Migraine and risk of stroke in older adults

Northern Manhattan Study

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ABSTRACT

Objective: To examine the association between migraine and stroke/vascular outcomes in a racially/ethnically diverse, older cohort.

Methods: Participants from the Northern Manhattan Study, a population-based cohort study of stroke incidence, were assessed for migraine symptoms using a self-report questionnaire based on criteria from the *International Classification of Headache Disorders, second edition*. We estimated the association between migraine and combined vascular events including stroke and stroke only over a mean follow-up of 11 years, using Cox models adjusted for sociodemographic and vascular risk factors.

Results: Of 1,292 participants (mean age 68 ± 9 years) with migraine data followed prospectively for vascular events, 262 patients (20%) had migraine and 75 (6%) had migraine with aura. No association was found between migraine (with or without aura) and risk of either stroke or combined cardiovascular events. There was an interaction between migraine and current smoking ($p = 0.02$ in relation to stroke and $p = 0.03$ for combined vascular events), such that those with migraine and smoking were at an increased risk. The hazard ratio of stroke for migraine among current smokers was 3.17 (95% confidence interval [CI] 1.13–8.85) and among current nonsmokers was 0.77 (95% CI 0.44–1.35). In relation to combined vascular events, the hazard ratio for migraine vs no migraine among current smokers was 1.83 (95% CI 0.89–3.75) and among current nonsmokers was 0.63 (95% CI 0.43–0.94).

Conclusion: In our racially/ethnically diverse population-based cohort, migraine was associated with an increased risk of stroke among active smokers but not among nonsmokers. *Neurology*® 2015;85:715–721

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **ICD-9** = *International Classification of Diseases, Ninth Revision*; **ICHD-2** = *International Classification of Headache Disorders, second edition*; **MI** = myocardial infarction; **NOMAS** = Northern Manhattan Study.

Migraine is a complex neurovascular syndrome resulting in an unstable trigeminal vascular system. It has been suggested that migraine and stroke exist on a continuum, and the vascular system may have important secondary consequences in migraine.¹ While the vascular theory of migraine has been disproved, migraine with aura, mostly in women younger than 45 years, has been shown to be an independent risk factor for ischemic stroke.² Some studies also suggest that migraine is associated with an unfavorable cardiovascular risk profile, cardiovascular disease events, and vascular death.^{3–8} However, there are no reliable indicators to predict which migraineurs will develop cerebrovascular ischemic insults and other vascular events. Moreover, migraine may be a potentially modifiable vascular risk factor, requiring further exploration in high-risk populations.

The objective of this study was to assess the association between migraine, including both migraine with and without aura, and stroke in the Northern Manhattan Study (NOMAS), an ethnically diverse, older, community-based cohort. As a secondary aim, we also explored the association between migraine and vascular events/mortality.

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METHODS Study participants. The NOMAS is a population-based prospective study designed to determine predictors of stroke recurrence and prognosis in a multiethnic, urban population. NOMAS includes 3,289 participants followed prospectively to determine stroke incidence, both novel and traditional risk factors, and prognosis. The study was approved by the institutional review boards of Columbia University and the University of Miami, and participants provided written informed consent. We used the same methodology as that employed in a previous study.⁹ Eligible participants were stroke-free, older than 40 years, and had resided in Northern Manhattan for 3 months or longer, with a telephone. Participants were identified by random-digit dialing (91% telephone response rate) and then recruited for an in-person baseline interview and assessment. The enrollment response rate was 75%, the overall participation rate was 69%, and a total of 3,298 participants were enrolled with an average annual contact rate of 95%. For our analysis, we excluded participants with a history of meningitis, head trauma, or radiation, to rule out individuals with the potential for secondary headache ($n = 378$), and those with a myocardial infarction (MI) before baseline ($n = 237$).

Baseline evaluation. Data were collected through interviews with trained bilingual research assistants in English or Spanish. Baseline data on demographics, socioeconomic factors, medical history and medication use, vascular risk factors, family history, migraine history, and other health-related information were collected. Race/ethnicity was determined through a series of questions modeled after the US census and conforming to standard definitions by Directive 15. Standard questions regarding hypertension, diabetes, cigarette smoking, and cardiac conditions were adapted using the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Prevention. Smoking was categorized as current (within the past year), former, or never smoker of cigarettes, cigars, or pipes. Our methods for measuring anthropomorphic indices, fasting blood specimens, and blood pressure were obtained as described previously.¹⁰ Briefly, diabetes mellitus was defined by the patient's self-report of such a history, use of insulin or oral antidiabetic medication, or fasting glucose >126 mg/dL. Hypertension was defined by multiple criteria: blood pressure $>140/90$ mm Hg, self-reported hypertension, or use of antihypertensive medication. Similarly, hypercholesterolemia was defined as having a total cholesterol level of >200 mg/dL, cholesterol-lowering medication use, or self-reported history of hypercholesterolemia. Body mass index (BMI) was calculated in kg/m^2 . Mild to moderate alcohol use and physical activity were defined previously.^{10,11}

Migraine diagnosis. Participants recruited after 1998 were interviewed about their migraine history (some participants enrolled between 1996 and 1997 were reinterviewed). We used the same methodology as that employed in our previous studies.^{12,13} Self-reported migraine was assessed with a questionnaire, with additional questions closely adhering to the *International Classification of Headache Disorders, second edition*, criteria for migraine as previously described.¹⁴ *Migraine without aura* was defined as recurrent headache with attacks lasting 4 to 72 hours: unilateral, pulsating, aggravated by physical activity, and associated with nausea and/or photophobia and phonophobia. *Migraine with aura* was defined as recurrent headache with attacks of completely reversible focal neurologic symptoms lasting less than 60 minutes following aura symptoms. Aura was defined as visual changes such as spots, stars, lines, or flashing lights.

Outcomes. The primary outcome was adjudicated stroke of all subtypes. The secondary outcomes were confirmed combined

vascular events (stroke, MI, or vascular death), MI, and vascular death. Follow-up procedures have been described previously.^{10,15} Participants were screened annually by telephone for changes in clinical status, and those who screened positive were invited for an interview and examination by a neurologist. Ongoing hospital surveillance of admission and discharge data were also reviewed, including screening of ICD-9 codes to detect outcome events, and available medical records were reviewed for all vascular outcome events. Stroke events were adjudicated by the study neurologists and defined by the first symptomatic occurrence of any type of stroke including infarct, intracerebral hemorrhage, and subarachnoid hemorrhage according to World Health Organization criteria. Similarly, a cardiologist adjudicated cardiac events, for which MI was defined by criteria adapted from the Cardiac Arrhythmia Suppression Trial and the Lipid Research Clinics Coronary Primary Prevention Trial.^{16,17} For MI, at least 2 of the 3 following criteria are required: (1) ischemic cardiac pain determined to be typical angina; (2) cardiac enzyme abnormalities defined as abnormal creatine phosphokinase MB fraction or troponin values; and (3) ECG abnormalities. The cause of death was classified as vascular or nonvascular based on family reporting, medical records, and death certificates. Vascular death included death due to stroke, MI, heart failure, pulmonary embolus, cardiac arrhythmia, or other vascular cause.

Statistical analysis. We examined the unadjusted associations between categories of migraine with sociodemographic and vascular risk factors using analysis of variance and χ^2 tests. The associations among migraine and stroke, MI, combined vascular events and vascular deaths were examined using Cox proportional hazards models. Migraine overall was the primary exposure of interest, and secondary analyses examined migraine with and without aura separately vs no migraine as the reference category. The person-time of follow-up was accrued from baseline to the most recent mean follow-up (11 ± 4.3 years), the time of outcome event, death, or loss of follow-up, whichever came first. We constructed the following models sequentially, adjusting for: (1) age at baseline, sex, race/ethnicity; (2) model 1 + smoking, moderate alcohol use, moderate to heavy physical activity, BMI; and (3) variables in model 2 + hypertension, hypercholesterolemia, and diabetes. We assessed potential effect modification by age, sex, race/ethnicity, and vascular risk factors (smoking, moderate alcohol use, moderate to heavy physical activity, BMI, hypertension, hypercholesterolemia, and diabetes) by including interaction terms between migraine and these variables in model 3.

RESULTS The study included 1,292 participants with information on migraine status; 262 (20%) of participants had migraine (with aura = 75, without aura = 187). Individuals with migraine were younger and more likely to be women and have Medicaid/no insurance and several vascular risk factors (table 1). Over a mean follow-up of 11 years ($\text{SD} = 4$), there was a total of 294 combined vascular events, 114 of which were strokes, 94 MIs, and 178 vascular deaths. In the full cohort, migraine was not associated with risk of both combined vascular events including stroke or stroke only outcomes (table 2). Furthermore, when migraine with aura and migraine without aura were examined as separate exposures, using no migraine as the reference, no associations were observed in relation to both combined vascular events including stroke or

Table 1 Demographics and cardiovascular risk factors by migraine diagnosis

	No migraine	Migraine	p Value
Overall cohort	1,292 (80)	262 (20)	
Sex			<0.0001
Women	615 (60)	199 (76)	
Men	415 (40)	63 (24)	
Race/ethnicity			0.2276
Black	197 (19)	40 (16)	
White	160 (14)	35 (11)	
Hispanic	657 (64)	185 (71)	
Hypertension	753 (73)	212 (81)	0.0094
Diabetes	223 (22)	54 (21)	0.7142
Hypercholesterolemia	614 (60)	177 (68)	0.0184
Body mass index			0.6477
Normal (<25 kg/m ²)	273 (27)	66 (25)	
Overweight (25–29.9 kg/m ²)	462 (45)	114 (44)	
Obese (30+ kg/m ²)	284 (28)	80 (31)	
Smoking			0.4871
Never	490 (48)	134 (51)	
Former	376 (37)	93 (36)	
Current	163 (16)	35 (14)	
Moderate alcohol use	382 (37)	80 (31)	0.0482
Moderate to heavy physical activity	76 (8)	9 (4)	0.0215
Medicaid and no insurance	518 (50)	160 (61)	0.0022
High school completion	424 (41)	82 (31)	0.0035
Age at baseline, y			0.0062
<60	224 (22)	77 (29)	
60–69	390 (38)	97 (37)	
70–79	263 (26)	67 (26)	
80+	152 (15)	21 (8)	

Data are n (%).

stroke only outcomes. There was no effect modification by age at baseline, sex, race/ethnicity, smoking, moderate alcohol use, moderate to heavy physical activity, BMI, hypertension, hypercholesterolemia, or diabetes. There was an interaction with current smoking ($p = 0.02$) in relation to stroke. An interaction was also found with current smoking ($p = 0.03$) in relation to combined vascular events.

The association between migraine and stroke stratified by smoking, hypertension, obesity, and diabetes is shown in the figure. In the stratified analysis, the hazard ratio of stroke for migraine vs no migraine among current smokers was 3.17 (95% confidence interval [CI] 1.13–8.85). Among former smokers, the hazard ratio was 0.87 (95% CI 0.41–1.84), and among never smokers, the hazard ratio was 0.49 (95% CI 0.19–1.27) when controlling for socioeconomic and vascular risk factors (model 3).

DISCUSSION Overall, we did not find an association between migraine and stroke or combined vascular events in our racially/ethnically diverse, older cohort. However, current smokers with a self-reported history of migraine were more likely to have strokes and combined vascular events than those without migraine, similar to other reports.^{4,18} Another study found that smoking was associated with a 7-fold increase of ischemic stroke in women with probable migraine and visual aura in combination with oral contraceptives.² Recommendations for smoking cessation have been limited to migraine with aura, as there does not appear to be a substantial risk of stroke in migraine without aura. We thought that factors associated with a greater migraine burden, such as obesity, may put migraineurs more at risk of vascular events but this was not the case.¹⁹

Our study results differ from a recent meta-analysis suggesting that migraine with aura is a risk factor for stroke.⁴ However, previous studies suggested that in young patients with ischemic stroke, migraine with aura is an independent risk factor of recurrent ischemic stroke and other vascular events.²⁰ Stroke risk associated with migraine with aura was greater in younger than in older women (45–49 years of age) in the Women's Health Study.²¹ Perhaps our participants were too old to display such a relationship between migraine with aura and stroke in both men and women of postmenopausal age. Moreover, the cerebrovascular burden may have been too high to detect a difference, which would be in alignment with another study in which an association was found between migraine with aura and ischemic stroke among women only in the lowest Framingham risk score group.²¹ Even though we found double the risk of silent brain infarctions in an MRI subsample with migraine in our ethnically diverse, older cohort, our findings are consistent with previous reports that suggest migraine is not a significant risk factor for stroke among older subjects.¹²

The association between migraine and stroke may be attributable to differences in traditional vascular risk factors or genetics. Regarding vascular risk factors, we found an association between migraine and several vascular risk factors (hypertension, hypercholesterolemia, physical inactivity); however, traditional cardiovascular risk factors other than smoking did not interact with migraine to increase stroke risk. Furthermore, recent work has begun to elucidate a genetic basis for migraine with typical aura.²² Cortical spreading depression, the physiologic correlate of migraine with aura, has also been suggested as an underlying link between migraine with aura and ischemic stroke.²³ Moreover, both animal models of familial hemiplegic migraine (FHM type 1 mutant mice), and inherited monogenic vasculopathies such as

Table 2 Migraine and risk of stroke and other vascular outcomes

	Stroke	Combined vascular events	MI	Vascular death
No migraine	Ref.	Ref.	Ref.	Ref.
Migraine (all)				
Model 1	1.09 (0.67-1.77)	0.80 (0.57-1.12)	1.03 (0.59-1.78)	0.67 (0.42-1.08)
Model 2	1.06 (0.66-1.72)	0.77 (0.55-1.08)	0.95 (0.54-1.67)	0.66 (0.41-1.07)
Model 3	1.04 (0.64-1.70)	0.76 (0.54-1.07)	0.92 (0.52-1.63)	0.65 (0.40-1.04)
Migraine with aura				
Model 1	0.41 (0.10-1.68)	0.60 (0.28-1.28)	1.06 (0.38-2.95)	0.75 (0.27-2.05)
Model 2	0.40 (0.10-1.65)	0.50 (0.22-1.14)	0.78 (0.24-2.51)	0.73 (0.27-2.01)
Model 3	0.40 (0.10-1.63)	0.49 (0.22-1.12)	0.76 (0.23-2.46)	0.72 (0.26-1.99)
Migraine without aura				
Model 1	1.31 (0.79-2.16)	0.86 (0.60-1.23)	1.02 (0.55-1.89)	0.66 (0.39-1.11)
Model 2	1.28 (0.77-2.11)	0.85 (0.59-1.22)	1.00 (0.54-1.85)	0.65 (0.38-1.10)
Model 3	1.24 (0.75-2.06)	0.83 (0.58-1.20)	0.97 (0.52-1.81)	0.63 (0.37-1.06)

Abbreviations: MI = myocardial infarction; Ref. = reference.

Data are hazard ratio (95% confidence interval). Model 1: adjusted for age at baseline, sex, race/ethnicity. Model 2: adjusted for variables in model 1 and smoking, moderate alcohol use, moderate to heavy physical activity, body mass index. Model 3: adjusted for variables in model 2 and hypertension, hypercholesterolemia, diabetes.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), for which migraine with aura is a feature, support the hypothesis that transient hypoperfusion or ischemic depolarization is associated with increased stroke susceptibility and migraine.²⁴ Molecular genetics has revealed associations between migraine and genetic polymorphisms of angiotensin I-converting

and enzyme, 5, 10 methylenetetrahydrofolate (*MTHFR*), suggesting the potential of shared genetic risks for stroke.²⁵ Further research may reveal subtypes of migraine, often with aura, at risk for stroke and vascular complications.²⁶

The mechanisms explaining why migraine was associated with vascular events only in smokers in our population are unclear. Statistically, we could

Figure Migraine and stroke: Stratified analysis of cerebrovascular risk factors

Multivariable-adjusted hazard ratios show the influence of vascular risk factors on the association between migraine and stroke outcomes. Current smoking was the only vascular risk factor that significantly influenced the relationship between migraine and stroke. Adjustments were made for age at baseline, sex, race/ethnicity, smoking, moderate alcohol use, moderate to heavy physical activity, body mass index, hypertension, hypercholesterolemia, and diabetes.

not rule out the possibility that the relationship between migraine and stroke in smokers was due to chance; however, we believe the association is biologically plausible. One possible mechanism of increased stroke risk may be oxidative stress, which has been theorized to have a role in migraine and may lead to increased susceptibility to vascular events among active smokers.²⁷ Second, smoking is a known risk factor for atherosclerosis; although increased arterial stiffness, carotid intima-media thickness, and impaired endothelial-dependent vasoreactivity have been associated with migraine, an increased association between atherosclerosis and migraine is not evident.^{28,29} Finally, prothrombotic states, decreased platelet hemostasis time, and endothelial dysfunction associated with migraine are all plausible mechanisms for which stroke risk may be enhanced in active smokers.³⁰ Taken together, we suspect that a synergic action may occur between vascular changes of migraine and smoking as an effect modifier although further work is necessary to elucidate this association.

In addition to stroke, migraine has been associated with an increased risk of vascular mortality,⁶ while the association between migraine with aura and coronary artery disease is supported in a few reports, although confirmation is needed.³¹ Of note, in our cohort of self-reported migraine, a history of never smoking appeared to be associated with fewer combined vascular events. One possibility is that participants reported migraine more often because they were generally healthier so that migraine diagnosis was not obscured by other more serious medical conditions. Nonsmokers with migraine may have also limited certain foods, such as meats (nitrosamines) and cheeses (tyramine) that are high in saturated fats, excessive salty foods (monosodium glutamate), or diet soft drinks (aspartame), that trigger both migraines and contribute to combined vascular outcomes.^{32,33} Migraineurs were also less likely to engage in moderate to heavy physical activity, but were less likely to use alcohol moderately. Potentially, migraineurs that did not smoke may have been more health conscious or may have had better access to medical care, in part motivated by pain. Although debatable, migraine has been theorized as an evolutionary advantage or as a tradeoff between genetic harms and benefits.³⁴ The usefulness of estimating the American Heart Association ideal cardiovascular health metrics in migraineurs is unknown but of considerable interest.

The strengths of this study include the large stroke-free, population-based, racially/ethnically diverse, older cohort, which includes a large proportion of Hispanic participants, who are typically underrepresented in studies of migraine. There were also several limitations. Migraine was identified by self-report, although the details of the history of headache

allowed classification based on the *ICHD-2* criteria without selection bias. Some evidence suggests that migraine treatments (i.e., triptans, ergotamines) may lead to an increased risk of vascular complications but this is unlikely to be a major factor because the risk of serious vascular side effects is quite low.^{35,36} Information on the duration of migraine and attack frequency was not available to confirm previous findings suggesting migraine of recent onset and high attack frequency are risk factors for ischemic events.^{2,37,38} Modest statistical power was an additional important limitation, and therefore negative findings should be interpreted with caution and underscore the need for future large prospective analyses. The power to detect significant associations was particularly limited in relation to the analyses of migraine subtypes and the tests of effect modification by demographic variables and vascular risk factors. Therefore, the latter analyses were considered exploratory. Moreover, we did not investigate the association between migraine and TIAs because of the challenges of distinguishing between transient neurologic events of migraine aura vs ischemic etiologies. Finally, the association between migraine and stroke was found in older adults; thus, the findings may not be generalizable to younger populations.

Our data suggest that vascular changes in migraine may be an important subclinical vascular marker for stroke and combined vascular events among active smokers. While some traditional vascular risk factors are associated with migraine, active smoking appears to be an important interaction leading to vascular events in our cohort. Future prospective studies are needed that determine the associations among active migraine status, the effects of migraine treatments, lifestyle behaviors, age-related cerebrovascular disease, and vascular events. As smoking may be common among migraineurs, smoking cessation counseling should be encouraged as a part of routine migraine care throughout the lifetime including in older age groups. Taken together, the identification of modifiable vascular risk factors and treatments may have beneficial outcomes for stroke reduction in the elderly population with migraine.

AUTHOR CONTRIBUTIONS

T.S. Monteith: study design, obtaining funding, interpretation of data, draft manuscript. H. Gardener: study design, data analysis, interpretation of data, draft manuscript. T. Rundek: study design, interpretation of data, draft manuscript. M.S.V. Elkind: obtaining funding, interpretation of data, critical review of manuscript. R.L. Sacco: study design, obtaining funding, interpretation of data, draft manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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This Week's *Neurology*® Podcast

Migraine and risk of stroke in older adults: Northern Manhattan Study (see p. 715)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the August 25, 2015, issue of *Neurology*. In the second segment, Dr. Andy Southerland talks with Dr. Teshamae Monteith about her paper on migraine and risk of stroke in older adults. Dr. Adam Numis reads the e-Pearl of the week about neurosyphilis. In the next part of the podcast, Dr. Alberto Espay focuses his interview with Dr. Keith Josephs on his Frontiers in Neuroscience Lecture at the AAN Annual Meeting on the topic of antemortem signatures of neurodegenerative proteinopathies.

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