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Magnesium intake was inversely associated with hostility among American young adults

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Abstract

Hostility is a complex personality trait associated with many cardiovascular risk factor phenotypes. Although magnesium intake has been related to mood and cardio-metabolic disease, its relation with hostility remains unclear. We hypothesize that high total magnesium intake is associated with lower levels of hostility because of its putative antidepressant mechanisms. To test the hypothesis, we prospectively analyzed data in 4,716 young adults aged 18–30 years at baseline (1985–1986) from four U.S. cities over five years of follow-up using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Magnesium intake was estimated from a dietary history questionnaire plus supplements at baseline. Levels of hostility were assessed

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Author Statement

The authors thank the other investigators and the staff of the CARDIA Study for valuable contributions. The authors' responsibilities were as follows—Chen Lyu: interpreted the data, drafting the manuscript, and had primary responsibility for the final content; Pengcheng Xun: analysis and interpretation of data; drafting the manuscript; Yongjia Pu: Analysis and interpretation of data; Ka Kahe: designed the study, acquisition of data, drafting the manuscript; and all authors: critical revision of manuscript regarding intellectual content. None of the authors had a conflict of interest.

CONFLICT OF INTEREST

The authors confirm that none of the authors had a conflict of interest.

using the Cook-Medley scale at baseline and year 5 (1990–1991). Generalized estimating equations were applied to estimate the association of magnesium intake with hostility as repeated measures at the two time-points (baseline and year 5). General linear model was used to determine the association between magnesium intake and change in hostility over 5 years. After adjustment for socio-demographic and major lifestyle factors, a significant inverse association was observed between magnesium intake and hostility level over 5 years of follow-up. Beta coefficients (95% CI) across higher quintiles of magnesium intake were 0 (reference), -1.28 (-1.92, -0.65), -1.45 (-2.09, -0.81), 1.41 (-2.08, -0.75) and -2.16 (-2.85, -1.47), respectively ($P_{linear\text{-}trend}<0.01$). The inverse association was independent of socio-demographic and major lifestyle factors, supplement use, and depression status at year 5. This prospective study provides evidence that in young adults, high magnesium intake was inversely associated with hostility level independent of socio-demographic and major lifestyle factors.

Keywords

Hostility; Magnesium intake; Prospective study; CARDIA; Generalized estimating equations

1. INTRODUCTION

Hostility is a complex personality trait characterized by three components: 1) cynicism and a mistrusting attitude, 2) anger and contempt emotion, and 3) overt or repressed aggressive behavior [1]. These manifestations of hostility are not mutually exclusive and expression of these components can take a wide range of forms. Evidence suggests both a psychological and physiological source of hostility, and many view these etiologies as complementary rather than competing. The etiology of hostility is particularly important, since it has shown associations with multiple health outcomes, including coronary heart disease [2], metabolic syndrome [3], and all-cause mortality [4]. Therefore, identifying factors that mitigate hostility may provide new insight into chronic disease prevention.

Diet may play an important role in regulating hostility levels, since diet has been shown to improve mood [5]. Magnesium is an essential mineral involved in energy production, protein synthesis, and cell signaling. A deficiency of magnesium has been linked to a variety of neuropathologies leading to irritability and hyperexcitability in mood [6]. Because of its role in protecting against excessive excitatory neurotransmitters [7], regulating the hypothalamic-pituitary-adrenal (HPA) axis activity [8], and anti-inflammation properties [9], magnesium has been implicated as one such potential regulator of hostility [6]. Clinical practitioners have recognized the utility of this mineral in treating “agitated” depression as far back as the 1920s, and today it is still used frequently as a homeopathic treatment for emotional issues like anxiety, depression, discontent, irritability, restlessness, oversensitivity, and insecurity in both adults and children. One review article has even suggested a potential link between Type A personality, highlighted by an individual’s hypersensitivity to stress, and magnesium deficiency [10].

Because magnesium is not synthesized in the human body, it must be obtained via the diet or supplementation. Even with the various dietary sources of magnesium, including coffee,

green leafy vegetables, legumes, nuts, and whole grains, only half of Americans are achieving the recommended daily amount [11]. For these reasons, magnesium deficiency is not uncommon. Furthermore, because symptoms of this deficiency tend to be non-specific, many cases of hypomagnesemia go undetected, putting many at risk for a variety of chronic diseases [12, 13].

A number of observational studies have examined the association between magnesium and mood in humans. However, most of these studies are cross-sectional analyses focusing on symptoms of depression, which generally overlap with the characteristics of hostility (e.g., aggression, irritability, agitation, mood swings); the results of these studies are inconsistent. Of those cross-sectional studies, some have revealed a significant inverse correlation between magnesium and symptoms of depression across a variety of magnesium measures [14–16], including serum and plasma, cerebrospinal fluid, and diet; other studies conversely demonstrated a positive association [17, 18], and a few more showed no relation [19, 20]. In addition, one prospective study with an average of 5.8 years of follow-up showed no significant association between magnesium intake and incident depression [21], while a recent prospective study found that individuals with higher magnesium intake were less likely to receive a depression diagnosis after a 20-year follow-up [22]. Despite moderate to high correlation between depression and hostility (r=0.27~0.71) [23, 24], no published study has directly linked magnesium status to hostility levels.

We hypothesized that high total magnesium intake is associated with lower levels of hostility because of its putative antidepressant mechanisms. The present study aimed to prospectively examine the association between baseline total magnesium intake from dietary and supplemental sources and the five-year changes in hostility in young adulthood using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study. We applied generalized estimating equations (GEE) to estimate the association of interest given the repeated measures of hostility at baseline and exam year 5. To take the temporal sequence into consideration, we also used general linear model to determine the association between magnesium intake and change in hostility over 5 years.

2. METHODS AND MATERIALS

2.1 Study Population

The CARDIA study is an ongoing prospective cohort study designed to investigate the evolution of cardiovascular disease risk beginning in young adulthood. The study is registered and the ClinicalTrials.gov identifier is NCT00005130. The detailed study design and procedures have been described elsewhere [25]. Briefly, recruitment was conducted in 1985–1986 in four US metropolitan locations: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Kaiser Permanente Division of Research, Oakland, California. A sample of 5,115 eligible young adults aged 18–30 years was enrolled with balanced representation by age (18–24 vs. 25–30 years), race (black vs. white), gender (male vs. female), and education level (≤ high school vs. >high school). Follow-up examinations were conducted in 1987–1986 (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), with high participant retention of 91%, 86%, 81%, 79%, 74%, 72%, 72% and

71%, respectively. The study was approved by the institutional review committee. Informed consent was obtained from all participants. The protocol number for the current study was 1907082670.

Among the 5,115 participants, we excluded 4 participants with no information on magnesium intake, 128 participants with implausible energy intake (<800 or >8000 kcal/d for men, <600 or >6000 kcal/d for women), 195 with missing data on hostility measurement at baseline, and 1 for withdrawing consent. Since pregnancy may change diet practice, 6 women who were pregnant during the baseline examination were excluded. Furthermore, we excluded participants with missing values in some important covariates at baseline including body mass index (BMI) information (n=15), smoking status (n=31), and alcohol consumption (n=19). After these exclusions, a total of 4,716 participants remained in the main analysis for determining the association of baseline magnesium intake with repeatedly measured hostility. In addition, 3,902 participants with hostility data available at year 5 were available for assessing baseline magnesium intake in relation to change in hostility. The selection procedure of our study population was shown in a flowchart (Figure 1).

2.2 Measures

2.2.1 Primary Exposure—Diet information was collected at baseline using the CARDIA Diet History Questionnaire, which was conducted by a validated interviewing method to assess habitual diet pattern. The validity and reproducibility of the questionnaire have been described elsewhere [26]. Dietary as well as supplemental magnesium were estimated by translating the partially pre-coded CARDIA diet history using the database (version 10) developed by the Nutrition Coordinating Center at the University of Minnesota. Total magnesium intake, the primary exposure, was calculated summing dietary and supplemental intake of magnesium and represented as a nutrient density (mg/1000kcal/day). Minimum and maximum cutoffs of total energy intake were applied to match the normal lifestyle (600–6000 kcal/d in women and 800–8000 kcal/d in men).

To validate the magnesium intake, we conducted a pilot study in 99 randomly selected participants from the CARDIA Chicago Field Center. Toenail magnesium concentrations from clippings collected at year 2 were measured with the use of inductively coupled plasma mass spectrometry. The Pearson correlation coefficient was 0.37 between toenail magnesium and magnesium intake [27]. Also, whole grain is the major food source of magnesium [28]. In the current study, the Spearman rank correlation coefficient between baseline intakes of whole grain and total magnesium was 0.365. Although coffee is not a good source of vitamins and minerals, 1–2 cups contain 7–14 mg of magnesium. The Spearman rank correlation coefficient between baseline coffee and total magnesium was 0.153. In addition, a Spearman correlation of 0.50 was observed for magnesium intake measured at baseline and year 7.

2.2.2 Outcome—Hostility profile was measured at baseline and year 5 using the Cook-Medley Hostility Scale (CM Scale), which represents hostility as a multidimensional construct with cognitive (cynicism and mistrust of others), affective (anger and contempt) and behavioral (aggression) components. The validity of CM Scale has been examined

elsewhere [29]. The CM Scale is a self-administered questionnaire consisting of 50 items derived from the Minnesota Multiphasic Personality Inventory. Each item required a binary response (0 or 1); thus, raw scores ranged from 0 to 50. Higher scores indicated a higher level of hostility with convergent and discriminant validity. In this study, a high Pearson correlation coefficient (0.67) was observed for hostility measured at baseline and year 5.

2.2.3 Covariates—Socio-demographic data (age, gender, race, and education) were collected using an interviewer-administered questionnaire at baseline. Physical activity was assessed by asking the frequency of participation in 13 specific activities during the past year. Frequency of activity was weighted by intensity to come up with an overall physical activity score, expressed in exercise units, with 300 exercise unit (EU) representing moderate-to-vigorous activity for 30 minutes, 5 days/week. Smoking status was identified using the Tobacco Use Questionnaire and classified as current, former, or never-smoker. Alcohol consumption (mL/d) was estimated using the Alcohol Use Questionnaire based on different alcohol concentrations for wine, beer and hard liquor. Height (cm) without shoes was measured using a vertical ruler. Weight (kg) in light clothing was measured using a calibrated balance beam scale, and BMI (kg/m^2) was calculated.

Other covariates of interest in the present study included blood pressure, fasting glucose and insulin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), long chain omega-3 polyunsaturated fatty acid (LCn3PUFA), diet quality, and depression score. Blood pressure (systolic and diastolic) was measured in triplicate using random-zero sphygmomanometry. The mean of the second and third blood pressure measurements at baseline was used for analysis. Fasting blood samples were collected at baseline. Fasting glucose was determined in serum using the hexokinase ultraviolet method. Insulin concentrations were analyzed using a radioimmunoassay with an overnight, equilibrium-incubation format. The glucose and insulin measurements were performed at LINCO Research. Plasma HDL-C was measured after dextran-sulfate-magnesium precipitation of other lipoproteins and HDL-C and total cholesterol were measured by enzymatic assay in Northwest Lipid Research Laboratories (Seattle, WA). LDL-C was calculated using the Friedewald equation after excluding triglyceride values greater than 500 mg/dL. Dietary intake of LCn3PUFA as well as food groups such as fruits, green vegetables, yellow vegetables, other vegetables, processed meat, red meat, organ meat, fried meat dish, fish, and lean fish at baseline were assessed using the Diet History Questionnaire. A priori diet quality score was derived from 46 foods groups as a measure of overall diet quality at baseline. Depression score was measured at year 5 using the Center for Epidemiological Studies-Depression (CES-D) Questionnaire [30], ranging from 0 to 60. Higher scores indicated greater depressive symptoms.

2.3 Statistical Analysis

Baseline characteristics of participants were expressed as means ± standard deviations, medians with interquartile ranges (IQR), or percentages, and were compared across quintiles of total magnesium intake by using analysis of variance [31], chi-squared test [32], or Kruskal-Wallis test [33] as appropriate.

Generalized estimating equations [34] were used to evaluate the associations between baseline magnesium intake and hostility assessed at 2 time-points. The initial analysis (model 1) was adjusted for time, age, gender, race, and study center. In model 2 (final model), we further adjusted for education, smoking, alcohol consumption, BMI, physical activity, and systolic blood pressure. In model 3, we performed a series of sensitivity analyses based on model 2. We additionally adjusted for LCn3PUFA intake in model 3a to eliminate the potential confounding effect of LCn3PUFA. In model 3b, we replaced LCn3PUFA with a priori diet quality score to further examine the isolated effect of magnesium from diet. In model 3c, we additionally adjusted for LDL-C/HDL-C ratio, total cholesterol, and insulin to determine whether they are the potential mediators of the magnesium-hostility relation. Moreover, since depression and hostility are highly correlated, we adjusted for depression in model 3d to determine whether the association of magnesium with hostility was independent of depressive symptoms. Furthermore, to eliminate the possible confounding by supplemental magnesium use, we replaced total magnesium with dietary magnesium intake and adjusted for supplement use in Model 4. In addition, we examined the association between whole grain intake and hostility in model 5 and the association between coffee intake and hostility in model 6. P for linear trend was tested using the continuous values of exposure of interest with its extreme values > 99^{th} excluded.

To take the temporal sequence into consideration, the general linear model was used to determine the association of baseline magnesium intake with change in hostility over 5 years after adjusting for the same covariates as those in the above model 2 plus baseline hostility.

Finally, we examined potential effect modification based on a few pre-specified factors such as race, gender, BMI, magnesium supplementation status and LCn3PUFA intake. People with different race, gender and BMI often have different glucose metabolism and cholesterol level, which may influence the association of magnesium with hostility. In addition, use of dietary supplements may indicate differences in lifestyle and health. Whether the potential interaction with magnesium and hostility exists or not is interesting to know. For each, interaction terms were created, and p-value for interaction was calculated using the likelihood ratio test by comparing models with and without the interaction terms.

All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, North Carolina, USA). $P \leq 0.05$ and $P \leq 0.10$ were considered statistically significant for detecting main effect and interaction, respectively.

3. RESULTS

Baseline characteristics of the 4,716 participants by quintile of total magnesium intake are shown in Table 1. The average magnesium intake (mg/1000 kcal/day) of each quintile (lowest to highest) was 93.2, 113.5, 132.3, 155.7 and 198.5, respectively. Participants in the highest quintile of magnesium intake tended to be older, females, and Caucasians with a higher level of education, and lower likelihood of smoking compared with those in the lowest quintile ($P<0.0001$). Additionally, individuals with higher magnesium intake also tended to have a lower BMI, systolic blood pressure, LDL-C, and insulin concentration, as well as a higher HDL-C and physical activity level ($P<0.05$). Finally, those in the highest

quintile of magnesium intake tended to have higher intakes of LCn3PUFA, whole grain and coffee, higher priori diet quality score, as well as lower baseline hostility scores assessed by CM scale (P<0.0001).

The multivariable-adjusted association between total magnesium intake and the Cook-Medley score over 5 years of follow-up is presented in Table 2. After adjusting for time, age, gender, race, center, education level, smoking status, alcohol consumption, **BMI**, physical activity, and systolic blood pressure in Model 2 (final model), a significant inverse linear trend was evident between total magnesium intake and hostility levels ($\mathbf{P}_{\text{linear-trend}}$<0.0001). For those in the highest magnesium intake quintile, the CM score was significantly lower by 2.16 (95 % CI: 1.47, 2.85) as compared with those in the lowest quintile of magnesium intake.

In the sensitivity analysis, we further adjusted for LCn3PUFA intake since LCn3PUFA was reported associated with the potential hostility-reduction effect [35] and dietary fatty acids may alter the magnesium metabolism [36]. The result was not materially changed (Model 3a). In addition, the inverse trend remained when we replaced the LCn3PUFA with a priori diet qualify score in the model (Model 3b), though the association was attenuated (Q5 vs. Q1: ß = -1.55, 95% CI: -2.31, -0.78). Moreover, no appreciable change was observed when we further adjusted for LDL-C/HDL-C ratio, total cholesterol and insulin (Model 3c). However, when depression was adjusted for (Model 3d), the inverse magnesium-hostility association was attenuated, but remained significant (Q5 vs. Q1: ß = 1.43, 95% CI: -2.19, -0.67). Furthermore, to eliminate the possible confounding effect induced by supplement use, we replaced the total magnesium with dietary magnesium intake and additionally adjusted for supplementation status (Model 4), and the inverse association was attenuated but remained significant (Q5 vs. Q1: *ß* = -1.02, 95% CI: -1.78, -0.25). Similarly, the inverse linear trend remained significant but attenuated (Q5 vs. Q1: *ß* = -0.54, 95% CI: -1.21, 0.12) ($\mathbf{P}_{\text{linear-trend}}$<0.01) when we replaced total magnesium intake with whole grain intake (Model 5). Nevertheless, such inverse association was attenuated to null (*ß* = 0.68, 95% CI: -0.08, -1.45) ($\mathbf{P}_{\text{linear-trend}}$=0.41) when total Mg intake was replaced with coffee intake (Model 6).

To take the temporal sequence into account, we examined baseline magnesium intake in relation to changes in hostility over 5 years of follow-up with adjustment for covariates in Model 2 plus baseline hostility levels. The multivariable adjusted association remained inversely significant (Q5 vs. Q1: *ß* = -1.09, 95% CI: -1.75, -0.43) ($\mathbf{P}_{\text{linear-trend}}$<0.05).

In the stratified analysis, we found that the observed inverse association was more pronounced among participants with high LCn3PUFA intake [>0.07 g/day (median level)] (*ß* = -2.54; -3.57, -1.52) comparing to those with low LCn3PUFA intake (=0.07 g/day) (*ß* = 1.85; -2.80, -0.99) (*P*interaction=0.09) (Figure 2). No effect modification was found by race, gender, BMI or magnesium supplementation (all *P* values for interaction > 0.10) (data not shown).

4. DISCUSSION

In this large prospective U.S. cohort study, our results support the hypothesis and we observed an inverse dose-response relationship between total magnesium intake and hostility level among young adults, independent of socio-demographic and major lifestyle factors, supplement use, and depression status. This inverse association was more pronounced among those with higher LCn3PUFA intake.

To the best of our knowledge, the relation between magnesium and hostility has never been directly addressed in any previous epidemiological study. However, our study is consistent with a recent prospective study in 2,320 Eastern Finnish men aged 41–62 years with 20 years of follow-up that showed greater magnesium intake was associated with a significantly lower risk of receiving a hospital unipolar depression diagnosis, which manifested with symptoms closely related to hostility. Conversely, a similar prospective study of 12,939 Spanish university graduates looking at magnesium intake and depression with a follow-up period similar to ours (i.e., 5 years) failed to corroborate our findings. However, depression in that study was self-reported, and self-reporting incident mental illness may be prone to a social desirability bias, in which individuals prefer to portray themselves more favorably on questionnaires. While more prospective research is required, our study provides a crucial first step in the area of magnesium intake and hostility levels.

The inclusion of depression symptoms score in the model attenuated the association of magnesium intake with hostility in the present study, but did not eliminate it. This finding suggested a significant association between magnesium intake and feelings of hostility independent of depression. Animal studies show similar results, which support our findings. Historically, rodent studies have revealed a complex association between magnesium and aggression. In mice, a step-wise increase in magnesium deficiency was shown to be inversely associated with a dose-dependent response in aggressive behaviors [37]. Similarly, a separate study in mice revealed that animals who were injected with high amounts of magnesium chloride showed reduced levels of aggression [38]. These early studies were pivotal in highlighting the role of magnesium and activity of the HPA axis [39] and sympathetic system.

There are several plausible biological mechanisms supporting an inverse association between magnesium and hostility. First, magnesium plays a role in downregulating the HPA axis to alter the stress hormones associated with hostility, including cortisol and catecholamine [40]. For example, increased HPA axis activity, such as increased epinephrine and norepinephrine concentrations, was found to be associated with hypomagnesemia [41] and global aggressive hostility [42]. Second, literatures indicate that magnesium supplementation may induce a functional block in serotonin metabolism and downregulate central nervous system serotonin in depressed people compared with those who are healthy [43]. This is particularly important since serotonin reuptake inhibitors have been used as antidepressive treatment for decades. Thirdly, numerous observational studies have demonstrated the role of magnesium as N-methyl D-aspartate (NMDA) receptor blocker to regulate glutamate and GABA pathway and perform neuroprotective and anti-depression function [44]. Accumulating evidence indicated the essential contribution of NMDA

receptor to human major depression [45]. In addition, an animal study suggested that anti-depressant-like action of magnesium was antagonized by NMDA [46]. Finally, inflammation may also link the magnesium-hostility association. There are numerous studies suggesting an inverse association between magnesium and inflammatory markers, such as interleukine-6, tumor necrosis factor-α, C-reactive protein, and soluble intercellular adhesion molecule-1 [47]. On the other hand, hostility can be induced by cytokine immunotherapy in patients. Significantly increased depression, anger and hostility were observed among patients with chronic hepatitis C infection after receiving interferon alfa therapy [48].

We performed a number of sensitivity analyses in this study. Total cholesterol and LDL-C were reported positively associated with hostility and depressive symptoms [49], and magnesium exhibits a total cholesterol and LDL-C -lowering effect [50]. Meanwhile, dyslipidemia, in the form of low HDL-C, was associated with greater hostility [51], and magnesium could increase HDL-C. These associations are implied in the present study, though not statistically significant (data not shown). On the other hand, hostility was found to be associated with impaired glucose metabolism [52], which could be improved with increased magnesium intake [53]. Thus, we included LDL-C/HDL-C, total cholesterol and insulin in the model to evaluate their potential mediating role. However, no substantial change was observed to support such a hypothesis.

In addition, the intake of LCn3PUFA has been shown to be associated with a lower incidence of hostility in another CARDIA study. Similar findings were also reported in a randomized trial and a review article [54, 55]. However, including LCn3PUFA in the model in our study did not appreciably change the association between magnesium intake and hostility. Of note, effect modification by LCn3PUFA intake was observed in the present study. Since LCn3PUFA and magnesium target a similar pathway to lower hostility level, the synergistic effect may be one possible reason to explain the stronger association with magnesium seen in the higher LCn3PUFA subgroup. Moreover, one animal study indicated that LCn3PUFA could significantly decrease magnesium excretion and increased the bioavailability of magnesium so as to enhance the effect of magnesium in the system. Further human studies are needed to confirm this interaction.

Furthermore, minerals like calcium, sodium, potassium, zinc, and phosphorus are closely related to magnesium metabolism and they were found relevant to depression in previous studies [56]. Nevertheless, adjusting for those variables did not induce any substantial change in the magnesium-hostility association (data not shown).

A notable null association was observed between coffee intake and hostility in our study, while a large prospective cohort study in 2011 revealed a significant inverse dose-response association of coffee intake and depression [57]. However, the baseline coffee consumption in our study was as low as 0.1 serving/day on average. Even in the group in highest quintiles of magnesium, the coffee consumption was slightly over 1 serving/day, corresponding to about 7 mg of magnesium. The dose might be too low to detect any possible beneficial effect on mood or hostility. The low correlation (0.15) between magnesium and coffee also support that coffee is not a major source of magnesium.

To the best of our knowledge, there is no study that has investigated the association between magnesium intake and hostility among American young adults. Our relatively large sample size provides sufficient statistical power for the current analysis. Based on the GLM power calculation in SAS, a minimal sample size of 210 was required to achieve a statistical power of 80% to detect any difference across quintiles of magnesium intake. Besides, the prospective design allowed us to take the temporal sequence into consideration and assess the longitudinal association. In addition, we were able to adjust for a number of potential confounders that are possibly associated with both magnesium homeostasis and hostility.

Several limitations should also be noted. First, because magnesium intake was assessed using a diet history questionnaire, recall bias, interviewer bias, and inaccurate estimates cannot be completely ruled out. However, the Diet History Questionnaire used in this study has been validated and is considered reliable. Also, only baseline dietary magnesium intake was used in the present analysis. However, it is reasonable to believe that dietary assessment of total magnesium intake was reliable and quite consistent during the 5 years of follow-up considering a Spearman correlation of 0.50 between two measurements at baseline and year 7. Besides, replacing magnesium intake at baseline with the average intake between baseline and year 7, the findings were essentially unchanged (Q5 vs. Q1: $ß$ = -2.54, 95% CI: -3.33, -1.75) ($\mathbf{P}_{\text{linear-trend}}$<0.0001). In addition, magnesium intake is different from intracellular magnesium (active magnesium). However, the assessment by Diet History Questionnaire should enable us to rank participants based on their total magnesium intake and estimate the association of interest. Finally, the study is mainly focusing on urban population. Therefore, the generalizability may be limited.

In conclusion, we observed an inverse dose-response relationship between magnesium intake and hostility levels independent of socio-demographic and lifestyle factors as well as depression status in this large U.S. young adult cohort. This inverse association was more pronounced with higher LCn3PUFA intake. Since hostility is associated with many health conditions, findings from this study highlight another pathway for the potential benefit of magnesium intake to the development of chronic diseases such as diabetes and cardiovascular disease.

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Abbreviations

CARDIA	Coronary Artery Risk Development in Young Adults
HPA	hypothalamic-pituitary-adrenal
BMI	body mass index

CM Scale	Cook-Medley Hostility Scale
EU	exercise unit
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
LCn3PUFA	long-chain omega-3 polyunsaturated fatty acids
CES-D	Center for Epidemiological Studies-Depression
NMDA	N-methyl D-aspartate
IQR	inter-quartile range
No.	number
Q	quintile
CI	confidence interval

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Highlights

- Magnesium intake was inversely associated with hostility in a dose-response manner
- The observed association was independent of socio-demographic and lifestyle factors
- The observed association was independent of depression status
- The observed association was more pronounced among those with higher omega-3 intake

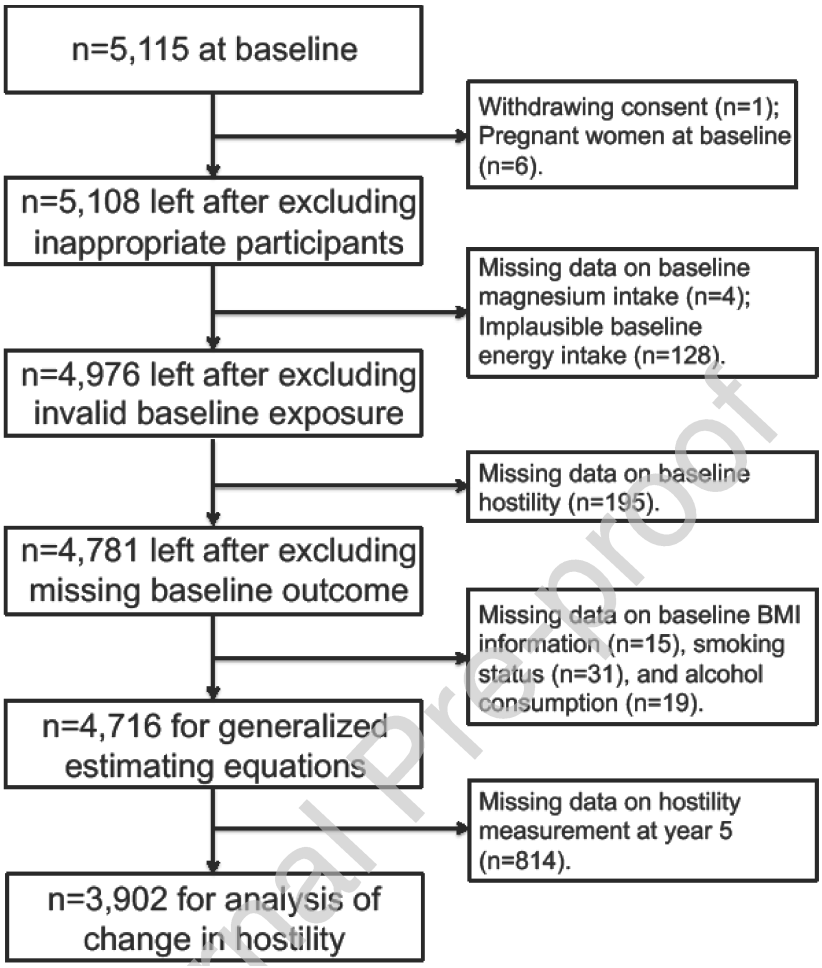

Figure 1.
The flowchart for selection procedure of study population.

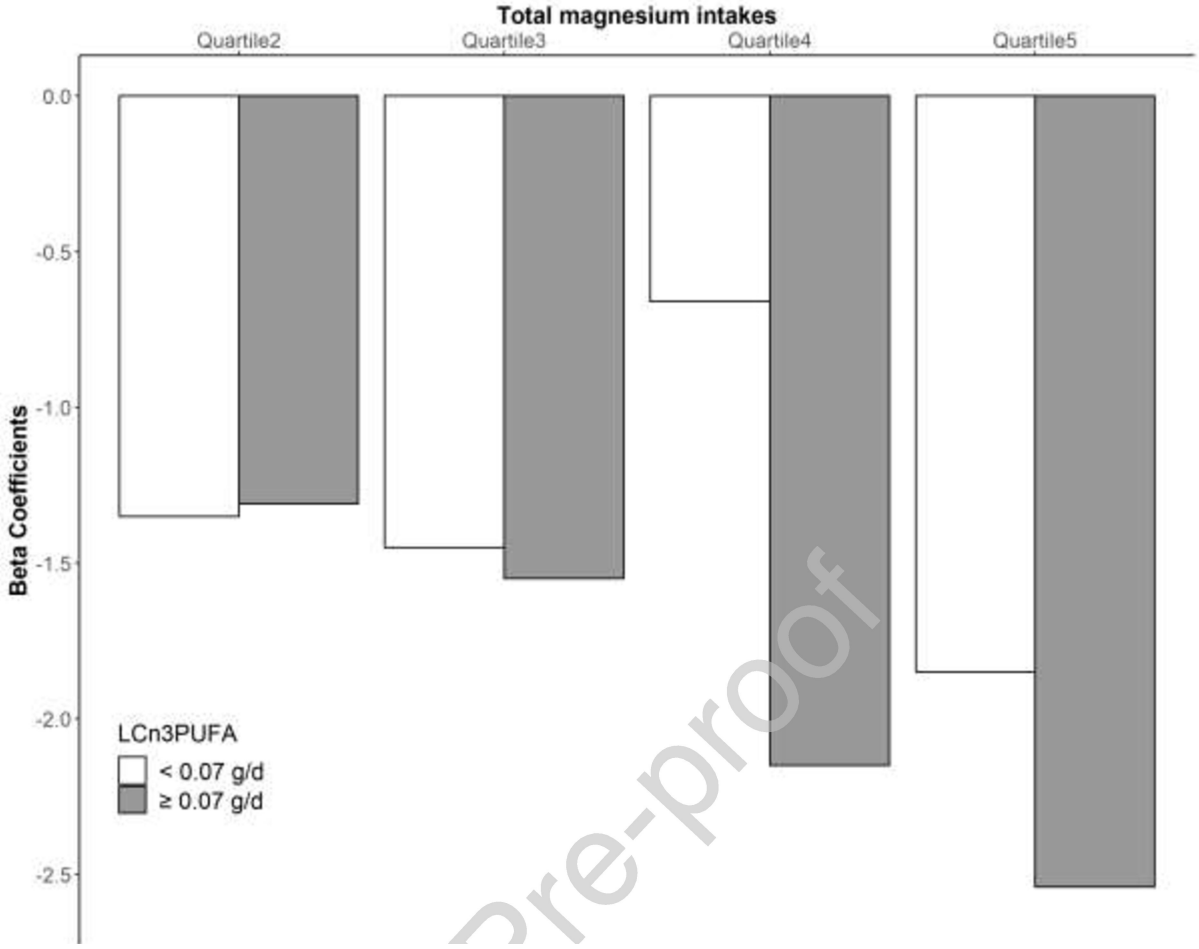

Figure 2.

Stratified analysis of the association between total magnesium intake and the Cook-Medley hostility scale by LCn3PUFA intake over a 5-year follow-up.

*The study population included 4,716 individuals from the CARDIA study. The magnesium-hostility associations were stratified by different LCn3PUFA intake groups (<0.07 vs. ≥0.07 g/day). P for interaction = 0.09.

Table 1

Baseline characteristics of the participants by quintiles of total magnesium intake *

Characteristics	Total	Quintiles of total magnesium intake (mg/1000 kcal/day)					*P*-value†
		Q1(lowest)	Q2	Q3	Q4	Q5(highest)	
No. of participants	4, 716	943	943	944	943	943	--
Total magnesium intake (mg/1000 kcal/day)	132.3 (108.8–164.0)	93.2 (85.1–99.1)	113.5 (108.8–118.2)	132.3 (127.6–137.5)	155.7 (149.3–164.0)	198.5 (182.9–225.2)	--
Magnesium supplement (%)	16.2	2.7	5.1	11.3	19.0	43.1	<0.0001
Whole grain, serving/week	6.5 (2.0–14.0)	2.0 (0.2–6.1)	4.7 (1.2–10.0)	7.0 (2.2–14.5)	8.5 (4.0–15.2)	11.2 (5.5–18.3)	<0.0001
Coffee, serving/day	0.1 (0.0–1.4)	0.0 (0.0–0.3)	0.0 (0.0–0.7)	0.1 (0.0–1.3)	0.4 (0.0–1.7)	1.3 (0.0–3.0)	<0.0001
Cook-Medley scale	19.5±8.5	22.5±8.5	20.7±8.3	19.4±8.1	18.4±8.3	16.6±8.2	<0.0001
Age (years)	24.9±3.6	23.8±3.8	24.2±3.7	25.0±3.6	25.4±3.5	26.2±3.1	<0.0001
Female gender (%)	54.8	57.3	51.3	50.5	52.1	62.9	<0.0001
Black (%)	50.6	79.1	68.6	51.7	33.7	20.0	<0.0001
Education (years)	13.8±2.3	12.9±1.9	13.3±2.0	13.8±2.2	14.4±2.3	14.8±2.3	<0.0001
LCn3PUFA intake (g/day)	0.11±0.17	0.09±0.11	0.11±0.13	0.11±0.13	0.13±0.24	0.13±0.19	<0.0001
A Priori diet quality score	62.6±13.6	51.1±8.3	57.1±9.3	62.2±9.9	67.9±10.9	74.9±11.5	<0.0001
Smoking Status (%)							
Never	56.8	58.4	57.6	58.2	57.5	52.5	<0.0001
Former	13.5	7.5	9.6	13.2	15.8	21.4	
Current	29.6	34.0	32.8	28.6	26.7	26.1	
Alcohol Intake (ml/day)	4.8 (0–14.5)	2.4 (0–10.0)	4.77 (0–15.13)	4.8 (0–15.5)	5.1 (0–17.0)	4.9 (0–15.8)	<0.0001
Physical Activity (EU)	357.0 (195.0±573.0)	269.5 (140.0±471.0)	334.0 (169.0±544.0)	369.0 (197.5±606.0)	390.0 (220.0±580.0)	427.0 (258.0±648.0)	<0.0001
BMI (kg/m^2)	24.5±5.0	25.0±6.0	24.9±5.3	24.6±4.9	24.3±4.6	23.7±4.1	<0.0001
SBP (mmHg)	110.2±10.8	110.6±10.6	110.9±10.8	111.0±10.8	109.9±10.6	108.7±11.1	<0.0001
Cholesterol (mg/dL)	176.7±33.4	173.3±33.7	177.7±34.0	178.6±33.9	178.3±32.8	175.8±32.4	<0.01
LDL-C (mg/dL)	109.2±31.1	107.6±31.8	110.4±31.8	111.1±31.7	111.0±30.5	106.9±29.6	<0.05
HDL-C (mg/dL)	53.0±13.2	51.6±12.3	53.0±13.0	52.7±13.2	52.8±13.6	55.2±13.4	<0.0001
LDL-C/HDL-C ratio	2.2±0.9	2.2±0.9	2.2±0.9	2.3±0.9	2.2±0.9	2.1±0.9	<0.0001
Glucose (mg/dL)	82.5±16.0	81.8±14.7	82.6±20.1	82.2±14.0	83.5±18.4	82.3±11.0	0.25
Insulin (μU/mL)	10.8±8.0	12.5±9.1	11.7±8.3	10.8±8.6	10.1±6.9	9.0±6.1	<0.000

Abbreviations: BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; EU, exercise unit; HDL-C: high-density lipoprotein cholesterol; IQR, inter-quartile range; LCn3PUFA, long-chain omega-3 polyunsaturated fatty acids; LDL-C: low-density lipoprotein cholesterol; No., number; Q, quintile;

SBP, systolic blood pressure; SD, standard deviation.

* The study population included 4,716 individuals from the CARDIA study. The summary statistics were reported as means ± SDs, medians (IQRs), or percentages.

† *P* values were obtained for any difference across the quintiles of total magnesium intake by using analysis of variance, Kruskal-Wallis test, or chi-squared test as appropriate.

Table 2

Multivariable-adjusted association between total magnesium intake and the Cook-Medley hostility scale over a 5-year follow-up [*]

	Quintiles of total magnesium intake (mg/1000 kcal/day)					$P_{\text{linear-trend}}$ [†]
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	
No. of participants	943	943	944	943	943	--
No. of observations	1,724	1,723	1,723	1,724	1,724	--
Total magnesium intake (mg/1000 kcal/day)						
Median	93.4	114.0	133.2	156.5	199.4	--
Range	41.8 105.0	105.0–123.0	123.1–144.2	144.2–173.2	173.2–887.7	--
Model 1 [‡]	0(Ref.)	−1.33 (−1.98, −0.67)	−1.71 (−2.37, −1.05)	−1.80 (−2.49 −1.12)	−2.62 (−3.33, −1.90)	<0.0001
Model 2 [§]	0(Ref.)	−1.28 (−1.92, −0.65)	−1.45 (−2.09, −0.81)	−1.41 (−2.08, −0.75)	−2.16 (−2.85, −1.47)	<0.0001
Model 3a [//]	0(Ref.)	−1.31 (−1.95, −0.68)	−1.48 (−2.12, −0.84)	−1.47 (−2.14, −0.80)	−2.21 (−2.91, −1.52)	<0.0001
Model 3b [**]	0(Ref.)	−1.01 (−1.65, −0.36)	−0.97 (−1.65, −0.30)	−0.82 (−1.54, −0.10)	−1.55 (−2.31, −0.78)	<0.001
Model 3c [††]	0(Ref.)	−0.98 (−1.63, −0.33)	−0.98 (−1.6 7, −0.29)	−0.81 (−1.54, −0.08)	−1.45 (−2.23, −0.67)	<0.05
Model 3d [††]	0(Ref.)	−1.01 (−1.64, −0.37)	−0.94 (−1.60, −0.27)	−0.75 (−1.46, −0.04)	−1.43 (−2.19, −0.67)	<0.05
Model 4 [§§]	0(Ref.)	−0.81 (−1.44, −0.18)	−0.70 (−1.37, −0.03)	−1.13 (−1.84, −0.42)	−1.02 (−1.78, −0.25)	<0.05
Model 5 [////]	0(Ref.)	0.11 (−0.52, 0.73)	−0.11 (−0.75, 0.54)	−0.63 (−1.27, 0.01)	−0.54 (−1.21, 0.12)	<0.01
Model 6 [***]	0(Ref.)	−0.30 (−0.80, 0.20)	0.15 (−0.48, 0.78)	−0.09 (−0.75, 0.56)	0.68 (−0.08, 1.45)	0.41

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CES-D, Center for Epidemiological Studies-Depression; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LCn3PUFA, long-chain omega-3 polyunsaturated fatty acids; LDL-C: low-density lipoprotein cholesterol; No., number; Ref., reference; Q, quintile.

[*] The study population included 4,716 individuals from the CARDIA study. The statistics for each model were reported using β coefficients and 95% confident intervals (CIs). All models were constructed using generalized estimating equations method.

[†] P for linear trend was tested using the continuous values of exposure of interest with its extreme values >99th excluded.

[‡] Model 1 was adjusted for time (year 0 and 5), age (continuous), gender, race (white or black), and center.

[§] Model 2 was additionally adjusted for education level (continuous), smoking status (never, ever, or current smokers), alcohol consumption (0, 0.1–11.9, 12.0–23.9 or ≥ 24 g/day), body mass index (<18.5, 18.5–24.9, 25–29.9, or ≥30 kg/m^2), physical activity (quintiles), and systolic blood pressure (quintiles).

[//] Model 3a was additionally adjusted for LCn3PUFA intake (quintiles).

[**] Model 3b replaced LCn3PUFA intake with a priori diet quality score (quintiles).

[††] Model 3c was additionally adjusted for LDL-C/HDL-C ratio (quintile), cholesterol (quintile), and insulin (quintile).

[††] Model 3d was additionally adjusted for depression (CES-D<16, or ≥16).

[§§] Model 4 replaced total magnesium with dietary magnesium intake (in nutrient density form) with additional adjustment for supplementation status (yes, or no).

////Model 5 replaced total magnesium with whole grain intake (quintiles).

***Model 6 replaced total magnesium with coffee consumption [0(ref.), 0.1–0.9, 1.0–1.9, 2.03.9, ≥4 servings/day)].