Review Article

The Role of Diet and Nutrition in Migraine Triggers and Treatment: A Systematic Literature Review

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Background.—Migraine is a disabling primary headache disorder often associated with triggers. Diet-related triggers are a common cause of migraine and certain diets have been reported to decrease the frequency of migraine attacks if dietary triggers or patterns are adjusted.

Objective.—The systematic literature review was conducted to qualitatively summarize evidence from the published literature regarding the role of diet patterns, diet-related triggers, and diet interventions in people with migraine.

Methods.—A literature search was carried out on diet patterns, diet-related triggers, and diet interventions used to treat and/or prevent migraine attacks, using an a priori protocol. MEDLINE and EMBASE databases were searched to identify studies assessing the effect of diet, food, and nutrition in people with migraine aged \geq 18 years. Only primary literature sources (randomized controlled trials or observational studies) were included and searches were conducted from January 2000 to March 2019. The NICE checklist was used to assess the quality of the included studies of randomized controlled trials and the Downs and Black checklist was used for the assessment of observational studies.

Results.—A total of 43 studies were included in this review, of which 11 assessed diet patterns, 12 assessed diet interventions, and 20 assessed diet-related triggers. The overall quality of evidence was low, as most of the (68%) studies assessing diet patterns and diet-related triggers were cross-sectional studies or patient surveys. The studies regarding diet interventions assessed a variety of diets, such as ketogenic diet, elimination diets, and low-fat diets. Alcohol and caffeine uses were the most common diet patterns and diet-related triggers associated with increased frequency of migraine attacks. Most of the diet interventions, such as low-fat and elimination diets, were related to a decrease in the frequency of migraine attacks.

Conclusions.—There is limited high-quality randomized controlled trial data on diet patterns or diet-related triggers. A few small randomized controlled trials have assessed diet interventions in preventing migraine attacks without strong results. Although many patients already reported avoiding personal diet-related triggers in their migraine management, high-quality research is needed to confirm the effect of diet in people with migraine.

Key words: migraine, diet, triggers, patterns, intervention

Abbreviations: BMI body mass index, CI confidence interval, DASH dietary approaches to stop hypertension, HR hazard ratio, IgG immunoglobulin G, IRR incident rate ratio, NHANES National Health and Nutrition Examination Survey, NICE National Institutes for Health and Care Excellence, OR odds ratio, PRISMA Preferred Reporting Items for Systematic reviews and Meta-analyses, RCT randomized controlled trial, SD standard deviation, VAS visual analog scale

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INTRODUCTION

Migraine is a disabling primary headache disorder with 2 major subtypes: migraine without aura and migraine with aura.¹ The clinical presentation of a migraine attack varies widely among patients, including the intensity of pain and the pattern of associated symptoms, such as photophobia, phonophobia, osmophobia, nausea, vomiting and movement sensitivity.² Migraine is associated with a number of comorbidities, including psychiatric disorders (eg, depression and anxiety), sleep disorders, fatigue, cardiovascular risk factors (eg, hypertension, diabetes, high cholesterol, and obesity), and cardiovascular and cerebrovascular diseases.³⁻⁵

While the pathophysiology of migraine is not completely understood, evidence suggests that dietary factors may play a role in several possible mechanisms. Diet may have an effect on the modulation of neuropeptides, neuroreceptors and ion channels, sympathetic nervous system and cerebral glucose metabolism, and/ or by causing inflammation, release of nitric oxide, and vasodilation.⁶

Certain foods, such as chocolate, caffeine, milk, cheese and alcoholic beverages, have been identified as common triggers of migraine attacks.⁷⁻⁹ Hoffmann and Recober (2013) stated in their review that foods and drinks are the most commonly reported triggers for migraine and these often include chocolate, cheese, nuts, citrus fruits, processed meats, monosodium glutamate, aspartame, fatty foods, coffee, and alcohol.¹⁰ A systematic review revealed fasting and alcohol as triggers in 44% and 27% of people with migraine, respectively.¹¹ Patients with triggers have been reported to be more prone to have a functional disability compared to those without trigger $(2.41 \pm 0.68 \text{ vs } 2.04 \pm 0.72, \text{ on a})$ 0-4 scale, with a higher score indicating higher impairment, P = .03). The number of triggers also correlates with functional disability in people with migraine, with an increase in the number of triggers leading to higher disability (r = 0.23, P = .002).¹²

Despite not being part of the current diagnostic criteria for headache disorders, triggers form an important component in the characterization of the migraine phenotypes.¹³ There is often difficulty in reliably identifying migraine triggers. Studies have aimed at identifying triggers in people with migraine using natural experimentation, which involves the covariation assessment of presence or absence of triggers with headache attacks, and formal experimentation or diary studies which use advanced statistical modeling techniques.^{14,15} Paper diaries have been included traditionally, and although electronic diaries may reduce recall bias and improve compliance, only a few headache diary studies have used smartphones or handheld devices to evaluate the association between triggers and migraine attacks.¹⁴

Limited evidence suggests that different kinds of diet interventions may offer a promising approach in the management of migraine. Diet interventions, such as high folate diet, low-fat diet, high omega-3, and low omega-6 fatty acid diets, ketogenic diet, Atkins diet, and low sodium diet, have been reported to reduce migraine attacks.^{6,16} Therefore, it is important to increase the awareness of existing evidence to aid the optimal use of dietary interventions in the management of migraine.

The aim of the present systematic literature review was to qualitatively summarize data from randomized controlled trials (RCTs) or observational studies on the role of diet patterns, diet-related triggers, and dietary interventions in adults with migraine. Evidence from published literature on the correlation or association of dietary patterns with migraine, the effect of diet as triggers, and the effect of diet interventions on migraine-related outcomes (frequency, intensity, duration, and pain) were assessed in efforts to aid providers in integrating dietary considerations in the migraine management.

METHODS

Search Strategy.—The systematic review was performed using an a priori protocol. The format of this review was based on the Preferred Reporting Items for

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Conflict of Interest: L. Lombard and P. Banerjee are full-time employees and hold stock or stock options at Eli Lilly and Company. M. Farrar and S. Aurora are former employees of Eli Lilly and Company, Indianapolis. N. A. Hindiyeh serves on the speaker's bureaus for Amgen, Eli Lilly, and Electrocore, and serves on advisory boards for Amgen, Eli Lilly, and Zosano Pharma. N. Zhang does not have any conflicts of interest.

Systematic reviews and Meta-analyses (PRISMA).¹⁷ A literature search was conducted in MEDLINE and EMBASE in the OVID platform to identify studies assessing the effect of diet on migraine. The search strategies combined free-text and controlled vocabulary terms for the disease and outcomes of interest. The search terms are outlined in the Appendix. The literature search was limited to articles in the English language, involving adult human subjects (\geq 18 years old) and published from January 1, 2000 to March 5, 2019. Inclusion and exclusion criteria were determined as depicted in Table 1.

Study Selection.—*Eligibility Criteria*.—RCTs, non-RCTs, prospective or retrospective observational studies, systematic literature reviews and surveys, in which diet, food, and nutrition were assessed as patterns, triggers or an intervention, in people with migraine aged \geq 18 years were included (Table 1).

Study Selection.—The studies were selected based on a 2-level screening process. Level 1 screening entailed a broad screening based on the titles and abstracts of the citations retrieved. The full text of all citations passing level 1 screening was retrieved for full-text article screening in level 2 and screened for final eligibility for the review. One reviewer completed level 1 screening (MF or PB), while a second reviewer conducted a quality check of a random sample of abstracts. Level 1 screening was verified by 2 expert reviewers (NAH and NZ). Level 2 screening was conducted by 2 independent reviewers (MF and PB) and discrepancies were resolved by consensus within the team or by involving a third team member (LL, NAH, or NZ). All screenings were recorded using prior developed eligibility criteria as described above. Bibliographic searches of systematic literature reviews were conducted to identify relevant studies.

Data Extraction.—Data were manually extracted from the reports by 2 researchers (MF and PB) and independent reviewers (LL, NAH, NZ or SA) further verified the extractions. A standardized data extraction form was used to extract the data from each included study and studies were categorized as diet patterns, diet-related triggers, and dietary interventions. The articles were searched for the type of diet, type of study, sample size, migraine type, results of outcome measures as reported by the articles for dietary patterns and triggers (correlation and association measures, prevalence, number or percentage of triggers), and the effect of interventions (effect on intensity, frequency or duration of headache or migraine attacks, pain or other medication use, number of migraine days).

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Patient population (P)	People with migraine aged ≥18 years	Pediatric patients (≤18 years), any other disease condition, studies not reporting data specifi- cally for people with migraine
Intervention (I)	Diet, food, and nutrition	_
Comparators (C)	All interventions, placebo or usual care	_
Outcomes (O)	 Diet, food, and nutrition: As triggers or predisposing factors for migraine Used for the prevention or treatment of migraine 	Supplements, nutritional supplements, natural medications, vitamins
Study design/publication type (S)	Randomized controlled trial (RCT) or pragmatic trials, non-RCT, prospective or retrospective observational studies, systematic literature reviews (SLRs)†	Editorial, letter, note, comment, book chapter or case reports
Time frame	January 1, 2000-March 5, 2019	_
Language	English	Non-English

Table 1.—PICOS and Eligibility Criteria

[†]Bibliographic searching of SLRs was conducted to identify additional relevant articles.

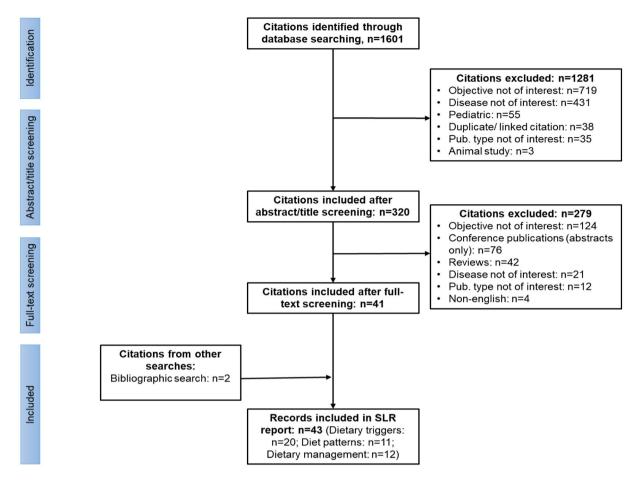


Fig. 1.—PRISMA diagram. [Color figure can be viewed at wileyonlinelibrary.com]

Quality Assessment of Included Studies.--All included RCT studies were assessed for quality by the National Institutes for Health and Care Excellence (NICE) checklist for RCTs.¹⁸ The items of the NICE checklist were rated as "yes", "no", "unclear", or "N/A". A "yes" response for an item indicates that the design/conduct of the study minimizes the risk of bias for that item. A "no" response denotes high risk of bias for an item. An "unclear" response to a question may arise when the item is not reported or not clearly reported. "N/A" was used when an RCT cannot give an answer of "yes" regardless of how well it has been designed. The risk of bias was determined according to the responses for each item. The disagreement between researchers was resolved by consensus. The Modified Downs and Black checklist^{19,20} was used to assess the quality of the observational studies. The checklist was modified for the scoring of item 27 that refers to the power of the study. Instead of rating according to an available range of study powers (0-5), the rating was performed based on whether or not the study performed power calculation (1 or 0). Therefore, the highest possible score for the check-list was 28 (instead of 32), with higher scores indicating higher study quality.

RESULTS

Study Selection.—A total of 1601 articles were identified, of which 320 were selected for full-text screening based on the inclusion criteria. Forty-three articles were finally included in this systematic literature review (Fig. 1). Of the studies included in the review, 11 outlined the evidence on diet patterns, 20 outlined the evidence on diet-related triggers, and 12 outlined evidence on diet as interventions in people with migraine.

Study Characteristics and Finding.—Majority of the included studies (81.4%) were observational studies.

Quality appraisals of RCT and observational studies are presented in Supplementary Tables S1-S3 and explained separately in the sections for diet patterns, diet-related triggers, and dietary interventions. All the RCT studies in the review (n = 8) assessed the effect of diet interventions.

Diet Patterns.—Study characteristics and a narrative summary of the results of studies evaluating diet patterns are summarized in Table 2. Diet patterns are features of a patient's diet that are observed either more or less frequently in people with migraine compared to those without. Diet patterns include multiple factors associated with diet in people with migraine. The overall quality of studies assessing diet patterns was low and it was hard to generalize a complete consensus. Most of the studies were completed at 1 site and none were rigorous RCT or prospective observational surveys. Most were point-in-time surveys and were, therefore, susceptible to recall bias.

General Diet Patterns.—There was conflicting evidence regarding the general diet patterns in people with migraine. The Prospective Analysis of Factors Related to Migraine Attacks Swiss study conducted in 327 patients stated that limited evidence exists on the effect of nutrition in the precipitation of migraine. No unfavorable impact of any nutritional factor was noted.²¹ A daily diary data analysis from a National Institutes of Health study reported that night time snacking and eating a late dinner reduced the odds of headache by 40% (hazard ratio [HR]: 0.60; 95% confidence interval [CI]: 0.40, 0.90; P = .013) and 21% (HR: 0.79; 95% CI: 0.55, 1.15; P = .22), respectively, in people with migraine.²² A case-control study conducted in Iran observed that females with migraine were more likely than females without migraine to report no regular diet program (37.6% vs 17.6%; P = .004), irregular schedule of meals (37.6% vs 23.5%; P = .046), and less than 3 meals per day (29.4% vs 9.4%; P = .001).²³

Several cross-sectional studies and surveys also reported the association of diet patterns with migraine. In a United States cross-sectional study, people with migraine with aura were reported to be more likely to have a low intake of chocolate (P = .005), cheese (P = 0.008), ice cream (P = .003), hot dogs (P < .001) and processed meats (P = .009), as compared to those

with migraine without aura.²⁴ In a Swedish populationbased survey, an increased prevalence of migraine was observed among those who skipped breakfast.²⁵ The National Health and Nutrition Examination Survey (NHANES) reported that the diet quality was significantly higher in women of normal weight (body mass index [BMI]: 18.5-24.9 kg/m²) without migraine compared to women of normal weight with migraine (P < .0001).²⁶

Specific Diet Patterns.—Unlike general diet patterns, specific diet patterns showed a more consistent relationship with migraine. Smoking and alcohol consumption had an association with migraine, with a retrospective analysis of annual health survey data reporting that the correlation of migraine prevalence with daily smoking was positive (Spearman coefficient, $r_s = 0.49$) and the correlation with alcohol consumption was negative ($r_s = -0.52$).²⁷ The Prospective Analysis of Factors Related to Migraine Attacks study reported that the risk of headache and migraine, as well as the risk of headache persistence, was reduced by the consumption of beer on days before headache onset.²¹

A cohort study conducted in Rome reported that increased consumption of whole-grain bread (P = .04) and whole grain pasta (P = .004), and decreased consumption of white bread (P = .004) was associated with a statistically significant reduction in migraine attack frequency and pharmacological rescue drug usage per month.²⁸

Several cross-sectional and survey studies also reported correlation between specific diet patterns and migraine. A study reported a significant positive association of consumption of fried food with migraine headache.²⁹ Similarly, another study showed that the migraine attack frequency is inversely proportional to adherence toward "healthy" eating pattern (high consumption of fruits, fish, vegetable pickles, vegetables, and legumes) (P for trend = .04) and directly proportional to adherence toward "western" eating pattern (high consumption of cola, salted nuts, processed meat, and fast foods) (P for trend = .02).³⁰ An inverse relationship between dietary sodium intake and the odds of probable migraine history was reported; however, in women, the relationship was limited to those with lower BMI (P = .007).³¹

Topic Author, year	Study Design, N	Outcome Summary
General Diet Patterns Overall dietary pattern	Prospective analysis of factors related to migraine attacks study, N = 327	There was limited evidence with regard to nutrition in the precipitation of migraine. Risk of migraine, headache, and headache persistence was lowered with consumption
Wober, 2007 ²¹ Eating habits	Case-control study, randomly selected, N = 170	of beer on days before headache onset More people with migraine had no regular diet, did not eat meals on a regular schedule, and ate less than 3 meals per
Nazari, 2010 ²³ Night-time snacking	Daily diary data analysis from NIH observational study, N = 34	day than the control group without migraine Night-time snacking and eating a late dinner were associated with reduction in the odds of headache
Turner, 2014 ²² Overall dietary pattern	NHANES cross-sectional survey, N = 3023	Women with or without migraine did not have any signifi- cant difference in dietary intake patterns, including total energy intake, percent of energy from macronutrients, sodium, caffeine, omega-3 fatty acids, omega-6 to omega-3 fatty acid ratio and eating frequency. However, women with migraine have higher odds of being alcohol consumers. Women of normal weight without migraine had significantly higher diet quality§ than women of
Evans, 2015 ²⁶ Dietary patterns,	Cross-sectional survey in the Women's Health Study, N = 7042	normal weight with migraine People with migraine reported low intake of total alcohol compared to those without any headache history. People with migraine with aura were more likely to have a low intake of chocolate, cheese, ice cream, hot dogs and processed meats compared to those with migraine without
Rist, 2015 ²⁴ Overall dietary pattern Molarius, 2008 ²⁵	Population-based survey, N = 1782	aura Increased prevalence of RH/M was found among women who often or sometimes drank heavily and those who skipped breakfast
Specific Diet Patterns "Healthy Eating Plate" diet	Cohort study, N = 101	There was a statistically significant decrease in migraine frequency and rescue drugs per month with increased consumption of whole-grain bread and whole-grain pasta
Altamura, 2018 ²⁸ Smoking and alcohol	Retrospective data analysis of the National Statistics Institute of Spain	and decreased consumption of white bread Migraine prevalence was positively associated with daily smoking and negatively associated with alcohol consump-
Matias-Guiu, 2014 ²⁷ Dietary patterns	database, NR Cross-sectional study, N = 285	tion (in the preceding 12 months Subjects with high adherence to western† eating pattern had more attack frequency, whereas subjects with high adher-
Hajjarzadeh, 2018 ³⁰ Dietary Sodium intake	National cross-sectional study, N = 8819	ence to healthy [‡] eating pattern had lower attack frequency Probable migraine history decreased with an increasing dietary sodium intake; however, it was found only in
Pogoda, 2016 ³¹ Dietary risk factors	Cross-sectional study, N = 750	women with lower BMI Consumption of fried food has a significant positive association with migraine headache
Najaf Zare, 2012 ²⁹		

BMI = body mass index; N = number of patients; NHANES = National Health and Nutrition Examination Survey; NIH = National Institutes of Health; NR = not reported; RH/M = recurrent headache/migraine.

†Western diet consists of high consumption of cola, salted nuts, processed meat, and fast foods and snacks.

‡Healthy diet consists of high consumption of fruits, fish, vegetable pickles, vegetables, and legumes.

\$Diet quality was measured using Healthy Eating Index 2005 [HEI-2005] total scores, where higher scores reflect higher consumption of fruits, vegetables, legumes, grains, milk, meat, beans, and oils, and lesser intake of saturated fat, sodium, and energy from solid fat, alcohol, and added sugars as per the standards specified by HEI-2005.

The association of alcohol intake and migraine varied across several cross-sectional studies. A cross-sectional study conducted in the United States reported that people with migraine had a low intake of total alcohol (P < .001) compared to those without any headache history.²⁴ The NHANES cross-sectional survey and Swedish population-based survey reported a positive association of alcohol consumption and migraine in women^{25,26}; however, no association between heavy alcohol use and migraine was noted in men.²⁵

Diet-Related Triggers.-Study characteristics and a narrative summary of the results of studies evaluating diet-related triggers are summarized in Table 3. Diet-related triggers for migraine identified included alcohol, caffeine, fasting, and a wide variety of specific foods. No RCT studies assessing diet as triggers were identified. Comparison between studies is limited, as some studies focused on 1 specific trigger (such as alcohol), while others assessed a variety of triggers. In addition, some studies presented a list to patients to assess triggers vs patients recalling triggers on their own. No study involved patient or assessor blinding. Due to the survey or questionnaire nature of these studies, patients were susceptible to recall bias. Most of the studies were of poor-tomedium quality due to the lack of complete reporting of study design or patient characteristics (Supplementary Table S2).

Alcohol.—Alcohol was reported to be significantly associated with migraine compared to nonmigraine headaches in a Korean prospective observational study (odds ratio [OR] = 2.5, 95% CI = 1.3, 5.0; P < .001).¹⁴ Another prospective cohort study reported alcohol to be associated with migraine in 3.9% (N = 126) patients.³²

Several cross-sectional studies reported the association of alcohol with migraine. Alcohol use was found to be associated with migraine in 17.5%, 20.5% and 35.6% participants in 3 questionnaire studies.³³⁻³⁵ One study reported red wine (77.8%) as the most common trigger among alcoholic beverages.³³ Alcohol was found to be associated with migraine in a Chinese cross-sectional study.³⁶ However, the association was less likely to be present in women compared to men.³⁶ Also, a Japanese population-based

survey reported no association of alcohol and migraine after age and gender adjustment,³⁷ and a cross-sectional study reported that alcohol was associated with migraine in only a small percentage of patients.³⁸

Fasting.—A cohort cross-over migraine diary study showed that during the month of Ramadan, there was an increase in the average number of migraine days among observant people with migraine compared to the following (control) month (9.4 ± 4.3 vs 3.7 ± 2.1 ; P < .001).³⁹

This finding was supported by a patient survey conducted in Iraq which reported that fasting in the month of Ramadan is a trigger for headaches in people with migraine.⁴⁰ Another prospective questionnaire study also reported fasting as a major trigger among people with migraine who reported any triggers.¹²

Food Allergens.—One study assessed the effect of food allergens on migraine. The prospective observational study conducted in Turkey showed that food allergens, such as fish, egg whites, egg yolks, nuts, orange, and strawberry, were not related to migraine attacks; however, people with migraine were found to have more pollen allergies compared to the people without migraine.⁴¹

Caffeine.—A prospective cohort study conducted in Turkey (N = 126) revealed that caffeine was a trigger in 6.3% people with migraine.³² Caffeine was found to be a a trigger for migraine-associated vertigo attacks in 69.6% of patients in a Turkish retrospective, observational study.⁴²

The association between caffeine and migraine was also reported in another prospective observational, cross-sectional study.⁴³

Dietary Triggers.—Dietary factors (43.6%), including hunger (53.9%) and consumption of milk and cheese (10.3%) and chocolate (18.3%), were found to be associated with migraine in a prospective cohort study conducted in Turkey. However, no statistical difference in dietary triggers was noted between migraine with and without aura (P = .753) or between genders (P = .081).³² In another Korean prospective, observational study, overeating was significantly associated with migraine compared to nonmigraine headaches (OR = 2.4; 95% CI = 1.1, 5.7; P = .001).¹⁴ A Turkish prospective cohort study

Study Design, N Author, year Outcome Summary Alcohol Park, 2016¹⁴ Prospective observational study, N = 62Alcohol use was significantly associated with migraine Mollaoglu, 2013³² Prospective cohort study, N = 126Triggers for migraine included alcohol Onderwater, 2019³³ Cross-sectional, questionnaire study, The most common alcohol-related trigger was red wine N = 2197Panconesi, 201338 Cross-sectional study, N = 448Very few patients indicated alcohol as a trigger Wang, 2013³⁶ Cross-sectional study, N = 394 Alcohol drinking was associated with migraine. Alcohol as a trigger was less common in females than males Yokoyama, 201249 Cross-sectional study, N = 419People with migraine drank less alcohol than those with TTH Alcohol triggers were red wine, liquor, champagne or spar-Hauge, 2011³⁵ Questionnaire survey, N = 126kling wine, white wine, and beer Andress-Rothrock, Ouestionnaire survey, N = 200Triggers included alcohol. Specific types of alcohol (e.g., red 2010^{34} wine) may trigger attacks Takeshima, 200437 Population-based survey, N = 5740Risk for migraine or TTH was not influenced by the consumption of alcohol, after age and gender adjustment Fasting Abu-Salameh, 201039 Cohort cross-over migraine diary study, During Ramadan, fasting was associated with an increase in N = 30migraine headache Yadav, 201012 Prospective questionnaire study, N = 182Fasting was one of the most commonly reported triggers Al-Shimmery, 2010⁴⁰ Patient interview/survey, N = 200Fasting during Ramadan and other days of the year were significantly associated with migraine Food allergens Bektas, 201741 Prospective observational study, N = 49Food allergen frequency did not differ between migraine and control groups (not exposed to allergens); however, an allergy to pollen was frequently found in the migraine group compared to the control group Caffeine Mollaoglu, 2013³² Prospective cohort study, N = 126Triggers for migraine included coffee Omer Saglam, 2015⁴² Retrospective observational study, N = 23Excessive caffeine intake (all forms) was reported by patients as one of the food triggers. Tai, 201843 Prospective observational, cross-sec-Coffee was one of the most common dietary factor associated tional study, N = 684 (migraine = 319) with migraine Dietary triggers Park. 2016¹⁴ Overeating was significantly associated with migraine Prospective observational study, N = 62Mollaoglu, 2013³² Prospective cohort study, N = 126Triggers for migraine included dietary factor, hunger, milk and cheese, and chocolate Omer Saglam, 201542 Prospective cohort study, N = 23Patients reported the following food triggers: Cheese/cheese products, excessive nuts intake, excessive fresh/dry fruits intake, high dairy products consumption, more processed food consumption, and high baked food consumption Kelman, 200744 Retrospective observational analysis, Food was a very frequently observed trigger in people with N = 1750migraine Tai. 201843 Prospective observational, cross-sectional Some dietary factors including chocolate and foods rich in study, N = 684 (migraine = 319) monosodium glutamate were most commonly associated with migraine Hauge, 2011³⁵ Questionnaire survey, N = 126Food and seasoning[†] usage was associated with migraine Andress-Rothrock, Questionnaire survey, N = 200Missing meals and use of specific foods including chocolate, 2010^{34} cheese, and hot dogs was associated with migraine Baldacci, 201347 Prospective observational, cross-sec-People with migraine seemed to better recognize triggers like tional study. N = 120particular food and stress Camboim Rockett, Cross-sectional survey, N = 123Only few patients reported no susceptibility to any dietary 2012⁴⁶ trigger Hauge, 2010⁴⁵ Questionnaire survey, N = 629Hunger/missing a meal, dehydration, and use of food/seasoning was associated with migraine Zivadinov, 200348 Population-based survey, N = 2039Significant positive association of food items noted in people (migraine = 720) with migraine with aura compared to migraine without aura

Table 3.—Diet-Related Triggers

N = number of patients; TTH = tension-type headache. †Seasoning was not defined by the article. included 23 people with migraine-associated vertigo. The most common triggers that may have triggered vertigo attacks included cheese or cheese products (100%) and excessive intake of nuts (56.5%), fresh or dry fruits (39.1%), dairy products (39.1%), processed food (30.4%), baked yeast foods (21.7%), and processed meat (21.7%).⁴²

A retrospective, observational study assessing the triggers or precipitants of migraine attacks reported the frequency of food triggers in people with migraine to be 26.9%. Food was identified as one of the very frequently occurring (>66% of headaches) triggers. Food was a more common trigger in people with migraine vs those with probable migraine (P = .017), in episodic migraine compared to chronic migraine (P = .025) and in migraine with aura compared to migraine without aura (P = .010).⁴⁴

Several cross-sectional studies and questionnaire surveys also reported the association of dietary factors with migraine. In a questionnaire survey assessing the effect of diet-related triggers, the number of people with at least 1 trigger was significantly higher in people with migraine attacks than those with no attacks within the last year (P < .001).⁴⁵ A cross-sectional survey reported that migraine was commonly associated with dietary triggers, with only 2.4% of people with migraine (N = 123) not experiencing susceptibility to any dietary trigger.⁴⁶ In an Italian cross-sectional study, people with migraine were reported to be better in recognizing triggers, such as particular foods and alcohol.⁴⁷ A questionnaire survey reported food and seasonings to be associated with migraine.³⁵ Another questionnaire survey reported missing meals and the use of certain foods including chocolate, cheese and hot dogs to be associated with migraine.³⁴ Chocolate and foods rich in monosodium glutamate were reported to be the most common dietary factors associated with migraine in a prospective, cross-sectional study.⁴³ Chocolate was found to be significantly associated with migraine compared to tension-type headache.43 A Croatian population-based survey reported a significant positive association of various food items (chocolate, cheese, alcoholic drinks, fried fatty foods, vegetables, and coffee) with migraine with aura compared to migraine without aura.48

Diet Interventions.—Study characteristics and a narrative summary of the results of studies evaluating diet interventions are summarized in Table 4. Diet interventions refer to the adjustment of a patient's diet by adding or eliminating a specific type of food that might influence the frequency and severity of migraine attacks. The quality of studies included was higher for diet interventions and included 8 RCTs which mostly had a low risk of bias in the quality assessment, allowing for possible claims of causation.

Specific Diets.—In a randomized, controlled study, in the first month after restriction to low glycemic index diet, monthly attack frequency significantly decreased from baseline in both diet and medication (control) groups (P < 0.05). The mean frequency and severity of attacks as measured by the visual analog scale (VAS) decreased significantly after 3 months in the diet group compared with those in the medication group (P < .05).⁵⁰ In another randomized, cross-over dietary interventional trial, a low-lipid (lipid content <20% of the total daily energy intake) or a normal-lipid (between 25% and 30% of the total daily energy intake) diet was assigned randomly for 3 months and then the diets were crossed over for the following 3 months. A significant correlation between low-lipid diet and decrease in migraine attacks (2.9 ± 3.7 ; P < .001 vs baseline and P < .05 vs normal-lipid diet) was established. The low-lipid diet was effective in reducing the mean (\pm standard deviation [SD]) severity of attacks (1.7 ± 0.9) vs 1.2 ± 0.9 , P = .001) and the number of severe pain attacks $(1.8 \pm 1.6 \text{ vs } 0.4 \pm 1.3, P = .01)$ vs the normal-lipid diet.⁵¹

Another randomized, cross-over study compared 2 treatments: dietary instruction with a placebo supplement. Each treatment period was 16 weeks, with a 4-week washout period before the cross-over to the alternate treatment. During the diet period, patients were prescribed a low-fat vegan diet for 4 weeks, after which they were asked to follow an elimination diet to identify possible specific migraine -triggering foods. During the elimination diet period, patients continued the low-fat vegan diet along with the elimination of common trigger foods, chosen based on previous studies. The elimination diet was continued until no further improvement was noted or until the midpoint of the period (typically 10 to 21 days), after which

Table 4.—Diet Interventions

Author, year	Study Design, N	Intervention-Comparator	Outcome Summary
<i>Specific diets</i> Evcili, 2018 ⁵⁰	RCT, N = 350	Low glycemic index diet vs. Control (medication group)	In the first month after dietary restriction, the number of monthly attacks significantly decreased in both groups but not in severity, based on a VAS score.
Ferrara, 2015 ⁵¹	Randomized cross- over N = 83	Low-lipid diet vs. Habitual diet (normal-lipid diet)	The mean scores of VAS significantly decreased later in the diet group compared with those in the medication group (after 3 months) People with migraine on a low-lipid diet had a signifi- cant reduction in the number of migraine attacks, as well as the severity of attack compared to those on a normal-lipid die
Bunner, 2014 ⁵²	Randomized cross- over interventional trial, N = 42	Low-fat vegan diet vs. Placebo sup- plement (a capsule containing alpha-linolenic acid and vitamin E)	1
Spigt, 2005 ⁵³	Pilot-RCT, N = 18	Increased water intake (1.5 L) vs. Placebo (normal water intake)	Water seemed to have an effect on the total number of hours of headache and headache intensity, although the effects were not statistically significan
Di Lorenzo, 2016 ⁵⁴	Prospective observa- tional study, N = 18	Ketogenic diet vs. Normal diet	After 1-month of the ketogenic diet, the mean attack frequency and duration significantly reduced
Sanders, 2018 ⁵⁵	Cross-sectional obser- vational, N = 12317	Measured daily intake of EPA/ DHA	Greater intake of omega-3 PUFAs was associated with a lower prevalence of severe headache or migrain
Mirzababaei, 2018 ⁵⁶	Questionnaire, cross- sectional, N = 266	Level of adherence to the DASH diet (high intake of fruits, vegetables, whole grains, poultry, fish, and nuts, restricting satu- rated fat, red meat, sweet bever- ages, and refined grains)	The results of analysis in the crude model showed that individuals with the greatest adherence to the DASH diet displayed lower prevalence in severe headaches, compared to those with the lowest adherence
Elimination diet.			
Ozon, 2018 ⁶⁰	Randomized cross- over study (Using headache diary), N = 50	Diet strict with trigger removal vs. Diet relaxed with trigger removal	Monthly attack frequency, attack duration, and attack severity were found to have decreased to a statisti- cally significant extent compared to those in the period before diet implementation in patients with diet restriction (removal of triggers from diet)
Aydinlar, 2013 ⁵⁷	RCT, Double-blind, randomized, cross- over trial, N = 21	IgG-based elimination vs. Baseline (usual diet)	Compared with baseline (usual diet), the elimination diet was associated with significant reductions in attack count, attack duration, attack severity, and acute medication use during attacks
Alpay, 2010 ⁵⁹	RCT, double-blind, cross-over, N = 30	Excluding (Elimination diet) or in- cluding (Provocation diet) foods with high IgG antibody level	Number of headache days reduced from baseline in the elimination diet group. Elimination diet was also superior in terms of attack count, number of attacks with acute medication, and total medication intake
Mitchell, 2011 ⁵⁸	RCT, single blind, N = 167	True diet (n = 84) vs. Sham diet (n = 83) based on IgG antibodies reactivity-related elimination	There were significant differences in median number of headache days between true diet and sham diet at week 4 but not at week 12
Arroyave Hernandez, 2007 ⁶¹	Prospective cohort study, N = 56	Elimination diet based on IgG food allergy positive reactiv- ity vs. Control group without migraine	After 6 months on the elimination diet, the majority of patients had remission of migraine (no migraine) and only a few observe a decreased in intensity and frequency. There was statistically significant difference between patients and the control group regarding level IgG food reactivity

DASH = dietary approaches to stop hypertension; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; IgG = immunoglobulinG; N = number of patients; PUFA = polyunsaturated fatty acid; RCT = randomized controlled trial; VAS = visual analog scale.

the omitted foods were reintroduced one at a time. Improvement in headache pain, as measured by the patient's global impression of change and change in pain question scale (5-point Likert-style scale ranging from "much worse" to "much better"), was significantly greater after the diet period (P < .001). Pain relief medication use decreased significantly during the diet period compared to the placebo supplement period (19 vs 3 absolute percentage point decrease in medicated headaches, P = .004). Improvement in average headache intensity and average headache frequency was not significantly higher in the diet period compared to the supplement period (P = .20 and P = .61, respectively).⁵²

An association of water intake on migraine was reported in an RCT, with an observed reduction of headache hours and headache intensity with higher water intake (1.5 liters) vs control (no water intake recommendations, continued normal water intake); however, the effects were not statistically significant. Headaches reduced by 21 hours (95% CI: -48, 5) within 2 weeks in the higher water intake group compared to the control group. The mean headache intensity was measured using the visual analog scale (VAS; 0-100 mm scale, higher scores indicating severe headache). The observed difference in mean improvement in headache intensity at 12 weeks was 13 mm (95% CI: -32, 5) on the VAS in the group with high water intake vs the control group.⁵³

Ketogenic diet administration for 1 month was also significantly related to the reduction in the mean attack frequency and duration compared to baseline (all P < .001) as shown in a small, prospective observational study.⁵⁴

Evidence of the association between specific diets and migraine was noted in cross-sectional studies. Greater intake of omega-3 polyunsaturated fatty acids was found to be statistically significantly associated with lower prevalence of severe headache or migraine.⁵⁵ Also, highest adherence to dietary approaches to stop hypertension (DASH) diet displayed a 30% lower prevalence in severe headaches compared to those with the lowest adherence.⁵⁶

Elimination Diets.—The importance of an Immunoglobulin G (IgG)-based elimination diet was shown in a double-blind, randomized, controlled, cross-over study which included baseline (usual diet) for 6 weeks, first diet (elimination [IgG-negative food] or provocation [IgG-positive food] diets) phase of 6 weeks, and second diet (interchange of elimination or provocation diets) phase of 6 weeks (with a 3-week washout phase with usual diet at the end of the first diet phase). There was a significant reduction with the elimination diet when compared to the baseline levels in the mean $(\pm SD)$ number of attacks (4.8 \pm 2.1 vs 2.7 \pm 2.0; P < .001), maximum attack duration $(2.6 \pm 0.6 \text{ vs } 1.4 \pm 1.1 \text{ days}; P < .001)$, mean attack duration $(1.8 \pm 0.5 \text{ vs } 1.1 \pm 0.8 \text{ days};$ P < .01), maximum attack severity (VAS 8.5 ± 1.4 mm vs VAS 6.6 \pm 3.3 mm; P < .001) and number of attacks with acute medication $(4.0 \pm 1.5 \text{ vs } 1.9 \pm 1.8;$ P < .001).⁵⁷

In a single-blind, randomized clinical trial, a significant difference in the median number of migraine-like headache days at 4 weeks (incident rate ratio [IRR] 1.23, 95% CI 1.01, 1.50; P = .04) was observed between true diet and sham diet, which included IgG antibody reactivity-related elimination diet (identified using enzyme-linked immunosorbent assay). However, the difference in the median number of migraine-like headache days over 12 weeks was not significantly different between the true and sham diet groups (IRR 1.15, 95%) CI 0.94, 1.41; P = .18).⁵⁸ Another double-blind, crossover study evaluated the importance of elimination of foods with a high IgG antibody level (elimination diet) by showing a significant reduction in the attack count, number of attacks with acute medication, and total medication intake with elimination diet compared to provocation diet that consisted of food with high IgG antibody levels (P = .006).⁵⁹

Another randomized, cross-over study showed the importance of diet implementation (restriction of triggers like wheat, orange, egg, caffeine, cheese, chocolate, and milk) in people with migraine. The migraine-triggering foods were excluded from the diet of 2 groups of patients and then the diet restriction was relaxed in group 1 after the second month and continued in group 2. Assessments were made before the start of diet restriction, and at 2 and 4 months. Monthly attack frequency, attack duration, and attack severity were found to decrease significantly after 2 months of diet implementation compared to the period before diet implementation in group 1 (P = .011, P = .041, and P = .003, respectively) and group 2 (P = .015, P = .037, and P = .003, respectively). In the 4th month evaluation, the significant decrease was maintained only in patients who continued the diet restriction (group 2) (P < .05).⁶⁰

In another prospective cohort study, the specific elimination diet (elimination of IgG-positive food) for 1 to 6 months was shown to be effective in 56 people with migraine who were positive on immunoassay for food IgG. Remission (no migraine) was achieved in 43 patients; the intensity and frequency were decreased in 4 patients, while 9 patients had no changes. The IgG food reactivity was significantly different between people with migraine and the control group (people without migraine) (P < .01), suggesting people with migraine may be more sensitive to IgG food reactivity.⁶¹

DISCUSSION

In this systematic literature review for the effect of diet on migraine, limited high-quality evidence was found. Evidence regarding the effect of general diet patterns in people with migraine varied in the studies identified. One study reported no unfavorable impact of any nutritional factor ²¹; whereas a few studies observed an association between eating behaviors and a reduction in headache occurrence.^{23,25} Some studies suggest that there may be a relationship between meal timing and migraine attacks. A study identified in this review showed that night time snacking and eating a late dinner could reduce the odds of headache.²² Although the data quality was generally low to medium, these studies suggest that maintaining steady glucose levels by eating more frequent, small meals and snacks could be a strategy that might prevent headaches triggered by fasting.⁶²

Earlier reviews have mentioned that about 12% to 60% of subjects in different studies have reported foods as trigger for migraine, with many subjects reporting more than 1 dietary trigger.⁶³ Avoiding triggers is a general recommendation to people with migraine; however, there is a lack of scientific evidence to support this therapeutic recommendation. Several studies identified in this review suggest that diets containing less fried foods, dairy products, caffeine, and processed foods, such as white bread and

processed meat, may be beneficial in reducing migraine symptoms or frequency.^{24,28-30} Diets high in fats, carbohydrates or caffeine cause activation of the sympathetic nervous system or parasympathetic withdrawal, which might contribute to the precipitation of migraine.⁶⁴

Alcohol consumption had conflicting associations with migraine.^{14,27,36} Alcohol was one of the most frequently reported triggers identified in this review ^{14,32} and in a vast majority of prior studies.⁶⁵ However, some studies also reported an inverse correlation between alcohol consumption and risk of migraine.^{21,27} The inconsistent findings suggest that some individuals or people from specific cultures may be more susceptible to alcoholic triggers. The inconsistencies may also be attributable to the fact that people with migraine have generally limited their intake of alcohol because they know it is a trigger. People with migraine may benefit from limiting alcohol, particularly red wine, if this is identified as a trigger for an individual.

Overall, many patients reported multiple dietary triggers and relatively inconsistent associations were observed, which suggest some dietary factors may not precipitate a migraine attack in isolation or that the association between food and migraine attacks is multifactorial and complex. The lifetime benefit would be substantial in people with migraine if an understanding of their own triggers leads to even a small effect on the severity, duration or frequency of attacks. The usage of migraine diaries in future studies may be a useful tool in identifying individual triggers.

Several studies identified in this review showed that dietary interventions can have a statistically significant effect on decreasing migraine attack frequency, severity or both. Data from most of the observational studies and RCTs showed no statistical significance in the number of headache days; however, a trend toward the reduction in the number of headache days was observed.

Low-fat or low-lipid vegan diets were reported to be beneficial in improving outcomes in people with migraine.^{51,52} An omega-3 polyunsaturated fatty acid and eicosapentaenoic acid-rich diet resulted in lower prevalence of severe headache or migraine.⁵⁵ An earlier RCT also reported that a high omega-3 and low omega-6 fatty acid diet leads to the reduction of headache days, frequency and pain in people with chronic headaches.⁶⁶ Ketogenic⁵⁴ and low-glycemic index⁵⁰ diets have also been reported to be beneficial in certain people with migraine.⁶⁷ The benefit of these diets was expected given that earlier studies have reported a significant correlation between obesity and migraine headache^{68,69} and avoiding unhealthy food has led to better outcomes in people with migraine. Data do not support the use of one of these diets over another in people with migraine, but comorbidities such as diabetes, hypertension, and cardiovascular diseases may be considered, while recommending a specific diet. Also, physicians may consider recommending these diets for a specific duration to enable optimal benefit, while avoiding nutritional deficiencies. Furthermore, compliance with the dietary recommendations would be crucial to achieve better outcomes.

Elimination of specific foods, such as wheat, orange, egg, caffeine, cheese, chocolates, and milk, from a person's diet was found to be associated with a reduction in the frequency, onset, and severity of migraine attacks.⁶⁰ The findings were similar to a prior study which reported a decrease in headache frequency in people with migraine who had an elimination diet based on positive skin prick test for food allergens.⁹ However, an earlier review reported that the widespread belief of avoiding chocolates and cocoa products in migraine is not supported by robust scientific literature.⁷⁰ The IgG-based elimination diet was associated with a significant reduction in attack duration and number and severity of attacks, and the number of headache days in some people with migraine.^{57,58,61}

Overall, preliminary evidence from some RCTs suggest that people with migraine may benefit from low-fat, low-lipid diet, ketogenic diet, or elimination diet of IgG-positive foods; however, an individualized approach to these dietary interventions may be needed. Furthermore, more long-term studies involving large samples examining the effect of diet interventions are needed to see if there is a place for diet in migraine management guidelines.

The studies included in this review were conducted on varied patient populations with different study designs. Most studies were cross-sectional and therefore, not designed for identifying causal relationships between migraine and possible diet-related triggers or diet patterns. The overall study quality of the observational studies was poor to medium. Most studies were point-in-time patient surveys or questionnaires with limited conclusions and were susceptible to recall bias. In addition, none of the observational studies involved blinding and very few discussed power or confounding. There is limited evidence from high-quality RCTs that assessed the effect of diet intervention on migraine. Overall, there were very few studies that lasted longer than 12 weeks, so the long-term effectiveness of the diet interventions included in the review remains unknown. Furthermore, the studies were completed in a wide variety of countries from Europe, Asia, and the United States. This made comparisons between studies difficult due to cultural and religious variations among different countries. Our review included adults with migraine and was focused on studies published in or after the year 2000; however, reviews assessing data in migraine and other types of headaches have reported similar findings.^{6,71} Despite these limitations, the individual studies identified in this review suggest that certain dietary factors can act as triggers. The review presents a body of evidence on the beneficial effect of diet interventions, which may aid clinicians in developing a holistic management plan for people with migraine. Longitudinal and high-quality RCTs and longer-term studies are needed to confirm the preliminary results reported by various studies on the effect of diet in migraine.

CONCLUSION

Migraine is a disabling primary headache disorder with high societal impact. Several studies have reported a link between diet triggers and migraine, but the associations need to be confirmed by high-quality longitudinal studies. Certain dietary interventions may help to improve clinical outcomes in some people with migraine, but these findings still need to be supported with robust evidence before being recommended for use in clinical practice.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

APPENDIX

Terms Included in OVID Medline and EMBASE Search

Migrain*[.ti/ ab];Tension-type adj1 headache[.mp]; (diet* or food).mp; (beverage or alcohol* or additive or preservative).ti,ab; (treat* or prevent* or prophyl* or effect* or trigger or risk* or sensiti* or induce or relation*).ti,ab,kw; (associat* or management or guideline or relate or (food adj1 allergy)).ti.

Filters:

- Publication year: From 01/01/2000 to 05/03/2019
- Language: English
- Population: adults, human, humans