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Original Article

ORIGINAL ARTICLE

Association of magnesium intake with sleep duration and sleep quality: findings from the CARDIA study

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Abstract

Study Objectives: As an antagonist of calcium (Ca), magnesium (Mg) has been implicated in the regulation of sleep. We aimed to examine the longitudinal associations of Mg intake and Ca-to-Mg intake ratio (Ca:Mg) with sleep quality and duration.

Methods: The study sample consisted of 3,964 participants from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Dietary and supplementary intake of Mg were obtained using the CARDIA Dietary History at baseline (1985–1986), exam years 7 and 20. Self-reported sleep outcomes were measured at years 15 and 20. Sleep quality was rating from 1 (very good) to 5 (very bad). We categorized sleep duration to <7, 7–9, and >9 h. Generalized estimating equation was used to examine the associations of interest as repeated measures at the two time points.

Results: After adjustment for potential confounders, Mg intake was borderline associated with better sleep quality [highest quartile (Q4) vs. intake quartile (Q1): odds ratio (OR) = 1.23; 95% CI = 0.999, 1.50, p_{trend} = 0.051]. Participants in Q4 were also less likely to have short sleep (<7 h) compared to those in Q1 (OR = 0.64; 95% CI = 0.51, 0.81, p_{trend} = 0.012). The observed association with short sleep persisted among participants without depressive disorders (Q4 vs. Q1: OR = 0.64; 95% CI = 0.49, 0.82, p_{trend} < 0.001), but not among individuals with depressive disorder. Ca:Mg was not associated with either outcomes, regardless of depression status.

Conclusions: Mg intake was associated with both sleep outcomes in this longitudinal analysis. Randomized controlled trials with objective measures of sleep are warranted to establish the potential causal inference.

Statement of Significance

Magnesium (Mg) participates in the regulation of numerous biochemical reactions in human body and is associated with decreased risk of several diseases. Sleep is a vital mediator between various exposures and downstream health outcomes. Our study is the first to demonstrate the long-term association between Mg intake and sleep quality and sleep duration in a large cohort of young American adults. This may help elucidate the potential physiological mechanism between magnesium intake and disease outcomes. Future studies with objective measures of sleep are warranted.

Key words: magnesium; Ca:Mg; sleep quality; sleep duration; depression; CARDIA

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Introduction

Sleep disturbance, such as sleep deprivation and poor sleep quality, has become a common health disorder in modern society. According to the Centers for Disease Control and Prevention (CDC), the prevalence of short sleep (<7 h/night) in adults by states in the United States ranged from 24.3% to 48.5% in 2014 [1]. Sleep disturbance is a major risk factor for chronic diseases such as obesity, diabetes, cardiovascular disease (CVD) and certain cancers [1–3] through interrupting glucose and insulin metabolism, and energy balance [4].

Magnesium (Mg) is the second most abundant mineral in the human body and serves as a cofactor for numerous enzymatic reactions [5]. Mg may play a role in sleep via the regulation of the glutamatergic and gamma-aminobutyric acid (GABA) ergic system. It binds to GABA receptors and activates GABA to reduce excitability of the nervous system [6]. Also, Mg can inhibit the N-methyl-D-aspartate receptor, promoting muscle relaxation via suppression of intracellular calcium (Ca) concentration in the muscle cell [7–10]. Additionally, it has been shown in rats that Mg deficiency resulted in a decrease in the concentration of plasma melatonin, a sleep-promoting hormone [11]. Moreover, studies have shown that Mg supplementation can decrease the concentration of serum cortisol, a stress hormone, [10, 12] resulting in calming the central nervous system [13] and potentially better sleep.

Since Ca and Mg homeostasis share some common regulatory hormones and ion transporters for absorption, Mg bioavailability may depend on the concentration of Ca or the Ca-to-Mg ratio (Ca:Mg) [14]. Although research on the association between Ca:Mg and sleep is scarce, some studies suggested that dietary Ca:Mg may be a better predictor than a single element for several health outcomes, including CVD [15, 16] and certain cancers [17–19].

Some short-term randomized controlled trials (RCT) in older adults provided mixed findings regarding the association of Mg supplementation with sleep quality and duration [12, 20–24]. Presumably, the inconsistency is explained by a variety of factors such as placebo effect, insufficient study duration, and different study populations. To date, no epidemiological evidence is available with regards to the association between Mg intake and sleep in young adults, who may be more vulnerable to sleep deprivation compared to older adults [25]. Additionally, sleep problems encountered at young adulthood may proceed to mature ages [26]. Therefore, we aimed to examine the longitudinal associations between Mg intake (including both dietary and supplementary sources) as well as Ca:Mg in relation to sleep quality and duration in a large-scale cohort study consisting of young adults in the United States.

Methods

Study population

Coronary Artery Risk Development in Young Adults (CARDIA) study is an ongoing multicenter prospective cohort study that aims to investigate the clinical trajectories of CVD and its associated risk factors [27]. In 1985–1986, 5,115 young Americans, aged 18–30 years, were recruited from four sites: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. This cohort utilized a sampling scheme that ensured balanced number of individuals from various demographic subgroups: race, sex, educational level, and age. The follow-up exams took place every 2–5 years. Detailed information on study design was published elsewhere [27]. Currently, data are available at 9 time points across 30 years: 1985–1986 (baseline), 1987–1988 (year 2), 1990–1991 (year 5), 1992–1993 (year 7), 1995–1996 (year 10), 2000–2001 (year 15), 2005–2006 (year 20), 2010–2011 (year 25), and 2015–2016 (year 30) [28]. The retention of the surviving cohort for each follow-up time were 91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71%, respectively.

The present study used data from baseline to year 20 because the most recent outcome variables (sleep quality and duration) were measured at year 20. The initial sample size was 5,114 (one participant dropped out after recruitment). We excluded 108 participants with extreme energy intake (<600 or >6,000 kcal/day for women; <800 or >8,000 kcal/day for men), 18 participants with implausible sleep duration (>24 h), and 1,024 participants with missing outcome measures at year 15 and 20. The final dataset included a total of 3,964 participants. Written informed consent was obtained from all participants. The institutional review boards of CARDIA participating institutions approved this study protocol.

Dietary assessment

The CARDIA diet history questionnaire is a validated instrument (https://www.cardia.dopm.uab.edu/images/more/pdf/D10006.PDF), assessing habitual dietary pattern [29]. Dietary information was collected in person by trained and certified interviewers at baseline, years 7 and 20 [29]. The questionnaire asked participants to report food eaten during the past month including information on cooking methods and frequency of consumption. Then, the trained personnel translated the pre-coded dietary items to estimate the individual nutrient intake (dietary and supplemental intake) using the Nutrition Data System for Research (NDSR, versions 10, 20, and 36 for baseline, year 7, and year 20, respectively) developed by the Nutrition Coordinating Center at the University of Minnesota [30].

We combined the dietary and supplemental intake of the nutrients as total intake and used it as the measure of the exposure variable. For the intake of all the nutrients including Ca:Mg, cumulative statistics were calculated by averaging the repeated measurements from baseline until the year of or the most recent year before the sleep measurements. Thus, in our analyses, the average of nutrient intake at baseline and year 7, and the average of nutrient intake at baseline, year 7, and 20 were used as the measures for exposure variables for sleep measures at years 15 and 20, respectively.

Assessment of sleep quality and duration

In CARDIA, sleep measures were available at years 15 and 20. For sleep quality, participants self-rated the quality from 1 (very good) to 5 (very bad) by answering the question "During the past month, how would you rate your sleep quality overall?" Sleep duration was obtained from participants' recall of the average number of hours of sleep during the past month. Participants were allowed to give fractions. We categorized the sleep duration into three groups: <7, 7–9, and >9 h based on the recommendation from the National Sleep Foundation [31].

Other covariates assessments

Information on age, sex, race, education level, physical activity, alcohol consumption and smoking status were collected using interviewer-administered questionnaires. Depression, as scoring of depressive symptoms, was measured by the modified Center for Epidemiologic Studies Depression Scale (CES-D) [32]. A higher score indicates more severe depressive symptoms. We dichotomized the variable into two categories based on the established cutoff points. Therefore, those with CES-D above 16 were considered with depressive disorder [32]. Participants' height and body were measured during clinical examinations and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Age, race, sex, and study site at baseline were used in the analyses. Smoking status was measured as never smoker, past smoker, and current smoker. For variables of smoking, educational level, and BMI, we used the most recent assessments in the analyses. For all other covariates, including alcohol consumption, depression status, and physical activity, similarly to nutritional variables, cumulative statistics were calculated by averaging the repeated measurements from baseline to the year of, or the most recent year before sleep measures were taken.

Statistical analysis

All analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA). $p \leq 0.05$ is considered statistically significant for a hypothesis test and $p \leq 0.10$ is considered statistically significant for a test of effect modification.

Total Mg intake was categorized into quartiles. Characteristics of participants were presented as mean values with standard deviations (SDs) or medians with interquartile ranges (IQR) in the whole sample and by quartiles of total Mg intake. The main characteristics of the four exposure groups were compared using the analysis of variance (ANOVA) (age and BMI), chi-squared test (sex, race, and smoking), or Kruskal–Wallis test (all other variables).

Generalized estimating equations (GEE) were used to evaluate the associations between exposure variables (in quartiles) and two sleep outcomes at two time points (years 15 and 20). Cumulative logistic regression was used for the outcome sleep quality, which was a self-reported score ranging from 1 (very good) to 5 (very bad) measured at two time points. Multinomial logistic regression was used to assess the association between exposures (in quartiles) and sleep duration categories (7–9 h as the reference level). Stratified analysis was used to assess the potential effect modification by depression.

In our sample, the frequency of Mg supplementation use was 43.4%. As a sensitivity analysis, we created a new variable which was indicative of Mg supplementation status (yes/no) and added this variable in the models assessing the associations of Mg intake in relation to both sleep outcomes.

Results

The characteristics of the 3,964 participants by quartile of total Mg intake are summarized in Table 1. The median Mg intakes (mg/1,000 kcal/day) in quartiles 1 through 4 were 105.5, 129.8, 155.8, and 195.8, respectively. Compared to participants

Table 1. Demographic and personal characteristics by quartiles of total magnesium intake, the CARDIA study

		Quartiles of magnesium intake (mg/1,000 kcal/day)				
	Total	Q1 (lowest)	Q2	Q3	Q4 (highest)	P-value
No. of participants	3,964	991	991	991	991	–
Mg intake (mg/1,000 kcal/day)	142.9 (118.6–172.1)	105.5 (96.2–112.2)	129.8 (123.9–136.6)	155.8 (149.6–163.3)	195.8 (182.9–223.4)	–
Ca intake (mg/1,000 kcal/day)	411.6 (331.9–529.7)	319.3 (267.0–375.4)	392.8 (331.9–476.9)	449.3 (369.9–545.1)	541.7 (441.4–665.7)	<0.0001
Ca/Mg	3.0 (2.5–3.5)	3.2 (2.6-3.6)	3.1 (2.6–3.7)	2.9 (2.4–3.5)	2.7 (2.2–3.3)	<0.0001
Age at baseline	25.0±3.6	24.0±3.8	24.7±3.7	25.4±3.4	26.0±3.2	<0.0001
Female (%)	56.1	54.6	49.8	53.2	66.9	<0.0001
Blacks (%)	47.8	81.1	56.0	34.0	20.2	<0.0001
Education levels (year)	14.5±2.3	13.4±2.0	14.2±2.2	15.0±2.3	15.4±2.2	<0.0001
Current smokers (%)	19.7	25.8	22.1	15.8	14.8	<0.0001
Alcohol intake (ml/day)	5.0 (0.7–14.3)	3.6 (0–13.1)	4.7 (0.5–15.5)	5.7 (0.9–14.5)	5.8 (1.2–14.4)	0.001
Physical activity (EU)	320.9 (197.5–489.1)	247.5 (151.0–413.6)	293.0 (180.4–466.7)	349.7 (224.3–517.3)	376.8 (257.8–536.2)	<0.0001
BMI at baseline (kg/m^2)	24.5±5.0	25.0±5.8	25.0±5.3	24.3±4.6	23.8±4.1	<0.0001
Depressive symptom (CES-D score)	9.0 (5.3–13.7)	10.0 (6.3–15.7)	9.3 (6.0–14.3)	8.3 (5.0–12.3)	8.0 (4.7–12.0)	<0.0001

Current smokers (%) was measured at year 15. All other variables, if not specified, were cumulative average of all the available measurements from baseline to year 15.

Results are presented by mean±SDs, medians (IQRs) or proportions. *P* values were calculated for any differences across quartiles of Mg intake levels using analysis for variance, Kruskal–Wallis test, or chi-squared test, as appropriate

Abbreviations: BMI, body mass index; Ca, calcium; CARDIA, Coronary Artery Development in Young Adults; CES-D, Center for Epidemiologic Studies Depression Scale; EU, exercise unit; IQR, interquartile ranges; Mg, magnesium; No., number; Q, quartile; *SD*, standard deviation

in the lowest quartile of Mg intake, those in the highest quartile were slightly older, more likely to be female and White, and have higher level of education. They were less likely to be current smokers, and had higher alcohol consumption and higher physical activity level. They described themselves with fewer depressive symptoms measured by CES-D. Sleep outcomes by categories of Mg intake and Ca:Mg are presented in Supplementary Tables 1 and 2.

The association between Mg intake and sleep quality

The multivariable-adjusted associations between Mg intake and sleep quality are summarized in Table 2. In model 1, which accounted for age, race, center, and time (years 15 and 20), there was a significant positive association between total Mg intake and sleep quality (p_{trend} = 0.02). Those in the highest quartile of Mg intake were more likely to have better sleep quality [odds ratio (OR) = 1.22; 95% confidence interval (CI) = 1.04, 1.42]. After additional adjustment for education, current smoking status, alcohol consumption, physical activity, BMI, and intakes of total energy, caffeine, zinc, vitamin D, and carbohydrate (model 3), the association was attenuated and became borderline significant (OR = 1.23; 95% CI = 0.999, 1.50, p_{trend} = 0.051). The results from the sensitivity analysis did not change substantially after adding the variable of magnesium status (OR = 1.25; 95% CI = 1.02, 1.54, p_{trend} = 0.03).

The interaction between Mg intake and depression status was significant ($p_{interaction}$ = 0.005). In the stratified analysis by depression status (Table 3), among individuals without depressive disorder, those in the highest quartile of Mg intake were more likely to have better sleep quality (OR = 1.30; 95% CI = 1.04, 1.63, p_{trend} = 0.02). No association was observed between Mg intake and sleep quality among those with depressive disorder.

The association between Mg intake and sleep duration

Table 2 presents the multivariable-adjusted associations between Mg intake and sleep duration. In model 1, individuals in the highest quartile of Mg intake were less likely to have a sleep duration <7 h (OR = 0.72; 95% CI = 0.61, 0.85, p_{trend} < 0.0001). The association remained significant even after additional adjustment for behavior variables and other nutrient intakes such as caffeine, zinc, vitamin D, and carbohydrate in model 3 (OR = 0.64; 95% CI = 0.51, 0.81, p_{trend} = 0.004). The results from the sensitivity analysis did not change substantially after adding the variable of magnesium status (OR = 0.64; 95% CI = 0.50, 0.80, p_{trend} = 0.004).

In the stratified analysis by depression status (Table 3), the association was observed only among individuals without depressive disorder. Participants in the highest Mg intake quartile were less likely to have a sleep duration <7 h (OR = 0.64; 95% CI = 0.49, 0.82, p_{trend} < 0.0001).

The association between Ca:Mg and sleep

Based on the available data, there was no significant association between Ca:Mg and sleep quality or duration (Table 4), regardless of depression status (Table 5).

Discussion

Findings from this longitudinal study support the hypothesis that Mg intake was associated with better sleep quality and the recommended sleep duration (i.e. 7–9 h), particularly among the participants without depressive disorders. The observed associations do not exist among the participants with depressive disorder. Ca:Mg was not associated with either sleep quality or sleep duration regardless of depression status.

Table 2. Multivariable-adjusted ORs and 95% CIs of sleep outcomes by quartiles of magnesium intake levels

		Quartiles of magnesium intake (mg/1,000 kcal/day)				
		Q1 (lowest)	Q2	Q3	Q4 (highest)	P_{trend}
No. of participants		991	991	991	991	–
No. of observations		1,982	1,982	1,982	1,982	–
***Outcome: sleep quality* (ORs of better sleep quality score)**						
Model 1		1(Ref.)	1.09 (0.95, 1.24)	1.11 (0.96, 1.29)	**1.22 (1.04, 1.42)**	**0.01**
Model 2		1(Ref.)	1.06 (0.93, 1.22)	1.03 (0.89, 1.20)	1.09 (0.92, 1.29)	0.36
Model 3		1(Ref.)	1.08 (0.93, 1.25)	1.09 (0.91, 1.29)	**1.23 (0.999, 1.50)**	**0.051**
***Outcome: sleep duration* (ORs compared to the reference group: 7–9 h)**						
Model 1	<7 h vs. ref	1(Ref.)	0.93 (0.81, 1.08)	**0.80 (0.68, 0.93)**	**0.72 (0.61, 0.85)**	**<0.0001**
	>9 h vs. ref	1(Ref.)	0.75 (0.45, 1.24)	0.62 (0.34, 1.16)	0.62 (0.32, 1.22)	0.11
Model 2	<7 h vs. ref	1(Ref.)	1.01 (0.87, 1.19)	0.87 (0.74, 1.04)	**0.81 (0.67, 0.98)**	**0.01**
	>9 h vs. ref	1(Ref.)	0.88 (0.53, 1.47)	0.90 (0.46, 1.77)	0.99 (0.48, 2.04)	0.87
Model 3	<7 h vs. ref	1(Ref.)	0.97 (0.82, 1.15)	**0.78 (0.64, 0.94)**	**0.64 (0.51, 0.81)**	**0.004**
	>9 h vs. ref	1(Ref.)	0.91 (0.55, 1.53)	0.87 (0.41, 1.86)	0.88 (0.36, 2.16)	0.20

All models were constructed using generalized estimating equation method. *P* for trend was examined using the medians of magnesium quartiles for sleep quality and ranks as continuous variable for sleep duration. The values of covariates, unless specified, were calculated as the cumulative average of repeated measurements by sleep quality at year 15 and year 20, respectively.

Model 1 was adjusted for age at baseline (continuous), sex (female or male), race (blacks or whites), study center, and time.

Model 2 was additionally adjusted for education (continuous), smoking status (current vs. no), alcohol consumption (continuous), BMI at baseline (<18.5, 18.5–24.9, 25–29.9, or ≥30 kg/m^2), physical activity (continuous), and total energy intake (quartiles).

Model 3 was additionally adjusted for caffeine intake (quartiles), zinc intake (quartiles), vitamin D intake (quartiles), carbohydrate intake (quartiles).

Abbreviations: BMI, body mass index; CI, confidence interval; h, hours; OR, odds ratio; Q, quartile; ref, reference.

Table 3. Multivariable-adjusted ORs and 95% CIs of sleep outcomes by quartiles of magnesium intake levels stratified by depression status

		Quartiles of magnesium intake (mg/1,000 kcal/day)				
		Q1 (lowest)	Q2	Q3	Q4 (highest)	P_{trend}
***Outcome: sleep quality* (ORs of better sleep quality score)**						
CES-D <16		1(Ref.)	1.13 (0.96, 1.32)	1.15 (0.95, 1.39)	**1.30 (1.04, 1.63)**	**0.02**
CES-D ≥16		1(Ref.)	0.81 (0.59, 1.11)	0.71 (0.48, 1.05)	0.79 (0.48, 1.29)	0.34
$p_{interaction}$		**0.005**				
***Outcome: sleep duration* (ORs compared to the reference group: 7–9 h)**						
CES-D<16	<7 h vs. ref	1(Ref.)	0.98 (0.81, 1.18)	**0.73 (0.59, 0.91)**	**0.64 (0.49, 0.82)**	**<0.0001**
	>9 h vs. ref	1(Ref.)	0.77 (0.42, 1.42)	0.62 (0.26, 1.47)	0.73 (0.27, 1.95)	0.39
CES-D≥16	<7 h vs. ref	1(Ref.)	1.02 (0.70, 1.49)	1.24 (0.77, 1.99)	0.66 (0.38, 1.15)	0.33
	>9 h vs. ref	1(Ref.)	1.22 (0.45, 3.30)	1.86 (0.48, 7.18)	1.21 (0.20, 7.19)	0.68
$p_{interaction}$		**0.07 (<7 h)** 0.14 (>9 h)				

All models were constructed using general estimation equations with adjustment for covariates in Model 3, Table 2. *P* for trend and *p* for interaction were examined using the medians of magnesium quartiles for sleep quality and using the continuous variable of ranks of magnesium intake (1 to 4) for sleep duration.
Abbreviations: CI, confidence interval; CES-D, Center for Epidemiologic Studies Depression Scale; h, hours; OR, odds ratio; Q, quartile; ref, reference.

Table 4. Multivariable-adjusted ORs and 95% CIs of sleep outcomes by quartiles of calcium-to-magnesium ratio levels

		Quartiles of calcium-to-magnesium ratio				
		Q1 (lowest)	Q2	Q3	Q4 (highest)	P_{trend}
No. of participants		991	991	991	991	–
No. of observations		1,982	1,982	1,982	1,982	–
***Outcome: sleep quality* (ORs of better sleep quality score)**						
Model 1		1(Ref.)	1.01 (0.89, 1.15)	1.07 (0.93, 1.22)	1.09 (0.95, 1.26)	0.16
Model 2		1(Ref.)	1.00 (0.88, 1.14)	1.04 (0.91, 1.20)	1.08 (0.93, 1.24)	0.24
Model 3		1(Ref.)	0.99 (0.87, 1.13)	1.01 (0.88, 1.16)	1.03 (0.89, 1.20)	0.60
***Outcome: sleep duration* (ORs compared to the reference group: 7–9 h)**						
Model 1	<7 h vs. ref	1(Ref.)	0.96 (0.84, 1.11)	0.93 (0.81, 1.07)	1.02 (0.88, 1.18)	0.77
	>9 h vs. ref	1(Ref.)	0.69 (0.39, 1.25)	0.92 (0.52, 1.62)	1.30 (0.75, 2.27)	0.24
Model 2	<7 h vs. ref	1(Ref.)	1.01 (0.87, 1.17)	0.92 (0.79, 1.08)	1.01 (0.86, 1.18)	0.92
	>9 h vs. ref	1(Ref.)	0.74 (0.41, 1.36)	1.00 (0.56, 1.79)	1.29 (0.73, 2.29)	0.27
Model 3	<7 h vs. ref	1(Ref.)	1.03 (0.89, 1.19)	0.97 (0.83, 1.13)	1.10 (0.93, 1.30)	0.36
	>9 h vs. ref	1(Ref.)	0.80 (0.43, 1.48)	1.12 (0.61, 2.06)	1.68 (0.91, 3.12)	0.07

All models were constructed using generalized estimating equation method. *P* for trend was examined using the medians of Ca:Mg quartiles. The values of covariates, unless specified, were calculated as the cumulative average of repeated measurements by sleep quality at year 15 and year 20, respectively.
Model 1 was adjusted for age at baseline (continuous), sex (female or male), race (blacks or whites), study center, and time.
Model 2 was additionally adjusted for education (continuous), smoking status (current vs. no), alcohol consumption (continuous), BMI at baseline (<18.5, 18.5–24.9, 25–29.9, or ≥30 kg/m^2), physical activity (continuous), and total calorie intake (quartiles).
Model 3 was additionally adjusted for caffeine intake (quartiles), vitamin D intake (quartiles), carbohydrate intake (quartiles).
Abbreviations: BMI, body mass index; Ca, calcium; CI, confidence interval; h, hours; Mg, magnesium; OR, odds ratio; Q, quartile; ref, reference.

Mg and sleep quality

Although the association between Mg and sleep quality is biologically plausible and supported by previous animal and human research, [10, 33, 34] the association was only borderline significant in our study. One explanation is that the measurement of sleep quality, which was assessed by one question asking participants to rate their sleep quality in the past 30 days from 1 to 5. This one-item subjective measure may not fully capture the characteristics of sleep quality, a complex construct including several aspects such as "easy to fall asleep, less wakening in between, and easy to drift back after initial wakening". Self-reported sleep quality can be more accurately measured by validated instruments such as the Pittsburg Sleep Quality Index [35]; objective sleep quality can be measured conveniently from smart watches or actigraphy devices that are widely available. With the aid of technology, researchers can obtain more accurate data in future studies. Of note, CARDIA sleep study (an ancillary study) collected PSQI and actigraphy data one time between year 15 and year 20. However, our power calculation indicated that the sample size was not enough to achieve the objective in this study.

Mg and sleep duration

Our finding is in agreement with previous research in both animal models [11] and humans [12, 36]. It has been shown that feeding rats with a Mg-deficient diet induced more wakefulness [11]. In humans, the results from a large-scale cross-sectional study suggested that higher Mg intake was associated with normal hours of sleep and low level of consumption was linked to both shorter and longer sleep [36]. Additionally, findings from a clinical trial showed that 500 mg elemental Mg supplementation

Table 5. Multivariable-adjusted ORs and 95% CIs of sleep outcomes by quartiles of calcium-to-magnesium ratio levels stratified by depression status

		Quartiles of calcium-to-magnesium ratio				
		Q1 (lowest)	Q2	Q3	Q4 (highest)	P_{trend}
***Outcome: sleep quality* (ORs of better sleep quality score)**						
CES-D <16		1(Ref.)	1.00 (0.86, 1.16)	1.00 (0.86, 1.17)	0.99 (0.84, 1.17)	0.97
CES-D ≥16		1(Ref.)	0.96 (0.71, 1.30)	0.96 (0.69, 1.32)	1.09 (0.76, 1.54)	0.65
$p_{interaction}$		.91				
***Outcome: sleep duration* (ORs compared to the reference group: 7–9 h)**						
CES-D <16	<7 hrs *vs.* ref	1(Ref.)	0.98 (0.83, 1.15)	1.00 (0.84, 1.18)	1.09 (0.91, 1.31)	0.29
	>9 hrs *vs.* ref	1(Ref.)	1.03 (0.47, 2.25)	1.43 (0.68, 3.02)	**2.49 (1.23, 5.01)**	**0.008**
CES-D ≥16	<7 hrs *vs.* ref	1(Ref.)	1.21 (0.83, 1.77)	0.81 (0.54, 1.21)	1.22 (0.78, 1.90)	0.70
	>9 hrs *vs.* ref	1(Ref.)	0.53 (0.18, 1.62)	0.70 (0.22, 2.18)	0.89 (0.25, 3.18)	0.92
$p_{interaction}$		0.79 (<7 h) 0.16 (>9 h)				

All models were constructed using general estimation equations with adjustment for covariates in model 3, Table 3. *P* for trend and *p* for interaction were examined using the medians of Ca:Mg quartiles for sleep quality and using the continuous variable of ranks of Ca:Mg (1 to 4) for sleep duration.
Abbreviations: Ca, calcium; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; h, hours; Mg, magnesium; OR, odds ratio; Q, quartile; ref, reference.

(equivalent to 250 mg/1,000/day, assuming on a 2,000 kcal diet) for 8 weeks significantly increased the sleep duration and decreased the sleep latency in the elderly [12].

Mg may influence sleep duration via regulation of the circadian clock [37]. Mg is crucial in neuronal processes given its important physiological role [34]. A study conducted in rats suggested that Mg concentrations in the forebrain were highly correlated with sleep duration [34]. Additionally, Mg is associated with the production of melatonin, a key hormone involved in the regulation of the sleep–wake cycle [38]. It has been shown in rats that Mg deficiency resulted in a decrease in plasma melatonin concentrations [11].

Ca:Mg

In this study, the median Ca:Mg was 3 (IQR: 2.5–3.5), which was higher than the optimal 2:1 ratio proposed by some researchers [39]. Thus, one possible explanation of the null association observed in the study is that the Ca:Mg of the participants were all higher than the optimal ratio, and the potential associations of Ca:Mg and sleep outcomes may have reached plateau. Noted, we observed an association between Ca:Mg (highest *vs.* lowest quartile) and sleep duration >9 h. However, the small number of participants with sleep duration >9 h resulted in the wide confidence interval with large margin of errors. Therefore, our ability to determine the potential association between Ca:Mg and sleep duration was limited by the relatively small sample size. Given that the research on the association of Ca:Mg in relation to sleep quality and duration is scarce, future studies with large sample size are warranted.

Effect modification of depression status

The complex relation between depression and sleep disorders has been well established. Sleep disturbance is one of the major symptoms of depression [40], and research has shown that sleep structures, in terms of the duration and characteristics of rapid eye movement (REM) sleep, varied between depression patients and the controls [40]. In the participants without depression status, the association of Mg intake and sleep quality became significant. Thus, obtaining measures such as stress in the participants may help examine the potential mediating role of stress with depression and sleep quality. For the participants with higher level of depressive symptoms, the dysfunction of sleep may result from the imbalance of multiple neurotransmitters [41]. Therefore, nutrition strategies, such as increasing Mg intake, may not be sufficient to reverse the disruptions of the corresponding biological pathways [42]. Additionally, some causes remotely associated with nutritional intake, such as stressful events and genetic vulnerability, could potentially trigger sleep disturbance among depressive participants. Thus, understanding the potential effect of modification of depression status on the association between Mg and sleep may help health professionals develop sleep remedies, for example, nutritional and pharmacological approaches tailored to different populations.

Strengths and limitations

To the best of our knowledge, this is the first study to assess the long-term association between Mg intake and sleep in a large cohort of young American adults. To maximize data utility, we include all participants with available data in the analyses, which gives us sufficient statistical power (>99.9%) to detect the associations of interest. Also, from a statistical perspective, the longitudinal study design (repeated measurement analysis) retained all available outcome information for each participant and increased the precision of the OR estimation [43]. In our analysis, a marginal model (i.e. GEE) was used, which accounts for the correlation of the sleep outcomes of the same subject.

However, this study also has several limitations. First, objective measures of Mg and Ca, for example, biomarkers, were not available. However, the CARDIA diet history has been validated in previous research and the correlation between the dietary Mg intake (year 0 and 7) and toenail Mg concentration (year 2) is moderate ($r = 0.37$) [44]. Second, the timing of Mg or Ca ingestion was not available, which may be an issue as one of the potential mechanisms linking Mg and sleep is melatonin synthesis [11]. Third, outcome measures, that is, sleep quality and duration in the whole cohort

were both subjective. While a moderate correlation (r = 0.46) has been shown between self-reported sleep duration and objective duration in CARDIA participants, researchers also indicated that subjective sleep duration was longer than the one measured by wrist actigraphy [45]. This may result in the misclassification of outcome categories and move the estimates of the associations to either directions. Additionally, the assessment of sleep quality in this study was based on one question, rather than validated questionnaire such as Pittsburgh Sleep Quality Index. This self-perceived sleep quality is acceptable although may not be thorough and informative. Future studies with validated instruments or technology-assisted objective measure of sleep quality are warranted. Forth, due to the nature of secondary data analysis, we were not able to control for some variables that have been shown to be associated with sleep duration/quality in young adults. For example, family relationship has a large influence on sleep in adults [46]. The requirement of caregiving for young children may disrupt the normal sleep pattern of parents [47].

Summary

As sleep disturbance has become a common concern for daily lives, research on sleep, along with sleep-associated diseases, may be more important than ever. Further examining sleep as a mediator may help elucidate the physiological mechanism linking upstream factors and a variety of downstream health outcomes. The present study suggested that individuals with higher Mg intake are more likely to have the recommended duration of sleep. However, due to the potential measurement errors associated with exposures and outcomes, RCTs with objective sleep measures are warranted.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Authors' Contributions

Y.Z.: Data curation; Formal analysis; Methodology; Writing – original draft. C.C.: Validation; Writing – review and editing. L.L., K.L.K., M.R.C., A.D.F., J.L., D.M.H., J.M.S.: Writing – review and editing. K.K.: Conceptualization; Funding acquisition; Writing – review and editing.

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Data Availability

The data underlying this article were provided by CARDIA under license/ by permission. Data will be shared on request to the corresponding author with permission of CARDIA.

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