

ORIGINAL RESEARCH

Magnesium Intake and Depression in Adults

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Background: Depression is a common and often disabling disorder. Magnesium supplementation has been linked to improvement in depressive symptoms, but consensus on the relationship between magnesium and depression has not been reached.

Methods: The purpose of this study was to test the existence of an association between dietary magnesium intake and depression in the adult US population. A cross-sectional, population-based data set (National Health and Nutrition Examination Survey) was used to explore the relationship of magnesium intake and depression in 8894 US adults (mean age, 46.1 years; 47.4% men) from 2007 to 2010. Using logistic regression to model the relationship between the presence of depression (Patient Health Questionnaire score ≥ 5) and low magnesium intake (< 184 mg/day), we examined the risk ratio (RR) of magnesium intake and its 95% confidence interval.

Results: After adjusting for all potential confounders, the strength of the association of very low magnesium intake with depression was statistically significant (RR = 1.16; 95% CI, 1.06–1.30). Adjusting for all other covariates, low magnesium intake was associated with depression in subjects younger than age 65 (RR, 1.22; 95% CI, 1.06–1.40; $P = .007$) but seemed to be protective in seniors (RR, 0.75; 95% CI, 0.56–0.98; $P = .032$).

Conclusions: We found a significant association between very low magnesium intake and depression, especially in younger adults. The finding of the potential protective effect of low magnesium intake in older adults is surprising and warrants further investigation. (J Am Board Fam Med 2015;28:249–256.)

Keywords: Depression, Dietary Supplements, Nutritional Sciences

Depression is a common and disabling disorder. Almost 11% of adults older than 60 and 18.8% of those younger than 60 suffer from depression.¹ Although both pharmacologic and behavioral therapies are effective for many patients, they have important limitations. Medications can take weeks to have an effect, often have significant adverse effects, and fail to help many patients.² Nonpharmacologic approaches such as cognitive behavioral therapy also are effective³ but require highly

trained therapists and weeks to achieve effectiveness.

As a result of the need for additional treatment options, interest in the role of nutrition in modulating depressive symptoms has grown. Magnesium plays a role in many of the pathways involved in the pathophysiology of depression and is found in several enzymes, hormones, and neurotransmitters.⁴ Depression and magnesium both are associated with systemic inflammation.^{5,6} National data indicate a significant portion of the population has a magnesium intake below the estimated average requirement (EAR).⁷

Magnesium supplementation has been linked to improvements in symptoms of major depression,⁸ premenstrual symptoms,⁹ postpartum depression,⁸ and chronic fatigue syndrome.¹⁰ Low magnesium status has been associated with increased depressive symptoms in several different age groups and ethnic populations.^{11–14}

Issues in study design have led to inconclusive results and skepticism about the role of magnesium in depression. Serum magnesium concentrations

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were used to indicate magnesium status in some studies,^{11,15} but their reliability is questionable.^{16,17} Clinical trials have suffered from limited sample sizes,^{10,11} the use of the supplement magnesium oxide¹⁸ (which is poorly absorbed),¹⁷ and restrictive inclusion criteria.¹¹ With varying outcomes, different populations and age ranges, and limited sample sizes, consensus on the relationship between magnesium intake and depression has not been reached.

Some cross-sectional studies have reported an inverse relationship between magnesium intake and standardized depression scores in populations with low magnesium intake.^{12-14,19} Because these studies were conducted outside of the United States, their results should be validated in a US population. One longitudinal study²⁰ did not find an inverse relationship, although the study was underpowered to detect a significant reduction in depression.

If proven effective, increased magnesium consumption through diet or supplementation might address some of the limitations of currently available treatment. Magnesium is found in many common foods, and consumption of these foods can easily affect magnesium status. Although it can lead to hypermagnesemia and diarrhea, magnesium supplementation is, in general, a safe treatment with few unanticipated side effects. Magnesium supplementation provides quick results. Case studies of magnesium supplementation reported improvements in depression, anxiety, and sleep within 1 week.^{8,11} Therefore, we sought to test the existence of a relationship between dietary magnesium intake and depression using a large, cross-sectional, population-based data set from the United States.

Subjects and Methods

Data Source and Subjects

To investigate the question of whether there is an association between depression and magnesium intake, we conducted a cross-sectional study using the National Health and Nutritional Examination Survey (NHANES). NHANES participants undergo extensive interviews and laboratory assessments, including measures of dietary intake, dietary supplements, socioeconomic factors, clinical characteristics, and personal habits.²¹ By applying a weighting scheme supplied by the Centers for Disease Control and Prevention, NHANES can be used to represent the sex-, age-, race-, and ethnic-

ity-adjusted noninstitutionalized population of the United States. To increase the power of the analyses, we combined data from 2 separate waves of the survey (2007 to 2008 and 2009 to 2010).²² We included all subjects at least 20 years old with complete data for the outcome, predictor, and all candidate confounders.

Variables

The main predictor variable was total magnesium intake in milligrams per day calculated from 24-hour dietary and supplement recall data. Intake was used because of the unreliability of serum magnesium concentrations¹⁶ and because it is directly modifiable and could serve as an intervention. Low magnesium intake was defined as intake in the lowest quintile (<184 mg/day). Magnesium deficiency was defined with age- and sex-varying thresholds taken from the EAR as intake <350 mg/day for men >30 years old, <330 mg/day for younger men, <265 for women >30 years old, and <255 mg/day for younger women.²³

The outcome variable was the score on the 9-item Patient Health Questionnaire (PHQ-9), a validated survey tool for measuring the presence and severity of depression in adults.²⁴ The PHQ-9 score is the sum of the responses to 9 items representing symptoms of depression. Each is graded by the patient according to how often they have experienced the symptoms over the previous 2 weeks, from 0 (not at all) to 3 (nearly every day). PHQ-9 scores range from 0 to 27 and were dichotomized into depressed (PHQ-9 score of 5-27) or not (PHQ-9 score of 0-4).

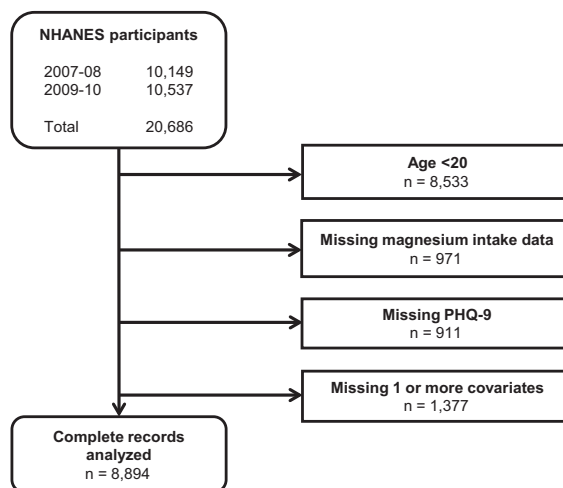
Based on a review of the literature and our clinical experience, we considered age, sex, race, ethnicity, education, marital status, household income, food security, tobacco use, alcohol intake, diabetes, kidney disease, and folate intake as potential confounders of the relationship between depression and magnesium intake. Race and ethnicity were combined into a single dichotomous variable of non-Hispanic white versus all others. Education was dichotomized as having a high school diploma (or equivalent) versus not. Marital status was characterized as married or living as married versus single, divorced, widowed, or separated. Household income was dichotomized as low if it was reported to be ≤\$35,000 per year. Food insecurity was present if the subject endorsed any of the following 3 statements: "(I/we) worried whether (my/our) food

would run out before (I/we) got money to buy more” or “The food that (I/we) bought just did not last, and (I/we) did not have money to get more” or “(I/we) could not afford to eat balanced meals.” Tobacco use was considered present if the patient endorsed current smoking versus absent for former smokers and those who never smoked. Alcohol use was coded as the average number of units consumed per day over the past year. A unit of alcohol is 1 can of beer, 1 glass of wine, or 1 ounce of liquor. Nondrinkers were coded as zero. Diabetes and kidney disease were considered present if the patient endorsed that a doctor or other health professional had told them they had such a diagnosis. Folate intake (micrograms/day) included dietary folate equivalents of food plus supplements and was dichotomized at $<230 \mu\text{g}/\text{day}$ (the lowest quintile of daily folate intake).

Statistical Analysis

The primary hypothesis was that depression is associated with magnesium intake while adjusting for possible confounders. We used unadjusted non-parametric Wilcoxon tests of trend to assess the relationships between quintiles of magnesium intake and other subject characteristics.²⁵ We used logistic regression to model the relationship between the presence of depression (PHQ-9 score ≥ 5) and low magnesium intake ($<184 \text{ mg}/\text{day}$, the lowest quintile) and tested the hypothesis by examining the odds ratio (OR) and relative risk²⁶ (RR) of magnesium intake and their 95% confidence intervals (CIs). Each potential confounder was tested in a separate univariate logistic regression for association with the outcome (depression) and the main predictor (low magnesium intake). If the variable was associated with both the outcome and predictor (each $P < .1$), it was considered a potential confounder and included in the multivariate model. We also explored the use of magnesium as a function of energy intake (milligrams of magnesium/1000 calories) as the predictor by following the same procedure. Because both magnesium intake²⁷ and depression¹ vary with age and sex, we constructed additional models including interaction terms to explore the possibility of interactions of magnesium with sex and magnesium with age. All analyses used the stratification and weighting scheme recommended for NHANES by the National Center for Health Statistics²² using Stata software version 13.1 (StataCorp, College Station,

Figure 1. Inclusion flow diagram. NHANES, National Health and Nutrition Examination Survey; PHQ-9, 9-item Patient Health Questionnaire.



TX). P values $<.05$ were considered statistically significant.

Results

Of the adult subjects in the NHANES data set, 73% met eligibility criteria, for a final sample size of 8894 (Figure 1). The characteristics of the sample are described in Table 1. All the selected covariates showed significant trends across the quintiles of magnesium intake. Depression was most prevalent in the lowest quintile of magnesium intake.

The univariate regression of low magnesium intake and depression demonstrated a strong, statistically significant association, with an OR of 1.73 (95% CI, 1.48–2.02) and an RR of 1.49 (95% CI, 1.35–1.66) (Table 2). All the potential confounders were associated with both low magnesium and depression ($P < .1$) and were retained in the multivariate model (except household income because it was highly correlated with food insecurity). After adjusting for all potential confounders, the strength of the association of low magnesium intake with depression was attenuated but remained statistically significant, with an OR of 1.21 (95% CI, 1.02–1.42) and an RR of 1.16 (95% CI, 1.06–1.30). The use of magnesium as a function of energy gave similar results.

Over half of the population (54%) reported deficient magnesium intake (less than the EAR). Deficiency was significantly associated with depression

Table 1. Subject Characteristics by Quintile of Magnesium Intake*

Characteristics	Quintile					Total
	1	2	3	4	5	
Sample size (n)	1,681	1,727	1,834	1,816	1,836	8,894
Magnesium intake						
Mean (mg/day)	138	216	281	361	581	334
Range (mg/day)	0–183	184–246	247–315	316–417	418–2437	0–2437
Deficient intake (%)	100	100	58.5	18.1	0	54.0
Depression (PHQ-9 score)						
Mean	4.1	3.3	2.8	2.8	2.8	3.1
Range	0–27	0–27	0–24	0–25	0–27	0–27
Depressed (score ≥ 5) (%)	32.2	24.5	20.5	20.5	21.1	23.2
Mean age (years)	44.6	45.8	46.2	46.9	46.5	46.1
Senior (≥ 65 years old) (%)	16.6	16.5	16.7	14.7	13.9	15.5
Race/ethnicity (%)						
Mexican-American	15.9	17.4	18.5	18.2	17.7	17.6
Other Hispanic	12.6	12.4	11.1	9.3	8.7	10.8
Non-Hispanic white	39.2	44.1	46.6	52.1	57.3	48.1
Non-Hispanic black	28.7	21.8	18.9	15.9	12.1	19.3
Other	3.6	4.2	4.9	4.5	4.3	4.3
Male sex (%)	26.9	38.8	46.2	53.5	63.2	47.4
Social (%)						
High school graduate	73.6	80.8	82	86.5	86.7	82.5
Married (or living as married)	54.9	58.2	62.7	66.1	68.0	62.6
Food insecurity	23.4	16.3	13.5	11.0	10.8	14.4
Household income $< \$35,000$ /year	47.8	33.2	29.6	23.2	24.4	30.5
Habits						
Current smoker (%)	31.2	20.9	20.5	20	17.7	21.5
Mean drinks per day	0.4	0.5	0.5	0.7	0.7	0.6
Chronic disease (%)						
Diabetes	11	9.6	8.4	8.4	8.2	9
Kidney disease	3.7	1.9	1.2	0.7	1.1	1.6
Dietary folate equivalent intake [†] (%)	58.6	23.2	9.1	3.4	1.5	16.5

*The trend across quintiles of magnesium intake is significant with $P \leq .001$ for all characteristics using an unadjusted nonparametric test of trend.²⁵

[†]Lowest quintile ($< 230 \mu\text{g/day}$).

PHQ-9, 9-item Patient Health Questionnaire.

in the univariate model (OR, 1.13 [95% CI, 1.01–1.27]; RR, 1.10 [95% CI, 1.01–1.20]) but not in the multivariate-adjusted analyses (OR, 0.97 [95% CI, 0.85–1.09]; RR, 0.98 [95% CI, 0.88–1.07]).

Only one of the covariates had a significant interaction. Older age interacted significantly with low magnesium intake (OR, 0.51; 95% CI, 0.37–0.72). Adjusting for all other covariates, low magnesium intake was associated with depression in subjects younger than age 65 (OR, 1.31 [95% CI, 1.08–1.58]; RR, 1.22 [95% CI, 1.06–1.40]) but seemed to be protective in seniors (OR, 0.69 [95% CI, 0.49–0.97]; RR, 0.75 [95% CI, 0.56–0.98]) (Figure 2).

Discussion

Overall, we found a significant association between low magnesium intake and depression, especially in younger adults. The increased prevalence of depression was confined to the lowest levels of magnesium intake. Nonetheless, the effect is very strong, with a $> 50\%$ higher rate of depression in the lowest quintile of intake compared with those consuming greater amounts. A very different pattern among seniors was observed (Figure 2 and Table 3). First, the overall rates of depression were lower. Second, the spread in rates across the levels of magnesium intake were much higher for younger

Table 2. Logistic regressions on depression

Independent Variables	Odds Ratio	95% CI	P Value
Univariate model			
Low magnesium	1.73	1.48–2.02	<.001
Multivariate model			
Low magnesium	1.21	1.02–1.42	.026
Male	0.61	0.53–0.70	<.001
Age ≥65 years	0.65	0.54–0.77	<.001
Non-Hispanic white	0.95	0.68–1.32	.75
High school graduate	0.77	0.64–0.93	.007
Married	0.70	0.61–0.80	<.001
Drinker	1.06	0.99–1.12	<.073
Chronic kidney disease	2.50	1.66–3.79	<.001
Smoker	1.78	1.52–2.10	<.001
Diabetes	1.63	1.29–2.06	<.001
Food insecurity	2.30	1.90–2.78	<.001
Low folate intake	1.11	0.92–1.35	.28

CI, confidence interval.

adults (23% to 37%) than in seniors (15% to 21%). Third, the lowest quintile of intake among seniors did not have the highest prevalence of depression. Rather, the highest rates occurred in the group with the highest intake. Although the adjusted odds of depression were significantly greater in the group with the highest intake compared with the lowest quintile, there was no clear dose–response relationship, and the clinical significance of this

Figure 2. Prevalence of depression adjusted by magnesium intake and age. The prevalence estimates for each quintile of magnesium intake for each age group were adjusted for sex, race, ethnicity, education, marital status, alcohol intake, smoking, kidney disease, diabetes, food insecurity, and low dietary folate. Quintiles of magnesium intake (by age) are presented as milligrams per day.

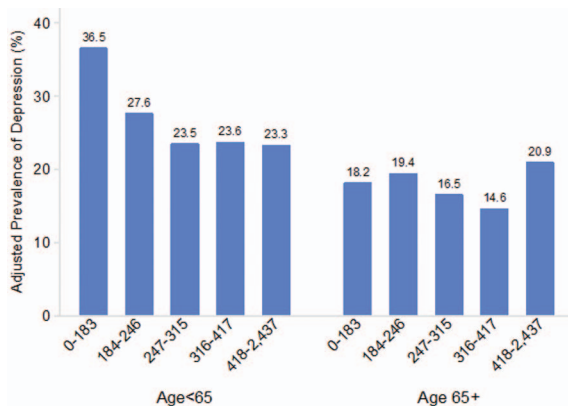


Table 3. Adjusted Odds of Depression by Age and Magnesium Intake*

Magnesium Intake (mg/day)	Odds Ratio	95% CI	P Value
Age <65			
0–183	1		
184–246	0.81	0.67–0.98	0.032
247–315	0.69	0.52–0.92	0.012
316–417	0.76	0.63–0.91	0.005
418–2437	0.80	0.59–1.09	0.15
Age ≥65			
0–183	1		
184–246	1.38	0.87–2.18	0.17
247–315	1.29	0.79–2.10	0.29
316–417	1.30	0.83–2.03	0.24
418–2437	2.15	1.34–3.45	0.002

*Odds ratios and confidence intervals (CIs) were adjusted for sex, race, ethnicity, education, marital status, alcohol intake, smoking, kidney disease, diabetes, food insecurity, and low dietary folate.

finding is uncertain. The large sample size available for analysis (372 to 435 seniors in each quintile of magnesium intake) may be responsible for making a small or even negligible effect seem statistically significant. Even if we discount the seemingly adverse effect of high magnesium intake in seniors, however, there is little doubt that the increased prevalence of depression with low intakes seen in younger subjects is absent after age 65.

By 2030, close to 20% of the population will be older than 65 (up from the current 12.9%).²⁸ Therefore, the number of people with late-life depression also will increase. Depression later in life increases the risk for cardiovascular disease and mortality,^{29–31} and depressive symptoms lasting >1 year are associated with a significant increased risk of mortality.²⁹ Newly depressed older adults are at a higher risk for mortality, and those with worsening depression have a 70% increase in mortality risk compared with patients with stable depression scores.²⁹ Therefore, understanding modifiable risk factors for depression in the older population is particularly useful.

Our data show over half of adults do not consume adequate amounts of magnesium. This finding is similar to other US population studies.⁷ Magnesium excretion increases while absorption decreases with age³² because of various chronic diseases and decreased intake of foods high

in magnesium. Compared with imipramine, magnesium supplementation was effective in treating depression in older adults with hypomagnesemia and type 2 diabetes in a randomized controlled trial.¹¹ The current analysis differs by suggesting a detrimental effect of higher magnesium intake in older adults. The differences may be because this is a study of a general US population with low intake rather than a group selected for low serum magnesium concentrations and diabetes.

Little is known about the mechanism of the possible effect of magnesium on depression. Even less is known about this mechanism in the elderly and why the association might differ between age groups. The current findings might be due to unidentified confounders, reverse causality, or data error. The PHQ was comparable with the Geriatric Depression Screen in a convenience sample of elderly primary care patients.³³ The existence of an emotional paradox in elders,³⁴ however, in which older adults experience higher levels of well-being despite cognitive and physical decline, may influence how depression is identified and scaled in this group and may make the PHQ less sensitive.

Several studies have looked at whether overall dietary pattern is more important than specific nutrients when considering the influence of nutrition on depression. Among adults with mood disorders, mineral intakes may be associated with psychiatric disorders more so than vitamin intakes.³⁵ We cannot rule out that a specific dietary pattern or combination of nutrients would show a synergistic effect and a stronger relationship with depression than magnesium alone. For instance, residents of Greece, where most people follow a Mediterranean diet, have a lower rate of depression and mental disorders.^{36,37} Changing dietary patterns takes time, however, as well commitment on the part of the patient. Emphasis on the consumption of foods high in magnesium, such as green leafy vegetables, legumes, nuts, seeds, and whole grains, could offer a dietary approach to controlling symptoms of depression. Advocating for increased magnesium intake through food can lead to a healthier overall diet and might be attractive to patients who have previously experienced unwanted side effects from medications for depression. Magnesium supplementation may be effective in as little as 1 week⁸ but may lead to gastrointestinal upset such as nausea, vomiting, or diarrhea in some people. However, toxic concentrations are unlikely to occur

when the recommended dose of magnesium is given and kidney function is normal.¹⁶ Whether increased dietary magnesium would lead to an improvement in symptoms as quickly as supplements is unknown.

Strengths and Limitations

This study has several strengths. The sample size was large and representative of almost 180 million American adults. The analysis includes the most recent available data from 2007 to 2010 and captures both dietary and supplemental intake. Although the assessment of magnesium intake at only one time point may not reflect long-term intake, trained interviewers collected the data, and the methods were validated and consistent over the 4 years of data collection.³⁸ In addition to social, demographic, behavioral, and clinical covariates, this analysis also controlled for folate intake, which has not been included in many previous analyses.

As with all observational studies, we cannot exclude the possibility of additional confounding not accounted for by the analysis. Likewise, we cannot rule out reverse causality to explain the association between magnesium intake and depression. In other words, poor dietary intake of magnesium could be a result of mental illness.

Conclusion

This study enlarges on previous research that found a relationship between magnesium intake and depression. Although very low magnesium intake seemed to be protective against depression among seniors, it was associated with higher rates of depression in younger adults. Rigorous, randomized clinical trials with adequate power to analyze subgroups are needed to confirm the effects of magnesium on depression.

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