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Magnesium Depletion Score (MDS) Predicts Risk of Systemic Inflammation and Cardiovascular Mortality among US Adults

Lei Fan,[1] Xiangzhu Zhu,[1] Andrea Rosanoff,[2] Rebecca B Costello,[2] Chang Yu,[3] Reid Ness,[4] Douglas L Seidner,[5] Harvey J Murff,[6] Christianne L Roumie,[6] Martha J Shrubsole,[1] and Qi Dai[1]

[1]Department of Medicine, Division of Epidemiology, Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; [2]Center for Magnesium Education and Research (CMER), Pahoa, HI, USA; [3]Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, USA; [4]Department of Medicine, Division of Gastroenterology, Vanderbilt University School of Medicine, Nashville, TN, USA; [5]Center for Human Nutrition, Department of Gastroenterology, Hepatology, and Nutrition, Digestive Disease and Surgical Institute, Cleveland Clinic, OH, USA; and [6]Veterans Health Administration–Tennessee Valley Healthcare System Geriatric Research Education Clinical Center (GRECC), HSR&D Center, Nashville, TN, USA

ABSTRACT

Background: Kidney reabsorption of magnesium (Mg) is essential for homeostasis.

Objectives: We developed and validated models with the kidney reabsorption-related magnesium depletion score (MDS) to predict states of magnesium deficiency and disease outcomes.

Methods: MDS was validated in predicting body magnesium status among 77 adults (aged 62 ± 8 y, 51% men) at high risk of magnesium deficiency in the Personalized Prevention of Colorectal Cancer Trial (PPCCT) (registered at clinicaltrials.gov as NCT01105169) using the magnesium tolerance test (MTT). We then validated MDS for risk stratification and for associations with inflammation and mortality among >10,000 US adults (weighted: aged 48 ± 0.3 y, 47% men) in the NHANES, a nationally representative study. A proportional hazards regression model was used for associations between magnesium intake and the MDS with risks of total and cardiovascular disease (CVD) mortality.

Results: In the PPCCT, the area under the receiver operating characteristic (ROC) curve (AUC) for magnesium deficiency was 0.63 (95% CI: 0.50, 0.76) for the model incorporating the MDS with sex and age compared with 0.53 (95% CI: 0.40, 0.67) for the model with serum magnesium alone. In the NHANES, mean serum C-reactive protein significantly increased with increasing MDS (P-trend < 0.01) after adjusting for age and sex and other covariates, primarily among individuals with magnesium intake less than the Estimated Average Requirement (EAR; P-trend < 0.05). Further, we found that low magnesium intake was longitudinally associated with increased risks of total and CVD mortality only among those with magnesium deficiency predicted by MDS. MDS was associated with increased risks of total and CVD mortality in a dose-response manner only among those with magnesium intake less than the EAR.

Conclusions: The MDS serves as a promising measure in identifying individuals with magnesium deficiency who may benefit from increased intake of magnesium to reduce risks of systemic inflammation and CVD mortality. This lays a foundation for precision-based nutritional interventions. *J Nutr* 2021;151:2226–2235.

Keywords: magnesium depletion score, magnesium tolerance test, C-reactive protein, NHANES, cardiovascular mortality

Introduction

The US-Canadian Joint Federal Dietary Reference Intake (DRI) Committee selected magnesium (Mg) for updating the recommended intake levels for chronic disease endpoints (1). While over half of US adults do not meet the Estimated Average Requirement (EAR) of magnesium intake (2), lack of accurate measures of body magnesium status has impacted the research of health outcomes by magnesium status. Epidemiological studies indicate that serum or intake of magnesium is related to a reduced risk of clinical outcomes such as type 2 diabetes (3, 4) and cardiovascular disease (CVD) (5, 6). However, the results have been inconsistent (7). Magnesium deficiency induces an inflammatory response, including the release of C-reactive protein (CRP) in mice (8). Human studies, including randomized trials (9, 10) and observational studies (11–16), have also generated inconsistent results on the effect of magnesium on serum CRP concentration.

Serum magnesium, clinically used to diagnose magnesium deficiency, is a poor measure of total body magnesium

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status because serum magnesium is tightly regulated (17–22). Further, >80% of plasma magnesium is ultra-filtrated and reabsorbed in the kidneys; thus, reabsorption of magnesium in the kidney plays an essential role in maintaining magnesium homeostasis (23). No previous studies have taken into account the pathophysiological factors influencing the kidneys' reabsorption capability. Several factors prevalent in the US population, including alcohol consumption (24), diuretic use (25), proton pump inhibitor (PPI) use (26), and kidney disease (27), diminish the magnesium reabsorption capacity of the kidney. We therefore implemented the magnesium depletion score (MDS), a composite score aggregating these risk factors. The total-body magnesium status is further impacted by the intake of calcium (Ca) (28–30), age (31), and sex (32).

The magnesium tolerance test (MTT) is the reference standard measure of magnesium status. The MTT, is however, impractical for widespread use in both clinical practice and research (33, 34) as it requires a 24-h urine collection, followed by an intravenous infusion of magnesium for 4 h and a second 24-h urine collection (33). In the current study, our aim was to validate MDS as a predictor of magnesium deficiency using MTT. As further validation, we examined whether *1*) the MDS is associated with serum CRP concentrations; *2*) low magnesium intake was longitudinally associated with increased risks of total and CVD mortality, particularly among those with magnesium deficiency defined by the MDS; and *3*) the MDS is prospectively associated with risks of total and CVD mortality, especially among those with low magnesium intake, in the NHANES.

Methods

MDS calculation

The MDS was calculated by aggregating 4 factors: *1*) diuretic use (current use for 1 point), *2*) PPI use (current use for 1 point), *3*) kidney function [60 mL/(min · 1.73 m^2) ≤ estimated glomerular filtration rate (eGFR) <90 mL/(min · 1.73 m^2) for 1 point; eGFR <60 mL/(min · 1.73 m^2) for 2 points], and *4*) alcohol drinking (heavy drinker for 1 point).

In the Personalized Prevention of Colorectal Cancer Trial (PPCCT), prior to baseline, participants completed a telephone interview that ascertained alcohol drinking history including usual number of drinks per week. A standard drink was defined as a drink with 14 g (0.6 fluid ounces) of ethanol (35). Current moderate drinkers were defined as up to 1 drink/d for women and up to 2 drinks/d for men. Heavy drinkers were defined as >1 drink/d for women and >2 drinks/d for men (36). Information on the participant's use of medications such as diuretics and PPIs and alcohol consumption was collected at each of 3 study visits. Current use of diuretics and PPIs were defined as self-reported regular use of diuretics or PPIs on a daily basis through the end of the trial. Serum creatinine was measured and used to determine the eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (37). We classified participants into 3 eGFR categories: participants with normal renal function with eGFR ≥90 mL/(min · 1.73 m^2), mildly decreased renal function with eGFR ≥60 and <90 mL/(min · 1.73 m^2), and chronic kidney disease (CKD) with eGFR <60 mL/(min · 1.73 m^2) (38). In the NHANES, current use of diuretics and PPIs was defined as self-reported use over the past 30 days. Kidney function and alcohol drinking were categorized in accordance with that in the PPCCT.

MDS validation in the PPCCT

The PPCCT (registered at clinicaltrials.gov as NCT01105169) is a double-blind 2 × 2 factorial randomized controlled trial conducted at the Vanderbilt University Medical Center, Nashville, TN. A detailed study design of the PPCCT has been published previously (39, 40). All study procedures were performed in accordance with relevant guidelines and regulations as approved by the Vanderbilt Institutional Review Board. Of the 250 participants enrolled in the PPCCT study, 78 completed the MTT at the end of the trial, of whom 77 had valid MTT results and were included in the analysis.

Participants completed 2 dietary recalls during weeks 1–6 and 2 additional recalls during weeks 6–12 of the study intervention (41). All 4 recalls were used to estimate total intakes of magnesium and calcium by summing dietary intakes and supplementation of magnesium and calcium (42). Serum and urine were collected at the study visit immediately prior to the MTT. Serum and urine magnesium were measured by standard analytic methods on the Beckman DXC 800 chemistry analyzer provided by the Vanderbilt Pathology Laboratory Services with an intra-assay CV of 2.0 (43).

MTT measurement

For the MTT, participants collected a 24-h urine sample at home. The next day, at their clinic visit, after confirmation of adequate renal function, participants received 0.2 mmol Mg sulfate/kg body weight in 500 mL of 5% glucose by intravenous infusion over a 4-h period. A second 24-h urine sample began at the time of the infusion and continued through the next day. For the MTT, the participant's retention rate was calculated by the following formula:

$$[1 - (\text{postinfusion Mg excretion} - \text{preinfusion Mg excretion})/\text{total Mg infused}] \times 100 \quad (1)$$

A retention rate ≥50% indicates magnesium deficiency (44).

Survey design and data sources for the NHANES

The NHANES is a serial, cross-sectional study in ongoing 2-y cycles designed to assess the health and nutritional status of adults and children in the United States. Details of the NHANES study design and methods have been published previously (45). The NHANES uses a complex, multistage, probability sampling design to obtain a nationally representative sample among the noninstitutionalized US population. NHANES combines survey interviews in participants' homes and physical examinations in a standardized mobile examination center. The National Center for Health Statistics Research Ethics Review Board approved the study protocol, and the study adhered to the Declaration of Helsinki. All participants provided written informed consent.

To study the association between MDS and concentrations of CRP, the data analysis was restricted to US adults aged ≥20 y who participated in 1 of 3 cycles (from 2005/2006 to 2009/2010; no CRP measure after 2010) with a total of 27,614 participants. Participants who were aged <20 y old ($n = 12,034$), self-reported current illegal drug use ($n = 1139$), self-reported current pregnancy or lactation ($n = 470$), and those with missing data on magnesium intake or serum CRP

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Address correspondence to QD (e-mail: qi.dai@vanderbilt.edu).
Abbreviations used: AMPM, Automated Multiple Pass Method; CRP, C-reactive protein; CVD, cardiovascular disease; EAR, Estimated Average Requirement; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; ICD-10, International Classification of Diseases, Tenth Revision; MDS, magnesium depletion score; MTT, magnesium tolerance test; PPCCT, Personalized Prevention of Colorectal Cancer Trial; PPI, proton pump inhibitor.

concentration ($n = 2278$) were excluded, leaving 11,693 individuals available for the statistical analyses.

To examine the longitudinal relation between MDS and mortality, the analysis was restricted to US men and nonpregnant women aged ≥20 y who participated in 1 of 5 cycles (from 2005/2006 to 2013/2014) with a total of 44,336 participants. Participants who were aged <20 y old ($n = 18,982$), self-reported current illegal drug use ($n = 1999$), self-reported current pregnancy or lactation ($n = 608$), no available mortality data ($n = 11,447$), with a single 24-h diet recall ($n = 15$), and missing data on sampling weights or records of medication use ($n = 1236$) were excluded, leaving 10,049 individuals available for the statistical analyses.

Total and dietary intakes of magnesium and calcium in the NHANES

The dietary methods in NHANES have been previously published (46–48). In brief, NHANES used the Automated Multiple Pass Method (AMPM) to conduct two 24-h dietary recalls collected 10 d apart. The USDA's Food and Nutrient Database for Dietary Studies (FNDDS) was used to code dietary intake data and calculate nutrient intake. Participants were also asked to provide detailed information on supplement use over the past 30 d. The reported supplement products were linked to NHANES Dietary Supplement Database (NHANES-DSD), the largest publicly available database, which provided ingredient information on nutrients as reported on the product label (49). For each nutrient, the daily supplement dose was calculated by combining the frequency with the product information on the ingredient, the amount per serving, and the units (50). Total intakes of nutrients, such as energy, magnesium, and calcium, were estimated from the average intake from two 24-h dietary recalls and intake amount from supplements collected via the AMPM. To achieve a biologically and clinically meaningful interpretation, we used the age- and sex-specific EAR (36) and RDA (36) to classify magnesium intakes. Participants were classified into the following exposure groups: participants with total magnesium intake ≥RDA, participants with total magnesium intake ≥EAR but <RDA, and participants with total magnesium intake <EAR. Participants with total magnesium intake <EAR were further divided into 2 subgroups: one with total magnesium intake at or above the median of those with magnesium intake <EAR (<EAR1) and the other with total magnesium intake below the median (<EAR2).

Assessment of high-sensitivity CRP in the NHANES

In the NHANES, high-sensitivity CRP (hs-CRP) concentrations were assayed by latex-enhanced nephelometry at the University of Washington Medical Center. Details on the methodology can be found on the NHANES website (51). Specimens were maintained at 20–25°C during testing. The within- and between-assay quality-control procedures were prepared by Behring Diagnostics and standardized against the WHO International Reference Preparation of CRP serum, available from the National Institute of Biological Standards and Controls, United Kingdom. The CVs through the period of data collection were 3.4% to 6.7%, 3.2% to 9.3%, and 3.6% to 7.5% in 2005/2006, 2007/2008, 2009/2010, respectively. The detection limit of CRP was 0.2 mg/L and values below this concentration were calculated as the detection limit divided by the square root of 2. CRP increases dramatically in response to acute inflammation and remains elevated if the inflammation remains active (52). To predict risk of systemic inflammation and CVD, the American Heart Association and the CDC have recommended categorizing subjects using hs-CRP cutoffs of <1, 1–3, and >3 mg/L into low-, moderate-, and high-risk categories, respectively (53).

Mortality

Mortality outcomes were obtained through linkage to the National Death Index from the date of survey participation through 31 December 2015 using probabilistic techniques (54). The 10th version of the International Classification of Diseases, Tenth Revision (ICD-10), guidelines were used to code for all deaths. In addition to total mortality, we focused on mortality due to CVD because of sample size consideration and its potential association with magnesium status (55, 56). Underlying cause of death with ICD-10 codes of I00–I09, I11, I13, I20–I51, and I60–I69 were defined as death from CVD. Follow-up time was calculated using person-months from the date of interview to the date of death or the end of 2015 for censored participants.

Statistical analysis

Validation of the MDS in the PPCCT.

The first-stage validation in the current study is a post hoc analysis of the PPCCT study. We examined how well MDS plus other factors [i.e., total magnesium intake, total calcium intake (28–30), sex (32), and age (31)] related to magnesium status as determined by the MTT. We primarily evaluated the following 5 models—*1*) model 1: the MDS alone; *2*) model 2: the model with MDS, age, and sex; *3*) model 3: adding intake of magnesium and calcium into model 2; *4*) model 4: adding serum magnesium into model 3; and *5*) model 5: adding urine magnesium into model 3. We assessed the ability of our models to differentiate participants with and without magnesium deficiency classified by magnesium retention rate from MTT using the AUC.

We used logistic regression models to estimate the AUCs for each prediction model using the magnesium retention rate ≥50%, which was considered as an appropriate indicator for magnesium deficiency in previous studies (44). However, as the magnesium retention rate rises, the severity of magnesium deficiency increases. To evaluate the performance of prediction models as severity of magnesium deficiency increased, we plotted corresponding AUC estimates by ordinal magnesium retention rate ranging from 50% to 75% (57).

Magnesium intake, MDS, and serum hs-CRP concentration in the NHANES.

Baseline characteristics of NHANES participants were compared using descriptive statistics. hs-CRP was highly skewed, and was log transformed. We used multiple linear regression models to examine the associations between MDS and magnesium intake and hs-CRP concentrations. Adjusted geometric means are presented for results on CRP. The categorical variables of total magnesium intake or MDS were added into the model as continuous variables to test for the linear trend. Multiple models were constructed including *1*) a crude without any adjustment; *2*) adjustment for age, sex, and race; and *3*) additional adjustment for total calcium intake, total energy intake, education, marital status, poverty to income ratio, physical activity, alcohol drinking, smoking status, cycle year, and BMI. Multivariable-adjusted geometric means of serum CRP by MDS and magnesium intake were calculated and tests for linear trends were conducted across magnesium intake, MDS, and joint categories of both factors. In addition, tests for multiplicative interactions were conducted by adding corresponding interaction terms in the models.

HRs and 95% CIs were estimated in Cox proportional hazard regression models for associations between magnesium intake and the MDS with risks of total and CVD mortality. Stratified analyses were further conducted to examine whether the associations differed by the MDS and magnesium intake, respectively. We adjusted for the same covariates as we did for CRP analyses in model 3. Since underlying disease conditions for use of medications, particularly use of diuretics, may confound the associations between the MDS and total mortality, particularly CVD mortality, we conducted sensitivity analysis by removing those who used diuretics or PPIs from the analysis.

All analyses accounted for NHANES sampling weights, nonresponse, cluster, strata, and the day of the week when dietary interview occurred. All analyses were conducted using SAS version 9.4 (SAS Institute) and all hypothesis testing was 2-sided, with $P < .05$ indicating statistical significance.

Results

The characteristics of study participants in the PPCCT stratified by MTT are presented in **Supplemental Table 1** . In the PPCCT, the AUC and the 95% CI for correctly categorizing participants

as magnesium deficient as measured by the MTT (magnesium retention rate ≥50% as magnesium deficiency) are presented in Table 1 for each prediction model. The AUC for the model containing the MDS alone was 0.60 (95% CI: 0.48, 0.72), which had the highest AUC estimate among models with single predictors, compared with 0.53 (95% CI: 0.40, 0.67) for the model with serum magnesium alone and 0.58 (95% CI: 0.45, 0.71) for urine magnesium alone. The AUC improved from 0.60 to 0.63 (95% CI: 0.50, 0.76) after adding age and sex. The AUC was 0.64 (95% CI: 0.51, 0.77) for the model with the MDS, age, sex, and intakes of magnesium and calcium. The AUC of the model remained unchanged with the further addition of serum magnesium (0.64; 95% CI: 0.51, 0.77) and the AUC for the model was 0.67 (95% CI: 0.54, 0.80) after further adding urine magnesium.

As shown in Figure 1, we found that the performance (i.e., AUC estimates) of the model with MDS, particularly the model with MDS plus sex and age, consistently exceeded any other model as the ordinal magnesium retention rates increased from 50% to 75% (i.e., severity of magnesium deficiency increased). Using the magnesium retention rate ≥75% to categorize magnesium deficiency, the AUCs for the model with the MDS alone and for the one with MDS, age, and sex were 0.68 (95% CI: 0.53, 0.83) and 0.76 (95% CI: 0.58, 0.93), respectively (Table 1).

Supplemental Tables 2, 3 and supplemental Figure 1 and 2 show the characteristics and covariates of the study population by MDS in the NHANES. Compared with participants with the lowest MDS (MDS = 0), those with the highest MDS (MDS >2) were older and more likely to be male, non-Hispanic White, former smokers, and current drinkers and had lower educational achievement, lower family income, lower physical activity, higher BMI, and were less likely to be married. In addition, they were more likely to use PPIs, diuretics, and have CKD.

The relation of the MDS and magnesium intake with CRP concentrations was evaluated in NHANES. With decreasing magnesium intake, the proportion of participants with a CRP concentration >3 mg/L slightly increased in each magnesium intake category (**Supplemental Figure 3**A). In contrast, with increasing MDS, the proportion of participants with a CRP concentration >3 mg/L apparently increased within each score category, particularly when the MDS reached 2 and >2 (**Supplemental Figure 3B**).

hs-CRP concentrations significantly increased with decreasing magnesium intake in the crude model (P-trend < 0.001) (Table 2). The dose–response relation remained after adjusting for age, sex, and race (P-trend < 0.001) and also after conducting a fully adjusted model (P-trend < 0.001). Concentrations of hs-CRP significantly increased with worsening magnesium status as measured by the MDS in a dose–response manner (P-trend < 0.001). The dose–response association remained after incorporating age, sex, and race in the model (P-trend < 0.001) and after including additional covariates in the fully adjusted model (P-trend < 0.01).

The geometric means and 95% CIs of serum CRP by MDS and magnesium intake are shown in Table 3 and **Supplemental Figure 4**. The association between MDS and CRP concentrations only appeared significant among individuals with magnesium intake less than the EAR (P-trend < 0.05) and was of borderline significance among those with an magnesium intake between the EAR and RDA (P-trend = 0.0538). The interaction between magnesium intake and MDS was not statistically significant.

During a median follow-up of 68.3 months, a total of 823 deaths occurred, including 160 deaths due to CVD (Table 4, **Supplemental Figure 5**). After multiple adjustments, the associations between magnesium intake and the risk of all-cause mortality and CVD mortality were not statistically significant. However, in the stratified analysis by the MDS, low magnesium intake was significantly associated with increased risks of all-cause mortality and CVD mortality among individuals with MDS ≥2 (P-trend < 0.05, respectively). No significant associations were observed in those with MDS <2.

In a fully adjusted model, the association between MDS and the risk of all-cause mortality was of borderline significance (P-trend = 0.0597), with an HR of 1.29 (95% CI: 0.88, 1.90) comparing individuals with MDS >2 with those with MDS = 0 (Table 5, **Supplemental Figure 5**). A significant association was found and became stronger for CVD mortality (P-trend < 0.05), with a corresponding HR of 3.13 (95% CI: 1.28, 7.66). In stratified analyses by magnesium intake, the associations remained significant only among individuals with magnesium intake less than the EAR for total morality (P-trend < 0.01; HR = 1.63; 95% CI: 1.07, 2.47) comparing individuals with MDS >2 with those with MDS = 0 and for CVD mortality (P-trend < 0.01; corresponding HR = 4.14; 95% CI: 1.32, 13.1). The interaction between MDS and magnesium intake was not statistically significant.

In sensitivity analysis, we found that, although P-trends were not statistically significant, the association pattern remained similar after removing those who use diuretics or those who used PPIs (data not shown). For example, after excluding those who used diuretics from the analysis, the corresponding HR (95% CI) for CVD mortality was 4.81 (1.14, 20.2) comparing individuals with MDS >2 with those with MDS = 0 among individuals with an magnesium intake below the EAR.

Discussion

In the post hoc analysis of the PPCCT, we proposed to develop and validate an MDS in predicting magnesium deficiency measured by MTT. Although the model containing the MDS alone had the highest AUC estimator among models with single predictors including serum magnesium and urine magnesium, most of the prediction models containing the MDS did not perform significantly better than chance. While the model with MDS along with age and sex became statistically significant compared with a random classifier, the CIs were relatively broad. Nevertheless, we found the performance for models with MDS, particularly MDS plus sex and age, was consistently better than other models as severity of magnesium deficiency increased. Due to the invasive nature and labor burden of conducting the MTT, the sample size for 77 participants with available MTT data is relatively small, which may lead to a largely reduced power to infer conclusive estimations. However, this is one of the largest studies conducting the MTT to date (58). To rule out the possibility that the findings were solely by chance, we conducted the second and third stages of studies to confirm the findings from the PPCCT. At the second stage, we conducted the MDS in the NHANES, a nationally representative sample of US adults, in which we demonstrated that hs-CRP concentrations significantly increased in a dose–response manner with worsening magnesium status as measured by the MDS. Furthermore, at the third stage, we found that magnesium intake was associated with an increased risk for

TABLE 1 AUC of prediction models for magnesium deficiency measured by the MTT in the PPCCT[1]

Predictors	AUC (95% CI) using MTT ≥50%[2]	AUC (95% CI) using MTT ≥75%[3]
MDS	0.60 (0.48–0.72)	0.68 (0.53–0.83)
Serum magnesium	0.53 (0.40–0.67)	0.53 (0.31–0.74)
Urine magnesium	0.58 (0.45–0.71)	0.49 (0.23–0.74)
Age	0.55 (0.42–0.68)	0.51 (0.31–0.71)
Sex	0.53 (0.42–0.65)	0.62 (0.43–0.81)
Total magnesium intake	0.54 (0.41–0.67)	0.52 (0.33–0.72)
Total calcium intake	0.54 (0.40–0.67)	0.52 (0.30–0.75)
Serum magnesium and age and sex	0.57 (0.44–0.70)	0.61 (0.35–0.86)
Urine magnesium and age and sex	0.60 (0.47–0.73)	0.66 (0.41–0.91)
MDS and age and sex	0.63 (0.50–0.76)	0.76 (0.58–0.93)
MDS and age and sex and urine magnesium	0.66 (0.54–0.79)	0.77 (0.59–0.74)
MDS and age and sex and magnesium and calcium intakes	0.64 (0.51–0.77)	0.77 (0.60–0.95)
MDS and age and sex and magnesium and calcium intakes and serum magnesium	0.64 (0.51–0.77)	0.75 (0.55–0.94)
MDS and age and sex and magnesium and calcium intakes and urine magnesium	0.67 (0.54–0.80)	0.77 (0.60–0.95)
MDS and age and sex and magnesium and calcium intakes and urine magnesium and serum magnesium	0.67 (0.54–0.80)	0.76 (0.57–0.95)

[1]A logistic regression model was used to estimate the AUCs for each prediction model. MDS, magnesium depletion score; MTT, magnesium tolerance test; PPCCT, Personalized Prevention of Colorectal Cancer Trial.
[2]A magnesium retention rate ≥50% indicates magnesium deficiency.
[3]A magnesium retention rate ≥75% indicates magnesium deficiency.

total and CVD mortality among individuals with an MDS ≥2. We also found that the MDS was associated with an increased risk of total and CVD mortality among individuals who do not meet the EAR of magnesium intake, indicating jointly using MDS with magnesium intake is critical to further improve the prediction of chronic disease risk.

We developed the MDS by aggregating 4 established factors (i.e., alcohol consumption, PPI use, diuretic use, and CKD), which were shown to reduce magnesium reabsorption. For example, alcohol consumption causes a prompt increase in the urinary excretion of magnesium (24). The magnesium-wasting effect of loop-blocking diuretics has been demonstrated

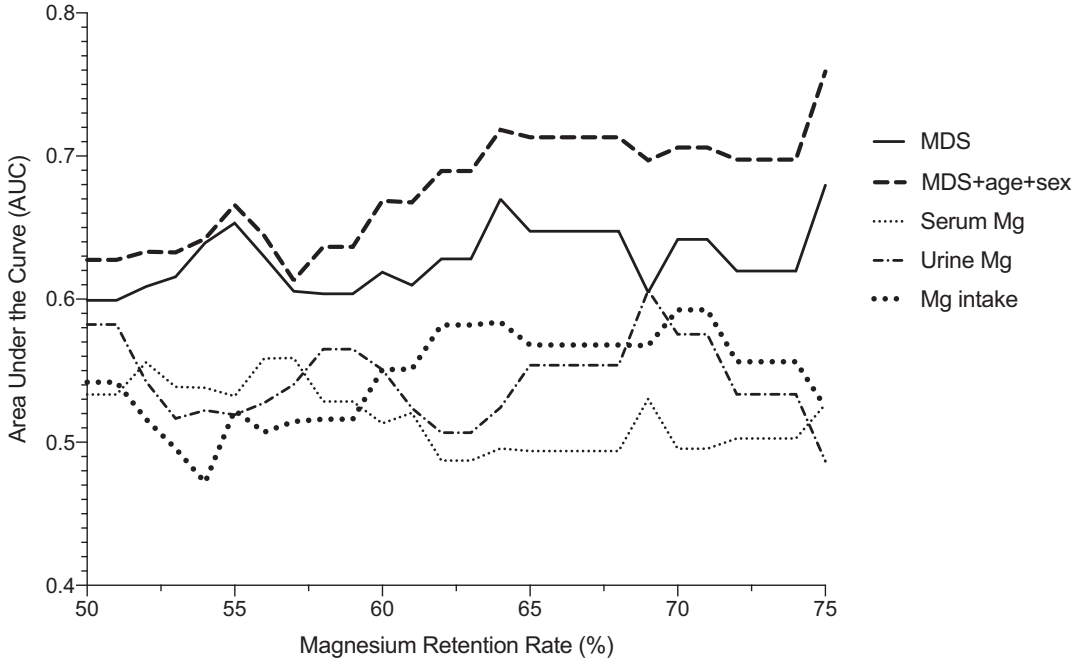

FIGURE 1 Area under the ROC curve (AUC) of prediction models for magnesium deficiency determined by ordinal magnesium retention rate ranging from 50% to 75% in the PPCCT. MDS, magnesium depletion score; PPCCT, Personalized Prevention of Colorectal Cancer Trial; ROC, receiver operating characteristic.

TABLE 2 Multivariable-adjusted serum CRP concentrations by magnesium intake and MDS in the NHANES 2005–2010[1]

	Mg intake,[2] mg/d				
hs-CRP, mg/L	≥RDA ($n = 2641$)	EAR∼RDA ($n = 1968$)	<EAR1 ($n = 3289$)	<EAR2 ($n = 3795$)	*P*-trend
Model 1	1.35 (1.25–1.46)	1.70 (1.56–1.85)	1.82 (1.71–1.94)	2.06 (1.92–2.20)	<0.001
Model 2	1.48 (1.37–1.60)	1.85 (1.70–2.00)	1.95 (1.83–2.09)	2.18 (2.02–2.34)	<0.001
Model 3	2.93 (1.86–4.59)	3.38 (2.17–5.28)	3.45 (2.26–5.26)	3.63 (2.38–5.54)	<0.001
			MDS		
	0 ($n = 4100$)	1 ($n = 4879$)	2 ($n = 1944$)	>2 ($n = 770$)	
Model 1	1.51 (1.42–1.61)	1.69 (1.59–1.80)	2.05 (1.89–2.21)	2.86 (2.55–3.22)	<0.001
Model 2	1.71 (1.59–1.83)	1.88 (1.76–2.00)	2.12 (1.95–2.30)	2.67 (2.35–3.02)	<0.001
Model 3*	3.10 (2.07–4.63)	3.28 (2.19–4.89)	3.28 (2.19–4.93)	3.86 (2.56–5.84)	<0.01

[1] CRP values are geometric means (95% CIs). Model 1: crude value. Model 2: adjusted for age, sex, and race. Model 3: adjusted for age, sex, race, education, marital status, poverty to income ratio, total energy intake, total calcium intake, physical activity, alcohol drinking, smoking status, cycle year, and BMI. Model 3*: adjusted for age, sex, race, education, marital status, poverty to income ratio, total energy intake, total calcium intake, physical activity, smoking status, cycle year, and BMI. A multiple linear regression model was used and CRP concentrations were log transformed. CRP, C-reactive protein; EAR, Estimated Average Requirement; hs-CRP, high-sensitivity C-reactive protein; MDS, magnesium depletion score.

[2] Age- and sex-specific EAR (36) and RDA (36) were used to classify magnesium intakes. ≥ RDA: total magnesium intake ≥RDA. EAR∼RDA: total magnesium intake ≥EAR but <RDA. Participants with total magnesium intake <EAR were further divided into 2 subgroups: total magnesium intake at or above the median of those with magnesium intake <EAR (<EAR1) and total magnesium intake below the median (<EAR2).

inducing magnesium loss through alterations in the renin-angiotensin-aldosterone system and concentrations of calcium and parathyroid hormone (59). Administration of PPIs was shown to reduce kidney reabsorption of magnesium through downregulated activity of the epithelial Mg^{2+} transient receptor potential channel subfamily M, member 6 (TRPM6) (60, 61). In addition to the use of alcohol and medications, magnesium reabsorption in the kidney can be drastically altered under certain pathophysiological conditions. CKD is accompanied with increased renal Mg^{2+} wasting (27) and, thus, impaired kidney function has been recognized as an essential pathway underlying magnesium depletion from the urine. Although magnesium deficiency has been associated with type 2 diabetes in epidemiological studies, a study comparing patients with type 2 diabetes with healthy control subjects using stable isotopes found that magnesium absorption and kidney retention are not impaired in patients with reasonably well-controlled type 2 diabetes (62). The high frequency of magnesium deficiency among patients with type 2 diabetes may result from secondary diabetic nephropathy due to inadequate glycemic control. In the current study, we found that kidney function measured by eGFR is significantly correlated with magnesium status measured by MTT (Pearson correlation coefficient $= -0.27$, $P < 0.05$). Furthermore, we found that mildly reduced kidney function started to affect magnesium status measured by MTT compared with normal kidney function [i.e., eGFR ≥90 mL/(min · 1.73 m^2)] (data not shown). Thus, we assigned 1 point for those with mildly reduced kidney function [i.e., 60 mL/(min · 1.73 m^2) ≤ eGFR <90 mL/(min · 1.73 m^2)] and 2 points for those with CKD [i.e., eGFR <60 mL/(min · 1.73 m^2)].

Our findings that serum magnesium and magnesium intake had an AUC ≤0.54 in predicting body magnesium status compared with 0.58 for urinary magnesium may provide an explanation for the findings from previous studies. A recent meta-analysis of cohort studies found that, compared with the lowest intake category, the highest intake of magnesium was associated with 10% (RR = 0.90; 95% CI: 0.80, 0.99) reduced risk of CVD (3). Likewise, another recent meta-analysis found that the corresponding reduction in risk of coronary heart disease for serum magnesium was 14% (RR = 0.86; 95% CI: 0.74, 0.996) (4). The inverse association between urinary magnesium and risk of CVD was much stronger than that of serum magnesium or magnesium intake with an HR (95% CI) of 1.60 (1.28, 2.00) comparing the lowest quintile of urine magnesium with the upper 4 quintiles, whereas in the same study, plasma concentrations of magnesium were not significantly related to the risk of CVD (63). In the current study, using the MDS with an AUC of 0.60, we found the associations between MDS with CRP and risk of CVD mortality are much stronger than the associations between magnesium intake with CRP and risk of CVD mortality.

Low-grade inflammation has been indicated as a risk factor for the development of numerous chronic metabolic disorders (64). CRP is a sensitive biomarker for low-grade or chronic inflammation and remains elevated while the underlying inflammation remains active (52). Previous studies found inconsistent results between serum magnesium concentrations and CRP concentration (65–67). Likewise, observational studies (11–15) and randomized trials (10) also generated inconsistent findings (9, 16) on magnesium intake and magnesium supplementation

TABLE 3 Multivariable-adjusted serum CRP concentrations by MDS and magnesium intake in the NHANES 2005–2010[1]

	MDS				
Mg intake,[2] mg/d	0	1	2	>2	*P*-trend[3]
≥RDA	2.86 (1.80–4.54)	2.90 (1.83–4.59)	2.82 (1.77–4.51)	2.97 (1.79–4.92)	0.624
EAR∼RDA	3.12 (1.99–4.90)	3.30 (2.08–5.24)	3.61 (2.25–5.81)	4.16 (2.59–6.70)	0.054
<EAR	3.27 (2.13–5.02)	3.51 (2.30–5.37)	3.47 (2.24–5.37)	4.14 (2.64–6.50)	<0.05

[1] CRP values (mg/L) are geometric means (95% CI). CRP, C-reactive protein; EAR, Estimated Average Requirement; MDS, magnesium depletion score.

[2] Age- and sex-specific EAR (36) and RDA (36) were used to classify magnesium intakes. ≥RDA: total magnesium intake ≥RDA. EAR∼RDA: total magnesium intake ≥EAR but <RDA. <EAR: total magnesium intake <EAR.

[3] Models were adjusted for age, sex, race, education, marital status, poverty to income ratio, total energy intake, total calcium intake, physical activity, smoking status, cycle year, and BMI. *P*-interaction = 0.5401.

TABLE 4 Multivariable-adjusted HRs and 95% CIs for magnesium intake in relation to all-cause and cardiovascular mortality in NHANES 2005–2014[1]

	Mg intake,[2] mg/d			
MDS	≥EAR	<EAR1	<EAR2	*P*-trend
All-cause mortality				
All				
Deaths	243	215	365	
Person-months	280,940	188,081	222,681	
HR (95% CI)	1.00 (ref)	0.98 (0.75–1.28)	1.21 (0.91–1.61)	0.194
MDS <2				
Deaths	148	105	167	
Person-months	228,866	142,839	168,071	
HR (95% CI)	1.00 (ref)	0.82 (0.56–1.20)	0.99 (0.64–1.51)	0.929
MDS ≥2				
Deaths	95	110	198	
Person-months	51,829	45,217	53,471	
HR (95% CI)	1.00 (ref)	1.26 (0.89–1.78)	1.54 (1.08–2.19)	<0.05
P-interaction				0.563
Cardiovascular mortality				
All				
Deaths	39	43	78	
Person-months	268,898	178,346	207,108	
HR (95% CI)	1.00 (ref)	1.09 (0.56–2.12)	1.18 (0.56–2.47)	0.668
MDS <2				
Deaths	24	15	31	
Person-months	221,389	137,566	160,405	
HR (95%CI)	1.00 (ref)	0.65 (0.27–1.60)	0.65 (0.27–1.54)	0.326
MDS ≥2				
Deaths	15	28	47	
Person-months	47,372	40,939	46,058	
HR (95% CI)	1.00 (ref)	2.21 (0.93–5.25)	2.44 (1.13–5.27)	<0.05
P-interaction				0.208

[1] EAR, Estimated Average Requirement; MDS, magnesium depletion score; ref, reference.
[2] Age- and sex-specific EAR (36) was used to classify magnesium intakes. ≥EAR: total magnesium intake ≥EAR. Participants with total magnesium intake <EAR were further divided into 2 subgroups: total magnesium intake at or above the median of those with magnesium intake <EAR (<EAR1) and total magnesium intake below the median (<EAR2).

with serum CRP concentration. Of note, the previous studies that used magnesium intake alone did not consider kidney reabsorption. Although increasing MDS was related to significantly increased CRP among individuals with magnesium intake below the EAR, we found the association disappeared among individuals with magnesium intake that met the EAR. This finding may provide an interpretation for the inconsistent results in previous studies.

There have been accumulating studies investigating magnesium status in relation to CVD mortality. However, meta-analyses generated conflicting results (6, 7); 1 analysis of 6 prospective studies with >200,000 participants found no significant differences (7) and another analysis including >400,000 adults reported a 14% reduced risk of CVD mortality (6). We found that low magnesium intake was not related to risk of total and CVD mortality. Although not significant, the point estimate for the HR was 1.18 for those with the lowest intake, which is very close to the HR found in the meta-analysis for magnesium intake in relation to risk of CVD mortality (6). We found that low magnesium intake was associated with increased risks of total and CVD mortality only among individuals with MDS ≥2, whereas the inverse association disappeared with an MDS <2, suggesting that sufficient magnesium intake may have benefits to reduce mortality risk among those at high risk of magnesium deficiency (i.e., with MDS ≥2). Thus, our finding may provide an explanation for the inconsistency in previous studies on the associations between magnesium intake and CVD mortality.

Also, we found that higher MDS was associated with an increased risk of CVD mortality, primarily among individuals consuming magnesium less than the EAR, whereas the association disappeared among individuals who met the EAR. Furthermore, these findings are consistent with our observations on the relation between MDS and serum CRP, an independent predictor of cardiovascular risk (68, 69). These findings indicate that magnesium intake at the EAR may have a modifying effect for eliciting potential benefits on systemic inflammation and CVD mortality, particularly among those with increased MDS.

This study has a number of strengths. We validated the MDS and other magnesium status–related factors (e.g., sex and age) in predicting magnesium status measured by the MTT in one of the largest studies thus far conducting the MTT (58). Subsequently, in a nationally representative sample, we examined the associations between magnesium intake and risks of total and CVD mortality stratified by the MDS as well as the body magnesium status measured by the MDS in relation to serum CRP concentrations and risks of total and CVD mortality stratified by magnesium intake. The findings were biologically plausible and internally consistent. Recall

TABLE 5 Multivariable-adjusted HRs and 95% CI for MDS in relation to all-cause and cardiovascular mortality in NHANES 2005–2014[1]

	MDS				
Mg intake,[2] mg/d	0	1	2	>2	*P*-trend
All-cause mortality					
All					
Deaths	124	296	231	172	
Person-months	254,681	284,700	109,174	40,872	
HR (95% CI)	1.00 (ref)	0.90 (0.65–1.26)	1.03 (0.72–1.46)	1.29 (0.88–1.90)	0.0597
<EAR					
Deaths	67	205	170	138	
Person-months	143,631	166,752	68,858	29,666	
HR (95% CI)	1.00 (ref)	1.14 (0.78–1.68)	1.41 (0.94–2.10)	1.63 (1.07–2.47)	<0.01
≥EAR					
Deaths	57	91	61	34	
Person-months	111,083	117,817	40,250	11,311	
HR (95% CI)	1.00 (ref)	0.69 (0.41–1.17)	0.68 (0.34–1.36)	1.01 (0.47–2.18)	0.863
P-interaction					0.656
Cardiovascular mortality					
All					
Deaths	15	55	49	41	
Person-months	248,159	270,716	99,557	34,218	
HR (95% CI)	1.00 (ref)	1.92 (0.83–4.40)	2.02 (0.83–4.92)	3.13 (1.28–7.66)	0.0245
<EAR					
Deaths	9	37	40	35	
Person-months	140,322	157,109	62,169	24,727	
HR (95% CI)	1.00 (ref)	2.02 (0.66–6.22)	2.54 (0.76–8.45)	4.14 (1.32–13.1)	<0.01
≥EAR					
Deaths	6	18	9	6	
Person-months	107,882	113,537	37,420	9694	
HR (95% CI)	1.00 (ref)	1.52 (0.49–4.75)	1.02 (0.32–3.23)	1.61 (0.31–8.24)	0.994
P-interaction					0.166

[1] Models were adjusted for age, sex, race, education, marital status, poverty to income ratio, total energy intake, total calcium intake, physical activity, smoking status, cycle year and BMI. EAR, Estimated Average Requirement; MDS, magnesium depletion score; ref, reference.
[2] Age- and sex-specific EAR (36) was used to classify magnesium intakes. <EAR: total magnesium intake <EAR. ≥EAR: total magnesium intake ≥EAR.

bias and interviewer bias were minimized because neither the participants nor the interviewers were aware of the study hypothesis when the data were collected. Since the NHANES data are derived from national population-based surveys that accounted for nonresponse, selection bias was also largely reduced.

There are some limitations of our study that need to be addressed. First, due to the nature of the cross-sectional design for CRP analysis, it is difficult to infer a causal relation between magnesium intake and MDS and serum CRP concentrations. However, it is unlikely that serum CRP concentrations led to the difference in magnesium intake or MDS (i.e., alcohol drinking, PPI use, diuretic use, and CKD). Also, previous randomized trials indicated that magnesium deficiency increases serum CRP concentrations. Furthermore, we found the similar longitudinal associations between the MDS and risk of total and CVD mortality.

Second, the association of MDS in relation to CRP concentrations and risk of total and CVD mortality may be confounded by underlying pathological conditions for the factors aggregating the MDS. However, we validated that the model with MDS plus sex and age is a statistically significant predictor of body magnesium status measured by the gold-standard approach. The performance of the model became better as the severity of magnesium deficiency increased. In our sensitivity analysis, we found, after excluding those who used diuretics or PPIs, that the associations between the MDS and risks of total and CVD mortality were attenuated, but the association pattern remained similar, indicating the associations were not solely confounded by the underlying conditions related to use of diuretics or PPIs. We also conducted additional analyses to examine if the associations were driven by kidney function. We found that, although kidney function measured by eGFR is significantly correlated with magnesium status measured by MTT, it is not significantly linked to the risk of total or CVD mortality (data not shown). Collectively, these findings indicate that the combined MDS, but not a single factor, leads to the associations.

Third, in the validation study of MDS among 77 participants with MTT data, the relatively small sample size may reduce the power to detect a significant difference between prediction models. However, this is the initial validation based on post hoc analysis from a randomized controlled trial, and the focus of this study is to validate if the association between magnesium intake and mortality differs by the MDS and if the MDS is linked to clinical outcomes including CRP and total and CVD mortality. Moreover, we consistently found the associations of the MDS with both CRP and risk of total and CVD mortality were only present in those with magnesium intake below the EAR, indicating that magnesium status linked to the MDS accounts for the associations. If the associations were completely confounded by the underlying diseases or

conditions, the associations would still exist in those with magnesium intake meeting the EAR.

Fourth, using the average of two 24-h dietary recalls to estimate individuals' long-term usual intake may be subject to nondifferential misclassification (i.e., excess within-person variation from day-to-day diets), which usually biases the results towards the null. Finally, we cannot fully exclude the possibility of bias due to residual confounding, although a large number of covariates have been adjusted in the analysis.

In summary, the model including the MDS plus sex and age may serve as a promising measure in identifying subsets of individuals with magnesium deficiency and at higher risk of systemic inflammation and CVD mortality. Future randomized trials are needed to confirm these findings. If confirmed, these findings indicate that the combined use of MDS with magnesium intake further improves the prediction of chronic disease risk and lay a foundation for precision-based nutritional interventions (i.e., increasing magnesium intake among those with higher MDS). This concurs with the precision nutrition paradigm emphasized by the 2020–2030 Strategic Plan for NIH Nutrition Research, which has listed nutrition–drug interaction as research focus (70). Future studies are warranted to investigate whether the combination of MDS with serum magnesium and urinary magnesium also improves the prediction of magnesium status in association with chronic diseases.

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