HHS Public Access

Author manuscript

Eur J Nutr. Author manuscript; available in PMC 2021 June 01.

Published in final edited form as:

Eur J Nutr. 2021 February ; 60(1): 465–474. doi:10.1007/s00394-020-02267-4.

Association of magnesium intake and vitamin D status with cognitive function in older adults: an analysis of US National Health and Nutrition Examination Survey (NHANES) 2011 to 2014

Noah C. Peeri[1], **Kathleen M. Egan**[2], **Weiwen Chai**[3], **Meng-Hua Tao**[1]

[1]Department of Biostatistics and Epidemiology, University of North Texas Health Science Center, Fort Worth, TX, 76107, USA

[2]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, 33612, USA

[3]Department of Nutrition and Health sciences, University of Nebraska-Lincoln, Lincoln, NE, 68583, USA

Abstract

Purpose: Reduced cognitive function associated with aging has gained increasing attention as the US population ages. Magnesium plays a critical role in vitamin D biosynthesis and metabolism; and deficiencies in magnesium and vitamin D show associations with poor cognition. However, no study has examined their interaction. This study aimed to evaluate the associations of magnesium intake and serum 25-hydroxyvitamin D (25(OH)D) concentrations, indicating vitamin D status, with cognition, and interaction between these nutrients in older adults.

Methods: Based on the National Health and Nutrition Survey (NHANES) 2011-2014, the study included 2,466 participants aged ≥60 years who completed the Digit Symbol Substitution Test (DSST) and had data available on serum 25(OH)D and magnesium intake. Cognitive impairment was defined as a DSST score lower than the lowest quartile. Serum 25(OH)D concentrations were measured by HPLC-tandem mass spectrometry.

Results: Higher total magnesium intake was independently associated with higher DSST scores (highest quartile *vs* lowest: β=4.34, 95% CI, 1.14-7.54). The association of total magnesium intake with high DSST score was primarily observed among women, non-Hispanic whites, physically active participants and those with sufficient vitamin D status, although the interactions were not significant. The odds of cognitive impairment was reduced with increasing intake of total magnesium (p trend<0.01) and higher level of serum 25(OH)D (p trend=0.05).

Correspondence to: Dr. Meng-Hua Tao, Department of Biostatistics and Epidemiology, University of North Texas Health Science Center, 3500 Camp Bowie, Fort Worth, TX, 76107, Tel: 817-735-0520, menghua.tao@unthsc.edu.

Author contributions: NCP conducted the statistical analyses and wrote the paper; KE and WC contributed to data interpretation, and the critical review of the manuscript; MHT designed the study, supervise the study process and wrote the paper; and all authors read and approved the final manuscript.

Conflict of interests: No potential conflicts of interests were disclosed.

Conclusions: Findings suggest that high magnesium intake alone may improve cognitive function in older adults, and the association may be stronger among subjects with sufficient vitamin D status. Further studies are needed to confirm these findings.

Keywords

magnesium intake; vitamin D status; cognitive function; older adults

Introduction

The search for lifestyle factors associated with cognitive function has gained importance over the last few decades as the U.S. population ages and incidence of dementia rises [1]. It is important to identify modifiable risk factors that may delay the progression of cognitive decline associated with the aging process [2], and prevent or retard the occurrence of cognition impairment or dementia. A number of studies with inconsistent results have investigated the associations of dietary factors with cognitive function [3]. However, few studies have considered complex interaction between nutrients that impact cognitive health.

Vitamin D is involved in many cellular activities in the body including cell apoptosis, oxidative stress, inflammation, and excitotoxicity [4]. Vitamin D is metabolized in the liver into 25-hydroxyvitamin D (25(OH)D) [5]. 25(OH)D then is converted into 1,25-dihydroxyvitamin D ($1,25[OH]_2$ D), and the conversion is regulated by parathyroid hormone and magnesium levels [5]. Serum 25(OH)D is often used to assess vitamin D status in the body. Despite food fortification and dietary supplementation, studies have shown that a large proportion of US adults had vitamin D intake below the Estimated Average Requirements (EARs) [6], and around 30% of older US adults had serum 25(OH)D less than 50 nmol/l [7].

Magnesium, the second most abundant intracellular cation, plays a critical role in numerous biological reactions including energy production, protein synthesis, nucleic acid metabolism [8-12], maintenance of muscle and nerve membranes functions, participation of neurochemical transmission and nerve transmission [13]. Low intake of magnesium has been linked to risk of metabolic syndrome, type 2 diabetes, cardiovascular disease [14], and decreased cognition [9,11]. Magnesium also plays a critical role in the synthesis and metabolism of vitamin D, with magnesium deficiency resulting in reduced $1,25[OH]_2$ D levels [15]. $1,25[OH]_2$ D can increase intestinal absorption of magnesium [16]. Previous studies have indicated possible interactions between magnesium and vitamin D status on mortality [17]. A recent randomized controlled trial reported that an optimal magnesium intake may be important for optimizing circulating 25(OH)D levels, highlighting the importance of the interaction between these micronutrients [18].

Previous observational studies have suggested that deficiencies in vitamin D and magnesium were associated with cognitive impairment and risk of dementia [3,9-11,19]; however, results from randomized controlled trials are inconsistent. Several recent vitamin D trials reported no effects of vitamin D supplementation on cognitive performance compared to the placebo groups [20,21]. A trial in healthy older adults found significant improvements in nonverbal (visual) memory with 4,000 IU/day vitamin D supplementation among subjects with insufficient levels at baseline [22]. Potential explanations for the inconsistent results

include the elusiveness of the optimal concentrations of serum 25(OH)D for cognitive health, short-term interventions to produce beneficial effects in clinical trials, and the fact that prior studies did not consider magnesium status and its interaction with vitamin D. Therefore, in this study, we investigated the association of magnesium intake and vitamin D status with cognitive impairment in older adults and tested for possible interaction between magnesium intake and vitamin D status on cognition utilizing data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2014.

Methods

Study Population

This study utilized data from the continuous NHANES survey from two survey cycles, conducted between 2011 and 2014 in which cognitive function testing among older adults was conducted. 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 [23]. 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 and older at time of the survey, had information of serum 25(OH)D, completed the 24-hour dietary recall, and had completed Digit Symbol Substitution Test (DSST) information described previously [24] were included in the study population. Participants with unreliable dietary data, missing data for total magnesium intake, or potential confounders were further excluded from the analyses, leaving a total of 2,466 subjects included in the analysis. All participants provided written informed consent and the Institutional Review Board of the NCHS approved the survey protocol.

Assessment of serum 25(OH)D

Blood was drawn from participants in Mobile Examination Centers (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 HPLC-tandem mass spectrometry. This method of mass spectrometry offers a cost effective, sensitive, and rapid test for 25(OH)D levels in nanomolar concentrations [25]. Blood serum levels of 25(OH)D were captured in nmol per liter (nmol/l).

Assessments of magnesium intake

Details of the protocol and dietary intake assessed in the MEC by trained interviewers have been described previously [26]. Briefly, daily dietary intake information was obtained via 24-hour recalls [27], 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 3-10 days after the MEC interview [26]. 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.

Cognitive Function

Cognitive function was assessed among participants aged 60 years and older using the DSST, which has been described previously [24]. Briefly, the DSST is a well-established and validated measure of cognitive performance that assesses executive function and processing speed. It is a test provided on paper and completed using pencil to assess psychomotor performance. It contains a table with numbers (1-9) and matching symbols as well as a test section of numbers with empty boxes where participants are asked to fill in the empty boxes with the symbols corresponding to the numbers provided. The score is the total number of correct symbols drawn within 2 minutes, with one point given for a correct response and a maximum score of 133. Because there is no well-defined threshold of DSST score for detecting cognitive impairment, the lowest unweighted quartile in the study population (DSST ≤ 34) was used to define cognitive impairment or low cognitive function, consistent with methods previously used [28]. Subjects with DSST scores > 34 were considered not to be cognitively impaired.

Statistical Analysis

The NHANES employs multistage clustered probability sampling to obtain results representative of the US population. Given the complex study design of the NHANES, the “Survey” procedure in SAS 9.4 software (SAS Institute, Cary, NC, USA) was used to estimate variance after incorporating the sampling weights in the multistage clustered probability sampling design. Covariates were compared between two groups with and without cognitive impairment to evaluate the potential for confounding using Rao-Scott chi-square test for categorical variables and t-tests for continuous variables. Linear and logistic regression models were conducted to examine the associations of magnesium intake and vitamin D status with cognitive function, separately. In the first, linear regression models were conducted for associations between total magnesium intake and vitamin D status and cognitive function evaluated as a continuous DSST score, with adjustment for potential confounders. In the second, we modeled cognitive impairment status as a dichotomized outcome and total magnesium intake and vitamin D status with logistic regression models. Serum 25(OH)D concentration and total magnesium intake were categorized into quartiles based on the distributions among subjects without cognitive impairment, and the lowest category was used as the reference. Tests for dose-response relationship were estimated by fitting models with exposure variables included as continuous variables.

Several factors were considered as potential confounders in multivariable modeling including sex, race/ethnicity, education, body mass index (BMI), cigarette smoking status, alcohol use status, physical activity level, as well as daily intakes of total energy and total calcium. Age, BMI, and intakes of total energy and total calcium were included in the models as continuous variables. In the NHANES, race/ethnicity was categorized by survey questions on race and Hispanic origin: non-Hispanic White referring to whites who are not of Hispanic origin; non-Hispanic Black referring to blacks without Hispanic origin; Hispanic referring all Hispanics regardless of race; non-Hispanic Asian including Asians without

Hispanic origin; and Other Race including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and multiracial persons [29]. Previous studies have reported associations between weak handgrips muscle strength and cognitive decline in older adults [30,31]. Therefore, in the current study we also assessed potential confounding by handgrips strength, and this factor did not alter point estimates by ≥10% and were excluded from final models. We only included physical activity, a proxy indicator of overall physical state, in final models, and categorized physical activity into two strata: no and low level, and moderate and high level, defined as no vigorous or moderate physical activity in the past 30 days, and at least ten minutes of sustained moderate or vigorous physical activity, respectively. Previous studies have shown correlation between type 2 diabetes and cognitive function [32]. Therefore, in the current study we also assessed possible confounding by type 2 diabetes, defined as having hemoglobin A1C concentration ≥ 6.5% based upon World Health Organization (WHO) guidelines [33]. Stratified analyses by potential effect modifiers and tests for multiplicative interactions using the Wald test were conducted. All reported *p*-values were two-tailed, and statistical significance was set at 0.05.

Results

Selected demographic and potential confounding factors by cognitive impairment status are presented in Table 1. 583 participants (23.6%) were defined as having cognitive impairment with an unweighted DSST score ≤ 34. Compared to subjects without cognitive impairment, those with cognitive impairment were older, less likely to be non-Hispanic white, physically active and never alcohol users, and more likely to be current smokers, and to have less education and lower serum 25(OH)D levels. Subjects with cognitive impairment consumed less calcium, magnesium, had lower total energy intake, and were less likely to take dietary supplements compared to those without cognitive impairment. All of the above variables were considered to be potential confounders and were adjusted for in subsequent analyses.

Linear and logistic regression models investigating associations of vitamin D status and total magnesium intake with cognitive function are presented in Table 2. In linear regression models, after adjustment for age, other confounding factors, intakes of total energy and total calcium, and vitamin D status, participants with the highest quartile of total magnesium intake scored an average of 4.34 points higher on the DSST than those in the lowest quartile (β =4.34, 95% CI: 1.14-7.54, *p* trend<0.01). For vitamin D status, there was no linear association between serum 25(OH)D level and DSST score (compared to Q_1, Q_2 β= −0.82, 95% CI: −3.08-1.44; Q_3 β= −0.00, 95% CI: −2.05-2.04; Q_4 β=0.90, 95% CI: −0.52-2.32; *p* trend=0.17). Increased intake of total magnesium was also associated with a reduced odds of cognitive impairment, the corresponding odds ratios (ORs) and 95% confidence intervals (95% CIs) for the third and highest quartiles *vs.* the lowest quartile of total magnesium intake were 0.42 (0.27-0.66) and 0.71 (0.38-1.33), respectively. A similar pattern was observed for the association between serum 25(OH)D concentrations and odds of cognitive impairment (OR=0.56; 95% CI: 0.36-0.87; OR = 0.73, 95% CI: 0.48-1.10, respectively for the third quartile and highest quartile). A significant dose-response relationship was observed for the intake of total magnesium (*p* trend<0.01) and serum 25(OH)D level (*p* trend=0.05) in logistic regression models.

The linear association of total magnesium intake with cognitive function was further evaluated stratifying by selected factors (Table 3). After adjustment, the association between higher total magnesium intake and better DSST score appeared stronger among females (compared to Q_1, Q_2: β= 3.20, 95% CI: 0.42-5.99; Q_3: β= 3.80, 95% CI: 0.82-6.77; Q_4: β= 5.61, 95% CI: 1.58-9.63; *p* for trend <0.01), non-Hispanic Whites (compared to Q_1, Q_2 β= 2.53, 95% CI: 0.13-4.95; Q_3 β= 4.40, 95% CI: 1.97-6.84; Q_4 β= 4.97, 95% CI:1.37-8.57; *p* for trend <0.01), and those with moderate or high level of physical activity (compared with Q_1, Q_2 β= 3.17, 95% CI: 1.32-5.03; Q_3 β= 3.66, 95% CI: 1.63-5.70; Q_4 β= 5.68, 95% CI: 2.66-8.70; *p* for trend <0.01). However, there was no statistically significant interaction between total magnesium intake and gender, race/ethnicity, or physical activity. Additional stratified analyses were conducted by serum 25(OH)D levels. Improved DSST scores associated with high intake of total magnesium was limited to subjects with vitamin D status ≥50 nmol/l (compared with Q_1, Q_2 β=2.87, 95% CI: 0.53-5.21; Q_3 β=4.45, 95% CI: 1.91-7.00; Q_4 β= 4.77, 95% CI: 1.08-8.46; *p* for trend <0.01). No statistically significant interaction was observed between vitamin D status and total magnesium intake. We further conducted stratified analyses for vitamin D status, and the patterns for associations between serum 25(OH)D level and DSST score did not vary by gender, race/ethnicity or physical activity levels (data not shown).

In additional stratified analyses by total magnesium intake and vitamin D status, joint effects on cognitive function were analyzed (Table 4). We found that when compared to subjects with insufficient vitamin D status (<50 nmol/l) and low total magnesium intake (<232 mg/day), on average, a 5-point increase in DSST score was observed among those subjects with a sufficient vitamin D status and in the third and fourth quartile of magnesium intake (311-412 mg/day, and >412 mg/day) (β: 5.07; 95% CI: 2.65-7.49; and β=5.44; 95% CI: 1.88-9.01, respectively). However, no significant interaction was observed between magnesium intake and vitamin D status on cognitive function (*p* interaction = 0.62).

Discussion

Utilizing data from two recent continuous NHANES cycles, we found that high total magnesium intake was independently associated with better DSST scores. Moreover, the positive association between magnesium intake and DSST score appeared stronger among women, non-Hispanic whites, subjects who were moderately or highly physically active, and subjects with a sufficient vitamin D status, although interactions were not statistically significant. In addition, we found participants in the third quartile of either serum 25(OH)D levels (81-98 nmol/L) or magnesium intake (311-412 mg/day) had reduced odds of cognitive impairment compared to those in the lowest quartiles. Our results from the joint analysis suggest a combination of sufficient magnesium intake (i.e. ≥311 mg/day comparable to Recommended Dietary Allowance (RDA): 400 mg for men; 310 mg for women) and adequate vitamin D status (≥50 nmol/L) were associated with higher DSST score in this older population.

Consistent with previous studies [3,10,19], our findings showed an inverse association between serum 25(OH)D level and odds of cognitive impairment (*P* trend = 0.05). The association was stronger for the third quartile (81-98 nmol/L), which was consistent with

previous reports that have suggested a non-linear (i.e. J-shaped *vs.* U-shaped) relationship of vitamin D status with cognitive function and mortality [34-36]. However, a recent randomized controlled trial found that vitamin D intake higher than the RDA had no effect on preventing cognitive decline [21]. Vitamin D has been shown to elicit neuroprotective effects by preventing oxidative stress, and this protective effect is concentration dependent and is attained at moderate but not at low or high vitamin D concentrations [37,38]. Accordingly, our findings suggested that serum 25(OH)D concentration between 81-98 nmol/l may suggest an optimal level for reducing the risk of cognitive impairment in older adults. However, prospective cohort studies are needed to confirm our results.

Magnesium has been found to interact with N-methyl-D-aspartate (NMDA) signaling, prevent synapse loss, and reverse memory deficits in aged rats [39]. Experimental studies have suggested that low magnesium levels may potentiate glutamatergic neurotransmission, which creates a supportive environment for excitotoxicity, increasing oxidative stress and neuronal cell death [40]. Abnormal glutamatergic neurotransmission has been implicated in many neurological disorders [41]; therefore, magnesium may be an important nutrient in the prevention and/or treatment of these conditions. The protective associations between high magnesium intake and cognitive function or risk of dementia have been investigated in a few epidemiologic studies [9-11]. In agreement with prior research [10,11,39], our study found that higher intake of total magnesium was associated with a significantly higher DSST score and reduced odds of cognitive impairment. In particular, we found that subjects with sufficient vitamin D status and sufficient total magnesium intake had the strongest increases in DSST score. Our novel findings are biologically plausible because body status of magnesium and vitamin D and their interaction are critical for cognitive maintenance in older adults. Animal and human studies have shown that higher serum 25(OH)D level increased magnesium absorption in the intestine [16], and retention [42]. It is possible that optimal magnesium intake produces beneficial effects on cognitive function only when vitamin D status is sufficient, suggesting the important interactions between vitamin D and magnesium homeostasis. However, another possible explanation is that the joint effect of sufficient magnesium and vitamin D status could be the result of a healthy lifestyle effect, those with healthier lifestyles are more likely to possess better cognitive function. In the analyses we have adjusted multiple lifestyle factors to control their possible confounding effects. Further studies are necessary to confirm this association, and to further assess the biological mechanisms of the joint effects of magnesium and vitamin D on cognition.

A recent systematic review showed a positive correlation between physical activity and cognitive function in the elderly [43]. In the current study, we found that higher magnesium intake was associated with high DSST score only among those with moderate or high physical activity level. This finding is plausible because magnesium plays an important role in energy metabolism, and maintenance of skeletal muscle function and overall physical functioning [13]. In a recent randomized controlled trial investigating effects of multi-domain intervention on prevention of cognitive decline among older adults [44], subjects receiving four intervention components including diet, exercise, cognitive training, and vascular risk monitoring had significant improvements in overall cognition, executive functioning, and processing speed compared to the control group over a two-year period [44]. Meanwhile, nutrition counselling, one of the intervention domains, significantly

increased dietary magnesium intake [45]. These results including current finding suggest potential combined effect between magnesium and physical activity in older adults, although the interaction was not statistically significant. More studies with larger sample size are needed to replicate our findings.

In the current study, we found that total magnesium intake among older women was positively associated with DSST score. This finding is biologically meaningful because of the interactions between magnesium and estrogen in the brain. In older women, estrogen deficiency has been reported to accelerate aging of the brain, cause diminution of brain functional capacity, and increases the risk of brain degenerative processes [46]. Neuroprotective effects of magnesium include its antioxidant activity and blockage of the calcium ion carrying channel which is regulated by beta-amyloid, the pathogenic factor for Alzheimer's disease [46]. Considering the evidence of a greater increasing rate of calcium relative to magnesium intake in US women [47], and reduced cerebral blood flow observed in older women, it is possible that high magnesium intake may show beneficial effects on cognition through increasing cerebral blood flow and blocking of calcium. Further studies are necessary to better understand potential modification of associations by gender.

The positive association between total magnesium intake and DSST score was stronger among non-Hispanic whites in our study. One previous study found that non-Hispanic whites had higher cognitive scores than Hispanics and non-Hispanic blacks across all age groups [48], which may be in part due to disparities in socioeconomic status, educational attainment, and differences in genetic or neurophysiological risk factors between racial/ethnic groups. The relative small number of minority participants still limited our ability to detect weak associations in each minority group. Further studies with a larger sample of older minority adults are needed to understand the association in these populations.

The strengths of this study include NHANES study with nationally representative samples, and a relatively large number of older adults providing the power to detect relative weak associations. 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. Although the DSST is highly sensitive for the detection of cognitive dysfunction and assessed several cognitive domains, and impairment in any one of these domains could result in poorer scores. The single DSST score limited our ability to determine which particular cognitive domain has been impacted [49], and limited our ability to examine associations of magnesium intake and vitamin D status with function of individual cognitive domain. Accompanying tests would improve the assessment of cognitive function in this population, including the supplemental use of the Mini Mental Status Examination (MMSEE) [50], or a more intensive measurement such as magnetic resonance imaging (MRI) to assess clinical signs of cognitive impairment. Furthermore, misclassification may occur in logistic analysis since there is no well-defined cutoff for cognitive impairment utilizing the DSST. However, this misclassification is likely to be nondifferential. Additional limitation is that vitamin D status was reliance on single rather than serial measurements of serum 25(OH)D level, which may not accurately reflect an individual's long-term vitamin D status. However, serum 25(OH)D is a more stable metabolite with a half-life of 10-50 days, it has been considered as a reliable indicator of vitamin D status [51]. Further, the method used in the

NHANES has been considered to be the most accurate method and the gold standard to measure vitamin D status [52]. Although multiple 24-hour dietary recalls are used as a gold standard measure in nutritional epidemiological studies, a one-time 24-hour dietary recall may not capture long-term dietary exposures. Self-reported dietary recall may result in both random and systematic errors with the potential for recall bias to occur. We have adjusted for many potential confounding factors, including total calcium intake and several medical conditions associated with cognitive dysfunction, which enabled us to capture the associations more accurately. However, the magnesium content of drinking water could not be calculated. This may lead to nondifferential misclassification of total magnesium intake.

In conclusion, our findings suggest that participants who had high intake of magnesium or those with optimal vitamin D status ranging from 81-98 nmol/l are associated with better cognitive function. In particular, among those who had sufficient vitamin D status (≥50 nmol/l), daily total magnesium intake meeting the RDA was related to better cognitive performance, indicating that both optimal levels of serum 25(OH)D and adequate magnesium intake may be required to protect against cognitive decline in older adults. Further studies, such as long-term clinical trials of magnesium and vitamin D supplement, are warranted to confirm the present results and to test the optimal range of serum 25(OH)D level and healthy dosage of daily magnesium intake for older adults to prevent cognitive decline.

Acknowledgement:

We thank the investigators, the staff and the participants of NHANES for their valuable contribution.

Funding: Dr. Tao's effort was partially supported by the National Institute on Minority Health and Health Disparities of the National Institute of Health under Award U54MD006882.

References

1. Derby CA, Katz MJ, Lipton RB, Hall CB (2017) Trends in Dementia Incidence in a Birth Cohort Analysis of the Einstein Aging Study. JAMA Neurol 74 (11):1345–1351. doi:10.1001/jamaneurol.2017.1964 [PubMed: 28873124]
2. Glisky EL (2007) Changes in Cognitive Function in Human Aging In: Riddle DR (ed) Brain Aging: Models, Methods, and Mechanisms. Frontiers in Neuroscience. Boca Raton (FL),
3. van der Schaft J, Koek HL, Dijkstra E, Verhaar HJ, van der Schouw YT, Emmelot-Vonk MH (2013) The association between vitamin D and cognition: a systematic review. Ageing Res Rev 12 (4):1013–1023. doi:10.1016/j.arr.2013.05.004 [PubMed: 23727408]
4. Vonder Haar C, Peterson TC, Martens KM, Hoane MR (2016) Vitamins and nutrients as primary treatments in experimental brain injury: Clinical implications for nutraceutical therapies. Brain Res 1640 (Pt A):114–129. doi:10.1016/j.brainres.2015.12.030 [PubMed: 26723564]
5. DeLuca HF (2004) Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 80 (6 Suppl):1689S–1696S. doi:10.1093/ajcn/80.6.1689S [PubMed: 15585789]
6. Health UDo, Services H (2017) Dietary guidelines for Americans 2015–2020. Skyhorse Publishing Inc.,
7. Liu X, Baylin A, Levy PD (2018) Vitamin D deficiency and insufficiency among US adults: prevalence, predictors and clinical implications. Br J Nutr 119 (8):928–936. doi:10.1017/S0007114518000491 [PubMed: 29644951]
8. Costello R, Wallace TC, Rosanoff A (2016) Magnesium. Adv Nutr 7 (1):199–201. doi:10.3945/an.115.008524 [PubMed: 26773023]

9. Cherbuin N, Kumar R, Sachdev PS, Anstey KJ (2014) Dietary Mineral Intake and Risk of Mild Cognitive Impairment: The PATH through Life Project. Front Aging Neurosci 6:4. doi:10.3389/fnagi.2014.00004 [PubMed: 24550825]
10. Huskisson E, Maggini S, Ruf M (2007) The influence of micronutrients on cognitive function and performance. J Int Med Res 35 (1):1–19. doi:10.1177/147323000703500101 [PubMed: 17408051]
11. Ozawa M, Ninomiya T, Ohara T, Hirakawa Y, Doi Y, Hata J, Uchida K, Shirota T, Kitazono T, Kiyohara Y (2012) Self-reported dietary intake of potassium, calcium, and magnesium and risk of dementia in the Japanese: the Hisayama Study. J Am Geriatr Soc 60 (8):1515–1520. doi:10.1111/j.1532-5415.2012.04061.x [PubMed: 22860881]
12. Richard EL, Laughlin GA, Kritz-Silverstein D, Reas ET, Barrett-Connor E, McEvoy LK (2018) Dietary Patterns and Cognitive Function among Older Community-Dwelling Adults. Nutrients 10 (8). doi:10.3390/nu10081088
13. Zhang Y, Xun P, Wang R, Mao L, He K (2017) Can Magnesium Enhance Exercise Performance? Nutrients 9 (9). doi:10.3390/nu9090946
14. Rosanoff A, Weaver CM, Rude RK (2012) Suboptimal magnesium status in the United States: are the health consequences underestimated? Nutr Rev 70 (3):153–164. doi:10.1111/j.1753-4887.2011.00465.x [PubMed: 22364157]
15. Reddy V, Sivakumar B (1974) Magnesium-dependent vitamin-D-resistant rickets. Lancet 1 (7864):963–965 [PubMed: 4133647]
16. Hardwick LL, Jones MR, Brautbar N, Lee DB (1991) Magnesium absorption: mechanisms and the influence of vitamin D, calcium and phosphate. J Nutr 121 (1):13–23. doi:10.1093/jn/121.1.13 [PubMed: 1992050]
17. Deng X, Song Y, Manson JE, Signorello LB, Zhang SM, Shrubsole MJ, Ness RM, Seidner DL, Dai Q (2013) Magnesium, vitamin D status and mortality: results from US National Health and Nutrition Examination Survey (NHANES) 2001 to 2006 and NHANES III. BMC Med 11:187. doi:10.1186/1741-7015-11-187 [PubMed: 23981518]
18. Dai Q, Zhu X, Manson JE, Song Y, Li X, Franke AA, Costello RB, Rosanoff A, Nian H, Fan L, Murff H, Ness RM, Seidner DL, Yu C, Shrubsole MJ (2018) Magnesium status and supplementation influence vitamin D status and metabolism: results from a randomized trial. Am J Clin Nutr 108 (6):1249–1258. doi:10.1093/ajcn/nqy274 [PubMed: 30541089]
19. Pavlovic A, Abel K, Barlow CE, Farrell SW, Weiner M, DeFina LF (2018) The association between serum vitamin d level and cognitive function in older adults: Cooper Center Longitudinal Study. Prev Med 113:57–61. doi:10.1016/j.ypmed.2018.05.010 [PubMed: 29753804]
20. Jorde R, Kubiak J, Svartberg J, Fuskevag OM, Figenschau Y, Martinaityte I, Grimnes G (2019) Vitamin D supplementation has no effect on cognitive performance after four months in mid-aged and older subjects. J Neurol Sci 396:165–171. doi:10.1016/j.jns.2018.11.020 [PubMed: 30472553]
21. Owusu JE, Islam S, Katumuluwa SS, Stolberg AR, Usera GL, Anwarullah AA, Shieh A, Dhaliwal R, Ragolia L, Mikhail MB, Aloia JF (2019) Cognition and Vitamin D in Older African-American Women- Physical performance and Osteoporosis prevention with vitamin D in older African Americans Trial and Dementia. J Am Geriatr Soc 67 (1):81–86. doi:10.1111/jgs.15607 [PubMed: 30359476]
22. Pettersen JA (2017) Does high dose vitamin D supplementation enhance cognition?: A randomized trial in healthy adults. Exp Gerontol 90:90–97. doi:10.1016/j.exger.2017.01.019 [PubMed: 28167237]
23. Johnson CL, Dohrmann SM, Burt VL, Mohadjer LK (2014) National health and nutrition examination survey: sample design, 2011–2014. Vital Health Stat 2 (162):1–33
24. Hoyer WJ, Stawski RS, Wasylyshyn C, Verhaeghen P (2004) Adult age and digit symbol substitution performance: a meta-analysis. Psychol Aging 19 (1):211–214. doi:10.1037/0882-7974.19.1.211 [PubMed: 15065945]
25. Saenger AK, Laha TJ, Bremner DE, Sadrzadeh SM (2006) Quantification of serum 25-hydroxyvitamin D(2) and D(3) using HPLC-tandem mass spectrometry and examination of reference intervals for diagnosis of vitamin D deficiency. Am J Clin Pathol 125 (6):914–920. doi:10.1309/J32U-F7GT-QPWN-25AP [PubMed: 16690491]

26. Ahluwalia N, Dwyer J, Terry A, Moshfegh A, Johnson C (2016) Update on NHANES Dietary Data: Focus on Collection, Release, Analytical Considerations, and Uses to Inform Public Policy. Adv Nutr 7 (1):121–134. doi:10.3945/an.115.009258 [PubMed: 26773020]
27. Moshfegh AJ, Rhodes DG, Baer DJ, Murayi T, Clemens JC, Rumpler WV, Paul DR, Sebastian RS, Kuczynski KJ, Ingwersen LA, Staples RC, Cleveland LE (2008) The US Department of Agriculture Automated Multiple-Pass Method reduces bias in the collection of energy intakes. Am J Clin Nutr 88 (2):324–332. doi:10.1093/ajcn/88.2.324 [PubMed: 18689367]
28. Chen SP, Bhattacharya J, Pershing S (2017) Association of Vision Loss With Cognition in Older Adults. JAMA Ophthalmol 135 (9):963–970. doi:10.1001/jamaophthalmol.2017.2838 [PubMed: 28817745]
29. NHANES 2011–2012 Demographics Data. CDC/Natonal Center for Health Statistics. https://wwwn.cdc.gov/nchs/nhanes/Search/DataPage.aspx?Component=Demographics&CycleBeginYear=2011. Accessed Feburary 14 2020
30. Liberman K, Forti LN, Beyer I, Bautmans I (2017) The effects of exercise on muscle strength, body composition, physical functioning and the inflammatory profile of older adults: a systematic review. Curr Opin Clin Nutr Metab Care 20:30–53 [PubMed: 27755209]
31. Fritz NE, McCarthy CJ, Adamo DE (2017) Handgrip strength as a means of monitoring progression of cognitive decline - A scoping review. Ageing Res Rev 35:112–123 [PubMed: 28189666]
32. Moheet A, Mangia S, Seaquist ER (2015) Impact of diabetes on cognitive function and brain structure. Ann N Y Acad Sci 1353:60–71. doi:10.1111/nyas.12807 [PubMed: 26132277]
33. Forouhi NG, Wareham NJ (2014) Epidemiology of diabetes. Medicine (Abingdon) 42 (12):698–702. doi:10.1016/j.mpmed.2014.09.007 [PubMed: 25568613]
34. Amrein K, Quraishi SA, Litonjua AA, Gibbons FK, Pieber TR, Camargo CA Jr., Giovannucci E, Christopher KB (2014) Evidence for a U-shaped relationship between prehospital vitamin D status and mortality: a cohort study. J Clin Endocrinol Metab 99 (4):1461–1469. doi:10.1210/jc.2013-3481 [PubMed: 24423347]
35. Durup D, Jorgensen HL, Christensen J, Tjonneland A, Olsen A, Halkjaer J, Lind B, Heegaard AM, Schwarz P (2015) A Reverse J-Shaped Association Between Serum 25-Hydroxyvitamin D and Cardiovascular Disease Mortality: The CopD Study. J Clin Endocrinol Metab 100 (6):2339–2346. doi:10.1210/jc.2014-4551 [PubMed: 25710567]
36. McGrath J, Scragg R, Chant D, Eyles D, Burne T, Obradovic D (2007) No association between serum 25-hydroxyvitamin D3 level and performance on psychometric tests in NHANES III. Neuroepidemiology 29 (1–2):49–54. doi:10.1159/000108918 [PubMed: 17898524]
37. Groves NJ, Burne THJ (2017) The impact of vitamin D deficiency on neurogenesis in the adult brain. Neural Regen Res 12 (3):393–394. doi:10.4103/1673-5374.202936 [PubMed: 28469647]
38. Ibi M, Sawada H, Nakanishi M, Kume T, Katsuki H, Kaneko S, Shimohama S, Akaike A (2001) Protective effects of 1 alpha,25-(OH)(2)D(3) against the neurotoxicity of glutamate and reactive oxygen species in mesencephalic culture. Neuropharmacology 40 (6):761–771. doi:10.1016/s0028-3908(01)00009-0 [PubMed: 11369030]
39. Slutsky I, Abumaria N, Wu LJ, Huang C, Zhang L, Li B, Zhao X, Govindarajan A, Zhao MG, Zhuo M, Tonegawa S, Liu G (2010) Enhancement of learning and memory by elevating brain magnesium. Neuron 65 (2):165–177. doi:10.1016/j.neuron.2009.12.026 [PubMed: 20152124]
40. Kirkland AE, Sarlo GL, Holton KF (2018) The Role of Magnesium in Neurological Disorders. Nutrients 10 (6). doi:10.3390/nu10060730
41. Olloquequi J, Cornejo-Cordova E, Verdaguer E, Soriano FX, Binvignat O, Auladell C, Camins A (2018) Excitotoxicity in the pathogenesis of neurological and psychiatric disorders: Therapeutic implications. J Psychopharmacol 32 (3):265–275. doi:10.1177/0269881118754680 [PubMed: 29444621]
42. Pointillart A, Denis I, Colin C (1995) Effects of dietary vitamin D on magnesium absorption and bone mineral contents in pigs on normal magnesium intakes. Magnes Res 8 (1):19–26 [PubMed: 7669504]

43. Carvalho A, Rea IM, Parimon T, Cusack BJ (2014) Physical activity and cognitive function in individuals over 60 years of age: a systematic review. Clinical interventions in aging 9:661–682. doi:10.2147/CIA.S55520 [PubMed: 24748784]
44. Ngandu T, Lehtisalo J, Solomon A, Levalahti E, Ahtiluoto S, Antikainen R, Backman L, Hanninen T, Jula A, Laatikainen T, Lindstrom J, Mangialasche F, Paajanen T, Pajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H, Kivipelto M (2015) A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 385 (9984):2255–2263. doi:10.1016/S0140-6736(15)60461-5 [PubMed: 25771249]
45. Lehtisalo J, Ngandu T, Valve P, Antikainen R, Laatikainen T, Strandberg T, Soininen H, Tuomilehto J, Kivipelto M, Lindström J (2017) Nutrient intake and dietary changes during a 2-year multi-domain lifestyle intervention among older adults: Secondary analysis of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) randomised controlled trial. British Journal of Nutrition 118 (4):291–302
46. Rosanoff A, Seelig MS (2004) Comparison of mechanism and functional effects of magnesium and statin pharmaceuticals. Journal of the American College of Nutrition 23 (5):501S–505S [PubMed: 15466951]
47. Rosanoff A, Dai Q, Shapses SA (2016) Essential Nutrient Interactions: Does Low or Suboptimal Magnesium Status Interact with Vitamin D and/or Calcium Status? Adv Nutr 7 (1):25–43. doi:10.3945/an.115.008631 [PubMed: 26773013]
48. Diaz-Venegas C, Downer B, Langa KM, Wong R (2016) Racial and ethnic differences in cognitive function among older adults in the USA. Int J Geriatr Psychiatry 31 (9):1004–1012. doi:10.1002/gps.4410 [PubMed: 26766788]
49. Jaeger J (2018) Digit Symbol Substitution Test: The Case for Sensitivity Over Specificity in Neuropsychological Testing. J Clin Psychopharmacol 38 (5):513–519. doi:10.1097/JCP.0000000000000941 [PubMed: 30124583]
50. Mitchell AJ (2009) A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res 43:411–431. [PubMed: 18579155]
51. Heaney RP (2011) Serum 25-hydroxyvitamin D is a reliable indicator of vitamin D status. Am J Clin Nutr 94:619–620 [PubMed: 21775574]
52. Zerwekh JE (2008) Blood biomarkers of vitamin D status. Am J Clin Nutr 87:1087S–1091S. [PubMed: 18400739]

Table 1.

Participant characteristics by cognitive function status, NHANES 2011-2014 (n=2,466)

Characters	Cognitive Impairment		
	Yes (n = 583)	No (n = 1,883)	*p*-value
Age (years) ǂ	73.8 (1.08) ǂ	66.8 (0.38) ǂ	<0.01
Serum 25(OH)D (nmol/l) ǂ	72.6 (2.41)	80.0 (1.18) ǂ	<0.01
Daily nutrient intake ǂ			
Total magnesium (mg)	239.5 (6.20) ǂ	310.7 (5.32) ǂ	<0.01
Total calcium (mg)	869.3 (30.70) ǂ	1101.5 (24.92) ǂ	<0.01
Total energy intake (kcal)	1478.7 (34.6) ǂ	1849.3 (22.1) ǂ	<0.01
BMI (kg/m^2) ǂ	27.7 (0.44) ǂ	30.0 (0.23) ǂ	0.96
Dietary supplement use, n (%) *			<0.01
Yes	105 (18.0)	483 (25.7)	
No	478 (82.0)	1400 (74.3)	
Race/ethnicity, n (%) *			<0.01
Non-Hispanic White	179 (30.7)	1073 (57.0)	
Non-Hispanic Black	193 (33.1)	351 (18.6)	
Hispanic	184 (31.6)	268 (14.2)	
Others *1*	27 (4.6)	191 (10.2)	
Sex, n (%) *			<0.01
Male	327 (56.1)	880 (46.7)	
Female	256 (43.9)	1003 (53.3)	
Education, n (%) *			<0.01
Less than high school	330 (56.6)	258 (13.7)	
High school	132 (22.6)	444 (23.6)	
Some college	83 (14.2)	623 (33.1)	
College graduate	38 (6.5)	558 (29.6)	
Physical activity level, n (%) *			<0.01
No and low	419 (71.9)	992 (52.7)	
Moderate and high	164 (28.1)	891 (47.3)	
Season of Exam, n (%) *			0.14
November to April	279 (47.9)	836 (44.4)	
May to October	304 (52.1)	1047 (55.6)	
Smoking Status, n (%) *			<0.01
Never	273 (46.8)	939 (49.9)	
Former	213 (36.5)	728 (38.7)	
Current	97 (16.6)	216 (11.5)	
Alcohol Use, n (%) *			<0.01

Characters	Cognitive Impairment		
	Yes (n = 583)	No (n = 1,883)	*p*-value
Never	114 (19.6)	249 (13.2)	
Former	232 (39.8)	447 (23.7)	
Current	237 (40.7)	1187 (63.1)	

[≠] Values shown are median and (standard error)

[*] Unweighted frequency counts and weighted percentages shown.

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

Table 2.

Linear and logistic regression models for associations of vitamin D status and total magnesium intake with DSST score and cognitive impairment status in NHANES 2011-2014

	Yes/No	β (95% CI)[1]	OR (95% CI)[2]
Serum 25(OH)D level (nmol/L)			
Q_1 <63	252/624	Referent	Referent
Q_2 63-80	138/427		
M_1		−0.72 (−2.94, 1.50)	0.86 (0.57, 1.30)
M_2		−0.82 (−3.08, 1.44)	0.86 (0.57, 1.30)
Q_3 81-98	96/432		
M_1		0.29 (−1.83, 2.41)	0.56 (0.36, 0.86)
M_2		−0.00 (−2.05, 2.04)	0.56 (0.36, 0.87)
Q_4 >98	97/400		
M_1		1.21 (−0.14, 2.56)	0.72 (0.47, 1.09)
M_2		0.90 (−0.52, 2.32)	0.73 (0.48, 1.10)
p_{trend}		0.17	0.05
Total magnesium intake (mg/day)			
Q_1 <232	263/543		
Q_2 232-310	153/463		
M_1		2.51 (0.55, 4.48)	0.80 (0.51, 1.25)
M_2		2.48 (0.48, 4.47)	0.80 (0.52, 1.25)
Q_3 311-412	79/450		
M_1		4.12 (2.08, 6.16)	0.43 (0.28, 0.66)
M_2		4.04 (2.03, 6.04)	0.42 (0.27, 0.66)
Q_4 >412	88/427		
M_1		4.44 (1.25, 7.63)	0.72 (0.39, 1.33)
M_2		4.34 (1.14, 7.54)	0.71 (0.38, 1.33)
p_{trend}		<0.01	<0.01

[1] Survey linear regression models used to estimate β and 95% CIs.

[2] Survey logistic regression models used to estimate ORs and 95% CIs.

M_1 were adjusted for age, sex, race/ethnicity, education, season of exam, BMI, smoking status, physical activity, alcohol use, diabetes status, history of cancer, history of heart attack, history of stroke, dietary intakes of total energy, and total calcium intake.

M_2 were additional mutually adjusted for serum vitamin D and total magnesium intake.

Table 3.

Linear associations of total magnesium intake with cognitive impairment status stratified by selected factors, NHANES, 2011-2014

Total Magnesium Intake (mg/day)	Low (n= 583)	High (n = 1,883)	β (95% CI)[≠]
Male			
Q_1 <232	130	193	Referent
Q_2 232-310	91	194	1.03 (−2.06, 4.12)
Q_3 311-412	44	235	3.42 (0.91, 5.93)
Q_4 >412	62	258	2.91 (−0.52, 6.34)
p_{trend}			0.61
Female			
Q_1 <232	133	350	Referent
Q_2 232-310	62	269	3.20 (0.42, 5.99)
Q_3 311-412	35	215	3.80 (0.82, 6.77)
Q_4 >412	26	169	5.61 (1.58, 9.63)
p_{trend}			0.01
$p_{interaction}$			0.45
Non-Hispanic White			
Q_1 <232	82	280	Referent
Q_2 232-310	49	266	2.53 (0.13, 4.95)
Q_3 311-412	19	268	4.40 (1.97, 6.84)
Q_4 >412	29	259	4.97 (1.37, 8.57)
p_{trend}			0.04
Other Race/Ethnicity [1]			
Q_1 <232	181	263	Referent
Q_2 232-310	104	197	1.40 (−1.02, 3.81)
Q_3 311-412	60	182	2.10 (0.21, 4.00)
Q_4 >412	59	168	0.55 (−3.24, 4.33)
p_{trend}			0.51
$p_{interaction}$			0.31
Low/No Physical Activity			
Q_1 <232	196	335	Referent
Q_2 232-310	110	257	2.01 (−0.90, 4.92)
Q_3 311-412	49	222	4.85 (1.26, 8.44)
Q_4 >412	64	178	3.91 (−0.43, 8.26)
p_{trend}			0.04
Moderate/High Physical Activity			
Q_1 <232	67	208	Referent
Q_2 232-310	43	206	3.17 (1.32, 5.03)

Total Magnesium Intake (mg/day)	**Low (n= 583)**	**High (n = 1,883)**	**β (95% CI)** [≠]
Q_3 311-412	30	228	3.66 (1.63, 5.70)
Q_4 >412	24	249	5.68 (2.66, 8.70)
p_{trend}			<0.01
$p_{interaction}$			0.17
Serum 25(OH)D level (<50 nmol/L)			
Q_1 <232	85	140	Referent
Q_2 232-310	34	67	−0.31 (−3.11, 2.48)
Q_3 311-412	18	69	1.23 (−3.84, 6.31)
Q_4 >412	19	45	0.86 (−6.54, 8.25)
p_{trend}			0.72
Serum 25(OH)D level (>=50 nmol/L)			
Q_1 <232	178	403	Referent
Q_2 232-310	119	396	2.87 (0.52, 5.21)
Q_3 311-412	61	381	4.45 (1.91, 7.00)
Q_4 >412	69	382	4.77 (1.08, 8.46)
p_{trend}			<0.01
$p_{interaction}$			0.68

[≠]Adjusted for age, sex, race/ethnicity, BMI, smoking status, activity, alcohol use, total calcium intake, history of cancer, education, season of exam, history of heart attack, diabetes status, history of stroke, total energy intake and serum 25(OH)D levels.

[1]Other race/ethnicity: included non-Hispanic Black, Hispanic, non-Hispanic Asian, and Other Race.

Table 4.

Joint effect of serum 25(OH)D level and magnesium on cognitive function measured as a DSST score

	Serum 25(OH)D <50 nmol/L	Serum 25(OH)D ≥50 nmol/L
Magnesium Intake (mg/day)	**β (95% CI)***	**β (95% CI)***
Q_1 <232	Referent	0.73 (−2.17, 3.63)
Q_2 232-310	1.44 (−2.86, 5.16)	3.43 (0.72, 6.15)
Q_3 311-412	3.91 (−0.86, 8.68)	5.07 (2.65, 7.49)
Q_4 >412	4.99 (−2.19, 12.16)	5.44 (1.88, 9.01)

*Adjusts for age, sex, race/ethnicity, education, season of exam, BMI, smoking status, physical activity, alcohol use, total calcium intake, history of cancer, history of heart attack, diabetes status, history of stroke, and total energy intake.