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Serum magnesium and risk of new onset heart failure in men: The Kuopio Ischemic Heart Disease Study

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Abstract

Serum magnesium is an essential intracellular cation involved in processes that regulate cardiovascular function and has been linked to the risk of several cardiovascular disease outcomes. We aimed to investigate the association of serum magnesium concentrations with risk of incident heart failure (HF). We studied 2,181 middle-aged men without prevalent HF (aged 42-61 years) enrolled in the Finnish Kuopio Ischemic Heart Disease prospective cohort study with serum magnesium measurements made at baseline. Hazard ratios (95% confidence intervals [CI]) for HF were assessed. During a median follow-up of 24.8 years, 278 HF events occurred. Baseline serum magnesium was weakly and inversely associated with several clinical markers and was continuously associated with risk of HF. The age-adjusted HR (95% CIs) for HF per 1 standard deviation (SD) higher serum magnesium levels was 0.86 (0.76-0.97). The HR (95% CIs) was 0.87 (0.76-0.98) after controlling for measures of adiposity, socio-economic variables, medical history, blood pressure, renal function, alcohol consumption, and lipids. These findings remained consistent in analyses accounting for incident coronary heart disease. The results were comparable across several clinically relevant subgroups and analyses with atrial fibrillation as a competing risk yielded similar results. Serum magnesium was continuously, inversely and independently associated with future risk of HF. Further research is needed to assess any potential relevance of serum magnesium in HF prevention.

Keywords: serum magnesium; heart failure; risk factor

Introduction

Magnesium is a key intracellular cation, involved in several homeostatic processes including enzymatic reactions, nucleic acid synthesis, and cell replication. It is also involved in processes that regulate cardiovascular function, including regulation of muscular function, endothelial cell function, myocardial excitability, and activation of sodium potassium ATPase.(1-4) Serum magnesium has been linked to chronic kidney disease (5, 6) and several cardiovascular disease (CVD) outcomes. Inverse associations have been demonstrated for atrial fibrillation,(7) sudden cardiac death,(8) coronary heart disease (CHD),(9, 10) stroke,(11) fatal CVD,(12) and all-cause mortality events.(12) Data on the etiological nature of the prospective association between serum magnesium levels and risk of heart failure (HF) is sparse. In the only population-based prospective study conducted till date, Lutsey and colleagues demonstrated a linear inverse and independent association between serum magnesium levels and risk of HF.(13) Magnesium may be related to HF risk through multiple pathways. Interestingly, several direct myocardial effects of magnesium have been demonstrated.(14) Thus, it is possible that magnesium may confer cardio-protective effects. Given that HF is associated with high morbidity and mortality[2] and imposes a significant economic burden on health systems, it is therefore necessary to further evaluate putative risk factors which may have predictive or causal relevance to the risk of HF and which could help tailor preventive and therapeutic interventions. In this context, our objective was to assess the shape, nature, and magnitude of the prospective association of serum magnesium with risk of HF and the consistency of the association in important clinical subgroups using a population-based cohort of 2,181 relatively healthy men from eastern Finland who were free of HF at baseline.

Methods

Study population

The study used data from the Kuopio Ischaemic Heart Disease (KIHD) risk factor study, a population-based prospective cohort study which was set up to investigate risk factors for CV and other chronic diseases in eastern Finland.(15) A baseline study was conducted between March 1984 and December 1989, which included a representative sample of 3,433 men aged 42-61 years living in the city of Kuopio and its neighbouring rural communities. Of the 3,433 randomly selected and eligible men, 2,682 (78%) volunteered to participate; 186 did not respond to the invitation and 367 declined to give informed consent. Men with a prevalent history of HF were excluded. The final cohort for the present analysis included 2,181 men with non-missing information on serum magnesium and several risk markers for HF. The KIHD study complies with the Declaration of Helsinki and was approved by the ethical committee of the University of Eastern Finland and each study participant gave written informed consent.

Ascertainment of outcomes

All HF events that occurred from the study entry to 2013 were included and there were no losses to follow-up. In the KIHD study, participants are under annual continuous surveillance for the development of new cardiovascular outcome events, including new incident HF cases.(16) Information on cardiovascular outcomes were obtained from the National Hospital Discharge Register data by computer linkage and a comprehensive review of hospital records and discharge diagnoses, inpatient physician claims data, study ECGs, and medico-legal reports. The events were coded according to ICD-10 codes (I50.0-I50.9, I11, I42.0-I42.9). The diagnosis of HF was based on symptoms, physical examination by a doctor, laboratory investigations including the determination of natriuretic peptides, chest radiography, echocardiography as well as electrocardiographic findings.(17) Documents were cross-checked in detail by two physicians. The Independent Events Committee, masked to clinical data, performed classification of outcomes.

Measurement of risk factors

Collection of blood specimens and the measurement of serum lipids, lipoproteins and glucose have been described in detail previously.(18) In addition to fasting, participants were instructed to abstain from drinking alcohol for at least 3 days and from smoking for at least 12 h prior to assessment. The serum samples were stored frozen at -80 °C for 0.2-2.5 years. Fasting plasma glucose (FPG) was measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany). Serum magnesium was measured using atomic absorption spectrometry (Perkin Elmer Zeeman 5000, Perkin Elmer, Norwalk, CT, USA) which involved the use of acetylene-air (1:4) flame technique. Serum magnesium was diluted in a ratio of 1:50 with distilled water. The wavelength was 185.2 nm for magnesium. The between-run Coefficient of Variation% for the method was 2.4 (37 assays).(19) Measurements of serum potassium and zinc have been described previously.(18, 20) Data on age, smoking, alcohol consumption, history of CVD, presence of hypertension, and use of medication was obtained using self-administered questionnaire. Re-interviews were conducted again by a physician to collect information on medical history.(18) Resting blood pressure was measured by a nurse on the first examination day with a random zero sphygmomanometer and the mean of all 6 measurements (3 supine, 1 standing, 2 sitting) was used as the final mean systolic and diastolic blood pressure. Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in metres. Physical activity was assessed using the validated KIHD 12-month leisure-time physical activity questionnaire.(21, 22)

Statistical analyses

Values of skewed variables were naturally logarithmically transformed to achieve approximately normal distributions. Descriptive data were presented in the form of mean (SD) or median (interquartile range) for continuous variables and percentages for categorical variables. Cross-sectional correlations of serum magnesium levels with various risk markers were determined using age-adjusted linear regression models.

Time-to-event analyses were conducted using Cox proportional hazard models. The proportional hazards assumptions were confirmed using Schoenfeld residuals as previously described.(23) To characterize the shape of the association, hazard ratios (HRs) were calculated within quartiles of serum magnesium levels and plotted against mean serum magnesium levels within each quartile. Floating variances were used to calculate 95% confidence intervals for the log hazard ratio in each group, including the reference group, to allow for comparisons across the groups irrespective of the arbitrarily chosen reference category (bottom quartile).(24) Multivariate-adjusted fractional polynomial models were also fitted to further characterize the shape of the association. As the association showed a continuous shape and given the sparse number of participants in the upper and lower quartiles of the distribution curve of serum magnesium levels (**Figure 1**), HRs were calculated per 1 standard deviation (SD) higher serum magnesium concentrations. The SD of serum magnesium concentration was 0.16 mg/dl. Hazard ratios were progressively adjusted for age, BMI, systolic blood pressure (SBP), prevalent CHD, smoking status, history of diabetes mellitus, use of medications (antihypertensive agents and lipid-lowering drugs), alcohol consumption, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), estimated glomerular filtration rate (eGFR), as calculated using the Chronic Kidney Disease Epidemiology Collaboration formula,(25) socio-economic status, physical activity, serum potassium and serum zinc . Further adjustment included incident coronary events as a time-varying covariate. Given that AF was higher than HF incidence in the KIHD cohort, we also performed additional analyses using the competing-risks extension of the Cox proportional hazards models, as proposed by Fine and Gray,(26) to estimate the baseline cumulative subhazard of HF considering AF as a competing outcome to HF. We performed subgroup analyses using interaction tests to assess statistical evidence of any differences in hazards across categories of pre-specified individual level characteristics. To avoid potential bias due to participants at high risk of HF or with underlying HF at baseline, we carried out sensitivity analyses that excluded the first 5 years of follow-up.

To assess whether adding information on serum magnesium measurements to established HF risk factors is associated with improvement in prediction of HF risk, we calculated measures of discrimination for censored time-to-event data (Harrell's C-index (27)) and reclassification (the continuous net-reclassification-improvement [NRI], a category-free version of the NRI).(28) All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

Results

Baseline characteristics and correlates of serum magnesium levels

The mean (SD) serum magnesium levels at baseline was 1.98 (0.16) mg/dl. **Figure 1** shows a histogram representing the frequency distribution of magnesium concentrations in the study sample. **Table 1** summarizes baseline characteristics of the study population (n=2,198).The mean (SD) of study participants was 53 (5) years. Serum magnesium levels were weakly and inversely correlated with physical measures (BMI and blood pressure) and with several lipid, metabolic, and renal markers. Weak positive correlations were observed for age, total cholesterol, creatinine, and zinc. Baseline serum magnesium levels were lower in people with diabetes compared with people without diabetes, people with a history of hypertension compared with people without a history of hypertension, and in current smokers compared with non-smokers.

Serum magnesium and risk of heart failure

During a median (interquartile range) follow-up of 24.8 (18.2-27.0) years, 278 incident HF events (annual rate 5.84/1,000 person-years at risk; 95% CI: 5.20 to 6.57) were recorded. In analyses adjusted for several established risk factors (age, BMI, SBP, prevalent coronary heart disease, smoking status, history of diabetes mellitus, use of antihypertensive agents and lipid-lowering drugs, and alcohol consumption), there was an inverse and continuous association between serum magnesium and incident HF, which was potentially consistent with either a curvilinear or approximately linear shape. However, statistical tests

suggested a better fit with a curvilinear shape (*P* for linearity > 0.05) (**Figure 2 and Supplementary Material**). The age-adjusted HR per 1 SD increase in serum magnesium levels was 0.86 (95% CI: 0.76 to 0.97; *P* = 0.015), which remained consistent on further adjustment for several established and emerging risk factors 0.87 (95% CI: 0.76 to 0.98; *P* = 0.028). The results persisted after further adjusting for incident coronary events as shown in **Table 2**. Analyses with AF as a competing risk event yielded similar results 0.79 (95% CI: 0.62 to 99; *P* = 0.048) per 1 SD increase in serum magnesium levels. There was evidence of effect modification by history of diabetes (*P* for interaction=0.023), and history of CHD (*P* for interaction = 0.013). Significant inverse associations were observed in individuals with a history of diabetes and individuals with no history of CHD compared to non-significant associations in individuals with no history of diabetes and those with a history of CHD respectively (**Figure 3**). There were no HF events recorded during the first five years of follow-up, therefore results for analyses that excluded the first five years of follow-up were unchanged and therefore not shown.

A HF risk prediction model containing established risk factors yielded a C-index of 0.7533 (95% CI: 0.7214 to 0.7852). After addition of information on serum magnesium in the model, the C-index was 0.7558 (0.7238 to 7878), a marginal increase of 0.0025 (-0.0035 to 0.0086; *P*=0.414), indicating that serum magnesium does not importantly improve prediction of HF risk beyond established risk factors. The NRI was 22.7% (-20.2 to 65.6%, *P*=0.299).

Comment

Summary of findings

In this population-based prospective study of middle-aged Finnish men without HF at baseline, our results show a decreased risk for incident HF with increasing serum magnesium levels; however, further work is needed to ascertain whether a curvilinear or linear shape better describes the relationship. This association persisted after controlling for baseline characteristics, predictors of incident HF, metabolic and renal

markers, and other related micronutrients. Our data adds to the growing literature on the role of serum magnesium in modulating cardiovascular risk and extend the results of the elegant study by the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Their results demonstrated that serum magnesium concentrations were associated with risk for HF after controlling for clinical characteristics, medical history, lipids, and renal function in a North American population, with the association remaining consistent across sex and race.(13) Taken together, these findings signal to the strength of the association between serum magnesium and incident HF. Our results also remained similar across several clinically relevant subgroups, except for evidence of effect modification by history of diabetes and prevalent CHD. Given the low event rate in some of the subgroups and the multiple statistical tests for interaction conducted, these subgroup results will require replication in further studies. Despite the high incidence of AF in our study cohort which might have hindered our event of interest, the association between serum magnesium and HF was similar when AF was adjusted for as a competing risk event. Finally, our analyses indicate that addition of information on serum magnesium measurements to conventional HF risk factors did not incrementally improve HF risk prediction.

Possible explanations for findings

A number of studies have demonstrated serum magnesium levels to be associated with several cardiovascular outcomes. Proposed mechanistic pathways linking low serum levels of magnesium to increased CVD risk include impaired glucose homeostasis and insulin resistance, high blood pressure, endothelial dysfunction, chronic inflammatory processes, diabetes, and impaired vascular tone and peripheral blood flow.(29, 30) Magnesium depletion also causes electrocardiogram abnormalities (eg, prolonged QTc interval) which increases the risk of cardiac arrhythmias.(30) Given that several CVD outcomes are closely related to the development of HF,(31-33) these same pathways may also play a role in the etiology between serum magnesium levels and HF. The broadly continuous and independent association of serum magnesium with HF may suggest a causal relationship, but this will need to be

demonstrated in a randomized controlled trial. A number of randomized controlled trials have shown that magnesium supplementation improves cardiovascular function in patients with heart failure; however, these do not prove causality. Establishing causality will require rigorous randomized controlled trials of magnesium supplementation with the appropriate endpoints. In the absence of clinical trials however, Mendelian randomisation (MR) studies of genetic variants specifically related to magnesium levels may also provide another route to assess causality.(34) Common genetic variants in the *TRPM6* gene and *ATP2B1* gene are associated with altered magnesium levels and risk for hypomagnesemia.(35) Further studies are needed to determine whether variants within these loci might be valid instrumental variables for MR studies of serum magnesium and HF.

Implications of findings

Collectively, these findings may have implications for clinical practice. Our findings further highlight the long-term association between baseline serum magnesium levels and risk of HF and suggest that magnesium might modify HF risk. Serum magnesium remains a promising though unproven strategy for HF risk prevention. Animal experiments have shown that inadequate intake of magnesium is associated with increased atherosclerotic plaque.(36) Evidence from experimental and animal models also shows that magnesium therapy is beneficial in the treatment of cardiac arrhythmias.(37, 38) Observational evidence consistently shows that increased dietary intake of magnesium is inversely associated with several cardiovascular outcomes.(39-43) Urinary excretion of magnesium, which is also an indicator of dietary magnesium intake, has also been shown to be inversely and independently associated with CVD.(44) A number of clinical studies have also shown a beneficial effect of magnesium infusion on the incidence of cardiovascular outcomes.(45) Given that serum magnesium concentration depends on magnesium intake from food and water, the overall evidence supports the possibility that increasing the intake of dietary magnesium resulting in increased serum magnesium concentrations, might protect from the development of CVD outcomes including HF and also form the basis of treatment strategies. Well-designed

intervention trials are warranted to investigate the potential therapeutic implications of serum magnesium in HF prevention. Assessing serum magnesium concentration is a simple, practicable, and inexpensive test and its potential usefulness in HF risk prediction deserves further investigation. Formal risk assessment analyses involving larger-scale individual participant data are warranted to assess the usefulness of serum magnesium in HF risk prediction.

Strengths and limitations

The strengths include a large population-based sample that was selected to be a nationally representative, involved a high response rate, and there were no losses during follow-up. We had reliable definitions of HF outcomes which were based on ICD-10 diagnoses and information on outcomes were from established and reliable databases. Assay methods for serum magnesium measurements employed atomic absorption spectrometry which has a high level of accuracy. The mean follow-up of over 20 years was sufficiently long to ascertain the risk for HF. We adjusted for a comprehensive panel of lifestyle and biochemical markers to allow adequate adjustment for potential confounding, enabling reliable assessments of the associations. The limitations of the present study also deserve mention. Serum magnesium levels does not necessarily reflect total body magnesium content,(1) however, it is the best estimate of magnesium status as it correlates with ionized and intracellular magnesium.(46) We were unable to correct for within-person variability in serum magnesium levels as we had no data on repeat measurements. Due to the distribution of magnesium concentrations in the KIHD, we were unable to assess the associations at extremely low levels of magnesium and by clinical categories of magnesium levels. We were unable to assess the differential impact of serum magnesium on risk of specific forms of HF (eg. systolic versus diastolic HF and HF with preserved versus reduced ejection fractions), because of the absence of such data. Though we adjusted for several confounders, there was a possibility of residual confounding due to other unmeasured confounders (such as proton pump inhibitors and other medications that affect serum magnesium levels(47) and are associated with risk of CVD(48)), which could in part explain the association between

serum magnesium and HF. The study included only male Caucasians and cannot necessarily be extrapolated to women and other ethnicities.

Conclusion

In this middle-aged population of Finnish men, serum magnesium was found to be continuously, inversely and independently associated with future risk of HF. Further research is needed to assess any potential relevance of serum magnesium in HF prevention.

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Conflict of interest

The authors declare they have no conflict of interest.

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Figure 1. Frequency distribution of magnesium concentrations in the study sample

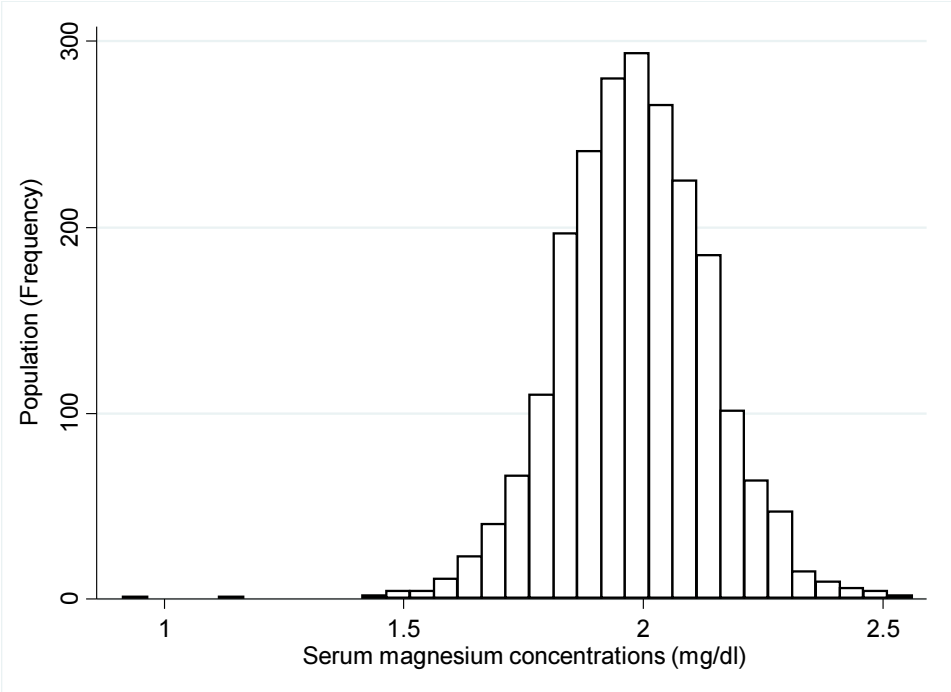
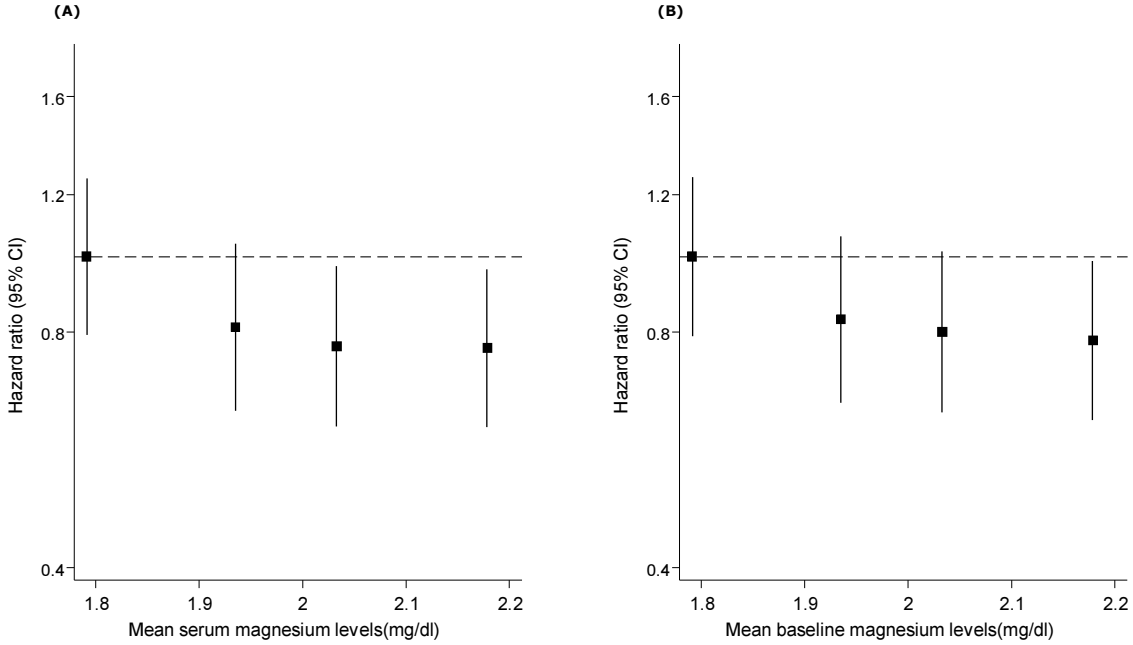
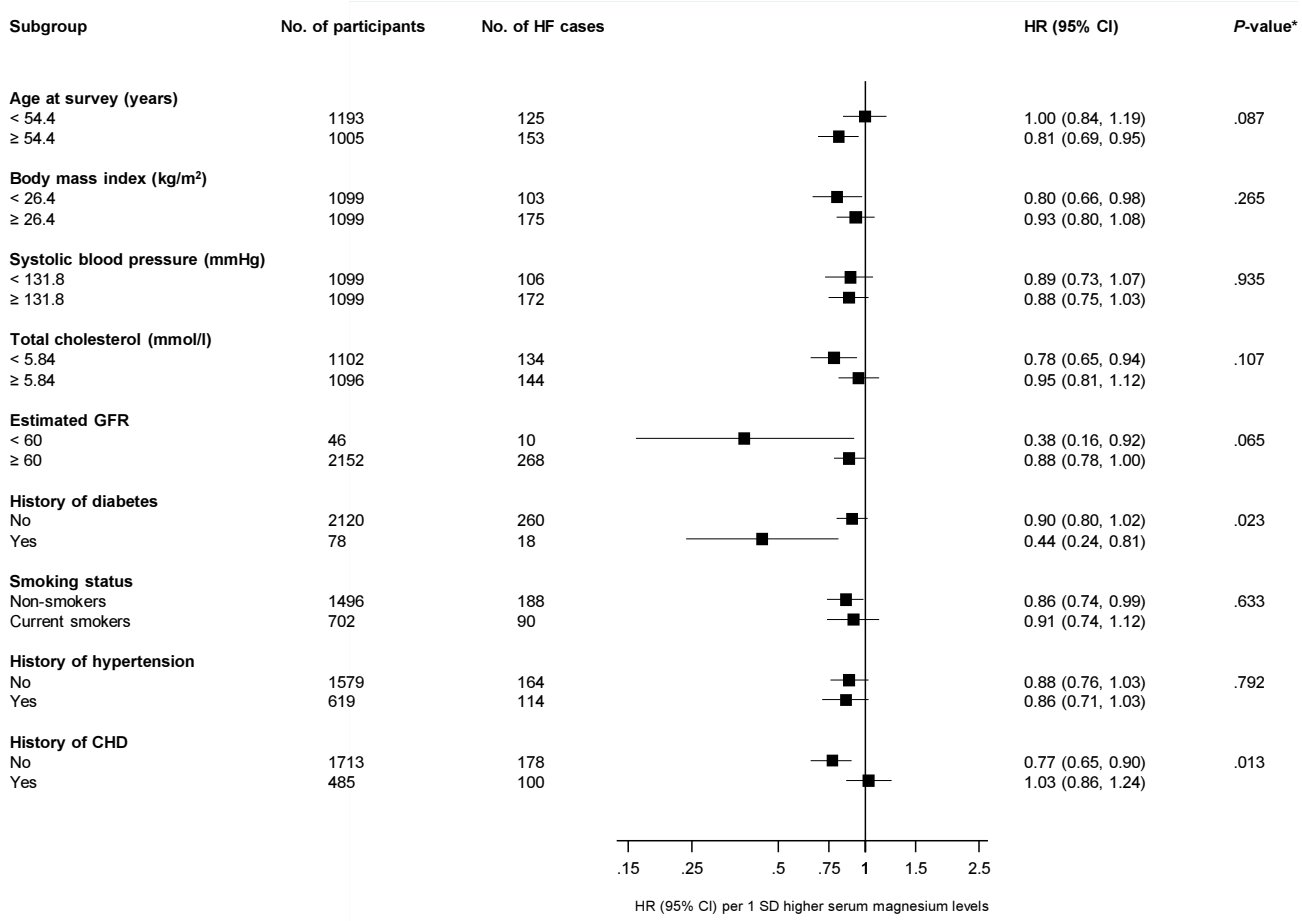


Figure 2. Hazard ratios for heart failure, by quartiles of serum magnesium levels



A, adjusted for age; **B**, adjusted for age, body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, use of medications (antihypertensive agents and lipid-lowering drugs), and alcohol consumption; the mean magnesium level (mg/dl) was 1.79 for the lowest quartile; 1.94 for the second quartile; 2.03 for the third quartile; and 2.18 for the top quartile

Figure 3. Hazard ratios for serum magnesium levels and heart failure risk by several participant level characteristics



Hazard ratios were adjusted age, body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, use of medications (antihypertensive agents and lipid-lowering drugs), and alcohol consumption; CHD, coronary heart disease; CI, confidence interval; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; SD, standard deviation; *, *P*-value for interaction; Cut-offs used for age, body mass index, systolic blood pressure, total cholesterol, estimated GFR, and follow-up time are median values.

Table 1. Baseline characteristics and cross-sectional correlates of serum magnesium

	Mean (SD), median (IQR), or %	Pearson correlation r (95% CI)†	Percentage difference (95% CI) in magnesium levels per 1 SD higher or compared to reference category of correlate‡
Magnesium (mg/dl)	1.98 (0.16)	-	-
Questionnaire/Prevalent conditions			
Age at survey (years)	53.0 (5.0)	0.06 (0.02, 0.10)*	1% (0, 2)*
Alcohol consumption (g/week)	76.3 (139.2)	-0.09 (-0.13, -0.04)***	-1% (-2, -1)***
History of diabetes			
No	96.4	-	Ref
Yes	3.6	-	-7% (-10, -3)**
Smoking status			
Other	68.1	-	Ref
Current	31.9	-	-1% (-2, 0)
History of hypertension			
No	72.0	-	Ref
Yes	28.0	-	-2% (-3, -0)*
History of CHD			
No	77.9	-	Ref
Yes	22.1	-	0% (-1, 2)
Use of anti-hypertensives			
No	81.3	-	Ref
Yes	18.7	-	-1% (-3, 0)
Medication for dyslipidemia			
No	99.4	-	Ref
Yes	0.6	-	-6% (-14, 2)
Physical measurements			
BMI (kg/m^2)	26.8 (3.5)	-0.03 (-0.07, 0.01)	-0% (-1, 0)
SBP (mmHg)	133.7 (16.7)	-0.04 (-0.09, -0.00)	-1% (-1, -0)*
DBP (mmHg)	88.6 (10.4)	-0.03 (-0.07, 0.01)	-0% (-1, 0)
Physical activity (kj/day)	1,512.8 (1,368.1)	0.00 (-0.04, 0.04)	0% (-1, 1)
Lipid markers			
Total cholesterol (mmol/l)	5.90 (1.10)	0.08 (0.04, 0.12)***	1% (1, 2)**
HDL-C (mmol/l)	1.31 (0.30)	-0.03 (-0.07, 0.01)	-0% (-1, 0)
Triglycerides (mmol/l)	1.08 (0.79-1.52)	-0.00 (-0.04, 0.04)	-0% (-1, 1)
Metabolic, biochemical, and renal markers			
Fasting plasma glucose (mmol/l)	5.33 (1.18)	-0.14 (-0.19, -0.10)***	-2% (-3, -2)***
Serum creatinine (μmol/l)	89.5 (21.0)	0.14 (0.10, 0.18)***	2% (2, 3)***
Serum potassium (mmol/l)	3.92 (0.30)	-0.01 (-0.05, 0.04)	-0% (-1, 1)
Serum zinc (mg/l)	0.94 (0.12)	0.11 (0.07, 0.15)***	2% (1, 2)***
Estimated GFR (ml/min/1.73 m^2)	87.3 (17.3)	-0.14 (-0.18, -0.10)***	-2% (-3, -2)***

BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SD, standard deviation; SBP, systolic blood pressure; †Pearson correlation coefficients between serum magnesium and the row variables;. ‡Percentage change in magnesium levels per 1-SD increase in the row variable (or for categorical variables, the percentage difference in mean magnesium levels for the category versus the reference) adjusted for age; asterisks indicate the level of statistical significance: *, p<0.05; **, p<0.01; ***, p<0.001

Table 2. Association of serum magnesium levels with heart failure

Magnesium, mg/dl	Events/ Total	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Per 1 SD increase	278 / 2,181	0.86 (0.76-0.97)	0.015	0.87 (0.77-0.98)	0.027	0.87 (0.76-0.98)	0.028	0.86 (0.76-0.98)	0.019

SD, standard deviation

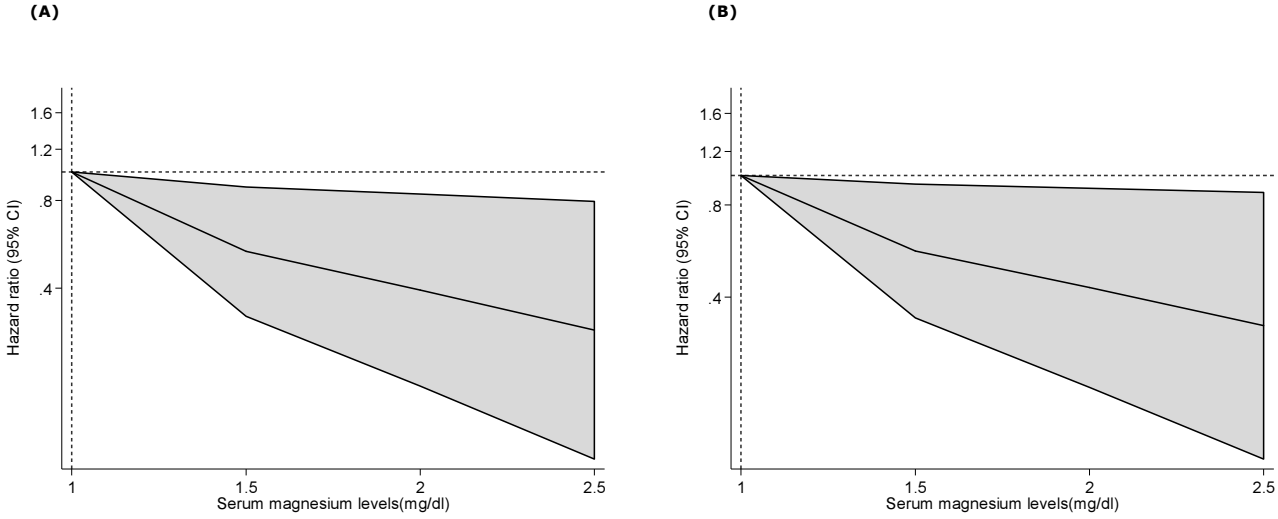
Model 1: Adjusted for age

Model 2: Model 1 plus body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, use of medications (antihypertensive agents and lipid-lowering drugs), and alcohol consumption

Model 3: Model 2 plus triglycerides, total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, socio-economic status, physical activity, serum potassium, and serum zinc

Model 4: Model 3 plus incident coronary heart disease as a time-dependent covariate

Supplementary Material: Hazard ratios for heart failure using multivariate-adjusted fractional polynomials



A, adjusted for age; **B**, adjusted for age, body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, use of medications (antihypertensive agents and lipid-lowering drugs), and alcohol consumption