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Association Between Magnesium Intake and Migraine Among Pre and Postmenopausal Women: A Cross-Sectional Study

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Objective: To investigate whether menopausal status modifies the association between magnesium intake and migraine in women, hypothesizing that hormonal differences between pre-menopausal and post-menopausal women would result in differential responses to magnesium intake.

Background: While magnesium's role in migraine management has gained attention, the relationship between magnesium intake and migraine across menopausal status remains poorly studied. This is the first study to compare this association between pre-menopausal and post-menopausal women specifically.

Methods: This cross-sectional study analyzed 3,248 women from the National Health and Nutrition Examination Survey (1999–2004), which achieved interview response rates of 79–84%. Menopausal status was determined by self-report: pre-menopausal (n=1,412) or post-menopausal (n=1,836). The exposure variable was total magnesium intake (dietary plus supplements); the outcome was self-reported migraine. Covariates included age, race, education, income, body mass index, smoking, drinking, hypertension, diabetes, C-reactive protein, estimated glomerular filtration rate, and calcium intake. Non-linear relationships were examined using piecewise logistic regression.

Results: Migraine prevalence was higher in pre-menopausal (31.3%) than post-menopausal women (15.6%). A significant non-linear relationship between magnesium intake and migraine was observed in pre-menopausal women, with odds of migraine decreasing by 36.0% per unit increase in magnesium intake below 325.41 mg/day (OR: 0.64, 95% CI: 0.42–0.98, P=0.042), with no significant association above the threshold. No significant association was found in post-menopausal women. Supplementary weighted analysis validated these findings.

Conclusion: Menopausal status may modify the relationship between magnesium intake and migraine. Adequate magnesium intake may be beneficial for reducing migraine risk in pre-menopausal women. Given that over half of American adults fail to meet recommended magnesium intake, these findings have significant public health implications for targeted dietary interventions in reproductive-age women, though prospective validation is needed.

Keywords: magnesium intake, migraine, menopause, National Health and Nutrition Examination Survey, cross-sectional study

Introduction

Migraine is a prevalent, debilitating neurological disorder that disproportionately affects women, with a two-to-threefold higher prevalence in females than in males.[1,2] This gender disparity becomes particularly pronounced during reproductive years, with migraine prevalence peaking in the third and fourth decades of life and declining after menopause.[1,3,4] The hormonal fluctuations characteristic of menopausal transition represent a critical juncture in women's neurological health, with nearly 40% of women experiencing migraine symptoms during their reproductive lifespan.[1,4] Understanding how menopausal status influences migraine pathophysiology and therapeutic responses is therefore paramount for developing targeted intervention strategies.

Magnesium, the second most abundant intracellular cation, has emerged as a promising therapeutic intervention for migraine prevention and management.[5,6] This essential mineral serves as a cofactor in over 600 enzymatic reactions, including

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ATP synthesis, and plays crucial roles in modulating neuronal excitability, neurotransmitter release, and vascular tone.[7] The neurobiological mechanisms underlying magnesium's anti-migraine effects include N-methyl-D-aspartate (NMDA) receptor antagonism, calcium channel modulation, and stabilization of neuronal membranes—processes directly implicated in migraine pathophysiology.[5,6,8] Despite its therapeutic potential, magnesium deficiency represents a significant and under-recognized public health concern, particularly among women.[9] Epidemiological data reveal a concerning finding that average magnesium intake in the American population has declined dramatically from approximately 500 mg/day a century ago to 175–225 mg/day currently, with approximately 50% of adults failing to meet recommended dietary allowances.[9,10] This widespread deficiency is especially pronounced in women.[9] The convergence of magnesium inadequacy with the female predominance in migraine prevalence suggests a potential relationship that warrants systematic investigation.

The biological rationale for investigating menopausal status as a modifier of magnesium-migraine associations lies in estrogen's dual role in magnesium homeostasis and migraine pathophysiology.[1,4,11] Estrogen regulates magnesium bioavailability through enhanced intestinal absorption and renal reabsorption.[10] Concurrently, magnesium exerts neuro-protective effects through voltage-dependent NMDA receptor antagonism and calcium channel blockade.[5,6,8] The distinct hormonal environments of pre-menopausal and post-menopausal women create divergent physiological contexts that may differentially modulate magnesium's therapeutic efficacy in migraine prevention.[9] Specifically, post-menopausal estrogen deficiency may attenuate estrogen-mediated magnesium homeostasis, thereby compromising magnesium's neuroprotective mechanisms and providing a plausible explanation for the heterogeneous therapeutic responses to magnesium supplementation observed across menopausal status.

Despite the biological rationale and clinical relevance, no studies have specifically examined whether the association between magnesium intake and migraine differs according to menopausal status. Previous research has largely treated women as a homogeneous population,[12,13] overlooking the profound hormonal and physiological changes that accompany menopausal transition. This represents a critical knowledge gap, as the effectiveness of magnesium supplementation may vary substantially between pre-menopausal and post-menopausal women due to estrogen-dependent differences in magnesium metabolism and neurological responsiveness.[4,9] Understanding these differential associations is essential for developing evidence-based, personalized dietary recommendations and therapeutic strategies.

Therefore, this study aims to investigate the association between magnesium intake and migraine in American women, specifically examining whether menopausal status modifies this relationship using comprehensive data from the National Health and Nutrition Examination Survey (NHANES). We hypothesize that hormonal differences between pre-menopausal and post-menopausal women would result in differential responses to magnesium intake. This is the first study to specifically compare the association between magnesium intake and migraine across menopausal status, addressing a critical knowledge gap in personalized migraine prevention strategies.

Methods

Study Population

This study utilizes NHANES data from 1999 to 2004, with interview response rates of 82.0%, 84.0%, and 79.0% for the 1999–2000, 2001–2002, and 2003–2004 cycles, respectively.[14] The following criteria were used to exclude participants from our analysis: (1) aged <20 years, male, pregnant (2) missing complete data about migraine, magnesium, and magnesium supplements. To eliminate interference, outliers in magnesium intake that did not fall within the range of the averages ± three standard deviations (SD) were removed.[15] An initial total of 31,126 participants took part in the study. After excluding younger than 20 years, male and pregnant participants (23,850), those with missing data on migraine, magnesium, and magnesium supplements (3,911), and 117 magnesium outliers, the analysis sample consisted of 3,248 participants (Figure 1).

Definition of Migraine

Migraine was defined based on participants' responses to the standardized NHANES questionnaire (Medical Conditions section, variable MCQ160c): "Have you experienced a severe headache or migraine in the past three months?" While this self-reported approach does not strictly adhere to International Classification of Headache Disorders (ICHD) criteria and may introduce misclassification bias, validation studies demonstrate 81.6–87.0% agreement with clinical diagnoses.[16,17] This limitation may

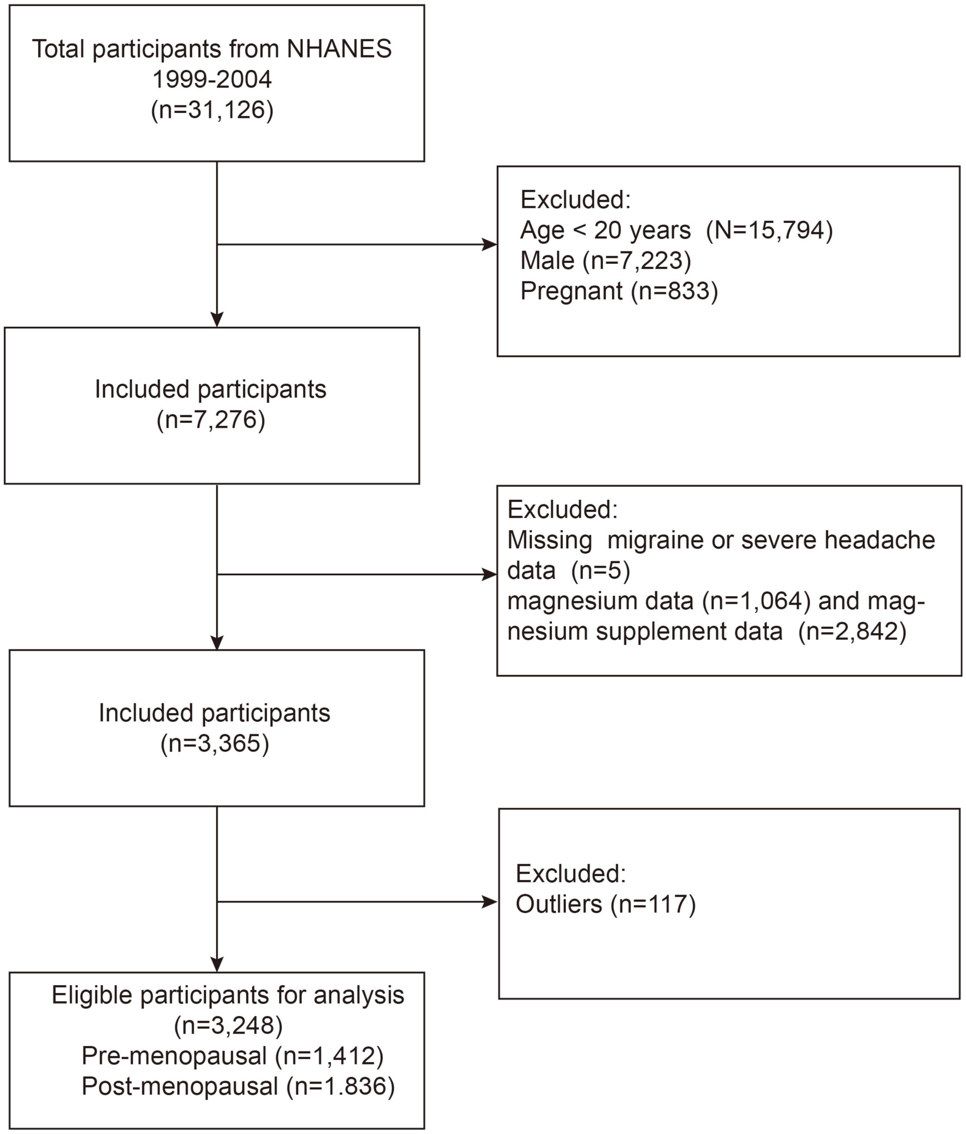

Figure 1 Flowchart of the participants.

result in some non-migraine headaches being classified as migraine, potentially attenuating observed associations. However, this approach is consistent with previous large-scale epidemiological studies using NHANES data.[18,19]

Assessment of Dietary Intake

The dietary intake data were extracted from the NHANES dietary survey. Trained interviewers asked participants about the types and amounts of all meals and beverages consumed within the previous 24 hours. Dietary recalls were collected using the United States Department of Agriculture Computer-Assisted Dietary Interview (CADI) from 1999 to 2002, and the Automated Multiple Pass Method (AMPM) was used from 2003 to 2004. These methods have been extensively utilized and validated in large-scale dietary assessment studies, ensuring reliable and accurate data collection.[20] Nutrient intake calculations involved summing the nutrient intake from food with the average daily amounts obtained from dietary supplements. Details of how NHANES assesses dietary supplement intake are provided in the eMethod 1.

Assessment of Menopausal Status

The reproductive health section of the NHANES questionnaire used self-reporting to determine menopausal status, which has been shown to have good validity and reproducibility.[21] Individuals who answered "no" to the question "Have you had at least one menstrual period in the past 12 months?" and selected "Menopause/hysterectomy" as the reason for not having a period in the past 12 months, were classified as post-menopausal (n = 1,836). If the participant's response to the first question was "yes" or if it was "no" and their response to the second question was "Breastfeeding", "Medical conditions/treatments", and/or "Other" and they were under the age of 55 years, they were considered pre-menopausal (n=1,412). For further details on the methodology employed to assess the post-menopausal population, please refer to eMethod 2.

Covariates

The selection of covariates was based on existing literature, biological plausibility, and observed differences between the migraine and control groups. These covariates were included to account for potential confounding effects and isolate the association between magnesium intake and migraine from other influencing factors. Age, race, education level, poverty-to-income ratio (PIR), body mass index (BMI), smoking status, drinking status, hypertension, diabetes, energy intake, C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), dietary calcium, supplemental calcium, and calcium intake were among the covariates in our study. We used missing continuous variables to be filled with dummy variables, and missing categorical variables to be analyzed as a separate group.

Statistical Analysis

The quintile ranges for magnesium intake were as follows: Quintile 1 < 158.0 mg/day; Quintile 2 = 158.0–207.8 mg/day; Quintile 3 = 207.8–263.0 mg/day; Quintile 4 = 263.0–345.0 mg/day; Quintile 5 ≥345.0 mg/day. Continuous variables were presented as mean±standard deviation (SD), while categorical variables were presented as percentages. We used the Chi-squared tests for categorical variables, one-way ANOVA for normally distributed continuous variables, and the Kruskal–Wallis test for skewed continuous variables. A log transformation was performed on the magnesium intake in order to correct for data skewness and normalize the results. To determine associations between increases in magnesium intake and migraine, we conducted unadjusted and multivariable-adjusted logistic regression analyzes. The regression coefficients and corresponding 95% confidence intervals (CI) were calculated to express the effect sizes as odds ratios (OR). Additionally, the independent association between migraine and magnesium intake increase, grouped into quintiles, was investigated using univariate and multivariable linear regression in three distinct models. In the minimally adjusted model, both age and race were added. The fully adjusted model incorporates additional covariates, including educational level, income-to-poverty ratio, lifestyle factors (smoking and drinking status), comorbidities (hypertension and diabetes), inflammatory markers (CRP), BMI, renal function (eGFR), and dietary factors (energy and calcium intake). Given the biological plausibility of threshold effects for magnesium supplementation, where benefits may plateau after reaching physiological requirements, and preliminary data visualization suggesting non-linear relationships, smoothed curve fitting was performed to visualize the relationship between magnesium intake and the odds of migraine. A two-piece piecewise logistic regression model was used to identify the optimal threshold point (K), with a likelihood ratio test comparing the one-line linear model (Model I) to the two-piece model (Model II). A P-value < 0.05 indicated a significant non-linear relationship.

Post-hoc power analyses were conducted using R software (pwr package) to assess the adequacy of our sample sizes for detecting clinically meaningful associations. Full details are provided in eMethod 3. To validate the robustness of our findings, we conducted supplementary weighted analyses incorporating NHANES sampling design parameters (sampling weights, strata, and primary sampling units). While our primary unweighted analyses focused on examining the biological association between magnesium intake and migraine, the weighted analyses assessed whether results remained consistent when accounting for the complex sampling design (eMethod 4). Statistical analyzes used R (http://www.r-project.org) and EmpowerStats (http://www.empowerstats.com) with a significance level of a two-sided P < 0.05.

Results

Baseline Characteristics of Participants

The study included 3,248 female participants, of whom 728 (22.4%) had migraine, including 1,412 pre-menopausal and 1,836 post-menopausal women. The mean age (±SD) was 39.0 ± 9.8 years for pre-menopausal women and 67.5 ± 12.5 years for post-menopausal women. The mean BMI was 28.0 ± 7.1 kg/m² and 28.1 ± 6.1 kg/m² for pre-menopausal and post-menopausal women, respectively. Tables 1 and 2 present subject characteristics stratified by quintiles of magnesium intake. Among pre-menopausal women, those in the highest quintile of magnesium intake (≥345.0 mg/day) were more likely to be non-Hispanic white (65.26%), to have higher education (72.81% above high school), and to have higher income (46.83% with PIR ≥3.5)

Table 1 Characteristics of Participants (Pre-menopausal N =1412)

	Magnesium Intake (mg/day)					P-value
	Q1 <158.0	**Q2 (158.0–207.8)**	**Q3 (207.8–263.0)**	**Q4 (263.0–345.0)**	**Q5 ≥345.0**	
N	278	278	257	268	331	
Age (years)	37.04 ± 9.56	39.15 ± 10.21	40.25 ± 9.77	39.47 ± 9.36	39.12 ± 9.96	0.003
Race (%)						<0.001
Mexican American	40 (14.39)	60 (21.58)	47 (18.29)	52 (19.40)	51 (15.41)	
Other Hispanic	11 (3.96)	16 (5.76)	14 (5.45)	9 (3.36)	12 (3.63)	
Non-Hispanic White	141 (50.72)	149 (53.60)	146 (56.81)	170 (63.43)	216 (65.26)	
Non-Hispanic Black	77 (27.70)	42 (15.11)	38 (14.79)	30 (11.19)	39 (11.78)	
Other Races	9 (3.24)	11 (3.96)	12 (4.67)	7 (2.61)	13 (3.93)	
Educational level (%)						<0.001
Less than high school	54 (19.42)	44 (15.83)	49 (19.07)	32 (11.94)	39 (11.78)	
High school	75 (26.98)	74 (26.62)	56 (21.79)	56 (20.90)	51 (15.41)	
Above high school	149 (53.60)	160 (57.55)	152 (59.14)	180 (67.16)	241 (72.81)	
PIR (%)						0.006
<1.3	63 (22.66)	52 (18.71)	56 (21.79)	44 (16.42)	38 (11.48)	
1.3–3.49	99 (35.61)	99 (35.61)	82 (31.91)	73 (27.24)	119 (35.95)	
≥3.5	98 (35.25)	110 (39.57)	101 (39.30)	131 (48.88)	155 (46.83)	
Unknown	18 (6.47)	17 (6.12)	18 (7.00)	20 (7.46)	19 (5.74)	
Smoking status (%)						0.025
Never	69 (24.82)	61 (21.94)	38 (14.79)	33 (12.31)	49 (14.80)	
Former	10 (3.60)	12 (4.32)	9 (3.50)	9 (3.36)	14 (4.23)	
Current	45 (16.19)	45 (16.19)	46 (17.90)	55 (20.52)	61 (18.43)	
Unknown	154 (55.40)	160 (57.55)	164 (63.81)	171 (63.81)	207 (62.54)	
Drinking status (%)						0.001
Light	65 (23.38)	83 (29.86)	59 (22.96)	76 (28.36)	108 (32.63)	
Moderate	50 (17.99)	56 (20.14)	44 (17.12)	64 (23.88)	78 (23.56)	
Excessive	76 (27.34)	50 (17.99)	58 (22.57)	56 (20.90)	46 (13.90)	
Unknown	87 (31.29)	89 (32.01)	96 (37.35)	72 (26.87)	99 (29.91)	
Hypertension (%)						0.691
Yes	55 (19.78)	53 (19.06)	55 (21.40)	57 (21.27)	57 (17.22)	
No	223 (80.22)	225 (80.94)	202 (78.60)	211 (78.73)	274 (82.78)	
Diabetes (%)						0.312
Yes	15 (5.40)	11 (3.96)	15 (5.84)	19 (7.09)	12 (3.63)	
No	263 (94.60)	267 (96.04)	242 (94.16)	249 (92.91)	319 (96.37)	
BMI (kg/m^2)	27.9 ± 6.63	28.71 ± 7.16	28.65 ± 7.32	28.31 ± 7.85	26.52 ± 6.29	<0.001
Energy (kcal/day)	1294.69 ± 459.42	1620.24 ± 475.81	1845.31 ± 553.94	2185.58 ± 623.75	2548.97 ± 843.97	<0.001
eGFR (mL/min/1.73m^2)	106.52 ± 16.22	107.89 ± 16.45	107.79 ± 15.77	106.12 ± 16.82	106.92 ± 16.90	0.682
CRP (mg/dL)	0.25 ± 0.40	0.30 ± 0.58	0.31 ± 0.51	0.29 ± 0.61	0.50 ± 1.66	0.028
Dietary calcium (mg/day)	431.32 ± 229.38	611.08 ± 328.18	742.20 ± 382.03	965.61 ± 518.54	1196.17 ± 631.69	<0.001
Dietary magnesium (mg/day)	124.53 ± 22.18	181.89 ± 15.97	234.60 ± 18.77	300.79 ± 24.65	419.41 ± 120.87	<0.001
Calcium supplement (mg/day)	87.75 ± 265.70	80.25 ± 237.31	162.07 ± 363.96	108.71 ± 246.90	230.31 ± 437.03	<0.001
Magnesium supplement (mg/day)	0.07 ± 1.01	0.98 ± 7.21	1.04 ± 11.29	0.85 ± 7.54	50.05 ± 135.43	<0.001
Calcium intake (mg/day)	844.01 ± 508.88	843.29 ± 595.93	1004.20 ± 648.04	1081.72 ± 686.84	1090.66 ± 666.95	<0.001
Migraine (%)						0.017
Yes	107 (38.49)	90 (32.37)	82 (31.91)	69 (25.75)	94 (28.40)	
No	171 (61.51)	188 (67.63)	175 (68.09)	199 (74.25)	237 (71.60)	

Notes: Continuous variables are presented as mean±standard deviation (SD). Categorical variables are presented as number (percentage).
Abbreviations: PIR, Income to poverty ratio; eGFR, Estimated glomerular filtration rate; CRP, C reactive protein; BMI, Body mass index.

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Table 2 Characteristics of Participants (Post-menopausal N =1,836)

	Magnesium Intake (mg/day)					P-value
	Q1 <158.0	Q2 (158.0–207.8)	Q3 (207.8–263.0)	Q4 (263.0–345.0)	Q5 ≥345.0	
N	368	368	400	381	319	
Age (years)	68.96 ± 12.16	67.50 ± 12.55	67.59 ± 12.98	66.20 ± 12.99	67.00 ± 11.66	0.048
Race (%)						0.041
Mexican American	73 (19.84)	73 (19.84)	62 (15.50)	68 (17.85)	49 (15.36)	
Other Hispanic	8 (2.17)	15 (4.08)	10 (2.50)	8 (2.10)	10 (3.13)	
Non-Hispanic White	217 (58.97)	237 (64.40)	265 (66.25)	256 (67.19)	228 (71.47)	
Non-Hispanic Black	57 (15.49)	34 (9.24)	53 (13.25)	43 (11.29)	24 (7.52)	
Other Races	13 (3.53)	9 (2.45)	10 (2.50)	6 (1.57)	8 (2.51)	
Educational level (%)						<0.001
Less than high school	146 (39.67)	125 (33.97)	111 (27.75)	96 (25.20)	68 (21.32)	
High school	101 (27.45)	120 (32.61)	124 (31.00)	99 (25.98)	78 (24.45)	
Above high school	121 (32.88)	123 (33.42)	165 (41.25)	186 (48.82)	173 (54.23)	
PIR (%)						<0.001
<1.3	117 (31.79)	78 (21.20)	83 (20.75)	72 (18.90)	60 (18.81)	
1.3–3.49	142 (38.59)	146 (39.67)	162 (40.50)	156 (40.94)	120 (37.62)	
≥3.5	71 (19.29)	108 (29.35)	124 (31.00)	114 (29.92)	110 (34.48)	
Unknown	38 (10.33)	36 (9.78)	31 (7.75)	39 (10.24)	29 (9.09)	
Smoking status (%)						0.617
Never	31 (8.42)	41 (11.14)	30 (7.50)	24 (6.30)	25 (7.84)	
Former	6 (1.63)	8 (2.17)	8 (2.00)	9 (2.36)	3 (0.94)	
Current	103 (27.99)	108 (29.35)	118 (29.50)	116 (30.45)	102 (31.97)	
Unknown	228 (61.96)	211 (57.34)	244 (61.00)	232 (60.89)	189 (59.25)	
Drinking status (%)						0.040
Light	112 (30.43)	105 (28.53)	148 (37.00)	128 (33.60)	127 (39.81)	
Moderate	34 (9.24)	40 (10.87)	42 (10.50)	50 (13.12)	38 (11.91)	
Excessive	16 (4.35)	18 (4.89)	21 (5.25)	23 (6.04)	14 (4.39)	
Unknown	206 (55.98)	205 (55.71)	189 (47.25)	180 (47.24)	140 (43.89)	
Hypertension (%)						0.044
Yes	200 (54.35)	206 (55.98)	190 (47.50)	187 (49.08)	150 (47.02)	
No	168 (45.65)	162 (44.02)	210 (52.50)	194 (50.92)	169 (52.98)	
Diabetes (%)						0.240
Yes	52 (14.13)	56 (15.22)	48 (12.00)	38 (9.97)	40 (12.54)	
No	316 (85.87)	312 (84.78)	352 (88.00)	343 (90.03)	279 (87.46)	
BMI (kg/m^2)	29.02 ± 6.88	27.90 ± 5.59	28.00 ± 5.72	28.44 ± 6.56	27.33 ± 5.57	<0.001
Energy (kcal/day)	1095.34 ± 356.69	1432.41 ± 390.95	1624.94 ± 485.84	1898.23 ± 513.47	2095.22 ± 618.93	<0.001
eGFR (mL/min/1.73m^2)	79.60 ± 23.62	81.54 ± 22.03	80.89 ± 20.43	85.61 ± 19.87	83.99 ± 19.69	<0.001
CRP (mg/dL)	0.32 ± 0.59	0.32 ± 0.57	0.47 ± 0.76	0.36 ± 0.82	0.36 ± 0.86	0.025
Dietary calcium (mg/day)	413.11 ± 249.24	572.34 ± 273.62	734.32 ± 366.02	884.52 ± 368.46	1074.33 ± 594.70	<0.001
Dietary magnesium (mg/day)	125.66 ± 23.08	183.96 ± 13.61	233.80 ± 18.82	297.29 ± 28.76	400.18 ± 117.50	<0.001
Calcium supplement (mg/day)	198.09 ± 365.30	224.07 ± 382.67	277.85 ± 519.73	224.30 ± 454.18	388.94 ± 558.05	<0.001
Magnesium supplement (mg/day)	0.38 ± 3.43	0.07 ± 0.64	1.36 ± 12.44	3.23 ± 19.76	68.96 ± 144.26	<0.001
Calcium intake (mg/day)	803.76 ± 517.19	861.84 ± 759.25	982.65 ± 684.80	1077.04 ± 708.84	1124.16 ± 775.48	<0.001
Migraine (%)						0.913
Yes	55 (14.95)	60 (16.30)	64 (16.00)	62 (16.27)	45 (14.11)	
No	313 (85.05)	308 (83.70)	336 (84.00)	319 (83.73)	274 (85.89)	

Notes: Continuous variables are presented as mean±standard deviation (SD). Categorical variables are presented as number (percentage).
Abbreviations: PIR, Income to poverty ratio; eGFR, Estimated glomerular filtration rate; CRP, C reactive protein; BMI, Body mass index.

than those in the lowest quintile (<158.0 mg/day). Similar patterns were observed in post-menopausal women, with those in the highest quintile having higher proportions of non-Hispanic whites (71.47%), higher education (54.23% above high school), and higher income (34.48% with PIR ≥3.5). Notably, the prevalence of migraine was higher in pre-menopausal women (31.3%) compared with post-menopausal women (15.6%), with significant differences between magnesium intake quintiles in pre-menopausal women (p=0.017) but not in post-menopausal women (p=0.913).

The Association Between Magnesium Intake and Migraine

In the multivariable logistic regression analysis, we observed distinct patterns between pre-menopausal and post-menopausal women regarding the association between magnesium intake and migraine (Table 3). The crude model showed that each unit increase in Ln-magnesium intake among pre-menopausal women was associated with a 28.0% lower odds of migraine (OR: 0.72, 95% CI: 0.57–0.91, P=0.005). This association remained significant after minimal adjustment for age and race (OR: 0.73, 95% CI: 0.58–0.93, P=0.011), but became non-significant in the fully adjusted model (OR: 0.87, 95% CI: 0.62–1.22, P=0.411). This attenuation suggests that the observed crude association may be partially explained by unmeasured confounders and warrants cautious interpretation of any potential causal relationship. When examining quintiles of magnesium intake in pre-menopausal women, we observed a notable inverse association, particularly in the fourth quintile. Compared to the lowest quintile (Q1), women in Q4 showed significantly lower odds of migraine across all models, with the association persisting even after full adjustment (OR: 0.63, 95% CI: 0.40–0.98, P=0.039). The trend analysis revealed significant dose-response relationships in both crude (P-trend=0.002) and minimally adjusted models (P-trend=0.005), though this trend was attenuated in the fully adjusted model (P-trend=0.224). In contrast, we found no significant associations among post-menopausal women between magnesium intake and migraine, either as a continuous variable or when analyzed by quintiles. The fully adjusted odds ratios across quintiles ranged from 1.06 (95% CI: 0.69–1.62) to 1.14 (95% CI: 0.71–1.83), with no clear trend pattern (P-trend=0.750). Notably, the migraine among post-menopausal women was substantially lower (15.6%) compared to pre-menopausal women (31.3%), and showed no significant variation across magnesium intake quintiles (p=0.913).

Table 3 Multivariable Logistic Analysis of Ln-Magnesium Intake and Migraine in Pre and Post-menopausal

	OR (95% CI), P-value		
	Crude Model	**Minimally Adjusted Model**	**Fully Adjusted Model**
Pre-menopausal			
Ln-magnesium intake (mg/day)	0.72 (0.57,0.91) 0.005	0.73 (0.58, 0.93) 0.011	0.87 (0.62, 1.22) 0.411
Quintile of Ln-magnesium intake			
Q1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	0.77 (0.54, 1.08) 0.132	0.76 (0.53, 1.08) 0.122	0.78 (0.54, 1.13) 0.196
Q3	0.75 (0.52, 1.07) 0.112	0.76 (0.53, 1.10) 0.145	0.80 (0.54, 1.19) 0.269
Q4	0.55 (0.38, 0.80) 0.002	0.56 (0.39, 0.81) 0.002	0.63 (0.40, 0.98) 0.039
Q5	0.63 (0.45, 0.80) 0.009	0.65 (0.46, 0.92) 0.015	0.78 (0.49, 1.26) 0.314
P for trend	0.002	0.005	0.224
Post-menopausal			
Ln-magnesium intake (mg/day)	0.91 (0.69,1.20) 0.511	0.73 (0.58, 0.93) 0.011	0.87 (0.62, 1.22)0.411
Quintile of Ln-magnesium intake			
Q1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1.11 (0.74, 1.65) 0.612	1.04 (0.69, 1.56) 0.859	1.06 (0.69, 1.62) 0.786
Q3	1.08 (0.73, 1.60) 0.687	1.04 (0.70, 1.56) 0.842	1.09 (0.71, 1.68) 0.702
Q4	1.11 (0.75, 1.64) 0.617	1.00 (0.66, 1.50) 0.989	1.14 (0.71, 1.83) 0.600
Q5	0.93 (0.61, 1.43) 0.756	0.89 (0.57, 1.38) 0.597	1.06 (0.61, 1.82) 0.842
P for trend	0.824	0.596	0.750

Notes: Crude model: we did not adjust other covariants. Minimally adjusted model: we adjusted age and race. Fully adjusted model: we adjusted age, race, educational level, PIR, smoking status, drinking status, hypertension, diabetes, CRP, BMI, eGFR, energy, and calcium intake. Ln-magnesium intake quintile ranges: Quintile 1 = 4.30 to 5.07; Quintile 2 = 5.07 to 5.34; Quintile 3 = 5.34 to 5.57; Quintile 4 = 5.58 to 5.84; Quintile 5 = 5.85 to 6.76.

Abbreviations: OR, Odd ratio; 95% CI, 95% Confidence interval; PIR, Income to poverty ratio; eGFR, Estimated glomerular filtration rate; CRP, C reactive protein; BMI, Body mass index.

The Non-Linear Relationship Between Magnesium Intake and Migraine

After controlling for all variables, a non-linear inverse relationship was observed in pre-menopausal women (Figure 2). The curve showed a decrease in migraine as magnesium intake increased from the low levels up to a threshold of about 5.79 ln mg/day (about 325.41 mg/day). Beyond this threshold, the association plateaued. In contrast, post-menopausal women (Figure 3) showed no clear association between magnesium intake and migraine probability across the entire range of intake levels.

After adjustment for variables, the threshold effect analysis (model II) identified notable non-linear relationships, particularly in pre-menopausal women, with the turning point occurring at K = 5.79. Below this threshold, each unit increase in Ln-magnesium intake was associated with a significant 36% reduction in the odds of migraine (OR: 0.64,

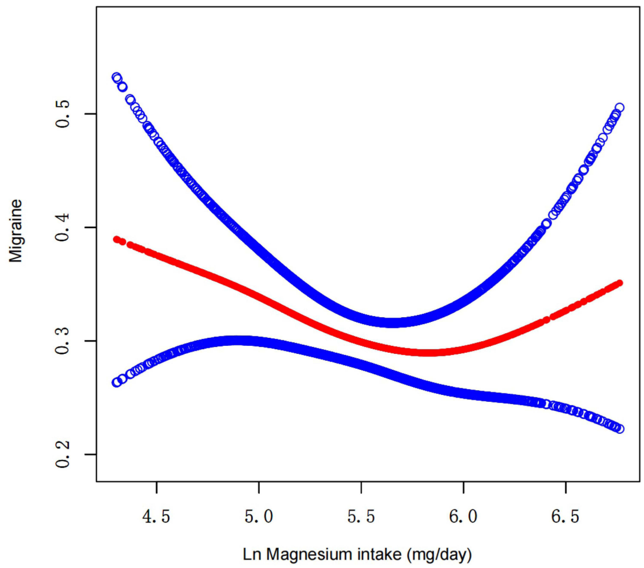

Figure 2 In pre-menopausal women, the generalized additive model detected a nonlinear relationship between Ln-magnesium intake and migraine. The model was adjusted for age, race, educational level, PIR, smoking status, drinking status, hypertension, diabetes, CRP, BMI, eGFR, energy, and calcium intake.
Abbreviations: PIR, Income to poverty ratio; eGFR, Estimated glomerular filtration rate; CRP, C-reactive protein; BMI, Body mass index.

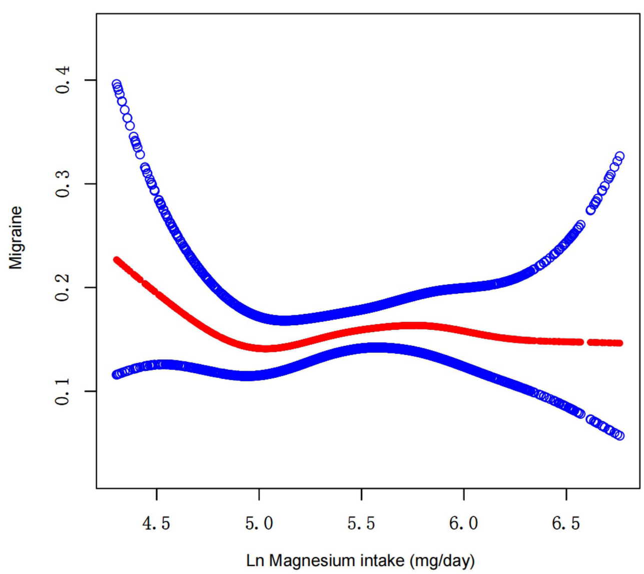

Figure 3 In post-menopausal women, the generalized additive model detected a nonlinear relationship between Ln-magnesium intake and migraine. The model was adjusted for age, race, educational level, PIR, smoking status, drinking status, hypertension, diabetes, CRP, BMI, eGFR, energy, and calcium intake.
Abbreviations: PIR, Income to poverty ratio; eGFR, Estimated glomerular filtration rate; CRP, C-reactive protein; BMI, Body mass index.

Table 4 Threshold Effect Analysis for the Relationship Between Ln-Magnesium Intake and Migraine

Models	Pre-menopausal		Post-menopausal	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Model I				
One line effect	0.87 (0.62, 1.22)	0.411	0.97 (0.66, 1.44)	0.900
Model II				
Turning point (K)	5.79		4.92	
<K effect 1	0.64 (0.42, 0.98)	0.042	0.25 (0.06, 1.05)	0.058
>K effect 2	1.88 (0.89, 3.97)	0.100	1.19 (0.77, 1.85)	0.426
Log-likelihood ratio test		0.028		0.060

Notes: Model I, linear analysis. Model II, non-linear analysis. Log likelihood ratio test: P-value < 0.05 means Model II is significantly different from Model I, which indicates a non-linear relationship.
Abbreviation: OR, Odd ratio; 95% CI, 95% Confidence interval.

95% CI: 0.42–0.98; P = 0.042). Above the turning point, there was a trend toward increased odds, though not statistically significant (OR = 1.88, 95% CI: 0.89–3.97, P = 0.100). The logarithmic likelihood ratio test (P = 0.028) confirmed a significant non-linear relationship in pre-menopausal women. For post-menopausal women, the relationship showed a different pattern with an inflection point at Ln-magnesium intake of 4.92. While the non-linear relationship approached significance (logarithmic likelihood ratio test P = 0.060), the associations were less pronounced (Table 4).

Power analysis revealed robust statistical power (99.6%) in pre-menopausal women but limited power (34.0%) in post-menopausal women due to very small effect sizes (Supplementary Table S1).

Validation of Findings Through Weighted Analysis

To validate the robustness of our primary findings, we conducted supplementary weighted analysis incorporating NHANES complex sampling design (Supplementary Table S2). The weighted analysis demonstrated consistent threshold effects in pre-menopausal women with a turning point at 365.04 mg/day (Ln-magnesium intake: 5.90), showing a significant protective association below the threshold (OR: 0.47, 95% CI: 0.24–0.90, P=0.035).

The concordance between unweighted and weighted analytical approaches in identifying threshold effects and protective associations confirms the biological validity of the observed dose-response relationship in pre-menopausal women. Both methods consistently identified significant protective effects below their respective thresholds (unweighted: 325.41 mg/day, OR: 0.64, P=0.042; weighted: 365.04 mg/day, OR: 0.47, P=0.035), with the weighted analysis yielding a slightly higher threshold value and stronger protective effect.

However, estimates in post-menopausal women exhibited wide confidence intervals in both analyses, particularly in the weighted analysis, suggesting limited precision in this subgroup and warranting cautious interpretation. No significant association was observed in post-menopausal women across both analytical approaches (unweighted P=0.060; weighted P>0.05), with consistent findings supporting the population-specific nature of the observed relationship.

Discussion

Our cross-sectional analysis of 3,248 women (1,412 pre-menopausal, 1,836 post-menopausal) revealed a menopausal status-dependent association between magnesium intake and migraine. In pre-menopausal women, we identified a non-linear protective relationship with a distinct threshold closely approximating current FDA recommendations (310–320 mg/day).[22] Beyond this threshold, the protective effect plateaued, suggesting an optimal intake range rather than a linear dose-response relationship. These cross-sectional findings suggest a potential association between dietary magnesium intake and reduced migraine odds among pre-menopausal women. However, the observational nature of this study precludes causal inference, and these results should be considered exploratory pending prospective validation.

These findings align with established research documenting magnesium's role in migraine pathophysiology. Clinical studies consistently demonstrate reduced magnesium concentrations in serum, cerebrospinal fluid, and saliva among migraine patients.[13,23–25]Most notably, Assarzadegan et al identified magnesium deficiency as an independent migraine risk factor, with reduced serum levels associated with a 35-fold increase in acute attack odds.[13] Meta-analytic evidence supports magnesium's therapeutic efficacy, demonstrating significant reductions in both attack frequency (OR = 0.20) and intensity (OR = 0.27) with supplementation.[12] This evidence base has translated into clinical practice guidelines, with both American and European neurological societies providing Level B recommendations for magnesium supplementation in migraine prevention.[26,27] This study provides the first menopausal status-stratified analysis of the magnesium-migraine relationship. Previous research by Slavin et al examined Americans aged 20–50 years and found no gender-specific effects, but did not consider menopausal status.[18] Our findings advance understanding by demonstrating that magnesium intake is associated with protective effects specifically in pre-menopausal women. The absence of this association in post-menopausal women suggests that alternative prevention approaches may be needed for this population.

The observed differential associations between magnesium intake and migraine across menopausal status may involve complex hormone-dependent neurobiological mechanisms, though direct evidence for estrogen-magnesium interactions remains limited. Magnesium functions as an endogenous NMDA receptor antagonist, blocking calcium influx and suppressing glutamate release, both critical processes implicated in migraine pathophysiology.[28,29] Additionally, magnesium influences vascular tone and platelet aggregation through calcium-dependent mechanisms while reducing circulating CGRP levels, representing important mechanisms in migraine pathophysiology.[10,30] The absence of significant associations in post-menopausal women likely reflects fundamental biological and statistical differences. Estrogen decline disrupts magnesium homeostasis through reduced intestinal absorption via TRPM6/7 channels and altered renal handling.[10] Concurrently, estrogen withdrawal modifies migraine pathophysiology by reducing NMDA receptor sensitivity and altering CGRP regulation, potentially diminishing magnesium's neuroprotective effects.[11] Statistical factors also contribute to null findings. The lower migraine prevalence in post-menopausal women (15.6% vs 31.3% in pre-menopausal women) resulted in reduced statistical power (34.0% vs 99.6%), limiting our ability to detect associations. Additionally, age-related decreases in magnesium absorption may further attenuate potential benefits.[31,32] While the precise mechanisms underlying the differential effects across menopausal status require further investigation, the convergence of magnesium's established neuroprotective pathways with known hormonal influences on migraine susceptibility may contribute to the protective association observed specifically in pre-menopausal women.

The potential role of magnesium supplementation aligns with growing interest in non-pharmacological migraine management approaches.[6] Recent evidence demonstrates the importance of manual trigger point treatment in comprehensive migraine management,[33] while studies reveal significant gaps in public awareness about alternative migraine treatments, including nutritional interventions.[34] These findings underscore the need for integrated approaches that combine dietary strategies with established therapeutic modalities.

The study presents several advantages. Most importantly, this is the first study to compare the association between magnesium intake and migraine in pre-menopausal and post-menopausal women to assess possible differences in menopausal status. Additionally, we conducted sensitivity analyses incorporating NHANES complex sampling design, with consistency between weighted and unweighted approaches validating the robustness of our primary findings and reducing the likelihood of false-positive results. Several limitations warrant consideration when interpreting these findings. First, the cross-sectional design precludes causal inference, limiting conclusions to associations rather than causal relationships. Second, migraine classification relied on self-reported data, which may introduce misclassification bias, though this approach is consistent with previous NHANES-based migraine research and shows reasonable agreement with clinical criteria.[18,19] Third, unmeasured confounding remains a concern. The variables unavailable in NHANES include: medication use (oral contraceptives, hormone replacement therapy, migraine prophylaxis) that could affect both magnesium metabolism and migraine occurrence; psychosocial factors (stress, sleep quality) known to influence both dietary patterns and migraine susceptibility; genetic polymorphisms affecting magnesium absorption; and detailed hormonal profiles in pre-menopausal women. Additionally, our analysis used total magnesium intake rather than bioavailable magnesium, which varies considerably based on individual absorption capacity and genetic factors. Fourth, generalizability may be limited to adult women in the United States, requiring validation in diverse populations before broader application.

These findings have important clinical and public health implications, though several limitations warrant consideration. These exploratory findings suggest that dietary assessment and counseling regarding magnesium-rich foods might warrant consideration as part of comprehensive migraine management in pre-menopausal women, particularly those with documented dietary magnesium inadequacy. However, healthcare providers should exercise caution when incorporating these findings into clinical practice until prospective studies establish causality and optimal intervention strategies. Future research priorities should include prospective cohort studies to establish temporal relationships, randomized controlled trials to determine optimal dosing and formulation, mechanistic studies examining magnesium-estrogen interactions, and validation studies in diverse populations. Additionally, cost-effectiveness analyses comparing magnesium-based interventions with conventional prophylaxis would inform evidence-based clinical decision-making and guide potential population-level interventions for reproductive-age women.

Conclusion

This cross-sectional analysis suggests that menopausal status may modify the association between magnesium intake and migraine in women. We identified a non-linear relationship between magnesium intake and migraine odds in pre-menopausal women, with a protective association below the threshold, while no significant association was observed in post-menopausal women. These exploratory findings suggest a potential association between adequate magnesium intake and reduced migraine odds among reproductive-age women, though the observational design limits causal inference. The clinical relevance of these findings requires validation through prospective cohort studies and randomized controlled trials to establish causality, determine optimal dosing strategies, and evaluate the efficacy of magnesium-based interventions for migraine prevention in pre-menopausal women.

Ethics Statement

The data used in this study were obtained from the publicly available National Health and Nutrition Examination Survey (NHANES) database. The NHANES study was conducted in accordance with the Declaration of Helsinki and approved by the National Center for Health Statistics Research Ethics Review Board. All participants provided written informed consent, and the publicly available data have been de-identified to protect participant privacy.

This secondary analysis was reviewed and approved by the Ethics Committee of Shangyu People's Hospital of Shaoxing, Zhejiang (Approval No. 202500101). The committee determined that this study met the criteria for expedited review as it involved analysis of existing, publicly available, de-identified data. Additional information regarding the original ethical approval for NHANES data collection can be found at: https://www.cdc.gov/nchs/nhanes/about/erb.html.

Disclosure

The authors report no conflicts of interest in this work.

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