI, and 1.07 (0.80-1.43; $P=.65$) for ischemic cardiovascular death. In addition, men who reported migraine had multivariable-adjusted HRs (95% CIs) of 1.05 (0.89-1.24; $P=.54$) for coronary revascularization and 1.15 (0.99-1.33; $P=.07$) for angina. The magnitude of association was similar for the 434 men classified as having frequent migraines compared with men without migraines.

The age-adjusted incidence of major CVD per 10 000 men per year was 8.5 for those who did not report migraine and 10.4 for those with migraine. Regarding MI, the age-adjusted incidence per 10 000 men per year was 3.6 for those without migraine and 4.9 for those with migraine. **Figure 1** shows the multivariable-adjusted cumulative incidence of major cardiovascular events, and **Figure 2** shows the multivariable-adjusted cumulative incidences of ischemic stroke, MI, coronary revascularization, and angina according to migraine status. The incidence curves diverge for major CVD, MI, and angina.

When we evaluated the association between nonmigraine headache and the various outcome events, we found no significant associations. The multivariable-adjusted HRs ranged from 0.92 (95% CI, 0.80-1.07) for death from ischemic CVD to 1.07 (95% CI, 0.91-1.25) for ischemic stroke. The associations between migraine and major CVD, ischemic stroke, and MI were not significantly modified by smoking and hypertension status or by randomized aspirin assignment. The association between migraine and ischemic stroke was significantly modified by age ($P=.03$). Compared with men who did not report migraine, the age-adjusted HR of ischemic stroke was 1.84 (95% CI, 1.10-3.08) for migraineurs younger than 55 years, whereas there was no significant association in the older age groups. Age did not significantly modify the association between migraine and major CVD and MI.

## COMMENT

In this large prospective cohort study of initially healthy middle-aged men who were free of CVD or angina at study entry and during the 5-year migraine ascertainment period, migraine was associated with a significantly in-

**Table 2. Age- and Multivariable-Adjusted Hazard Ratios for Ischemic Vascular Events According to Migraine Status in 20 084 Participants From the Physicians' Health Study***

| Event | No Migraine (n = 18 635) | Migraine† (n = 1449) | *P* Value | Frequent Migraine‡ (n = 434) | *P* Value |
|---|---|---|---|---|---|
| Major cardiovascular event,§ No. of patients (n = 2236) | 2067 | 169 | | 47 | |
| Age adjusted | 1.00 | 1.19 (1.02-1.40) | .03 | 1.16 (0.87-1.55) | .32 |
| Multiple adjusted‖ | 1.00 | 1.24 (1.06-1.46) | .008 | 1.23 (0.91-1.65) | .17 |
| Ischemic stroke, No. of patients (n = 750) | 699 | 51 | | 15 | |
| Age adjusted | 1.00 | 1.09 (0.82-1.44) | .57 | 1.14 (0.68-1.90) | .62 |
| Multiple adjusted‖ | 1.00 | 1.12 (0.84-1.50) | .43 | 1.17 (0.69-1.99) | .57 |
| Myocardial infarction, No. of patients (n = 1046) | 952 | 94 | | 28 | |
| Age adjusted | 1.00 | 1.36 (1.10-1.68) | .01 | 1.37 (0.94-2.00) | .10 |
| Multiple adjusted‖ | 1.00 | 1.42 (1.15-1.77) | <.001 | 1.52 (1.04-2.21) | .03 |
| Coronary revascularization,¶ No. of patients (n = 2257) | 2091 | 166 | | 43 | |
| Age adjusted | 1.00 | 1.05 (0.89-1.23) | .58 | 0.90 (0.67-1.22) | .50 |
| Multiple adjusted‖ | 1.00 | 1.05 (0.89-1.24) | .54 | 0.97 (0.71-1.31) | .82 |
| Angina, No. of patients (n = 2625) | 2424 | 201 | | 54 | |
| Age adjusted | 1.00 | 1.12 (0.97-1.29) | .14 | 1.00 (0.76-1.31) | >.99 |
| Multiple adjusted‖ | 1.00 | 1.15 (0.99-1.33) | .07 | 1.07 (0.82-1.41) | .61 |
| Cardiovascular disease death, No. of patients (n = 866) | 814 | 52 | | 10 | |
| Age adjusted | 1.00 | 1.00 (0.76-1.33) | .99 | 0.72 (0.38-1.34) | .30 |
| Multiple adjusted‖ | 1.00 | 1.07 (0.80-1.43) | .65 | 0.76 (0.40-1.48) | .42 |

*Data are presented as hazard ratio (95% confidence interval) unless otherwise indicated.
†Any indication of migraine during a 5-year exposure window.
‡Four or more migraine reports during a 5-year exposure window.
§A major cardiovascular event was defined as the first of any of the following events: nonfatal ischemic stroke, nonfatal myocardial infarction, or death from ischemic cardiovascular cause.
‖Adjusted for age, history of hypertension, diabetes mellitus, smoking status, exercise, body mass index (calculated as weight in kilograms divided by height in meters squared), alcohol consumption, a cholesterol level of 240 mg/dL (6.21 mmol/L) or greater, parental history of myocardial infarction before age 60 years, and randomized treatment assignments.
¶Includes reports of bypass surgery and percutaneous coronary angioplasty.

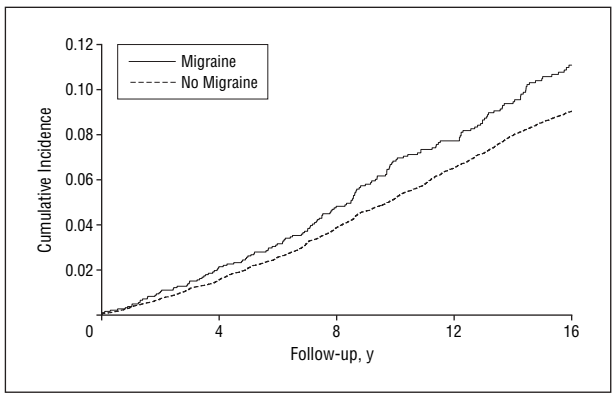


**Figure 1.** Multivariable-adjusted cumulative incidence of major cardiovascular disease, defined as the first of nonfatal ischemic stroke, nonfatal myocardial infarction, or ischemic cardiovascular disease death according to migraine status and adjusted for age, history of hypertension, diabetes mellitus, smoking status, exercise, body mass index (calculated as weight in kilograms divided by height in meters squared), alcohol consumption, a cholesterol level of 240 mg/dL (6.21 mmol/L) or greater, parental history of myocardial infarction before age 60 years, and randomized treatment assignments.

creased risk of major cardiovascular events, which was driven by an increased risk of MI. Compared with men who did not indicate migraine by the 5-year questionnaire and after adjustment for a variety of cardiovascular risk factors, men who reported migraine had a 24% increased risk of major CVD and a 42% increased risk of MI. Migraine was not statistically significantly associated with increased risk of ischemic stroke, death from ischemic CVD, or coronary revascularization and was marginally associated with angina. The association between migraine and ischemic stroke, however, was significantly modified by age, indicating an increased risk of ischemic stroke for men with migraine who were 40 to 54 years of age but not for older age groups. Men who indicated migraine 4 or more times during the 5-year exposure window did not have further increased risk of CVD.

The associations between migraine and major CVD, MI, and ischemic stroke are compatible with findings from the WHS.[22] In this prospective cohort of 27 840 apparently healthy women, any history of migraine was associated with a multivariable-adjusted HR of 1.42 (95% CI, 1.16-1.74) for major CVD, 1.41 (95% CI, 1.03-1.91) for MI, and 1.22 (95% CI, 0.88-1.68) for ischemic stroke compared with women with no history of migraine. In contrast, however, the study in women found significantly increased risk of coronary revascularization, angina, and CVD death for women with overall migraine compared with women who did not report migraine. More specifically, the results of the WHS indicate that the increased risk of any ischemic vascular events is only apparent for women with migraine with aura. Migraineurs without aura do not have increased risk of any ischemic vascular events.[22] In the PHS, there was no information on migraine aura recorded.

In a previous report from the PHS,[21] migraine was not associated with increased risk of CHD during a mean of 12 years of follow-up. Because migraine is less prevalent in men,[3] the association between migraine and CHD may not have been apparent because of the shorter follow-

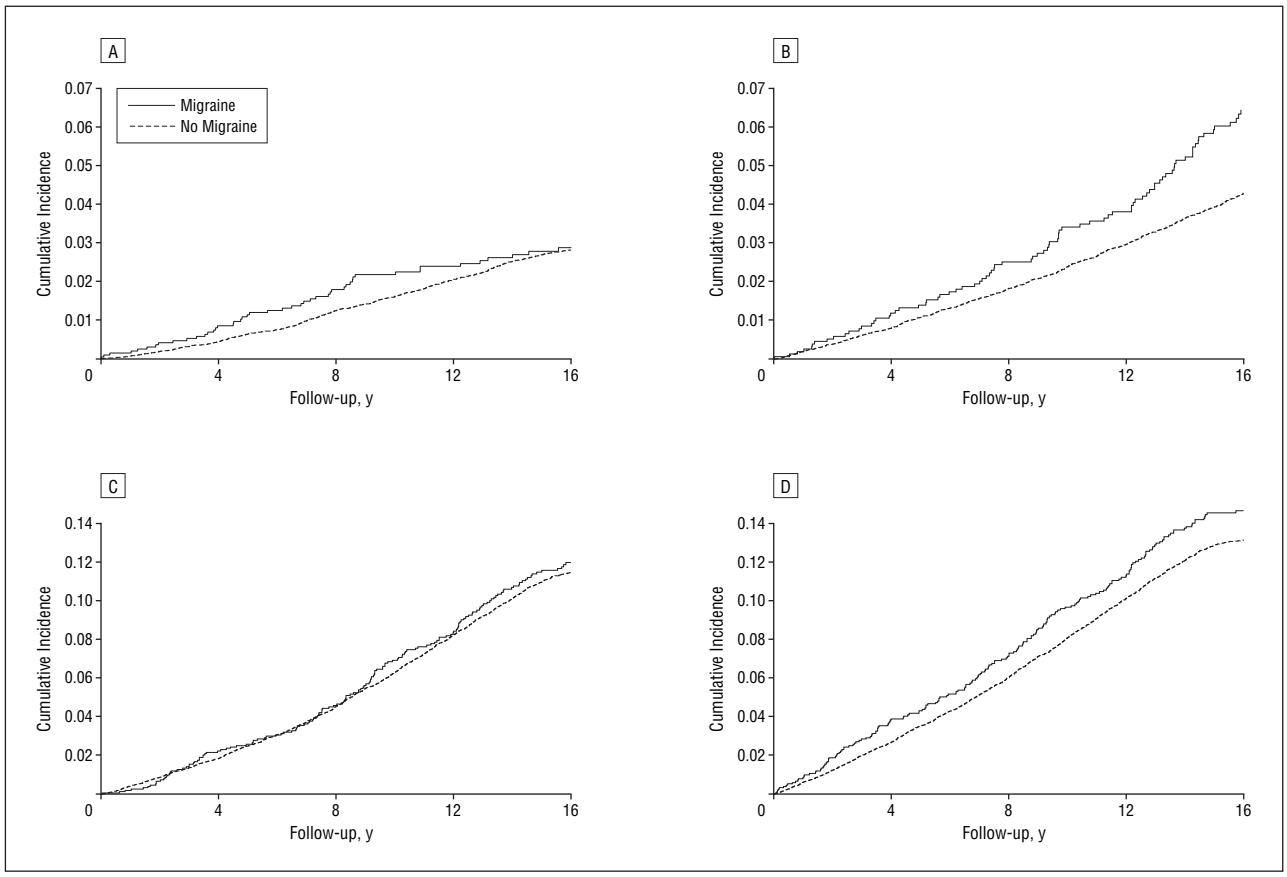


**Figure 2.** Multivariable-adjusted cumulative incidence of ischemic stroke (A), myocardial infarction (B), coronary revascularization (C), and angina (D) according to migraine status and adjusted for age, history of hypertension, diabetes mellitus, smoking status, exercise, body mass index (calculated as weight in kilograms divided by height in meters squared), alcohol consumption, a cholesterol level of 240 mg/dL (6.21 mmol/L) or greater, parental history of myocardial infarction before age 60 years, and randomized treatment assignments.

up. In addition, we used a different migraine definition than the previous study, which may indicate that different migraine patterns have different associations with CVD risk. This should be explored in future research studies.

Regarding ischemic stroke, the present finding is in contrast to a previous report from the PHS[14] that showed a 2-fold increased risk of ischemic stroke in men who reported migraine during mean follow-up of 5 years. The present data, however, are compatible with the findings from the WHS, which[17,22] did not show significant associations between overall migraine and ischemic stroke. Because in stratified analyses of the PHS data there was an apparent association between migraine and ischemic stroke in men younger than 55 years, these data support previous studies showing that the association between migraine and ischemic stroke is particularly apparent in younger individuals[28] but not in the elderly.[17,29] Thus, it may be that the association between migraine and ischemic stroke diminishes with increasing age and, thus, with increasing follow-up duration, which may explain the pattern of the cumulative incidence curve (Figure 2).

Regarding CHD, 2 population-based studies[6,30] found an association between migraine and prevalent CVD, and 1 study[31] found increased risk of non-MI ischemic heart disease. In contrast, several prospective studies[20,32] did not find associations between migraine and major coronary events. Results from the Atherosclerosis Risk in Communities Study[20] show an increased prevalence of angina in migraineurs but do not indicate an association between migraine and CHD in the 12 409 participants. A study[32] of 130 411 migraineurs and an equal number of matched nonmigraineurs from a US health plan insurance database showed an association between migraine and ischemic stroke, transient ischemic attacks, and angina but not MI. However, in that study the mean follow-up time was only 1.4 years. In a study[33] of 944 women with chest pain or symptoms suggestive of MI, women with migraine did not have increased risk of subsequent CVD or all-cause mortality during mean follow-up of 4.4 years.

Several mechanisms have been proposed supporting a biological link between migraine and vascular events. However, the precise mechanisms are currently unknown and are likely to be complex. For example, migraine has been associated with an unfavorable cardiovascular risk profile,[6] and migraine frequency and severity have been associated with increased body mass index.[34] Thus, it is possible that migraine is a marker of progressive atherosclerosis. However, the increased risk of vascular events remained after controlling for major cardiovascular risk factors in the present data and other studies.[17,18,22] However, it has recently been shown that in women with indications for coronary angiography, those with migraine had less severe angiographic coronary artery disease than those without migraine.[33] It is

also plausible that compared with individuals with the same degree of atherosclerosis, migraineurs have more vascular symptoms and events due to the migraine-specific vascular dysfunction[4,35] or that a synergistic effect exists between the vascular and endothelial dysfunction of migraine and factors that increase the risk of thrombotic vascular events.

Migraine has also been associated with biomarkers that have been linked with increased risk of CVD[7-11] and the release of vasoactive neuropeptides that may stimulate inflammatory responses.[36] Furthermore, genetic polymorphisms may predispose to migraine and CVD. A polymorphism in the methylenetetrahydrofolate reductase gene (C677T) has been associated with migraine[12] that has also been associated with increased levels of homocysteine, a risk factor for CVD. A previously described association between migraine and patent foramen ovale[37] may partly explain the association between migraine and ischemic stroke but unlikely explains the association between migraine and MI.

This study has several strengths, including the prospective design, large number of participants and outcome events, long follow-up, and homogeneous nature of the cohort, which may reduce confounding. Furthermore, except for coronary revascularization and angina, all of the outcome events were confirmed after medical record review.

Several limitations should be considered when interpreting these results. First, because information on aura was not recorded, we could not further evaluate whether, specifically, migraine with aura increases the risk of CVD in men, as suggested by findings from the WHS.[22] Second, migraine was self-reported by the participating physicians, and we had no further details to classify migraine based on the criteria established by the International Headache Society.[2] However, results from the WHS showed good agreement with these criteria.[22,38] Furthermore, we found no association between reports of nonmigraine headache and risk of any vascular events, indicating that potential misclassification of migraine would most likely lead to an underestimation of the association between migraine and CVD. Third, we had no information about the use of migraine-specific drugs (ie, triptans and ergot alkaloids), which owing to their vasoconstrictive ability may be associated with increased risk of ischemic vascular events. The current cardiovascular safety and postmarketing data[31,32,39,40] for migraine-specific drugs do not support a strong association with CVD. A recent study,[41] however, indicated that individuals with migraine who overuse ergotamines may have an increased risk of ischemic complications, in particular those who concomitantly use cardiovascular drugs. Fourth, despite controlling for a variety of potential confounders, residual and unmeasurable confounding is possible in this observational study. Fifth, the PHS was composed of middle-aged and mostly white physicians; thus, generalizability may be limited. However, based on current knowledge, we have no reason to believe that the biological mechanisms by which migraine may lead to CVD differs in other male populations.

In conclusion, in this large prospective cohort of apparently healthy middle-aged men, migraine was associated with increased risk of subsequent major CVD, which was driven by increased risk of MI.

**Accepted for Publication:** December 8, 2006.
**Correspondence:** Tobias Kurth, MD, ScD, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave E, Boston, MA 02215-1204 (tkurth@rics.bwh.harvard.edu).
**Author Contributions:** *Study concept and design:* Kurth. *Acquisition of data:* Gaziano and Buring. *Analysis and interpretation of data:* Kurth, Gaziano, Cook, Bubes, Logroscino, Diener, and Buring. *Drafting of the manuscript:* Kurth. *Critical revision of the manuscript for important intellectual content:* Kurth, Gaziano, Cook, Bubes, Logroscino, Diener, and Buring. *Statistical analysis:* Kurth, Cook, and Bubes. *Obtained funding:* Gaziano and Buring. *Administrative, technical, and material support:* Gaziano, Diener, and Buring. *Study supervision:* Gaziano and Buring.
**Financial Disclosure:** Dr Kurth has received investigator-initiated research funding as principal or co-investigator from the National Institutes of Health, Bayer AG, McNeil Consumer & Specialty Pharmaceuticals, and Wyeth Consumer Healthcare. He is also a consultant for i3 Drug Safety and has received an honorarium from Organon. Dr Gaziano has received investigator-initiated research funding and support as principal investigator from the National Institutes of Health, BASF, DSM Pharmaceuticals, Wyeth Pharmaceuticals, McNeil Consumer Products, and Pliva. He is also a consultant for Bayer, McNeil Consumer Products, Wyeth Pharmaceuticals, Merck, Nutraquest, and GlaxoSmithKline and has received honoraria from Bayer and Pfizer. Dr Cook has received investigator-initiated research funding and support as principal investigator from the National Institutes of Health and research support from Roche Molecular Systems. She has also served as a consultant for Bayer. Dr Logroscino has received investigator-initiated research funding from the National Institutes of Health and honoraria from Pfizer and Lilly Pharmaceutical. Dr Diener has received investigator-initiated research funding and support from the German Research Foundation, Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag, and Pfizer and honoraria from Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, Boehringer Ingelheim, Bristol-Meyers Squibb, GlaxoSmith Kline, Grünenthal, Janssen-Cilag, Lilly, La Roche, 3M Medica, MSD, Novartis, Johnson & Johnson, Pierre Fabre, Pfizer, Schaper & Brümmer, Sanofi-Aventis, and Weber & Weber. Dr Buring has received investigator-initiated research funding and support as principal investigator from the National Institutes of Health and Dow Corning Corporation, research support from Bayer Health Care and the Natural Source Vitamin E Association, and honoraria from Bayer. She also serves on an external scientific advisory committee for a study by Procter & Gamble.
**Funding/Support:** The PHS was funded by grants CA 34944, CA 40360, HL 26490, and HL 34595 from the National Institutes of Health.
**Acknowledgment:** We thank the participants in the PHS for their outstanding commitment and cooperation and the entire PHS staff for their expert and unfailing assistance.

## REFERENCES


1. Silberstein SD. Migraine. *Lancet*. 2004;363:381-391.
2. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24(suppl 1):9-160.
3. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41:646-657.
4. Hargreaves RJ, Shepheard SL. Pathophysiology of migraine: new insights. *Can J Neurol Sci*. 1999;26(suppl 3):S12-S19.
5. Goadsby PJ, Lipton RB, Ferrari MD. Migraine: current understanding and treatment. *N Engl J Med*. 2002;346:257-270.
6. Scher AI, Terwindt GM, Picavet HS, Verschuren WM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: the GEM population-based study. *Neurology*. 2005;64:614-620.
7. Tietjen GE, Al-Qasmi MM, Athanas K, Dafer RM, Khuder SA. Increased von Willebrand factor in migraine. *Neurology*. 2001;57:334-336.
8. Soriani S, Borgna-Pignatti C, Trabetti E, Casartelli A, Montagna P, Pignatti PF. Frequency of factor V Leiden in juvenile migraine with aura. *Headache*. 1998; 38:779-781.
9. Hering-Hanit R, Friedman Z, Schlesinger I, Ellis M. Evidence for activation of the coagulation system in migraine with aura. *Cephalalgia*. 2001;21:137-139.
10. Ferrari MD, Odink J, Tapparelli C, Van Kempen GM, Pennings EJ, Bruyn GW. Serotonin metabolism in migraine. *Neurology*. 1989;39:1239-1242.
11. Gallai V, Sarchielli P, Firenze C, et al. Endothelin 1 in migraine and tension-type headache. *Acta Neurol Scand*. 1994;89:47-55.
12. Scher AI, Terwindt GM, Verschuren WM, et al. Migraine and MTHFR C677T genotype in a population-based sample. *Ann Neurol*. 2006;59:372-375.
13. Collaborative Group for the Study of Stroke in Young Women. Oral contraceptives and stroke in young women: associated risk factors. *JAMA*. 1975;231: 718-722.
14. Buring JE, Hebert P, Romero J, et al. Migraine and subsequent risk of stroke in the Physicians' Health Study. *Arch Neurol*. 1995;52:129-134.
15. Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. *JAMA*. 2004;291:427-434.
16. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ*. 2005;330:63-65.
17. 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.
18. Stang PE, Carson AP, Rose KM, et al. Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. *Neurology*. 2005; 64:1573-1577.
19. Rosamond W. Are migraine and coronary heart disease associated? an epidemiologic review. *Headache*. 2004;44:S5-S12.
20. Rose KM, Carson AP, Sanford CP, et al. Migraine and other headaches: associations with Rose angina and coronary heart disease. *Neurology*. 2004;63: 2233-2239.
21. Cook NR, Benseñor IM, Lotufo PA, et al. Migraine and coronary heart disease in women and men. *Headache*. 2002;42:715-727.
22. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. *JAMA*. 2006;296:283-291.
23. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med*. 1989;321:129-135.
24. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996;334:1145-1149.
25. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II: a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. *Ann Epidemiol*. 2000;10:125-134.
26. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*. 1988;8(suppl 7):1-96.
27. Berger K, Kase CS, Buring JE. Interobserver agreement in the classification of stroke in the Physicians' Health Study. *Stroke*. 1996;27:238-242.
28. Schwaag S, Nabavi DG, Frese A, Husstedt IW, Evers S. The association between migraine and juvenile stroke: a case-control study. *Headache*. 2003;43:90-95.
29. Mosek A, Marom R, Korczyn AD, Bornstein N. A history of migraine is not a risk factor to develop an ischemic stroke in the elderly. *Headache*. 2001;41: 399-401.
30. Mitchell P, Wang JJ, Currie J, Cumming RG, Smith W. Prevalence and vascular associations with migraine in older Australians. *Aust N Z J Med*. 1998;28: 627-632.
31. Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology*. 2004;62:563-568.
32. Velentgas P, Cole JA, Mo J, Sikes CR, Walker AM. Severe vascular events in migraine patients. *Headache*. 2004;44:642-651.
33. Ahmed B, Bairey Merz CN, McClure C, et al. Migraines, angiographic coronary artery disease and cardiovascular outcomes in women. *Am J Med*. 2006;119: 670-675.
34. Bigal ME, Liberman JN, Lipton RB. Obesity and migraine: a population study. *Neurology*. 2006;66:545-550.
35. Uyarel H, Erden I, Cam N. Acute migraine attack, angina-like chest pain with documented ST-segment elevation and slow coronary flow. *Acta Cardiol*. 2005; 60:221-223.
36. Waeber C, Moskowitz MA. Migraine as an inflammatory disorder. *Neurology*. 2005; 64(suppl 2):S9-S15.
37. Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla Volta G. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. *Neurology*. 1999;52:1622-1625.
38. Benseñor IM, Cook NR, Lee IM, Chown MJ, Hennekens CH, Buring JE. Low-dose aspirin for migraine prophylaxis in women. *Cephalalgia*. 2001;21: 175-183.
39. Dodick DW, Martin VT, Smith T, Silberstein S. Cardiovascular tolerability and safety of triptans: a review of clinical data. *Headache*. 2004;44:S20-S30.
40. Martin VT, Goldstein JA. Evaluating the safety and tolerability profile of acute treatments for migraine. *Am J Med*. 2005;118(suppl 1):36S-44S.
41. Wammes-van der Heijden EA, Rahimtoola H, Leufkens HG, Tijssen CC, Egberts AC. Risk of ischemic complications related to the intensity of triptan and ergotamine use. *Neurology*. 2006;67:1128-1134.