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ORIGINAL ARTICLE

Relationship between magnesium intake and decline in kidney function, incident chronic kidney disease and incident cardiovascular disease

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ABSTRACT

Background and hypothesis. Higher magnesium (Mg) intake is associated with a lower risk of stroke, heart failure and mortality, while there are limited data with kidney disease outcomes. We hypothesized that higher dietary Mg intake would be associated with a lower incidence of cardiovascular disease (CVD), chronic kidney disease (CKD) and kidney function decline.

Methods. The Health, Aging, and Body Composition Study is an observational cohort of 3075 community-dwelling older adults. Dietary Mg intake was estimated using validated dietary surveys. Kidney outcomes included ≥30% decline in estimated glomerular filtration rate (eGFR) cystatin or incident CKD, which was defined as a subsequent eGFR <60 mL/min/1.73 m^2 and at least 1 mL/min/year decline from baseline. Incident CVD was defined as incident coronary disease, heart failure, stroke or cardiovascular mortality. Multivariable Poisson regression and Cox proportional hazards models were used to evaluate the association of Mg intake with kidney and cardiovascular outcomes, respectively.

Results. After excluding missing data, 2682 individuals were available for analysis. The median daily dietary Mg intake was 278 mg/day (11.4 mmol/day) (25th–75th percentile: 214–350 mg/day). Among 1871 individuals without baseline CKD, 522 developed incident CKD, while within the whole cohort, 394 (14.7%) had a ≥30% decline in eGFR over 10 years. Higher Mg intake was independently associated with lower risk of 30% eGFR decline [incidence rate ratio (IRR) per standard deviation (SD) higher Mg intake = 0.79 (95% confidence interval 0.66, 0.93)] and with a lower risk of incident CKD

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[IRR per SD higher Mg intake = 0.84 (95% confidence interval 0.73, 0.96)]. Among 1968 individuals without baseline CVD, 634 developed incident CVD. There was no association between Mg intake and overall incident CVD [adjusted hazard ratio 0.98 (95% confidence interval 0.85, 1.13)].
Conclusions. Higher Mg intake was associated with a lower risk of 30% decline in eGFR and incident CKD but not with incident CVD in a large cohort of older adults. The impact of Mg supplementation on kidney outcomes warrants further investigation.

Keywords: cardiovascular disease, kidney function, magnesium intake

KEY LEARNING POINTS

What was known:

- Higher magnesium (Mg) intake has been associated with a lower risk of stroke, heart failure, diabetes and all-cause mortality, while there are limited data on Mg intake and kidney disease outcomes.

This study adds:

- We demonstrated that higher Mg intake is associated with a lower risk for incident chronic kidney disease, and kidney function decline over 10 years.

Potential impact:

- Magnesium supplementation is inexpensive, widely available and safe.
- Based on the results of this study, the impact of Mg supplementation on kidney outcome should be tested in a randomized clinical trial.

INTRODUCTION

Magnesium (Mg) is an essential mineral for life as it acts as a cofactor for many enzymes involved in glucose, protein and energy metabolism. Humans depend on Mg consumption to keep up with losses in feces, sweat and urine; therefore, deficient dietary intake of Mg is one cause of hypomagnesemia, which is typically defined as serum Mg less than 1.8 mg/dL or 0.70 mmol/L and has a prevalence of up to 15% in the general population [1, 2]. Dietary Mg is mostly absorbed in the small intestine through passive paracellular transport [1].

In the general population, lower serum Mg has been associated with higher risk of congestive heart failure, stroke and diabetes, among other conditions [3–7]. In patients with chronic kidney disease (CKD), lower serum Mg is associated with greater vascular calcification and mortality, possibly due to interactions with other mineral metabolism markers [8–11]. Magnesium oxide oral supplementation appears to attenuate the progression of vascular calcification in patients with CKD suggesting a potential causal relationship between Mg intake and cardiovascular disease (CVD) in CKD [12–16]. The biological plausibility of a causal association is supported by experimental studies showing that Mg supplementation reduces vascular calcification and expression of bone biomarkers in vascular smooth muscle cells in the presence of a high phosphate diet [16–22].

Thus far, studies related to dietary Mg intake and health outcomes have been disparate. A dose–response meta-analysis including over a million participants concluded that higher reported dietary Mg intake was associated with a reduced risk of stroke, heart failure, diabetes and all-cause mortality, but not coronary artery disease or overall CVD [23]. Importantly, the relationships of Mg intake with kidney-related outcomes have not been fully evaluated. Furthermore, although inter-related mineral metabolism parameters such as fibroblast growth factor 23 (FGF-23) [24] and klotho [25] influence Mg metabolism and associate with both CVD and kidney outcomes, it remains unclear whether these parameters modify the impact of Mg intake on clinical outcomes [26]. In this context, we aimed to evaluate the relationship of reported dietary Mg intake with kidney function decline, incident CKD and CVD, including interaction analyses with key mineral metabolism parameters. We hypothesized that higher dietary Mg intake is associated with lower risk of kidney disease, particularly in participants with high FGF-23 or low klotho concentrations.

MATERIALS AND METHODS

All data used in this manuscript are publicly available as a de-identified dataset and accompanying data dictionary through the National Institute of Aging and can be accessed via the following website: https://healthabc.nia.nih.gov/.

Study population

The Health, Aging and Body Composition Study (Health ABC) is a prospective cohort recruited between 1997 and 1998 with a goal of determining the relation of body composition and weight-related health conditions to incident functional limitations. The study population consists of 3075 participants aged 70–79 years at baseline with a balanced number of men and women and was pre-specified to include a significant proportion of Black participants (38%). All persons included were determined to be free of disability in activities of daily living and free of functional limitation at baseline. All participants provided written consent for the study. The study was approved by institutional review boards at each of the participating institutions and meets the requirements of the Declaration of Helsinki.

Exposure

Magnesium intake

Dietary Mg intake was estimated using a semi-quantitative food frequency questionnaire (Block Dietary Data Systems, Berkley,

CA, USA), which was administered by trained interviewers at the second yearly study visit. The food lists contained in the questionnaire were based on National Health and Nutrition Examination Survey (NHANES) III dietary data for individuals 60 years and older, who were non-Hispanic White or Black and resided in the Northeast and South (the geographic areas from which the Health ABC cohort was assembled). Mg intake estimated by the questionnaire has correlated well with alternative methods such as a food diary [27]. Additional details regarding estimation of Mg intake in Health ABC have been published previously [28]. Total caloric intake, dietary calcium and phosphate intake were estimated using the same techniques described above and were examined as "control" dietary exposures in sensitivity analyses.

Outcomes

Kidney outcomes

Cystatin C was measured on three occasions (baseline, Year 3 and Year 10) from stored frozen serum samples at the Health ABC core laboratory (University of Vermont, Burlington, VT, USA) using a BNII nephelometer (Dade Behring Inc., Deerfield, IL, USA) and using a particle-enhanced immunonepholometric assay (N Latex Cystatin C) [29]. As in prior Health ABC studies [30, 31], serum cystatin C was used as the primary measure of kidney function rather than serum creatinine for two reasons. First, cystatin C measures were calibrated across all samples, whereas there was a shift in the creatinine assay from non-isotope dilution mass spectroscopy (IDMS) traceable (baseline) to IDMS traceable during the study (Years 3 and 10). Second, cystatin C is less influenced by age, sex and race [32], and in particular muscle mass, and has been shown to be more strongly associated with adverse outcomes in the elderly population [33, 34]. Among 61 healthy individuals with three cystatin C measurements over a 6-month period, the intra-individual coefficient of variation was 7.7%, reflecting long-term stability of the measurement. Estimated glomerular filtration rate (eGFR) was calculated using a validated cystatin C–based estimating equation [29, 35]. Using eGFR, three kidney outcomes were defined as follows:

- Decline in kidney function was defined as an eGFR decline of 30% or greater. When two follow-up measures of eGFR were available, the last available value (Year 10) was utilized. Recent publications have shown that a 30% decline in eGFR is an acceptable clinical endpoint for clinical trials, as it strongly and consistently predicts the development of end-stage renal disease [36, 37].
- Incident CKD was defined as onset of an eGFR $<$60 mL/min/1.73 m^2 at any point during follow-up and an annual absolute decline $>$1 mL/min/1.73 m^2 per year, with the latter requirement in place to avoid inclusion of participants with minor changes in eGFR. Participants with an eGFR $<$60 mL/min/1.73 m^2 at baseline (i.e. baseline CKD) were excluded from these analyses.

Cardiovascular disease

Participants were queried about any hospital stays, and every 6 months they were asked direct questions to elicit information about a possible interval cardiovascular event. When an event was reported, hospital stay records were collected and examined by the Health ABC Disease Adjudication Committee, with only confirmed events included. Coronary event was defined as admission to the hospital for myocardial infarction (MI), angina, or either percutaneous or surgical revascularization. MI was defined by coronary death or any overnight hospital stay for acute MI, documented by symptoms, electrocardiographic changes, troponin and CPK levels and other imaging. Similarly, all hospital admissions that were confirmed as related to decompensated heart failure (HF) or stroke were recorded. Events and diagnoses were adjudicated on the basis of hospital stay records and death records. Date of death was taken from the death certificate and hospital stay records. Underlying causes of death were determined by central adjudication. Coronary heart death (CHD) was defined as any death where the underlying cause of death was ascertained as atherosclerotic CVD, which included definite fatal MI, definite fatal coronary heart disease and possible fatal CHD. Cardiovascular death was defined as any death classified as coronary death, death due to HF or death due to stroke.

Covariates

All covariates, unless indicated below, were obtained at the Year 2 visit since this is the visit in which Mg intake was estimated. Prevalent CVD was defined as a prior history of coronary artery disease, stroke or HF. Diabetes was defined as use of hypoglycemic agents, self-reported history, fasting plasma glucose level $\geq$126 mg/dL, or 2-h oral glucose tolerance test result $\geq$200 mg/dL. Smoking status was obtained at Year 1 and was classified as current, past ($\geq$100 lifetime cigarettes) or never. Body mass index (BMI) was determined from height and weight at the Year 2 visit. Anti-hypertensive medications were recorded at each visit and were categorized into class of antihypertensive including: angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, calcium channel blocker or diuretic. Diuretics were subcategorized into loop diuretic, thiazide or other. Total caloric intake was estimated using the dietary questionnaire method described above.

Urine albumin was measured at the Year 1 visit using a particle-enhanced turbidimetric inhibition immunoassay allowing for direct albumin quantification (Siemens), while urine creatinine was measured by a modified Jaffé method on a clinical chemistry analyzer (Siemens). Urine albumin was indexed to urine creatinine to report urine albumin-to-creatinine ratio (UACR) in mg/g. Measures of mineral metabolism including calcium, phosphate, parathyroid hormone (PTH), 25-hydroxy [25(OH)] vitamin D, FGF-23 and soluble klotho were measured from frozen stored blood samples at Year 2. Intact PTH was measured in EDTA plasma using a two-site immunoradiometric assay kit (N-tact PTHSP; DiaSorin). Serum calcium and phosphate levels were measured using direct quantitative colorimetric determination (Stanbio Laboratory, Boerne, TX, USA). Serum 25(OH) vitamin D was measured using a two-step radioimmunoassay (25-Hydroxyvitamin D 125I RIA Kit, DiaSorin, Stillwater, MN, USA) in a laboratory participating in the Vitamin D External Quality Assessment Scheme. Serum FGF-23 was measured using a commercial enzyme-linked immunosorbent assay (ELISA) that detects the full-length intact peptide (Kainos Laboratories, Japan). Serum αklotho (klotho) was assayed using a commercially available sandwich ELISA test (IBL-International, Japan) from never thawed frozen samples stored at –70°C.

Statistical analysis

A complete case analysis was used for all models, thus for each outcome, the total number of participants differed. We

examined baseline characteristics of participants across quartiles of Mg intake. These were summarized with means and standard deviations (SD), or medians and interquartile ranges for highly skewed variables or proportions for categorical variables. For eGFR and UACR, we also included the proportion of participants in each quartile below or above clinically relevant cut points (eGFR <60 mL/min/1.73 m^2, UACR >30 mg/g). To understand the potential influence of Mg intake on key covariates, we determined the Spearman's correlation between Mg intake and serum calcium, phosphorus, PTH, FGF-23, klotho and eGFR.

Magnesium intake associations

To examine the functional form of the association between Mg intake and each study outcome, we fit unadjusted natural cubic splines with knots placed at the Mg intake quartiles while extreme values representing Mg intake <100 mg/day and >600 mg/day were excluded to avoid implausible extrapolation of shapes of the association.

Magnesium intake and decline in kidney function

Participants without a second or third eGFR (e.g. only baseline eGFR) were excluded. Multivariable Poisson regression models were used to assess the relationship between Mg intake and 30% decline in eGFR. Mg intake was examined as both a continuous variable (per 1 SD higher intake) and categorized by quartiles. Model 1 was unadjusted. Multivariable models were then sequentially constructed through a series of nested models using pre-specified variables as follows: Model 2 adjusted for age, sex, race, diabetes, hypertension, BMI, smoking status, total caloric intake, and loop and thiazide diuretic use; Model 3 additionally adjusted for baseline eGFR, urine ACR, calcium, phosphate, 25(OH) vitamin D, PTH, FGF-23 and klotho. We assessed for the following interactions with Mg intake and 30% eGFR decline: (i) sex and race (based on possible effects on dietary Mg intake); (ii) FGF-23 and klotho (based on prior data showing impacts of Mg intake on FGF-23 and klotho [26] as well as clinical outcomes); and (iii) eGFR, dichotomized as >60 vs ≤60 mL/min/1.73 m^2 (based on the potential for GFR to impact Mg concentrations).

Magnesium intake and incident CKD

Participants with CKD at baseline (eGFR <60 mL/min/1.73 m^2) were excluded. Poisson (log-link) regression was used to model the incidence rate ratio of CKD as a function of Mg intake with robust variance estimation and an offset for follow-up time. Mg intake was again examined as both a linear term and by category (quartiles) to assess for non-linear relationships based on our spline analysis. Identical multivariable models were constructed as described above, including interaction terms, except for eGFR, for which dichotomized eGFR could not be tested.

Magnesium intake and incident CVD

Cox proportional hazards regression was used to model the association between Mg intake and incident CVD events. Mg intake was again examined as both a linear term and by category (quartiles) to assess for non-linear relationships based on our spline analysis. Identical multivariable models were constructed as described above, including interaction terms. We then repeated analyses for each subcomponents of incident CVD: incident stroke, incident MI, incident CHD and incident HF.

Sensitivity analyses

We additionally examined the association between Mg intake with eGFR slope. Specifically, eGFR decline was treated as a continuous outcome, by examining the percentage decline per year. For this analysis, we employed a linear mixed effects model, which accounts for within-subject correlation and allows for more accurate estimation of eGFR decline over time. To confirm that Mg intake itself was associated with outcomes, versus dietary quality, dietary calcium and phosphate intake were examined as comparison or "control" exposures by repeating the same model structures described above.

Analyses were conducted using SPSS (IBM Corp., released 2015, IBM SPSS Statistics for Windows, Version 23.0; IBM Corp., Armonk, NY, USA) and Stata (StataCorp. 2013, Stata Statistical Software: release 13; StataCorp LP, College Station, TX, USA). A two-sided *P*-value of <.05 was considered statistically significant for all analyses including interaction terms.

RESULTS

Baseline characteristics

Among 3075 persons, 77 participants did not attend the Year 2 visit, 285 participants did not complete the dietary survey and 31 participants were missing covariates, leaving 2682 available for analysis. The mean (SD) age was 75 (3) years, with 1368 (51%) female and 1041 (39%) Black participants (Table 1). The distribution of Mg intake within the study population can be seen in Fig. 1. The median total Mg intake was 278 mg/day (interquartile range 214–350 mg/day). At baseline, 478 (18%) had prevalent coronary artery disease, 30 (1%) had prevalent HF and 183 (7%) had a prior history of cerebrovascular disease. The mean (SD) baseline eGFR was 72 (18) mL/min/1.73 m^2 and 644 (24%) participants had CKD by eGFR criteria (eGFR <60 mL/min/1.73 m^2) at baseline.

Across quartiles of Mg intake, participants in the highest quartile were more likely to be men, to have prevalent HF and to have higher baseline eGFR. There were no observed differences in age, race, diabetes, hypertension or measures of mineral metabolism across quartiles of Mg intake. Correlations between Mg intake and mineral metabolism markers, as well as eGFR are presented in Supplementary data, Table S1.

Magnesium intake and kidney outcomes

For 30% eGFR decline, of the 2429 participants, 1335 had an eGFR at all three visits, 1042 had an eGFR at Years 1 and 3 only, and 52 had an eGFR at Years 1 and 10 only. For incident CKD, of the 1871 participants, 1083 had an eGFR at all three visits, 740 had an eGFR at Years 1 and 3 only, and 48 had an eGFR at Years 1 and 10 only. Thus, in follow-up, 394 of 2429 individuals developed at least a 30% decline in eGFR over 10 years, while 522 of 1871 individuals developed incident CKD. Higher Mg intake was independently associated with lower risk of ≥30% eGFR decline {incidence rate ratio (IRR) per SD higher Mg intake = 0.79 [95% confidence interval (CI) 0.66, 0.93]} and with a lower risk of incident CKD [IRR per SD higher Mg intake = 0.84 (95% CI 0.73, 0.96)] in fully adjusted models (Table 2). When examined as quartiles of Mg intake, the highest quartile of Mg intake was associated with lower risks of both ≥30% eGFR decline and incident CKD [IRR = 0.54 (0.37, 0.78) and 0.67 (0.50, 0.91)] for highest vs lowest Mg intake quartile, respectively). The non-linear fully adjusted relationship between Mg intake and both kidney outcomes can be visualized in Figs 2 and 3.

Table 1: Demographics and clinical characteristics by quartiles of Mg intake.

Variable	Full cohort	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Range (mg/day)		3–213	214–277	278–350	351–1305
N	2682	667	675	673	667
Age (years)	75 (3)	75 (3)	75 (3)	75 (3)	75 (3)
Female	1368 (51)	399 (60)	358 (53)	336 (50)	275 (41)
Black	1041 (39)	310 (47)	234 (35)	233 (35)	264 (40)
Diabetes	976 (36)	247 (37)	228 (34)	247 (37)	254 (38)
Hypertension	2064 (77)	530 (80)	523 (78)	504 (75)	507 (76)
Smoking					
Former	1242 (46)	305 (46)	319 (47)	232 (48)	295 (44)
Current	250 (9)	71 (11)	53 (8)	58 (9)	68 (10)
Anti-hypertensive medications					
ACE-I	453 (17)	104 (16)	115 (17)	133 (20)	101 (15)
ARBs	94 (4)	22 (3)	27 (4)	18 (3)	27 (4)
Beta blockers	404 (15)	105 (16)	114 (17)	87 (13)	98 (15)
Calcium channel blockers	628 (24)	175 (26)	155 (23)	141 (21)	157 (24)
Diuretics					
Miscellaneous	277 (10)	91 (14)	69 (10)	61 (9)	56 (8)
Loop	190 (7)	56 (8)	45 (7)	40 (6)	49 (7)
Thiazide	520 (19)	142 (21)	142 (21)	126 (19)	100 (17)
Any anti-hypertensive med	1520 (57)	403 (60)	387 (58)	368 (55)	362 (54)
Coronary artery disease	478 (18)	138 (21)	122 (18)	109 (17)	109 (17)
Heart failure	30 (1.1)	5 (0.8)	10 (1.5)	7 (1.1)	8 (1.2)
Cerebrovascular disease	183 (6.9)	52 (7.9)	46 (6.9)	43 (6.5)	42 (6.4)
Systolic blood pressure (mmHg)	134 (21)	136 (22)	133 (20)	132 (20)	134 (21)
Diastolic blood pressure (mmHg)	70 (12)	71 (13)	70 (11)	70 (11)	70 (12)
BMI (kg/m^2)	27.2 (4.8)	27.7 (5.1)	27.0 (4.6)	27.0 (4.8)	27.1 (4.6)
C-reactive protein (mg/L)	2.95 (1.25, 6.41)	3.43 (1.34, 7.32)	2.83 (1.20, 5.81)	3.00 (1.32, 6.52)	2.73 (1.07, 6.04)
eGFR (mL/min/1.73 m^2)	72 (18)	71 (20)	72 (18)	73 (18)	75 (18)
eGFR <60	644 (24)	180 (27)	172 (26)	161 (24)	131 (20)
UACR (mg/g)	8 (4, 19)	8 (4, 20)	8 (4, 21)	7 (4, 15)	7 (4, 18)
UACR ≥30 mg/g	455 (17)	118 (18)	125 (19)	94 (14)	118 (18)
Vitamin D 25(OH)2 (ng/mL)	26 (11)	24 (12)	26 (10)	27 (13)	26 (10)
Calcium (mg/dL)	8.9 (0.4)	8.9 (0.4)	8.9 (0.4)	8.9 (0.4)	8.8 (0.4)
Phosphate (mg/dL)	3.55 (0.48)	3.59 (0.50)	3.56 (0.48)	3.54 (0.57)	3.51 (0.46)
PTH (pg/mL)	34 (25, 46)	36 (27, 49)	32 (25, 45)	32 (24, 43)	34 (24, 44)
FGF-23 (pg/mL)	47 (37, 60)	46 (36, 59)	48 (38, 62)	46 (36, 58)	46 (37, 59)
Klotho (pg/mL)	627 (478, 811)	624 (473, 803)	614 (477, 781)	621 (473, 814)	649 (495, 849)
Calcium intake (mg)	786 (400)	459 (196)	672 (217)	837 (270)	1176 (456)
Phosphate intake (mg)	1155 (491)	676 (200)	974 (178)	1223 (222)	1746 (483)
Total caloric intake (kcals)	1880 (775)	1196 (379)	1636 (362)	1976 (450)	2713 (840)

Data are presented as mean (SD), median (25th, 75th) or number (%) as appropriate.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

Magnesium intake and incident CVD

Among 1968 individuals who were free from CVD at baseline, 634 developed incident CVD for an incident rate of 3.5% per year. There was no association between Mg intake and incident CVD when examining Mg intake as a continuous variable [fully adjusted hazard ratio (HR) 0.98 (0.85, 1.13)] (Table 3). There was no association between quartiles of Mg intake and overall incident CVD or when examining the non-linear association between Mg intake with overall incident CVD (Fig. 4). When examining individual components of the composite CVD outcome, higher Mg intake was associated with a lower hazard of incident stroke in unadjusted analyses [HR 0.83 (0.72, 0.97)] (Table 4). The association became non-significant in subsequent models adjusting for demographics, CVD risk factors and measures of mineral metabolism. In quartile analyses, quartiles 2, 3 and 4 all carried a lower hazard for incident stroke; this association remained significant across all models. In contrast, no association was seen between Mg intake and incident MI, HF or CHD (Table 4).

Interactions

The only interaction observed to be statistically significant was the association of Mg intake and FGF-23, stratified at above or below the median of 44.6 pg/mL, with incident CKD. Among those with lower FGF-23 concentrations, higher Mg intake [IRR 0.80 (0.65, 0.98)] had a stronger association with incident CKD than among participants with higher FGF-23 [IRR 0.90 (0.74, 1.09)] (P for interaction = .02). All other tested interactions, including sex race, klotho and eGFR, had a P-value >.1.

Sensitivity analyses

When looking at the association between Mg intake and eGFR slopes, we found results consistent with the primary kidney

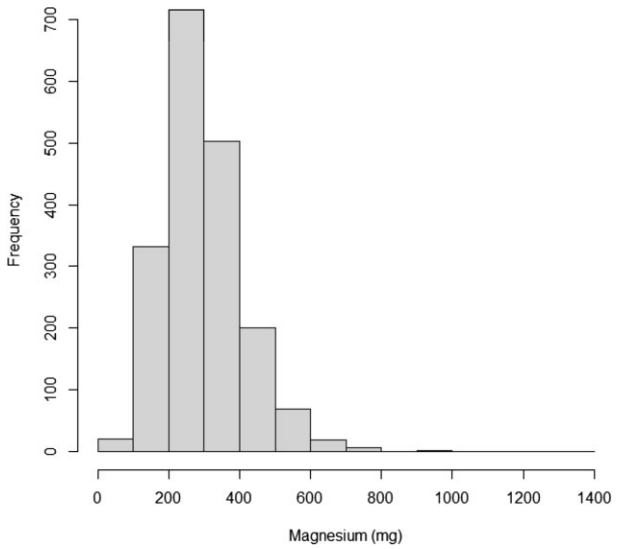

Figure 1: Distribution and frequency of Mg intake within Health ABC cohort participants.

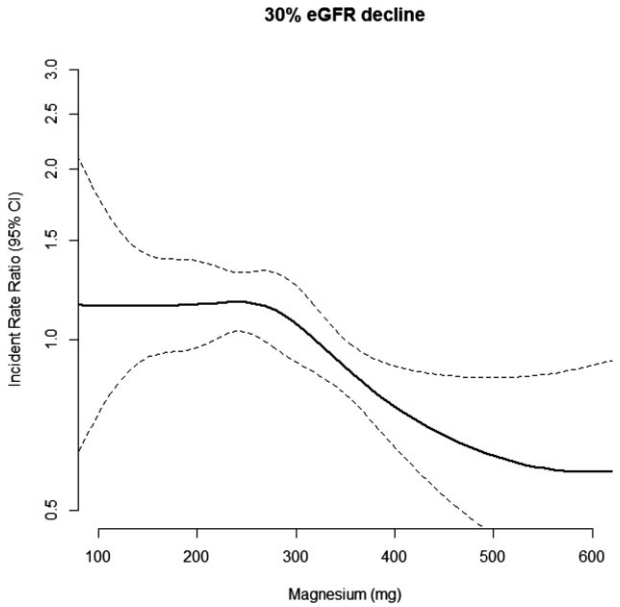

Figure 2: Relationship between Mg intake and 30% eGFR decline.

outcomes (Supplementary data, Table S2). Higher Mg intake was associated with slower/less steep eGFR decline; this was most pronounced in the highest Mg quartile. Dietary calcium intake and phosphate intake were not associated with 30% decline in eGFR, incident CKD or incident CVD across all models (Supplementary data, Table S3).

DISCUSSION

In a cohort of community dwelling older adults, we found that higher estimated Mg intake was independently associated with a lower risk of ≥30% decline in eGFR as well as a lower risk of incident CKD during 10 years of follow-up. There was no observed association between Mg intake and overall incident CVD across all models. For CVD components, higher Mg intake was only associated with a lower risk for stroke. No association was seen for analyses examining the association of calcium and phosphate intake with the same kidney and CVD outcomes. The effect of higher Mg intake on the lower risk of incident CKD appeared more significant in individuals with lower levels of FGF23 at baseline, which highlights the importance of patient selection (i.e. enrichment) when Mg-based interventions are evaluated in clinical trials.

There is a wealth of literature describing the association between dietary Mg intake and incident CVD. A recent meta-analysis by Fang *et al.* evaluated the relationship between Mg intake and CVD, type 2 diabetes and mortality [23]. A total of 40 studies comprising 1 million individuals were included. The authors found a significant association between higher Mg intake and lower risk of two sub-categories of CVD (heart failure and stroke), but not with total CVD or coronary disease. Higher Mg intake was also associated with a lower risk for type 2 diabetes

Table 2: Association of Mg intake with incident CKD and ≥30% eGFR decline.

Mg intake	N	# of events	Incident rate (%/year)	Model 1 IRR (95% CI)	Model 2	Model 3 IRR (95% CI)
Incident CKD						
Mg intake (per SD = 117)	1871	522	4.75	0.95 (0.88, 1.04)	**0.80 (0.69, 0.92)**	**0.84 (0.73, 0.96)**
Mg quartiles						
<214	441	133	5.21	1.00 (ref)	1.00 (ref)	1.00 (ref)
214–277	469	139	5.00	0.96 (0.77, 1.19)	0.85 (0.68, 1.06)	0.85 (0.68, 1.06)
278–350	474	130	4.71	0.90 (0.73, 1.13)	**0.76 (0.60, 0.97)**	0.82 (0.65, 1.04)
>350	487	120	4.13	**0.79 (0.63, 0.99)**	**0.55 (0.41, 0.75)**	**0.67 (0.50, 0.91)**
≥30% decline						
Mg intake (per SD = 117)	2429	394	2.68	**0.87 (0.78, 0.97)**	**0.79 (0.67, 0.94)**	**0.79 (0.66, 0.93)**
Mg quartiles						
<214	594	112	3.15	1.00 (ref)	1.00 (ref)	1.00 (ref)
214–277	619	109	2.86	0.90 (0.71, 1.14)	0.87 (0.68, 1.12)	0.85 (0.66, 1.09)
278–350	615	98	2.67	0.84 (0.66, 1.07)	0.81 (0.61, 1.08)	0.80 (0.60, 1.07)
>350	601	75	2.06	**0.65 (0.50, 0.85)**	**0.54 (0.37, 0.79)**	**0.54 (0.37, 0.78)**

Model 1 = unadjusted analysis.
Model 2 = adjusted for age, sex, race, diabetes, hypertension, BMI, smoking, total caloric intake, loop diuretics and thiazides.
Model 3 = Model 2 + eGFR, UACR, calcium, phosphate, 25(OH) vitamin D, PTH, FGF-23 and klotho.
Bold $p < 0.05$.

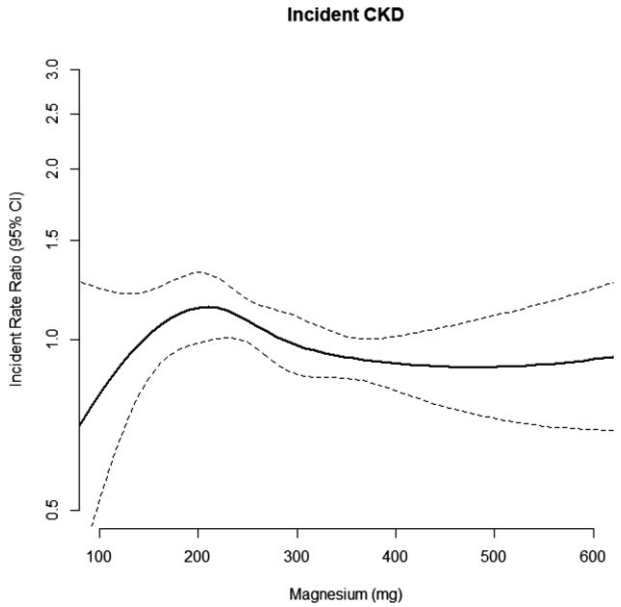

Figure 3: Relationship between Mg intake and incident CKD.

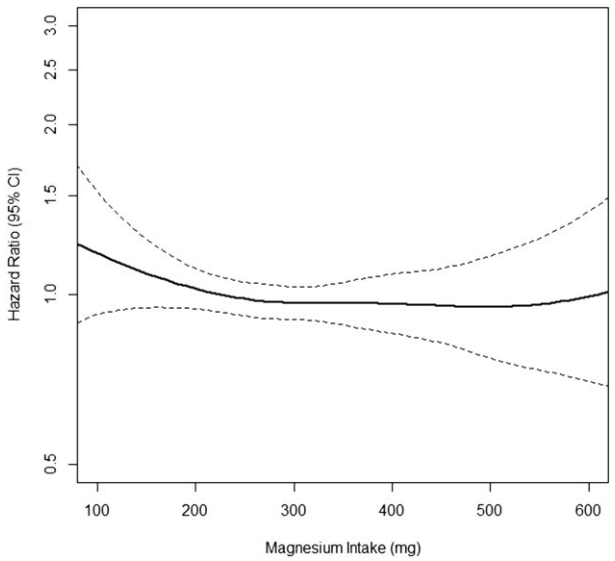

Figure 4: Relationship between Mg intake and overall incident CVD.

and all-cause mortality. The present study confirmed the association between higher Mg intake and a lower risk for stroke.

In contrast, there are relatively few studies examining the relationship between Mg intake and kidney-related outcomes. A study by Rebholz *et al*. included approximately 1200 individuals enrolled in the Healthy Aging in Neighborhoods of Diversity across the Life Span study and found that lower dietary Mg intake was associated with a higher risk for rapid eGFR decline defined as ≥3% eGFR decline per year [38]. Compared with our study, incident CKD and 30% decline in eGFR were not evaluated as study outcomes and the analyses were not adjusted for relevant mineral metabolism markers that could influence Mg homeostasis and outcomes. Another study by Farhadnejad *et al*. explored the association between dietary micronutrients and incident CKD, finding that those individuals in the highest quintile of Mg intake had a lower adjusted hazard [0.41 (95% CI 0.22, 0.76)] for incident CKD compared with those in the lowest Mg intake quintile [39]. The study defined incident CKD as a subsequent follow-up eGFR of <60 mL/min/1.73 m^2 but did not include any criteria for minimum absolute eGFR decline and did not adjust for either albuminuria or mineral metabolism markers.

There are several potential explanations for our findings. First, higher estimated dietary Mg intake may be protective against the development or progression of kidney disease by increasing total body Mg concentrations. Higher serum Mg concentrations appear to have a beneficial effect on endothelial function and vascular health, resulting in lower systemic blood pressures [40]. However, serum Mg concentrations may not reflect total body Mg content in some persons. An alternative explanation is that the observed association could be due to overall dietary quality as high Mg concentrations are most often observed in fruits and vegetables [41]. Individuals who consume a higher quality diet, which may overlap with well-studied diets and dietary patterns such as the DASH (Dietary Approaches to Stop Hypertension) and Mediterranean diets, may be at lower risk of kidney disease due to overall better health and/or access to healthcare information and services. In this study, to partially control for dietary quality, we adjusted for total caloric intake, as well as evaluated dietary calcium and phosphate intake as alternative risk exposures for study outcomes.

There are several limitations to our study. First, dietary Mg intake was estimated using a dietary survey at a single time point and therefore not directly measured. This method has the potential for imprecision due to recall bias and may not capture changes in dietary patterns over time. However,

Table 3: Association of Mg intake with incident CVD.

Mg intake	N	# of events	Incident rate (%/year)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Incident CVD						
Mg intake (per SD = 117)	1968	634	3.51	1.00 (0.92, 1.08)	0.95 (0.82, 1.09)	0.98 (0.85, 1.13)
Mg quartiles						
<214	469	168	3.92	1.00 (ref)	1.00 (ref)	1.00 (ref)
214–277	494	142	3.09	**0.78 (0.62, 0.98)**	**0.73 (0.58, 0.93)**	**0.74 (0.58, 0.95)**
278–350	511	173	3.73	0.95 (0.76, 1.18)	0.87 (0.68, 1.10)	0.92 (0.71, 1.19)
>350	494	151	3.31	0.85 (0.67, 1.07)	**0.71 (0.52, 0.98)**	0.76 (0.54, 1.05)

Model 1 = unadjusted analysis.
Model 2 = adjusted for age, sex, race, diabetes, hypertension, BMI, smoking, total caloric intake, loop diuretics and thiazides.
Model 3 = Model 2 + eGFR, UACR, calcium, phosphate, 25(OH) vitamin D, PTH, FGF-23 and klotho.
Bold $p < 0.05$.

Table 4: Association of Mg intake with individual CVD outcomes.

Mg intake	N	# of events	Incident rate (%/year)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Incident stroke						
Mg intake (per SD)	2437	275	1.16	**0.83 (0.72, 0.97)**	0.79 (0.62, 1.01)	0.85 (0.66, 1.10)
Mg quartiles						
<214	600	92	1.62	1.00 (ref)	1.00 (ref)	1.00 (ref)
214–277	610	70	1.16	**0.70 (0.52, 0.96)**	**0.69 (0.50, 0.96)**	**0.70 (0.51, 0.98)**
278–350	615	59	0.99	**0.59 (0.42, 0.82)**	**0.54 (0.37, 0.79)**	**0.61 (0.42, 0.89)**
>350	612	54	0.90	**0.54 (0.38, 0.75)**	**0.45 (0.29, 1.71)**	**0.49 (0.30, 0.78)**
Incident MI						
Mg intake (per SD)	2115	227	1.10	1.02 (0.87, 1.20)	0.93 (0.73, 1.20)	0.97 (0.75, 1.25)
Mg quartiles						
<214	506	59	1.20	1.00 (ref)	1.00 (ref)	1.00 (ref)
214–277	535	53	1.01	0.82 (0.57, 1.18)	0.71 (0.48, 1.04)	0.72 (0.49, 1.08)
278–350	547	64	1.20	0.97 (0.68, 1.38)	0.80 (0.54, 1.19)	0.86 (0.57, 1.29)
>350	527	51	0.99	0.83 (0.57, 1.21)	0.58 (0.34, 1.01)	0.65 (0.37, 1.13)
Incident CHD						
Mg intake (per SD)	2115	535	2.73	1.04 (0.95, 1.14)	0.98 (0.84, 1.14)	1.00 (0.86, 1.17)
Mg quartiles						
<214	506	134	2.84	1.00 (ref)	1.00 (ref)	1.00 (ref)
214–277	535	117	2.35	0.81 (0.63, 1.04)	0.76 (0.59, 1.00)	0.79 (0.60, 1.03)
278–350	547	148	2.94	1.02 (0.81, 1.29)	0.95 (0.73, 1.24)	1.01 (0.76, 1.32)
>350	527	136	2.8	1.00 (0.78, 1.26)	0.83 (0.59, 1.19)	0.89 (0.62, 1.28)
Incident HF						
Mg intake (per SD)	2567	530	2.00	1.00 (0.92, 1.09)	0.96 (0.83, 1.12)	1.03 (0.89, 1.20)
Mg quartiles						
<214	644	136	2.08	1.00 (ref)	1.00 (ref)	1.00 (ref)
214–277	644	133	1.98	0.93 (0.73, 1.18)	0.92 (0.71, 1.19)	0.97 (0.75, 1.25)
278–350	647	125	1.88	0.90 (0.71, 1.15)	0.92 (0.71, 1.20)	1.03 (0.78, 1.35)
>350	641	136	2.07	0.98 (0.77, 1.24)	0.91 (0.65, 1.28)	1.03 (0.73, 1.46)

Model 1 = unadjusted analysis.
Model 2 = adjusted for age, sex, race, diabetes, hypertension, BMI, smoking, total caloric intake, loop diuretics and thiazides.
Model 3 = Model 2 + eGFR, UACR, calcium, phosphate, 25(OH) vitamin D, PTH, FGF-23 and klotho.
Bold $p < 0.05$.

nearly every other large study of dietary micronutrient intake, including NHANES [41], uses a similar approach due to the difficulty and expense of direct measurements. The dietary survey method employed in this study is widely regarded as the "gold standard" of dietary estimation of micronutrients [42]. Notably, the estimated Mg intake for this study was similar to the one estimated in NHANES for the general US population [41]. In addition, we were unable to consistently determine the contribution of Mg supplements to total Mg intake in this cohort; we have therefore focused on dietary Mg intake alone. Second, we did not have serum Mg concentrations available for comparison or adjustment. Nonetheless, we did adjust for other mineral metabolism markers including calcium, phosphate, PTH, vitamin D, FGF-23 and soluble klotho. We additionally examined calcium and phosphate dietary intake as control dietary exposures; reassuringly, neither of these dietary measures was associated with any of the clinical outcomes. Third, we acknowledge that our analyses include multiple statistical comparisons that were not addressed with statistical corrective methods. We have attempted to focus on effect sizes, CIs and the robustness of results by transparently reporting all our findings, including null results. Additionally, we performed a limited number of *a priori*–determined interaction tests. Finally, there may be other unmeasured confounders that influenced the findings, including socioeconomic status. We attempted to address confounding by adjusting for all available cardiovascular and kidney disease risk factors, total caloric intake and relevant measures of mineral metabolism.

In conclusion, we found a significant relationship between higher Mg intake and a lower risk of ≥30% decline in eGFR and incident CKD in a large cohort of community dwelling older adults with up to 10 years of follow-up. These observations were independent of potential confounders including demographics, CVD and CKD risk factors, and relevant dietary exposures and mineral metabolism parameters. While there was no association between Mg intake and overall incident CVD, there was an association between higher Mg intake and a lower risk for stroke. Given that we can augment Mg intake through supplementation or dietary changes, further studies aimed at studying the impact of increased Mg intake on CKD incidence and progression are warranted.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

CONFLICT OF INTEREST STATEMENT

O.M.G. reports receiving honoraria from Amgen, Akebia, AstraZeneca and Ardelyx. M.G.S. reports receiving honoraria from Boehringer Ingelheim, AstraZeneca and Bayer and research support from Bayer. O.W.M. reports advisory board payments from Alnylam Pharmaceutical. M.J.S. attended an advisory board for Boehringer Ingelheim, is on the Steering Committee for Akebia and his spouse is employed by Eli Lilly. There are no other conflicts of interest to declare. The results presented in this paper have not been published previously, in whole or part.

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