Urinary and plasma magnesium and risk of ischemic heart disease

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ABSTRACT

Background: Previous studies on dietary magnesium and risk of ischemic heart disease (IHD) have yielded inconsistent results, in part because of a lack of direct measures of actual magnesium uptake. Urinary excretion of magnesium, an indicator of dietary magnesium uptake, might provide more consistent results.

Objective: The objective was to investigate whether urinary magnesium excretion and plasma magnesium are associated with IHD risk.

Design: We examined 7664 adult participants free of known cardiovascular disease in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study—a prospective population-based cohort study. Urinary magnesium excretion was measured in 2 baseline 24-h urine collections.

Results: Mean ± SD urinary magnesium excretion was 4.24 ± 1.65 mmol/24 h for men and 3.54 ± 1.40 mmol/24 h for women. During a median follow-up of 10.5 y (IQR: 9.9–10.8 y), 462 fatal and nonfatal IHD events occurred. After multivariable adjustment, urinary magnesium excretion had a nonlinear relation with IHD risk (P-curvature = 0.01). The lowest sex-specific quintile (men: <2.93 mmol/24 h; women: <2.45 mmol/24 h) had an increased risk of fatal and nonfatal IHD (multivariable HR: 1.60; 95% CI: 1.28, 2.00) compared with the upper 4 quintiles of urinary magnesium excretion. A similar increase in risk of the lowest quintile was observed for mortality related to IHD (HR: 1.70; 95% CI: 1.10, 2.61). No associations were observed between circulating magnesium and risk of IHD.

Conclusions: Low urinary magnesium excretion was independently associated with a higher risk of IHD incidence. An increased dietary intake of magnesium, particularly in those with the lowest urinary magnesium, could reduce the risk of IHD. Am J Clin Nutr doi: 10.3945/ajcn.112.054114.

INTRODUCTION

Magnesium is an essential, mainly intracellular, cation that has been favorably associated with markers of inflammation and endothelial dysfunction (1, 2) and risk of the metabolic syndrome (3, 4) and type 2 diabetes (5, 6). Despite these promising data, prospective studies on magnesium intake and risk of ischemic heart disease (IHD) have yielded inconsistent results, with some studies showing null (7, 8) or nonindependent associations (9) and others a weak inverse association (10–12). However, previous studies used circulating magnesium (10, 11), which is regulated within a narrow homeostatic range and may be compensated by magnesium from muscle and bone (13), which makes it less reflective of dietary intake. Other studies relied on subjective measures of magnesium intake assessed by dietary recall (7–10, 12) of uncertain validity and did not capture the increased gastrointestinal absorption of magnesium at lower dietary intakes (14, 15).

An alternative approach to assessing dietary magnesium is to measure urinary excretion of magnesium. Magnesium homeostasis is predominantly regulated via the balance between gastrointestinal uptake and renal excretion. Magnesium absorption can accurately be determined from 24-h urine collections (16), and clinical trials have shown that dietary manipulation of magnesium is reflected in urinary magnesium excretion (17). Thus, 24-h urinary magnesium excretion provides a measure of dietary magnesium uptake.

To examine the association of urinary magnesium excretion with incidence of IHD, we studied a large population-based sample of men and women who provided two 24-h urine collections at baseline and have now been followed for more than a decade.

SUBJECTS AND METHODS

Study design and population

The Prevention of Renal and Vascular End-Stage Disease (PREVEND) study is a prospective investigation of albuminuria, renal, and cardiovascular disease in a large cohort drawn from the general population. Details of this study were described elsewhere (18). In summary, from 1997 to 1998, all inhabitants of Groningen, Netherlands, aged 28–75 y (n = 85,421) were sent a questionnaire and a vial to collect a first-morning void urine sample. Pregnant women and subjects with type 1 diabetes mellitus were excluded. The urinary albumin concentration was assessed in 40,856
responders. Subjects with a urinary albumin concentration of \( \geq 10 \text{ mg/L} (n = 7768) \) were invited to participate, of whom 6000 were enrolled. In addition, a randomly selected group with a urinary albumin concentration of \( < 10 \text{ mg/L} (n = 3394) \) was invited to participate in the cohort, of whom 2592 were enrolled. These 8592 individuals constitute the PREVEND cohort.

For the current study, we excluded subjects with a history of cardiovascular disease (\( n = 451 \)) or dialysis (\( n = 18 \)) at baseline and those with missing data on urinary excretion of magnesium (\( n = 64 \)) or other cations (\( n = 29 \)), serum cholesterol (\( n = 223 \)), and lifestyle behaviors (\( n = 143 \)), which left 7664 subjects for the current analysis. The PREVEND study was approved by the medical ethics committee of the University Medical Center Groningen. Written informed consent was obtained from all participants.

Data collections

Participants underwent 2 visits to an outpatient research unit for the baseline survey. At the first visit, all participants completed a questionnaire on demographics, cardiovascular disease history, smoking habits, alcohol consumption, and medication use. Information on medication use was combined with information from a pharmacy-dispensing registry, which has complete information on drug use of \( > 90\% \) of subjects in the PREVEND study. Height and weight were measured on the first visit. Blood pressure (BP) was assessed during both visits while the subjects were in a supine position, every minute for 10 and 8 min, respectively, with an automatic Dinamap XL model 9300 series device (Johnson-Johnson Medical). The mean of the last 2 recordings from each visit was used. Standard 12-lead electrocardiograms were recorded. In addition, a fasting blood sample was drawn (stored at \(-80^\circ \text{C}\)), and subjects collected two 24-h urine samples after thorough oral and written instruction (stored at \(-20^\circ \text{C}\)).

Assessment of urinary and plasma magnesium

Urinary and plasma magnesium concentrations were both measured in specimens from the baseline examination by a xyldyl blue method. Urinary magnesium was determined on a MEGA clinical chemistry analyzer (Merck) with an interassay CV of 2.1%. Circulating magnesium was measured in plasma with lithium heparin as anticoagulant on a Modular analyzer (Roche Diagnostics) with an interassay CV of 1.3%.

Assessment of covariates

Calcium, sodium, potassium, and creatinine in urine and circulating calcium, sodium, potassium, creatinine, albumin, total cholesterol, HDL cholesterol, triglycerides, high-sensitivity C-reactive protein (CRP), and glucose were measured as previously described (19, 20). BMI was calculated as weight (kg) divided by the square of height (m\(^2\)). Hypertension was defined as a systolic BP of \( \geq 140 \text{ mm Hg} \), a diastolic BP of \( \geq 90 \text{ mm Hg} \), or the use of antihypertensive drugs (21). Hypercholesterolemia was defined as a cholesterol concentration of \( > 6.21 \text{ mmol/L} (\geq 240 \text{ mg/dL}) \) or the use of lipid-lowering drugs (22) and diabetes as a fasting plasma glucose concentration \( \geq 7.0 \text{ mmol/L} (\geq 126 \text{ mg/dL}) \) or the use of antidiabetic medication (23). The estimated glomerular filtration rate was calculated from the Chronic Kidney Disease Epidemiology Collaboration equation (24). Chronic kidney disease was defined as an estimated glomerular filtration rate \( < 60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2} \) or a urinary albumin excretion of \( \geq 30 \text{ mg/24 h} \). Minor ischemic changes on an electrocardiogram were defined by using the Minnesota code classification system for electrocardiographic findings, codes 4 and 5 (25). Left ventricular hypertrophy was identified by electrocardiogram by using the Cornell voltage–duration product, which was calculated as follows: RAVL + SV3 (with 6 mm added in women) times QRS-complex duration. A threshold of 2440 mm \cdot ms was used to identify left ventricular hypertrophy (26).

Ascertainment of IHD events

For IHD outcomes, we used the incidence of IHD morbidity and mortality after the baseline screening. Date and cause of death were obtained by record linkage with the Dutch Central Bureau of Statistics. Information on hospitalization for IHD morbidity was obtained from PRISMANT, the Dutch national registry of hospital discharge diagnoses. The validity of this database has been shown to be good, with 84\% of the primary diagnoses matching the diagnoses recorded in patients’ charts (27). The data were initially coded according to the International Classification of Diseases (ICD) 9th revision and were recoded according to the ICD 10th revision. For this study, IHD events were defined as follows: acute myocardial infarction (ICD-10 code I21), hospitalization for other acute ischemic heart disease (ICD-10 code I24), coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty. The ICD-10 codes for IHD-related mortality in this study included acute myocardial infarction (I21), chronic ischemic heart disease (I25), cardiac arrest (I46), ventricular fibrillation and flutter (I49), and heart failure (I50).

Statistical analysis

Baseline characteristics are presented according to sex-specific quintiles of urinary magnesium excretion. We created sex-specific categories to reflect the difference in magnesium recommendations between sexes set by the Institute of Medicine (28). Normally distributed variables are given as means ± SDs and skewed variables as medians (IQRs). We used Cox proportional hazards analyses to examine the association between urinary magnesium excretion and risk of IHD and mortality. Survival time was defined as the period from the date of urine collection of the participant to the date of first event, relocation to an unknown destination or 1 January 2009 (end of follow-up). For the primary outcome of nonfatal and fatal IHD, subjects were followed until the first coronary event and censored on noncoronary death. For IHD-related mortality, subjects were censored on non-IHD death but not on nonfatal events. Adjusted HRs are reported with 95\% CIs. All models took into account the sampling design of the study (presence or absence of albuminuria) by specifying stratum-specific baseline hazard functions. To determine the independent association of urinary magnesium excretion with risk, we adjusted for age and IHD risk factors, including smoking (current smoking or cessation <1 y), ratio of total to HDL cholesterol, BMI, sex, alcohol consumption (5 categories), and parental history of IHD (multivariable model 1) and additionally for urinary calcium, sodium, potassium, and creatinine excretion (multivariable model 2). If an association was present after multivariable adjustment, we
also investigated the effect of potential intermediate variables by adding log-transformed CRP, log-transformed urinary albumin excretion, systolic BP, antihypertensive treatment use, type 2 diabetes, ischemic ST-T segment changes, and prolonged QTc interval to our model (multivariable model 3). To test for a linear trend, we modeled urinary magnesium excretion as a continuous variable. We examined potential nonlinear relations using restricted cubic spline transformations (29) and tested nonlinearity by using the likelihood ratio test, comparing nested models with a linear or linear and cubic spline terms. Multiplicative interaction was assessed by fitting models containing both main effects and their cross-product terms. In sensitivity analyses, we excluded subjects with potentially altered magnesium absorption from the intestine (due to proton-pump inhibitor use or consumption of ≥4 alcoholic beverages/day) or excretion due to diuretic use and addressed the oversampling of subjects with elevated urinary albumin excretion by using design-based Cox proportional-hazards regression models that took into account the probability of selection by statistical weighting.
Similar analyses were performed for circulating magnesium. Given the restricted range of values for plasma magnesium, we used overall quintiles rather than sex-specific quintiles. We tested the association between magnesium in urine and plasma with age- and sex-adjusted Pearson partial correlation coefficients. Statistical analyses were performed by using PSAW (version 20.0; SPSS Inc) and SAS (version 9.2; SAS Institute) software.

RESULTS

Mean urinary magnesium excretion at baseline was 4.24 ± 1.65 mmol/24 h for men and 3.54 ± 1.40 mmol/24 h for women. The baseline characteristics of the study population, by sex-specific quintiles of urinary magnesium excretion, are shown in Table 1. Urinary magnesium excretion was inversely associated with age, systolic BP, and triglyceride and CRP concentrations and positively with HDL cholesterol and urinary excretion of calcium, sodium, potassium, albumin, and creatinine. In participants with higher urinary magnesium excretion, the prevalence of regular alcohol consumption was higher, whereas the prevalence of hypertension was lower. Urinary magnesium excretion was weakly and inversely correlated with plasma magnesium (r = −0.03, P = 0.02). Plasma magnesium was positively associated with other plasma cations and albumin (see Supplemental Table S1 under “Supplemental data” in the online issue).

During a median follow-up of 10.5 y (IQR: 9.9–10.8 y), we documented 462 cases of IHD. The association between quintiles of urinary magnesium excretion and risk of IHD is shown in Table 2. Urinary magnesium excretion was associated with a reduced risk of IHD in a nonlinear fashion after adjustment for age and selected IHD risk factors (multivariable model 1; P-curvature < 0.001) and excretion of urinary cations and creatinine (multivariable model 2; P-curvature = 0.01). Further adjustment for potential intermediate variables had a very modest effect (multivariable model 3). A restricted multivariable cubic spline plot for urinary magnesium excretion and adjusted risk of IHD is presented in Figure 1, which shows an increased risk especially at the lower range of urinary magnesium excretion.

Because of the nonlinear association between urinary magnesium excretion and IHD risk, we combined the upper 4 quintiles of magnesium excretion in all further analyses because the increased risk of IHD was observed only for the lowest quintile. Compared with the highest 4 quintiles, subjects in the lowest quintile of urinary magnesium excretion had a higher risk of IHD (HR: 1.60; 95% CI: 1.28, 2.00) after adjustment (multivariable model 2). When the lowest quintile of urinary magnesium excretion was further divided into 2 deciles, the lowest decile (HR: 1.73; 95% CI: 1.32, 2.27) and second-lowest decile (HR: 1.48; 95% CI: 1.10, 1.98) both had an increased risk of IHD compared with the remainder of the cohort. The increased risk of IHD associated with low urinary magnesium excretion was consistent across sex and several select IHD risk factors (Figure 2), without evidence of an interaction within subgroups (P-interaction >0.22 for all). The increased risk also persisted when we restricted the analyses to specific events of

TABLE 2

HRs (95% CIs) for IHD and mortality according to ranges of sex-specific quintiles of urinary magnesium excretion

<table>
<thead>
<tr>
<th>Sex-specific quintiles of urinary magnesium excretion (mmol/24 h)</th>
<th>1 (M: &lt;2.93; F: &lt;2.45)</th>
<th>2 (M: 2.93–3.74; F: 2.45–3.21)</th>
<th>3 (M: 3.75–4.50; F: 3.22–3.79)</th>
<th>4 (M: 4.51–5.46; F: 3.80–4.62)</th>
<th>5 (M: &gt;5.46; F: &gt;4.62)</th>
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</thead>
<tbody>
<tr>
<td>Fatal and nonfatal IHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>137</td>
<td>82</td>
<td>91</td>
<td>73</td>
<td>79</td>
</tr>
<tr>
<td>Person-years</td>
<td>14,116</td>
<td>14,564</td>
<td>14,541</td>
<td>14,643</td>
<td>14,681</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.57 (1.21, 2.05)</td>
<td>0.86 (0.64, 1.16)</td>
<td>1.00 (Ref)</td>
<td>0.90 (0.66, 1.22)</td>
<td>1.09 (0.81, 1.48)</td>
</tr>
<tr>
<td>Multivariable model 1</td>
<td>1.59 (1.21, 2.08)</td>
<td>0.91 (0.66, 1.29)</td>
<td>1.00 (Ref)</td>
<td>0.91 (0.67, 1.23)</td>
<td>1.05 (0.78, 1.43)</td>
</tr>
<tr>
<td>Multivariable model 2</td>
<td>1.50 (1.13, 1.99)</td>
<td>0.87 (0.64, 1.17)</td>
<td>1.00 (Ref)</td>
<td>0.91 (0.67, 1.25)</td>
<td>1.10 (0.80, 1.51)</td>
</tr>
<tr>
<td>Multivariable model 3</td>
<td>1.44 (1.07, 1.92)</td>
<td>0.85 (0.62, 1.16)</td>
<td>1.00 (Ref)</td>
<td>0.87 (0.63, 1.20)</td>
<td>1.05 (0.75, 1.47)</td>
</tr>
<tr>
<td>IHD-related mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>41</td>
<td>23</td>
<td>20</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Person-years</td>
<td>14,607</td>
<td>14,886</td>
<td>14,960</td>
<td>14,997</td>
<td>15,002</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>2.03 (1.19, 3.45)</td>
<td>1.07 (0.59, 1.95)</td>
<td>1.00 (Ref)</td>
<td>0.70 (0.33, 1.46)</td>
<td>1.22 (0.63, 2.36)</td>
</tr>
<tr>
<td>Multivariable model 1</td>
<td>2.01 (1.17, 3.43)</td>
<td>1.12 (0.62, 2.05)</td>
<td>1.00 (Ref)</td>
<td>0.70 (0.34, 1.47)</td>
<td>1.21 (0.62, 2.35)</td>
</tr>
<tr>
<td>Multivariable model 2</td>
<td>1.71 (0.97, 3.00)</td>
<td>1.05 (0.57, 1.93)</td>
<td>1.00 (Ref)</td>
<td>0.74 (0.35, 1.56)</td>
<td>1.44 (0.72, 2.87)</td>
</tr>
<tr>
<td>Multivariable model 3</td>
<td>1.59 (0.88, 2.86)</td>
<td>0.97 (0.52, 1.82)</td>
<td>1.00 (Ref)</td>
<td>0.66 (0.30, 1.48)</td>
<td>1.44 (0.70, 2.96)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>131</td>
<td>117</td>
<td>101</td>
<td>80</td>
<td>69</td>
</tr>
<tr>
<td>Person-years</td>
<td>14,607</td>
<td>14,886</td>
<td>14,960</td>
<td>14,997</td>
<td>15,002</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.31 (0.99, 1.67)</td>
<td>1.07 (0.82, 1.40)</td>
<td>1.00 (Ref)</td>
<td>0.89 (0.66, 1.20)</td>
<td>0.93 (0.68, 1.26)</td>
</tr>
<tr>
<td>Multivariable model 1</td>
<td>1.25 (0.96, 1.63)</td>
<td>1.12 (0.85, 1.47)</td>
<td>1.00 (Ref)</td>
<td>0.90 (0.67, 1.22)</td>
<td>0.91 (0.66, 1.22)</td>
</tr>
<tr>
<td>Multivariable model 2</td>
<td>1.04 (0.79, 1.38)</td>
<td>1.02 (0.77, 1.33)</td>
<td>1.00 (Ref)</td>
<td>0.93 (0.69, 1.26)</td>
<td>1.00 (0.72, 1.38)</td>
</tr>
</tbody>
</table>

1 HRs were derived from Cox proportional hazard models. Age-adjusted models took into account the sampling design of the study (presence or absence of a urinary albumin excretion <10 mg/L) by specifying stratum-specific baseline hazard functions. Multivariable model 1 was an age-adjusted model and was additionally adjusted for smoking status, sex, BMI, ratio of total to HDL cholesterol, parental history of IHD, and alcohol consumption. Multivariable model 2 was adjusted as for model 1 plus urinary calcium, sodium, potassium, and creatinine. Multivariable model 3 was adjusted as for model 2 plus potential intermediates of the association between urinary magnesium excretion and IHD incidence and mortality (C-reactive protein, systolic blood pressure, antihypertensive therapy, type 2 diabetes, urinary albumin, ischemic ST-T segment changes, and prolonged QT interval). IHD, ischemic heart disease; Ref, reference.

2 Derived from a Cox proportional hazard model by using urinary magnesium excretion as a continuous variable.

3 Derived by using the likelihood ratio test, comparing nested Cox proportional hazard models with a linear or linear and cubic spline terms.
myocardial infarction (HR: 1.50; 95% CI: 1.06, 2.14), ischemic heart disease (HR: 1.49; 95% CI: 0.99, 2.24), or revascularization procedures (HR: 1.90; 95% CI: 1.25, 2.90) separately in a comparison of quintile 1 with quintiles 2–5. We next evaluated the possibility of reverse causation by repeating the analysis excluding cases that occurred within the first 2 y of follow-up. This did not change the results (HR: 1.61; 95% CI: 1.25, 2.08). The increased IHD risk associated with low magnesium excretion remained when we excluded subjects who may have had a lower magnesium absorption as a result of proton-pump inhibitor use (HR: 1.60; 95% CI: 1.27, 2.90) or altered excretion due to diuretic use (HR: 1.52; 95% CI: 1.21, 1.92). Finally, the higher risk associated with low urinary magnesium excretion modestly attenuated when we reanalyzed the data using complex sampling to correct for the enrichment of subjects with albuminuria (HR: 1.43; 95% CI: 1.03, 1.96).

To explore whether low urinary magnesium excretion was a marker of poor health or underlying disease, we also investigated the association between urinary magnesium excretion and mortality. Similarly to risk of nonfatal and fatal IHD, the lowest quintile of urinary magnesium excretion had an increased risk of IHD-related mortality (HR: 1.70; 95% CI: 1.10, 2.61), but not for mortality related to cancer (HR: 0.91; 95% CI: 0.65, 1.27) or all-cause mortality (HR: 1.05; 95% CI: 0.84, 1.31) when compared with the upper 4 quintiles.

No associations were observed between plasma magnesium and risk of fatal and nonfatal IHD, IHD-related mortality, or all-cause mortality (Table 3). Plasma magnesium was also not associated with risk of fatal and nonfatal IHD when a lower cutoff point of <0.75 mmol/L (HR: 1.13; 95% CI: 0.80, 1.59) or <0.70 mmol/L (HR: 1.74; 95% CI: 0.95, 3.20) was used when compared with the reference category (quintile 3) (multivariable model 2). Furthermore, we found no evidence for interactions in the association between plasma magnesium and risk of fatal and nonfatal IHD by factors that may have influenced renal magnesium handling, ie, the presence or absence of hypertension, type 2 diabetes, and chronic kidney disease (P-interaction >0.18 for all). In sensitivity analyses, we found no associations between plasma magnesium and risk of fatal and nonfatal IHD when we excluded subjects receiving proton-pump inhibitor therapy, with excessive alcohol consumption, or receiving diuretic therapy.

DISCUSSION

In this prospective population-based study of men and women, urinary magnesium excretion—a biomarker of dietary magnesium uptake—was associated with risk of IHD in a nonlinear and threshold fashion. Low urinary magnesium excretion was associated with a 60% increased risk of IHD compared with the remainder of the cohort. No associations were observed between plasma magnesium and risk of IHD.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male (N=3741)</th>
<th>Female (N=3923)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>≤60 (N=6023)</td>
<td>&gt;60 (N=1641)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>≤27 (N=4921)</td>
<td>&gt;27 (N=2743)</td>
</tr>
<tr>
<td>Smoking</td>
<td>No (N=4742)</td>
<td>Yes (N=2922)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No (N=5249)</td>
<td>Yes (N=2415)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>No (N=5351)</td>
<td>Yes (N=2313)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No (N=7417)</td>
<td>Yes (N=247)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>≤3.0 (N=5906)</td>
<td>&gt;3.0 (N=1758)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>No (N=6337)</td>
<td>Yes (N=1327)</td>
</tr>
</tbody>
</table>

FIGURE 1. Urinary magnesium excretion and risk of IHD. Association estimated by Cox regression based on restricted cubic splines. The median urinary magnesium excretion is the reference standard. Dashed lines indicate the 95% CIs. The model was adjusted for age, smoking status, sex, BMI, ratio of total to HDL cholesterol, parental history of IHD, alcohol consumption, and urinary calcium, sodium, potassium, and creatinine excretion. The spline curve is truncated at the first percentile and 99th percentile of the distribution curve (n = 7511). IHD, ischemic heart disease.

FIGURE 2. Urinary magnesium excretion and risk of IHD stratified by selected characteristics. Adjusted HRs and 95% CIs for risk of IHD for the comparison of the lowest quintile with the upper 4 quintiles of urinary magnesium excretion. HRs were derived from Cox proportional hazard models and adjusted for age, smoking status, sex, BMI, ratio of total to HDL cholesterol, parental history of IHD, alcohol consumption, and urinary calcium, sodium, potassium, and creatinine excretion (unless the variable is stratified on). P-interactions were >0.10 for all. *Chronic kidney disease is defined as an estimated glomerular filtration rate <60 mL · min⁻¹ · 1.73 m⁻² or a urinary albumin excretion of ≥30 mg/24 h. IHD, ischemic heart disease.
The observed association with IHD risk appeared to be independent of other important urinary cations, which suggests that the effect is specific for low urinary magnesium. The association between urinary magnesium excretion and disease was confined to IHD morbidity and mortality and was not observed for cancer or all-cause mortality, which reduces the likelihood that low urinary magnesium excretion is a generic marker of poor food intake associated with underlying illnesses. In addition, the association was consistent across strata of sex and several important cardiovascular disease risk factors, with no evidence of any interactions. Taken together, these findings add to the biologic plausibility that low urinary magnesium excretion is a novel marker of increased risk of IHD.

To our knowledge, only the INTERMAP and INTERSALT studies have used 24-h urine collections to measure urinary magnesium excretion with compatible median magnesium excretion ranging between 3.2 and 4.2 mmol/24 h (30). Twenty-four–hour urine collections are an alternative way of assessing magnesium intake, although urinary excretion of magnesium does not necessarily correspond with the actual intake because of incomplete gastrointestinal uptake, it captures the amount of magnesium in food and supplements that has been available and relevant for biological activity in tissues and cells. When subjects are in steady state, as in this cohort of community-dwelling adults, 24-h urinary magnesium excretion will reflect overall magnesium uptake from the gut—the product of overall dietary intake and the fractional absorption rate.

The increased risk of IHD associated with low urinary magnesium excretion complements and extends previous dietary studies showing weak inverse associations (7–10, 12) and autopsy reports of low intracellular magnesium in myocardial tissue after ischemic heart disease (31–34). Several pathways could explain the beneficial role of magnesium on the heart. Intracellular magnesium acts as a cofactor for sodium and potassium ATPase, which is responsible for maintaining muscle membrane potential and action potential propagation (35). As a consequence, magnesium deficiencies can result in muscle weakness, cramping, and spasm (36). Also, magnesium inhibits tonic contraction of human coronary arteries (37), which could prevent coronary spasm (38) and, in turn, ischemic heart disease. Experimental studies have shown that low magnesium intake causes arrhythmias, such as supraventricular ectopy (39) and atrial fibrillation (40), which ultimately may explain the increased risk of sudden cardiac death associated with low magnesium (41, 42). However, adjustment for electrocardiogram deviations at baseline (ie, ST-T segment changes and QTc interval prolongation) did not affect the observed association, possibly because these factors are more important in sudden cardiac death rather than nonfatal cardiac events.

Besides magnesium’s muscle-specific effects, in vitro studies have linked magnesium to inhibition of platelet aggregation (43) and enhanced synthesis of nitric oxide—a potent endothelial vasodilator (44). This seems to correspond with magnesium’s favorable effect on some endothelial markers (1, 2). In addition, clinical trials have reported impaired glycemic control (40) after magnesium depletion and lower C-peptide concentrations (45) after magnesium supplementation that may account for the lower risk of diabetes associated with dietary magnesium (5). Antiatherosclerotic properties of magnesium through lipoproteins, however, seem unlikely because dietary magnesium manipulation does not favorably alter cholesterol concentrations (40, 46).
In previous studies with comparable cutoff values for the lowest category, circulating magnesium was also not associated with total IHD (10, 11), although it was associated with IHD mortality (11) and with sudden cardiac death (41, 42) in particular. In this analysis, we were unable to evaluate the later association. Similarly to the correlation between dietary and circulating magnesium studies (10, 42), we noted a very weak and even inverse correlation between magnesium in urine and plasma. Despite being responsive to magnesium supplementation (17), plasma magnesium may also reflect non-dietary sources, particularly when magnesium intake is low. In a 78-d trial of magnesium depletion among women, serum magnesium concentrations paradoxically increased relative to baseline after an initial decrease (40), perhaps reflecting increased mobilization from internal magnesium stores from muscle and bone. Regardless, our results suggest that urinary magnesium excretion is apt to be a more useful marker of effective magnesium balance than are plasma concentrations.

In 2 recent iterations of NHANES (47, 48), as much as 20% of the US population did not meet the Recommended Dietary Allowances of magnesium intake set by the Institute of Medicine (28). The prevalence of inadequate magnesium intake by millions of US adults combined with the substantial increased risk of IHD associated with low urinary magnesium excretion—an indirect marker of dietary magnesium uptake—highlights an important, yet under-recognized, potential for primary prevention.

The strengths of our study were the long duration of follow-up, the large number of subjects with both urinary and plasma magnesium measurements, extensive information on subject characteristics, medication use and potential confounders, and the use of confirmed events of IHD. Some limitations warrant consideration. The 24-h urinary collections provided no information about the dietary origin of the excreted magnesium. Magnesium is abundant in green leafy vegetables and whole grains, and diets low in these food groups could in turn have accounted for the increased risk of IHD rather than the low magnesium excretion itself. However, the observed association appeared to be independent of (inadequate excretion of) potassium—another cation highly present in such healthy and fiber-rich foods. Second, urinary magnesium excretion and plasma magnesium were measured only at baseline. Therefore, changes in urinary or plasma magnesium over time could not be taken into account. However, this is expected to lead to under- rather than overestimation of the true association between these variables and IHD events. Finally, as with any observational study, residual confounding could, in part, explain the association between magnesium excretion and risk of IHD, despite the substantial number of factors that we adjusted for.

In conclusion, low urinary magnesium excretion as a marker of low dietary magnesium uptake was associated with an increased risk of IHD in this prospective cohort of men and women. The association appeared to be independent of other urinary cations and traditional IHD risk factors and was limited to risk of IHD morbidity and mortality. Given the substantial number of individuals who have inadequate magnesium intakes, an increased consumption of magnesium-rich foods, particularly by those with the lowest urinary magnesium excretion, may be a promising approach for the primary prevention of IHD.

The authors’ responsibilities were as follows—MMJ, RTG, KJM, and SJLB: concept and design of the study; RTG, PavH, GN, and SJLB: acquisition of the data; MMJ: statistical analyses and writing of the first draft of the manuscript; and RTG, KJM, PavH, MGJ, EJMFe, GN, and SJLB: critical review and advice and consultation throughout. None of the authors reported a conflict of interest. The funders of the work had no role in the conception, execution, or analysis of the research and had no role in drafting the manuscript.

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