

Plasma and dietary magnesium and risk of sudden cardiac death in women^{1–3}

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ABSTRACT

Background: Magnesium has antiarrhythmic properties in cellular and experimental models; however, its relation to sudden cardiac death (SCD) risk is unclear.

Objective: We prospectively examined the association between magnesium, as measured in diet and plasma, and risk of SCD.

Design: The analysis was conducted within the Nurses' Health Study. The association for magnesium intake was examined prospectively in 88,375 women who were free of disease in 1980. Information on magnesium intake, other nutrients, and lifestyle factors was updated every 2–4 y through questionnaires, and 505 cases of sudden or arrhythmic death were documented over 26 y of follow-up. For plasma magnesium, a nested case-control analysis including 99 SCD cases and 291 controls matched for age, ethnicity, smoking, and presence of cardiovascular disease was performed.

Results: After multivariable adjustment for confounders and potential intermediaries, the relative risk of SCD was significantly lower in women in the highest quartile compared with those in the lowest quartile of dietary (relative risk: 0.63; 95% CI: 0.44, 0.91) and plasma (relative risk: 0.23; 95% CI: 0.09, 0.60) magnesium. The linear inverse relation with SCD was strongest for plasma magnesium (P for trend = 0.003), in which each 0.25-mg/dL (1 SD) increment in plasma magnesium was associated with a 41% (95% CI: 15%, 58%) lower risk of SCD.

Conclusions: In this prospective cohort of women, higher plasma concentrations and dietary magnesium intakes were associated with lower risks of SCD. If the observed association is causal, interventions directed at increasing dietary or plasma magnesium might lower the risk of SCD. *Am J Clin Nutr* 2011;93:253–60.

INTRODUCTION

Sudden death from cardiac causes accounts for >50% of all coronary artery disease (CAD) deaths, with estimates ranging from 184,000 to 462,000 deaths annually (1). Most patients who suffer sudden cardiac death (SCD) are not at high risk on the basis of established criteria (2), and up to 55% of men and 68% of women have no clinically recognized heart disease before sudden death (3, 4). Therefore, low-cost primary preventive strategies are needed to markedly reduce the incidence of SCD in the general population (1).

Magnesium, an intracellular cation that is easily and routinely measured in blood, plays an important role in cardiac electrophysiology as an activator of sodium potassium ATPase (5). This channel regulates ion currents across cell membranes (6), thereby maintaining the cell's resting membrane potential, membrane

stability, and excitability (5, 7). Evidence from experimental and animal models suggests that magnesium has antiarrhythmic properties (8, 9), whereas chronic magnesium deficiency may be proarrhythmic (10).

Prospective epidemiologic studies have reported variable associations between magnesium and risk of cardiovascular disease (CVD) (11–15). In general, relations were stronger for plasma than for dietary magnesium. Furthermore, the association between plasma magnesium and CAD risk appears stronger for fatal than for nonfatal events (11), which could be explained if magnesium was protective against fatal ventricular arrhythmias and thus SCD. This hypothesis is supported further by ecologic studies, which reported inverse associations between regional drinking water hardness and sudden death (16) and autopsy studies, which reported lower myocardial magnesium concentrations in victims of SCD as compared with trauma (17, 18). However, prospective data regarding the association between magnesium and SCD are sparse, with only one study reporting an inverse association between serum magnesium and SCD (19). Therefore, we prospectively examined the association between magnesium, both in the diet and plasma, and risk of SCD in women in the Nurses' Health Study (NHS).

SUBJECTS AND METHODS

Study population

The NHS is a cohort study of 121,700 female nurses aged 30–55 y at baseline in 1976 (20). Detailed information on lifestyle

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habits, medical history, and newly diagnosed disease was updated biennially, and dietary information was collected by using a semiquantitative food-frequency questionnaire (FFQ) in 1980, 1984, 1986, and every 4 y through 2002. Between 1989 and 1990, 32,826 women in this cohort provided a blood sample. Participants who provided blood samples were similar to those who did not (21). Informed consent was obtained from all participants, and the study was approved by the institutional review board at Brigham and Women's Hospital.

Endpoint ascertainment and definitions

Details for the classification of SCD were described previously (4, 22). Briefly, cardiac deaths were considered sudden if the death or cardiac arrest occurred within 1 h of symptom onset, as documented by medical records or through reports from next of kin. Deaths were also classified as arrhythmic or nonarrhythmic based on the definition of Hinkle and Thaler (23). We included arrhythmic deaths, even if symptoms lasted >1 h, and excluded nonarrhythmic deaths, even if symptoms lasted <1 h. Unwitnessed deaths or deaths that occurred during sleep and the participant was documented to be symptom free when last observed within the preceding 24 h were considered probable, if circumstances suggested that the death could have been arrhythmic. Results were not substantially different when we excluded these probable cases (data not shown).

Assessment of nutrients and lifestyle factors

For each food item on the FFQ, a commonly used portion size was specified, and participants were asked how often, on average, they had consumed that quantity over the past year. Average nutrient intake was calculated by multiplying the frequency of consumption of each food by its nutrient content and then summing across all foods. Magnesium intake was the sum of magnesium from food and supplemental sources, including multivitamins and magnesium supplements. Nutrient values were obtained from the Harvard University Food Composition Database (24). All nutrients were adjusted for total energy intake by using the residual method (25). Information on anthropometric, lifestyle, and CVD risk factor status was ascertained from biennial questionnaires.

Measurement of biochemical variables

Blood samples were collected and stored in a liquid nitrogen freezer as previously described (26). Plasma magnesium was measured with the Siemens Dimension Vista 1500 System from Dade Behring (now Siemens Health Care Diagnostics Inc, Newark, DE) by using a modified methylthymol blue procedure (27). In addition, we measured triglycerides, total cholesterol, HDL and LDL cholesterol, *N*-terminal pro-B type natriuretic peptide (NT-proBNP), and high-sensitivity C-reactive protein (hsCRP) as described previously (22). Glomerular filtration rate was estimated by using the Modification of Diet in Renal Disease formula. The CV for plasma magnesium was 4%. The intraclass correlation for plasma magnesium from samples taken 1 y apart was 0.63.

Dietary magnesium data analysis

The association between magnesium intake and SCD was analyzed by using a prospective cohort design among women

who returned the 1980 FFQ. Women with prior diagnosis of cancer or who had invalid dietary data (ie, left ≥ 10 food items blank or had implausible energy intake [< 600 or > 3500 kcal/d]) were excluded, leaving 88,375 women for analysis. Women with a history of prior CVD (angina, myocardial infarction, coronary revascularization, or stroke) at baseline or who developed CVD during follow-up were not excluded from the primary analysis. Instead, we controlled for prior report of CVD in the analysis. Women contributed person-time in this analysis, from date of return of the 1980 questionnaire until the date of death or end of follow-up (1 June 2006), whichever came first.

We calculated the cumulative average of magnesium intake and other nutrients from repeated dietary assessments to reduce measurement error (28). Because we hypothesized that short-term intake would have the greatest influence on SCD risk, we gave more weight to the most recent diet. For example, magnesium intake from the 1984 FFQ was used to estimate SCD risk between 1984 and 1986, whereas an average of the 1984 and 1986 magnesium intake was used to predict SCD risk occurring between 1986 and 1990. To estimate disease risk between 1990 and 1994, we used the average of magnesium intake in 1984 and 1986 and magnesium intake in 1990 (28). In multivariable models, other covariates were updated at various time points; if data were missing at a given time point, the last observation was carried forward for 1 cycle.

The means and proportions of baseline characteristics and CVD risk factors across quartiles of magnesium intake were calculated for descriptive purposes only. Cox proportional hazards models were used to analyze the association between magnesium intake and the risk of SCD, with adjustment for CVD risk factors and nutrients that may influence magnesium metabolism (potassium, calcium, and vitamin D) or were previously associated with risk of SCD [marine omega-3 (*n*-3) fatty acids], all in quartiles. In separate models, we furthered adjusted for intermediate endpoints, including diabetes, hypertension, and hypercholesterolemia, to address potential mechanistic pathways through which magnesium intake may influence risk of SCD. Further adjustment for cholesterol or blood pressure-lowering medication use did not alter the results (data not shown). To test for a linear trend, we assigned the median value of plasma magnesium to each quartile and modeled this variable as a continuous variable in separate regression models. We also examined the possibility of a non-linear relation between magnesium intake and SCD risk non-parametrically by using restricted cubic spline transformations (29) and tested for nonlinearity by using the likelihood ratio test, comparing the model with the linear term with the model with the linear and the cubic spline terms combined.

In prespecified secondary analyses, we explored whether the relation between magnesium intake and SCD was modified by preexisting CAD (myocardial infarction, angina, or coronary revascularization). To test formally for interaction, we modeled the cross-product term between magnesium intake and CAD history and used a likelihood ratio test to compare models with and without the interaction term.

Plasma magnesium data analysis

To estimate the association between plasma magnesium and risk of SCD, we used a prospective nested case-control study in the 32,826 women who provided a blood sample between 1989

and 1990. From among these women, 99 cases of SCD occurred after return of the blood sample and before 1 June 2006. Using risk-set sampling (30), we randomly selected controls in a 3:1 ratio, matched to cases on age (± 1 y), ethnicity, smoking status (current, never, or past), time and date of blood sampling, fasting status, and CVD before death. Matched case-control pairs were shipped to the laboratory in the same batch, and magnesium and other biochemical assays were performed in the same analytic run. The order of each case-control pair was random to keep the laboratory personnel blinded to case-control status.

We calculated the means and proportions of baseline characteristics, CVD risk factors, and biomarkers across quartiles of plasma magnesium concentration among the controls. We also compared the means and proportions of baseline characteristics in cases and controls and tested the significance of these associations using repeated-measures analysis of variance (Proc Mixed in SAS; SAS Institute Inc, Cary, NC) for continuous variables and generalized estimating equations for categorical variables. Age-adjusted Spearman correlations were used to assess the association between plasma and dietary magnesium.

The association between plasma magnesium and the risk of SCD was assessed by using multivariable conditional logistic regression. With risk-set analysis, the odds ratio derived from the conditional logistic regression directly estimates the hazard ratio (30) and thus the relative risk (RR). The quartiles of plasma magnesium were created based on the distribution of plasma magnesium among the controls, and cases were assigned to the appropriate category. However, given the restricted range of values for plasma magnesium, the participants were not evenly distributed in each quartile. Tests for linear trend across quartiles

and deviations from linearity were performed, as described above. Models were adjusted for various nutritional and other risk factors ascertained on the 1990 questionnaire (the year the blood samples were collected) and biomarkers associated with SCD (total:HDL cholesterol, glomerular filtration rate, hsCRP, and NT-proBNP). Further adjustment for blood pressure- and cholesterol-lowering medications, triglycerides, and uric acid did not alter the risk estimates (data not shown). Because thiazide diuretic use can alter plasma magnesium concentrations, we conducted a separate analysis excluding women who reported use of these medications at the time of blood draw. All analyzes were carried out by using SAS version 9.1 (SAS Institute Inc).

RESULTS

Dietary magnesium analysis

The distribution of selected characteristics in 1980 in this population across quartiles of magnesium intake is detailed in **Table 1**. Women with a greater intake of magnesium tended to be older, to smoke, to have a slightly lower BMI, to exercise more, and to have a higher intake of potassium, calcium, vitamin D, long-chain omega-3 fatty acids, and alcohol at baseline. Data on magnesium supplement use were first collected in 1984. Approximately 4% of the women reported taking a magnesium supplement, and the results were similar when these supplement users were excluded (data not shown).

In this cohort, 505 cases of SCD ($n = 295$ definite, $n = 210$ probable) were identified over 26 y of follow-up. In the age-adjusted model, magnesium intake was inversely associated with

TABLE 1
Cardiovascular disease risk factors and selected nutrient intakes in 88,375 women in the Nurses' Health Study in 1980 according to quartile (Q) of magnesium intake¹

	Magnesium intake (mg/d)			
	Q1	Q2	Q3	Q4
Range of magnesium (mg/d)	<261	261–300	301–345	>345
Median magnesium (mg/d)	235	281	321	383
No. of subjects	30,071	21,415	19,182	17,707
Age (y)	46 \pm 7 ²	47 \pm 7	47 \pm 7	48 \pm 7
Current smoker (%)	27	28	30	31
Parental history of MI (%)	13	12	13	14
History of hypertension (%)	18	16	15	16
History of diabetes (%)	2	2	2	3
History of high cholesterol (%)	5	5	6	7
BMI (kg/m ²)	24.6 \pm 4.8	24.3 \pm 4.4	24.3 \pm 4.2	24.3 \pm 4.2
Physical activity (MET-h/wk)	3.6 \pm 2.8	3.8 \pm 2.9	4.0 \pm 2.9	4.4 \pm 2.9
Current use of postmenopausal hormones (%)	8	8	8	8
Current aspirin use >22 d/mo (%)	15	14	15	15
Current use of thiazide diuretics (%)	10	10	10	11
Nutrients				
Potassium (mg/d)	2209 \pm 349	2690 \pm 320	2996 \pm 371	3488 \pm 527
Calcium (mg/d)	574 \pm 236	717 \pm 272	804 \pm 308	940 \pm 341
Vitamin D (IU/d)	274 \pm 252	323 \pm 279	354 \pm 290	403 \pm 322
Long-chain omega-3 fatty acids (% of total energy)	0.06 \pm 0.04	0.08 \pm 0.08	0.09 \pm 0.07	0.11 \pm 0.10
Saturated fat (% of total energy)	16.7 \pm 3.6	15.9 \pm 3.3	15.2 \pm 3.3	13.7 \pm 3.4
Fiber (g/d)	11.2 \pm 3.6	13.2 \pm 3.8	14.6 \pm 4.3	17.5 \pm 5.5
Alcohol (g/d)	5.8 \pm 10.6	6.4 \pm 10.2	6.8 \pm 10.7	6.8 \pm 10.7

¹ All nutrients, except alcohol, were energy adjusted. MI, myocardial infarction; MET-h, metabolic equivalent task hours.

² Mean \pm SD (all such values).

SCD (P for trend = 0.003), and women in the highest quartile of magnesium intake had a significantly lower risk of SCD than did women in the lowest quartile (RR: 0.62; 95% CI: 0.48, 0.79) (Table 2). Further adjustment for CVD risk factors, diet, lifestyle, medication use (multivariable model 1), and potential intermediate diseases (multivariable model 2) did not appreciably alter this result (RR for the highest compared with the lowest quartile: 0.66; 95% CI: 0.46, 0.95); however, the P for linear trend across quartiles became nonsignificant (P for trend = 0.09, multivariable model 2). The inverse association was significant in the second quartile of magnesium intake, with minimal change in the RRs at higher levels of consumption. Thus, in a post hoc analysis, we explored a potential threshold relation by comparing the risk of SCD in the top 3 quartiles with that in the lowest quartile. The RR in women in the top 3 quartiles, compared with quartile 1, for magnesium intake was 0.71 (95% CI: 0.53, 0.93); however, no significant deviation from linearity was detected (P for deviation from linearity = 0.76) when cubic spline transformations were used. No significant interactions between magnesium intake and prior CAD diagnosis were found (P for interaction = 0.89).

Plasma magnesium analysis

Of the controls selected for the nested case-control analysis, women with higher plasma magnesium concentrations tended to have a lower prevalence of CVD, diabetes, and hypertension; were less likely to use aspirin, postmenopausal hormone therapy, and thiazide diuretics; and tended to have a lower concentration of hsCRP, a lower glomerular filtration rate, and higher concentrations of total, LDL, and HDL cholesterol (Table 3). Plasma magnesium was not significantly correlated with dietary magnesium ($r = 0.07$, $P = 0.23$) or associated with any other CVD risk factors or nutrients. As compared with controls, cases of SCD were more likely to have a parental history of MI, have a personal history of diabetes and/or hypertension, or use thiazide diuretics (Table 4). Plasma magnesium concentrations were lower in the cases than in the controls ($P = 0.009$).

After adjustment for matching factors, plasma magnesium concentrations were inversely associated with SCD (P for trend = 0.006). Women in the highest compared with the lowest quartile

of plasma magnesium had a significantly lower risk of SCD (RR: 0.39; 95% CI: 0.20, 0.78) (Table 5), and no deviations from linearity in the relative risks was detected (P for deviation from linearity = 0.64). This association was strengthened after adjustment for CVD risk factors, thiazide diuretics, dietary nutrients, biomarkers, and potential intermediate diseases (multivariate model 4) (RR for the comparison of quartile 4 with quartile 1: 0.23; 95% CI: 0.09, 0.60). When analyzed as a continuous variable, each 0.25-mg/dL (1-SD) increment in plasma magnesium was associated with an RR of 0.59 (95% CI: 0.41, 0.85) after adjustment for CVD risk factors, nutrients, and biomarkers.

This association remained significant in secondary analyses in which women who had developed CVD by the time of the blood draw were excluded ($n = 30$). The multivariate RR for the comparison of the highest with the lowest quartile of plasma magnesium was 0.26 (95% CI: 0.08, 0.87). Additionally, the association between plasma magnesium and SCD remained significant among women who did not report thiazide diuretic use (RR for the comparison of extreme quartiles: 0.22; 95% CI: 0.06, 0.70).

DISCUSSION

In this large prospective cohort of women, magnesium measured in diet and plasma was associated with a lower risk of SCD. Women in the highest compared with the lowest quartile of dietary and plasma magnesium had a 34% and 77% lower SCD risk, respectively. The relation was stronger for plasma magnesium, for which the inverse association appeared linear across the normal range of plasma magnesium, with a 41% lower risk of SCD with each 1-SD increase. The relatively consistent inverse association found between these 2 measures of magnesium and SCD risk is supportive of the hypothesis that magnesium might modify SCD risk.

Inverse associations between magnesium and total CAD have been reported previously in some, but not in all, prior prospective studies. Weak associations between dietary magnesium and CAD have been reported solely among men (12–14), whereas serum magnesium was inversely associated with CAD only among women in the Atherosclerosis Risk in Communities (ARIC) Study.

TABLE 2

Relative risk (95% CI) of sudden cardiac death by quartile (Q) of magnesium intake¹

	Magnesium intake (mg/d)				<i>P</i> for trend ²
	Q1	Q2	Q3	Q4	
Median magnesium intake (mg/d)	235	281	321	383	
No. of cases	124	96	146	139	
Person-years	568,020	567,696	567,670	566,412	
Age-adjusted model	1.0 (ref)	0.61 (0.47, 0.80)	0.81 (0.64, 1.03)	0.62 (0.48, 0.79)	0.003
Multivariate model 1	1.0 (ref)	0.63 (0.47, 0.86)	0.82 (0.60, 1.13)	0.63 (0.44, 0.91)	0.06
Multivariate model 2	1.0 (ref)	0.64 (0.47, 0.87)	0.85 (0.62, 1.17)	0.66 (0.46, 0.95)	0.09

¹ ref, reference. Multivariate model 1 was a Cox proportional hazards model adjusted for age; history of cardiovascular disease (yes or no); total calories; smoking; BMI (in kg/m²; <25, 25–29.9, or ≥30); parental history of myocardial infarction before age 60 y (yes or no); alcohol intake (<0.1, 0.1–14.9, 15–29.9, or ≥30 g/d); physical activity (quintiles of metabolic equivalent task hours/wk); use of postmenopausal hormones, thiazide diuretics, and aspirin >22 d/mo (yes or no); and intakes of long-chain omega-3 fatty acid (% of energy), calcium (mg/d), potassium (mg/d), and vitamin D (IU/d) (all in quartiles). Multivariate model 2 was adjusted as for model 1 plus hypertension, hypercholesterolemia, and diabetes.

² P for linear trend estimated by assigning the median value of plasma magnesium in each quartile and modeling this as a continuous variable in Cox proportional hazards models.

TABLE 3

Cardiovascular biomarkers and selected nutrient intakes in 1990 according to quartile (Q) of plasma magnesium in 291 controls in a nested case-control study in the Nurses' Health Study¹

	Plasma magnesium (mg/dL)			
	Q1	Q2	Q3	Q4
Range of magnesium (mg/dL)	<1.9	1.9–2.0	2.1–2.1	>2.1
Median magnesium (mg/dL)	1.7	1.9	2.1	2.3
No. of subjects	54	86	56	95
Age (y)	61 ± 6 ²	61 ± 6	61 ± 6	60 ± 6
Current smoker (%)	20	29	9	24
Parental history of MI (%)	17	28	16	15
History of hypertension (%)	55	43	51	38
History of diabetes (%)	15	12	1	5
History of cardiovascular disease (%)	48	46	34	37
BMI (kg/m ²)	27.3 ± 5.6	26.0 ± 4.2	27.5 ± 5.2	25.8 ± 5.0
Physical activity (MET-h/wk)	18.0 ± 20.2	15.0 ± 15.6	20.3 ± 24.0	165.1 ± 18.7
Current use of postmenopausal hormones (%)	41	39	37	29
Current aspirin use >22 d/mo (%)	31	16	12	18
Current use of thiazide diuretics (%)	18	18	20	10
Current use of magnesium supplements (%)	7	3	1	1
Nutrients				
Magnesium (mg/d)	295 ± 65	303 ± 64	332 ± 85	307 ± 66.5
Potassium (mg/d)	2884 ± 502	2924 ± 501	3023 ± 538	2922 ± 554
Calcium (mg/d)	1024 ± 548	985 ± 439	971 ± 507	1040 ± 518
Vitamin D (IU/d)	384 ± 251	384 ± 255	363 ± 253	362 ± 240
Long-chain omega-3 fatty acids (% of total energy)	0.15 ± 0.14	0.15 ± 0.13	0.18 ± 0.14	0.15 ± 0.15
Alcohol (g/d)	8.0 ± 16	6.5 ± 14	5.9 ± 10.6	5.4 ± 9.8
Cardiovascular biomarkers				
Cholesterol (mg/dL)				
Total	212 ± 38	225 ± 35	234 ± 34.7	242 ± 47
LDL	135 ± 39	148 ± 32	153 ± 29	162 ± 44
HDL	64 ± 14	62 ± 14	66 ± 14	68 ± 17
Triglycerides (mg/dL)	161 ± 109	161 ± 72	169 ± 102	154 ± 58
C-reactive protein (mg/L)	6.6 ± 8.6	4.9 ± 4.9	4.7 ± 5.5	3.9 ± 4.6
N-Terminal pro-B type natriuretic peptide (pg/mL)	128 ± 133	163 ± 327	135 ± 119	109 ± 122
Glomerular filtration rate (mL · min ⁻¹ · 1.73 m ⁻²)	117 ± 105	92 ± 21	96 ± 28	86 ± 23

¹ All nutrients, except alcohol, were energy adjusted. MI, myocardial infarction; MET-h, metabolic equivalent task hours.

² Mean ± SD (all such values).

In the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study (11), plasma magnesium was associated with fatal, but not with nonfatal ischemic heart disease events. One potential explanation for this latter finding was that magnesium may be associated more strongly with fatal arrhythmias and SCD than with the development of atherosclerosis.

Despite promising autopsy and ecologic data supporting a specific association with SCD (16–18), to our knowledge, only one other study prospectively examined the association between magnesium and SCD. Similar to our findings, higher serum magnesium concentration was associated with a lower risk of SCD within the multiethnic ARIC population over 12 y of follow-up (19). In the ARIC Study, the corresponding RR of SCD for the comparison of the fourth to first quartiles of serum magnesium was less extreme (RR: 0.62; 95% CI: 0.42, 0.93). In further contrast with our data, dietary magnesium was not associated with SCD risk in the ARIC Study (19); however, repeated measures of dietary intake were not available, and the number of SCDs was smaller ($n = 264$) than in our dietary analysis.

In addition to these prospective studies, several lines of evidence support a specific antiarrhythmic action of magnesium. Extra-

cellular magnesium influences cardiac ion channel properties (31) and regulates potassium homeostasis through activation of sodium potassium ATPase (5). Magnesium administration suppresses early after depolarizations and dispersion of repolarization (8, 9), whereas magnesium deficiency results in polymorphic ventricular tachycardia and SCD in animal models (10). In clinical studies, magnesium therapy is efficacious in the treatment of arrhythmias secondary to acquired torsades de pointes (32) or hypomagnesemia (33). Apart from antiarrhythmic actions, magnesium may also influence SCD risk through other pathways, including improvements in vascular tone, lipid metabolism, endothelial function, inflammation, blood pressure, diabetes, and inhibition of platelet function (34–36).

As in previous studies (12, 37), plasma and dietary magnesium are not strongly correlated in this population. Plasma magnesium concentrations are under tight homeostatic regulation by a variety of mechanisms, most notably by renal excretion; therefore, plasma magnesium is a poor surrogate for magnesium intake. However, magnesium supplementation increases plasma (38) and intracellular (39) magnesium concentrations, particularly among patients with hypomagnesemia. Thus, magnesium intake may have a greater influence on plasma magnesium at more extreme



TABLE 4
Baseline characteristics of the study participants according to case status¹

	Cases (n = 99)	Controls (n = 291)	P value ²
Matching factors			
Age (y)	61 ± 6 ³	61 ± 6	NA
Current smoker (%)	23	23	NA
History of cardiovascular disease (%)	40	40	NA
Cardiovascular disease risk factors			
Parental history of coronary disease (%)	28	19	0.06
History of hypertension (%)	61	45	0.01
History of diabetes (%)	21	8	<0.001
BMI (kg/m ²)	27.1 ± 5.4	26.4 ± 5.0	0.29
Activity (MET-h/wk)	16.5 ± 18.9	16.6 ± 19.3	0.97
Drug therapy (%)			
Hormone therapy at blood draw	32	37	0.36
Aspirin use >22 d/mo	25	18	0.10
Thiazide diuretics	27	16	0.02
Magnesium supplements	2	3	0.75
Nutrients			
Plasma magnesium (mg/dL)	2.0 ± 0.2	2.1 ± 0.3	0.009
Magnesium intake (mg/d)	296 ± 65	308 ± 70	0.11
Potassium intake (mg/d)	2956 ± 629	2934 ± 525	0.92
Calcium intake (mg/d)	1023 ± 483	1007 ± 498	0.78
Vitamin D intake (IU/d)	311 ± 208	373 ± 248	0.06
Omega-3 fatty acid intake (% of energy)	0.13 ± 0.13	0.15 ± 0.14	0.29
Alcohol (g/d)	6.5 ± 11.9	6.3 ± 12.7	0.92

¹ MET-h, metabolic equivalent task hours; NA, not applicable.² P values were calculated by using repeated-measures linear regression models (Proc Mixed in SAS; SAS Institute Inc, Cary, NC) for continuous variables and generalized estimating equations for categorical variables.³ Mean ± SD (all such values).

intakes than seen in our population. Alternatively, a stronger correlation with diet may have been observed if intracellular magnesium concentrations had been measured.

If the observed association between magnesium and SCD risk is ultimately found to be causal through randomized trials, these findings would have important public health implications. The estimated magnesium intake from food sources in 2005–2006 was 261 mg in women and 347 mg in men (40), which is well below the Recommended Dietary Allowance (RDA) (320 mg for

women and 420 mg for men), and most Americans do not meet the RDA, even with the use of magnesium-containing supplements (41, 42). Therefore, increases in magnesium intake would likely require supplementation or fortification of water or food supplies. Such public health strategies may be effective in preventing SCD and other CVD outcomes associated with low magnesium intake. Although short-term administration of intravenous magnesium in the setting of acute myocardial infarction did not reduce the risk of cardiac arrest or mortality in a large-scale

TABLE 5
Relative risk (95% CI) of sudden cardiac death by quartile (Q) of plasma magnesium¹

	Plasma magnesium (mg/dL)				P for trend ²
	Q1	Q2	Q3	Q4	
Range of magnesium (mg/dL)	<1.9	1.9–2.0	2.1–2.1	>2.1	
Cases/controls (n)	30/54	31/89	14/56	24/95	
Median magnesium in cases (mg/dL)	1.8	1.9	2.1	2.2	
Median magnesium in controls (mg/dL)	1.7	1.9	2.1	2.3	
Multivariate model 1	1.0 (ref)	0.61 (0.33, 1.12)	0.42 (0.20, 0.90)	0.39 (0.20, 0.78)	0.006
Multivariate model 2	1.0 (ref)	0.47 (0.23, 0.95)	0.31 (0.13, 0.74)	0.23 (0.10, 0.53)	0.001
Multivariate model 3	1.0 (ref)	0.50 (0.23, 1.09)	0.33 (0.13, 0.86)	0.19 (0.08, 0.50)	0.001
Multivariate model 4	1.0 (ref)	0.56 (0.25, 1.25)	0.41 (0.15, 1.10)	0.23 (0.09, 0.60)	0.003

¹ ref, reference. Multivariate model 1 was a Cox proportional hazards model adjusted for age and fasting. Multivariate model 2 was adjusted as for model 1 plus BMI (in kg/m²; <25, 25–29.9, or ≥30), parental history of myocardial infarction before age 60 y (yes or no), alcohol intake (<0.1, 0.1–14.9, 15–29.9, or ≥30 g/d), physical activity (quintiles of metabolic equivalent task hours/wk), postmenopausal hormone use, use of thiazide diuretics (yes or no), aspirin use >22 d/mo (yes or no), and intake of magnesium (mg/d), long-chain omega-3 (n–3) fatty acids (% of energy), calcium (mg/d), potassium (mg/d), and vitamin D (IU/d) (all in quartiles). Multivariate model 3 was adjusted as for model 2 plus total:HDL cholesterol, glomerular filtration rate, C-reactive protein, and N-terminal pro-B type natriuretic peptide. Multivariate model 4 was adjusted as for model 3 plus history of diabetes and hypertension.

² Estimated by assigning the median value of plasma magnesium in each quartile and modeling this as a continuous variable in regression models.

randomized trial (43), it is plausible that chronic long-term magnesium supplementation might still be beneficial in a more general population. We must emphasize that observational studies cannot establish causality and, ultimately, randomized controlled trials will be needed to definitively test this hypothesis.

Strengths of the present study include the prospective design, the large well-characterized cohort with repeated assessments of diet and long-term follow-up, and the large number of rigorously confirmed sudden and/or arrhythmic cardiac deaths—a difficult phenotype to classify in population studies. Potential study limitations also require discussion. First, the selective nature of the cohort, primarily white US female nurses, may limit the generalizability of the findings to other groups of women, ethnicities, or men. However, the good health status of this population also minimizes potential confounding due to preexisting comorbidities.

Second, although plasma magnesium is used routinely to assess magnesium status, <1% of magnesium circulates in the blood (44) and plasma magnesium may not be reflective of total body stores. However, if plasma magnesium is low, magnesium deficiency is usually present (44). Also, our analysis was based on a single baseline determination of plasma magnesium. Whereas our results remain strongly supportive of an association between magnesium and SCD risk, serial measurements or a measure of intracellular magnesium, such as that in lymphocytes, erythrocytes, or myocytes, may have provided a more precise assessment of the true relation. In addition, the FFQ does not capture magnesium intake from drinking water, which may account for 20–30% of a person's daily requirement (37, 45), and likely underestimates total magnesium intake. These sources of non-differential misclassification should underestimate the strength of the relation between magnesium and SCD in our data.

Finally, as with any observational study, residual confounding by other factors could explain, in part, the association between magnesium and SCD. We do not have complete data on drug therapies, specifically during the early follow-up years, or direct clinical measurements of heart rate and blood pressure, and therefore could not control for these parameters in our models. However, control for a variety of other coronary risk factors, biomarkers, and nutrients in our models had little effect on the risk estimates. Furthermore, although we controlled for dietary potassium in our models, we did not measure and were unable to control for plasma potassium in our case-control analysis. However, plasma potassium did not confound or modify the association between plasma magnesium and SCD in the ARIC Study (19).

In summary, both plasma concentrations and dietary intake of magnesium are inversely associated with SCD risk in this large cohort of women. Because most individuals who die suddenly have no clinically recognized heart disease, prevention of SCD will require efforts to lower risk in the general population as well as in high-risk individuals. Given that most Americans do not meet the RDA for magnesium, increasing intake of magnesium presents a potential opportunity for SCD prevention in the general population. If further studies replicate these findings, this hypothesis may warrant testing in randomized trials.

Data for the NHS were collected by investigators at the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

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