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A prospective study of migraine history and venous thromboembolism in older adults

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Abstract

Background: Limited evidence suggests that migraine might be a risk factor for venous thromboembolism (VTE). We conducted an epidemiologic study to assess whether migraine history is associated prospectively with VTE or cross sectionally with hemostatic risk markers for VTE.

Methods: In a population-based US cohort, 11 985 participants free of VTE reported headache symptoms in 1993-1995. We classified participants as having either migraines with or without aura, severe nonmigraine headaches, or no severe headaches. We followed them through 2015 for incident VTE verified by medical records.

Results: Participants' mean age at baseline was 60 years (SD: 6). Eleven percent were classified as having a migraine history (932 without aura and 396 with aura). Over a mean of 18 years and 211 913 person-years at risk, 688 participants developed VTE. Participants with a migraine history had no greater risk of VTE compared with those free of severe headache (adjusted hazard ratio [HR]: 1.06, 95% confidence interval [CI]: 0.82-1.36). Those with migraine history with aura had an HR of 1.25 (95% CI: 0.85-1.85). Self-reported physician diagnosis of migraine carried an HR of 1.22 (0.96-1.55). At baseline, those with a history of migraine, furthermore, did not have a higher frequency of elevated hemostatic risk factors or a higher genetic risk score for VTE.

Conclusion: This study does not support the hypothesis that migraine history is an important risk factor for VTE in older adults.

KEYWORDS

deep vein thrombosis, epidemiology, migraine, prospective study, pulmonary embolism, venous thromboembolism

Essentials

- A few studies suggested that migraine increases venous thromboembolism (VTE) risk.
- We conducted a prospective US population-based study.
- Migraine history did not appear to increase risk of VTE.
- Older patients with migraine should require only standard VTE prophylaxis.

1 | INTRODUCTION

Migraine is a common chronic condition associated with increased risk of stroke and possibly other cardiovascular diseases involving the arteries or heart.[1–4] At least 4 reports[4–7] have suggested that migraine history also may carry an increased risk of venous thromboembolism (VTE)—that is, deep vein thrombosis (DVT) and/or pulmonary embolism (PE). A recent large, record-based, prospective Danish study (median age: 35 years) showed that VTE incidence over 19 years of follow-up was 1.59 times more frequent in those with clinically recognized migraine than those with no evidence of migraine[4]; the associations were similar for migraine with and without aura. A prospective clinical study in Taiwan (mean age = 42 years) reported that migraine with aura, but not migraine without aura or total migraine, was associated >2-fold increased risk of VTE over 4 years of follow-up compared with having no headache.[5] A cross-sectional population-based German study showed that 55- to 94-year-old participants with migraine had a 2-fold higher age- and sex-adjusted history of VTE than did nonmigraine patients.[6] Additionally, in a large, population-based, cross-sectional sample of pregnant women, VTE discharge codes during pregnancy were 3-fold more common in those with peripartum migraine vs no migraine.[7]

Migraine may trigger ischemic stroke via cerebral vasoconstriction, arterial thrombi, or cortical spreading depression,[1–4] but VTE has a different pathophysiology—more related to venous stasis and coagulation factor activation. Thus, how migraine might "cause" VTE is unclear. Migraine is not consistently associated with plasma hemostatic factors or genetic variants that predispose to VTE.[8,9] High estrogen states can contribute to migraine and VTE, but in that case, hyperestrogenemia would be the cause of VTE, not migraine. Perhaps migraine could lead to immobility, predisposing to VTE. On the other hand, previous cross-sectional, clinical, or record-based studies showing an association of migraine with VTE may have suffered from misclassification, uncontrolled confounding, or a positive publication bias.

The large population-based prospective Atherosclerosis Risk in Communities (ARIC) study queried participants about migraine symptoms and identified and validated VTE events by medical record review. Using these data, we assessed (a) whether migraine history is a risk factor for future VTE and (b) whether migraine history is associated with hemostatic risk markers for VTE—namely, plasma factor VIII, factor XI, von Willebrand factor, activated partial thromboplastin time (aPTT), D-dimer, and a 5-single nucleotide polymorphism genetic risk score for VTE.

2 | MATERIALS AND METHODS

2.1 | Study design and sample

We reported elsewhere details of the overall ARIC study design, methods, and baseline participation,[10,11] as well as the VTE incidence rates.[12] In brief, 15 792 men and women aged 45-64 years enrolled in the ARIC study in 1987-1989 (visit 1). ARIC performed subsequent examinations in 1990-1992, 1993-1995 (visit 3), 1996-1998, 2011-2013, and 2016-2017, as well as annual or semiannual telephone contact. At each visit, ARIC measured risk factors and obtained and stored plasma at −80°C. The institutional review committees at each study center approved the methods, and ARIC staff obtained written informed participant consent.

2.2 | Ascertainment of headache status

At ARIC visit 3, but at no other visit, interviewers administered a headache questionnaire.[13] The first question asked, "Have you had headaches lasting more than 4 hours?" For those answering "Yes," subsequent questions asked about migraine symptoms. We classified *migraine headache history* for headaches (a) lasting 4 or more hours; (b) typically throbbing, pounding, or pulsating, or being unilateral; (c) accompanied by nausea, vomiting, or sensitivity to light or sound; and (d) occurring over at least 1 year. We classified *severe nonmigraine headache history* as lasting at least 4 hours but not meeting all of the other criteria. We classified *no severe headache history* as those who denied ever having headaches lasting at least 4 hours. The questionnaire also allowed us to subclassify migraine as *without or with visual aura* (ie, spots, jagged lines, or heat waves in 1 or both eyes). Separately, ARIC asked participants, "Have you ever been told by a physician that you have migraine headaches?"

2.3 | Measurement of other VTE risk factors

Except where noted, our analysis included VTE risk factors documented previously in ARIC and measured at ARIC visit 3. Participants reported race, smoking status, history of cancer, and use of hormone replacement therapy (HRT), blood pressure (BP) medication, or aspirin in the past 2 weeks. ARIC staff measured sitting BP thrice after a 5-minute rest via a random-zero sphygmomanometer, and we used the mean of the last 2 measures. Staff measured weight and height. We defined diabetes as a fasting blood glucose of 126 mg/dL or higher, nonfasting blood glucose of 200 mg/dL or higher, a self-reported physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks. The Laboratory for Clinical Biochemistry Research at the University of Vermont measured plasma factor XI and D-dimer.[14,15] ARIC isolated genomic DNA and measured 5 key variants important for VTE: *F5* Leiden rs6025, *F2* rs1799963, *ABO* rs8176719 (O vs non-O groups), *FGG* rs2066865, and *F11* rs2036914, and a weighted genetic risk score was created, as previously reported.[16]

We used visit 1 and 2 ARIC data for laboratory assays not available at visit 3. At visit 1, ARIC measured aPTT, FVIII, and von Willebrand factor.[17,18] At visit 2, ARIC estimated glomerular filtration rate from creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) algorithm.[19]

2.4 | VTE occurrence

Atherosclerosis Risk in Communities staff contacted participants annually or semiannually by telephone and asked about all

hospitalizations in the previous year. Additionally, ARIC annually reviewed local hospital discharge lists and surveys of state and national death indices. Staff then retrieved hospital records for possible VTE events through 2015. As previously reported, to validate VTE events, 2 physicians reviewed the records using standardized criteria, [12] requiring positive imaging tests for diagnosis of DVT and PE. The reviewers subclassified VTE events as unprovoked (no obvious cause) or provoked (associated with cancer, major trauma, surgery, marked immobility). For this report, we restricted DVTs to those in the lower extremity or vena cava, because upper extremity DVTs were relatively few and almost always the result of venous catheters.

2.5 | Statistical methods

Of the 12 887 ARIC cohort participants examined at visit 3, we excluded 57 with missing headache information, 303 whose first VTE occurred before visit 3 (because of our interest in incident VTE after

TABLE 1 Baseline VTE risk factor levels (mean or %) by headache history status, ARIC, 1993-1995

	Headache history status			
	No severe headache	Severe, nonmigraine headache	Migraine without aura	Migraine with aura
n	9442	1215	932	396
Self-reported physician-diagnosed migraine, %	5	13	39	67
Age, y	60	59	58	58
Sex, % female	51	64	75	82
Race, % African American	24	16	12	18
Height, cm	169	167	165	164
Weight, kg	81	78	76	79
Diabetes, %	16	12	11	13
Hormone replacement therapy, % of females	15	26	33	33
Smoking status, %				
Current	18	17	16	17
Former	42	42	36	36
Never	40	41	48	48
Systolic blood pressure, mm Hg	125	123	121	124
Antihypertensive medication, %	38	31	34	43
Aspirin use, %	42	53	51	45
History of cancer, %	9	10	11	12
Estimated glomerular filtration rate, mL/min/1.73 m^2[a]	96	97	98	98
Factor XI, %[b]	113	113	115	114
D-dimer, μg/mL[b]	0.50	0.49	0.45	0.54
Activated partial thromboplastin time, s[b,c]	29	29	29	29
Factor VIII, %[b,c]	129	125	127	128
von Willebrand factor, %[b,c]	116	110	110	111
Weighted genetic risk score (*F5*, *F2*, *ABO*, *F11*, *FGG* variants)[b]	1.44	1.44	1.44	1.45

ARIC, Atherosclerosis Risk in Communities; VTE, venous thromboembolism.
Means and percentages are adjusted for age, sex, and race, except for hormone replacement therapy (adjusted for age and race).
[a]From ARIC visit 2, 1990-1992.
[b]Sample size modestly smaller due to additional missing data.
[c]From ARIC visit 1, 1987-1989.

visit 3), 38 who were of race groups other than black or white, 136 who were taking anticoagulants at visit 3, and 368 missing information on visit 3 covariates used in modeling. This left 11 985 participants. Person-time accrued from visit 3 until the first VTE, loss to follow-up, death, or else December 31, 2015.

We used generalized linear models to test for differences in means or frequencies of VTE risk factors, including hemostatic factors, between participants with a migraine history and those with no severe headache history. We used Kaplan-Meier methods to plot cumulative incidence of VTE among headache groups. We then performed proportional hazards regressions to estimate the hazard ratio (HR) of VTE in relation to headache status, with no severe headache history being the reference. Follow-up for VTE began at ARIC visit 3 and went until the date of first VTE occurrence, loss to follow-up, death, or else December 31, 2015. The proportional hazard assumption was not violated. Model 1 adjusted for age, race, and sex. Model 2 adjusted for age, race, HRT-sex (women-current user, women-nonuser, women-unknown status, men), weight (continuous), height (continuous), diabetes (yes, no), smoking status (current, former, never), systolic BP (continuous), BP medications (yes, no), cancer history (yes, no), aspirin use (yes, no), and visit 2 eGFR (continuous). We also tested 2-way interactions of headache status with key VTE risk factors—age, race, weight, height, and the VTE genetic risk score. None was significant ($P > 0.3$). As a secondary analysis, we also calculated HRs of VTE, comparing those who self-reported a physician diagnosis of migraine headaches vs those reporting no diagnosis. We used SAS version 9.4 (SAS Inc., Cary, NC) for all analyses.

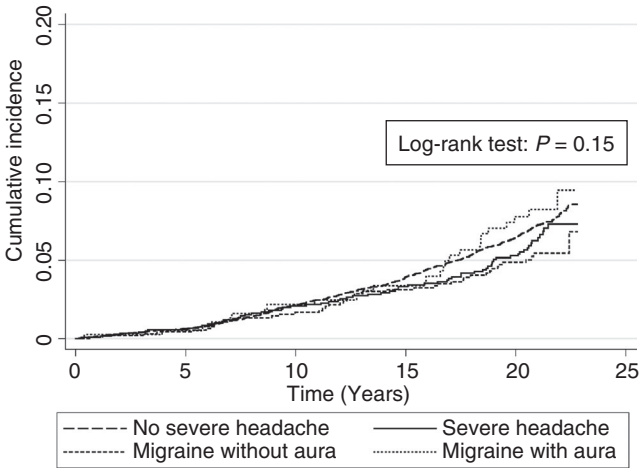

FIGURE 1 Cumulative incidence of venous thromboembolism by headache status, Atherosclerosis Risk in Communities, 1993-1995 through 2015

3 | RESULTS

At baseline among participants free of VTE, the mean age was 60 years (SD: 6), and 11% were classified by the ARIC headache questionnaire as having a migraine history (n = 932 without aura and 396 with aura). Those having a migraine history were more likely to self-report a physician diagnosis of migraines, more often women than men, and more often whites than blacks (Table 1). Several other baseline characteristics differed for migraineurs vs the no headache group (Table 1), but after adjustment for age, race, and sex (not shown in Table 1), the only characteristics that remained significantly different were that migraineurs had more use of HRT (women) and aspirin, compared with participants with no history of severe headache. After accounting for age, race, and sex, those with a history of migraines did not have higher frequency of elevated hemostatic risk factors or a higher genetic risk score for VTE.

Over a mean of 18 years of follow-up (maximum 23 years) and 211 913 person-years at risk, 688 participants developed VTE, for a crude incidence rate of 3.2 per 1000 person-years. The VTE incidence was quite similar across headache groups (Figure 1). As shown further in Table 2, there was no evidence that participants with a migraine history, overall, had a greater risk of VTE compared with those free of severe headache (Model 2, HR: 1.06, 95% confidence interval [CI]: 0.82-1.36). Migraine history with aura had a Model 2 HR of 1.25 (0.85-1.85), compared with no severe headache. When we repeated this analysis adjusting for the competing

TABLE 2 Hazard ratios (95% CIs) of VTE by headache history status, ARIC, 1993-1995 through 2015

	Headache history status			Migraine history subset	
	No severe headache	Severe, nonmigraine headache	Migraine	Migraine without aura	Migraine with aura
n at risk	9442	1215	1328	932	396
Person-years at risk	165 041	22 268	24 604	17 501	7103
Incident VTE, n	550	67	71	44	27
Model 1 HR[a] (95% CI)	1 (reference)	1.05 (0.82-1.36)	1.03 (0.80-1.33)	0.91 (0.67-1.24)	1.34 (0.90-1.97)
Model 2 HR[b] (95% CI)	1 (reference)	1.09 (0.85-1.42)	1.06 (0.82-1.36)	0.97 (0.71-1.32)	1.25 (0.85-1.85)

ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.
[a]Model 1: Adjusted for age, race, and sex.
[b]Model 2: Adjusted for age, race, sex–hormone replacement therapy, weight, height, diabetes, smoking status, systolic blood pressure, antihypertensive medications, aspirin use, history of cancer, and estimated glomerular filtration rate.

risk of death (not shown), Figure 1 and Table 2 results were nearly identical.

The statistically nonsignificant patterns shown in Table 2 were similar for DVT and PE and for unprovoked and provoked VTE, when analyzed separately (Tables S1 and S2).

In the secondary analysis (Table 3), VTE also was not significantly associated with a self-reported physician diagnosis of migraine headaches (Model 2, HR for yes vs no: 1.22, 95% CI: 0.96-1.55).

4 | DISCUSSION

This prospective population-based study of older adults showed no significant association between migraine history and incident VTE. This was true for migraine history both with aura and without aura. Furthermore, a self-reported physician diagnosis of migraine headaches was not associated with VTE. In addition, we found no apparent association of migraine history with important plasma hemostatic factors or with a 5-single nucleotide polymorphism genetic risk score for VTE. These lines of evidence suggest that migraine is not an important risk factor for VTE in older adults.

Our findings contrast with 4 previous reports associating a migraine diagnosis with VTE.[4–7] These studies differed from ours in many ways—study design (2 cohort, 2 cross sectional), population and age sampled, exposure and outcome definitions, and control of confounding variables. Our study was population based, prospective, queried migraine symptoms in all (as opposed to only capturing individuals who sought medical care), was well controlled for confounding variables, and studied validated VTEs rather than relying solely on International Classification of Diseases codes. Yet our study had some drawbacks. First, ARIC defined migraine history by standard questions about headache duration and symptoms obtained 1 time and did not obtain physician confirmation of migraine diagnosis. Thus, migraine history is undoubtedly somewhat

TABLE 3 Hazard ratios (95% CIs) of VTE by self-reported physican-diagnosed migraine, ARIC, 1993-1995 through 2015

	Physician-diagnosed migraine status	
	No migraine	Diagnosed migraine
n at risk	10 732	1244
Person-years at risk	189 398	22 388
Incident VTE, n	610	77
Model 1 HR[a] (95% CI)	1 (reference)	1.20 (0.95-1.53)
Model 2 HR[b] (95% CI)	1 (reference)	1.22 (0.96-1.55)

ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

[a]Model 1: Adjusted for age, race, and sex.

[b]Model 2: Adjusted for age, race, sex–hormone replacement therapy, weight, height, diabetes, smoking status, systolic blood pressure, antihypertensive medications, aspirin use, history of cancer, and estimated glomerular filtration rate.

TABLE 4 Prospective studies of migraine history and incidence of VTE

Sample	Migraine definition	VTE definition	HR and 95% CI
Danish study[4] of 51 032 migraineurs and 510 320 random people from the general population. Median age 35. Maximum follow-up 19 y	ICD 8-CM code 346 or ICD-10-CM code G43 from nationwide inpatient and outpatient records	ICD-8-CM codes 451.00 and 450.99 or ICD-10-CM codes I26, I80.1-I80.3	Adjusted HR: 1.59 (1.45-1.74) overall but 2.48 (1.91-3.22) in first 2 years of follow-up
Taiwanese study[5] of 102 159 migraineurs and 102 159 random headache-free subjects matched on sex and migraine propensity score. Mean age 42. Maximum follow-up 6 y	ICD-9-CM code 346 among neurologist visits nation-wide	ICD-9-CM codes 415.1x or 453.x, and prescription for anticoagulant	Matched HR: 1.12 (0.92-1.35) overall; 2.42 (1.40-4.19) for those with aura, 0.81 (0.55-1.20) for those without aura, and 1.07 (0.84-1.36) for unspecified as to aura
ARIC study (this study) of 11 985 US adults, of whom 1328 had migraine history. Mean age 60. Maximum follow-up 23 y	(1) Headache history and symptoms from interviewer-administered questionnaire (2) Self-reported physician diagnosis of migraines	Hospitalized VTE by ARIC criteria and physician review	(1) Adjusted HR: 1.06 (0.82-1.36) for migraine history vs no headache history (2) Adjusted HR: 1.22 (0.96-1.55) for self-reported physician diagnosis (yes, no)

ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

misclassified. Because migraine in ARIC is associated with increased stroke risk,[20] as in other studies,[1–4] the validity of the ARIC migraine classification may be adequate. Second, as summarized in Table 4, compared with the 2 previous cohort studies showing positive associations of migraine with VTE,[4,5] the ARIC sample was older (mean age: 60), which may be relevant because migraine prevalence peaks between ages 20 and 50 years and decreases greatly after age 60 years.[21] Yet the ARIC questionnaire asked about *ever* having prolonged headaches, and doing so should have captured migraines earlier in life. Moreover, our secondary analysis showed self-reporting a physician diagnosis of migraines was also not associated with VTE. Third, we identified hospitalized VTE cases only, thus missing cases managed as outpatient; yet pilot data suggest that the vast majority of patients with first VTEs in ARIC were hospitalized.

Fourth, ARIC follow-up for VTE occurrence was long. This is relevant because Adelborg et al[4] found that the association of migraine with VTE was stronger in the short term (0-1 year) than in the long term (up to 19 years) after diagnosis. Our study did not have year of migraine onset and, in any case, was not large enough to examine VTE incidence in the 2-year period following the migraine assessment. Finally, 3 of the 4 prior studies suggested the association between migraine and aura might be at least 2-fold,[5–7] and the other 1.6-fold.[4] Our study with 688 VTEs provided HRs that were relatively imprecise but should have had sufficient statistical power to rule out migraine doubling the risk of VTE. Power was certainly limited to determine whether migraine is a weak VTE risk factor (eg, HR: 1.2), and especially so when evaluating subsets of migraine with vs without aura. However, if migraine were such a weak risk factor for VTE, the association would be of little clinical or public health importance.

We did not find the VTE genetic risk score or several plasma hemostatic factors to be associated with migraine history, thus providing no additional mechanistic support for an association of migraine with VTE. Admittedly, we cannot rule out the possibility that a migraine episode may change hemostatic factors acutely and thereby trigger a VTE. All in all, the methodologic flaws and inconsistent findings of existing studies prevents firm conclusions about whether migraine affects hemostasis.[8]

In summary, in contrast to 2 previous cohort studies of younger migraineurs, this study does not support the hypothesis that migraine history is an important risk factor for VTE in older adults. However, imprecision of our HRs prevents firm conclusions about whether migraine might be a modest VTE risk factor.

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RELATIONSHIP DISCLOSURE

The authors report nothing to disclose.

AUTHOR CONTRIBUTIONS

Manuscript conceptualization, data collection, and drafting manuscript: AF. Manuscript conceptualization and critical review of manuscript: PL. Data analysis and critical review of manuscript: JM. Data collection and critical review of manuscript: MC.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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