Migraine and Functional Outcome From Ischemic Cerebral Events in Women

Pamela M. Rist, MSc; Julie E. Buring, ScD; Carlos S. Kase, MD; Markus Schürks, MD, MSc; Tobias Kurth, MD, ScD

Background—Studies have linked migraine with aura to an increased risk of ischemic stroke, particularly among women. Data on the relationship of migraine and functional outcome from ischemic cerebral events are sparse.

Methods and Results—This was a prospective cohort study among 27 852 women enrolled in the Women’s Health Study for whom we had information on migraine and measured cholesterol values and who had no prior stroke or transient ischemic attack (TIA) at baseline. Migraine was classified into no history of migraine, active migraine with aura, active migraine without aura, and past history of migraine. Possible functional outcomes were no stroke or TIA, TIA, and stroke with modified Rankin Scale (mRS) score 0 to 1, mRS 2 to 3, and mRS 4 to 6. We used multinomial logistic regression to evaluate the relationship of migraine with functional outcomes after ischemic stroke. During a mean of 13.5 years of follow-up, 398 TIs and 345 ischemic strokes occurred. Compared with women without history of migraine and who did not experience a TIA or stroke, women who reported migraine with aura had adjusted relative risk (95% confidence interval) of 1.56 (1.03 to 2.36) for TIA, 2.33 (1.37 to 3.97) for stroke with mRS 0 to 1, 0.82 (0.30 to 2.24) for mRS 2 to 3, and 1.18 (0.28 to 4.97) for mRS 4 to 6. The risk of any outcome was not significantly elevated for women who experienced migraine without aura or who had a past history of migraine.

Conclusions—Results of this large prospective cohort suggest that women with migraine with aura are at increased risk of experiencing TIA or ischemic stroke with good functional outcome. (Circulation. 2010;122:2551-2557.)

Key Words: epidemiology • ischemic stroke • longitudinal studies • migraine • women

Migraine is a chronic-intermittent primary headache disorder that affects ≈18% of the female population. Up to one third of migraineurs have transient neurological symptoms that usually manifest as visual disturbances known as migraine aura. Migraine, in particular migraine with aura, has been shown to be a risk factor for ischemic stroke, a leading cause of morbidity and mortality in the United States and worldwide. A recent meta-analysis found an increased risk of ischemic stroke among subjects with any migraine (relative risk, 1.73; 95% confidence interval [CI], 1.31 to 2.29). This risk was further increased for women (relative risk, 2.08; 95% CI, 1.13 to 3.84) and especially among those with migraine with aura (relative risk, 2.16; 95% CI, 1.53 to 3.03).

Clinical Perspective on p 2557

Population-based research has shown evidence of an increased risk of lacunar stroke among women who experience migraine with aura. Because lacunar strokes are usually less severe than other ischemic stroke subtypes, one can hypothesize that migraine with aura may be associated with milder levels of disability after stroke. However, little research has been done on the association between migraine with aura and functional outcome after stroke. Such an association would be of importance, particularly for women, who are 3 to 4 times more likely to suffer from migraine and who are at increased likelihood of being more disabled after stroke than men. Thus, we sought to analyze the association between migraine and functional outcome from incident ischemic cerebral events in the Women’s Health Study (WHS), a large prospective cohort of female health professionals.

Methods

Study Population

The WHS was a randomized, placebo-controlled trial of the effects of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. The design of the WHS has been published in detail previously. Briefly, at baseline (1993–1996), 39 876 US female health professionals aged ≥45 years without a history of cardiovascular disease, cancer, or other major illnesses were randomized to receive active aspirin and placebo vitamin E, active vitamin E and placebo aspirin, both active agents, or both placebos. The clinical trial of the WHS ended in March 2004, and the women have been followed on an observational basis since the end of the trial. At baseline, participants were sent a questionnaire asking about personal characteristics, medical history (including migraine), and health habits. Participants were sent a

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From the Division of Preventive Medicine, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass (P.M.R., J.E.B., M.S., T.K.); Department of Epidemiology, Harvard School of Public Health, Boston, Mass (P.M.R., J.E.B., T.K.); Department of Neurology, Boston University School of Medicine, Boston, Mass (C.S.K); and INSERM Unit 708–Neuroepidemiology and University Pierre et Marie Curie, Paris, France (T.K.).

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Correspondence to Tobias Kurth, MD, ScD, INSERM Unit 708–Neuroepidemiology, Hôpital de la Pitié-Salpêtrière, 47 boulevard de l’Hôpital, 75651 Paris Cedex 13, France. E-mail tkurth@rics.bwh.harvard.edu

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questionnaire twice within the first year and yearly thereafter asking about study compliance and study outcomes (including stroke and transient ischemic attacks [TIAs]).

In the baseline questionnaire, women were asked whether they would be willing to provide a venous blood sample by mail. A total of 28,345 women (71.1%) provided samples, 27,939 of which could be assayed for total cholesterol, high-density lipoprotein cholesterol, and directly obtained low-density lipoprotein cholesterol. For this analysis, we used information collected until March 2, 2009. Informed consent was obtained from all participants, and the institutional review board at Brigham and Women's Hospital approved the WHS.

Exposure Assessment
On the baseline questionnaire, women were asked, "Have you ever had migraine headaches?" and "In the past year, have you had migraine headaches?" Women who experienced migraine headaches within the past year were asked further about the frequency of the attacks and characteristics of their migraine, including the presence of aura or any other indication that a migraine is coming. From this information, we divided the women into 4 possible categories: (1) "no migraine history"; (2) "active migraine with aura," which included those who reported migraine within the past year and who reported presence of aura or any indication that a migraine is coming; (3) "active migraine without aura"; and (4) "history of migraine," which included those who reported ever having migraines but did not experience any migraines within the past year.

In a previous study, we have shown that among WHS participants who reported active migraine, 83.5% fulfilled all but 1 International Classification of Headache Disorders-I criteria for migraine (code 1.7, migraine disorder), and 46.6% fulfilled all International Classification of Headache Disorders-I criteria for "migraine without aura" (code 1.1, migraine without aura). In addition, we have shown that in a subsample of the WHS, 87.7% of women with self-reported active migraine could be diagnosed as having migraine without aura (71.5%) or probable migraine without aura (16.2%) according to International Classification of Headache Disorders-II criteria.

Outcome Assessment
After a woman reported a stroke or a TIA in her yearly questionnaire, she was asked for permission to review her medical records. An End Points Committee of physicians (including a board-certified vascular neurologist) reviewed the medical records and confirmed cases of stroke and TIA. A nonfatal stroke was defined as a focal neurological deficit of sudden or rapid onset and vascular mechanism that lasted >24 hours. A TIA was defined as a focal neurological deficit of sudden or rapid onset and vascular mechanism that resolved within 24 hours. To confirm cases of fatal stroke, all available sources, including death certificates and hospital records, were used to find evidence of a cerebrovascular mechanism. We classified the stroke according to major subtypes (ischemic, hemorrhagic, or unknown). Interobserver agreement for major stroke subtype classification was excellent (Cohen's κ statistic = 0.96). Additionally, all ischemic strokes were further classified into subtypes on the basis of their mechanism (atherothrombotic, atheroembolic, cardiogenic embolism, lacunar, infarct of unknown mechanism, or cerebral infarct related to a procedure). For all confirmed strokes, the End Points Committee also assigned a modified Rankin Scale (mRS) score on the basis of the degree of impairment experienced by the participant at hospital discharge. The mRS is a 7-point scale (0 = no symptoms at all; 1 = no significant disability despite symptoms; 2 = slight disability; 3 = moderate disability; 4 = moderately severe disability; 5 = severe disability; 6 = death)14,15 that has strong test-retest reliability, interrater reliability, and validity.16,17 We categorized the mRS score into 3 levels (0 to 1, 2 to 3, 4 to 6) to avoid possible problems with model convergence due to sparse data.18,19 When we examined the association between migraine status and incident ischemic cerebral events, our possible functional outcomes were no stroke or TIA, TIA, and ischemic stroke with the 3 possible categories of the mRS.

Analysis
Of the 27,939 women from whom plasma cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol could be assessed, we excluded 79 with missing information on migraine status and 8 who reported having had a TIA before receiving the baseline questionnaire, leaving 27,852 women for this analysis. Because of differences in the age distribution according to migraine status, we calculated age-standardized distributions and proportions of baseline characteristics.

We used Cox proportional hazards models to determine the relative risk of TIA and ischemic stroke, using women without a history of migraine as the reference group. To test the assumption of proportional hazards, we included an interaction term between the log transformation of time in the study and migraine status. No significant violation was found.

We used multinomial logistic regression to calculate odds ratios and 95% CIs as a measure of the relative risk of the relationship between migraine status and functional outcome from incident ischemic cerebral events. Multinomial logistic regression is an extension of binary logistic regression, in which the dependent variable is allowed to have >2 categories and each category is simultaneously compared with 2 reference categories. 1 for the exposure and 1 for the outcome. Our reference categories were women with no migraine history (the reference category for the exposure) and who had not experienced a stroke or TIA (the reference category for the outcome). Women who experienced a hemorrhagic stroke (n = 82) or a stroke of unknown type (n = 2) were excluded from this analysis.

For our assessment of the risk of TIA and ischemic stroke and risk of functional outcome from ischemic stroke, we ran age- and multivariable-adjusted models. In our multivariable-adjusted models, we adjusted for the following possible confounders as obtained at baseline: age (continuous), history of hypertension >140/90 mm Hg (yes/no), baseline treatment with medication for high blood pressure (yes/no), midpoint of systolic blood pressure category (categories were defined by 10-mm Hg increments), history of high cholesterol >240 mg/dL (yes/no), baseline treatment with cholesterol-lowering medication (yes/no), alcohol consumption (rarely/never, 1 to 3 drinks per month, 1 to 6 drinks per week, >1 drink per day), postmenopausal status (premenopausal, postmenopausal, uncertain), ever used oral contraceptives >2 months (yes/no), smoking status (never, past, current), body mass index (continuous), exercise (rarely/never, <1 time per week, 1 to 3 times per week, >4 times per week), and total cholesterol levels in quartiles. In addition, we adjusted for randomized aspirin and vitamin E assignment. We decided not to adjust for high-density and low-density lipoprotein cholesterol levels because the results were very similar to the results when we only adjusted for total cholesterol.

In secondary analysis, we tested for effect modification of the association between migraine and functional outcome from ischemic cerebral events. To avoid problems with model convergence, we decided to further collapse our functional outcomes from ischemic stroke into 3 categories: no stroke or TIA, TIA or stroke with mRS 0 to 1, and stroke with mRS 2 to 6. An interaction term between migraine status and the possible effect modifiers was included in separate age-adjusted models. The possible effect modifiers were age (<55 years or ≥55 years), history of hypertension (yes/no), smoking status (never, past, current), randomized assignment to aspirin (yes/no), total serum cholesterol (quartiles), and Framingham Risk Score20 (<12 points/12 points).21,22 For all models, if a woman had missing information on body mass index (n = 344) or midpoint of systolic blood pressure category (n = 291), she was assigned to the median value of that variable. Fewer than 100 women were missing information on all other covariates. They were assigned to the reference category (ie, lowest exposure category) or to the past user category (smoking) or unclear exposure category (postmenopausal hormones).

To explore whether our method of handling missing data had an impact on our results, we performed sensitivity analyses in which we deleted all women with missing baseline covariate information. Results
of the 2 methods of handling missing information were similar in age- and multivariable-adjusted models (data not shown).

All statistical analyses were performed with the use of SAS 9.1. All P values are 2-tailed, and P<0.05 was considered statistically significant.

**Results**

Of the 27 852 women, 5129 (18.4%) reported any history of migraine, and 3612 had active migraine, of whom 1435 (39.7%) reported migraine with aura. The age-adjusted baseline characteristics of the participants according to their migraine status are summarized in Table 1. Women who experience migraine with aura were younger than those with no history or a past history of migraine and were more likely to be never smokers. Those with a past history of migraine were more likely to have a history of hypertension. Women with no migraine history were the least likely to have a history of high cholesterol.

During a mean of 13.5 years (377 329 person-years) of follow-up, 398 TIsAs and 345 ischemic strokes occurred. Women who reported migraine with aura had a statistically significant increased risk of TIA (relative risk, 1.55; 95% CI, 1.03 to 2.34; P=0.04) and ischemic stroke (relative risk, 1.63; 95% CI, 1.05 to 2.52; P=0.03) compared with those women without a history of migraine in multivariable-adjusted analysis. Women who experienced migraine without aura or who had a past history of migraine did not have a significant increase or decrease in their risk of TIA or ischemic stroke.

The association between migraine status and functional outcome from incident ischemic cerebral events is summarized in Table 2 and the Figure. Compared with women who had no

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**Table 1. Age-Adjusted Baseline Characteristics of Women According to Migraine Status in the WHS (n=27 852)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Migraine History (n=22 723)</th>
<th>Migraine With Aura (n=1435)</th>
<th>Migraine Without Aura (n=2177)</th>
<th>History of Migraine (n=1517)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SE), y</td>
<td>54.9 (0.05)</td>
<td>53.2 (0.19)</td>
<td>52.6 (0.15)</td>
<td>55.5 (0.18)</td>
</tr>
<tr>
<td>Body mass index, mean (SE), kg/m²</td>
<td>25.9 (0.03)</td>
<td>25.8 (0.13)</td>
<td>26.2 (0.11)</td>
<td>26.1 (0.13)</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>24.6</td>
<td>25.5</td>
<td>26.1</td>
<td>30.4</td>
</tr>
<tr>
<td>Antihypertensive medication use, %</td>
<td>13.0</td>
<td>13.9</td>
<td>14.2</td>
<td>17.2</td>
</tr>
<tr>
<td>History of high cholesterol, %</td>
<td>28.9</td>
<td>33.3</td>
<td>33.6</td>
<td>33.2</td>
</tr>
<tr>
<td>Cholesterol-lowering medication use, %</td>
<td>3.1</td>
<td>3.5</td>
<td>3.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Postmenopausal, %</td>
<td>54.4</td>
<td>53.3</td>
<td>54.3</td>
<td>55.1</td>
</tr>
<tr>
<td>Oral contraceptive use, %</td>
<td>69.1</td>
<td>72.3</td>
<td>71.3</td>
<td>71.8</td>
</tr>
<tr>
<td>Postmenopausal hormone use, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>47.4</td>
<td>37.2</td>
<td>42.8</td>
<td>43.6</td>
</tr>
<tr>
<td>Past</td>
<td>9.9</td>
<td>11.4</td>
<td>9.7</td>
<td>11.8</td>
</tr>
<tr>
<td>Current</td>
<td>42.7</td>
<td>51.4</td>
<td>47.4</td>
<td>44.6</td>
</tr>
<tr>
<td>Alcohol consumption, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely/never</td>
<td>43.5</td>
<td>48.3</td>
<td>47.3</td>
<td>45.2</td>
</tr>
<tr>
<td>1–3 drinks per month</td>
<td>13.1</td>
<td>13.1</td>
<td>15.4</td>
<td>14.2</td>
</tr>
<tr>
<td>1–6 drinks per week</td>
<td>32.7</td>
<td>30.3</td>
<td>30.1</td>
<td>30.3</td>
</tr>
<tr>
<td>≥1 drink per day</td>
<td>10.8</td>
<td>8.3</td>
<td>7.1</td>
<td>10.3</td>
</tr>
<tr>
<td>Randomized aspirin assignment, %</td>
<td>50.2</td>
<td>49.1</td>
<td>50.3</td>
<td>47.8</td>
</tr>
<tr>
<td>Randomized vitamin E assignment, %</td>
<td>50.1</td>
<td>51.5</td>
<td>47.8</td>
<td>50.0</td>
</tr>
<tr>
<td>Vigorous physical activity, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely/never</td>
<td>37.0</td>
<td>38.2</td>
<td>39.5</td>
<td>39.2</td>
</tr>
<tr>
<td>&lt;1 time per week</td>
<td>19.2</td>
<td>20.5</td>
<td>21.6</td>
<td>20.1</td>
</tr>
<tr>
<td>1–3 times per week</td>
<td>32.3</td>
<td>30.7</td>
<td>29.1</td>
<td>29.4</td>
</tr>
<tr>
<td>≥4 times per week</td>
<td>11.6</td>
<td>10.7</td>
<td>9.6</td>
<td>11.3</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>51.3</td>
<td>52.6</td>
<td>56.2</td>
<td>50.7</td>
</tr>
<tr>
<td>Past</td>
<td>37.0</td>
<td>37.4</td>
<td>34.5</td>
<td>35.3</td>
</tr>
<tr>
<td>Current &lt;15 cigarettes per day</td>
<td>4.4</td>
<td>3.9</td>
<td>3.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Current ≥15 cigarettes per day</td>
<td>7.3</td>
<td>6.2</td>
<td>5.7</td>
<td>8.9</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>2.5</td>
<td>1.8</td>
<td>1.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Total cholesterol, mean (SE), mg/dL</td>
<td>211.4 (0.27)</td>
<td>213.4 (1.08)</td>
<td>212.7 (0.88)</td>
<td>214.8 (1.05)</td>
</tr>
</tbody>
</table>

Numbers may not add up to 100% because of rounding or missing data.
We found no significant evidence of effect modification by age ($P_{\text{interaction}} = 0.46$), history of hypertension ($P_{\text{interaction}} = 0.45$), smoking status ($P_{\text{interaction}} = 0.54$), randomized aspirin assignment ($P_{\text{interaction}} = 0.69$), total serum cholesterol...
The first is a longitudinal study from Iceland showing that migraine with aura is associated with an increased risk of subclinical infarct-like lesions later in life among women.23 The second is a population-based cross-sectional study from the Netherlands and found an increase in posterior circulation infarct-like lesions among migraineurs.24 The authors hypothesize that these lesions are most likely ischemic in origin and may be caused by hypoperfusion and/or embolism and not by atherosclerosis or small-vessel disease based on the characteristics of the lesions.

In a recent publication from the Reykjavik Study, migraine was associated with increased risk of mortality from total stroke, a finding only apparent among male migraineurs with aura.25 Data from the WHS suggest that migraine with aura may increase the risk of fatal hemorrhagic stroke26 but not fatal ischemic stroke, as suggested from the present analysis. However, the number of fatal strokes in these 2 studies was small, and future studies are needed to evaluate whether migraine with aura differentially affects the functional outcome from ischemic and hemorrhagic stroke.

Current theories postulate that local vascular phenomena may underlie the association between migraine and ischemic stroke. For example, a previous study from the WHS showed that the association between migraine with aura and risk of stroke was strongest among women who had a rather healthy vascular health status as estimated by the Framingham Risk Score.22 This may support the idea that the biological mechanisms underlying the association between migraine with aura and stroke are different from atherosclerosis but may instead involve microvascular phenomena.22 Potential scenarios include local vascular processes leading to thrombosis or microemboli obliterating small vessels. There is further evidence of a complex interrelationship between migraine and the vascular system from an animal study demonstrating that cortical spreading depression, the likely physiological correlate of migraine aura, can be triggered by microemboli-induced hypoperfusion.27 Reduced cerebral blood flow activates local inflammatory mechanisms, which may cause cortical spreading depression and ultimately increase the risk of ischemic stroke.28

The results of the present study further support the idea that the association between migraine with aura and ischemic stroke may be due to microvascular phenomena instead of other mechanisms. First, no ischemic stroke with an atherothrombotic or atheroembolic mechanism occurred among women with migraine with aura, suggesting that large-vessel disease does not play an important role in the association between migraine with aura and stroke. Additionally, we observed a low frequency of cardioembolic-induced strokes, a group in which patent foramen ovale rather than atrial fibrillation would be likely to play a role in our middle-aged cohort of women. Finally, we observed a high proportion (>56%) of cases labeled as “infarct of unknown mechanism,” which corresponds to the “undetermined” ischemic stroke type of the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification. Infarcts of unknown mechanism are a nonlacunar type of infarcts that have no detectable cardiac/aortic source of embolism or evidence of “large-vessel” disease as the stroke mechanism.

Although our data support the idea that the association between migraine with aura and ischemic cerebrovascular
events is not due to large-vessel disease or a detectable cardiac/aortic source of embolism, the precise vascular mechanism underlying the association between migraine with aura and stroke remains unclear. Additionally, it is plausible that the reason for the observed low level of disability from an ischemic cerebral event observed among migraineurs with aura may be a function of the small size of the infarcts rather than of their specific underlying mechanism.

To assess functional outcome from stroke, we used the mRS. Because of its strong emphasis on mobility, the mRS is primarily a measure of disability or “global health index,”20,30 even though it claims to be a measure of handicap. Although there are limitations to the mRS,16,17 it is widely accepted for functional stroke outcome assessment in clinical trials31–34 and has several advantages in population-based studies. First, the mRS can be ascertained from medical records and takes prestroke disability into account when the poststroke mRS score is determined.15 Second, it is simple to administer and has strong test-retest reliability, interrater reliability, and validity.66 Finally, unlike the Barthel Index, the mRS does not have a “ceiling effect.”35

Strengths of our study include its prospective nature, the large number of participants and outcome events, the confirmation of reported TIA’s and strokes by medical record review, and high interobserver agreement on the classification of major stroke subtype.

Some limitations to our study should be noted. First, migraine status was self-reported. Although our cohort enrolled only female health professionals who likely report health information more accurately than the general population,36 and validation studies have shown good agreement of our migraine classification with International Headache Society criteria,11,12,28 some degree of misclassification may still be possible. However, such misclassification would likely be nondifferential and is thus an unlikely explanation of the observed associations. In addition, misclassification of migraine status could also occur if women who experience migraines only mention headache but no migraine features. However, because reports of nonmigraine headache were not associated with increased risk of ischemic stroke in the WHS,37 we believe that such potential misclassification is an unlikely reason for our findings. Second, ascertainment of the mRS was not done in a prespecified time frame after stroke, and we did not record information on the length of hospital stay. However, because patients with the most severe nonfatal stroke likely have the longest hospital stay, mRS score and hospital stay are expected to be correlated. Third, we did not have information on migraine-specific drug use, such as the use of triptans and ergot alkaloids, during follow-up. However, available evidence does not support the notion that migraine-specific drug use would confound the relationship between migraine status and risk of stroke or functional outcomes from stroke. Previous studies have shown associations only between migraine with aura and stroke risk, and migraine-specific drugs are used by all migraineurs, not just those patients who have migraine with aura. Moreover, other studies have not found a relationship between migraine-specific drug use and risk of stroke.38–41

Thus, it seems unlikely that migraine-specific drug use confounds the relationship between migraine status and stroke risk. Finally, because all WHS participants are primarily white women aged ≥45 years, the generalizability of our results to other populations with different age, sex, and racial distributions may be limited.

In conclusion, data of this large prospective study of initially apparently healthy women suggest that the association between migraine with aura and ischemic cerebrovascular events generally favors events with good functional outcomes. Future studies are warranted to further elucidate the biological mechanisms underlying this association and to determine whether treatment of migraine may help to reduce the risk of stroke.

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**CLINICAL PERSPECTIVE**

Migraine affects ≈20% of the female population, and up to one third of migraineurs experience transient neurological symptoms, primarily visual disturbances that are known as migraine aura. Previous research has linked migraine with aura with increased risk of ischemic stroke, particularly among women. However, little research has been done on whether the functional outcome from stroke, which can be more severe among women, is affected by migraine status. To explore this association, we used data from the Women’s Health Study, a large prospective cohort study of women aged ≥45 years at baseline without a history of stroke, transient ischemic attack, or other major diseases. We found that women who report migraine with aura are at increased risk of transient ischemic attack (relative risk = 1.56; 95% confidence interval, 1.03 to 2.36) and of ischemic stroke with good functional outcome, with modified Rankin Scale 0 to 1 (relative risk = 2.33; 95% confidence interval, 1.37 to 3.97). However, women who report migraine with aura do not appear to have an increased risk of a more unfavorable functional outcome after ischemic stroke. Women with migraine without aura did not have increased risks for any outcome. Although our data confirm migraine with aura as a risk factor for ischemic cerebrovascular events, results suggest that the functional outcome of these events is good.