CLINICAL RESEARCH STUDY

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Prospective Cohort Study of Caffeinated Beverage Intake as a Potential Trigger of Headaches among Migraineurs

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ABSTRACT

PURPOSE: We aimed to evaluate the role of caffeinated beverage intake as a potential trigger of migraine headaches on that day or on the following day.

METHODS: In this prospective cohort study, 101 adults with episodic migraine completed electronic diaries every morning and evening. Ninety-eight participants completed at least 6 weeks of diaries in March 2016-October 2017. Every day, participants reported caffeinated beverage intake, other lifestyle factors, and the timing and characteristics of each migraine headache. We compared a participant's incidence of migraines on days with caffeinated beverage intake to the incidence of migraines among the same individual on days with no intake, accounting for day of week. We used conditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals.

RESULTS: Among 98 participants (86 women, 12 men) with mean age 35.1 years, 83% white, and 10% Hispanic or Latino, the average age when headaches started was 16.3 years. In total, the participants reported 825 migraines during 4467 days of observation. There was a statistically significant nonlinear association between the number of caffeinated beverages and the odds of migraine headache occurrence on that day (*P*-quadratic trend = .024), though estimates for each level of intake were not statistically significant. The associations varied according to habitual intake and oral contraceptive use.

CONCLUSIONS: There was a nonlinear association between caffeinated beverage intake and the odds of migraine headache occurrence on that day. This suggests that high levels of caffeinated beverage intake may be a trigger of migraine headaches on that day.

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KEYWORDS: Caffeine; Case-crossover; Cohort studies; Headache; Migraine

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BACKGROUND

Migraine is a disabling primary headache disorder,[1] affecting approximately 1.04 billion adults worldwide. Migraine is the third most prevalent illness and sixth leading cause of years lived with disability.[2] In the United States, 14% of adults reported experiencing migraine or severe headache in the previous 3 months,[3] and headache is the most common pain condition causing lost productive time[4] and significant direct and indirect costs.[5,6] Widespread anecdotal evidence suggests that migraines can be immediately triggered by weather or lifestyle factors,[7,8] such as sleep disturbances and skipping meals, with 95% of migraineurs endorsing at least one trigger.[9] However, there has been limited research to prospectively evaluate the immediate effects of potential triggers. Based on our a priori hypothesis about the biological effects of caffeine, we aimed to evaluate the role of caffeinated beverages as a potential trigger of migraine headaches.

CLINICAL SIGNIFICANCE

- Widespread anecdotal evidence suggests that caffeinated beverages immediately trigger migraine headaches, but few studies prospectively examined this association.
- 1-2 servings of caffeinated beverages were not associated with headaches on that day, but = 3 servings may be associated with higher odds of headaches, even after accounting for daily alcohol intake, stress, sleep, activity, and menstrual bleeding.
- Associations between caffeinated beverages and headaches on the following day followed a similar pattern.

Approximately 87% of Americans consume caffeine daily, with an average intake of 193 mg per day.[10] Whereas some behavioral and environmental factors may only have potential harmful effects on migraine risk, the role of caffeine is particularly complex, because the impact depends on dose and frequency. It may trigger an attack but it is also an analgesic adjuvant.[11] Because there have been few prospective studies on the immediate risk of migraine headaches following caffeinated beverage intake, there is limited evidence to formulate dietary recommendations for people with migraines.

Most of the prior studies on caffeine and the risk of migraine headaches in the subsequent hours or days are based on animal models[12] or analyses on caffeine intake reported after migraine occurrence.[13] A few prospectively collected information on caffeine intake to examine the proportion of headaches with the presence of potential triggers,[14] and they did not account for potential confounding by factors associated with the timing of caffeine intake and the occurrence of migraine headaches, such as physical activity or hormonal changes.[15] Therefore, we conducted a prospective cohort study of patients with migraine who provided detailed information on daily caffeinated beverage intake, headaches, and other behavioral and psychological characteristics every morning and evening for 6 weeks. We conducted a within-person analysis to test the hypothesis that among people with episodic migraines, caffeinated beverage intake is associated with transiently higher odds of migraine headaches on that day or on the following day.

METHODS

Study Population

In 3 academic medical centers, we enrolled individuals who experience migraine headaches on 2-15 days per month for at least 3 months, with or without aura,[16] ≥ 18 years of age who were able to communicate in English. Exclusion criteria were: self-reported chronic pain, chronic opioid use, high risk for obstructive sleep apnea assessed via Berlin questionnaire or known untreated moderate or severe sleep apnea, pregnancy, and failure to complete 4/7 days of a run-in phase diary. Between March 2016 and October 2017, 131 individuals completed the screening visit, 101 met inclusion criteria and agreed to participate, and 3 withdrew with <21 days of diary data, resulting in a sample of 98 migraineurs who completed the study.

After a run-in phase to ensure compliance with completing daily diaries, participants wore Actiwatch-Spectrum actigraphs (Philips Respironics, Inc., Monroeville, Pa) on their nondominant wrist, and they completed secure Internet-based daily diaries every morning and evening to provide information about health behaviors and migraine headaches. Study data were collected using REDCap electronic data tools hosted at Beth Israel Deaconess Medical Center.[17] The study was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations. All participants provided written consent.

Caffeine and Covariates

At baseline, we collected information on demographics, medical history, medication use, typical servings of caffeinated beverages per day, typical servings of alcohol per week, and measures of depressive symptoms and psychological stress. Participants were presented with a list of commonly reported triggers of migraine headache, such as caffeine, irregular sleep, and weather changes, and they were asked to report which ones they believed had triggered their migraines in the past. Because most people consume caffeinated beverages during daytime hours, daily questions about intake were included in the evening questionnaire. In the hour prior to getting into bed every evening, participants were asked, "How many servings of caffeine (coffee, tea, soda, energy drinks) did you have today? For coffee and tea, one drink = 6-8 oz; soda with caffeine, one drink = 12 oz. Do not include decaffeinated or caffeine-free coffee/drinks."

The evening diary included questions about time spent that day engaged in moderate (eg, fast walking, average bicycling)

or vigorous (eg, running/jogging, fast bicycling) activities. Total daily activity time was objectively recorded with wrist actigraphy. With data from daily diaries and actigraphs, a trained technician blinded to headache records used a standardized protocol[18] to identify daily sleep/wake times. The evening diary included 2 scales of psychological stress. Participants responded to 7 items from the Positive and Negative Affect Schedule.[19] Using a Likert scale (very slightly or not at all, a little, moderately, quite a bit, extremely), they rated their current intensity of feeling upset, nervous, afraid, distressed, scared, enthusiastic, and alert. They also completed 7 questions from the Daytime Insomnia Symptom Scale.[20] Using a visual analog scale ranging from 0 (not at all) to 100 (as much as possible), they rated the intensity of their current feelings of anxiety, tension, sadness, relaxation, energy, and calmness. Premenopausal females reported whether they experienced menstrual bleeding that day. Because most people consume alcoholic beverages in the evening, the morning questionnaire asked about the number of servings of alcohol consumed on the prior day.

Migraine Headaches

At baseline, participants completed the Headache Impact Test-6[21] and reported whether they "know (or feel) that a migraine headache is coming before the head pain starts." Every morning and evening, they reported the onset, duration, pain intensity, and medications used for migraine headaches since previous diary completion. They reported the presence of any visual aura and accompanying symptoms (eg, throbbing or pounding head pain, nausea, vomiting, and sensitivity to light and sounds). Headaches reported as starting before the end of a prior headache were reclassified as extensions of earlier headaches. A study physician (SMB) reviewed the symptoms of each headache. If a participant reported a headache duration <4 hours, intensity $<40/100$, <1 migrainous feature (eg, photophobia), and no abortive medications, the headache was classified as unlikely to be a migraine.

Statistical Analysis

We conducted a self-matched analysis to examine whether caffeinated beverage intake is associated with the odds of migraine headaches on that day. We compared a participant's incidence of migraines on days with caffeinated beverage intake to the incidence of migraines among the same individual on days with no intake, further matching on day of week. This eliminates confounding by risk factors that are constant within individuals over the observation period but may differ among participants, such as sex and other long-term risk factors for migraine. In a self-matched analysis, only individuals with at least some variation in exposure contribute information to the estimate of the exposure effect.

We constructed conditional logistic regression models stratifying by participant and day of week to estimate odds ratios and 95% confidence intervals for the association between the number of servings of caffeinated beverages and occurrence of headaches. Self-matching eliminates confounding by fixed (eg, sex, genotype) or slowly varying (eg, age, hypertension) characteristics, and stratification by day of week eliminates confounding by weekend vs weekday habits that may impact intake and migraine occurrence, but there can be confounding by time-varying characteristics (eg, menstrual bleeding) related to the timing of caffeinated beverage intake and migraines.[22,23] Therefore, in secondary analyses, we adjusted for alcohol intake (continuous), psychological stress (continuous), self-reported and actigraphy-based measures of physical activity (continuous), day with menstrual bleeding (yes/no), and departures from each individual's usual wake time (continuous). We conducted a test for quadratic component of trend by determining the statistical significance of a term for the squared value of caffeinated beverage intake included in a model with a term for intake as a linear continuous variable.

In our primary analysis, we assessed caffeinated beverage intake and migraine headaches on that day, and in secondary analyses, we evaluated the association between intake and headaches on the following day. We evaluated whether the association varied by self-reported typical frequency of caffeinated beverage intake (<1 vs ≥ 1 servings per day), whether the participant typically knows or feels that a migraine headache is coming before head pain starts, and whether the participant believes that caffeine triggers the onset of migraines. Because oral contraceptives extend caffeine's half-life of elimination,[24,25] we examined whether, among premenopausal women, the association varied by oral contraceptive use. We calculated the product of indicator variables for caffeinated beverage intake and the potential modifier, and we conducted likelihood ratio tests of nested models with and without interaction terms.

In secondary analyses to examine the robustness of our findings: 1) we reclassified migraine headaches starting on consecutive days as a single event; 2) we excluded participants that typically used migraine prophylaxis medications; 3) headaches classified as unlikely to be migraines; or 4) headaches that began while participants were asleep.

Two-sided P values of $<.05$ were considered statistically significant. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics of the 98 participants (86 women, 12 men) are presented in Table 1. A majority of the sample was white (82.7%), not Hispanic or Latino (89.8%), and never smokers (82.7%). Participants reported that their headaches began at an average age of 16 years, experiencing 5 headaches per month, and 26.5% reported that they use migraine prophylaxis medications. At baseline, 20% of the participants reported that they typically do not consume caffeinated beverages, 66% reported consuming 1-2 servings per day, and 12% reported intake of 3-4 servings per day. During the study, participants reported consuming an average of 7.9 (standard deviation [SD] 5.6) servings per week on an average of 4.5 (SD 2.1) days per week. All participants had caffeinated beverages on at least one day during the study,

Table 1 Baseline Characteristics, Mean ± Standard Deviation or Frequency (%) Among 98 Participants with Episodic Migraines Followed for 6 Weeks*

	Female	Male	Total
	n = 86	n = 12	n = 98
Age, years	35.0 ± 11.6	35.8 ± 15.6	35.1 ± 12.1
Race			
White	70 (81.4%)	11 (91.7%)	81 (82.7%)
Ethnicity			
Hispanic or Latino	10 (11.6%)	0 (0.0%)	10 (10.2%)
Smoking status			
Never	72 (83.7%)	9 (75.0%)	81 (82.7%)
Past	10 (11.6%)	3 (25.0%)	13 (13.3%)
Current	2 (2.3%)	0 (0.0%)	2 (2.0%)
Menopausal status	11 (12.8%)		11 (11.2%)
Age when headaches started	16.0 ± 7.7	18.4 ± 11.9	16.3 ± 8.3
Self-reported migraines per month	5.4 ± 3.6	2.0 ± 0.6	5.0 ± 3.6
Headache Impact Test (range: 36-78)	61.4 ± 6.0	57.9 ± 7.5	61.0 ± 6.2
Know or feel that a migraine headache is coming before the head pain starts	62 (72.1%)	10 (83.3%)	72 (73.5%)
Visual aura	25 (29.1%)	7 (58.3%)	32 (32.7%)
Self-reported belief that caffeine is a migraine trigger	14 (16.3%)	0 (0.0%)	14 (14.3%)
Medications			
Migraine prophylaxis	25 (29.1%)	1 (8.3%)	26 (26.5%)
Stimulants	8 (9.3%)	2 (16.7%)	10 (10.2%)
Estrogen-contraception/hormone replacement	27 (31.4%)		27 (27.6%)
Cups of caffeine beverages per day			
0	17 (19.8%)	3 (25.0%)	20 (20.4%)
1-2	59 (68.6%)	6 (50.0%)	65 (66.3%)
3-4	9 (10.5%)	3 (25.0%)	12 (12.2%)
Servings of alcohol per week			
0	27 (31.4%)	4 (33.3%)	31 (31.6%)
1-3	41 (47.7%)	5 (41.7%)	46 (46.9%)
4-7	15 (17.4%)	1 (8.3%)	16 (16.3%)
8-14	2 (2.3%)	1 (8.3%)	3 (3.1%)
15 or more	0 (0.0%)	1 (8.3%)	1 (1.0%)
Frequency of moderate or vigorous exercise per week			
0	2 (2.3%)	1 (8.3%)	3 (3.1%)
1-2	24 (27.9%)	2 (16.7%)	26 (26.5%)
3-4	34 (39.5%)	7 (58.3%)	41 (41.8%)
5+	23 (26.7%)	2 (16.7%)	25 (25.5%)
Perceived Stress Scale (PSS) (range 0-40)	14.8 ± 6.5	14.4 ± 6.2	14.7 ± 6.4
CESD-20 Depressive Symptoms (range 0-60)	9.9 ± 7.8	9.6 ± 8.3	9.9 ± 7.8

CESD = Center for Epidemiological Studies Depression.

*Some participants had no data smoking status (n=2), headache impact test score (n=1), know or feel that a migraine headache is coming before the head pain starts (n=2), caffeinated beverages per day (n=1), alcohol per week (n=1), or exercise per week (n=3).

†Migraine prophylaxis medications include topiramate, metoprolol, propranolol, amitriptyline, and venlaxfaxine.[1]

‡Stimulants include amphetamines, methylphenidate, atomoxetine.

resulting in some within-person variation in exposure. Participants reported 825 headaches during 4467 days of observation, with an average of 8.4 (SD 4.6) headaches per participant.

There was a statistically significant nonlinear association between caffeinated beverage intake and the odds of migraine headaches on that day (P-quadratic trend = 0.024; Figure), though point estimates for each category of intake were not statistically significant. There was no association between 1-2 servings of caffeinated beverage intake and odds of headaches on that day, but estimated higher odds on days with ≥ 3 servings. Results were similar in secondary analyses further accounting for daily changes in alcohol intake, stress, sleep, physical activity, and menstrual bleeding.

Participants may have consumed more caffeinated beverages following the onset of a headache to treat pain, raising concerns of reverse causation. Therefore, we examined the association between caffeinated beverage intake and the occurrence of headaches on the following day, ensuring correct temporality. Although the estimated associations had wide

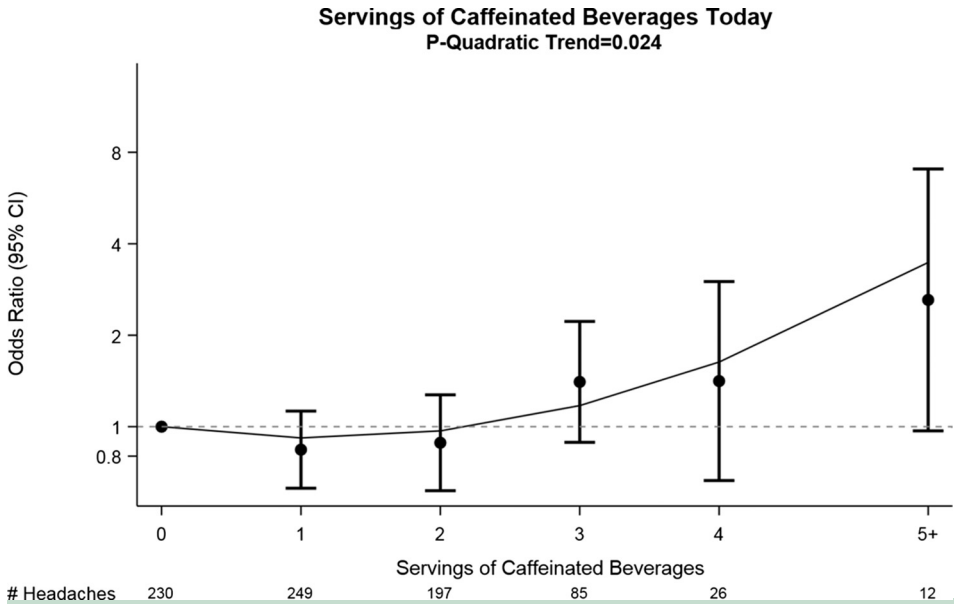

Figure Association between servings of caffeinated beverages compared with none and occurrence of migraine on the same day among 98 participants with episodic migraines followed for 6 weeks. The observed estimates of the association for each number of servings of caffeine are shown with the circles (odds ratios) and vertical lines (95% confidence intervals [CI]), and the quadratic association is shown with the solid line. The dashed line reflects the null value of no association between caffeinated beverages and occurrence of migraine headaches. There was no information on caffeinated beverage intake for 26 of the 825 migraines.

confidence intervals and *P*-quadratic trend = 0.30, point estimates above one indicating a potential higher odds of migraine headaches were evident only on days following ≥3 servings of caffeinated beverages (Table 2).

Table 3 presents results stratified by potential modifiers of the association between caffeinated beverage intake and headaches on that day. Among participants who reported that they typically consumed ≥1 servings per day, the association was apparent only on days with ≥3 servings of caffeinated beverages. However, among participants who reported that they typically consumed <1 serving per day, even 1-2 servings were associated with headaches on that day. Among premenopausal women, the association varied by oral contraceptive use. The associations varied according to whether or not participants believed that they typically know or feel that a headache is coming before the head pain starts. Results were similar regardless of whether or not participants reported at baseline that caffeine triggers their headaches. Results were not meaningfully altered in any of the sensitivity analyses.

Table 2 Association Between Servings of Caffeinated Beverages and the Odds of Migraine Headaches on the Current Day and on the Following Day in a Self-Matched Analysis of 825 Headaches Among 98 Participants Followed for at Least 6 Weeks

Servings of Caffeinated Beverages	Current Day	Following Day
0	1.00 (Reference)	1.00 (Reference)
1	0.84 (0.63-1.13)	0.91 (0.70-1.20)
2	0.89 (0.62-1.27)	0.95 (0.69-1.32)
3	1.40 (0.89-2.22)	1.03 (0.65-1.63)
4	1.41 (0.66-3.00)	1.11 (0.54-2.28)
5	2.61 (0.97-7.05)	1.89 (0.67-5.30)
	P-quadratic trend = .024	*P*-quadratic trend = .30

DISCUSSION

In this self-matched analysis of a prospective cohort study, there was no association between 1-2 servings of caffeinated beverage intake and the odds of headaches on that day, but higher odds were estimated on days with ≥3 servings, even after accounting for potential confounding by other triggers. Participants may consume caffeine for therapeutic purposes after migraines. If that had led to reverse causation, we would have expected to observe a higher risk on days with even 1-2 servings of caffeinated beverages. However, there was no higher risk on days with 1-2 servings. Furthermore, results were similar for intake and headaches on the following day, suggesting that reverse causation is unlikely to account for our findings.

Despite the high prevalence of migraines and their debilitating symptoms, effective prevention remains elusive for many patients. Migraines are often attributed to triggers including hormonal changes, acute psychological stress, sleep disturbances, skipping meals, humidity, caffeine, and medications,[26,27] and there is interindividual variation in which factors trigger migraines.[15,28] However, rather than prospectively reporting behaviors and subsequent migraine

Table 3 Association Between Servings of Caffeinated Beverages and the Odds of Migraine Headaches on the Current Day Stratified by Potential Modifiers in a Self-Matched Analysis of 825 Headaches Among 98 Participants Followed for at Least 6 Weeks

	Servings of Caffeinated Beverages						*P* Value*
	0	1	2	3	4	5	
# Headaches	230	249	197	85	26	12	
Baseline caffeine							.12
<1/day	1.00 (Ref)	1.39 (0.79-2.43)	1.97 (0.48-8.05)	11.65 (0.86-158.0)	9.78 (0.30-321.2)		
1+/day	1.00 (Ref)	0.69 (0.50-0.97)	0.74 (0.50-1.10)	1.14 (0.71-1.84)	1.15 (0.53-2.50)	2.16 (0.79-5.87)	
Typically know or feel a migraine headache is coming before pain starts							.64
Yes	1.00 (Ref)	0.98 (0.68-1.41)	1.09 (0.70-1.68)	1.62 (0.95-2.75)	1.75 (0.76-4.04)	3.78 (1.13-12.62)	
No	1.00 (Ref)	0.65 (0.39-1.10)	0.57 (0.28-1.17)	1.25 (0.46-3.45)	0.72 (0.11-4.61)	1.10 (0.16-7.73)	
Believe caffeine is a trigger							.98
Yes	1.00 (Ref)	0.86 (0.40-1.87)	0.97 (0.38-2.52)	1.47 (0.43-5.00)	2.15 (0.43-10.63)		
No	1.00 (Ref)	0.84 (0.61-1.15)	0.87 (0.59-1.30)	1.40 (0.85-2.29)	1.23 (0.51-2.96)	2.40 (0.85-6.73)	
Oral contraceptive use among premenopausal women							.77
Yes	1.00 (Ref)	0.58 (0.35-0.96)	0.45 (0.23-0.91)	0.77 (0.30-2.01)	0.65 (0.14-3.14)	1.45 (0.06-33.51)	
No	1.00 (Ref)	0.83 (0.53-1.29)	0.87 (0.51-1.48)	1.59 (0.81-3.13)	1.57 (0.50-4.90)	3.71 (0.48-28.75)	

* *P* value for interaction from likelihood ratio test of nested models with and without interaction.

headaches, most prior studies asked participants about potential triggers *after* their migraines occurred, raising concerns of recall bias. In attempting to find causes for their migraines,[13,29] participants may over-report lifestyle factors immediately preceding migraines even though these factors often occur in daily life with no ensuing migraine.[30,31]

In one study,[14] participants recorded headaches and suspected triggers for 3 months. The investigators compared the proportion of migraine vs nonmigraine headaches that participants attributed to suspected triggers. Travel, hormonal changes, noise, alcohol, overeating, and stress were reported more frequently for migraines than for nonmigraine headaches. Headaches attributed to triggers were associated with greater pain intensity than other headaches. In our study, we examined whether the amount of daily caffeinated beverage intake is associated with higher odds of migraine headaches on that day even after accounting for transient changes in alcohol, stress, sleep, activity, and menstrual bleeding.

The primary mechanism proposed for linking caffeine and migraine is caffeine's antagonism of adenosine receptors. As a pain regulator, adenosine inhibits or promotes pain, depending on the location (central or peripheral), type of pain (acute or chronic), and receptor subtype activated.[12] Chronic adenosine receptor antagonism from habitual intake of approximately 2 or more cups of coffee for >5 days causes upregulation of adenosine receptors and increasing extracellular adenosine content.[32] Due to the rapid development of caffeine tolerance, any interruption in regular consumption may lead to a caffeine withdrawal headache.[33]

We found that the transient impact of caffeinated beverages on daily headache risk was apparent only on days with ≥3 servings. This is concordant with prior evidence that caffeine dose impacts its pharmacodynamics. Whereas low doses (5 mg/kg) interact with central cholinergic pathways, medium to high intake (10-35 mg/kg) involves central amine systems, and high intake (75-100 mg/kg) central noradrenergic pathways.[34] Consistent with our findings that the heightened odds of migraines were stronger among people reporting lower typical levels of habitual caffeine consumption, chronic caffeine consumption results in a higher number of adenosine A_1 receptors.[35] Other mechanisms may also play a role in a tolerance to caffeine's effect on migraine occurrence.[34]

Comparing each individual's intake on different days eliminates confounding by fixed or slowly varying characteristics such as chronic risk factors for migraine, whether known or unknown. To minimize time-varying confounding by triggers temporally related to caffeine intake, we matched on day of week and adjusted for daily alcohol intake, physical activity, sleep changes, and menstrual bleeding. Although environmental factors may induce migraines, they are unlikely to affect caffeinated beverage intake. Caffeine may induce symptoms of anxiety[36] that would mediate rather than confound the association of interest.

Every day, participants reported the total servings of caffeinated beverages they had consumed, including coffee, tea, soda, and energy drinks. We cannot assess whether the association varies by beverage type. Additionally, one serving of caffeine is typically defined as 8 ounces or 1 cup of caffeinated coffee (~135-150 mg), 6 ounces of tea (~25-110 mg), or a 12-ounce can of soda (~46 mg),[37,38] and a 2-ounce can of an energy drink (~35 mg).[38] Because caffeine dose per serving varies by drink type and preparation method,[37,39] we cannot quantify the amount associated with heightened risk. However, in this self-matched analysis over only 6 weeks, each participant's types of caffeinated beverages should be fairly consistent. We did not collect information on chocolate intake and other foods containing caffeine, but these sources contribute relatively low amounts of caffeine. We did not collect information on skipping meals or screen time, which may be correlated with intake and the timing of migraine headaches. We did not have information on the timing of caffeinated beverage intake each day, so we could not explore potential immediate effects of intake on migraine risk in the subsequent hours. This may raise concerns of reverse causation from participants drinking caffeinated beverages to treat migraines. However, there were no higher odds of headache on days with 1-2 servings, and results were similar in analyses of intake and migraine headaches on the subsequent day.

Caffeine is widely consumed and may play a role in the prevention, occurrence, and treatment of migraine headaches. In this study, there was a nonlinear association between caffeinated beverage intake and the odds of migraine headache on that day. This suggests that high levels of caffeinated beverage intake may be a trigger of migraine headaches on that day. Additional research is needed to examine the potential effect of caffeine on symptom onset in the subsequent hours and the interplay of sleep, caffeine, anxiety, environmental factors, and migraine.

References

1. The International Classification of Headache Disorders. 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808.
2. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2018;17(11):954-76.
3. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. *Headache*. 2015;55(1):21-34.
4. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA*. 2003;290(18):2443-54.
5. Bonafede M, Sapra S, Shah N, Tepper S, Cappell K, Desai P. Direct and indirect healthcare resource utilization and costs among migraine patients in the United States. *Headache*. 2018;58(5):700-14.
6. Messali A, Sanderson JC, Blumenfeld AM, et al. Direct and indirect costs of chronic and episodic migraine in the United States: a web-based survey. *Headache*. 2016;56(2):306-22.
7. Peatfield RC. Relationships between food, wine, and beer-precipitated migrainous headaches. *Headache*. 1995;35(6):355-7.
8. Van den Bergh V, Amery WK, Waelkens J. Trigger factors in migraine: a study conducted by the Belgian Migraine Society. *Headache*. 1987;27(4):191-6.
9. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia*. 2007;27(5):394-402.
10. Frary CD, Johnson RK, Wang MQ. Food sources and intakes of caffeine in the diets of persons in the United States. *J Am Diet Assoc*. 2005;105(1):110-3.
11. Lipton RB, Diener HC, Robbins MS, Garas SY, Patel K. Caffeine in the management of patients with headache. *J Headache Pain*. 2017;18(1):107.
12. Fried NT, Elliott MB, Oshinsky ML. The role of adenosine signaling in headache: a review. *Brain Sci* 2017;7(3) https://doi.org/10.3390/brainsci7030030.
13. Lipton RB, Pavlovic JM, Haut SR, Grosberg BM, Buse DC. Methodological issues in studying trigger factors and premonitory features of migraine. *Headache*. 2014;54(10):1661-9.
14. Park JW, Chu MK, Kim JM, Park SG, Cho SJ. Analysis of trigger factors in episodic migraineurs using a amartphone headache diary applications. *PLoS One*. 2016;11(2), e0149577.
15. Wober C, Brannath W, Schmidt K, et al. Prospective analysis of factors related to migraine attacks: the PAMINA study. *Cephalalgia*. 2007;27(4):304-14.
16. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24(suppl 1):9-160.
17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-81.
18. Patel SR, Weng J, Rueschman M, et al. Reproducibility of a standardized actigraphy scoring algorithm for sleep in a US Hispanic/Latino population. *Sleep*. 2015;38(9):1497-503.
19. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol*. 1988;54(6):1063-70.
20. Buysse DJ, Thompson W, Scott J, et al. Daytime symptoms in primary insomnia: a prospective analysis using ecological momentary assessment. *Sleep Med*. 2007;8(3):198-208.
21. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res*. 2003;12(8):963-74.
22. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health*. 2000;21:193-221.
23. Mostofsky E, Coull BA, Mittleman MA. Analysis of observational self-matched data to examine acute triggers of outcome events with abrupt onset. *Epidemiology*. 2018;29(6):804-16.
24. Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives. *Eur J Clin Pharmacol*. 1985;28(4):425-8.
25. Patwardhan RV, Desmond PV, Johnson RF, Schenker S. Impaired elimination of caffeine by oral contraceptive steroids. *J Lab Clin Med*. 1980;95(4):603-8.
26. Goadsby PJ, Silberstein SD. Migraine triggers: harnessing the messages of clinical practice. *Neurology*. 2013;80(5):424-5.

27. Zaeem Z, Zhou L, Dilli E. Headaches: a review of the role of dietary factors. *Curr Neurol Neurosci Rep*. 2016;16(11):101.
28. Peris F, Donoghue S, Torres F, Mian A, Wober C. Towards improved migraine management: determining potential trigger factors in individual patients. *Cephalalgia*. 2017;37(5):452-63.
29. Baldacci F, Vedovello M, Ulivi M, et al. How aware are migraineurs of their triggers? *Headache*. 2013;53(5):834-7.
30. Hougaard A, Amin FM, Hauge AW, Ashina M, Olesen J. Provocation of migraine with aura using natural trigger factors. *Neurology*. 2013;80(5):428-31.
31. Varkey E, Gruner Svealv B, Edin F, Ravn-Fischer A, Cider A. Provocation of migraine after maximal exercise: a test-retest study. *Eur Neurol*. 2017;78(1-2):22-7.
32. Green A, Stuart CA, Pietrzyk RA, Partin M. Photochemical cross-linking of 125I-hydroxyphenylisopropyl adenosine to the A1 adenosine receptor of rat adipocytes. *FEBS Lett*. 1986;206(1):130-4.
33. Echeverri D, Montes FR, Cabrera M, Galan A, Prieto A. Caffeine's vascular mechanisms of action. *Int J Vasc Med*. 2010;2010, 834060.
34. Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev*. 1999;51(1):83-133.
35. Green RM, Stiles GL. Chronic caffeine ingestion sensitizes the A1 adenosine receptor-adenylate cyclase system in rat cerebral cortex. *J Clin Invest*. 1986;77(1):222-7.
36. Ribeiro JA, Sebastiao AM. Caffeine and adenosine. *J Alzheimers Dis*. 2010;20(suppl 1):S3-S15.
37. Advokat CD, Comaty JE, Julien RM. Caffeine and nicotine. A Primer of Drug Action: a Comprehensive Guide to the Actions, Uses, and Side Effects of Psychoactive Drugs. 13th ed. New York: Worth Publishers; 2014. p. 167-75. (Chapter 6).
38. Attipoe S, Leggit J, Deuster PA. Caffeine content in popular energy drinks and energy shots. *Mil Med*. 2016;181(9):1016-20.
39. Stavric B, Klassen R, Watkinson B, Karpinski K, Stapley R, Fried P. Variability in caffeine consumption from coffee and tea: possible significance for epidemiological studies. *Food Chem Toxicol*. 1988;26(2):111-8.