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Results from the Atherosclerosis Risk in Communities study suggest that low serum magnesium is associated with incident kidney disease

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Abstract

Low serum magnesium has been associated with kidney function decline in persons with diabetes as well as cardiovascular disease in the general population. Since the association of serum magnesium with incident kidney disease in the general population is unknown, we assessed this in 13,226 participants (aged 45 to 65) in the Atherosclerosis Risk in Communities study with baseline estimated glomerular filtration rate of at least 60 ml/min/1.73m² in years 1987–89 and followed through 2010. The risks for incident chronic kidney disease (CKD) and end-stage renal disease (ESRD) associated with baseline total serum magnesium levels were evaluated using Cox regression. There were 1,965 CKD and 208 ESRD events during a median follow-up of 21 years. In adjusted analysis, low serum magnesium levels (0.7mmol/L or less) had significant associations with incident CKD and ESRD compared with the highest quartile with adjusted hazard ratio of 1.58 (95% CI: 1.35–1.87) for CKD and 2.39 (95% CI: 1.61–3.56) for ESRD. These associations remained significant after excluding users of diuretics and across subgroups stratified by hypertension, diabetes, and self-reported race. Thus, in a large sample of middle-aged adults, low total serum magnesium was independently associated with incident CKD and ESRD. Further studies are needed to determine whether modification of serum magnesium levels might alter subsequent incident kidney disease rates.

Keywords

renal failure; chronic kidney disease; end-stage renal disease; magnesium

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Introduction

Chronic kidney disease (CKD) affects over 10% of U.S. adults¹ and is associated with excess mortality risk² and substantial economic cost, including 18% of the Medicare fee-for-service expenditure in 2011.¹ Although some risk factors for CKD have been established, including diabetes, hypertension, older age, and family history of CKD,^{3, 4} the identification of additional, novel risk factors for CKD may improve our understanding of the pathogenesis of CKD and allow the development of new CKD prevention strategies.

Magnesium deficiency is an emerging public health concern, even in developed countries.⁵ Several lines of evidence suggest low serum magnesium may be a risk factor for incident kidney disease. Low magnesium has been associated with higher production of inflammatory and pro-atherogenic cytokines in endothelial cells,⁶ a pathway that could contribute to kidney function decline. Indeed, low serum magnesium has been associated with kidney function decline in CKD patients⁷ and patients with diabetes^{8, 9} as well as decreased allograft survival in kidney transplant recipients,¹⁰ cardiovascular disease in the general population,¹¹ and mortality in hemodialysis patients.¹² However, lower serum magnesium levels are common in persons at high risk of kidney disease, such as those with diabetes or who are treated with diuretics for hypertension;^{13, 14} thus, whether low serum magnesium is a cause or consequence of CKD risk factors and/or treatment is unclear. Therefore, we investigated the association of total serum magnesium levels with incident CKD and ESRD in participants with estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m² in the Atherosclerosis Risk in Communities (ARIC) study, a community-based cohort, with particular attention to subgroups by diabetes status and diuretic use.

Results

Study population characteristics

Table 1 presents the baseline characteristics of the study population by five serum magnesium levels (Quartiles [Q] 1 to 4 with Q1 subdivided into Q1a [0.25–0.7mmol/L] and Q1b [0.75mmol/L]). Individuals with lower total serum magnesium levels were more likely to be African-American and female. They also tended to have lower education and income levels, higher prevalence of diabetes and hypertension, higher levels of triglycerides, and lower serum albumin levels. Among individuals with hypertension, those with lower total serum magnesium levels tended to have higher thiazide or loop diuretic use.

During a median of 21 years of follow-up, 1,965 incident CKD events and 208 ESRD events occurred in 13,226 individuals. The Kaplan-Meier curves for cumulative incidence of CKD or ESRD by five levels of serum magnesium are presented in Figures 1 and 2, respectively.

Association between Serum Magnesium and Incident CKD

Incident CKD was two-fold higher in individuals in the lowest serum magnesium category (Q1a, 0.7mmol/L) than in those in Q4 (0.9mmol/L) (13.09 versus 6.23 per 1000 person-years, Table 2). There was a graded and inverse relationship between serum magnesium levels and incident CKD (p trend <0.001). This graded relationship remained significant in all multivariable models (p trend <0.001 , Table 3), including those adjusting for diabetes and

diuretic use. With adjustment for race-center, age, gender, eGFR, diabetes and hypertension medication status (Model 2), individuals in the lowest quartile (Q1a or Q1b) of serum magnesium levels had over 1.5 times higher risk of developing CKD than those in Q4 (Q1a vs. Q4, adjusted hazard ratio [HR] 1.75, 95% confidence interval [CI]: 1.49–2.06; Q1b vs. Q4, adjusted HR 1.58, 95% CI: 1.36–1.83). Further adjustment for education levels, household income, medical insurance status, prevalent coronary heart disease, dyslipidemia, body mass index, smoking status, and serum albumin (Model 3) resulted in slight attenuation of the association (Q1a vs. Q4, adjusted HR 1.58, 95% CI: 1.35–1.87; Q1b vs. Q4, adjusted HR 1.47, 95% CI: 1.27–1.71; p for trend<0.001).

Significant associations between low serum magnesium and incident CKD were also found after excluding users of thiazide or loop diuretics as well as within subgroups stratified by prevalent hypertension or diabetes status or self-reported race (p for trend<0.001 for all subgroups, Supplementary Table 1). After excluding users of thiazide or loop diuretics, the association between low serum magnesium and incident CKD remained significant (Q1a vs Q4: adjusted HR 1.57, 95% CI: 1.31–1.89, p -trend< 0.001). Between individuals with and without prevalent hypertension, the associations between serum magnesium and incident CKD were not significantly different (no prevalent hypertension, Q1a vs Q4: adjusted HR 1.52, 95% CI: 1.18–1.96; prevalent hypertension, Q1a vs Q4: adjusted HR 1.63, 95% CI: 1.31–2.04). Between individuals with and without prevalent diabetes, the association between serum magnesium and incident CKD was slightly higher in individuals with prevalent diabetes (Q1a vs Q4: adjusted HR 2.12, 95% CI: 1.42–3.17) than in those without (adjusted HR 1.48, 95% CI: 1.22–1.79, p for interaction 0.05). Between African Americans and European Americans, the association between serum magnesium and incident CKD was slightly higher in African Americans (Q1a vs. Q4: adjusted HR 1.93, 95% CI: 1.43–2.62) than in European Americans (adjusted HR 1.35, 95% CI: 1.09–1.67, p for interaction 0.02), although the associations were similar at higher levels of serum magnesium (African Americans, Q1b vs. Q4: adjusted HR 1.47, 95% CI: 1.08, 2.01; European Americans, Q1b vs. Q4: adjusted HR 1.53, 95% CI: 1.30, 1.82).

Significant associations between low serum magnesium and incident CKD were also found in sensitivity analyses (Supplementary Table 1). The associations between serum magnesium levels and incident CKD were similar in analyses treating incident diabetes and hypertension during the follow-up period as time-varying covariates. In addition, the association between serum magnesium and incident CKD was largely unaffected by adjustment for serum calcium, phosphorus, and potassium. Serum magnesium had low correlations with calcium ($r=0.03$) and phosphorus ($r=0.04$), whereas serum magnesium and potassium had moderate correlation ($r=0.23$). The association between serum magnesium and incident CKD defined solely using visit-based eGFR captured over the first 9-years of follow-up was similar to the association using the composite definition. Lastly, using the 3-year visit (visit 2) as the baseline and including adjustment for hemoglobin A1c (HbA1c), parathyroid hormone, and high-sensitivity C-reactive protein (hsCRP) levels resulted in similar association between serum magnesium and incident CKD. In this latter analysis, individuals in Q1a (serum magnesium levels 0.7mmol/L) were approximately 1.5 times more likely to develop CKD than those in Q4 (adjusted HR 1.56, 95% CI: 1.28–1.89).

Association between serum Magnesium and Incident ESRD

Incident ESRD was six times higher in individuals in the lowest serum magnesium category (Q1a, 0.7mmol/L) than those in Q3 and Q4 combined (0.85mmol/L) (2.62 versus 0.44 per 1000 person-years, Table 2). Q3 and Q4 of serum magnesium levels were combined as the reference group in this analysis to ensure adequate number of individuals in each subgroup in multivariate analysis (see Methods section for details). The graded and inverse relationship between serum magnesium levels and incident ESRD was significant in all multivariate models (p trend<0.001, Table 4). With the adjustment of race-center, age, gender, eGFR, diabetes, and hypertension medication status (Model 2), individuals in Q1a (0.7mmol/L) had approximately 2.5 times higher risk of developing ESRD than those in Q3 and Q4 combined (adjusted HR 2.66, 95% CI: 1.80–3.93, p for trend<0.001). After further adjustment for other risk factors (Model 3), the association between serum magnesium and incident ESRD remained similar (Q1a vs. Q3 and Q4, adjusted HR 2.39, 95% CI: 1.61–3.56, p for trend<0.001).

In subgroup analyses excluding users of thiazide or loop diuretics, or stratified by prevalent hypertension or diabetes status or self-reported race, the association between the lowest serum magnesium category (Q1a, 0.7mmol/L) and ESRD was significant in all subgroups, and there were no statistically significant differences between subgroups (p for interaction for all >0.15, Supplementary Table 2). Adjustment for diabetes and hypertension status as time-varying covariates did not attenuate the associations between lower serum magnesium and the risk of ESRD (Q1a vs. Q3&4, adjusted HR 3.18, 95% CI: 2.16–4.68). Similarly, including serum calcium, phosphorus, and potassium, and as covariates or controlling for HbA1c, parathyroid hormone, and hsCRP levels with the 3-year visit (visit 2) as the baseline did not materially alter the association between serum magnesium and incident ESRD.

Discussion

Main Findings

In a community-based cohort of European and African Americans with eGFR ≥ 60 mL/min/1.73m², low serum magnesium levels were associated with incident CKD and ESRD after controlling for potential socio-economic and clinical confounders of kidney function decline. Individuals in the lowest serum magnesium category (Q1a, 0.7mmol/L) were approximately 1.6 times more likely to develop incident CKD than those in Q4 (0.9mmol/L) and 2.4 times more likely to develop ESRD than those in Q3 and Q4 combined (0.85mmol/L). These associations did not appear to be confounded by prevalent diabetes or the use of diuretics for hypertension treatment, nor did they appear mediated by incident diabetes or hypertension. Indeed, significant associations between low serum magnesium and incident CKD or ESRD existed across all subgroups stratified by prevalent diabetes and hypertension status, and self-reported race.

In the Context of the Literature

To our knowledge, this is the first study to show a prospective association of low serum magnesium with incident CKD and ESRD in a community-based cohort with eGFR ≥ 60 mL/min/1.73m². Several clinical-based studies have shown associations between low

serum magnesium levels and poor kidney outcomes. In patients with type 2 diabetes, low serum magnesium levels were associated with kidney function decline or ESRD.^{8,9} In critically ill patients with acute kidney injury, serum magnesium levels <0.7mmol/L were associated with non-recovery of kidney function.¹⁵ In kidney transplant recipients with chronic cyclosporine nephrotoxicity, serum magnesium levels <0.82mmol/L were associated with decreased graft survival.¹⁰ The present study expands upon prior work by investigating the association between serum magnesium and kidney function in a population-based cohort, identifying significant association overall and in individuals with and without prevalent diabetes or hypertension.

Although this study is observational and thus cannot provide evidence of a causal relationship between magnesium and adverse kidney outcomes, the mechanism underlying the association merits further investigation. Previous studies suggest serum magnesium may influence kidney function through the regulation of vascular and endothelial function.¹⁶ The rate of circulating magnesium transport into a cell varies depending on tissue and cell type.¹⁷ The endothelial cell, which expresses the magnesium transporter TRPM7,¹⁸ may be more readily influenced by circulating magnesium. In vitro studies have shown that low extracellular magnesium levels inhibit endothelial cell proliferation¹⁹ and promote the expression of inflammatory biomarkers.⁶ Low magnesium levels have also been shown to promote vascular calcification in both in vitro²⁰⁻²³ and in vivo studies.²⁰ Further, serum magnesium levels may affect the endothelium through a thrombotic process, since low circulating magnesium levels increase platelet aggregation²⁴⁻²⁶ and have a pro-thrombotic effect in animal studies.^{27, 28} Chronic inflammation and hemostatic biomarkers have been linked to kidney function decline.²⁹⁻³³

If circulating magnesium has a causal role in the regulation of vascular and endothelial functions, which, in turn, have been implicated in the development of chronic diseases, then low circulating magnesium levels could potentially contribute to disease in multiple organs in a parallel manner. Endothelial dysfunction has been linked to insulin resistance,^{34, 35} and vascular calcification has been recognized as a risk factor for coronary heart disease.³⁶ Low serum magnesium is an independent risk factor of diabetes,³⁷ hypertension,³⁸ and cardiovascular disease.¹¹ The potential regulatory role of serum magnesium on vascular and endothelial functions may partly explain these independent prospective associations between serum magnesium and multiple chronic diseases. On the other hand, serum magnesium levels are determined by a constellation of factors, including dietary intake and medications, and are regulated by multiple organs. Therefore, low total serum magnesium levels might be a marker of disturbances in metabolism or dysregulation of other solutes, which may lead to nephrotoxicity in independent ways.³⁹

Strengths and Limitations

Some limitations of our study warrant mention. This study is observational and thus cannot provide experimental mechanistic insight on the association between magnesium and adverse kidney outcomes. The main analysis was based on a one-time measure of serum magnesium with a measurement precision limited to 0.05 mmol/L. Measures of albuminuria were not available for adjustment or defining CKD. Biomarkers of chronic inflammation or

endothelial dysfunction were not available to evaluate the hypothesized pathway by which serum magnesium might confer renal risk. We cannot exclude the possibility of residual confounding from diuretic use and diabetes, although relevant variables were controlled for in the analysis. The strengths of our study include a large sample size with a follow-up period of over 20 years without weakening of the magnesium association, rigorous measurement of many potential confounding variables, and extensive subgroup and sensitivity analyses for evaluating potential confounding and mediating effects.

In summary, we have identified low serum magnesium as an independent risk factor for incident CKD and ESRD in a large cohort of middle aged adults with eGFR $< 60 \text{ mL/min/1.73m}^2$. Associations were robust to multiple sensitivity analyses. Further research is required to determine if low total serum magnesium is itself nephrotoxic. If so, our findings suggest that magnesium levels may be a novel therapeutic target for the prevention of CKD.

Methods

Study Population

The ARIC Study is a community-based prospective observational study of 15,792 individuals between the ages of 45 and 64 years. Participants were drawn from a probability-based sample from 4 US communities (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD). Participants took part in examinations starting with the baseline visit (visit 1) between 1987 and 1989. Details of the ARIC cohort have been published elsewhere.⁴⁰

The analyzed sample of 13,226 individuals included participants with baseline eGFR $< 60 \text{ mL/min/1.73m}^2$, fasting time ≥ 8 hours for blood drawn, and with data in all covariates for multivariate analysis. Details on the numbers of individuals not included in analysis are reported in Supplementary Table 3.

Incident CKD and ESRD Assessment

Incident CKD was defined using a validated definition as a composite outcome of: 1) a drop in eGFR to a level $< 60 \text{ mL/min/1.73m}^2$ at the 3- or 9-year follow-up visits (visits 2 and 4) with a concomitant 25% decline in eGFR from baseline (based on the Kidney Disease: Improving Global Outcome definition for CKD progression⁴¹), 2) a hospitalization or death with a diagnostic code indicating CKD (based on the observation that incident CKD was strongly associated with non-attendance at subsequent study visits⁴²), or 3) incident ESRD. Incident ESRD was identified through linkage with the U.S. Renal Data System (USRDS), a national ESRD registry that obtains information on all new ESRD patients through the nephrologist-completed Centers for Medicare & Medicaid Services Medical Evidence Report. In the ARIC study, active surveillance for hospitalizations and death is performed for all participants, and 26 *International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)* discharge diagnostic codes are abstracted (*ICD-10-CM* codes in the case of deaths).⁴⁰ The ICD-9-CM and ICD-10-CM codes used for classifying CKD-related events are reported in Supplementary Table 4. The sensitivity of discharge diagnostic code is low (35.5%), but the specificity is high at 95.7%, indicating few false positives.⁴²

Most incident CKD events in the present study were captured using hospitalization diagnostic codes after the 9-year visit. Of the 1965 incident CKD events reported in the present study, 1200 events (61%) were captured solely by the diagnostic codes. Of these 1200 incident CKD events, 1095 events (91%) occurred after the 9-year visit. The median follow-up time of these 1200 incident CKD events was 17 years (interquartile range: 7.2 years). Participants who died without an event, were lost to follow-up, or survived to the end of 2010 without an event were censored.

Measure of Serum Magnesium and Other Variables

Total serum magnesium was measured using the metallochromic dye, Calmagite, based on the procedure of Gindler and Heth.⁴³ The measurement precision was 0.05mmol/L. The coefficient of variation based on split specimens sent one week apart to the laboratory was 3%. The short term (<30 days) intra-individual variability as a proportion of the total variance of serum magnesium was 0.13.⁴⁴ The intra-class correlation of serum magnesium between the baseline and 3-year visits was 0.45.

Prevalent diabetes mellitus was defined as fasting glucose level at least 126 mg/dL, nonfasting glucose level at least 200 mg/dL, or having a self-reported diagnosis of or treatment for diabetes. Blood pressure measures were calculated from the last 2 measures of three seated blood pressure measures performed by certified technicians using a random-zero sphygmomanometer after the participant experienced 5 minutes of rest. Self-reported antihypertensive medication use was verified by the inspection of medication bottles. Hypertension was defined as systolic blood pressure >140mmHg or diastolic blood pressure >90mmHg or having a self-reported diagnosis of or treatment for hypertension. Hypertension medication status was coded as a four-category variable: no prevalent hypertension, hypertension with no medication, hypertension treated with thiazide or loop diuretics, and hypertension treated with other medications.

Prevalent coronary heart disease was defined as having a self-reported physician diagnosis or a myocardial infarction revealed on the electrocardiogram conducted during the baseline visit. Total plasma cholesterol and triglyceride levels were measured using enzymatic methods. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation⁴⁵ (excluding those with incalculable LDL because of triglyceride values >400 mg/dL). Smoking status was based on self-reported. Serum creatinine based eGFR was calculated using the equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)⁴⁶ after standardizing the serum creatinine measures obtained from modified kinetic Jaffe assay.⁴⁷

Statistical Analysis

Serum magnesium levels were categorized into quartiles. Given that 52% of the incident ESRD cases were in Q1, we further divided Q1 into sub-quartiles Q1a (< 0.7 mmol/L) and Q1b (0.7-0.75mmol/L). Baseline characteristics were compared by the five categories of serum magnesium levels using t-tests for non-skewed continuous variables, Wilcoxon tests for skewed continuous variable, and Chi-square tests for categorical variables. Kaplan-Meier estimates were plotted by serum magnesium categories. Cox proportional hazards regression

was used to estimate hazard ratios and 95% confidence intervals for incident CKD or ESRD by the five categories of serum magnesium levels. P-values for trend were obtained by coding the five categories of serum magnesium as an ordinal variable with values from 0 to 4. Proportional hazard analyses were performed using SAS 9.3. All other analyses were conducted using R.

Using Q4 as the reference group, we estimated the risk for incident CKD associated with lower serum magnesium levels in three proportional hazard regression models. The covariates were selected *a priori* based on literature review^{41, 48-51} and their availability in the ARIC study. Model 1 controlled for self-reported race, age, sex, and center. Model 2 added baseline eGFR, diabetes status, and hypertension medication status, well established risk factors of kidney function decline.⁴¹ Model 3 added other baseline covariates: education levels, household income, health insurance status, systolic blood pressure, prevalent coronary heart disease, smoking status, log-transformed triglycerides, high-density lipoprotein cholesterol level (HDL-C), log-transformed low density lipoprotein cholesterol level (LDL-C), and serum albumin. Although household income was missing in 5% of the population, dropping this variable from model 3 so that the study population included participants with missing household income led to no meaningful difference in results for either incident CKD or incident ESRD. We also considered novel risk factors of CKD that are available in the ARIC study, such as leukocyte count, hemostatic factors, and markers of heart rate variability.^{33, 52, 53} Including these variables as covariates had no meaningful effect on observed associations (data not shown).

Sensitivity analyses within subgroups were performed to evaluate whether the association between serum magnesium and incident CKD might differ by diuretic use, prevalent diabetes or hypertension status, or self-reported race. In addition, low serum magnesium levels have been shown to be associated with incident diabetes³⁷ or hypertension.³⁸ To evaluate potential mediating effects from these two factors, we repeated the analysis for Model 3 using incident diabetes and hypertension status as time-varying covariates. Incident diabetes and hypertension status were obtained from annual phone interviews up to 2010. We also examined whether serum calcium, phosphorus, or potassium might partly account for the association between serum magnesium and incident CKD. We calculated the Spearman correlation between serum magnesium and these three serum minerals and repeated the analysis for Model 3 after adding these serum minerals as covariates. To further consider potential confounding, three additional variables were available at the 3-year visit (visit 2): parathyroid hormone, hemoglobin A1c (HbA_{1c}), a measure of glycemic control, and hsCRP, an acute inflammation biomarker shown to be associated with rapid kidney function decline.³⁰ Therefore, we performed the analysis for Model 3 using the 3-year visit as the baseline and adding parathyroid hormone, HbA_{1c}, and hsCRP as covariates. We evaluated the association between magnesium and incident CKD defined using only visit-based eGFR as a drop in eGFR to a level <60 mL/min/1.73m² at the 3- or 9-year follow-up visits with a concomitant 25% decline in eGFR. A similar analysis defining incident CKD as a drop in eGFR to <60 ml/min/1.73 m² led to no meaningful difference in results (data not shown). Finally, because the proportion of persons with eGFR < 120 ml/min/1.73 m² was

slightly higher in the low magnesium group, we repeated analyses excluding those with eGFR < 120 ml/min/1.73 m², again with no difference in results (data not shown).

For incident ESRD, only four individuals had ESRD events in Q4 (< 0.9 mmol/L) in African-Americans. To ensure each category of serum magnesium had adequate number of events in multivariate analyses, we combined Q3 and Q4 as the reference group for incident ESRD analyses. Otherwise, the analyses for incident ESRD followed the same steps as outlined above for incident CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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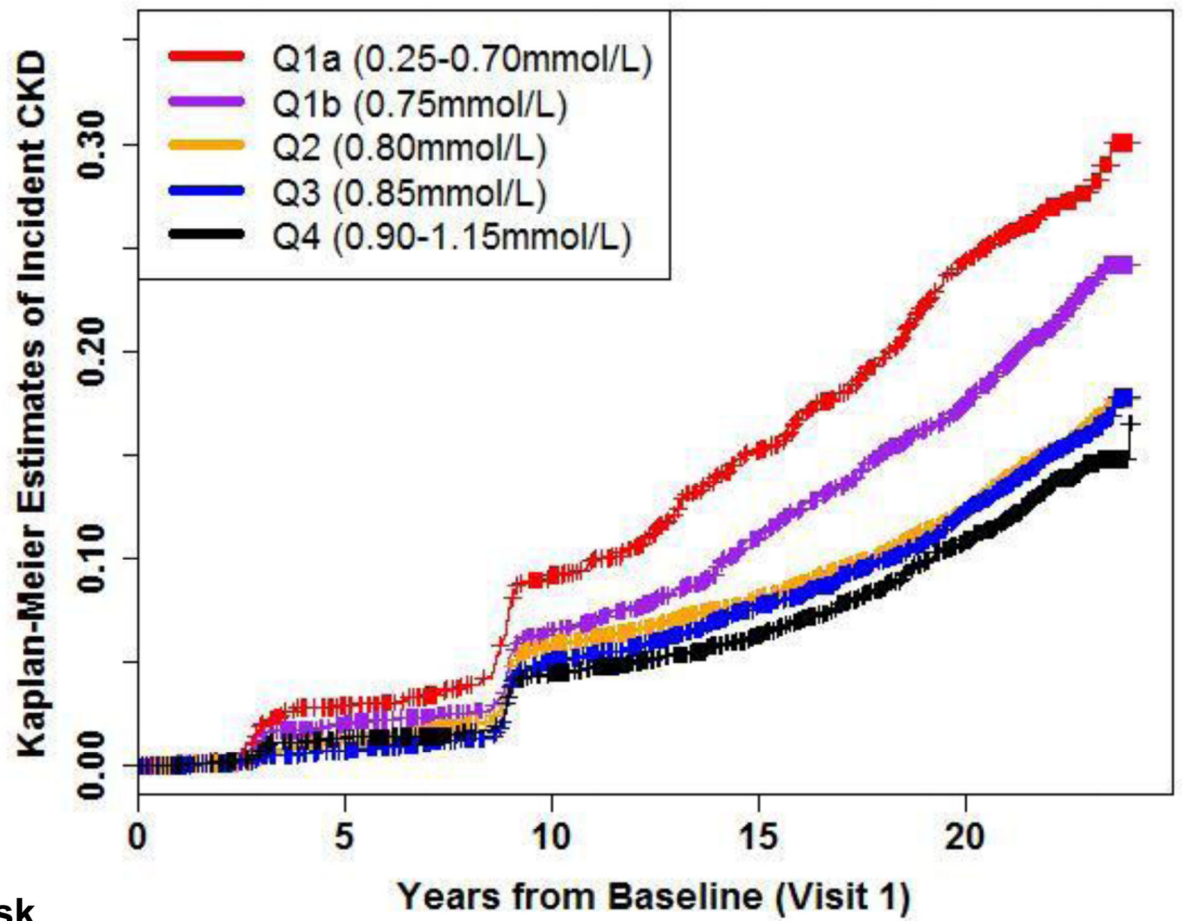
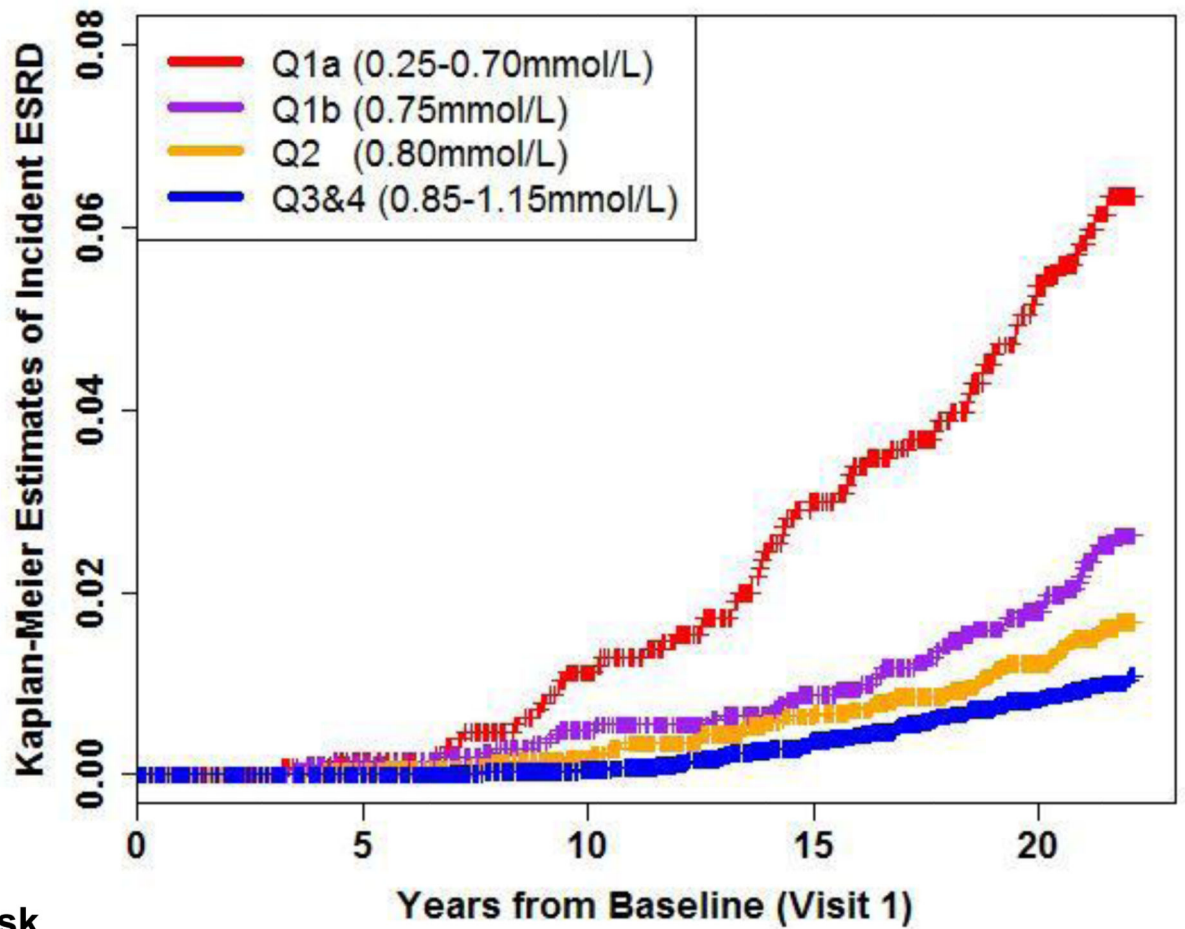


Figure 1.



No. at Risk

	0	5	10	15	20
Q1a	1370	1300	1188	1037	862
Q1b	2140	2062	1939	1751	1524
Q2	3461	3352	3165	2902	2562
Q3&4	6255	6087	5831	5398	4785

Figure 2.

Table 1

Baseline Characteristics of Study Population by Serum Magnesium Levels

	Quartile 1a	Quartile 1b	Quartile 2	Quartile 3	Quartile 4	P-Value
Range (mmol/L)	0.25–0.70	0.75	0.80	0.85	0.90–1.15	
Range (mg/dL)	0.61–1.70	1.82	1.95	2.07	2.19–2.80	
N	1370	2140	3461	3358	2897	
Variable						
Age (year)	54.1±5.8	53.8±5.8	54.0±5.8	54.3±5.7	54.3±5.6	0.04
Men, % (n)	40.3 (552)	40.6 (869)	45.5 (1575)	46.5 (1561)	48.0 (1391)	<0.001
African Americans, % (n)	46.6 (638)	30.3 (648)	23.7 (821)	17.5 (586)	15.8 (458)	<0.001
Education, % (n)						<0.001
< 12 years	31.7 (434)	26.0 (557)	21.4 (739)	20.6 (693)	18.8 (545)	
12–16 years	37.7 (516)	41.3 (883)	41.7 (1444)	42.1 (1414)	42.4 (1229)	
17 years or above	30.7 (420)	32.7 (700)	36.9 (1278)	37.3 (1251)	38.8 (1123)	
Household income, % (n)						<0.001
Under \$12,000	27.3 (374)	17.5 (375)	14.4 (499)	11.1 (372)	10.0 (290)	
\$12,000 to \$24,999	25.7 (352)	24.2 (517)	21.4 (741)	21.0 (706)	21.0 (607)	
\$25,000 or above	47.0 (644)	58.3 (1248)	64.2 (2221)	67.9 (2280)	69.0 (2000)	
Health insurance, % (n)	85.2 (1167)	89.4 (1914)	91.1 (3154)	93.1 (3127)	92.8 (2689)	<0.001
Smoking status, % (n)						0.09
Never	40.1 (549)	42.6 (911)	41.7 (1443)	41.7 (1399)	41.5 (1202)	
Former	30.9 (423)	31.9 (682)	32.2 (1113)	33.3 (1119)	34.0 (984)	
Current	29.1 (398)	25.6 (547)	26.1 (905)	25.0 (840)	24.5 (711)	
Coronary heart disease history, % (n)	6.1 (84)	4.7 (101)	4.3 (148)	4.5 (150)	4.1 (119)	0.04
Prevalent diabetes, % (n)	24.4 (334)	13.4 (287)	9.7 (336)	6.5 (218)	4.9 (143)	<0.001
Body mass index, kg/m²	29.0±6.1	28.3±5.8	27.4±5.2	27.2±4.9	26.9±4.8	<0.001
Triglycerides (mmol/L)	1.3 (0.9, 1.9)	1.3 (0.9, 1.8)	1.2 (0.9, 1.8)	1.2 (0.9, 1.7)	1.2 (0.9, 1.7)	<0.001
eGFR categories, % (n)						<0.001
>=120 ml/min/1.73m ²	12.8 (176)	6.4 (138)	4.3 (149)	2.4 (82)	2.0 (57)	

	Quartile 1a	Quartile 1b	Quartile 2	Quartile 3	Quartile 4
90–119 ml/min/1.73m ²	63.2 (866)	68.2 (1459)	66.0 (2284)	65.5 (2201)	64.0 (1854)
60–89 ml/min/1.73m ²	23.9 (328)	25.4 (543)	29.7 (1028)	32.0 (1075)	34.0 (986)
Systolic blood pressure (mm Hg)	125.8±20.7	122.7±19.0	120.4±18.5	119.2±17.6	118.8±17.4
Diastolic blood pressure (mm Hg)	75.9±11.8	74.2±11.5	73.3±11.2	72.6±10.8	72.9±10.8
Prevalent hypertension category, % (n)					
No prevalent hypertension	48.6 (666)	60.0 (1284)	67.9 (2351)	72.4 (2432)	73.6 (2131)
Hypertension, no medication	9.4 (129)	10.4 (222)	8.7 (300)	8.0 (268)	8.2 (239)
Hypertension, with thiazide or loop diuretics	18.8 (258)	10.5 (225)	7.9 (273)	6.7 (224)	5.9 (170)
Hypertension, with other medications	23.1 (317)	19.1 (409)	15.5 (537)	12.9 (434)	12.3 (357)
High-density lipoprotein cholesterol (mmol/L)	1.2 (1.0, 1.6)	1.3 (1.0, 1.6)	1.3 (1.0, 1.6)	1.3 (1.0, 1.6)	1.3 (1.0, 1.6)
Low-density lipoprotein cholesterol (mmol/L)	3.3 (2.7, 4.1)	3.4 (2.8, 4.1)	3.5 (2.8, 4.2)	3.5 (2.9, 4.2)	3.6 (3, 4.3)
Serum albumin (mg/dL)	3.78±0.3	3.8±0.3	3.9±0.3	3.9±0.3	3.9±0.3
Sodium (mmol/L)	140.3±2.6	140.7±2.4	140.9±2.4	141.1±2.3	141.4±2.3
Potassium (mmol/L)	4.2±0.5	4.3±0.5	4.4±0.5	4.5±0.5	4.6±0.5
Calcium (mg/dL)	9.80±0.5	9.75±0.5	9.77±0.4	9.79±0.4	9.81±0.4
Phosphorus (mg/dL)	3.41±0.5	3.39±0.5	3.42±0.5	3.42±0.5	3.45±0.5

Note: For continuous variables, either mean±standard deviation or median (1st quartile, 3rd quartile) are presented. P-Values were obtained by t-tests for non-skewed continuous variables, Wilcoxon tests for skewed continuous variable, and Chi-square tests for categorical variables.

Table 2

Incident CKD and ESRD by Serum Magnesium Levels

	Quartile 1a	Quartile 1b	Quartile 2	Quartile 3	Quartile 4	Total
Serum magnesium range (mmol/L)	0.25–0.70	0.75	0.80	0.85	0.90–1.15	
CKD Events	306	397	465	447	350	1965
Person-years	23369	39110	65136	64001	56159	247775
Incidence per 1000 person-years	13.09	10.15	7.14	6.98	6.23	7.93
Serum magnesium range (mmol/L)	0.25–0.70	0.75	0.80	0.85–1.15		
ESRD Events	65	43	46	54		208
Person-years	24834	41084	67446	124334		257698
Incidence per 1000 person-years	2.62	1.05	0.68	0.44		0.81

Note: Quartile 3 and 4 were combined for ESRD event for analysis because in African Americans only four ESRD events were observed in quartile 4.

Table 3
Adjusted Hazard Ratios (95% Confidence Intervals) for Incident CKD by Serum Magnesium Levels

Serum magnesium	Quartile 1a	Quartile 1b	Quartile 2	Quartile 3	Quartile 4	P-trend
mmol/L	0.25-0.70	0.75	0.80	0.85	0.90-1.15	
Model 1	2.14 (1.83, 2.50)	1.71 (1.48, 1.98)	1.17 (1.02, 1.35)	1.13 (0.98, 1.30)	1.00	<0.001
Model 2	1.75 (1.49, 2.06)	1.58 (1.36, 1.83)	1.13 (0.98, 1.30)	1.14 (0.99, 1.31)	1.00	<0.001
Model 3	1.58 (1.35, 1.87)	1.47 (1.27, 1.71)	1.06 (0.93, 1.22)	1.09 (0.95, 1.26)	1.00	<0.001

Model 1: controlling for race-center, age, and gender

Model 2: Model 1 + baseline eGFR, diabetes, and hypertension medication status

Model 3: Model 2 + education levels, household income, health insurance status, systolic blood pressure, prevalent coronary heart disease, smoking status, log-transformed triglycerides, HDL-C, log-transformed LDL-C, and serum albumin.

P-values for trend were obtained by coding serum magnesium levels as a continuous variable from 0 to 4.

Table 4
Adjusted Hazard Ratios (95% Confidence Intervals) for Incident ESRD by Serum Magnesium Levels

Serum magnesium mmol/L	Quartile 1a	Quartile 1b	Quartile 2	Quartiles 3 and 4	P-trend
	0.25-0.70	0.75	0.80	0.85-1.15	
Model 1	4.58 (3.14, 6.69)	2.10 (1.40, 3.16)	1.44 (0.97, 2.14)	1.00	<0.001
Model 2	2.66 (1.80, 3.93)	1.66 (1.10, 2.49)	1.30 (0.88, 1.93)	1.00	<0.001
Model 3	2.39 (1.61, 3.56)	1.50 (0.99, 2.27)	1.26 (0.84, 1.87)	1.00	<0.001

Model 1: controlling for race-center, age, and gender

Model 2: Model 1 + baseline eGFR, diabetes, and hypertension medication status

Model 3: Model 2 + education levels, household income, health insurance status, systolic blood pressure, prevalent coronary heart disease, smoking status, log-transformed triglycerides, HDL-C, log-transformed LDL-C, and serum albumin.

Quartiles 3 and 4 were combined for analysis because in African American, only four ESRD events were observed in quartile 4.

P-values for trend were obtained by coding serum magnesium levels as a continuous variable from 0 to 3.