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Migraine, Headache and the Risk of Depression: Prospective Cohort Study

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Abstract

Background—While cross-sectional studies have shown associations between migraine and depression, few studies have been able to evaluate the association between migraine and incident depression.

Methods—Prospective cohort study among 36,016 women without a history of depression enrolled in the Women's Health Study who provided information about migraine and headache at baseline. Women were classified as either having non-migraine headache, migraine with aura, migraine without aura, past history of migraine or no history of headache. Cox proportional hazards models were used to evaluate the association between migraine and headache status and incident depression.

Results—At baseline, 5115 women reported a history of non-migraine headache, 1805 reported migraine with aura, 2723 reported migraine without aura and 1896 reported a past history of migraine. During 13.8 mean years of follow-up, 3833 new cases of depression occurred. The adjusted relative risks of incident depression were 1.44 (95% CI: 1.32, 1.56) for non-migraine headache, 1.53 (95% CI: 1.35, 1.74) for migraine with aura, 1.40 (95% CI: 1.25, 1.56) for migraine without aura and 1.56 (95% CI: 1.37, 1.77) for past history of migraine compared to no history of headache.

Conclusions—Middle-aged women with migraine or non-migraine headache are at increased risk of incident depression.

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Conflicts of Interest

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Keywords

Migraine; depression; epidemiology

Introduction

Migraine and depression are common disorders in the general population and are associated with substantial disability burden.(1, 2) Studying the association between migraine and depression among women is particularly important because the prevalence of each disorder is more common among women than men.(3, 4) Several cross-sectional studies have suggested that migraine and depression may be comorbid disorders.(5) Since some studies have found evidence of a bidirectional association between migraine and depression,(6–9) longitudinal studies are necessary to quantify the risk of incident depression among those with migraine. Additionally, information on whether migraine with aura may exhibit stronger relationships with depression than migraine without aura is limited. One study found that the risk of depression is higher amongst those who experience migraine with aura compared to those who experience migraine without aura.(8)

Based on the hypothesis that migraine may increase the risk of depression through the intense and often long-lasting pain episodes, some studies have also examined whether the presence of non-migraine headache is associated with an increased risk of depression commensurate with the increase seen in migraine. A cross-sectional and a case-control study found an association between migraine as well as non-migraine headache and depression compared to no headache, although the association was stronger for migraine than for non-migraine headache.(10, 11) However, a prospective study found that severe headache did not result in a significant increase in the risk of developing depression.(7) To further elucidate the associations between migraine, including aura status, as well as non-migraine headache, and incident depression, we aimed to study these associations in the Women's Health Study (WHS), an ongoing prospective cohort study.

Methods

The Women's Health Study was a large, randomized, placebo-controlled trial designed to test the effects of aspirin and vitamin E on the primary prevention of cardiovascular disease and cancer. The design and main results of the trial have been described previously.(12–14) Briefly, at baseline 39,876 US female health professionals aged 45 years or older were randomized to receive active aspirin, active vitamin E, both active agents, or both placebos according to a two by two factorial design. At baseline women were asked about various health and lifestyle characteristics including information about migraine. Six months after baseline and yearly thereafter, women were again asked about various health conditions and events. Since the end of the trial in 2004, the women continued to be followed on an observational basis.

The WHS was approved by the institutional review board at Brigham and Women's Hospital and informed consent was obtained from all participants.

Migraine and Headache Assessment

At baseline the 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 for further details including "What is the approximate frequency of your migraines?" with possible response options of daily, weekly, monthly, every other month, and less than 6 times per year and "Do your migraines have any of the

following characteristics? (Mark all that apply.)” The response options included “Aura or any other indication a migraine is coming” which was used to classify women who experience migraine with aura. Since the baseline questionnaire did not ask about migraine headache, we used information from the six-month questionnaire to assess headache. On the six-month questionnaire, women were asked if they had had any headache since the baseline questionnaire. Using the women’s responses to these questions, we divided them into the following groups: any history of migraine (women who reported ever experiencing migraine headache), history of non-migraine headache (women who reported experiencing headache but did not report migraine headaches) and no history of headache (women who reported no history of migraine headache or non-migraine headache). Women with any history of migraine were further divided into the following categories: “migraine with aura” (women who reported migraine within the past year and who reported the presence of aura or any indication that migraine is coming); “migraine without aura”; and “past history of migraine” (women who reported ever having migraines but not within the past year). Women who reported experiencing migraine within the past year were also asked about the frequency of their attacks (<6 times per year, monthly, weekly, daily). A previous study in the WHS has shown good agreement between self-reported migraine without aura and classification of migraine without aura based on the International Classification of Headache Disorders(15) criteria.

Depression Assessment

Women were asked if they had ever been diagnosed with depression on the 48-month and 108-month questionnaire. Women who responded affirmatively were asked to provide the month and year of diagnosis. On the 120-month and first observational follow-up questionnaire, women were asked to report newly diagnosed depression within the past year and to include the month and year of diagnosis. Incident diagnosed depression and year of incident diagnosed depression were based on the earliest reported diagnosis date from these four questionnaires. Although depression diagnosis was self-reported, previous research has shown that health professionals report lifestyle characteristics and medical conditions accurately.(16–18)

Given the limitations to using self-reported physician diagnoses of depression, we performed sensitivity analyses using three related outcome measures. First, on the 60-month questionnaire, the women were asked questions from the Mental Health Inventory (MHI-5), a five item subscale of the Short-Form 36 health status survey(19) that measures global psychological distress. The five items ask the participants how much of the time over the past month (all, most, a good bit, some, little or none) they felt nervous, felt so down that nothing could cheer them up, felt calm and peaceful, felt down and blue or felt happy. We categorized the MHI-5 into four groups: 86–100, 76–85, 53–75 and <53 and designated scores <53 as evidence of significant psychological distress, similar to previous studies.(20–22) Our second outcome measure was self-reported anti-depressant medication use among those reporting depression at the 108-month questionnaire.

Analysis

Of the 39,876 women enrolled in the WHS, we excluded 119 women missing information on migraine status at baseline, 872 women who never provided information on depression status, and 2869 women who reported a history of depression prior to the 6 month questionnaire, leaving 36,016 women for this analysis. Using Cox proportional hazards models, we calculated the hazard ratio and 95% confidence interval (CI) as a measure of the relative risk (RR) of incident depression for women with any history of migraine or a history of non-migraine headache compared to those without a history of headache. We tested the

assumption of proportional hazards by including an interaction term between the log transformation of time and headache category and found no significant violation.

We further stratified the group of women reporting any history of migraine into migraine with aura, migraine without aura and past history of migraine. Additionally, we examined the association between migraine attack frequency and risk of incident depression.

We built age-adjusted (Model 1) and two multivariable-adjusted models. In our multivariable analyses, we first adjusted for the following potential confounders (Model 2): age (continuous in years), body mass index (BMI; continuous in kg/m²), systolic blood pressure (10 mmHg increments), diastolic blood pressure (<65, 65–74, 75–84, 85–89, 90–94, 95–104, 105 mmHg), history of hypertension (yes/no), use of antihypertensive medication (yes/no), menopausal status (premenopausal, postmenopausal, uncertain), ever used oral contraceptives 2 months (yes/no/not sure), alcohol use (rarely/never, 1–3 drinks per month, 1–6 drinks per week, 1 drink per day), vigorous physical activity (rarely/never, <1 time per week, 1–3 times per week, 4 times per week), baseline history of diabetes (yes/no), smoking (never, past, smoke <15 cigarettes per day, smoke 15 cigarettes per day), postmenopausal hormone use (never/past/current), history of high cholesterol (yes/no), and treatment for high cholesterol (yes/no). We also adjusted for randomized treatment assignments. We then additionally adjusted (Model 3) for income (\$10,000 increments), education (RN, LPN/LVN, Other, MD/MD equivalent, DDS/DMD, DVM) and marital status (single, married, divorced, widowed).

For our sensitivity analyses, we performed logistic regressions adjusting for all covariates listed above in Model 2. For the MHI-5 outcome, we excluded women who did not answer all five questions on the MHI-5. For the anti-depressant medication use outcome, we excluded women who did not return the 108-month questionnaire.

For all models, more than 100 women were missing information on systolic and diastolic blood pressure, income, education and marital status and were assigned to a separate category. Less than 100 women were missing information on all other covariates and were either assigned to the mean value (BMI), the reference category (i.e. lowest exposure category), to the past user category (smoking) or to the unclear exposure category (menopausal status and oral contraceptive use). The highest percentage of missing data was seen for diastolic blood pressure (1.4% of women were missing data on this covariate).

All statistical analyses were performed with the use of SAS 9.1.3. All p-values are 2-tailed and $p < 0.05$ was considered statistically significant.

Results

Of the 36,016 women eligible for inclusion in this study, 5115 (14.2%) reported a history of non-migraine headache, and 6424 (17.8%) reported any history of migraine, of whom 1805 (28.1%) reported migraine with aura, 2723 (42.4%) reported migraine without aura and 1896 (29.5%) reported a past history of migraine. The baseline characteristics of these women can be seen in Table 1. Compared to those without a history of any headache, those with a history of non-migraine headache or migraine were younger and less likely to consume alcohol. Those with a history of migraine were more likely to have a history of high cholesterol and hypertension than those without a history of any headache.

During a mean of 13.8 years of follow-up, 3833 cases of incident depression occurred. After adjusting for potential confounders (Model 2), those with a history of non-migraine headache and any history of migraine had a relative risk of depression of 1.44 (95%CI: 1.32, 1.56) and 1.48 (95%CI: 1.37, 1.60) respectively compared to those without a history of

headache or migraine. Additional adjustment for income, education and marital status did not impact our results (Table 2). Our results stratified by specific migraine subtypes (migraine with aura, migraine without aura and past history of migraine) can be found in Table 3. The increase in risk for depression was only slightly higher for those with migraine with aura (Model 2: RR=1.53, 95%CI 1.35, 1.74) or past history of migraine (Model 2: RR=1.56, 95%CI 1.37, 1.77) than for those with migraine without aura (Model 2: RR=1.40, 95%CI 1.25, 1.56) or non-migraine headache (Model 2: RR=1.44, 95%CI 1.32, 1.56) compared to women with no history of headache.

Table 4 shows our results stratified by migraine attack frequency (no history of headache, migraine attacks less than 6 times per year, monthly migraine attacks, and weekly or daily migraine attacks). The risk of incident depression was the highest amongst those women who reported weekly or daily migraine attacks compared to women who reported no history of migraine or headache (Model 2: RR=2.44, 95%CI: 1.85, 3.23).

Table 5 shows the results from our sensitivity analyses using the four categories of the MHI-5 stratified by specific migraine subtypes. Results were similar for all migraine subtypes. The relative risk for the MHI-5 <53 category was higher than the relative risk for any other MHI-5 category for all migraine subtypes.

Table 6 shows the effect estimates for significant psychological distress (MHI-5 <53) and anti-depressant medication use. Overall, the estimates are similar in magnitude to those seen for self-reported depression and we did not see large differences amongst the migraine categories.

Discussion

Results from this large, prospective study among middle-aged women showed that migraine, regardless of migraine subtype, and non-migraine headache was associated with an increased risk of incident depression compared to no history of headache. Frequent migraine attacks (weekly or daily) were associated with the highest risk for developing depression.

Few studies have been able to specifically address the direction of the relationship between migraine and depression. Some studies have suggested that migraine and depression may have a bi-directional association.(6–9) One study found evidence of a bidirectional association between migraine and depression but was unable to stratify their results by aura status and did not examine the association between non-migraine headache and depression. (6) Another study using data from the Detroit Area Study of Headache followed people with migraine within the past year, people with other severe headache within the last year and a subset of the remaining sample without migraine or severe headache in their lifetime for the occurrence of migraine, severe headache or depression. The study found that major depression at baseline was associated with the onset of migraine during follow-up (OR=3.4, 95%CI: 1.4, 8.7) and that migraine was associated with the onset of depression during follow-up (OR=5.8, 95%CI: 2.7, 12.3).(7) Given the insignificant associations seen between headache and depression in these analyses, the authors concluded that the association between migraine and depression is most likely due to shared etiologic factors, possibly related to the hormonal or neurotransmitter systems. However, the authors acknowledged that an association between severe headache and depression could not be conclusively ruled out.

Data from the Canadian National Population Health Survey also suggested a bidirectional association between migraine and depression. Those with migraine were 60% more likely to develop major depressive episodes compared to those without migraine while those with a

history of major depressive episodes were 40% more likely to develop migraine compared to those without major depressive episodes.(9)

While some studies have shown evidence of a bi-directional association between migraine and depression, data from the Baltimore Epidemiologic Catchment Area Follow-up Study did not find evidence of an association between depression and incident migraine.(23) However, this study did not examine the association between migraine and incident depression.

While our study confirmed a longitudinal association between migraine and depression, we also found an association between non-migraine headache and depression. The larger size of (36,016 women vs. 1186 women) and the longer follow-up in (13.8 years vs. 2 years) our study compared to the previous longitudinal study(7) may have resulted in an increased ability to detect a significant association between non-migraine headache and incident depression.

Most previous studies on migraine and depression could not stratify their results by migraine aura status. The Detroit Area Study of Headache observed an increase in the risk of incident depression for both migraine with aura (RR=4.90; 95% CI: 3.34, 7.19) and migraine without aura (RR=3.03; 95% CI: 2.23, 4.11).(8) We also found a slightly higher risk of depression among women who experience migraine with aura than among women who experience migraine without aura, although our effect estimates were lower than those observed in the Detroit Area Study of Headache. There are a few possible explanations for the difference in effect sizes. First, the age ranges of the two cohorts were different. The previous study enrolled people aged 20–55 while our study only included women who were 45 years of age or older. The risk for incident depression among migraineurs may be higher among young adults than middle-aged adults. Additionally, by relying on self-report of physician diagnosis of depression instead of using a structured interview, we may not have captured all cases of depression within our cohort. If this underreporting was non-differential with respect to our exposure status, we would expect our results to be biased towards the null, which might help to explain why our effect estimates were lower than those seen in the previous study.

Another study followed 379 subjects aged 19 to 20 at first interview for ten years. Using the Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology (SPIKE), they found that major depression and recurrent brief depression were more common among the migraine with aura group than among those with migraine without aura, tension type headache, headache symptoms only or no headache groups.(24)

Three different mechanisms have been proposed to explain why migraine is associated with depression in cross-sectional studies.(25) First, psychiatric disorders, like depression, may cause migraine. Second, migraine may cause psychiatric disorders like depression possibly because of the repeated episodes of intense and long-lasting pain associated with migraine or some other migraine-specific mechanism. Finally, migraine and depression may share etiologic factors or common causes.

Our findings that non-migraine headache in addition to migraine increases the risk for depression favors the concept that the pain aspect of migraine or some pain-related mechanism increases the susceptibility for depression. Two not mutually exclusive scenarios may be envisioned. First, repeated headache attacks (and chronic headache) are debilitating, may obviate social activities and thus impair quality of life to such an extent that depression develops. Second, headache and depression may share common neuroanatomical circuits, neurotransmitters, and/or genetic susceptibility factors. This agrees with findings from other pain conditions and depression.(26–28) If one or both conditions develop as well as when

and in which order they manifest may depend on additional factors. Given the increased risk of depression observed among those with migraine or headache, physicians should monitor these patients for the development of depressive symptoms.

The strengths to this study include its prospective, longitudinal design which allowed us to assess the temporal association between migraine or non-migraine headache and depression. The large size of the cohort and the classification of aura status also allowed us to stratify our results based on migraine subtype.

Despite these strengths, there are a few important limitations to this study. First, migraine status and incident depression are self-reported and misclassification of migraine or depression status is possible. However, previous research has shown that health professionals, similar to those enrolled in our cohort, report lifestyle characteristics and medical conditions accurately.^(16–18) Additionally, we observed good agreement between self-reported migraine and the classification of migraine status according to IHS criteria. While some misclassification of migraine status is still possible, this misclassification is more likely non-differential with respect to our outcome because information on incident depression was collected prospectively. Our sensitivity analysis using related outcomes (the MHI-5 which measures psychological distress and self-reported anti-depressant medication use) and found similar results to our primary analysis. We did not use self-reported anti-depressant medication use as our primary outcome because frequent migraine can be treated with anti-depressant medication. Other limitations include not having information on the aura status of women who report a prior history of migraine and only crude information on migraine attack frequency. Our study enrolls only middle-aged women, which may impact the generalizability of our findings to other populations. Finally while we attempted to control for confounding, the potential for unmeasured and residual confounding remains.

Migraine and non-migraine headache are associated with an increased risk of incident depression in middle-aged women. By incorporating information on the onset of migraine and depression relative to each other and also examining the impact of other pain disorders on the risk of depression, future studies can help to determine if the associations seen between migraine and depression may be causal or due to common etiologic factors.

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Table 1

Baseline characteristics of women according to headache status in the Women's Health Study (n=36,016).

Characteristic	No history of headache, n = 24,477	History of non-migraine headache, n = 5115	History of migraine, n = 6424
Mean age (SE), y	55.2 (7.3)	53.7 (6.4)	53.7 (6.5)
BMI (SE), kg/m ²	25.9 (5.0)	26.3 (5.2)	26.1 (5.1)
History of hypertension, %	25.3	25.9	26.9
Antihypertensive medication use, %	13.6	12.9	14.7
History of high cholesterol, %	28.6	28.9	31.5
Cholesterol lowering medication use, %	3.1	3.0	2.9
Postmenopausal status, %	56.8	49.9	50.9
Oral contraceptive use, %	67.1	71.1	73.7
Postmenopausal hormone use, %			
Never	49.7	47.6	44.5
Past	10.1	10.2	10.5
Current	40.1	42.1	44.8
Alcohol consumption, %			
Rarely/never	43.5	48.1	47.4
1–3 drinks/month	12.7	13.1	14.4
1–6 drinks/week	32.5	30.8	30.0
1 drinks per day	11.3	8.0	8.2
Vigorous physical activity, %			
Rarely/never	38.1	37.6	38.2
<1/week	19.0	20.4	22.0
1–3 times/week	31.5	33.2	30.2
4 times/week	11.4	8.7	9.7
Smoking status, %			
Never	50.9	52.3	53.8
Past	36.1	35.5	33.8
Current <15 cig/day	4.8	4.7	4.5
Current 15 cig/day	8.0	7.3	7.6
Baseline diabetes, %	2.5	2.9	1.9
Randomized to aspirin, %	50.3	48.5	49.1
Randomized to vitamin E, %	49.8	51.3	49.3

Numbers may not add up to 100% because of rounding or missing data.

Table 2

Age- and multivariable-adjusted relative risk of depression according to headache status (N=36,016). *

Headache status	Age-adjusted		First multivariable-adjusted model*		Second multivariable-adjusted model**	
	No. of cases	Relative risk (95%CI)	No. of cases	Relative risk (95%CI)	No. of cases	Relative risk (95%CI)**
No history of headache	2221	1.00	2221	1.00	2221	1.00
History of non-migraine headache	700	1.48 (1.36, 1.61)	700	1.44 (1.32, 1.56)	700	1.43 (1.31, 1.56)
History of migraine	912	1.54 (1.43, 1.67)	912	1.48 (1.37, 1.60)	912	1.46 (1.35, 1.58)

* Adjusts for age, randomized treatment assignment, BMI, systolic blood pressure (categories), diastolic blood pressure (categories), history of hypertension, hypertension medication use, menopausal status, oral contraceptive use, alcohol use, vigorous physical activity, baseline history of diabetes, smoking, postmenopausal hormone use, history of high cholesterol, and treatment for high cholesterol.

** Also adjusts for income, education and marital status.

Table 3

Age- and multivariable-adjusted relative risk of depression according to headache status (N=36,016).

Headache status	Age-adjusted (Model 1)		First multivariable-adjusted model (Model 2)*		Second multivariable-adjusted model (Model 3)**	
	No. of cases	Relative risk (95%CI)	No. of cases	Relative risk (95%CI)	No. of cases	Relative risk (95%CI)
No history of headache	2221	1.00	2221	1.00	2221	1.00
History of non-migraine headache	700	1.48 (1.36, 1.61)	700	1.44 (1.32, 1.56)	700	1.43 (1.31, 1.56)
migraine with aura	271	1.62 (1.42, 1.83)	271	1.53 (1.35, 1.74)	271	1.51 (1.33, 1.71)
migraine without aura	372	1.44 (1.29, 1.61)	372	1.40 (1.25, 1.56)	372	1.38 (1.24, 1.54)
Past history of migraine	269	1.64 (1.44, 1.86)	269	1.56 (1.37, 1.77)	269	1.53 (1.35, 1.74)

* Adjusts for age, randomized treatment assignment, BMI, systolic blood pressure, diastolic blood pressure, history of hypertension, antihypertensive medication use, menopausal status, oral contraceptive use, alcohol use, vigorous physical activity, baseline history of diabetes, smoking, postmenopausal hormone use, history of high cholesterol, and treatment for high cholesterol.

** Also adjusts for income, education and marital status.

Table 4

Age- and multivariable-adjusted relative risk of incident depression according to migraine attack frequency (N=28,949).

Migraine attack frequency	Age-Adjusted (Model 1)		Multivariate-adjusted (Model 2)*	
	No. of cases	Relative risk (95%CI)	No. of cases	Relative risk (95%CI)
No history of headache	2221	1.00	2221	1.00
Less than 6 times/yr	386	1.41 (1.27, 1.57)	386	1.35 (1.21, 1.50)
Every other month	71	1.63 (1.28, 2.06)	71	1.62 (1.28, 2.05)
Monthly	126	1.47 (1.23, 1.76)	126	1.45 (1.21, 1.74)
Weekly or Daily	51	2.66 (2.02, 3.52)	51	2.44 (1.85, 3.23)

* Adjusts for age, randomized treatment assignment, BMI, systolic blood pressure, diastolic blood pressure, history of hypertension, antihypertensive medication use, menopausal status, oral contraceptive use, alcohol use, vigorous physical activity, baseline history of diabetes, smoking, postmenopausal hormone use, history of high cholesterol, and treatment for high cholesterol.

Table 5

Multivariable-adjusted relative risk of psychological distress as measured by the MHI-5 according to headache status (N=32,026).

	MHI 86-100			MHI 76-85			MHI 53-75			MHI <53		
	n	%		n	%	RR (95% CI)	n	%	RR (95% CI)	n	%	RR (95% CI)
No migraine or headache	9367	43.1		7369	33.9	1.00	3896	17.9	1.00	1120	5.2	1.00
Headache only	1410	30.7		1717	37.4	1.47 (1.36, 1.59)	1088	23.7	1.71 (1.56, 1.87)	372	8.1	2.00 (1.75, 2.28)
Migraine with aura	526	33.5		575	36.6	1.29 (1.14, 1.46)	319	20.3	1.31 (1.13, 1.52)	152	9.7	2.14 (1.76, 2.60)
Migraine without aura	767	31.9		860	35.7	1.31 (1.18, 1.46)	579	24.1	1.60 (1.42, 1.79)	200	8.3	1.87 (1.58, 2.22)
Past history of migraine	639	37.4		600	35.1	1.20 (1.07, 1.35)	334	19.5	1.24 (1.08, 1.43)	136	8.0	1.73 (1.42, 2.11)

* Adjusts for age, randomized treatment assignment, BMI, systolic blood pressure, diastolic blood pressure, history of hypertension, antihypertensive medication use, menopausal status, oral contraceptive use, alcohol use, vigorous physical activity, baseline history of diabetes, smoking, postmenopausal hormone use, history of high cholesterol, and treatment for high cholesterol.

Table 6

Multivariable-adjusted relative risk of significant psychological distress (MHI-5 < 53) and anti-depressant medication use according to headache status.

Headache status	<u>Significant psychological distress (N=32,026)</u>		<u>Anti-depressant medication use (N=27,735)</u>	
	No. of cases	Relative risk (95%CI)	No. of cases	Relative risk (95%CI)
No history of headache	1120	1.00	852	1.00
History of non-migraine headache	372	1.51 (1.33, 1.70)	280	1.44 (1.25, 1.65)
Migraine with aura	152	1.82 (1.52, 2.18)	100	1.48 (1.19, 1.85)
Migraine without aura	200	1.50 (1.28, 1.76)	135	1.28 (1.06, 1.54)
Past history of migraine	136	1.54 (1.27, 1.85)	114	1.68 (1.37, 2.07)

* Adjusts for age, randomized treatment assignment, BMI, systolic blood pressure, diastolic blood pressure, history of hypertension, antihypertensive medication use, menopausal status, oral contraceptive use, alcohol use, vigorous physical activity, baseline history of diabetes, smoking, postmenopausal hormone use, history of high cholesterol, and treatment for high cholesterol.