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Migraine, weight gain and the risk of becoming overweight or obese: prospective cohort study

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Abstract

Background—Some cross-sectional studies have suggested an association between migraine and increased body weight. However, prospective data on the association are lacking.

Methods—We conducted a prospective cohort study among 19,162 participants in the Women's Health Study who had a body mass index (BMI) of 18.5–<25kg/m² at baseline. Migraine was self-reported by standardized questionnaires. Main outcome measures were: incident overweight (BMI 25kg/m²), incident obesity (BMI ≥30kg/m²), and mean weight change. Age- and multivariable-adjusted hazard ratios were calculated for the association between migraine and incident overweight and obesity. Differences in weight change were evaluated by ANCOVA.

Results—3,483 (18.2%) women reported any migraine history. After 12.9 years of follow-up, 7,916 incident overweight and 730 incident obesity cases occurred. Migraineurs had multivariable-adjusted HRs (95%CI) of 1.11 (1.05–1.17) for becoming overweight and 1.00 (0.83–1.19) for becoming obese. These associations remained stable after censoring for chronic diseases and were similar according to migraine aura status. Multivariable-adjusted mean weight change from baseline to the end of study was +4.7kg for migraineurs and +4.4kg for women without migraine (P=0.02).

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Conclusion—Results of this large prospective study of middle-aged women do not indicate a consistent association between migraine and incident overweight, obesity, or relevant weight gain.

Keywords

Migraine; body mass index; overweight; obesity; prospective study

Introduction

Migraine and obesity are both highly prevalent conditions that cause substantial individual and societal burden (1, 2). Several studies have evaluated the potential role of obesity on episodic and chronic migraine, migraine attack frequency and migraine features (3). Plausible shared pathophysiological mechanisms have also been proposed to link these two entities (4, 5).

Small clinical studies reported a high prevalence of episodic migraine among morbidly obese patients (6, 7). However, evidence from population-based cross-sectional studies are inconclusive. Some studies report a positive association between BMI and migraine prevalence (8–12), while others could not confirm these results (13–17). In addition, results of two large population-based studies suggest that obesity is associated with migraine attack frequency and migraine features including photophobia and phonophobia (13, 16). Furthermore, obesity is considered a risk factor for disease progression (18, 19).

In most previous studies obesity has been hypothesized as a risk factor of migraine (10, 11, 13, 16, 18, 20). However, the direction of any association remains unclear in cross-sectional studies. Migraine is a chronic condition which may lead to certain lifestyle modifications. Although some clinical studies report a beneficial effect of physical exercise on migraine (21), many migraineurs with frequent and/or disabling attacks may not be able to adhere to a regular exercise routine. Furthermore, migraine is associated with a variety of comorbid conditions and some migraine-related comorbidities such as depression are associated with weight gain and obesity (22). Considering that migraineurs may have resulting differences in lifestyle and a greater risk of certain obesity-related comorbidities, one can envision migraine as a risk factor for becoming obese. Prospective data that can address the temporal issue in the association between migraine, weight gain and incident obesity are lacking.

We therefore conducted a prospective cohort study among female health professionals in the Women's Health Study to examine whether having migraine is a risk factor for becoming overweight or obese.

Methods

Study Population

The Women's Health Study (WHS) was a randomized, placebo-controlled trial designed to test the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among apparently healthy women. The design, methods and results have been described in detail previously (23, 24). Briefly, a total of 39,876 US female health care professionals aged 45 years or older at study entry (1992–1995) and without a history of cardiovascular disease, cancer, or other major illnesses were randomly assigned to receive aspirin (100 mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both placebos. All participants provided written informed consent, and the institutional review board of the Brigham and Women's Hospital, Boston, Massachusetts, approved the WHS.

Baseline information was self-reported and collected by mailed questionnaires that asked about many cardiovascular risk factors and lifestyle variables. Every 6 months in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes and other information during the study period. For this analysis, we included follow-up information from the time of randomization through March 2004 (12.9 years of follow-up) of women with a baseline BMI between 18.5 and <25 kg/m².

Assessment of migraine

On the baseline questionnaire, participants were asked: “Have you ever had migraine headaches?” and “In the past year, have you had migraine headaches?” Women who experienced migraine headache in the past year were further asked details about their migraine attacks including attack duration of 4 to 72 hours; unilateral location and pulsating quality of pain; inhibition of daily activities; aggravation by routine physical activity; nausea or vomiting; and sensitivity to light or sound. Furthermore, participants who reported migraine during the past year were asked whether they had an “aura or any indication a migraine is coming” as well as details about their attack frequency (daily, weekly, monthly, every other month, <6 times/year). Based on this information, we categorized women into ‘women without migraine history’, ‘women who reported any migraine history’, ‘women who reported active migraine’ (migraine in the year prior completing the baseline questionnaire), and ‘women who reported prior migraine’, which includes women who reported ever having had a migraine but none in the year prior to completing the questionnaire. Women with ‘active migraine’ were further classified into ‘active migraine with aura’ and ‘active migraine without aura’, similar to previous studies (25, 26). Our ‘any migraine’ category included women with ‘active migraine’ (migraine with aura, migraine without aura) and ‘prior migraine’.

In previous studies of the WHS (25, 27), we have shown good agreement between our migraine classification and modified 1988 diagnostic criteria of the International Headache Society (IHS) (28). Furthermore, another study using a subsample of the WHS showed excellent agreement between self-reported migraine and migraine classification according to the 2004 IHS diagnostic criteria. Over 87% of women with active migraine could be diagnosed as migraine without aura (71.5%) or probable migraine without aura (16.2%) when applying 2004 diagnostic criteria (29).

Assessment of covariates

Participants were asked to report age, race, smoking status, exercise, menopausal status, postmenopausal hormone use, history of hypertension, history of hypercholesterolemia, and a history of diabetes on the baseline questionnaire. Information on depression has been assessed during follow-up. On the 48-month follow-up questionnaire, women were asked to report whether they have ever been diagnosed with depression.

39,310 of the 39,876 randomized participants completed a 131-item, self-administered semi-quantitative food frequency questionnaire at baseline. For each food item, a commonly used unit or portion size was specified and participants indicated on a 9 point scale, ranging from “never” to “six or more times per year”, how often they had consumed that specific amount, on average, during the last year. Nutrient scores were calculated by multiplying the intake frequency of each unit of food by the nutrient content of the specific portion size according to food composition tables from the Harvard School of Public Health, Boston, MA. Intake of each nutrient was further adjusted for total energy intake using the residual method. The semi quantitative food frequency questionnaire has demonstrated reasonable validity and reliability as a measure of long-term average dietary intake (30). We defined quintiles of food intake (fruit and vegetables, whole grain, refined grains, red meat, low fat dairy

products, high fat dairy products) and nutrient intake (total fat, saturated fat, monounsaturated fat, polyunsaturated fat, carbohydrates, protein, fiber).

Outcome ascertainment

Participants were asked to report their height and weight on the baseline questionnaire and information on weight was updated on 2-, 3-, 5-, 6-, 9-, 11-, 12- and 13-year follow-up questionnaire. Based upon this information, we calculated BMI values at baseline and at each of the 8 follow-up time-points. A BMI of 18.5 to $<25 \text{ kg/m}^2$ was considered as normal, a BMI of 25 to $<30 \text{ kg/m}^2$ was defined as overweight and a BMI $\geq 30 \text{ kg/m}^2$ as obese. Furthermore, we calculated the weight change between baseline and each follow-up time point.

Consistent with a previous study in the WHS (31), we defined women with a normal BMI at baseline who reported a BMI of $\geq 25 \text{ kg/m}^2$ at any follow-up point as incident cases of becoming overweight or obese. To estimate the time when the BMI crossed the cutoff point, a regression line was modeled from the last reported BMI of $<25 \text{ kg/m}^2$ to the first reported BMI of $\geq 25 \text{ kg/m}^2$ during follow-up. Using the same approach, we defined a subset of incident obesity cases using a BMI cut off point of 30 kg/m^2 .

Person-time was calculated from the date of randomization until the time when a person became overweight or obese, or the latest date when a BMI $<25 \text{ kg/m}^2$ (or $<30 \text{ kg/m}^2$ for analyses of incident obesity) was reported, whatever occurred first. Women who developed diabetes during follow-up prior to becoming overweight or obese were censored on the date of diabetes diagnosis since diabetes management typically includes weight control.

Statistical analysis

Of the 39,876 randomized participants, we excluded 20,313 women with a BMI $\geq 25 \text{ kg/m}^2$ or $<18.5 \text{ kg/m}^2$ at baseline, 128 women with no updated body weight during the entire follow-up period, 194 women with baseline diabetes, 53 women with missing information on migraine, and 26 women who reported cardiovascular disease or cancer events prior to receiving the baseline questionnaire, leaving a total of 19,162 women for this analysis.

We compared baseline characteristics with respect to migraine status using t-tests for continuous variables and chi-square tests for categorical variables. Cox proportional hazards models were used to evaluate the association between baseline migraine status and the risk of becoming overweight (BMI $\geq 25 \text{ kg/m}^2$), as well as the risk of becoming obese (BMI $\geq 30 \text{ kg/m}^2$). Age- and multivariable-adjusted hazard ratios (HRs) and their corresponding 95% confidence intervals (95% CIs) were calculated. To determine the mean change in body weight from baseline to each follow-up point according to migraine status, age and multivariable-adjusted analysis of covariance (ANCOVA) models were used.

We further used Cox proportional hazards models to evaluate the association between migraine frequency and the risk of becoming overweight or obese among 2,407 women with active migraine who provided migraine frequency information. Because of low cell counts in the daily and weekly migraine frequency categories we defined the following attack frequency categories: at least weekly, monthly, every other month and <6 times/year (reference category).

The multivariable Cox proportional hazards- and ANCOVA-models were adjusted for age (continuous), race (white/other), randomized treatment assignments, baseline BMI (continuous), smoking status (never, past, current), exercise (never, <1 time/week, 1–3 times/week, 4 times/week) alcohol consumption (never, 1–3 drinks/month, 1–6 drinks/week, 1 drink/day), history of hypertension (yes/no), history of hypercholesterolemia (yes/

no), total energy intake (<1600 kcal/day, 1600–2400 kcal/day, >2400 kcal/day), postmenopausal status (premenopausal, postmenopausal, biologically uncertain, unclear), postmenopausal hormone use (never, past, current), and history of depression (yes/no).

Further adjustment for quintiles of food intake (fruit and vegetables, whole grain, refined grains, red meat, low fat dairy products, high fat dairy products) and nutrient intake (total fat, saturated fat, monounsaturated fat, polyunsaturated fat, carbohydrates, protein, fiber), oral contraceptive use, family history of myocardial infarction, and caffeine intake did not substantially change the results and are therefore not included in the final models.

Because caloric intake and depression can also be viewed as a consequence of migraine we run separate multivariable models excluding these two covariates to prevent adjustment for potential mediating factors.

To test the proportional hazards assumption, we included an interaction term for migraine status with the logarithm of time and found no statistically significant violation.

Effect modification was evaluated for baseline age (<55, 55–<65, 65–<75, 75 years), smoking status (never, past, current) exercise (never, <1 time/week, 1–3 times/week, 4 times/week), and alcohol consumption (never, 1–3 drinks/month, 1–6 drinks/week, 1 drink/day). We tested statistically significant effect modification by contrasting models with and without an interaction term indicator variable using the likelihood ratio test.

We performed a sensitivity analysis by censoring participants who developed myocardial infarction (MI), stroke or cancer during follow-up in the Cox-proportional-hazards-models since these diseases are potentially associated with subsequent weight change. For the each ANCOVA model, we excluded women who developed myocardial infarction, stroke or cancer during the specific time period analyzed.

A missing value indicator was incorporated into the outcome models for covariates if the number of missing women was greater or equal to 100. We assigned participants with missing values to the covariate reference category if the number of missing information was less than 100.

For all analysis, we used SAS (version 9.1; SAS Institute Inc., Cary, NC, USA). All p-values were two-tailed and $p < 0.05$ was considered to be statistically significant.

Results

Among a total of 19,162 women having a BMI $18.5 < 25 \text{ kg/m}^2$ at baseline, 3,483 (18.2%) women reported any history of migraine of whom 974 reported migraine aura. In Table 1, baseline characteristics of the participants according to migraine status are presented. Migraineurs had a mean age of 53.6 years and were younger compared to women without migraine. They were more likely to rarely/never drink alcohol, to never smoke cigarettes, to exercise <1/week, to have a total calorie intake of 2400 kcal/day, to have a history of hypertension, a history of cholesterol 240 mg/dl and a history of depression.

During 12.9 years of follow-up, 7,916 initially normal weight women became overweight (BMI 25 kg/m^2) and 730 became obese (BMI 30 kg/m^2). In Table 2, age- and multivariable-adjusted HRs for incident overweight are shown. Women who reported any migraine had a multivariable-adjusted HR of 1.11 (1.05–1.17) for becoming overweight. The associations did not differ according to migraine aura status. Compared with women without migraine, those with any history of migraine were not at increased risk of becoming obese (Table 3).

In sensitivity analyses that censored participants with cardiovascular disease and cancer during follow-up, the associations between any migraine and incident overweight and obesity remained stable in multivariable-adjusted models (HR incident overweight: 1.10, 95% CI: 1.04–1.16, HR incident obesity: 0.97, 95% CI: 0.81–1.17).

When we excluded caloric intake and depression from the multivariable model, the association between any migraine and becoming overweight (HR = 1.13, 95% CI: 1.07–1.19) or becoming obese (HR = 1.04, 95% CI: 0.87–1.25) remained very similar.

The associations between migraine and incident overweight and obesity were not modified by age, smoking, alcohol consumption, or postmenopausal status (all p-values for interaction >0.09). The relationship between migraine and incident overweight appeared to be significantly modified by exercise (p interaction=0.03), indicating that women with migraine who exercised <1 times per week, but not those who exercised more may have an increased risk of becoming overweight (multivariable-adjusted HR of 1.17, 95% CI: 1.09–1.26).

In Table 4, age- and multivariable-adjusted mean weight change according to migraine status is presented. During follow-up, both migraineurs and women without migraine constantly gained weight. After 12.9 years of follow-up, women who reported migraine at baseline had a multivariable-adjusted mean weight change of 4.65 kg while women without migraine had a mean weight change of 4.36 kg (P=0.02). In sensitivity analyses, the differences in mean weight change between migraineurs and women without migraine decreased and lost statistical significance in multivariable adjusted models for most follow-up time points (data not presented).

In Table 5, the associations between migraine frequency and incident overweight and obesity are presented. Compared to women with a migraine attack frequency of <6 times/year, migraineurs who reported an attack frequency of every other months, monthly and weekly had multivariable-adjusted HRs of 1.31 (0.74–2.31), 0.95 (0.59–1.53) and 0.61 (0.24–1.53), respectively, for becoming obese.

Discussion

In this large prospective study of female health professionals aged 45 years or older at study entry, we did not find meaningful associations between any history of migraine and an increased risk for becoming overweight or obese. The associations did not differ according to migraine aura status. Within the first 5 years of follow-up, all women gained weight but the magnitude of weight change did not substantially differ between women with and without migraine after 12.9 years of follow-up. The differences in weight change were attenuated after excluding women who were diagnosed with chronic diseases during follow-up.

The potential relationship between episodic migraine and obesity has been studied frequently with inconsistent results. Several cross-sectional studies are in line with our finding of no association between migraine and obesity (13–17, 32). In a cross-sectional study among 31,865 Danish twin individuals, a BMI ≥ 30 kg/m² was not associated with migraine (OR: 0.98, 95% CI: 0.87–1.10), migraine with aura (OR: 0.92, 95% CI: 0.77–1.10) or migraine without aura (OR: 1.02, 95% CI: 0.88–1.17) after multivariable adjustment. One potential limitation of this large population-based study is that migraine diagnosis and BMI calculations were based upon self-reported information and misclassification is possible (14). Another cross-sectional study using measured BMI indices as well as a migraine diagnosis based on neurologist interviews found no relationship between BMI and migraine prevalence among 684 women aged 40–74 years. Migraine was divided into active (migraine during the past year) and inactive migraine (migraine in the past but not the year

preceding the interview) and BMI was not significantly associated with neither active (OR: 1.1, 95% CI: 0.6–1.8) nor inactive migraine (OR: 1.0, 95% CI: 0.6–1.7) (15).

Contrary to our results, several studies found modest associations between BMI and migraine (8, 11, 12). Windsvold et al. evaluated the association between migraine and cardiovascular risk factors among 48,713 participants of the HUNT Study. Migraine was defined according to modified IHS criteria and BMI was calculated using measured height and weight. Compared to a BMI <25 kg/m², a BMI ≥30 kg/m² was associated with a multivariable-adjusted OR of 1.17 (1.04–1.32) for migraine without aura and an OR of 1.32 (1.04–1.32) for migraine with aura after adjusting for age, gender and education level (12). A cross-sectional study evaluating data from the National Health and Nutrition Survey 1999–2002 found an association between BMI and severe headache or migraine. Among 7,601 participants aged ≥20 years, a BMI of ≥30 kg/m² was associated with an increased multivariable-adjusted OR of 1.37 (1.09–1.72). Information on measured BMI indices was available in this study, but migraine was not defined according to IHS criteria and combined with severe headaches (8).

Only few studies have specifically evaluated the relationship between migraine and weight gain. Recently, Vo et al. evaluated the association between BMI, weight gain and migraine among 3,733 participants of the Omega Study who were interviewed during early pregnancy. BMI was estimated using pregravid weight. A pregravid BMI ≥30 kg/m² was associated with a multivariable-adjusted OR of 1.28 (1.12, 1.96) for adult migraine. Women with pediatric migraine had an OR of 1.67 (1.13–2.47) for adult weight gain of ≥10 kg in this study. In our study, migraine diagnosis was associated with a slightly increased mean weight change, but we could not observe an association between migraine and obesity. The study population and design of the previous mentioned study differ from our study. The Omega study participants were younger and of reproductive age compared to our study population (9).

Age, gender, and postmenopausal status are important factors that may contribute to inconsistent results across studies. In a cross-sectional study of 21,783 participants of the National Health and Nutrition Examination Survey 1999–2004, Peterlin et al. reported an association between severe headache or migraine and total body obesity for those aged ≥55, but not >55 years (11). In an elderly Brazilian population, Bensenor et al. evaluated the association between cardiovascular risk factors and migraine and mean BMI values did not differ according to migraine status (32). The lack of association between migraine and incident obesity we have observed in our population could be due to the fact that participants in our study were 45 years and older at study entry and a high percentage of them was already postmenopausal. However, prospective data in younger populations evaluating the association between migraine and incident obesity are lacking.

Several studies evaluated the association between BMI and migraine attack frequency (13, 15, 16, 20). Two cross-sectional studies suggested a J-shaped association between BMI and migraine frequency (16, 20). A BMI of ≥35 kg/m² was associated with the highest effect estimates for a daily migraine frequency in a previous study using WHS data (OR 3.11, 95% CI: 1.12–8.67) and very frequent headache in the American Migraine Prevalence and Prevention Study (OR: 1.74, 95% CI: 1.41–1.93) (16, 20). In contrast, a cross-sectional study from Sweden found no association between BMI and migraine frequency (15). But these findings do not easily compare with our WHS data since women started with a BMI <25 kg/m² and we evaluated whether women with a high attack frequency are at increased risk for becoming overweight and/or obese. Our data suggest that among the lean, a high migraine attack frequency is associated with a decreased risk for becoming obese.

Our study has several strengths. We followed a large number of women with long-term follow-up of 12.9 years. In addition, migraine cases were defined according to diagnostic criteria of the IHS and we were able to distinguish migraine subtypes. In addition, comprehensive information on potential confounders was available for our analyses. Furthermore, we were able to evaluate the association between migraine and incident overweight and obesity in a population free of prevalent cardiovascular disease, cancer and other chronic conditions at baseline which may be associated with weight change. The following limitations should also be considered when interpreting our results. First, information on migraine was self-reported and misclassification is possible. However, we have shown excellent agreement between self-reported migraine and the 2004 diagnostic criteria in a previously published study of the WHS (29). Second, we cannot rule out misclassification of BMI due to the self reported height and weight information. However, our cohort consists of health professionals known to accurately report health information (33). Specifically, self-reported and measured weight information was highly correlated in ($r=0.97$) in a comparable cohort of female health professionals (34). Third, no information on migraine specific treatment known to be associated with weight gain or weight loss, such as topiramate and calcium-channel blockers, was available. However, since both drugs are used for preventive treatment of migraine, the effect of these drugs would probably not have a large impact on our results. Finally, our study population consists of female health professionals aged 45 years and older at study entry which may limit the generalizability of our results to other populations.

In conclusion, in this large, prospective study, we did not observe a meaningful association between migraine and becoming overweight or obese, nor did migraineurs have a relevant weight gain.

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Table 1

Baseline characteristics according to migraine status (n=19,162)

	No migraine history	Any migraine history	p-value
	n=15,679	n=3,483	
Demographic information			
Mean age, years (SD)	54.7 (7.2)	53.6 (6.5)	<0.01
Race, %			
White	14,903 (95.7)	3,288 (95.3)	0.26
Life style factors			
Mean baseline BMI, kg/m ² (SD)	22.4 (1.6)	22.5 (1.6)	<0.01
Alcohol consumption, %			<0.01
Rarely/never	5,910 (37.7)	1,413 (40.6)	
1–3 drinks/month	1,965 (12.5)	532 (15.3)	
1–6 drinks/week	5,658 (36.1)	1,151 (33.1)	
1 drink/day	2,141 (13.7)	387 (11.1)	
Smoking Status, %			0.06
Never	7,862 (50.2)	1,823 (52.4)	
Past	5,612 (35.8)	1,195 (34.4)	
Current	2,195 (14.0)	461 (13.3)	
Exercise, %			<0.01
Rarely/never	5,126 (32.7)	1,144 (32.9)	
<1/week	2,871 (18.3)	729 (20.9)	
1–3 times/week	5,476 (34.9)	1,157 (33.2)	
4 times/week	2,200 (14.0)	451 (12.7)	
Total calorie intake (kcal/day)			0.04
<1600	7,054 (46.3)	1,516 (45.0)	
1600–<2400	6,684 (43.8)	1,471 (43.7)	
2400	1,504 (9.9)	380 (11.3)	
Other covariates, %			
Postmenopausal status at baseline			<0.01
Premenopausal	4,564 (29.2)	1,002 (28.8)	
Postmenopausal	8,541 (54.6)	1,763 (50.7)	
Biological uncertain	1,947 (12.4)	578 (16.6)	
Unclear/subject unsure	604 (3.9)	135 (3.9)	
Postmenopausal hormone use. %			<0.01
Never	7,332 (46.8)	1,462 (42.1)	
Past	1,396 (8.9)	328 (9.4)	
Current	6,925 (44.2)	1,683 (48.5)	
History of hypertension	2,477 (15.8)	594 (17.1)	0.07
History of cholesterol ≥240mg/dl	3,849 (24.6)	949 (27.3)	<0.01

	No migraine history	Any migraine history	p-value
	n=15,679	n=3,483	
History of depression	1,310 (8.7)	474 (14.2)	<0.01

Percentages may not add up to 100% because of rounding or missing values

Table 2

Age- and multivariable-adjusted* HRs (95% CI) for becoming overweight according to migraine status (n=19,162)

	Total n	Incident overweight (BMI ≥ 25 kg/m ²)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)
			HR (95% CI)	HR (95% CI)
Any migraine	3,483	1,617	1.18 (1.12, 1.25)	1.11 (1.05, 1.17)
No migraine	15,679	6,299	1.00	1.00
Migraine subtypes				
Migraine with aura	974	459	1.18 (1.07, 1.30)	1.10 (1.00, 1.21)
Migraine without aura	1,464	686	1.18 (1.09, 1.28)	1.13 (1.05, 1.23)
Prior migraine	1,045	472	1.18 (1.08, 1.30)	1.07 (0.98, 1.18)
No migraine	15,679	6,299	1.00	1.00

* Multivariable models were adjusted for age, race, randomized treatment assignments, baseline BMI, total calorie intake, alcohol consumption, exercise, smoking status, postmenopausal hormone use, postmenopausal status, history of cholesterol >240 mg/dl, history of hypertension, history of depression.

Table 3

Age- and multivariable-adjusted* HRs (95% CI) for becoming obese according to migraine status (n=19,162)

	Total n	Incident obesity (BMI ≥ 30)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)
			HR (95% CI)	HR (95% CI)
Any migraine	3,483	155	1.16 (0.97, 1.39)	1.00 (0.83, 1.19)
No migraine	15,679	575	1.00	1.00
Migraine subtypes				
Migraine with aura	974	46	1.20 (0.89, 1.62)	1.02 (0.76, 1.38)
Migraine without aura	1,464	75	1.29 (1.01, 1.64)	1.11 (0.87, 1.41)
Prior migraine	1,045	34	0.92 (0.65, 1.31)	0.79 (0.56, 1.12)
No migraine	15,679	575	1.00	1.00

* Multivariable models were adjusted for age, race, randomized treatment assignments, baseline BMI, total calorie intake, alcohol consumption, exercise, smoking status, postmenopausal hormone use, postmenopausal status, history of cholesterol ≥ 240 mg/dl, history of hypertension, history of depression.

Table 4

Age- and multivariable-adjusted* mean weight change (kg) according to migraine status (N=19,162)

Follow-up duration	No migraine (n=15,679)	Any migraine (n=3,483)	p-value
2 yrs (n=18,942)	n=15,504	n=3,438	
Age-adjusted	1.34	1.44	0.15
Multivariable-adjusted	1.70	1.72	0.74
3 yrs (n=18,045)	n=14,755	n=3,290	
Age-adjusted	1.76	1.95	0.01
Multivariable-adjusted	1.99	2.09	0.23
5 yrs (n=18,012)	n=14,753	n=3,259	
Age-adjusted	2.44	2.80	<0.01
Multivariable-adjusted	3.13	3.35	0.01
6 yrs (n=17,724)	n=14,521	n=3,203	
Age-adjusted	2.73	3.12	<0.01
Multivariable-adjusted	3.19	3.43	0.01
9 yrs (n=15,297)	n=12,526	n=2,771	
Age-adjusted	3.16	3.56	<0.01
Multivariable-adjusted	4.13	4.34	0.06
11 yrs (n=16,274)	n=13,319	n=2,955	
Age-adjusted	3.17	3.62	<0.01
Multivariable-adjusted	4.05	4.30	0.04
12 yrs (n=15,945)	n=13,031	n=2,914	
Age-adjusted	3.24	3.75	<0.01
Multivariable-adjusted	4.04	4.36	0.01
13 yrs (n=15,590)	n=12,737	n=2,853	
Age-adjusted	3.26	3.74	<0.01
Multivariable-adjusted	4.36	4.65	0.02

* Multivariable models were adjusted for age, race, randomized treatment assignments, baseline BMI, total calorie intake, alcohol consumption, exercise, smoking status, postmenopausal hormone use, postmenopausal status, history of cholesterol >240 mg/dl, history of hypertension, history of depression

Table 5

Age- and multivariable-adjusted HRs (95% CI) for becoming overweight or obese according to migraine frequency (N=2,407)

Migraine frequency	Total n	Incident overweight (BMI 25)	Age-adjusted	Multivariable- adjusted
Daily + weekly	131	60	0.95 (0.73, 1.23)	0.97 (0.75, 1.27)
Monthly	496	224	0.93 (0.80, 1.08)	1.00 (0.86, 1.17)
Every other month	249	127	1.10 (0.91, 1.33)	1.34 (1.11, 1.63)
<6 times/year	1,531	720	1.00	1.00
Migraine frequency	Total n	Incident obesity (BMI 30)	Age-adjusted	Multivariable- adjusted
Daily + weekly	131	5	0.80 (0.32, 1.98)	0.61 (0.24, 1.53)
Monthly	496	23	0.90 (0.57, 1.44)	0.95 (0.59, 1.53)
Every other month	249	15	1.19 (0.68, 2.07)	1.31 (0.74, 2.31)
<6 times/year	1,531	75	1.00	1.00

Multivariable models were adjusted for age, race, randomized treatment assignments, baseline BMI, total calorie intake, alcohol consumption, exercise, smoking status, postmenopausal hormone use, postmenopausal status, history of cholesterol >240 mg/dl, history of hypertension, history of depression.