



Serum and dietary magnesium and incidence of atrial fibrillation in whites and in african americans - Atherosclerosis risk in communities (ARIC) study

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Serum and Dietary Magnesium and Incidence of Atrial Fibrillation in Whites and in African Americans – Atherosclerosis Risk in Communities (ARIC) Study –

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Background: Low serum magnesium (Mg) has been associated with an increased risk of cardiovascular disease (CVD), including ventricular arrhythmias, but the association between serum or dietary Mg and atrial fibrillation (AF) has not been investigated.

Methods and Results: A total of 14,290 men and women (75% white; 53% female; mean age, 54 years) free of AF at baseline participating in the Atherosclerosis Risk in Communities study in the United States, were studied. Incident AF cases through 2009 were ascertained from electrocardiograms, hospital discharge codes, and death certificates. Multivariate Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for AF associated with serum and dietary Mg quintiles. Over a median follow-up time of 20.6 years, 1,755 incident AF cases were identified. In multivariate models, lower serum Mg was associated with higher AF risk: compared to individuals in the middle quintile (≥ 0.80 – 0.83 mmol/L), the HR (95% CI) of AF in quintiles 1, 2, 4, and 5 were 1.34 (1.16–1.54), 0.99 (0.85–1.16), 1.04 (0.90–1.22), and 1.06 (0.91–1.23), respectively. There was no evidence of significant interactions between serum Mg and sex or race. No association between dietary Mg and AF risk was observed.

Conclusions: Lower serum Mg was associated with a higher AF risk, and this association was not different between whites and African Americans. Dietary Mg was not associated with AF risk. (*Circ J* 2013; **77**: 323–329)

Key Words: Atrial fibrillation; Dietary magnesium; Serum magnesium

Atrial fibrillation (AF), a common cardiac arrhythmia, affects >2 million individuals in the USA.¹ AF is also associated with an increased risk of cardiovascular disease (CVD), heart failure (HF), stroke, and overall mortality.² Numerous studies have identified risk factors for AF, including older age, male sex, white race, cigarette smoking, hypertension, obesity, diabetes, HF, coronary heart disease (CHD), left ventricular hypertrophy, metabolic syndrome, and inflammation,^{2–7} but a large proportion of the attributable risk of AF (44%) remains unexplained after accounting for one or more borderline or elevated risk factors.⁸

Magnesium (Mg) is an abundant cation in the body that plays a crucial role as a modulator of vasomotor tone, blood pressure, and peripheral blood flow. Consequently, Mg deficiency can affect the cardiovascular system. Previous epidemiologic

studies have found that higher levels of serum Mg were associated with a lower risk of hypertension,⁹ CHD,^{10,11} diabetes,¹² sudden cardiac death,¹³ and ischemic stroke.¹⁴ Results from studies examining dietary Mg intake with cardiometabolic outcomes, though, have been conflicting, with some identifying an inverse association and others finding no association.^{9–17} In addition, there is some evidence that serum Mg deficiency complicates cardiac surgery and is associated with increased risk of postoperative AF.¹⁸ As a result, Mg has been suggested as a possible prophylactic treatment to prevent postoperative AF events, but evidence of the effectiveness of this intervention is mixed.^{19–23} The association between serum or dietary Mg and incident AF in the general population, however, has not been investigated.

Using data from the Atherosclerosis Risk in Communities

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(ARIC) study, a community-based cohort including middle-aged whites and African Americans, we explored whether serum and dietary Mg were associated with the risk of incident AF. We hypothesized that individuals with lower serum Mg levels or dietary intake would have a higher risk for AF independent of other cardiovascular risk factors and that the association of Mg with AF risk would be of a similar magnitude in both white and African-American individuals.

Methods

Study Design and Subjects

The ARIC study is a prospective cohort study aimed to study risk factors of atherosclerosis and CVD.²⁴ In 1987–1989, an initial baseline examination including a home interview and clinical visit was conducted with 45–64-year-old participants in 4 US communities: Forsyth County, NC; Jackson, MS (African Americans only); the northwest suburbs of Minneapolis, MN; and Washington County, MD. At that time, 15,792 participants were enrolled in the study, and 3 further examinations occurred (with approximately 3 years between examinations) through 1998. Response rates for the follow-up triennial exams were 93%, 86%, and 80%, respectively. Participants are contacted yearly by telephone to obtain follow-up information related to hospital admissions and to determine vital status. Telephone interviews after exam 4 have seen an average response rate of >90%. Surveillance of death certificates and hospital discharges within pre-specified catchment areas is also continuous. The ARIC Study protocol was approved by the institutional review board of each participating university, and written informed consent was gathered from all enrolled participants.

Assessment of Mg and Covariates

Most risk factors for this analysis were ascertained at the baseline examination. Before the clinical examination, participants were asked to fast for 12 h, and blood was drawn from an antecubital vein of seated participants into vacuum tubes containing thylendiaminetetraacetic acid (for measurement of lipids) or a serum separator gel (Mg, potassium, creatinine, and glucose). Aliquots were stored at -70°C and were shipped to central laboratories for analysis. Serum Mg was measured at visits 1 and 2 and was based on the Gindler and Heth procedure of using the metallochromic dye calmagite (1-[1-hydroxy-4-methyl-2-phenylazo]-2-naphthol-4-sulfonic acid). Using split samples sent 1 week apart, laboratories were blind-tested for the laboratory coefficient of variation for Mg, and the result was 3%.²⁴ The correlation coefficient of serum Mg measured at visit 1 vs. visit 2 was 0.46.

Serum potassium (K) was assessed with a Coulter DACOS analyzer (Coulter Instruments, Hialeah, FL, USA) using a direct ion-selective electrode. Serum creatinine was measured using a modified kinetic Jaffe method described previously.^{24,25} Over several weeks, 40 participants were repeatedly tested, yielding a reliability coefficient of 0.69 for Mg, 0.66 for K, and 0.68 for creatinine.²⁶ Serum glucose was assayed using a hexokinase/glucose-6-phosphate dehydrogenase method. Prevalent diabetes mellitus was characterized by fasting glucose ≥ 126 mg/dl, non-fasting glucose ≥ 200 mg/dl, a self-reported physician diagnosis, or a current treatment for diabetes. High-density lipoprotein cholesterol (HDL-C) was determined using enzymatic methods while low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation.²⁷

Blood pressure was measured with a random-zero sphygmomanometer after 5 min of rest in the sitting position and

was defined as the average of the last 2 of 3 measurements. Questionnaires were used to assess education, smoking status, drinking status, and dietary information. Using an adapted version of the Willett 61-item food frequency questionnaire, usual dietary intake from the previous year was collected at baseline and at visit 3.²⁸ Dietary Mg intake was computed by multiplying the Mg content of each food item by the frequency of its daily consumption and summing over all items. In addition, all medications used in the preceding 2 weeks before each clinic visit were recorded from prescription bottles brought by the participant. At baseline, prevalent myocardial infarction (MI) was characterized as previously reported MI event or from electrocardiograms (ECG) while prevalent HF was defined by Gothenburg criteria 3 or the intake of HF medications. Prevalent stroke was designated as self-reported history of physician-diagnosed stroke. Incident cases of HF, MI, or stroke were identified through annual telephone interviews, triennial field center examinations, and the ongoing surveillance of ARIC community hospitals for any hospitalizations or deaths of any cohort participants and were then validated.

Incident AF Events

Incident AF cases were ascertained from 3 sources: ECGs completed during the study exams; hospital discharge codes; and death certificates. ECGs during study visits were performed with MAC PC Personal Cardiographs (Marquette Electronics, Milwaukee, WI, USA). A standard supine 12-lead resting ECG was transmitted to the ARIC ECG Reading Center for coding, interpretation, and storage. A trained cardiologist visually rechecked the ECGs automatically coded as AF to confirm the diagnosis.²⁹ Those identified with prevalent AF at visit 1 on ECG were excluded from further analysis.

Annual follow-up phone calls to the study participants were used to identify hospitalizations and deaths through the end of 2009,³⁰ and discharge lists from local hospitals were reviewed for any cardiovascular events. Using International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) codes, AF was identified when 427.31 or 427.32 was listed as a discharge diagnostic code. Any AF event identified during a hospitalization for cardiac surgery was excluded. In a physician review of discharge summaries from 125 possible AF cases, approximately 90% of the cases were confirmed.³ Last, AF was identified as a cause of death if ICD-9 code 427.3 or ICD-10 code I48 was listed on the death certificates. Most incident cases of AF (>98%) in this analysis were identified from hospital discharge codes while <1% of AF was identified from death certificates.

AF incidence date was defined as the date of the first ECG showing AF, the first hospital discharge date for an AF or atrial flutter diagnosis, or date when death occurred due to AF, whichever occurred first.

Statistical Analysis

From the initial 15,792 ARIC participants, the following were excluded: those who were races other than white or African-American ($n=48$); African Americans located in Minneapolis and Washington County ($n=55$); those with prevalent AF or atrial flutter identified by the baseline ECG ($n=37$); those with missing or unreadable ECG at baseline ($n=309$); those with missing baseline serum Mg data measurements ($n=124$); those not fasting at least 8 h for the baseline examination ($n=536$); and those missing any information on covariates ($n=393$).

Initially, we explored the shape of the association between Mg and AF risk using restricted cubic splines. Next, both serum and dietary Mg were divided into ranked quintiles. For serum

Table 1. Baseline Characteristics vs. Serum Mg Quintile: Atherosclerosis Risk in Communities, 1987–1989

	Serum magnesium (mmol/L)				
	<0.78 (n=3,118)	0.78–0.80 (n=2,620)	≥0.80–0.83 (n=3,100)	≥0.83–0.88 (n=2,739)	≥0.88 (n=2,713)
Magnesium median (mmol/L)	1.45	1.55	1.65	1.70	1.80
Age (years)	54.2±5.9	53.9±5.8	54.1±5.7	54.2±5.7	54.5±5.7
Female	59.6	57.8	54.0	52.5	52.6
African-American	41.0	23.3	22.5	18.3	16.0
BMI (kg/m ²)	28.9±6.2	27.5±5.2	27.4±5.1	27.2±5.0	26.8±4.7
LDL-C (mg/dl)	133.5±39.7	136.6±38.8	139.0±39.5	139.1±37.9	140.9±39.2
HDL-C (mg/dl)	52.1±18.0	52.3±17.1	51.5±16.4	51.9±16.7	52.0±16.6
Serum potassium (mmol/L)	4.2±0.4	4.3±0.3	4.3±0.4	4.4±0.4	4.4±0.4
Serum creatinine (mg/dl)	1.1±0.3	1.1±0.2	1.1±0.2	1.1±0.3	1.2±0.7
Current smoker	27.8	24.5	26.3	24.3	25.0
Current drinker	49.2	57.0	57.2	61.4	60.5
High school degree	38.6	43.2	43.2	42.5	40.0
Diabetes	20.3	9.4	8.6	6.2	4.8
SBP (mmHg)	125.2±20.3	120.2±17.6	120.3±18.5	119.2±18.2	119.0±17.6
Use of antihypertensive medications	43.0	28.0	27.4	24.3	30.0
Previous MI	4.9	3.4	3.5	3.8	3.6
Previous HF	6.6	4.1	3.9	3.2	3.2
Previous stroke	2.0	1.7	1.7	2.1	1.2
Dietary magnesium (mg/day)	247.1±87.2	252.9±87.1	253.4±85.7	255.9±88.3	257.6±87.3
Dietary potassium (mg/day)	2,596.7±929.8	2,646.7±885.0	2,641.0±879.9	2,665.9±896.7	2,687.8±892.5
Dietary calcium (mg/day)	641.3±343.8	660.9±342.0	657.3±332.0	669.2±340.4	663.7±340.2
Total energy intake (kcal/day)	1,614.1±573.7	1,615.4±550.4	1,619.6±547.2	1,616.5±557.8	1,626.7±553.4

Data given as mean±SD or %.

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure.

Mg, ranked quintiles were generated based on the mean 2 visit measurements (visit 1 and 2). For individuals who did not attend visit 2 (or were censored before the visit), their visit 1 serum Mg measurement was used for the purposes of ranking. For dietary Mg, visit 1 and visit 3 measurements were used to generate the ranked quintiles.

Adjusted hazard ratios (HR) and their 95% confidence interval (CI) for the association of serum Mg with incident AF were calculated using Cox proportional hazards regression. Follow-up time was defined as the time between the baseline visit and the date of AF incidence, death, loss to follow-up, or 31 December 2009, whichever came first. The initial model was adjusted for age, sex, race, and ARIC field center site at baseline. The second model was additionally adjusted for other baseline variables including smoking status (current, former, never), drinking status (current, former, never), education level (less than high school, high school graduate, at least some college), diabetes (yes, no), use of antihypertensive medications (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, other medications, none), and the following continuous variables: body mass index, HDL-C, LDL-C, serum K, serum creatinine, and systolic blood pressure. The third model further adjusted for prevalent MI, HF, or stroke at baseline. Finally, the fourth model was adjusted for incident MI, HF, and stroke as time-dependent covariates and potential mediators of the association between Mg and AF risk. Test for linear trend using the serum quintile number as an ordinal, continuous variable was examined for each model. Effect modification was evaluated by age, sex, and race conducting stratified analysis and including multiplicative terms between the effect modifier and Mg measures in the models. All potential

effect modifiers were found to be non-significant to a P-value cut-off of 0.05, although a modest interaction was identified between serum Mg and race (P=0.04). The proportional hazards assumption of the Cox models was tested with the inspection of log-negative log survival curves and was found not to be violated.

Dietary Mg and its association with incident AF was evaluated using the same Cox proportional hazard models. All 4 models were additionally adjusted for total energy intake (kcal), and models 2 through 4 included adjustment for other dietary covariates that are correlated with Mg intake: K, calcium, dietary fiber, protein, caffeine, and polyunsaturated to saturated fat ratio. All statistical analysis was done using SAS version 9.2 (SAS, Cary, NC, USA).

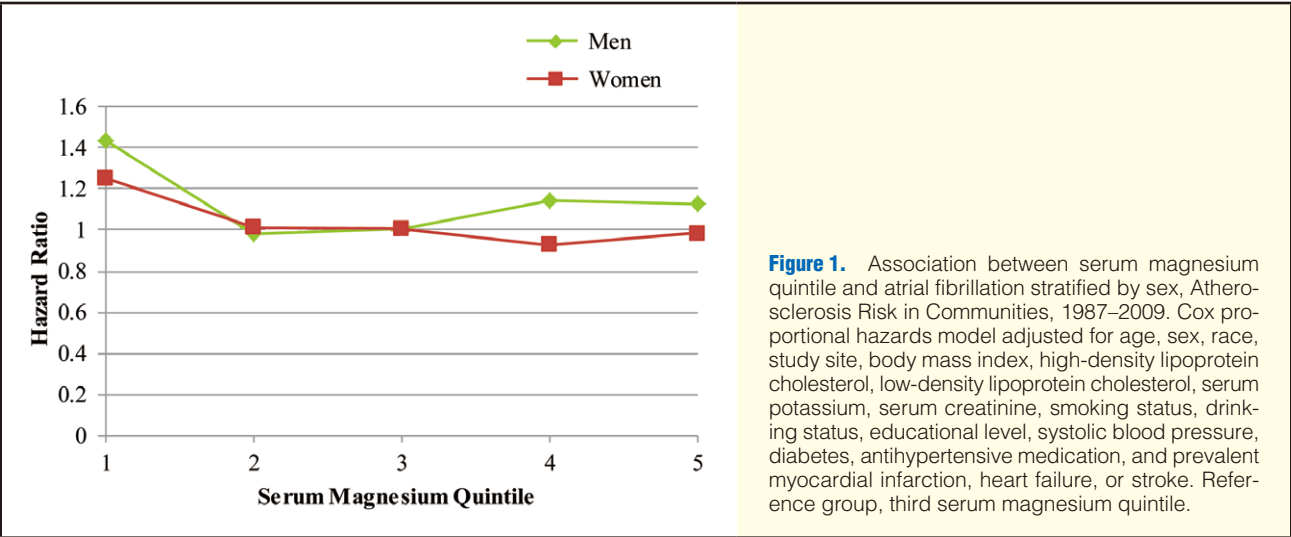
Results

At baseline, 7,911 women and 6,379 men aged 45–64 years free of AF met the inclusion criteria. The range for serum Mg from both visit 1 and 2 was 0.3–1.55 mmol/L and followed a normal distribution, with 98% of individuals having serum Mg between 0.6 and 1.0 mmol/L. Dietary Mg intake from both visit 1 and 3 also had a fairly normal distribution that ranged from 41.2 to 807 mg/day and included 98% of individuals between 101 and 505 mg/day. There was no linear association between serum and dietary Mg level (Pearson correlation coefficient=0.04).

Table 1 lists the characteristics of the ARIC participants at baseline by serum Mg quintile. LDL-C, serum K, current drinker, high school degree, and intake of K, Ca, and total energy were all positively associated with serum Mg. Many of the

	Serum magnesium (mmol/L)					P-value for trend†
	<0.78 (n=3,118)	0.78–0.80 (n=2,620)	≥0.80–0.83 (n=3,100)	≥0.83–0.88 (n=2,739)	≥0.88 (n=2,713)	
Cases	466	297	351	313	328	
Person-years	53,896	49,347	57,131	50,218	50,427	
Crude incidence rate (per 1,000 person-years)	8.65	6.02	6.14	6.23	6.50	
Model 1 HR (95%CI)	1.60 (1.39–1.84)	1.02 (0.87–1.19)	1.00 (Reference)	0.99 (0.85–1.15)	1.00 (0.86–1.17)	<0.0001
Model 2 HR (95%CI)	1.34 (1.16–1.54)	1.00 (0.85–1.16)	1.00 (Reference)	1.04 (0.89–1.21)	1.05 (0.90–1.22)	0.005
Model 3 HR (95%CI)	1.34 (1.16–1.54)	0.99 (0.85–1.16)	1.00 (Reference)	1.04 (0.90–1.22)	1.06 (0.91–1.23)	0.008
Model 4 HR (95%CI)	1.24 (1.08–1.43)	1.00 (0.85–1.16)	1.00 (Reference)	1.10 (0.94–1.28)	1.10 (0.94–1.28)	0.26

†Linear trend in quintile number.
Model 1, Cox proportional hazards model adjusted for age, sex, race, and study site. Model 2, model 1 with additional adjustment for BMI, HDL-C, LDL-C, serum potassium, serum creatinine, smoking status, drinking status, educational level, SBP, diabetes, and antihypertensive medication. Model 3, model 2 with additional adjustment for prevalent MI, HF, or stroke at baseline. Model 4, model 3 with additional adjustment for incident MI, HF, or stroke as time-varying covariates.
AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.



risk factors for CVD such as African-American race, diabetes mellitus, systolic blood pressure, use of antihypertensive medications, and a history of CVD were inversely associated with serum Mg.

Serum Mg and AF Risk

Over a median follow-up time of 20.6 years, 1,755 incident cases of AF were identified through 31 December 2009. The association of serum Mg with incident AF approximately followed an L-shaped curve, with the highest AF risk among individuals with low serum Mg and a lower risk among individuals with average or higher Mg level. After adjustment for age, race, sex, and field center, individuals in the lowest quintile (<0.78 mmol/L) had approximately a 60% higher risk of AF compared to those in the middle quintile of serum Mg (≥0.80–0.83 mmol/L; HR, 1.60; 95% CI: 1.39–1.84; Table 2, model 1). Additional adjustment for multiple confounders, including a history of CVD (Table 2, models 2,3) partially attenuated the association (HR of AF for the lowest compared to the middle quintile: 1.34, 95% CI: 1.16–1.54). Additional adjustment for incident CVD as a potential mediator further attenuated the association (HR of AF for the lowest compared

to the middle quintile: 1.24, 95% CI: 1.08–1.43; Table 2, model 4). Further adjustment for PR interval provided similar results (data not shown). Results were similar in men and women (Figure 1), white and African-American subjects (Figure 2), and younger and older individuals (Figure 3).

Several sensitivity analyses were conducted to examine the association between serum Mg and AF in more detail. First, because most cases were identified through hospitalizations, we repeated the analysis including only the 117 incident AF cases identified on ECGs performed in the 3 ARIC follow-up visits. The adjusted HR of ECG-defined AF was 1.60 (95% CI: 0.88–2.91) and 1.47 (95% CI: 0.81–2.68) for the first quintile and fifth quintile, respectively, compared to the middle quintile (Table S1). Second, because diuretics have been shown to decrease serum Mg concentration, the association between serum Mg and incident AF was examined excluding the 2,426 individuals who were using diuretics. These results were similar to the results of the full cohort (Table S2). In the fully adjusted models, the risk of AF was 27% higher in those in the lowest quintile of serum Mg (HR, 1.27; 95% CI: 1.07–1.50) and 11% higher in those in the fifth quintile (HR, 1.11; 95% CI: 0.93–1.32) compared to those in the middle quintile. Third,

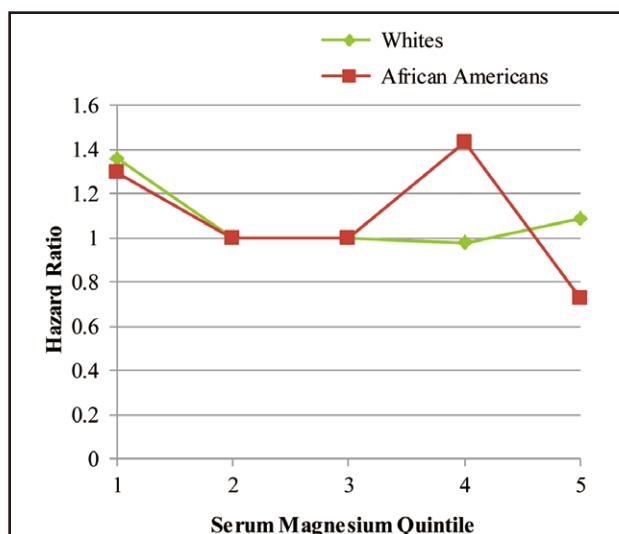


Figure 2. Association between serum magnesium quintile and atrial fibrillation stratified by race, Atherosclerosis Risk in Communities, 1987–2009. Cox proportional hazards model adjusted for age, sex, race, study site, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum potassium, serum creatinine, smoking status, drinking status, educational level, systolic blood pressure, diabetes, antihypertensive medication, and prevalent myocardial infarction, heart failure, or stroke. Reference group, third serum magnesium quintile. There was a reduced total of atrial fibrillation events in the fourth and fifth serum magnesium quintiles among African-American subjects ($n=52$ and $n=26$, respectively), and a modest interaction between serum Mg and race was identified ($P=0.04$).

due to an increase in measurement error the further away an Mg measurement is from the AF event, an analysis of only the first 10 years of follow-up was performed. With the occurrence of 526 incident AF cases, the resulting HRs were of similar magnitude to the full follow-up time analysis (results not shown). Fourth, we conducted an additional analysis excluding individuals with hypertension, diabetes, or a history of heart failure or MI at baseline to reduce potential residual confounding, and the results remained unchanged (data not shown). In a final analysis to examine the risk of AF among those with the lowest Mg level in more detail, the lowest serum Mg quintile was divided into 2 categories (≤ 0.73 mmol/L and 0.73 – 0.77 mmol/L; [Table S3](#)). This analysis resulted in the same association between serum Mg and AF risk, with a higher AF risk among individuals with lower serum Mg.

Dietary Mg and AF Risk

[Table 3](#) lists the HR of AF by quintile of dietary Mg. Overall, there was no association between dietary Mg and incident AF. When compared to those with a dietary Mg intake of 223.2–264.8 mg/day (middle quintile), those with an Mg intake of 320.1 mg/day or more (highest quintile) had an HR of 1.09 (95% CI: 0.86–1.36) while those with an Mg intake of <180.9 mg/day (lowest quintile) had an HR of 1.02 (95% CI: 0.83–1.24) in the multivariate models. No significant interaction was identified between dietary Mg and sex or race.

Discussion

In this prospective analysis of the ARIC cohort, an L-shaped

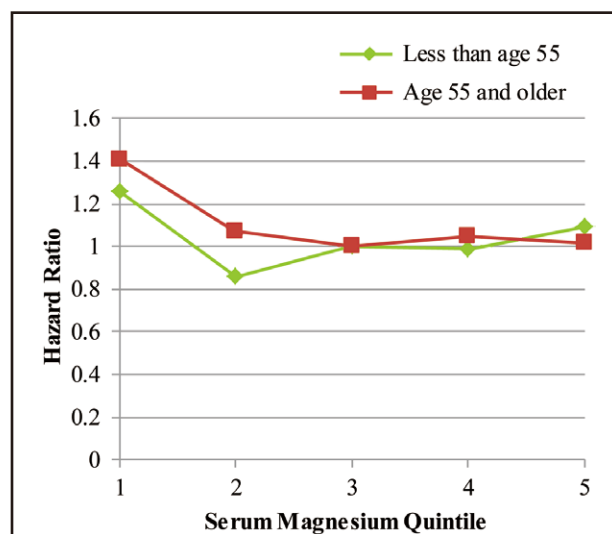


Figure 3. Association between serum magnesium quintile and atrial fibrillation stratified by age, Atherosclerosis Risk in Communities, 1987–2009. Cox proportional hazards model adjusted for age, sex, race, study site, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum potassium, serum creatinine, smoking status, drinking status, educational level, systolic blood pressure, diabetes, antihypertensive medication, and prevalent myocardial infarction, heart failure, or stroke. Reference group, third serum magnesium quintile.

association between serum Mg and incident AF was identified, with the highest risk of AF in individuals at the low end of the serum Mg distribution range, and a lower risk at more normal and elevated levels. This association was evident even after adjustment for the most important risk factors of AF and possible mediators of the serum Mg-AF relationship. The results did not differ significantly by race, sex, or age. Despite the association between serum Mg and AF, dietary Mg was not associated with the risk of AF, which may be due to limitations associated with the food frequency questionnaire being a less accurate measurement, yielding a higher degree of exposure misclassification. Serum Mg level also reflects intracellular levels and renal handling of whole-body Mg, and these factors may have a stronger effect on serum Mg than dietary Mg intake, especially given that only some dietary Mg is absorbed during digestion. Overall, the present results are consistent with previous analyses conducted on the ARIC cohort that have found an association of different cardiometabolic outcomes with serum Mg but not with dietary Mg.^{9,10,12–14}

Although this is the first study to report an association between serum Mg and AF in the general population to our knowledge, numerous studies, including randomized trials, have assessed the effect of i.v. Mg on prevention of AF in a postoperative setting. The findings, however, are inconclusive,^{19,31} and the potential effect mechanism is still not entirely understood.^{19–23} Intracellular Mg is frequently depleted after surgery,^{32,33} and this reduction in Mg has been linked to an increase in supraventricular and ventricular arrhythmias, including AF.³⁴ Kaplan et al have suggested that the decrease in Mg may be linked to an increase in the sensitivity of the atrial myocardium and the increased possibility of arrhythmias.²³ Indeed, i.v. Mg prolongs sinoatrial node conduction time, atrioventricular conduction and atrial refractoriness,^{35,36} which potentially

Table 3. HR and 95% CI of AF vs. Dietary Mg Quintile, Atherosclerosis Risk in Communities, 1987–2009

	Dietary magnesium (mg/day)					P-value for trend†
	<180.90 (n=2,711)	180.90–223.16 (n=2,711)	223.17–264.76 (n=2,712)	264.77–320.08 (n=2,711)	≥320.08 (n=2,711)	
Cases	295	335	315	343	359	
Person-years	49,579	49,852	50,303	50,474	48,473	
Crude incidence rate (per 1,000 person-years)	5.95	6.72	6.26	6.80	7.41	
Model 1 HR (95%CI)	1.09 (0.92–1.30)	1.10 (0.94–1.28)	1.00 (Reference)	1.03 (0.88–1.20)	1.05 (0.88–1.26)	0.51
Model 2 HR (95%CI)	1.07 (0.88–1.31)	1.10 (0.93–1.29)	1.00 (Reference)	1.05 (0.89–1.24)	1.09 (0.87–1.37)	0.80
Model 3 HR (95%CI)	1.10 (0.91–1.34)	1.12 (0.95–1.32)	1.00 (Reference)	1.04 (0.88–1.23)	1.07 (0.86–1.35)	0.55
Model 4 HR (95%CI)	1.02 (0.83–1.24)	1.04 (0.89–1.23)	1.00 (Reference)	1.05 (0.89–1.24)	1.09 (0.86–1.36)	0.82

†Linear trend in quintile number.

Model 1, Cox proportional hazards model adjusted for age, sex, race, study site, and total energy intake. Model 2, model 1 with additional adjustment for BMI, HDL-C, LDL-C, smoking status, drinking status, educational level, SBP, diabetes, antihypertensive medication, and intake of potassium, calcium, dietary fiber, protein, caffeine, and polyunsaturated to saturated fat ratio. Model 3, model 2 with additional adjustment for prevalent MI, HF, or stroke at baseline. Model 4, model 3 with additional adjustment for incident MI, HF, or stroke as time-varying covariates. Abbreviations as in Tables 1,2.

lowers the risk of AF. Mg also plays a role in cell membrane stabilization, modulation of calcium and potassium channels, and acts as a cofactor in numerous enzymatic reactions.³⁷

Some potential limitations related to the exposure in this study should be noted. First, serum Mg accounts for only <1% of all Mg in the body³⁸ and the correlation coefficient of 0.46 between visit 1 and visit 2 serum Mg suggests that there may be a large, intraindividual variation of serum Mg concentration. There is moderate correlation ($r=0.54$), however, between serum Mg level and the intracellular free Mg level.³⁹ Both circumstances likely lead to non-differential misclassification of serum Mg exposure. We expect this misclassification to bias the results toward the null and possibly underestimate the true association. Second, because the use of diuretics has been shown to reduce not only blood pressure but also serum Mg concentration,^{37,40} hypertension may be a potential confounder between serum Mg and AF incidence. In a sub-analysis excluding individuals on diuretics, however, the association between serum Mg and incident AF risk remained unchanged. Third, serum Mg was measured only during early follow-up; therefore, this may not be reflective of usual serum Mg or of the level immediately preceding an AF event, which may be more relevant as a predictor of AF. In an analysis restricted to the first 10 years of follow-up, however, results were similar to those for the entire period.

In addition, the ascertainment of AF in the ARIC cohort was not without limitations. The majority of AF cases were identified through hospitalization discharges, which does not account for asymptomatic AF or AF managed in outpatient settings. As a result, there may be an underascertainment of incident AF cases. To examine the differential ascertainment of AF, a sensitivity analysis including AF cases identified from study ECGs of all study participants was performed and showed an association between serum Mg and AF of a similar magnitude. Also, the ascertainment of AF cases through hospitalizations in ARIC and other cohorts has shown acceptable validity.^{3,41} Finally, AF incidence rates in the ARIC cohort are consistent with other cohort studies, further supporting the case ascertainment validity.³

Unmeasured or residual confounding could partly explain the observed association. Individuals with low levels of serum Mg were more likely to be hypertensive, diabetic or present a previous history of CVD, all established risk factors for AF. We adjusted for these covariates and others in the multivariate anal-

ysis, however, making confounding a less likely explanation for the present results. Also, in a sensitivity analysis, the results remained unchanged even after excluding individuals with hypertension, diabetes, or a history of HF or MI at baseline.

Despite these limitations, some important strengths related to the present analysis should be highlighted: the large, biracial sample with a long follow-up time, a large number of AF events, and the detailed measurement of key covariates in this cohort.

Conclusion

Overall, this study has identified an association between low serum Mg and higher AF risk but no association between dietary Mg and incidence of AF. Future studies are needed to examine the specific mechanisms underlying this association and to explore the effect of changes in serum Mg level over time on AF risk.

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Supplementary Files

Supplementary File 1

Table S1. HR and 95% CI of Electrocardiogram AF by Serum Magnesium Quintile, Atherosclerosis Risk in Communities, 1987–2009

Table S2. HR and 95% CI of AF by Serum Magnesium Quintile Excluding Participants on Diuretics, Atherosclerosis Risk in Communities, 1987–2009

Table S3. HR and 95% CI of AF by Serum Magnesium Quintile, With Lowest Quintile Split in 2 Categories, Atherosclerosis Risk in Communities, 1987–2009

Please find supplementary file(s);
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