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RESEARCH ARTICLE

Association between magnesium intake and cognition in US older adults: National Health and Nutrition Examination Survey (NHANES) 2011 to 2014

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Abstract

Introduction: Identifying nutrition- and modifiable lifestyle-based risk factors for cognitive decline and dementia may contribute future primary prevention strategies. This study aimed to evaluate the associations between magnesium intake and cognition in older adults in the United States.

Methods: Based on the National Health and Nutrition Survey (NHANES) between 2011 and 2014, the study included 2508 participants aged 60 years and older. Linear regression models were used to examine the association of total magnesium intake with cognition.

Results: After adjusted demographic and other confounding factors, intakes of energy and total calcium, and serum vitamin D level, higher intake of total magnesium was independently associated with 0.15 higher global cognitive *z*-score (95% confidence interval, 0.02 to 0.28 for highest vs. lowest quartile, *P* trend = .037). The positive association of total magnesium intake with global cognition was primarily presented among women, non-Hispanic Whites, and those with sufficient serum vitamin D levels (≥50 nmol/L), although interactions were not significant. There were no clear linear associations for global cognition with serum vitamin D level.

Discussions: Our findings suggest that high magnesium intake alone may improve cognition in older adults, particularly among non-Hispanic Whites and subjects with sufficient levels of serum vitamin D. Further studies are needed to confirm the findings.

KEYWORDS
cognitive function, magnesium intake, older adults, race/ethnicity, serum vitamin D, sex

1 | BACKGROUND

With an aging population in the United States, cognitive impairment and dementia have rapidly become one of the most daunting healthcare and public health challenges.[1] Except the recently approved drug for Alzheimer's disease (AD),[2] there are no other effectively pharmacologic therapies to target and affect the process of dementia. Therefore, identifying primary prevention strategies through modifiable risk factors, such as dietary factors, has public health and clinical significance to prevent or retard the occurrence of cognition impairment and dementia.

Magnesium, the second most abundant intracellular cation in the human body, plays an important role in numerous physiologic activities, including energy production; lipid and glucose metabolism; synthesis of

DNA, RNA, and protein; and inflammation.[3–5] In addition, magnesium plays a critical role in the regulation of N-methyl-D-aspartate (NMDA) receptor excitability in the brain.[5,6] NMDA receptors are essential for excitatory synaptic transmission, neuronal plasticity, and neurodegeneration, and can be blocked by magnesium ions.[5] Previous studies have shown that intake of magnesium supports normal functions of neurons through protecting neurons from degeneration by NMDA-induced excitotoxicity.[5,7]

A few observational studies with inconsistent results have examined the association between low intake of magnesium and cognitive function and risk of dementia and AD.[8–11] The inconsistency may be due to the discrepancies in study design, sample size, study population, statistical methods, and assessments of magnesium intake and cognition. In particular, many previous studies failed to consider the possible interactions between magnesium and other nutrients, such as vitamin D, on cognition. Accumulative evidence has described the role of vitamin D in the brain.[12] The conversion of vitamin D from its storage or inactive form into an active form is dependent on the bioavailability of magnesium.[13,14] There is evidence that vitamin D also can stimulate intestinal absorption of magnesium,[15] while magnesium deficiency results in a decreased in serum 1,25-dihydroxyvitamin D ($1,25[OH]_2D$).[16] A recent randomized controlled trial reported that an optimal magnesium intake may be important for optimizing circulating 25-hydroxyvitamin D (25[OH]D) levels, highlighting the interaction between these micronutrients and the importance of adequate balance of magnesium and vitamin D.[17]

Moreover, variations in dietary habits and quality by sex and race/ethnicity may partially explain the inconsistency in the existing evidence.[18] Magnesium intake has been historically low in the US population.[4] Women consume less magnesium than men, and non-Hispanic Blacks (NHBs) consume less than non-Hispanic White (NHW) counterparts.[19–21] Disparities in cognitive decline and dementia risk based on sex and race/ethnicity also exist in older adults. There is evidence that dementia affects more Hispanics and NHBs than NHWs,[22] and females have higher risk of dementia than males.[23,24]

To grow our understanding of the role of magnesium intake in cognition, we studied the association between magnesium intake and cognition in older adults, and estimated whether the magnesium–cognition associations vary by possible effect modifiers, such as race/ethnicity, sex, and serum 25(OH)D level, using data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2014.

HIGHLIGHTS

- Based on data of participants aged 60 years and older from the National Health and Nutrition Survey (NHANES) 2011 to 2014, high magnesium intake was independently associated with better cognition.
- The positive association between magnesium intake and cognition was limited in women but not in men, as well as in non-Hispanic Whites but not in other racial/ethnic groups.
- Among participants with sufficient serum vitamin D (≥50 nmol/L), high magnesium intake was positively associated with better cognition.

RESEARCH IN CONTEXT

1. Systemic review: The authors reviewed the literature using traditional (e.g., PubMed) sources. Potential association between magnesium intake and cognitive health has been investigated; however, many previous studies failed to consider the possible interactions between magnesium and vitamin D status on cognition.
2. Interpretation: Our findings showed independent protective effects of high magnesium intake on cognitive health in a nationally representative sample of the US elderly population, and the positive association between magnesium intake and cognition was primarily presented among women, non-Hispanic Whites, and those with sufficient serum vitamin D levels.
3. Future directions: Further studies including prospective studies with a larger sample of minority older adults are necessary to confirm our findings and to test the optimal levels of serum vitamin D and magnesium intake.

2 | METHODS

2.1 | Study population

This study used data from the continuous NHANES survey from two survey cycles, conducted between 2011 and 2014, in which cognitive functioning among older adults was assessed. The NHANES is a survey designed to assess health and nutrition in a nationally representative sample of the non-institutionalized US population. A detailed description of the study design has been published previously.[25] The survey is maintained and administered by the National Center for Health Statistics (NCHS) under the purview of the Centers for Disease Control and Prevention (CDC). Participants who were aged < 60 years at time of the survey were excluded in the study population. Participants with unreliable dietary data, missing data for total magnesium intake, serum 25(OH)D, cognition tests, or potential confounders were further excluded from the analyses, leaving a total of 2508 subjects included in the analysis. All participants provided written informed consent and the institutional review board of the NCHS approved the survey protocol.

2.2 | Cognitive function

To assess cognitive functioning, NHANES used three cognitive tests among participants aged 60 years and older in the 2011 to 2014 cycles, including the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word Learning subset assessing immediate and delayed learning ability for new verbal information (memory sub-domain); the animal fluency (AF) test to examine categorical verbal fluency (component of executive function); and the Digit Symbol Substitution Test (DSST) to assess processing speed, sustained attention, and working memory.[26]

The modules from CERAD consist of three consecutive learning trials and a delayed recall. Participants were asked to recall as many words as possible immediately after 10 unrelated words were read in the learning trials. The delayed word recall occurred after the other two cognitive tests were completed (≈8–10 minutes from the start of the learning trials). The immediate recall (CERAD-IR) score was calculated as the sum of the three immediate recall assessments, ranging from 0 to 30, and the delayed recall (CERAD-DR) score ranged from 0 to 10. Participants taking the AF test were asked to name as many animals as possible in 1 minute. A point was given for each named animal. The DSST test has been described previously.[27] Briefly, participants were asked to copy, in 2 minutes, as many number-corresponding symbols as possible in 133 empty boxes that adjoin the number on paper. The score was the total number of correct matches, ranging from 0 to 133.

We calculated a composite *z*-score for global cognition by averaging the standardized scores of each cognitive test.

2.3 | Assessments of magnesium intake

Details of the protocol and dietary intake assessed in the Mobile Examination Center (MEC) by trained interviewers have been described previously.[28] Briefly, daily dietary intake information was obtained via 24-hour recalls,[29] and 30-day dietary supplement questionnaire interviews. Information about type, consumption frequency, duration, and amount taken over the past 30 days was collected for each reported dietary supplement. Two 24-hour recalls were conducted in NHANES 2011 to 2014. The first dietary recall was administered in person by trained interviewers in NHANES MEC and the second dietary recall was completed by trained interviewers via telephone 3 to 10 days after the MEC interview.[28] To keep intake information consistent, only the in-person dietary recall for all subjects was used in the present analysis. Total intakes of magnesium and other nutrients were calculated by summing intake from diet and supplements.

2.4 | Assessment of serum 25(OH)D

Blood was drawn from participants in MEC by certified phlebotomists. Serum 25 hydroxyvitamin D2 and D3 (25[OH]D_2, and 25[OH]D_3) analysis was performed at multiple government and contract labs using high-performance liquid chromatography–tandem mass spectrometry. This method of mass spectrometry offers a cost-effective, sensitive, and rapid test for 25(OH)D levels in nanomolar concentrations.[30] Blood serum levels of 25(OH)D were captured in nanomolar per liter (nmol/L).

2.5 | Covariates

We considered a number of risk factors for cognitive decline as potential confounding factors, including sex (male, female); race/ethnicity (NHW, NHB, Hispanic, and other races); education (less than high school, high school, and at least some college); cigarette smoking status (never, former, current), alcohol use status (never, former, current), physical activity level (no and low level, moderate, and high level); depression (yes [the brief Patient Health Questionnaire (PHQ-9) score ≥10], no [the PHQ-9 score <10]); history of diabetes, heart attack, or stroke (ever, never); and season of exam (November–April, May–October). Age, body mass index (BMI), daily intakes of total energy (kcal), and total calcium (mg) were included as continuous variables for adjustment in the models.

2.6 | Statistical analysis

Given the complex nature of the NHANES multistage sampling design, the "Survey" procedure in SAS 9.4 software (SAS Institute) was used to estimate variance after incorporating the sampling weights in the multistage sampling design. Characteristics of participants were described by magnesium quartiles as means and proportions for continuous and categorical variables, respectively. The association of magnesium intake with cognitive performance was examined using linear regression models. In addition to examining serum 25(OH)D as a potential confounding factor, we also examined whether serum 25(OH)D was related to global cognitive *z*-score. In the linear regression models, global cognitive *z*-score was the dependent variable, and the predictors, total magnesium intake and serum 25(OH)D level, were categorized into quartiles with the lowest quartile as the reference. Magnesium intake and serum 25(OH)D were mutually adjusted to each other to assess the independent association of total magnesium intake and serum vitamin D level, respectively. Tests for dose–response relationship were estimated by fitting models with median values to each quartile of exposure variables and included as continuous variables. Additionally, stratified analyses by potential effect modifiers and tests for multiplicative interactions using the Wald test were conducted.

Post hoc analyses were performed for individual CERAD-IR, CERAD-DR, and AF score similar to the analysis for global cognitive score. Sensitivity analysis was performed through further excluding participants who self-identified to have difficulties in thinking and remembering in the past 12 months. We did not include analysis for DSST score here, because we have examined the association between

magnesium intake and DSST score previously.[27] All reported *P*-values were two-tailed, and statistical significance was set at .05.

3 | RESULTS

Participants with lower magnesium intake were more likely to be female, NHB, and have less education than those with higher intake of magnesium (Table 1). Those with lower magnesium intake were also more likely to be physical inactive, current smokers, never drinkers, and to have greater body mass index (BMI), lower intakes of total energy and calcium, and lower serum 25(OH)D levels.

Compared to those in the lowest quartile, subjects with the highest quartile of total magnesium intake had higher global cognitive score after adjustment for age, other confounding factors, intakes of total energy and total calcium, and serum 25(OH)D (β = 0.15, 95% confidence interval [CI]: 0.02 to 0.28, *P* trend = .037; Table 2). The positive association was also observed for AF and DSST[27] test scores, but not for CERAD tests. Serum 25(OH)D was neither associated with global cognitive score nor the scores of all individual cognitive tests.

The association of total magnesium intake with cognitive function was further examined stratifying by potential modifiers (Table 3). Among subjects with serum 25(OH)D level ≥50 nmol/L, compared to those with the lowest quartile intake, subjects who consumed total magnesium at the highest quartile had higher scores on global cognitive function (β = 0.17, 95% CI: 0.01 to 0.32; *P* for trend = .049) and AF test (β = 1.24, 95% CI: 0.03 to 2.45; *P* for trend = .076). However, no significant interactions between magnesium intake and serum 25(OH)D level were observed on global cognitive function and in all individual cognition tests. After adjustment, the association between higher total magnesium intake and increased global cognitive function score appeared stronger among NHWs and women, while the positive magnesium intake–AF test association was primarily limited to NHWs and men. However, there were no significant interactions between total magnesium intake and sex and race/ethnicity. We further evaluated the associations across age groups. Similar patterns of associations between total magnesium intake and global cognitive function were observed among subjects aged ≥65 years and relatively young subjects (≥60 to <65 years; *P* for interaction = .65; data not shown).

We also conducted stratified analyses of serum 25(OH)D by sex and race/ethnicity (Table 4). In stratified analyses by sex, we found a marginal interaction between serum 25(OH)D quartile and sex in CERAD-DR score (*P* for interaction = .069). Serum 25(OH)D level was not significantly associated with global cognitive score and all individual cognitive test scores in different racial/ethnic groups.

We further tested the joint effect of magnesium intake and serum 25(OH)D on cognition (Table S1 in supporting information). Compared to those with insufficient magnesium intake (<350 mg/d) and the lowest quartile serum 25(OH) D level, a significant increase in global cognitive score was observed among subjects with a sufficient total magnesium intake (≥350 mg/d) and highest quartile of serum vitamin D. Excluding participants with difficulties in remembering or thinking, the associations with total magnesium intake were attenuated slightly, but remained significant for global cognition. Results of stratified analyses in sensitivity analyses were similar to the main results (data not shown).

4 | DISCUSSION

Using data from two recent continuous NHANES cycles, we found that high total magnesium intake was independently associated with better cognition in older adults. Moreover, the positive association between magnesium intake and cognition was primarily presented among women, NHWs, and subjects with a sufficient serum vitamin D level; however, interactions were not statistically significant. In addition, there were no clear linear associations for global cognition with serum vitamin D level.

Magnesium may target different pathways in dementia pathology. NMDA receptors, an inotropic glutamatergic receptor, play important roles in developmental plasticity, learning, and long-term memory.[31] Activated by glutamate, NMDA receptors are permeable to calcium, sodium, and potassium ions, and blocked by magnesium ions at a normal membrane potential.[5] Under reduced extracellular magnesium ion concentrations, fewer NMDA channels are blocked and NMDA receptor activity will be abnormally enhanced.[31] Over activated NMDA receptors can cause hyperexcitability of the neurons and neuronal necrosis.[5,31] In addition, magnesium has a critical role in the regulation of oxidative stress and neuroinflammation. Magnesium deficiency has been shown to increase the release of substance P, a neuroinflammatory tachykinin, and stimulate secretion of inflammatory mediators such as interleukins, tumor necrosis factor alpha, and nitric oxide.[5,32] The crosstalk between these mediators and amyloid beta in glial cells and neurons could ultimately aggravate the development and progression of cognitive impairment and dementia.[5,32] Our findings are consistent with previous studies that reported better cognitive function or lower risk of dementia among subjects with a higher magnesium intake.[8–10] Another retrospective study also found protective association between magnesium oxide, a commonly prescribed laxative, and risk of dementia.[33] These studies, including our findings, suggest that high magnesium intake seems to be associated with better cognitive function, regardless of the resources of magnesium intake.

In addition, we found that the positive association between magnesium intake and global cognition was primarily among subjects with sufficient serum 25(OH)D level. Higher vitamin D level seems to increase magnesium absorption in the intestine,[15] and retention[34] in both animal and human models. It is possible that optimal magnesium intake produces beneficial effects on cognitive function when serum vitamin D status is sufficient. In the joint analysis, we further observed that subjects with sufficient total magnesium intake and a higher serum 25(OH)D level had the highest increase in global cognitive score. The sufficient magnesium intake (i.e., ≥350 mg/d) was comparable to 320 mg/d, the Recommended Dietary Allowance for women aged >50 years.[35] Several randomized trial studies have reported magnesium to have synergic action on vitamin D metabolism in the body,[17,36] emphasizing the effect of sufficient intake of magnesium on optimal 25(OH)D levels. Our results indicated that there may be a synergistic interaction

TABLE 1 Participant characteristics by magnesium intake status, NHANES 2011 to 2014 (n = 2508)

Characters	Magnesium intake status			
	Q1 (<221.92) (n = 739)	Q2 (221.91–300.33) (n = 621)	Q3 (300.34–406.29) (n = 606)	Q4 (≥406.30) (n = 542)
Age (years)[a]	68.3 (0.52)	67.2 (0.49)	67.8 (0.88)	66.3 (0.73)
Serum 25(OH)D (nmol/L)[a]	72.0 (1.72)	77.5 (1.59)	80.4 (2.40)	85.2 (0.61)
Daily nutrient intake[a]				
Total calcium (mg)	606.1 (31.68)	946.0 (33.23)	1206.9 (38.55)	1476.1 (33.21)
Total energy intake (kcal)	1201.2 (37.02)	1762.6 (34.57)	2032.7 (39.47)	2394.1 (62.96)
Race/ethnicity, n (%)[b]				
Non-Hispanic White	324 (43.8)	320 (51.5)	312 (51.5)	306 (56.5)
Non-Hispanic Black	220 (29.8)	145 (23.4)	110 (18.1)	86 (15.9)
Hispanic	134 (18.7)	109 (17.5)	132 (21.8)	93 (17.1)
Others[c]	57 (7.7)	47 (7.6)	52 (8.6)	57 (10.5)
Sex, n (%)[b]				
Male	292 (39.5)	288 (46.4)	314 (51.8)	341 (62.9)
Female	447 (60.5)	333 (53.6)	292 (48.2)	201 (37.1)
Education, n (%)[b]				
Less than high school	235 (31.8)	153 (24.6)	111 (18.3)	97 (17.9)
High school	187 (25.3)	162 (26.1)	138 (22.8)	105 (19.4)
More than high school	317 (42.9)	306 (49.3)	357 (58.9)	340 (62.7)
Season of exam, n (%)[b]				
November to April	351 (47.5)	253 (40.7)	275 (45.4)	257 (47.4)
May to October	388 (52.5)	368 (59.3)	331 (54.6)	285 (52.6)
Physical activity level, n (%)[b]				
Inactive	488 (66.0)	373 (60.1)	312 (51.5)	259 (47.8)
Moderate	229 (31.0)	218 (35.1)	244 (40.3)	219 (40.4)
High	22 (3.0)	30 (4.8)	50 (8.2)	64 (11.8)
Smoking status, n (%)[b]				
Never	361 (48.9)	322 (51.9)	298 (49.2)	238 (43.9)
Former	250 (33.8)	217 (34.9)	224 (37.0)	245 (45.2)
Current	128 (17.3)	82 (13.2)	84 (13.9)	59 (10.9)
Alcohol use, n (%)[b]				
Never	125 (16.9)	101 (16.3)	87 (14.4)	57 (10.5)
Former	253 (34.2)	157 (25.3)	158 (26.1)	126 (23.3)
Current	361 (48.9)	363 (58.4)	361 (59.6)	359 (66.2)
BMI (kg/m^2)[a]	29.2 (0.42)	28.0 (0.37)	28.1 (0.44)	27.2 (0.41)
Diagnosis of diabetes, n (%)				
Yes	278 (37.6)	184 (29.6)	147 (24.3)	130 (24.0)
History of heart attack, n (%)				
Yes	79 (10.7)	49 (7.9)	51 (8.4)	41 (7.6)
History of stoke, n (%)				
Yes	55 (7.4)	37 (6.0)	39 (6.4)	35 (6.5)
Depression, n (%)				
Yes	87 (11.8)	43 (6.9)	46 (7.6)	47 (8.7)
Dietary supplement use, n (%)[b]				
Yes	127 (17.2)	210 (33.8)	279 (46.0)	327 (60.3)

[a]Values shown are median and (standard error).
[b]Unweighted frequency counts and weighted percentages shown.
[c]Others: included non-Hispanic Asian and other race.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; NHANES, National Health and Nutrition Examination Survey.

TABLE 2 Linear regression models for associations total magnesium intake and 25(OH)D level with cognitive tests score in NHANES 2011 to 2014

Cognitive test	Magnesium intake level				P_{trend}
	Q1 (<221.92) (n = 739)	Q2 (221.91–300.33) (n = 621)	Q3 (300.34–406.29) (n = 606)	Q4 (≥406.30) (n = 542)	
Global *z*-score					
β (95% CI)[a]	Reference	0.09 (−0.01, 0.20)	0.19 (0.11, 0.28)	0.23 (0.13, 0.32)	<.001
β (95% CI)[b]	Reference	0.06 (−0.05, 0.16)	0.14 (0.03, 0.25)	0.15 (0.02, 0.28)	.037
CERAD-IR					
β (95% CI)[a]	Reference	0.39 (−0.26, 1.04)	0.73 (0.05, 1.41)	0.81 (0.18, 1.44)	.011
β (95% CI)[b]	Reference	0.17 (-0.52, 0.86)	0.36 (−0.42, 1.13)	0.24 (−0.60, 1.09)	.624
CERAD-DR					
β (95% CI)[a]	Reference	−0.13 (−0.48, 0.22)	0.21 (−0.11, 0.53)	0.28 (−0.02, 0.58)	.015
β (95% CI)[b]	Reference	−0.17 (−0.50, 0.17)	0.15 (−0.23, 0.53)	0.19 (−0.25, 0.62)	.225
AF[a]					
β (95% CI)[a]	Reference	0.91 (0.19, 1.62)	1.20 (0.48, 1.93)	1.64 (0.79, 2.49)	.001
β (95% CI)[b]	Reference	0.71 (−0.02, 1.45)	0.94 (0.04, 1.85)	1.24 (0.18, 2.30)	.045
	Serum 25(OH) D level				
	Q1 (<62.60) (n = 844)	Q2 (62.60–79.29) (n =	Q3 (79.30–98.25) (n =	Q4 (≥98.26) (n = 513)	
Global *z*-score					
β (95% CI)[a]	Reference	−0.03 (−0.14, 0.09)	0.02 (−0.07, 0.10)	0.09 (−0.02, 0.19)	.056
β (95% CI)[c]	Reference	−0.06 (−0.18, 0.05)	−0.04 (−0.13, 0.04)	0.03 (−0.07, 0.12)	.394
CERAD-IR[a]					
β (95% CI)[a]	Reference	−0.09 (−0.90, 0.73)	0.01 (−0.63, 0.64)	0.38 (−0.24, 1.00)	.166
β (95% CI)[c]	Reference	−0.21 (−1.03, 0.60)	−0.26 (−0.91, 0.39)	0.12 (−0.54, 0.77)	.652
CERAD-DR					
β (95% CI)[a]	Reference	−0.31 (−0.72, 0.11)	−0.10 (−0.44, 0.23)	0.12 (−0.20, 0.44)	.259
β (95% CI)[c]	Reference	−0.35 (−0.74, 0.04)	−0.17 (−0.49, 0.14)	0.05 (−0.25, 0.35)	.405
AF					
β (95% CI)[a]	Reference	0.21 (−0.38, 0.79)	0.25 (−0.41, 0.90)	0.52 (−0.21, 1.25)	.203
β (95% CI)[a]	Reference	−0.03 (−0.62, 0.57)	−0.15 (-0.76, 0.46)	0.13 (−0.49, 0.74)	.753

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AF, animal fluency; BMI, body mass index; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease-delayed recall; CERAD-IR, Consortium to Establish a Registry for Alzheimer's Disease-immediate recall; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.

[a]Model 1: adjusted for age, sex, race/ethnicity, and education.

[b]Model 2: additionally adjusted for BMI; physical activity level; alcohol drinking; smoking status; history of diabetes, heart attack, or stroke; depression status; season of exam; intakes of total energy and calcium; and serum 25(OH)D level.

[c]Model 3: additionally adjusted for BMI; physical activity level; alcohol drinking; smoking status; history of diabetes, heart attack, or stroke; season of exam; depression status; intakes of total energy, calcium, and magnesium.

between magnesium and serum vitamin D on cognitive function. Further studies, particularly prospective studies, are warranted to replicate our findings, and to further assess the interaction between magnesium and vitamin D on cognition.

There has been evidence that minorities have higher prevalence and incidence of dementia and AD than NHWs.[22] Consistent with previous findings on diet and cognition,[37] our results showed a stronger protective role of total magnesium intake on cognition in NHWs than in other racial/ethnic groups. However, the Atherosclerosis Risk in Communities (ARIC) cohort reported similar non-significant associations of serum magnesium level with risk of dementia in NHBs and NHWs,[38] while recent results from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort found a stronger inverse association between serum magnesium level and risk of incident cognitive impairment in NHBs than in NHWs.[39] Except for the differences in study designs, assessments for magnesium status, and sample size, serum vitamin D was not adjusted as a confounding factor in these studies. Although NHANES oversampled minority groups and older

TABLE 3 Associations of total magnesium intake with cognitive tests stratified by selected factors, NHANES, 2011 to 2014

	Magnesium intake level					
Cognitive test	**Q1 (n = 739)**	**Q2 (n = 621)**	**Q3 (n = 606)**	**Q4 (n = 542)**	P_{trend}	$P_{interaction}$
Global *z*-score						
Serum 25(OH)D[b] (nmol/L)						
<50	Reference	−0.01 (−0.18, 0.16)	0.15 (−0.07, 0.37)	0.11 (−0.24, 0.46)	.280	
≥50	Reference	0.06 (−0.04, 0.18)	0.14 (0.02, 0.26)	0.17 (0.01, 0.32)	.049	.190
Sex[c]						
Males	Reference	0.10 (−0.07, 0.27)	0.15 (0.00, 0.31)	0.15 (−0.03, 0.32)	.203	
Females	Reference	0.02 (−0.10, 0.12)	0.12 (0.01, 0.24)	0.18 (0.02, 0.34)	.043	.274
Race/ethnicity[c]						
NHW	Reference	0.05 (−0.07, 0.18)	0.16 (0.03, 0.29)	0.17 (0.02, 0.32)	.043	–
NHB	Reference	0.71 (0.01, 0.32)	0.01 (−0.15, 0.16)	−0.03 (−0.33, 0.27)	.563	.604
Hispanics	Reference	−0.08 (−0.22, 0.06)	0.09 (−0.08, 0.27)	−0.01 (−0.24, 0.21)	.727	.902
Others[a]	Reference	0.06 (−0.21, 0.33)	0.12 (−0.08, 0.33)	0.34 (0.004, 0.67)	.051	.556
CERAD-IR						
Serum 25(OH)D[b] (nmol/L)						
<50	Reference	−0.07 (−1.19, 1.04)	0.63 (−0.82, 2.07)	0.39 (−1.33, 2.12)	.435	
≥50	Reference	0.20 (−0.58, 0.98)	0.31 (−0.51, 1.13)	0.28 (−0.69, 1.26)	.626	.164
Sex[c]						
Males	Reference	0.70 (−0.56, 1.95)	0.83 (−0.47, 2.12)	0.51 (−0.87, 1.88)	.783	
Females	Reference	−0.14 (−0.82, 0.53)	0.03 (−0.63, 0.68)	0.25 (−0.83, 1.33)	.572	.670
Race/ethnicity[d]						
NHW	Reference	0.12 (−0.71, 0.95)	0.41 (−0.54, 1.36)	0.26 (−0.79, 1.32)	.644	
NHB	Reference	1.06 (−0.00, 2.12)	−0.29 (−1.38, 0.81)	−0.58 (−2.21, 1.06)	.204	.465
Hispanics	Reference	−0.48 (−1.56, 0.59)	0.45 (−0.85, 1.75)	−0.18 (−2.02, 1.67)	.920	.652
Others[a]	Reference	0.59 (−0.80, 1.98)	0.29 (−1.15, 1.73)	1.55 (−0.15, 3.26)	.095	.639
CERAD-DR						
Serum 25(OH)D[b] (nmol/L)						
<50	Reference	−0.23 (−0.75, 0.29)	0.23 (−0.46, 0.92)	−0.19 (−1.12, 0.73)	.983	
≥50	Reference	−0.16 (−0.54, 0.22)	0.15 (−0.28, 0.58)	0.27 (−0.24, 0.78)	.149	.385
Sex[c]						
Males	Reference	0.12 (−0.28, 0.53)	0.15 (−0.46, 0.76)	0.24 (−0.29, 0.77)	.447	
Females	Reference	−0.38 (−0.80, 0.03)	0.15 (−0.26, 0.56)	0.21 (−0.42, 0.85)	.243	.391
Race/ethnicity[d]						
NHW	Reference	−0.21 (−0.63, 0.21)	0.16 (−0.29, 0.60)	0.18 (−0.33, 0.69)	.284	
NHB	Reference	0.29 (−0.16, 0.75)	−0.10 (−0.74, 0.53)	0.04 (−0.75, 0.83)	.824	.820
Hispanics	Reference	−0.42 (−0.83, −0.001)	0.04 (−0.41, 0.50)	−0.26 (−0.81, 0.29)	.713	.902
Others[a]	Reference	0.42 (−0.50, 1.34)	0.32 (−0.31, 0.94)	0.90 (−0.09, 1.90)	.094	.880
AF						
Serum 25(OH)D[b] (nmol/L)						
<50	Reference	0.55 (−0.98, 2.09)	1.41 (0.04, 2.78)	1.65 (−1.39, 4.69)	.164	
≥50	Reference	0.72 (−0.11, 1.55)	0.85 (−0.19, 1.88)	1.24 (0.03, 2.45)	.076	.146
Sex[c]						
Males	Reference	1.09 (−0.53, 2.72)	1.28 (−0.16, 2.71)	1.53 (0.16, 2.89)	.045	
Females	Reference	0.43 (−0.45, 1.31)	0.72 (−0.20, 1.65)	1.21 (−0.24, 2.67)	.142	.652

(Continues)

TABLE 3 (Continued)

Cognitive test	Magnesium intake level				P_{trend}	$P_{interaction}$
	Q1 (n = 739)	Q2 (n = 621)	Q3 (n = 606)	Q4 (n = 542)		
Race/ethnicity[d]						
NHW	Reference	0.70 (−0.23, 1.64)	1.07 (−0.08, 2.21)	1.40 (0.16, 2.64)	.041	
NHB	Reference	0.63 (−0.46, 1.71)	0.30 (−1.01, 1.60)	−0.43 (−2.46, 1.60)	.604	.580
Hispanics	Reference	0.54 (−0.53, 1.62)	1.03 (−0.63, 2.69)	0.98 (−0.77, 2.72)	.285	.527
Others[a]	Reference	−0.02 (−2.31, 2.26)	0.23 (−2.19, 2.65)	2.26 (−0.95, 5.48)	.122	.338

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AF, animal fluency; BMI, body mass index; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease-delayed recall; CERAD-IR, Consortium to Establish a Registry for Alzheimer's Disease-immediate recall; NHANES, National Health and Nutrition Examination Survey; NHB, Non-Hispanic Black; NHW, Non-Hispanic White.

[a]Others: included non-Hispanic Asian, and Other Race.

[b]Adjusted for age; education; sex; race/ethnicity; season of exam; BMI; physical activity level; alcohol drinking; smoking status; history of diabetes, heart attack, or stroke; season of exam; depression status; and intakes of total energy and calcium.

[c]Adjusted for age; education; race/ethnicity; season of exam; BMI; physical activity level; alcohol drinking; smoking status; history of diabetes, heart attack, or stroke; season of exam; depression status; intakes of total energy and calcium; and serum 25(OH)D level.

[d]Adjusted for age; education; sex; season of exam; BMI; physical activity level; alcohol drinking; smoking status; history of diabetes, heart attack, or stroke; season of exam; depression status; intakes of total energy and calcium; and serum 25(OH)D level.

adults in the 2011 to 2014 cycles, the relatively small sample size of NHB and Hispanic subjects still limited our ability to detect weak associations in these minority groups. More studies with a large sample of minority older adults are needed to understand the independent magnesium–cognition association.

Sex differences in magnesium consumption[19,21] and risk of dementia[23,24] have been documented. Considering the evidence that high magnesium ion concentrations can antagonize calcium in the neurons and American women experienced a greater rising rate of calcium intake than magnesium,[4,5] women might benefit from high magnesium intake through inhibition of the excessive influx of calcium ion and prevention of production of toxic reactive oxygen species in the neurons.[5,32] We found a positive association between total magnesium intake and cognition among women but not in men, although the interaction was not statistically significant. To date, several previous studies have reported inconsistent results on the magnesium–sex interaction on cognition.[9,38,39] Further investigations of sex differences in effects of magnesium on cognition are warranted which may impact the development of personalized prevention of cognitive aging and dementia.

Accumulative evidence has described the role of vitamin D in the pathology of cognitive impairment and dementia.[12] Previous results on serum vitamin D in relation to cognitive impairment or risk of dementia have not been entirely consistent,[40–45] particularly results from randomized trials showing little evidence on the preventive effects of vitamin D supplementation on cognitive decline.[44] However, intake of magnesium was not adjusted as a confounding factor in most previous studies. With additional adjustment of magnesium intake, we previously found an inverse association between serum vitamin D levels and odds of cognitive impairment assessed by DSST.[27] In this extension of our prior work, our present study assessed cognition using a global *z*-score based on more cognitive tests; our results are consistent with the recent null association between serum 25(OH)D level and cognition assessed by multiple neuropsychological tests.[41,42] Moreover, our results suggested that the association between serum vitamin D and CERAD-DR may vary by sex. As more evidence showed that sex significantly affects vitamin D status through clothing practices, outdoor activities, and estrogenic hormone pathways,[46] further studies are warranted to assess the modification effect of sex on the association of serum 25(OH)D level with cognition.

The strengths of this study include use of the NHANES study with nationally representative samples and a relatively large number of older adults providing the power to detect relatively weak associations. Standardized and detailed information on a wide range of potential confounders were collected in NHANES and were adjusted in our analyses. In addition, the 24-hour dietary recall used in NHANES was validated and able to capture usual foods and dietary habits including race and culturally specific foods in the United States. However, several limitations common to observational studies should be mentioned. Due to the nature of cross-sectional studies, the temporal sequences may not be clear. The cognitive assessments in NHANES were chosen for ease of administration and periodical use in other cycles, but they may not be comprehensive enough to capture the entire cognitive function of an individual and not sufficient for identifying cognitive impairment or dementia. Moreover, serum 25(OH)D levels were only assessed at one time point and therefore may not accurately reflect an individual's long-term vitamin D status. However, serum 25(OH)D has been considered a reliable indicator of vitamin D status because of its long half-life (10–50 days); the method used in the NHANES has been considered to be the most accurate method and the gold standard to measure 25(OH)D.[36,47] In addition, a recent study found that magnesium intake is not a precise measure in predicting body magnesium status due to pathophysiological factors influencing magnesium (re)absorption and storage in the body.[48] Using one-time 24-hour dietary recall in the current study may not adequately capture long-term dietary intake of magnesium. Because inter-day variation in magnesium intake is random, any residual inter-day variation in current analyses may lead to nondifferential misclassification, which usually

TABLE 4 Stratified analyses on associations between serum 25(OH)D level and cognitive tests, NHANES, 2011 to 2014

	Serum 25(OH)D level					
Cognitive test	Q1 (n = 736)	Q2 (n = 509)	Q3 (n = 487)	Q4 (n = 450)	P_{trend}	$P_{interaction}$
Global *z*-score						
Sex[b]						
Males	Reference	−0.08 (−0.21, 0.05)	−0.04 (−0.17, 0.09)	−0.08 (−0.20, 0.05)	.287	
Females	Reference	−0.06 (−0.24, 0.12)	−0.06 (−0.18, 0.06)	0.07 (−0.05, 0.19)	.088	.090
Race/ethnicity[c]						
NHW	Reference	−0.10 (−0.24, 0.05)	−0.07 (−0.17, 0.04)	0.02 (−0.10, 0.14)	.444	
NHB	Reference	0.06 (−0.05, 0.17)	0.05 (−0.13, 0.23)	0.01 (−0.14, 0.17)	.683	.896
Hispanics	Reference	0.05 (−.08, 0.19)	−0.04 (−0.20, 0.11)	−0.09 (−0.28, 0.11)	.385	.293
Others[a]	Reference	0.05 (−0.16, 0.25)	0.04 (−0.18, 0.27)	−0.14 (−0.35, 0.08)	.256	.324
CERAD-IR						
Sex[b]						
Males	Reference	−0.22 (−1.11, 0.67)	−0.05 (−0.89, 0.79)	−0.37 (−1.20, 0.47)	.469	
Females	Reference	-0.28 (-1.39, 0.82)	-0.48 (-1.34, 0.38)	0.22 (−0.59, 1.04)	.390	.231
Race/ethnicity[c]						
NHW	Reference	−0.33 (−1.37, 0.71)	−0.31 (−1.06, 0.43)	0.13 (−0.67, 0.93)	.546	
NHB	Reference	0.04 (−0.59, 0.66)	−0.18 (−1.62, 1.26)	−0.28 (−1.14, 0.57)	.511	.651
Hispanics	Reference	0.38 (−0.57, 1.33)	−0.20 (−1.10, 0.70)	−1.22 (−3.11, 0.66)	.209	.195
Others[a]	Reference	0.98 (−0.45, 2.41)	0.58 (−1.06, 2.21)	0.38 (−1.05, 1.82)	.689	.873
CERAD-DR						
Sex[b]						
Males	Reference	−0.59 (−1.08, −0.09)	−0.17 (−0.61, 0.27)	−0.40 (−0.85, 0.05)	.206	
Females	Reference	−0.14 (−0.64, 0.35)	−0.24 (−0.70, 0.22)	0.25 (−0.12, 0.63)	.066	.069
Race/ethnicity[c]						
NHW	Reference	−0.52 (−1.02, −0.01)	-0.27 (−0.67, 0.12)	−0.02 (−0.39, 0.36)	.496	
NHB	Reference	0.09 (−0.33, 0.52)	0.24 (−0.22, 0.69)	−0.12 (−0.63, 0.39)	.863	.705
Hispanics	Reference	0.02 (−0.53, 0.56)	−0.03 (−0.50, 0.44)	−0.10 (−0.83, 0.62)	.781	.765
Others[a]	Reference	0.70 (−0.11, 1.52)	0.60 (−0.13, 1.34)	0.50 (−0.09, 1.08)	.123	.640
AF						
Sex[b]						
Males	Reference	0.07 (−0.78, 0.94)	−0.04 (−1.10, 1.03)	0.10 (−0.97, 1.18)	.915	
Females	Reference	−0.23 (−1.28, 0.81)	−0.36 (−0.93, 0.22)	−0.02 (−0.71, 0.68)	.937	.951
Race/ethnicity[c]						
NHW	Reference	−0.13 (−0.92, 0.65)	−0.25 (−0.98, 0.49)	0.11 (−0.62, 0.85)	.748	
NHB	Reference	0.66 (−0.68, 1.99)	0.38 (−1.02, 1.77)	0.72 (−0.49, 1.93)	.206	0.705
Hispanics	Reference	0.51 (−0.57, 1.59)	−0.40 (−1.68, 0.87)	0.09 (−1.24, 1.42)	.901	.768
Others[a]	Reference	−0.39 (−2.61, 1.83)	−0.95 (−3.36, 1.46)	−3.31 (−5.50, −1.22)	.005	.058

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AF, animal fluency; BMI, body mass index; CERAD-DR, Consortium to Establish a Registry for Alzheimer's Disease-delayed recall; CERAD-IR, Consortium to Establish a Registry for Alzheimer's Disease-immediate recall; NHANES, National Health and Nutrition Examination Survey; NHB, Non-Hispanic Black; NHW, Non-Hispanic White.

[a]Others: included non-Hispanic Asian, and other race.

[b]Adjusted for age; education; race/ethnicity; season of exam; BMI; physical activity level; alcohol drinking; smoking status; history of diabetes, heart attack, or stroke; season of exam; depression status; and intakes of total energy, calcium, and magnesium.

[c]Adjusted for age; education; sex; season of exam; BMI; physical activity level; alcohol drinking; smoking status; history of diabetes, heart attack, or stroke; season of exam; depression status; intakes of total energy, calcium, and magnesium.

biases the results toward the null. Finally, the intake of magnesium from water has not been calculated and this may lead to nondifferential misclassification. Further studies are needed to replicate these associations.

In conclusion, our findings suggest that high intake of magnesium may be associated with better cognitive function in the US elderly population. Our preliminary results indicate that the positive association between total magnesium intake and cognition may be stronger among women, NHWs, and those with sufficient vitamin D status. In addition, among those with sufficient total magnesium intake, high 25(OH)D level may be related to better cognitive function, indicating that both optimal levels of serum vitamin D and adequate magnesium intake may be required to protect against cognitive decline in older adults. Further studies, including prospective cohort studies, are warranted to confirm our findings.

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CONFLICTS OF INTEREST

Jialiang Liu has no interests to declare. Meng-Hua Tao serves on the Editorial Board for *Scientific Reports*, and as Advisory Committee member for the Texas Cancer Registry. Diana Cervantes has received support from the Agency for Healthcare Research and Quality under Award AHRQ75Q8012C00003. She serves as Research Committee member for the Association of Professionals in Infection Control and Epidemiology. No potential conflicts of interest were disclosed.

AUTHOR CONTRIBUTIONS

Meng-Hua Tao designed the study, conducted the statistical analyses, and drafted the paper; Jialiang Liu contributed to statistical analyses and the critical review of the manuscript; Diana Cervantes contributed to critical review of the manuscript; all authors read and approved the final manuscript.

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SUPPORTING INFORMATION

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