MAGNESIUM INTAKE AND ODDS OF MIGRAINE OCCURRENCE IN PRE- AND PERI-MENOPAUSAL WOMEN PARTICIPATING IN THE STUDY OF WOMEN'S HEALTH ACROSS THE NATION (SWAN)

by

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Magnesium Intake and Odds of Migraine Occurrence in Pre- and Peri-Menopausal Women Participating in the Study of Women's Health Across the Nation (SWAN)

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DEDICATION

This is dedicated to my loving husband, Emery, for motivating me with encouragement and affirmation, and being my constant in the uncertainties of life.

To my parents, Vasudha Khatri and Mansukh Ram Khatri, for supporting my goals and ambitions, and trusting me every step of the way.

To my sisters, Alpna Khatri, Ratna Khatri, and Daksha Khatri, for being the true cheerleaders of my personal and professional life.

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LIST OF ABBREVIATIONS

ATP, Adenosine Triphosphate
BMI, Body Mass Index
CGRP, Calcitonin gene-related peptide
CI, Confidence Interval
CSD, Cortical Spreading Depression
DDE, Daily Dietary Estimate
EAR, Estimated Average Requirement
FFQ, Food Frequency Questionnaire
FNDDS, Foundation Foods, Food and Nutrition Database for Dietary Studies
HEI, Healthy Eating Index
ICHD, International Classification of Headache Disorders
IHS, International Headache Society
NHANES, National Health and Nutrition Examination
NMDA, *N*-methyl-D-aspartate
NSAIDS, Nonsteroidal anti-inflammatory drugs
OR, Odds Ratio
RDA, Recommended Dietary Allowance
SE, Standard Error
SoFAAS, Solid Fats, Alcohol, and Added Sugar
SR, Standard Reference
SWAN, Study of Women's Health Across the Nation
USDA, United States Department of Agriculture
USHC, United States Headache Consortium

ABSTRACT

MAGNESIUM INTAKE AND ODDS OF MIGRAINE OCCURRENCE IN PRE- AND PERI-MENOPAUSAL WOMEN PARTICIPATING IN THE STUDY OF WOMEN'S HEALTH ACROSS THE NATION (SWAN)

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Background: Migraine is a neurological disorder that causes disabling headaches that can impede day-to-day normal activities. It is three times more prevalent in women than men following puberty. Menstrual migraine, a subtype of migraine that occurs during the perimenstrual period, is typically more difficult to treat than non-menstrual migraine and can be exacerbated during peri-menopause. Magnesium supplementation has shown promising results in reducing the occurrence and intensity of migraine attacks, including menstrual migraines, but information on dietary magnesium intake in pre- and peri-menopausal women in relation to migraine and menstrual migraine is scarce.

Objective: The overall aim of the study was to observe the association between dietary magnesium intake and migraine status in pre- and peri-menopausal women.

Methods: This analysis included cross-sectional data from 3,022 pre- and peri-menopausal women, aged 42-52 years old participating in the Study of Women's Health

Across the Nation (SWAN). Migraine status was determined from an interview questionnaire, and individuals were classified into four groups: menstrual migraine (n=794), non-menstrual migraine (n=43), history of migraine (n=181), and never migraine (control) (n=2,004). Dietary magnesium intake was determined through the Block Food Frequency Questionnaire. Odds ratios and 95% confidence intervals were calculated using multinomial logistic regression, and p-trends were calculated using median regression. Variables adjusted in different regression models included BMI, race/ethnicity, menstrual status, alcohol consumption, total family income, health insurance, and food group (fruit, vegetable, dairy, grain, and meat) and magnesium intake.

Results: Mean dietary intake of magnesium at baseline was below the recommended age-based and gender-based dietary allowance in all migraine status groups. In the unadjusted model, women had higher odds of non-menstrual migraine (OR_{Q4}=2.69 [1.11-6.49], p_{trend}=0.014) with increasing dietary magnesium intake quartiles as compared to controls. The relationship remained consistent when the model was adjusted for food groups and demographics. For dietary magnesium intake, no statistically significant relationship was observed (p_{trend}>0.05) in the unadjusted and adjusted models for the menstrual migraine group and the history of migraine group. Except for meat, the mean intake of all other food groups was below the recommended age-based and gender-based food group servings for all the migraine status groups.

Conclusions: Dietary magnesium intake and food group intake of pre- and peri-menopausal women with different migraine status are lower than the recommended

intake levels. The debilitating nature of migraine might affect the dietary choices of individuals which could lead to inadequate intake of healthy food groups and micronutrients such as magnesium. A statistically significant difference was observed in the non-menstrual migraine group in relation to dietary magnesium. These findings suggest this group may not have been limiting their food choices to avoid triggers or in response to symptoms as they indicated they consumed medication for migraine. However, the results in our study did not show any statistically significant difference in the menstrual migraine group in relation to dietary magnesium intake. Menstrual migraine is harder to treat and does not respond well to migraine medication. This could indicate that diet alone may not prevent menstrual migraine symptoms and may require supplemental treatment(s), which is to be expected given current understanding of migraine pathophysiology. Limited studies that have observed improved symptoms in women with menstrual migraine have made use of supplemental magnesium in high doses. More research is needed on the effect of dietary magnesium intake on features of migraine such as frequency, intensity, and attack duration in this population, particularly in relation to hormonal fluctuations and other pathophysiological mechanisms specific to this population.

CHAPTER 1. LITERATURE REVIEW

An estimated 1 in 4 women will experience migraine disease in their lifetime, and approximately 28 million women in the U.S. have migraine.[1] Research suggests a potential relationship between diet and migraine,[2] but the evidence is limited. Supplemental magnesium has been implicated to prevent migraine symptoms in individuals,[3] but there is a scarcity of research examining the relationship between dietary magnesium intake and migraine. This chapter will review aspects of migraine disease and the evidence for a potential relationship between diet and migraine, with an emphasis on magnesium, with the intention of identifying opportunities for exploring this relationship.

Migraine

Migraine disease is a neurological disorder that causes recurrent disabling headaches that affect day-to-day normal activities of individuals. The pain can range from moderate to severe[4] and can last up to 72 hours.[5] The attack is associated with several other symptoms such as photophobia (sensitivity to light), phonophobia (sensitivity to sound), nausea, and vomiting.[6] According to the Global Burden of Disease survey 2019, migraine is the second most disabling condition in respect to years lived with a disability, and the first cause of global disability in young adult women (aged 15-49).[7] Migraine can have substantial effect on the quality of life, and contributes to the socioeconomic burden.[8] A U.S. wide study showed that the total cost of episodic

migraine was $2649/year, whereas the total cost of chronic migraine was $8243/year.[9] Of these costs, 60-64% are due to direct costs such as medical needs.[9]

Classification of Migraine

Migraine has been classified by The International Headache Society (IHS), and according to their third edition of the International Classification of Headache Disorders (ICHD-3), there are two major types of migraine: migraine without aura and migraine with aura. Migraine without aura is described as recurrent headaches with attacks lasting 4-72 hours. The migraine headaches are characterized by their unilateral location, pulsating nature, intensity ranging from moderate to severe, and exacerbation due to physical activity. They are also associated with nausea and/or photophobia, and phonophobia.[10] Migraine with aura is described as recurrent attacks that last for a few minutes. The attacks are characterized by visual, sensory, speech and/or language, motor, brainstem, or retinal unilateral reversible aura symptoms. These symptoms are usually followed by a headache and other migraine symptoms.[11]

Classification and diagnostic criteria of "menstrual migraine" has been placed in the appendix of ICHD-3 and is still considered an area that needs further research for validation.[12] Menstrual migraine has been defined as migraine "occurring in the perimenstrual period, i.e. on day -2 to +3 of menstruation in at least two out of three menstrual cycles."[12] Two types of menstrual migraine have been recognized by ICHD-3: pure menstrual migraine (PMM) and menstrually-related migraine (MRM).[12] PPM occurs exclusively in the perimenstrual period, whereas MRM is experienced by individuals

both in and outside of the perimenstrual period. Like other types of migraine, PPM and MRM can occur in women with or without aura.[12] Non-menstrual migraine (with or without aura), on the other hand, occurs exclusively outside of the perimenstrual period.[13,14]

Prevalence

Prevalence of migraine increases steadily through childhood, and with puberty a shift occurs in the male-to-female ratio where the prevalence becomes significantly higher in females as compared to males, and remains so throughout their lives.[15] Migraine is three times more common in women as compared to men worldwide.[15]

According to most headache centers, almost 85% of their migraine patients are women.[15] Among women with migraine, almost 70% report experiencing menstrual migraine.[12] Women who are diagnosed with menstrual migraine often describe the migraine attacks as more painful and disabling, longer lasting, and comparatively less responsive to treatment than non-menstrual migraine.[12] Estrogen plays a key role in both the menstrual cycle and the occurrence of migraine in women, and its fluctuation during puberty, pregnancy, peri-menopause, and post-menopause impacts migraine.[16]

In particular, women with migraine who are going through the peri-menopausal transition have greater risk for experiencing increased headache frequency than pre-menopausal women with migraine.[17] Prevalence of migraine has been estimated to be between 16% to 29% in peri-menopausal women.[18] This indicates that fluctuating menstrual cycles during peri-menopause may increase the number of events when

estrogen fluctuation occurs, making the women going through the transition more prone to migraine headaches.

Diagnosis

Migraine can be diagnosed using the IHS criteria, in combination with family history of the patient, neurological examination, and a headache diary.[19] Even so, migraine is often underdiagnosed. More than half of the population living with migraine is never diagnosed with migraine because majority of them do not seek medical care. Of those who are diagnosed, only 4% seek care from headache and pain specialists, and out of the 25% who could be eligible for preventative treatment, only 12% receive it.[1]

Pathophysiology

In order to understand the potential ways in which diet may influence migraine, it is important to first review the current proposed theories of migraine pathophysiology. Later, ways in which nutrients may interact with this pathophysiology will be discussed.

Calcitonin Gene-Related Peptide

The theory for patients genetically susceptible to migraine is based in the hyperexcitable trigeminovascular complex and possibly cortex. Trigeminovascular neurons produce neuropeptides calcitonin gene-related peptide (CGRP) and substance P, which are released during migraine. As a result, vasodilation, mast cell degranulation, increased vascular permeability, and blood vessel edema takes place that causes meningeal neurogenic inflammation. Pain results when the brainstem trigeminal nucleus

caudalis sends nociceptive information resulting from this inflammation through the trigeminal nerve to the thalamic nuclei and the cortex.[20]

Cortical Spreading Depression

Cortical Spreading Depression (CSD) is the proposed theory for the aura experienced by migraine patients. When the cerebral cortex experiences electrical or chemical stimuli, excitation followed by depolarization takes place that further spreads throughout the cortex.[20] Evidence suggests that CSD is associated with the release of glutamate in the extracellular space. The released glutamate acts on the presynaptic *N*-methyl-D-aspartate (NMDA) receptor which further releases more glutamate,[21] and higher concentration of glutamate increases neuronal excitability.[22]

Mitochondrial Dysfunction

Dysfunction of the mitochondria has also been believed to contribute to migraine pathophysiology. Mitochondria carry out oxygen metabolism, and impairment of this organelle can lead to reduction in mitochondrial phosphorylation potential in between headaches.[23] The main role of mitochondria in the body is to produce adenosine tri-phosphate (ATP) through the electron transport chain. A pathogenic mutation of any kind can negatively affect the function of mitochondria in producing energy and in maintaining ion homeostasis in neurons leading to several abnormalities.[24] Reduction in mitochondrial phosphorylation means reduction in ATP production, therefore, in migraine patients, the energy metabolism in the brain might be less consistent.

Estrogen Withdrawal

Estrogen decline in the perimenstrual period along with prostaglandin release is a widely accepted theory for menstrual migraine in some women. Several biological conditions where estrogen decline occurs in women have been associated with migraine including the time period immediately before menses.[25] Decline in estrogen levels may increase susceptibility to prostaglandins which can cause neurogenic inflammation.[12] The inflammation can lead to increase in neuropeptides including CGRP.[12] Prostaglandin levels have been found to be elevated threefold times in the luteal phase of menstrual cycle, and even more during menstruation.[16] Although the pathophysiological difference between pure menstrual migraine and menstrually-related migraine needs further exploration, inflammatory response is generally accepted as the pathophysiological mechanism for menstrual migraine.[26] Considering menstrual cycles are irregular during perimenopause, hormonal fluctuations, especially of estrogen, increases the severity and frequency of migraine attacks in peri-menopausal women.[16]

Current Treatment

According to the United States Headache Consortium (USHC), patients with migraine should use migraine specific medications, but only two-third of those who have sought care from a health-care provider were prescribed migraine-specific treatments.[27] The three important factors of successful treatment of migraine are: 1) abortive therapy (treatment of acute attacks), 2) prevention of episodic attacks, and 3) reduction of the likelihood of episodic migraines progressing to chronic migraines.[27]

The purpose of abortive treatment is to abort the headaches and the associated symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDS), triptans and anti-CGRP antibodies are types of first-line abortive therapy which play a role in mitigating mild to moderate episodic migraines that occur a few times per month.[27]

On the other hand, the purpose of preventive therapy is to decrease the severity and frequency of future migraine headaches in individuals with more frequent attacks. For chronic migraine prophylaxis, beta-blockers and antiepileptic drugs are prescribed more frequently, and have shown 50% reduction in migraine frequency in half of the treated patients.[27] A new class of anti-CGRP antibodies has also been recently approved for prevention of migraine attacks.[28]

Along with these abortive and prevention medications, some minerals (such as magnesium) and vitamins (such as B2, B12, D) have shown promising results in migraine prevention.[29,30] Unlike the medications that may have side effects, use of nutraceuticals might be a reasonable choice as they may have less adverse effects. Micronutrients play a role in the prevention of migraine by reducing inflammatory factors, positively affecting the mitochondrial function and ameliorating antioxidant status.[4]

Magnesium

Magnesium, an essential micronutrient, is the second most abundant intracellular divalent cation in human bodies. It plays a crucial role as a cofactor in many enzymatic reactions in the body, is involved in many cellular functions,[31] and participates in the physiological function of the brain, heart, and skeletal muscles.[32] Following are some of

the processes in which magnesium acts as a cofactor: protein synthesis, cellular energy production and storage, reproduction, DNA and RNA synthesis, and stabilization of mitochondrial membranes.[33]

In an average adult human body, there is about 24 grams of magnesium of which 67% is located in the skeleton, 31% is present intracellularly (20% in the skeletal muscle), and 1 to 2% is present extracellularly. Of this extracellular amount, one half is ionized, and 20 to 30% is bound to protein.[31] The balance of magnesium in the body is maintained by the intestine, the bones, and the kidneys.[34]

Absorption of dietary magnesium occurs mainly in the small intestine, but some occurs in the large intestine. Two pathways for magnesium absorption have been identified in the human intestine. The first pathway is paracellular transport where magnesium is absorbed passively through the small spaces between the epithelial cells. In the second pathway (a tightly regulated transport pathway), magnesium is actively transported to the blood through the interior of the epithelial cell.[35]

The Recommended Dietary Allowance (RDA) for magnesium for female adults aged 19-30 years is 310 mg/day and for female adults aged 31+ years is 320 mg/day.[36] However, almost entire half (48%) of the U.S. population does not consume the suggested daily requirement of magnesium through foods, and the daily intake continues to decrease.[37]

A healthy diet including magnesium-rich foods can play a key role in fulfilling the body's need of magnesium. Magnesium can be found in many plant and animal foods, and foods with the highest amount of magnesium include unrefined (whole)

grains, vegetables (such as spinach and potato), nuts, seeds, and legumes.[33,36] Supplemental magnesium is another source through which body's magnesium needs can be met, especially for individuals that are deficient in magnesium or have low levels of magnesium.

The following sections will discuss several mechanisms where the role of magnesium has been recognized in the pathogenesis of migraine, as well as review the accumulated evidence of supplemental magnesium for preventing migraine symptoms in patients.

Magnesium in Relation to Migraine

The United States Headache Consortium (USHC) has categorized magnesium as a suggested mineral to prevent migraine.[38] It has also been recommended by the American Academy of Neurology and American Headache Society for migraine prevention, according to the 2nd highest level of evidence (Level B).[39]

Potential Mechanisms of Magnesium's Influence on Migraine

There are several opportunities for magnesium to influence migraine pathophysiology. Some key examples are discussed below.

Calcitonin Gene-Related Peptide

CGRP, a neuropeptide, is believed to play a significant role in the pathogenesis of migraine. After it is released from the activated trigeminal sensory nerves, it causes dilation of the intracranial blood vessels and may increase the transmission of nociceptive

information to the brain stem and spinal cord.[31] Serum CGRP levels have been observed to be high during a migraine attack, and levels return to normal when the migraine pain subsides.[31] Magnesium has shown to decrease the circulating level of CGRP,[31] and this could possibly be effective in aborting migraine attacks by decreasing the cranial vasodilation induced by CGRP.[20]

N-Methyl-D-Aspartate Blockage

A neurological function of magnesium is its interaction with the NMDA receptor. NMDA plays a role in the initiation and propagation of the CSD. Excessive activation of NMDA glutamate receptors releases glutamate in the cerebral cortex which induces CSD. Magnesium acts as a 'plug' in the NMDA receptor controlling the release of glutamatergic neurotransmission. Low levels of magnesium increase the effect of glutamate on the NMDA receptor which further releases more glutamate inducing glutamatergic-dependent transmission of a CSD.[31,38,40]

Mitochondrial Dysfunction

Magnesium cations bind to phospholipids present in the cell membrane, reducing their mobility in the membrane. This leads to the membrane being less fluid and less permeable.[41] Magnesium therefore plays a role in cellular energy production, i.e. maintenance of oxidative phosphorylation. When magnesium levels are low in the body, it affects the ATP production negatively because the permeability of the cell membranes increases.[42] A possible reason for migraine occurrence can be associated to decreased neuronal energy, and since magnesium plays a role in energy production, deficiency of this mineral in the body can be a plausible cause of migraine.

Estrogen and Progesterone

Magnesium concentration and female sex hormones (estrogen and progesterone) have been accounted to affect cerebral vascular smooth muscles.[43] Although the relationship between estrogen and magnesium needs to be further explored in context of menstrual migraine in women, a group of researchers found that exposure to higher concentration of estrogen and progesterone resulted in lower levels of magnesium concentration in single cultured canine cerebral vascular smooth muscle cells.[43] Serum levels of magnesium ions and total magnesium have also been found to be inversely related to estrogen concentration in menopausal women.[44] This limited evidence demonstrating an inverse relationship between female sex hormone concentration and magnesium status suggests the presence of a potential complicating factor in the metabolic relationship between magnesium and migraine pathophysiology.

Magnesium Deficiency

Magnesium deficiency has been associated with migraine. It can occur due to inadequate intake, gastrointestinal malabsorption, renal loss, and excretion due to stress.[40,45] Although the exact mechanism for magnesium deficiency in migraine patients is still unknown, evidence has suggested that prevalence of magnesium deficiency is higher in the migraine patients as compared to healthy controls.[45]

Evidence of Magnesium Supplementation for Alleviating Migraine Symptoms

Due to the potential role of magnesium in the pathophysiology of migraine, several studies have observed the role of magnesium in relation to frequency, severity, and duration of migraine attacks. They are presented and summarized in **Table 1**. However, the results are mixed,[46] and the possible reason for the discrepancy could partly be due to different magnesium formulations, dosages of magnesium supplements, and duration of supplementation. In addition, difference in the base magnesium levels in the serum of participants could also affect the end results obtained in the studies. [47]

Table 1. Summary of Studies that Observed Effects of Oral Supplemental Magnesium on Prophylaxis of Migraine

Study	**Design**	**Subjects (n)**	**Dose**	**Results**
Facchinetti et al.[48] (1991)	Double-blinded, placebo-controlled, study	Women with menstrual migraine (20) Age = 28 - 36 years old	360 mg/day of magnesium pyrrolidone carboxylic acid	Magnesium reduced number of days with headache
Taubert et al.[49] (1994)	Double-blinded, crossover design study	Migraine patients (43) Age = Unknown	600 mg/day of trimagnesium dictrate	Magnesium reduced incidence of migraine attacks
Peikert, Wilimzig, and Kohne-Volland[50] (1996)	Double-blinded randomized trial	Migraine patients (81) Age = 18 - 65 years old	600 mg/day of trimagnesium dicitrate	Magnesium reduced migraine attack frequency, number of days with migraine, and drug consumption for symptomatic treatment
Pfaffenrath et al.[51] (1996)	Randomized, double blinded, placebo-controlled study	Migraine patients (69) Age = 18 - 60 years old	486 mg/day of magnesium-u-aspartate-hydrochloride-trihydrate	Magnesium did not reduce number of days of migraine or migraine attacks

Trauninger et al.[52] (2002)	Clinical trial	Migraine patients (20) Age = 16 - 52 years old	3000 mg of magnesium lactate during 24-hour interictal period	24-hour urinary magnesium excretions were lower in migraine patients
Mauskop et al.[53] (2002)	Cohort Study	Women with menstrual migraine (61) Age = 20 - 51 years old	-	Ionized magnesium deficiency was higher during menstrual attack
Esfanjani et al.[47] (2012)	Clinical trial	Migraine patients (133) Age = 18 - 55 years old	500 mg/day of magnesium oxide	Magnesium reduced mean number of migraine frequency, severity, and migraine index, and mean migraine days/month
Köseoglu et al.[54] (2018)	Double blind, randomized, placebo controlled study	Migraine patients (30) Age = 22 - 55 years old	600 mg/day of magnesium citrate	Magnesium reduced migraine attack frequency and severity

The studies mentioned above focused on administering supplemental magnesium to the participants to observe its prophylactic effect on migraine symptoms. Most of the studies observed that after taking oral magnesium supplementation, migraine patients (including women with menstrual migraine) had improvements in various migraine symptoms. These results highlight that magnesium somehow contributes to the pathophysiology of migraine and plays some role in preventing and improving migraine symptoms. All the same time, these results also raise many questions regarding dietary magnesium in relation to migraine. It is possible that individuals with migraine have diets

that are deficient in magnesium, their dietary magnesium needs are different than the general population, or their body does not metabolize magnesium properly.

While evidence has helped us understand the effects of supplemental magnesium in improving and preventing migraine symptoms, the influence of dietary magnesium in relation to migraine remains relatively unexplored. A recent study by Slavin et al. observed the dietary magnesium intake of individuals with migraine (aged 20-50 years old), and the researchers found that the mean dietary magnesium intake of adults with migraine was lower than the RDA. According to their results, with increasing dietary magnesium intake, the odds of migraine decreased.[55] These outcomes indicate that dietary magnesium intake and dietary intake, in general, in the population with migraine needs to be further investigated as dietary magnesium might contribute in the prophylaxis of migraine.

The study above observed the intake of dietary magnesium in a large group of migraine patients and included both the genders, however, dietary magnesium intake in relation to migraine has not be explored exclusively in peri-menopausal women. Considering this population experiences higher frequency of migraine attacks due to inconsistent menstrual cycle and estrogen withdrawal, it is also important to understand their dietary magnesium intake and diets in general.

Migraine and Diet

Diet is one of the most important factors that can play a key role in preventing and improving chronic health conditions, such as diabetes and cardiovascular disease.[56] There

is a broad expectation that diet may have a similar impact for migraine disease, but evidence to strongly support this relationship remains sparse. Some patients experiencing migraine can associate its onset to many foods that act as triggers for the migraine attacks, but this evidence is anecdotal. Many of these patients are asked to monitor their diets and eliminate the foods that lead to migraine attacks. This can lead to nutritional deficiencies in the body, and a decreased diet quality.

For a healthy dietary patten, and nutritional balance, dietary guidelines have been established. The dietary recommendations for number of servings per day for different food groups are: fruits: 4 servings/day, vegetables: 5 servings/day, dairy: 3 servings/day, grains: 6 servings/day, and meat: 1 serving/day.[57]

Research suggests that individuals with migraine have lower dietary quality as compared to individuals without migraine. A few studies that have investigated the relationship between dietary quality/intake and migraine have found significantly lower Healthy Eating Index (HEI) scores[58] and lower dietary intake of fruits, vegetables and milk[59] in women with migraine as compared to women without migraine. Significant decreases in migraine disability scores, frequency of migraine attacks per month, and use of abortive drugs per month has also been observed in participants with migraine with increased consumption of whole-grain foods.[60] These results suggest that women with migraine may have less a balanced diet as compared to the women without migraine, and it may be possible that improvement in diet quality may alleviate the frequency and intensity of migraine in some patients, but further research is required for concrete evidence. These results also yield the question if there is bidirectional relationship

between migraine and diet, and if presence of migraine influences the dietary choices made by individuals.

Another dietary factor that has been associated with migraine is alcohol consumption. Alcohol is commonly reported as a trigger for migraine attacks.[61] Some studies indicate that patients with migraine tend to limit their alcohol consumption due to its triggering effect,[61] while other studies have observed higher intake of alcohol in patients with migraine as compared to individuals without migraine.[58] The contrasting results further need to be evaluated to understand the association between alcohol and migraine.

Assessment of Food and Nutrients

Dietary assessments are conducted by health professionals and researchers to observe and measure the usual dietary intake of individuals and are an important tool for both researching the potential diet-migraine connection and providing clinical nutrition care. They are tools that gather information about foods and drinks consumed by individuals over a specified time.[62] The foods and drinks are coded and processed to calculate energy intake, nutrient intake, and other dietary components[62] which give a deeper understanding of the nutritional and food group intakes of individuals. The overall dietary intake or dietary intake of individual nutrients and food groups helps researchers understand connection between human health and diet or disease and diet.

Twenty-four-hour recalls measure the food and beverage intake consumed by an individual in past 24 hours. It is a structured interview that helps collect detailed

information about not only the type of food and beverage consumed by the individual but also portion size and preparation method of food and beverage, and the time of the day it was consumed. It is usually administered by a trained interviewer, but automated self-administered tools have been developed.[62] The drawback of this method is that it does not capture day-to-day variation in diet unless multiple days are recorded, and it relies on participant memory. Hence, two or more recalls on non-consecutive day are required to estimate usual dietary intake.[63]

Food diaries collect dietary data consumed by individuals over one day or more days.[64] Food, beverage, and supplement intakes are self-reported by the individuals. Respondents are encouraged to record the foods, beverages, and supplements as they are consuming them throughout the day. Although the data is collected in real time and does not rely on memory, the coding of self-reported food record tends to be expensive.[64] Multi-day diets from food diaries are a reasonable choice for collecting reliable dietary intake data, but they require expertise, commitment, and respondent time.

Food Frequency Questionnaires (FFQs) ask participants to indicate their frequency of consumption of foods and beverages in pre-specified categories over a given period of time.[65] Additionally, they may also measure frequency and dosage of dietary supplement intake. The aim of administering a FFQ is to evaluate the usual dietary intake of individuals. Nutrient composition databases are often used to translate the food and beverage intake into nutrient intake and food group intake equivalents.[65]

FFQs are often used in nutritional epidemiological studies because they are time-saving and cost-effective for large sample sizes as compared to the other methods of

collecting dietary data. They capture and give insight on the long-term diet of individuals as compared to the 24-hour recalls and food diaries. Because they are collected at a single point in time, FFQs also pose lower burden on study participants. However, the limitations of FFQs include that they do not capture detailed information about specific foods and beverages and brands, they include a pre-specified food list that might not effectively reflect the dietary intake of the population, and they include systematic error due to incomplete or inappropriate list of foods and reliance on memory.[65]

FFQs need to be developed and validated for a specific population because diet can be influenced by ethnicity, socioeconomic status, and preferences of individuals.[66] Hence, validation of FFQ is critical to assess the dietary pattern of a given population. Sometimes they are validated against biomarkers which provide unbiased estimates of true intake, but this process is usually conducted in a small population and selected groups because it is expensive. A more frequently used method of validating a FFQ is evaluating it against other dietary intake methods such as 24-hour recalls and food records which helps understand if two individual instruments produce comparative results.[67]

Assessment of Magnesium

Assessment of individual macronutrients and micronutrients gives insight into the potential relationship between the specific health issue and nutrient of interest. Nutritional assessment is a process in which nutritional information is collected and interpreted to understand and draw conclusions regarding nutrition related health issues

experienced by individuals.[68] There are few ways in which magnesium levels can be assessed in individuals.

The gold standard to measure magnesium status of individuals is a magnesium tolerance test which determines magnesium retention (through urine collection) after intravenously administering magnesium. However, the invasive nature of this method makes it difficult to use.[69] Another clinical method of assessing magnesium is through plasma ionized magnesium which reflects the physiologically active magnesium, but it is still not known if it reflects the actual body stores.[69]

Other methods of assessing magnesium include serum magnesium concentration, urinary magnesium concentration, and dietary magnesium intake. About 30 to 40% of dietary magnesium is absorbed in the body, but it may vary based on the amount ingested and the composition of food.[69] Collecting dietary data is a commonly used method in epidemiological studies as compared to other clinical methods because the ease of administering dietary assessment tools allows data collection from a larger population.

FFQs can be a better choice for collecting dietary data in epidemiologic and clinical studies because they are easier to administer, provide valid results, and are less expensive.[70] Block and Willett FFQs or their modified versions are widely used in epidemiological studies to collect dietary data.[71] Block FFQ has been validated for estimating magnesium intake by Subar and colleagues.[71] The researchers in the study compared three different types of FFQs (Block FFQ, Diet History Questionnaire [DHQ] - a modified version of the Block FFQ, and Willett FFQ) to the gold standard multiple 24-hour recalls in their study. The median intake of magnesium in women according to the

24-hour recalls and Block FFQ was 235 mg/d and 232 mg/d respectively, and the median intake of magnesium in men according to the 24-hour recalls and Block FFQ was 350 mg/d and 282 mg/d respectively. The researchers measured the deattenuated correlation of magnesium between the results from the 24-hour recall and Block FFQ in women and men. In women, the unadjusted value and adjusted value was 0.60 and 0.81 respectively. In men, the unadjusted value and adjusted value was 0.64 and 0.76 respectively.[71] Considering these correlation values, there is a moderate to strong positive relation between 24-hour recalls and Block FFQ in calculating magnesium intake in men and women. The relationship, after adjustment, was higher in women than in men. The results of this study suggest that Block FFQ is a reliable method of assessing magnesium intake through diet.

Summary

Migraine is a neurological disorder that is more prevalent in women as compared to men.[15] During the peri-menopausal stage of life, women experience more episodes of migraine attacks due to fluctuating withdrawal of estrogen and release of prostaglandins.[17] An inverse correlation between estrogen and magnesium has been observed in serum levels of women with migraine,[44] and supplemental magnesium has shown to improve migraine symptoms in migraine patients [47,50,54] and menstrual migraine patients.[48,53] However, dietary magnesium has not been explored enough to understand the relationship between magnesium and migraine occurrence, especially in pre- and peri-menopausal women. Supplemental magnesium has been observed to ameliorate migraine

symptoms, yielding the question of whether patients with migraine consume adequate dietary magnesium in the first place. Hence, the dietary magnesium intake of pre- and peri-menopausal women needs further exploration to understand if the dietary magnesium intake has any relationship with odds of migraine. Research has also shown that patients with migraine have poor diets as compared to individuals without migraine,[58,59] but literature observing dietary quality of pre- and peri-menopausal women with menstrual migraine and non-menstrual migraine is scarce.

CHAPTER 2. A CROSS-SECTIONAL ANALYSIS OF MIGRAINE AND DIETARY MAGNESIUM INTAKE IN THE STUDY OF WOMEN'S HEALTH ACROSS THE NATION (SWAN)

Rationale and Significance

Several randomized controlled trials, as mentioned in the literature review, have indicated the possible role of supplemental magnesium in prophylaxis of migraine and menstrual migraine.[47,48,50,53] However, baseline dietary magnesium intake in relation to migraine has not been assessed extensively, especially in pre- and peri-menopausal women.

Previous studies that investigated the dietary pattern and dietary quality of patients with migraine found that the intake of different food groups (fruit, vegetable, legumes, dairy) was lower in individuals with migraine as compared to those without migraine.[58] In general, these food groups contain foods high in magnesium. Thus, it appears that individuals with migraine are consuming low amounts of food groups high in magnesium. However, dietary magnesium intake in relation to migraine in pre-and peri-menopausal women has not been reported in the literature to date.

Furthermore, deficiency of magnesium has been associated with menstrual migraine[53] and migraine[52] in general. Although the reason for presence of magnesium deficiency in migraine patients remains unclear, possible etiologies for this deficiency include reduced dietary intake, malabsorption in intestine, defect in transport membrane, stress, genetic impairment in cell regulation, and hormonal status (in women).[52] This may indicate that individuals with migraine may require higher amounts of dietary magnesium

than the RDA of 320 mg/day. Additionally, dietary magnesium might not only address migraine symptoms, but it may also aid in other comorbidities that are associated with migraine such as cardiovascular disease, hypertension, gastrointestinal disorders, and depression.[27]

Studies have found that during peri-menopause, women with migraine have increased vulnerability to migraine headache attacks.[17] There are very few studies that have examined prophylaxis of menstrual migraine in relation to magnesium supplementation, and the subjects included in those studies had a wide age range (20 – 51 years old).[48,53] One study that did explore the association between dietary magnesium and migraine also focused on a wide age range (20 – 50 years old), and included both male and female migraine patients.[55] Lack of studies examining migraine and menstrual migraine in relation to dietary magnesium in pre- and peri-menopausal women warrants investigation considering the withdrawal of estrogen in that stage of life leads to increased headaches experienced by the women. Furthermore, both magnesium concentration and sex hormones have been observed to alter cerebral vascular reactivity which is associated with migraine,[43] and inverse correlation has also been observed between serum levels of magnesium and estrogen in menopausal women.[44] These associations highlight the vital need to understand the dietary magnesium intake of women in relation to migraine and menstrual migraine, as well as menopausal status. Therefore, to address the gap in the literature, a secondary analysis was carried out using the data from the Study of Women's Health Across the Nation (SWAN).

Objectives

The overall aim of our study was to observe the association between dietary magnesium intake and migraine status in pre- and peri-menopausal women.

Hypothesis: Pre- and peri-menopausal women who report consuming high levels of dietary magnesium will have lower odds of migraine than their counterparts who consume low levels of dietary magnesium.

Methods

Study of Women's Health Across the Nation (SWAN)

Our study used publicly available data collected for SWAN. SWAN was carried out to study women's health as they approach the years of pre- and peri-menopause. It is a longitudinal and epidemiological study that took place at multiple sites in the United States. The study began in 1994 and selected participants in three phases. The SWAN study protocols can be found here (https://www.swanstudy.org/about/swan-history/). Between the years 1996 and 1997, 3,302 participants joined SWAN through designated research centers located at Ann Arbor, MI (University of Michigan), Boston, MA (Massachusetts General Hospital), Chicago, IL (Rush University Medical Center), Alameda and Contra Costa County, CA (University of California Davis and Kaiser Permanente), Los Angeles, CA (University of California at Los Angeles), Jersey City, NJ (Albert Einstein College of Medicine), and Pittsburgh, PA (University of Pittsburgh).[72]

Along with other health information, SWAN also collected dietary information from the participants through a 137-item FFQ.[73] The assessment was a modified version

of 1995 Block Food Frequency Questionnaire that was administered at baseline to collect data of eating habits and average use of foods.[74] The questionnaire was administered in four languages (English, Spanish, Chinese, or Japanese), and collected usual dietary pattern from previous year.

Subjects

Our study used the publicly available baseline data collected by SWAN researchers in 1996-1997.[75,76] A total of 3,302 women were included in our study, and their age ranged from 42-52 years old. Participants who had missing data (including those who refused to answer questions), and those who chose "do not know" as the answer for the following characteristics were excluded from our analysis: age, BMI, menstrual status, total family income, migraine status, migraine medication use, alcohol intake, dietary magnesium, daily calorie intake, daily fruit serving, daily vegetable serving, daily dairy serving, daily grain serving, and daily meat serving. Pre- and peri-menopausal women reporting use of hormones (including birth control pills, estrogen, progestin, patches, and vaginal hormones) were excluded. Participants reporting alcohol intake of >35 drinks per week (drinks/wk) were also excluded. The majority of exclusions occurred due to missing dietary data. After all the exclusions (n=280), a total of 3,022 were included in this secondary analysis (**Figure 1**).

At the time of the original SWAN study, participants provided written consent to participate. We employed a secondary analysis using de-identified publicly available SWAN data and did not include any personally identifiable information of participants. The use of publicly available, de-identified data is not subject to further review by the

George Mason University Institutional Review Board, and therefore no further approval was required for this study.

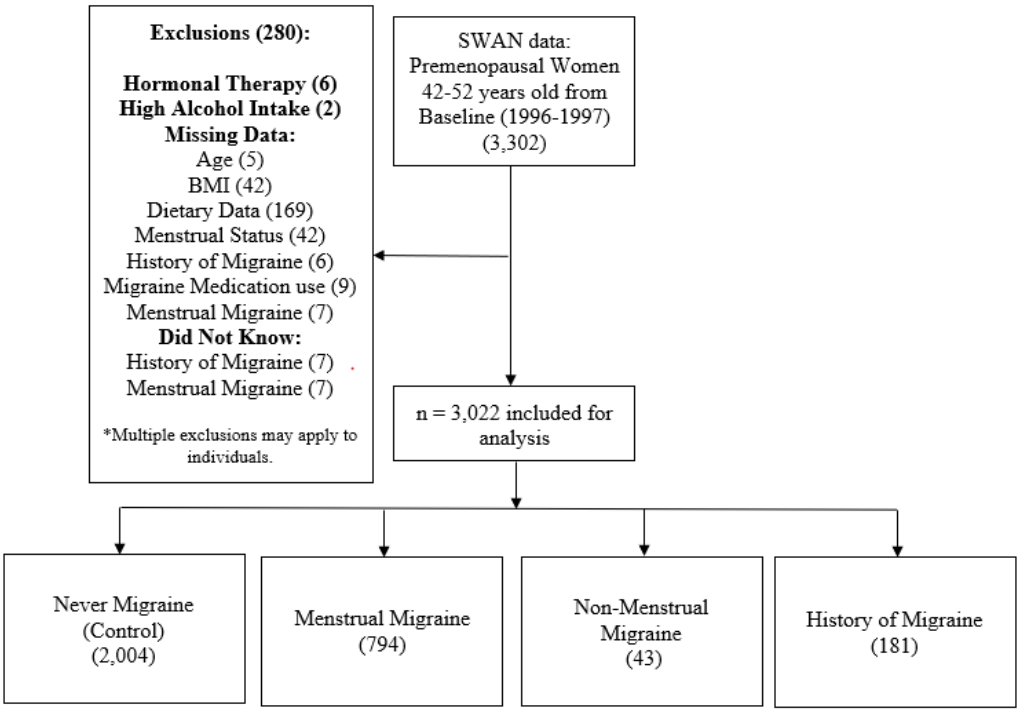

Figure 1. Exclusion and Inclusion Criteria

Demographics

For this analysis, the following demographic variables were considered: age, race/ethnicity, total family income, and health insurance. Race/ethnicity categories from the SWAN dataset were used, except the Chinese/Chinese American and Japanese/Japanese American groups were combined in our analysis due to small numbers. The categories used in this analysis were: Black/African American, Chinese/Chinese American or Japanese/Japanese American, Caucasian/White Non-

Hispanic, and Hispanic. Four categories were also created for the total family annual income variable: less than $19,999, $20,000 to $49,999, $50,000 to $99,999, and $100,000 or more. Health insurance was categorized in three groups: private insurance only or combination of private and public, public insurance only or military insurance or other insurance, and no insurance or missing insurance or unknown.

Anthropometrics

Anthropometric measurements assessed by the original study included weight and height, and BMI was calculated by dividing weight (in kilograms) by square of height (in meters).[76] For our analysis, the BMI was categorized into three categories: underweight and normal weight (n=1183) (<25 kg/m^2), overweight (n=780) (25-<30 kg/m^2), and obese (n=972) (≥30 kg/m^2). The underweight category contained few individuals (n=48) and was thus combined with the normal weight category for analysis.

Migraine Assessment

Migraine status and migraine medication use was determined according to each participant's answers to SWAN's in-person interview questions at baseline. All the participants were asked the following question at baseline:

1. Has a doctor, nurse practitioner, or other health care provider ever told you that you have any of the following conditions: Migraine headaches?[76]

If the participants answered yes to the above migraine question, they were asked the following question:

2. Do you currently take medication for migraine headaches?[76]

Menstrual migraine status was determined from the following separate question:

3. During the last year, have you had any of the following during at least half of your menstrual periods or in the week before them: Severe headaches (including migraine)?[76]

Based on the answers of the above three questions at baseline, the participants in our study were divided into four groups for analysis: menstrual migraine, non-menstrual migraine, history of migraine, and never migraine (control).

Table 2. Criteria for Participants to be Placed in Individual Analysis Groups

Migraine Status	**Criteria**
Menstrual Migraine	Participants Reported: • Yes, to taking migraine medication, and • Yes, to having symptoms of menstrual migraine OR • No, to taking migraine medication or medication question was not applicable, and • Yes, to having symptoms of menstrual migraine
Non-Menstrual Migraine	Participants Reported: • Yes, to taking migraine medication, and • No, to having symptoms of menstrual migraine
History of Migraine	Participants Reported: • No, to taking migraine medication, and • No, to having symptoms of menstrual migraine, and • Yes, to being diagnosed with migraine in the past
Never Migraine (Control)	Participants Reported: • No, to having symptoms of menstrual migraine, and • No, to being diagnosed with migraine in the past

Based on their responses (**Table 2**), women classified in the menstrual migraine group included women with pure menstrual migraine (i.e., having migraine exclusively in perimenstrual period) or menstrually-related migraine (i.e. having migraine both in

perimenstrual period and at other times of the cycle). Women classified in the non-menstrual migraine group included women who had migraine at other times in the cycle but not during perimenstrual period. Women were classified in the history of migraine group on the assumption that they were diagnosed with migraine in the past but since they were not taking migraine medication at the time data was collected, they did not have active symptoms of migraine in the past year. Lastly, women classified in the never migraine group included women who did not have symptoms of migraine in the perimenstrual period, and they were never diagnosed with migraine in the past.

Dietary Assessment

Daily intake amounts of dietary magnesium and food groups (fruit, vegetable, dairy, grain & meat) servings was estimated from the Block FFQ that was administered by the original study at baseline (1996-1997).[76] The publicly available SWAN data did not contain any information regarding magnesium supplementation.

Statistical Analysis

The statistical analysis was carried out using the data analysis tool, Stata version 16.1 (College Station, Texas).[77] Descriptive categorical data including BMI, race/ethnicity, menstrual status, alcohol consumption, total family income, and health insurance were reported as frequencies and percent distribution. Descriptive continuous data including age, magnesium, fruit serving, vegetable serving, dairy serving, grain serving, and meat serving were reported as means and standard errors.

Multinomial logistic regression models were used to model migraine status with dietary magnesium intake as the predictor variable and the “never migraine” group as the

reference group. The potential confounding factors that were adjusted in different models included: race/ethnicity, BMI, menstrual status, alcohol consumption, total family income, and health insurance. Adjusted odds ratio (OR) and 95% confidence intervals (CI) were calculated for the migraine status groups, and a p-trend was computed using median regression as similarly performed by Slavin and colleagues.[55] A p-value less than 0.05 was considered to be significantly different for the statistical tests.

Results

Participants were classified into four groups: menstrual migraine (n=794), non-menstrual migraine (n=43), history of migraine (n=181), and control (n=2,004) (**Table 3**). Demographic characteristics are summarized in **Table 3**. The mean age and standard error of the total sample was 45.83 ± 0.05 years. In terms of menstrual status, 54.2% of the women in the total sample were pre-menopausal and 45.8% were early peri-menopausal. However, in menstrual migraine group, 52.4% of the women were early peri-menopausal and 47.6% were pre-menopausal. In terms of alcohol consumption, 7.5% of the total sample consumed 7-35 drinks/wk, but from those in the non-menstrual group, 11.6% consumed 7-35 drinks/wk.

The total mean dietary intake and standard error of dietary magnesium in the total sample was 258.49 ± 1.74 mg/day. When the groups were categorized, the highest mean intake of 286.08 ± 15.37 mg/day was observed in the non-menstrual migraine group (**Table 3**).

The mean and standard error servings per day of fruit, vegetable, dairy, grain, and meat in the total sample were as follows: 1.32 ± 0.02, 1.77 ± 0.02, 1.38 ± 0.02, 5.21 ± 0.05, and 1.81 ± 0.02, respectively (**Table 3**).

Distribution of participants in magnesium group quartiles and food group quartiles can be found in **Table 4**. The ranges of dietary magnesium intake quartiles were: Q1 (68.6-190.0 mg), Q2 (190.1-244.6 mg), Q3 (244.6-312.3 mg), and Q4 (312.7-915.9 mg).

Table 3. Demographic Characteristics of Participants According to Migraine Status (SWAN)

	Total		**Menstrual Migraine**		**Non-Menstrual Migraine**		**History of Migraine**		**Non-Migraine (Control)**	
	(n=3,022)		**(n=794)**		**(n=43)**		**(n=181)**		**(n=2,004)**	
	Mean [SE] or n (%)		**Mean [SE] or n (%)**		**Mean [SE] or n (%)**		**Mean [SE] or n (%)**		**Mean [SE] or n (%)**	
Age, years, mean	45.83 [0.05]		45.69 [0.09]		45.42 [0.38]		46.02 [0.22]		45.88 [0.06]	
BMI (kg/m^2)										
<25	1213	(40.1)	300	(37.8)	14	(32.6)	59	(32.6)	840	(41.9)
25 - <30	814	(26.9)	210	(26.5)	8	(18.6)	52	(28.7)	544	(27.2)
≥30	995	(32.9)	284	(35.8)	21	(48.8)	70	(38.7)	620	(30.9)
Race/Ethnicity										
Black/African American	826	(27.3)	211	(26.6)	11	(25.9)	50	(27.6)	554	(27.6)
Chinese/Chinese American and Japanese/Japanese American	488	(16.2)	102	(12.9)	6	(14.0)	16	(8.8)	364	(18.2)
Caucasian/White Non-Hispanic	1454	(48.1)	375	(47.2)	26	(60.5)	105	(58.0)	948	(47.3)
Hispanic	254	(8.4)	106	(13.4)	0	(0.00)	10	(5.5)	138	(6.9)
Menstrual Status										
Early Peri	1385	(45.8)	416	(52.4)	19	(44.2)	75	(41.4)	875	(43.7)
Pre-menopausal	1637	(54.2)	378	(47.6)	24	(55.8)	106	(58.6)	1129	(56.3)
Alcohol Consumption										
<1 drinks/wk	2194	(72.6)	609	(76.7)	26	(60.5)	135	(74.6)	1424	(71.1)
1-7 drinks/wk	601	(19.9)	149	(18.8)	12	(27.9)	36	(19.9)	404	(20.2)
7-35 drinks/wk	227	(7.5)	36	(4.5)	5	(11.6)	10	(5.5)	176	(8.8)
Total Family Income										

Less than $19,999	419	(13.9)	150	(18.9)	5	(11.6)	22	(12.2)	242	(12.1)
$20,000 to $49,999	1002	(33.2)	255	(32.1)	15	(34.9)	76	(42.0)	656	(32.7)
$50,000 to $99,999	1080	(35.7)	269	(33.9)	13	(30.2)	59	(32.6)	739	(36.9)
$100,000 or more	438	(14.5)	97	(12.2)	9	(20.9)	22	(12.2)	310	(15.5)
Refused, Do not know or Missing	83	(2.8)	23	(2.9)	1	(2.3)	2	(1.1)	57	(2.8)
Insurance										
Private Insurance Only OR Combination of Private & Public	2465	(81.6)	588	(74.1)	40	(93.0)	142	(78.5)	1695	(84.6)
Public Insurance Only OR Military Insurance OR Other	300	(9.9)	108	(13.6)	2	(4.7)	21	(11.6)	169	(8.4)
No insurance or Missing or Unknown[a]	257	(8.5)	98	(12.3)	1	(2.3)	18	(9.9)	140	(7.0)
Magnesium Intake, mg/day, mean	258.49 [1.74]		261.19 [3.55]		286.08 [15.37]		269.40 [7.85]		255.84 [2.07]	
Fruit Intake, servings/day, mean	1.32 [0.02]		1.32 [0.03]		1.14 [0.11]		1.25 [0.07]		1.33 [0.02]	
Vegetable Intake, servings/day, mean	1.77 [0.02]		1.72 [0.05]		1.76 [0.15]		1.93 [0.12]		1.77 [0.03]	
Dairy Intake, servings/day, mean	1.38 [0.02]		1.43 [0.04]		1.69 [0.29]		1.53 [0.10]		1.34 [0.03]	
Grain Intake, servings/day, mean	5.21 [0.05]		5.16 [0.09]		5.81 [0.49]		5.29 [0.22]		5.21 [0.06]	
Meat Intake, servings/day, mean	1.81 [0.02]		1.83 [0.03]		1.81 [0.13]		1.86 [0.07]		1.79 [0.02]	

[a] Fewer than 15 were missing or were unknown

BMI: body mass index; SWAN: Study of Women's Health Across the Nation; SE: standard error

Table 4. Distribution of Participants in Magnesium and Food Group Intake Quartiles Based on Migraine Status

	Menstrual Migraine (n=794)		**Non-Menstrual Migraine (n=43)**		**History of Migraine (n=181)**		**Non-Migraine (Control) (n=2,004)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Magnesium Intake, mg/day								
Q1 (68.6-190.0)	195	(24.6)	7	(16.3)	44	(24.3)	510	(25.5)
Q2 (190.1-244.6)	191	(24.1)	9	(20.9)	38	(21.0)	517	(25.8)
Q3 (244.6-312.3)	208	(26.2)	9	(20.9)	50	(27.6)	489	(24.4)
Q4 (312.7-915.9)	200	(25.2)	18	(41.9)	49	(27.1)	488	(24.4)
Fruit Serving/day								
Q1 (0.0 - 0.6)	225	(28.3)	13	(30.2)	59	(32.6)	508	(25.4)
Q2 (0.7 – 1.1)	184	(23.2)	12	(27.9)	40	(22.1)	473	(23.6)
Q3 (1.2 – 1.8)	200	(25.2)	12	(27.9)	44	(24.3)	560	(27.9)
Q4 (1.9 – 5.9)	185	(23.3)	6	(14.0)	38	(21.0)	463	(23.1)
Vegetable Serving/day								
Q1 (0.0 - 0.9)	216	(27.2)	7	(16.3)	44	(24.3)	489	(24.4)
Q2 (0.9 – 1.3)	205	(25.8)	11	(25.6)	40	(22.1)	499	(24.9)
Q3 (1.3 – 2.2)	179	(22.5)	12	(27.9)	43	(23.8)	522	(26.1)
Q4 (2.2 – 10.6)	194	(24.4)	13	(30.2)	54	(29.8)	494	(24.7)
Dairy Serving/day								
Q1 (0.0 - 0.5)	181	(22.8)	8	(18.6)	42	(23.2)	525	(26.2)
Q2 (0.5 – 1.1)	201	(25.3)	15	(34.9)	45	(24.9)	494	(24.7)
Q3 (1.1 – 1.8)	207	(26.1)	10	(23.3)	39	(21.6)	500	(25.0)
Q4 (1.8 – 11.6)	205	(25.8)	10	(23.3)	55	(30.4)	485	(24.2)
Grain Serving/day								
Q1 (0.2 – 3.3)	192	(24.2)	11	(25.6)	54	(29.8)	499	(24.9)
Q2 (3.3 – 4.7)	208	(26.2)	12	(27.9)	36	(19.9)	499	(24.9)

Q3 (4.7 – 6.5)	187	(23.6)	5	(11.6)	45	(24.9)	519	(25.9)
Q4 (6.5 – 27.5)	207	(26.1)	15	(34.9)	46	(25.4)	487	(24.3)
Meat Serving/day								
Q1 (0.1 – 1.2)	205	(25.8)	10	(23.3)	44	(24.3)	497	(24.8)
Q2 (1.2 – 1.6)	178	(22.4)	13	(30.2)	48	(26.5)	516	(25.8)
Q3 (1.7 – 2.2)	201	(25.3)	8	(18.6)	39	(21.6)	508	(25.4)
Q4 (2.2 – 7.9)	210	(26.5)	12	(27.9)	50	(27.6)	483	(24.1)

A statistically significant trend was observed in the non-menstrual migraine group in the unadjusted dietary magnesium intake model (p_{trend}=0.014) (**Table 5**) where increasing quartiles of magnesium indicated increasing odds of non-menstrual migraine. Women consuming dietary magnesium intake in the range of Q4 were 2.69-times more likely to be in the non-menstrual migraine group as compared to the control group (OR=2.69 [1.11-6.49]). No statistically significant difference was observed in the menstrual migraine group and the history of migraine group in the unadjusted model.

Table 5. Multinomial Logistic Regression Analysis for Odds of Migraine Status[a] as Predicted by Dietary Magnesium Intake (Unadjusted)

	Menstrual Migraine		**Non-Menstrual Migraine**		**History of Migraine**	
	(n=794)		**(n=43)**		**(n=181)**	
Predictor Variable	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Magnesium Intake, mg/day						
P-trend[b]	0.385		0.014		0.272	
Q1 (68.6-190.0)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (190.1-244.6)	0.97	(0.76-1.22)	1.27	(0.47-3.43)	0.85	(0.54-1.34)
Q3 (244.6-312.3)	1.11	(0.88-1.40)	1.34	(0.50-3.63)	1.19	(0.78-1.81
Q4 (312.7-915.9)	1.07	(0.85-1.35)	2.69	(1.11-6.49)	1.16	(0.76-1.78)

[a] Reference category is: Never Migraine group

[b] p_{trend}: Median regression, statistical significance set at $p<0.05$

CI: 95% Confidence Interval; OR: Odds ratio.

In the model where demographics were adjusted (**Table 6**), and in the model where food groups, magnesium and demographics were adjusted (**Table 7**), the odds of being obese as compared to the control group were higher for all the groups. Obese women were 2.68-times and 2.87-times more likely to be in the non-menstrual migraine group than the control group in both the models, respectively.

Though not statistically significant, in the model where demographics were adjusted (**Table 6**), and in the model where food groups, magnesium and demographics were adjusted (**Table 7)** women reporting 7-35 drinks/wk were 54% and 50% (respectively) more likely to be in the non-menstrual migraine group than the control group.

In both the models (**Table 6 and Table 7**), pre-menopausal women had 29% lower odds of being in menstrual migraine group as compared to control (OR=0.71 [0.60-0.85]).

In both the models (**Table 6 and Table 7**), women reporting public insurance only (or military insurance or other insurance) and no insurance (or missing or unknown) had 60% and 68% (respectively) lower odds of being in the non-menstrual migraine group as compared to the control, but the results were not statistically significant.

In the demographics adjusted model (**Table 6**), and the food groups, magnesium, and demographics adjusted model (**Table 7**), the association between dietary magnesium quartiles and the non-menstrual migraine group did not change (p_{trend}=0.025, and p_{trend}=0.002, respectively).

In the model where food groups, magnesium, and demographics were adjusted (**Table 7**), the association between fruit servings/day and the non-menstrual migraine group and the history of migraine group was statistically significant (p_{trend}=0.025 and p_{trend}=0.029 (respectively)). Women consuming fruit servings in Q4 were 68% less likely to have non-menstrual migraine as compared to the controls (OR=0.32 [0.11-0.92]). Women consuming fruit servings in Q3 and Q4 were 37% (OR=0.63 [0.41-0.96]) and 40% (OR=0.60 [0.37-0.96]), respectively, less likely to have history of migraine as compared to the controls.

Table 6. Multinomial Logistic Regression Analysis for Odds of Migraine Status[a] as Predicted by Dietary Magnesium Intake and Adjusted for Demographic Characteristics

	Menstrual Migraine		**Non-Menstrual Migraine**		**History of Migraine**	
	(n=794)		**(n=43)**		**(n=181)**	
Predictor Variable	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Magnesium Intake, mg/day						
P-trend[b]	0.142		0.025		0.217	
Q1 (68.6-190.0)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (190.1-244.6)	0.98	(0.77-1.25)	1.28	(0.47-3.48)	0.87	(0.55-1.37)
Q3 (244.6-312.3)	1.15	(0.91-1.46)	1.23	(0.45-3.36)	1.24	(0.81-1.90)
Q4 (312.7-915.9)	1.15	(0.91-1.46)	2.51	(1.03-6.13)	1.20	(0.78-1.85)
BMI (kg/m^2)						
<25	1.00 (ref)		1.00 (ref)		1.00 (ref)	
25 - <30	0.94	(0.75-1.17)	1.04	(0.42-2.57)	1.27	(0.85-1.90)
≥30	1.03	(0.83-1.27)	2.68	(1.22-5.87)	1.34	(0.90-1.99)
Race/Ethnicity						
Black/African American	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Chinese/Chinese American OR Japanese/Japanese American	0.84	(0.62-1.14)	1.26	(0.40-3.97)	0.63	(0.34-1.18)
Caucasian/White Non-Hispanic	1.18	(0.95-1.46)	1.50	(0.70-3.22)	1.42	(0.97-2.07)
Hispanic	1.75	(1.26-2.44)	---	---	0.68	(0.32-1.44)
Menstrual Status						
Early Peri	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Pre-menopausal	0.71	(0.60-0.85)	1.06	(0.57-1.96)	1.17	(0.86-1.60)
Alcohol Consumption						
<1 drinks/wk	1.00 (ref)		1.00 (ref)		1.00 (ref)	
1-7 drinks/wk	0.83	(0.67-1.03)	1.59	(0.78-3.25)	0.91	(0.61-1.35)
7-35 drinks/wk	0.47	(0.32-0.69)	1.54	(0.56-4.22)	0.59	(0.30-1.16)
Total Family Income						

Less than $19,999	1.00 (ref)		1.00 (ref)		1.00 (ref)	
$20,000 to $49,999	0.92	(0.69-1.23)	0.61	(0.20-1.88)	1.55	(0.88-2.73)
$50,000 to $99,999	0.97	(0.71-1.32)	0.41	(0.13-1.33)	1.12	(0.61-2.08)
$100,000 or more	0.88	(0.61-1.27)	0.74	(0.21-2.60)	1.08	(0.53-2.21)
Refused, Do not know or Missing	0.91	(0.53-1.58)	0.60	(0.07-5.47)	0.45	(0.10-2.02)
Insurance						
Private Insurance Only OR Combination of Private & Public	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Public Insurance Only OR Military Insurance OR Other	1.57	(1.16-2.11)	0.40	(0.08-1.85)	1.62	(0.95-2.77)
No insurance or Missing or Unknown[c]	1.56	(1.12-2.17)	0.32	(0.04-2.58)	1.87	(1.03-3.40)

[a] Reference category is: Never Migraine group.

[b] p_{trend}: Median regression, statistical significance set at $p<0.05$

[c] Fewer than 15 were missing or were unknown

BMI: Body Mass Index; CI: 95% Confidence Interval; OR: Odds ratio.

Table 7. Multinomial Logistic Regression Analysis for Odds of Migraine Status[a] as Predicted by Dietary Magnesium Intake and Adjusted for Food Group Intake and Demographic Characteristics

	Menstrual Migraine		**Non-Menstrual Migraine**		**History of Migraine**	
	(n=794)		**(n=43)**		**(n=181)**	
Predictor Variable	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Magnesium Intake, mg/day						
P-trend[b]	0.389		0.002		0.417	
Q1 (68.6-190.0)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (190.1-244.6)	1.01	(0.78-1.32)	1.93	(0.66-5.63)	0.99	(0.60-1.63)
Q3 (244.6-312.3)	1.19	(0.88-1.60)	2.69	(0.84-8.58)	1.43	(0.83-2.44)
Q4 (312.7-915.9)	1.14	(0.80-1.64)	7.88	(2.25-27.59)	1.24	(0.64-2.38)
Fruit Serving/day						
P-trend[b]	0.152		0.025		0.029	
Q1 (0.0 - 0.6)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (0.7 – 1.1)	0.89	(0.70-1.13)	1.00	(0.44-2.31)	0.73	(0.48-1.13)
Q3 (1.2 – 1.8)	0.79	(0.62-1.00)	0.72	(0.31-1.66)	0.63	(0.41-0.96)
Q4 (1.9 – 5.9)	0.82	(0.64-1.07)	0.32	(0.11-0.92)	0.60	(0.37-0.96)
Vegetable Serving/day						
P-trend[b]	0.413		0.623		0.060	
Q1 (0.0 - 0.9)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (0.9 – 1.3)	1.05	(0.83-1.34)	1.59	(0.60-4.25)	1.02	(0.65-1.62)
Q3 (1.3 – 2.2)	0.97	(0.75-1.25)	1.47	(0.54-4.02)	1.08	(0.68-1.74)
Q4 (2.2 – 10.6)	1.13	(0.85-1.49)	1.53	(0.53-4.40)	1.51	(0.92-2.48)
Dairy Serving/day						
P-trend[b]	0.793		0.169		0.748	
Q1 (0.0 - 0.5)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (0.5 – 1.1)	1.08	(0.84-1.38)	1.80	(0.73-4.42)	1.04	(0.66-1.64)

Q3 (1.1 – 1.8)	1.04	(0.80-1.34)	0.97	(0.35-2.63)	0.82	(0.50-1.34)
Q4 (1.8 – 11.6)	0.99	(0.75-1.32)	0.67	(0.23-1.98)	1.09	(0.66-1.80)
Grain Serving/day						
P-trend[b]	0.140		0.583		0.634	
Q1 (0.2 – 3.3)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (3.3 – 4.7)	1.11	(0.87-1.42)	1.04	(0.44-2.48)	0.67	(0.42-1.06)
Q3 (4.7 – 6.5)	1.00	(0.77-1.30)	0.31	(0.10-0.97)	0.76	(0.48-1.21)
Q4 (6.5 – 27.5)	1.27	(0.96-1.67)	0.79	(0.31-2.05)	0.84	(0.51-1.39)
Meat Serving/day						
P-trend[b]	0.552		0.225		0.889	
Q1 (0.1 – 1.2)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (1.2 – 1.6)	0.78	(0.61-1.00)	0.88	(0.37-2.12)	1.01	(0.65-1.57)
Q3 (1.7 – 2.2)	0.89	(0.69-1.14)	0.48	(0.17-1.35)	0.84	(0.52-1.37)
Q4 (2.2 – 7.9)	0.87	(0.65-1.15)	0.53	(0.18-1.51)	1.08	(0.64-1.81)
BMI (kg/m^2)						
<25	1.00 (ref)		1.00 (ref)		1.00 (ref)	
25 - <30	0.94	(0.76-1.17)	1.03	(0.41-2.59)	1.28	(0.86-1.92)
≥30	1.03	(0.83-1.29)	2.87	(1.26-6.51)	1.30	(0.86-1.94)
Race/Ethnicity						
Black/African American	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Chinese/Chinese American OR Japanese/Japanese American	0.79	(0.57-1.08)	1.09	(0.33-3.60)	0.55	(0.29-1.05)
Caucasian/White Non-Hispanic	1.17	(0.93-1.47)	1.40	(0.62-3.15)	1.41	(0.94-2.10)
Hispanic	1.85	(1.31-2.61)	---	---	0.74	(0.34-1.61)
Menstrual Status						
Early Peri	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Pre-menopausal	0.71	(0.60-0.85)	1.15	(0.61-2.16)	1.16	(0.84-1.59)
Alcohol Consumption						
<1 drinks/wk	1.00 (ref)		1.00 (ref)		1.00 (ref)	

1-7 drinks/wk	0.84	(0.67-1.04)	1.58	(0.76-3.29)	0.89	(0.60-1.33)
7-35 drinks/wk	0.47	(0.32-0.69)	1.50	(0.54-4.15)	0.58	(0.30-1.14)
Total Family Income						
Less than $19,999	1.00 (ref)		1.00 (ref)		1.00 (ref)	
$20,000 to $49,999	0.93	(0.69-1.25)	0.64	(0.21-2.02)	1.57	(0.89-2.77)
$50,000 to $99,999	0.99	(0.72-1.36)	0.43	(0.13-1.42)	1.17	(0.63-2.17)
$100,000 or more	0.89	(0.61-1.29)	0.78	(0.22-2.80)	1.11	(0.54-2.28)
Refused, Do not know or Missing	0.90	(0.52-1.57)	0.53	(0.56-4.99)	0.44	(0.10-1.97)
Insurance						
Private Insurance Only OR Combination of Private & Public	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Public Insurance Only OR Military Insurance OR Other	1.54	(1.14-2.07)	0.39	(0.08-1.81)	1.58	(0.91-2.71)
No insurance or Missing or Unknown[c]	1.59	(1.14-2.22)	0.32	(0.04-2.63)	1.81	(0.99-3.30)

[a] Reference category is: Never Migraine group.

[b] p_{trend}: Median regression, statistical significance set at $p<0.05$

[c] Fewer than 15 were missing or were unknown

BMI: Body Mass Index; CI: 95% Confidence Interval; OR: Odds ratio.

In the model where food groups and magnesium were adjusted (**Table 8**), the association between dietary magnesium quartiles and the non-menstrual migraine group did not change (p_{trend}=0.001).

In the same model (**Table 8**), both the non-menstrual migraine group and history of migraine had a statistically significant difference for fruit servings per day (p_{trend}=0.014 and p_{trend}=0.030, respectively). Participants in the non-menstrual migraine group consuming fruit servings in Q4 were 70% less likely to have non-menstrual migraine as compared to controls (OR=0.30 [0.11-0.82]). Participants in the history of migraine group consuming fruit servings in Q3 and Q4 were 37% and 39% (respectively) less likely to have a history of migraine as compared to controls (OR=0.63 [0.41-0.96] and OR=0.61 [0.38-0.97]). Women in all the quartiles of fruit servings and vegetable servings had lower odds of being in the menstrual migraine group, but the results were not statistically significant.

Table 8. Multinomial Logistic Regression Analysis for Odds of Migraine Status[a] as Predicted by Dietary Magnesium Intake and Adjusted for Food Group Intake

	Menstrual Migraine		**Non-Menstrual Migraine**		**History of Migraine**	
	(n=794)		**(n=43)**		**(n=181)**	
Predictor Variable	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Magnesium Intake, mg/day						
P-trend[b]	0.569		0.001		0.458	
Q1 (68.6-190.0)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (190.1-244.6)	1.00	(0.77-1.30)	1.84	(0.64-5.36)	0.98	(0.60-1.60)
Q3 (244.6-312.3)	1.16	(0.87-1.55)	2.72	(0.87-8.52)	1.34	(0.79-2.29)
Q4 (312.7-915.9)	1.09	(0.77-1.54)	7.71	(2.26-26.33)	1.20	(0.63-2.27)
Fruit Serving/day						
P-trend[b]	0.326		0.014		0.030	
Q1 (0.0 - 0.6)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (0.7 – 1.1)	0.89	(0.70-1.12)	0.89	(0.39-2.01)	0.71	(0.46-1.09)
Q3 (1.2 – 1.8)	0.80	(0.64-1.02)	0.66	(0.29-1.50)	0.63	(0.41-0.96)
Q4 (1.9 – 5.9)	0.88	(0.68-1.13)	0.30	(0.11-0.82)	0.61	(0.38-0.97)
Vegetable Serving/day						
P-trend[b]	0.230		0.809		0.180	
Q1 (0.0 - 0.9)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (0.9 – 1.3)	0.92	(0.73-1.16)	1.56	(0.59-4.10)	0.95	(0.60-1.49)
Q3 (1.3 – 2.2)	0.76	(0.60-0.97)	1.56	(0.58-4.13)	0.99	(0.62-1.56)
Q4 (2.2 – 10.6)	0.85	(0.66-1.11)	1.36	(0.49-3.78)	1.31	(0.82-2.10)
Dairy Serving/day						
P-trend[b]	0.273		0.263		0.173	
Q1 (0.0 - 0.5)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (0.5 – 1.1)	1.19	(0.94-1.51)	1.93	(0.80-4.65)	1.18	(0.76-1.84)
Q3 (1.1 – 1.8)	1.20	(0.94-1.53)	1.08	(0.41-2.85)	1.00	(0.63-1.61)
Q4 (1.8 – 11.6)	1.21	(0.93-1.58)	0.80	(0.29-2.23)	1.44	(0.89-2.32)

Grain Serving/day						
P-trend[b]	0.896		0.535		0.315	
Q1 (0.2 – 3.3)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (3.3 – 4.7)	1.08	(0.85-1.37)	0.92	(0.39-2.17)	0.65	(0.41-1.02)
Q3 (4.7 – 6.5)	0.91	(0.70-1.17)	0.29	(0.09-0.88)	0.73	(0.46-1.15)
Q4 (6.5 – 27.5)	1.07	(0.82-1.40)	0.75	(0.30-1.88)	0.74	(0.46-1.21)
Meat Serving/day						
P-trend[b]	0.497		0.201		0.907	
Q1 (0.1 – 1.2)	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Q2 (1.2 – 1.6)	0.83	(0.65-1.05)	1.02	(0.43-2.41)	1.03	(0.67-1.60)
Q3 (1.7 – 2.2)	0.96	(0.75-1.23)	0.56	(0.21-1.50)	0.85	(0.53-1.37)
Q4 (2.2 – 7.9)	1.03	(0.79-1.33)	0.59	(0.22-1.58)	1.06	(0.65-1.72)

[a] Reference category is: Never Migraine group.

[b] p_{trend}: Median regression, statistical significance set at $p<0.05$

CI: 95% Confidence Interval; OR: Odds ratio.

Discussion

This study explored the relationship between dietary magnesium intake and odds of migraine in pre- and peri-menopausal women. The hypothesis predicted that pre- and peri-menopausal women with higher dietary magnesium intake would have lower odds of appearing in any migraine status group than women with low magnesium intake.

The hypothesis was not supported by the analysis. Interestingly, in the non-menstrual migraine group, the opposite relationship was observed: with increasing magnesium intake, women had higher odds of appearing in the non-menstrual migraine group. This merits further discussion below, along with other nuanced findings, including that (1) overall dietary magnesium intake and food group intake of pre- and peri-menopausal women are lower than the recommended intake levels, regardless of migraine status, and (2) pre- and peri-menopausal women with menstrual migraine or history of migraine had dietary magnesium intake levels similar to the never migraine (control) group. The following sections further explore the possible reasonings for the results obtained, and the potential prospects for future studies to enhance the understanding of dietary magnesium intake and migraine subtypes in pre- and peri-menopausal women.

Magnesium

While supplemental magnesium has been investigated in prophylaxis of migraine in literature, dietary magnesium intake remains unexplored in pre- and peri- menopausal women with migraine. The recommended dietary magnesium intake for women over the age of 31 years is 320 mg/day,[36] and the Estimated Average Requirement (EAR) for women aged 31-50 years old is 265 mg/day.[78] Magnesium has been recognized by the

2015-2020 Dietary Guidelines of America as an under consumed nutrient in women aged 19-50 years.[79] By using 2011-2016 NHANES data, Devarshi et al. estimated usual dietary intake of nutrients of women in peri-menopausal age group (40-50 years), and they found the average dietary intake of magnesium was 274.1 mg/day and 50% of the women consumed dietary magnesium less than the EAR of 265 mg/day.[79] Our study found similar results. The average dietary intake of magnesium of our total sample was 258.49 mg/day which is below the RDA and EAR. When the total sample was divided into different migraine status groups, the average baseline dietary magnesium intake remained relatively low as compared to the RDA in all the migraine status groups. Almost 75% of the individuals in the menstrual migraine group, 58% in the non-menstrual migraine group, 73% in the history of migraine group, and 76% in the control group had magnesium intake below the RDA (Q1 – Q3) (**Table 3**). These results also align with literature that individuals with migraine consume less dietary magnesium as compared to individuals without migraine.[55]

The range of magnesium dose in clinical trials that administered oral supplemental magnesium to the participants for prophylaxis of migraine was 360 mg – 600 mg.[47,48,50,54] These doses are higher than the RDA of 320 mg/day for women indicating that current guidelines for magnesium might not be sufficient for prevention of migraine. The high oral doses of supplemental magnesium were also given to the individuals once or twice a day, whereas in reality, dietary magnesium is distributed in meals eaten throughout the day. Therefore, further research may be required to

understand the effect of gradual intake of dietary magnesium throughout the day on the prophylaxis of migraine.

A statistically significant difference was observed in the non-menstrual migraine group in relation to dietary magnesium intake i.e., with increasing dietary magnesium quartile consumption, the odds of being in the non-menstrual migraine group increased. Women in the non-menstrual migraine group did not experience symptoms of menstrual migraine, but they did consume medication for migraine. It is possible that this group had severe migraine which prompted them to seek medication to treat it. The possible reason for the association observed could be that because these women had access to medication, they might not have been limiting their food choices. Several foods have been considered as triggers for migraine attacks including chocolate, nuts, tomatoes, figs, beans, onions, citrus fruits, banana, dairy products, coffee, alcohol, and monosodium glutamate,[2,80] and some of them are high in magnesium. Hence, access to medication might not have prevented them to avoid the foods that may trigger migraine attacks as well as being high in magnesium. Although it is not known from the data the type of medication these women were consuming for migraine, it should be noted that it was in the 1990s that triptans, an acute treatment for migraine, were introduced and revolutionized the treatment for migraine.[81] Furthermore, the dietary magnesium range in the fourth quartile was also relatively wider than the other quartiles, ranging from 312.7 – 915.9 mg/day. Considering this wide range, individuals in this quartile might have had considerably different diets that cannot be further elucidated with available data; therefore, this association needs further investigation. Furthermore, the small sample size (n=43) of this

group, and wide confidence intervals in Q4 (in the unadjusted and adjusted models) makes this association imprecise and impedes concrete conclusions.

The results in our study did not show any statistically significant difference in the menstrual migraine group in relation to dietary magnesium intake. Menstrual migraine is harder to treat and does not respond well to migraine medication.[25] This could indicate that diet alone may not prevent menstrual migraine symptoms and may require supplemental treatment(s), which is to be expected given current understanding of migraine pathophysiology. Studies that have observed improved symptoms in menstrual migraine women have made use of supplemental magnesium in high doses.[48,82]

The history of migraine group also did not show any statistically significant difference in relation to dietary magnesium intake. This group had been diagnosed for migraine at some point in their lives, but they were not taking any medication nor reporting menstrual migraine symptoms at the time data was collected in the original study, and their current status of migraines was unclear. Due to limited publicly available data, it was not possible to decipher when in the past individuals in this group were diagnosed for migraine. Hence, it was assumed that since they were not intaking any medication nor reporting menstrual migraine symptoms, they probably did not have active symptoms of migraine. Therefore, it is not unexpected that there is no difference from the control group in terms of their dietary magnesium intake.

Diet Quality

To further understand the relationship between magnesium and migraine, analysis of diet quality of pre- and peri-menopausal women was carried out. A healthy diet

consists of different food groups, and the recommended number of servings per day for different food groups are: fruits: 4 servings/day, vegetables: 5 servings/day, dairy: 3 servings/day, grains: 6 servings/day, and meat: 1 serving/day.[57] The results of our study found that, except for the meat food group, the baseline servings of other food groups in all the migraine status groups were relatively lower than what is recommended (**Table 2**). This agrees with prior research in the sense that dietary quality of individuals with migraine has been demonstrated to be lower than nutritional recommendations. However, prior research has also shown that patients with migraine have poor dietary quality as compared to individuals without migraine,[58] which was not demonstrated in the current study.

Considering that the baseline intake of different food groups of the women with migraine was not very different from that of the controls, it is possible that there may be other factors in this population that are contributing to migraine including eating frequency,[83,84] sodium dysregulation,[85,86] dehydration,[87] and macronutrient composition.[88,89] For example, several experimental studies have found that skipping meals or fasting can trigger migraine attacks in some individuals, possibly because the blood-glucose levels fall too low.[83,84] This particular eating pattern would not have been evident in the SWAN dataset and could therefore confound our results. Similar intakes might also indicate that the pathophysiology and mechanism of migraine in these women might be unique and different. Hence, their dietary and magnesium needs might be different than the women without migraine.

However, it is also possible that migraine symptoms might affect the dietary choices that people make. The debilitating nature of migraine can affect day-to-day activities of individuals including dietary choices, and these dietary choices may impact intake of different food groups. There might be a potential bidirectional relationship between migraine and diet as migraine may influence not only the dietary choices of individuals but also the "amount, quality, timing, and patterns of dietary intake."[90] Another factor that could potentially influence dietary intake is subtype of migraine. Rist et al. observed intake of certain foods such as wine, chocolate, dairy products, and processed foods was influenced by the presence or absence of aura.[91] Evidence for how migraine may influence dietary choices according to migraine subtypes is limited and warrants further investigation to understand if diet and migraine subtypes are interrelated. Furthermore, many foods have been associated as triggers for migraine attacks, and it is possible that patients with migraine limit or eliminate those foods from their diet. Currently, there are no set dietary guidelines for individuals with migraine,[80] and patients are often recommended to eliminate foods that trigger migraine attacks. Elimination of foods further leads to nutritional deficiencies of micronutrients and lower intake of healthy food groups.[2]

Similar to the results of Evans et al. where they found that dietary quality of women with migraine did not meet the dietary guidelines,[58] we also observed that baseline dietary intake of different food groups in this population did not meet the recommendations of servings. Our study also observed the women consuming fruits in the fourth quartile of fruit serving had lower odds of being the non-menstrual migraine

group and the history of migraine group. Some studies have observed that higher consumption of fruits, vegetables and grains and lower consumption of fats may be associated with lower frequency and severity of migraine headaches.[92]

Although the evidence is limited, improvement in diet quality has shown to improve migraine symptoms in some patients. Altamura et al. found in their study that when patients with migraine were educated about healthy eating, they had significant improvement in headache frequency, abortive drug use, and migraine disability scales.[60] They even found that patients statistically ate less sweets, white bread, and red or processed meat, and more whole grain cereals and legumes.[60] Hence, it might be beneficial to encourage and inform patients with migraine about different food groups—particularly those with high magnesium content like whole grains, dairy and certain vegetables—and healthy eating as it may impact their dietary lifestyle and improve their migraine symptoms.

Magnesium is naturally present in a wide variety of plant and animal foods; however, some varieties of fruits, vegetables, and whole grains have higher magnesium content than others. Food group servings in publicly available SWAN data referred to average daily intake of the food group where portion size and frequency of consumption were added.[76] Based on the fruit and vegetable serving variable, it not specifically known which fruits and vegetables were consumed by these women in different migraine status groups as only composite variables of all the food groups were publicly available. Therefore, along with intake of healthy food groups, it is equally important that variety of foods from those food groups are included in the diet as different foods have different

nutritional composition. Following a diet that does not involve different food groups and a variety of foods might also lead to lower levels of dietary magnesium intake.

Additional Observations

In the adjusted models, women in the non-menstrual migraine group were more likely to be obese as compared to the controls. Although these results are independent of the dietary magnesium intake results, it is worth noting that research has observed association between severity of migraine and obesity.[93,94] Additionally, adjusted models also showed that women consuming 1-7 drinks/wk and 7-35 drinks/wk had higher odds of being in the non-menstrual migraine group as compared to the controls, and the results align with literature.[58] Alcohol is a common trigger associated with migraine occurrence, hence, further research is needed to understand this relationship and why it did not appear in the menstrual migraine group. In the adjusted models, women in the non-menstrual migraine group were also more likely to have private insurance only or combination of private and public insurance as compared to the controls. Research suggests people with insurance are more likely to take medication as compared to people with no insurance due to high costs of medication.[95]

A higher proportion of women in the early peri-menopausal stage were found in the menstrual migraine group as compared to controls. These proportions align with research that frequency of menstrual migraine is higher during peri-menopausal stage of life due to fluctuating estrogen levels as compared to pre-menopausal stage of life.[17]

Strengths and Limitations

Research suggests that menstrual migraine attacks are more severe and harder to treat as compared to migraine attacks occurring at other times of the cycle.[96] The results of our study revealed that the dietary magnesium intake and food group intake of women with menstrual migraine is not different than that of the control group suggesting that physiology of menstrual migraine might be different than other types of migraine. Hence, the dietary needs of women with menstrual migraine might be different. Previous studies that have observed dietary magnesium intake and dietary quality of individuals with migraine had wide age group range and sometimes both male and females included in analysis. This study, however, sheds light onto the magnesium intake and dietary intake pattern of pre- and peri-menopausal women (42-52 years old) in relation to migraine. Women at this stage of life have shown to have increased migraine symptoms[17] and might have different nutritional needs based on their age and hormonal fluctuations. The study is further strengthened by the use of Block FFQ that has been validated for calculating dietary magnesium by Subar et al.[71] Furthermore, the large data set allowed selection of exclusion and inclusion criteria, and adjustment of several potential covariates.

Although the total sample size was large enough to observe the baseline dietary magnesium intake and diet quality of pre- and peri-menopausal women with migraine, the sample size in individual groups, especially the non-menstrual migraine group was very small (n=43) which led to loss in statistical power.

Other than the questions asked about diagnoses of migraine, migraine medication use, and menstrual migraine status at baseline, diagnoses could not be verified using available data against diagnostic criteria. However, this approach in accepting self-diagnoses of migraine has been used in previous studies[55] and similar demographics[97] i.e. majority of individuals who self-report migraine diagnoses meet the ICHD diagnostic criteria. Migraine prevalence during the pre- and peri-menopausal stages has been estimated to be between 16% - 29%,[18] and the prevalence observed in our study i.e. 33.7% is close to this estimate. Considering migraine is underdiagnosed in the population[98] and the diagnostic criteria for menstrual migraine is not fully established and is present in the Appendix of ICHD-3 requiring further research,[99] it was reasonable to use the menstrual migraine question in an attempt to capture more women who had menstrual migraine but were never diagnosed.

Migraine data and dietary data was self-reported by the participants in the SWAN study which could have led to bias and inaccuracy in recall. Furthermore, data was not available for magnesium supplement intake and water intake in this population. Therefore, the dietary estimate of magnesium at baseline cannot be evaluated in relation to total magnesium intake from a combination of diet and supplements. However, at the time SWAN data was collected, magnesium's role in pathophysiology and prophylaxis of migraine was beginning to be recognized and clinical studies observing supplemental magnesium in relation to migraine characteristics had mixed results, hence, it might have been unlikely for the women to be intaking magnesium supplementation specifically with

the intention of preventing migraine and therefore there is no reason to expect that their intake was influenced.

Conclusion

This study highlighted the magnesium intake and dietary pattern of pre- and peri-menopausal women, indicating that dietary magnesium intake in this population is lower than the recommended intake in the total sample as well as in individual migraine status groups. Even though baseline dietary magnesium intakes were low for the migraine status groups, levels were very similar to the control group without migraine, indicating that there are likely other factors (i.e., pathophysiology or other confounders) that might be contributing to the migraines experienced by these women. Since a statistically significant difference was observed in the non-menstrual migraine group, a future study exclusively observing this population (i.e., those taking medication for migraine but without menstrual migraine) might help in understanding their dietary pattern and behaviors, and the association between dietary magnesium and migraine medication use. Future studies can further expand upon these results by exploring diet in further detail, possibly by observing the specific types of foods consumed by these women within individual food groups or by utilizing diet quality indices, such as the Healthy Eating Index, to explore overall diet quality. Further, there are limited studies observing the bidirectional role of migraine and diet, and future, prospective studies could explore this, in addition to exploring whether the type of migraine has any influence on the dietary choices made by individuals with migraine. From this analysis, nutritional

recommendations of dietary magnesium and different food groups cannot be devised for pre- and peri-menopausal with migraine, but the results suggests that dietary magnesium intake influences migraine status. The results tap into the compelling rationale that magnesium influences migraine disease, but significant questions of relevance of dietary magnesium for migraine in this population still remain. Hence, future studies are warranted to untangle the complexities that could not be addressed from this study.

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