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Association of Dietary Magnesium Intake with Fatal Coronary Heart Disease and Sudden Cardiac Death

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Abstract

Background: Postmenopausal women represent the highest population-based burden of cardiovascular disease, including sudden cardiac death (SCD). Our understanding of the etiology and risk factors contributing to fatal coronary heart disease (CHD) and SCD, particularly among women, is limited. This study examines the association between dietary magnesium intake and fatal CHD and SCD.

Materials and Methods: We examined 153,569 postmenopausal women who participated in the Women's Health Initiative recruited between 1993 and 1998. Magnesium intake at baseline was assessed using a validated food frequency questionnaire, adjusting for energy via the residual method. Fatal CHD and SCD were identified over an average follow-up of 10.5 years.

Results: For every standard deviation increase in magnesium intake, there was statistically significant risk reduction, after adjustment for confounders, of 7% for fatal CHD (hazard ratio [HR] 0.93, 95% confidence interval [CI] 0.89–0.97), and 18% risk reduction for SCD (HR 0.82, 95% CI 0.58–1.15) the latter of which did not reach statistical significance. In age-adjusted quartile analysis, women with the lowest magnesium intake (189 mg/day) had the greatest risk for fatal CHD (HR 1.54, 95% CI 1.40–1.69) and SCD (HR 1.70, 95% CI 0.94–3.07). This association was attenuated in the fully adjusted model, with HRs of 1.19 (95% CI 1.06–1.34) for CHD and 1.24 (95% CI 0.58–2.65) for SCD for the lowest quartile of magnesium intake.

Conclusions: This study provides evidence of a potential inverse association between dietary magnesium and fatal CHD and a trend of magnesium with SCD in postmenopausal women. Future studies should confirm this association and consider clinical trials to test whether magnesium supplementation could reduce fatal CHD in high-risk individuals.

Keywords: sudden cardiac death, magnesium, coronary heart disease

Introduction

Postmenopausal women represent the highest population-based burden of cardiovascular disease, including sudden cardiac death (SCD).[1] Our understanding of the etiology and risk factors for fatal coronary heart disease (CHD) and SCD, particularly among women, is limited.[2] The sudden, unexpected, and dynamic nature of SCD presupposes that majority of SCD events occur in the community.[3]

Magnesium plays an important role in cardiac electrophysiology. Both extracellular magnesium and intracellular magnesium have significant effects on cardiac ion channels,

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especially calcium and potassium channels.[4] These effects may have important consequences on action potential duration, cell excitability, and contractility.[4] Therefore, magnesium, and in particular hypomagnesemia, is thought to play an important role in the pathophysiology of many cardiovascular diseases. Magnesium was shown to reduce infarct size in whole heart models of ischemia/reperfusion,[4–7] and to protect the *in vitro* heart against ischemia by significantly increasing duration of cell survival during ischemia.[8] However, subsequent clinical studies and trials remained inconclusive.[9,10] Many studies suggested a relationship between magnesium and arrhythmias, particularly ventricular arrhythmias.[11] A recent meta-analysis by Del Gobbo et al. showed that high levels of dietary magnesium were associated with a significantly lower risk of total cardiovascular disease and ischemic heart disease and demonstrated a nonlinear association with fatal ischemic heart disease.[12] Chiuve et al. showed that women with the highest intake of magnesium in the Nurses' Health Study had a 39% lower risk of fatal CHD.[13] SCD is the mechanism of death in more than 60% of patients with known CHD—the leading cause of mortality among Americans.[5,14,15,16]

The Women's Health Initiative (WHI) study population is advantageous due to it being a large, geographically dispersed, multirace/ethnic cohort with multiple years of follow-up.[17] The primary purpose of this WHI study is to examine the prospective association of dietary magnesium intake with fatal CHD and SCD in a well-characterized cohort of postmenopausal women, and to examine whether women with the lowest quartile daily magnesium intake compared with women with the highest quartile were associated with higher adjusted incident rates of fatal CHD and SCD.

Materials and Methods

Study participants

A total of 161,808 postmenopausal women participated in the WHI, including 93,676 women in the WHI observational study (OS) and 68,132 women in 1 or more of the following 3 clinical trials (CT): the hormone therapy, calcium and vitamin D, or dietary modification trials.[17] These women enrolled at 40 study sites across the United States and were aged 50–79 years at baseline (1993–1998). We examined all WHI participants in the OS and CT in the control and intervention arms of the randomized trials in our analyses for SCD and fatal CHD. Details of WHI death were previously well characterized.[17] All women (OS and CT participants) completed the WHI food-frequency questionnaire (FFQ) at baseline. Women were excluded from our analysis if they were missing FFQ data, body mass index (BMI) <18.5, or did not have follow-up, creating an analysis sample of 153,569.

Outcome measurements

Fatal CHD events were captured by WHI follow-up according to procedures. Physician adjudicated events for fatal CHD and SCD. Fatal CHD was defined as one of the following: (1) death within 28 days of hospitalized myocardial infarction (MI); (2) no known nonatherosclerotic cause of death, at least one of the following: postmortem diagnosis of CHD, chest pain within 72 hours of death, a history of chronic ischemic heart disease (defined by a previous hospitalization for an MI, angina, or revascularization procedure); and (3) no know nonatherosclerotic cause of death and a death certificate consistent with CHD as the underlying cause.

The 2010 NHLBI consensus definition of SCD[3] was used to readjudicate fatal CHD death for SCD, which was defined as (1) witnessed sudden loss of consciousness; (2) unwitnessed but within one hour of the onset of symptoms in a previously stable individual without evidence of noncardiac cause of the arrest; (3) autopsy-documented SCD; (4) as last seen without symptoms in the past 24 hours and no known nonatherosclerotic cause of death. SCD events in this analysis occurred out of the hospital or in the emergency room. Deaths that occurred in the nursing home care or in hospital were not considered SCD deaths. Subjects with life-threatening noncardiac comorbidities, such as end-stage chronic obstructive pulmonary disease, pulmonary emboli, or sepsis, were not considered SCD. Available data from informant interviews, coroner's report, autopsy reports, emergency medical services, and emergency room and hospital discharge summaries were reviewed as well as circumstances surrounding the event, to accurately classify whether the subjected had experienced SCD. All adjudications were done in duplicate. If the two adjudicators did not agree, a third adjudicator (C.B.E.) reviewed the case and confirmed the presence or absence of SCD.

Assessment of magnesium intake

The WHI used a validated, semiquantitative FFQ designed specifically for postmenopausal women to measure dietary intake.[18] The WHI FFQ asked participants to recall diet over the past 3 months and includes 122 line items and 350 unique foods. We adjusted each dietary intake of magnesium for total energy by using the residual method.[16,19] The residual method computed energy-adjusted nutrient intake as the residuals of a regression model of total energy intake (independent variable) and absolute nutrient intake (dependent variable). This approach isolated the variation in nutrient intake attributed to the composition of the diet from the variation in nutrient intake attributed to the total amount of energy consumed. An additional strength of the residual method was that it removed the problem of collinearity, which could occur when the multivariable approach was used and the total energy intake was correlated with the nutrient of interest. Total magnesium intake was adjusted for energy with the use of the residual method, before categorizing intake into quartiles.

Covariates

Age, ethnicity, income, education, smoking status, and disease history (MI, CHD excluding MI, heart failure, diabetes mellitus, and hypertension) were self-reported at baseline using standardized questionnaires. Trained certified staff measured height, weight, and BMI at the baseline examination. Height was measured with the use of a stadiometer, weight was measured with participants wearing light clothing, and BMI was calculated as weight divided by the square of height (kg/m^2). Hypertension was defined by self-report and taking antihypertensive medications or systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg. Diabetes mellitus was defined by self-report of physician diagnosis and/or taking hypoglycemic medications. Participants were also assessed for use of proton pump

inhibitors, which could affect magnesium absorption. The FFQ was used to derive total energy intake or biomarker-calibrated energy intake, carbohydrate (% of energy), protein (%of energy), fat (% of energy), dietary fiber (g), total magnesium intake (mg/day), dietary magnesium intake (mg/day), dietary calcium (mg/day), and dietary potassium (mg/day).

Statistical analysis

Participant characteristics were described overall and by quartiles of energy-adjusted magnesium intake. Magnesium intake was modeled both as continuous and quartiles in time-to-event regression models (with highest quartile as reference), stratified on study assignment (OS or CT). We developed Cox proportional hazards models. Crude, age-adjusted, and a final model adjusting for age, ethnicity, BMI, history of comorbidities (MI, CHD excluding MI, heart failure, diabetes, and hypertension), smoking, dietary calcium, and dietary potassium and use of proton pump inhibitor were constructed. Complete case analysis was used; those with missing data on covariates were not included in final adjusted models. Non-CHD deaths were censored. A sensitivity analysis using a competing risk model was performed. All analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics of our study population are shown in Table 1. Among the 153,569 women, the mean age was 63.2 years. Participants in the lowest quartile of magnesium residual intake ($n = 38,392$) had higher numbers of comorbidities (MI, CHD excluding MI, heart failure, diabetes mellitus, and hypertension), higher BMI, and lower intake of dietary calcium and potassium.

Table 2 shows the associations between the quartiles of magnesium intake and mortality due to CHD and SCD. In the fatal CHD model, low dietary magnesium was associated with a 54% statistically significant, higher hazard ratio (HR) after adjustment for age (HR 1.54, 95% confidence interval [CI] 1.40–1.69) and an attenuated, statistically significant, 19% higher HR after adjustment for all confounders (HR 1.19, 95% CI 1.06–1.34). We found a statistically significant linear inverse association of fatal CHD with residual magnesium intake adjusting for age (HR 0.85, 95% CI 0.82–0.88 with an increase per 1 standard deviation [SD] of residual magnesium), and this association remained statistically significant after adjustment for all confounders (HR 0.93, 95% CI 0.89–0.97).

In the SCD model, participants with low magnesium intake showed a 70% higher HR for SCD (CI 0.94–3.07) after

Table 1. Characteristics Among Women by Quartiles of Magnesium Intake

	Total	*Q1*	*Q2*	*Q3*	*Q4*	
Characteristics	n = *153,569*	n = *38,392*	n = *38,392*	n = *38,393*	n = *38,392*	p
Median dietary magnesium (mg/day)	244	189	206	249	330	
Residual magnesium (mg/day)[a]	–4	–58.1	–19.7	12.9	62.3	
Interquartile range of residual magnesium (mg/day)[a]	–362 to 437	–362 to –36.6	36.6 to –4.0	–4.0 to 32.9	32.9 to 437	
Age (years), mean (SD)	63.2 (7.2)	62.1 (7.2)	63.2 (7.2)	63.5 (7.2)	64.0 (7.2)	<0.001
BMI (kg/m^2), mean (SD)	28.1 (5.9)	29.7 (6.4)	28.2 (5.8)	27.5 (5.5)	26.8 (5.4)	<0.001
Ethnicity, *n* (%)						
American Indian or Alaskan Native	638 (0.4)	225 (0.6)	185 (0.5)	129 (0.3)	99 (0.3)	<0.001
Asian or Pacific Islander	3,801 (2.5)	1,046 (2.7)	1,116 (2.9)	948 (2.5)	691 (1.8)	
Black or African American	13,241 (8.6)	6,158 (16.1)	3,208 (8.4)	2,178 (5.7)	1,697 (4.4)	
Hispanic/Latino	5,789 (3.8)	2,291 (6.0)	1,517 (4.0)	1,146 (3.0)	835 (2.2)	
White, not of Hispanic origin	127,996 (83.6)	28,085 (73.3)	31,781 (83.0)	33,509 (87.5)	34,621 (90.4)	
Other	1,726 (1.1)	493 (1.3)	476 (1.2)	390 (1.0)	367 (1.0)	
History of comorbidities, *n* (%)						
MI	3,413 (2.2)	919 (2.4)	834 (2.2)	810 (2.1)	850 (2.2)	0.049
CHD, excluding MI	9,449 (6.2)	2,510 (6.6)	2,339 (6.2)	2,292 (6.1)	2,308 (6.1)	0.002
Heart failure	1,882 (1.2)	567 (1.5)	466 (1.2)	414 (1.1)	435 (1.1)	<0.001
Diabetes mellitus	6,705 (4.4)	1,816 (4.7)	1,676 (4.4)	1,648 (4.3)	1,565 (4.1)	<0.001
Hypertension	47,933 (31.2)	13,258 (34.5)	12,173 (31.7)	11,493 (30.0)	11,009 (28.7)	<0.001
Smoking, *n* (%)						
Never	77,100 (50.9)	18,826 (49.7)	19,349 (51.1)	19,410 (51.2)	19,515 (51.5)	<0.001
Former	64,158 (42.3)	14,804 (39.1)	15,858 (41.8)	16,579 (43.7)	16,917 (44.6)	
Current	10,344 (6.8)	4,239 (11.2)	2,686 (7.1)	1,951 (5.1)	1,468 (3.9)	
Dietary calcium (mg/day), mean (SD)	826 (450)	666 (372)	697 (354)	824 (382)	1,118 (523)	<0.001
Dietary potassium (mg/day), mean (SD)	2,626 (964)	2,115 (853)	2,273 (742)	2,666 (725)	3,448 (919)	<0.001
Use of proton pump inhibitor, *n* (%)	12,767 (8.3)	3,949 (10.3)	3,412 (8.9)	2,894 (7.5)	2,512 (6.5)	<0.001

p-Value, chi-square for categorical variables and analysis of variance for continuous variables.
[a]Total magnesium intake was adjusted for energy using the residual method, before categorizing intake into quartiles.
BMI, body mass index; CHD, coronary heart disease; MI, myocardial infarction; SD, standard deviation.

Table 2. Hazard Ratios for Fatal Coronary Heart Disease (Top) and Sudden Cardiac Death (Bottom) by Quartiles of Magnesium Intake and Per 1 Standard Deviation Difference (55 U) in Magnesium Intake

		Residual magnesium intake					
		Q1	*Q2*	*Q3*	*Q4*		*Mg continuous*[a]
	Events	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*Reference*	p[b]	*HR (95% CI)*
Fatal CHD							
Age adjusted	3,428	1.54 (1.40–1.69)	1.25 (1.14–1.38)	1.08 (0.98–1.19)	1	<0.001	0.85 (0.82–0.88)
Adjusted model[b]	3,277	1.19 (1.06–1.34)	1.07 (0.95–1.20)	1.00 (0.90–1.11)	1	0.004	0.93 (0.89–0.97)
SCD							
Age adjusted	73	1.70 (0.94–3.07)	0.82 (0.41–1.68)	0.94 (0.47–1.87)	1	0.072	0.77 (0.57–1.03)
Adjusted model[b]	71	1.24 (0.58–2.65)	0.70 (0.31–1.55)	0.89 (.041–1.89)	1	0.34	0.82 (0.58–1.15)

[a]HR for Mg continuous is per each SD.
[b]Overall p-value for quartiles from type 3 chi-square test.
[c]Adjusted for age, ethnicity, body mass index, history of comorbidities (MI, CHD excluding MI, heart failure, diabetes, and hypertension), smoking, dietary calcium, dietary potassium, and use of proton pump inhibitor.
CI, confidence interval; HR, hazard ratio; Mg, magnesium; MI, myocardial infarction; SCD, sudden cardiac death.

adjustment for age. The higher HR is attenuated to 24% (CI 0.58–2.65) when adjusted for all confounders. We found a statistically insignificant linear inverse association of SCD with magnesium intake adjusting for age (HR 0.77, 95% CI 0.57–1.03 per 1 SD of residual magnesium). This association is attenuated with adjustment for all confounders (HR 0.82, 95% CI 0.58–1.15). Competing risk analysis showed similar results (Supplementary Table S1).

Discussion

Our prospective cohort study shows that postmenopausal women in WHI had a lower risk for CHD death (statistically significant 7% lower risk per SD) with higher magnesium intake. In quartile analysis, we found a trend of an increased risk in the lowest quartile of magnesium for CHD death, which with multiple variable adjustment was attenuated and lost statistical significance. The association of low magnesium with SCD showed a similar point estimate but was underpowered to show statistical significance, as there are fewer SCD events (Table 2).

The pathobiology of CHD in women may be different from men, which contributes to fatal CHD and SCD in women. For example, women who suffer out-of-hospital arrest were on average older, more likely to present with pulseless electrical activity, and to experience arrests at home.[20] Women, especially those at younger age, have higher rates of successful resuscitation from shockable rhythms, possibly due to body stature and estrogen on the success of defibrillation and post-resuscitation measures.[20] Low-cost primary preventive strategies are needed to reduce incidence of fatal CHD and SCD.

Our results regarding CHD deaths are consistent with that of the Nurses' Health Study by Chiuve et al., who found an inverse association between magnesium intake and fatal CHD, and increased risk of CHD death comparing highest and lowest quartile of magnesium intake.[13] The Rotterdam Study found an association between low serum magnesium and fatal CHD in a cohort of 9,820 participants, ages 45 years or older, 96% of whom were of European descent and 56.8% were women.[21] Magnesium plays a role in inflammation,[22] endothelial dysfunction,[22] thrombosis,[23] and vascular smooth muscle calcification[24] and may influence fatal CHD through these mechanisms.

We showed that low residual dietary magnesium intake was associated with a 22% higher risk for SCD, although due to a small sample size this did not reach statistical significance. Arrhythmias are a significant cause of SCD.[25] Magnesium has antiarrhythmic properties[26,27] while chronic hypomagnesemia may be proarrhythmic[28,29] and has been associated with a higher risk of SCD.[13,30] Magnesium supplementation to correct hypomagnesemia reduces ventricular arrhythmias in heart failure patients and may reduce the risk of SCD.[11] Ventricular arrhythmias are a significant cause of SCD post-MI, and correcting hypomagnesemia is recommended for the management of refractory ventricular fibrillation, to which hypomagnesemia is suspected to contribute.[11]

The strengths of our study include its prospective design, a cohort of women of multiple ethnicities from 40 centers geographically distributed in the United States, physician-adjudicated SCD and fatal CHD, and the use of a residual method and FFQ to calculate dietary magnesium intake. Dietary magnesium may be a marker for fatal CHD and SCD; however, the limitation of our study is that this association may not be causal, as dietary magnesium may not directly correlate with serum magnesium and is affected by other dietary factors, medication use, and comorbidities.

This study provides evidence of a lower risk for women with higher dietary magnesium intakes for fatal CHD and potentially an increased risk between low dietary magnesium and fatal CHD and SCD in postmenopausal women. Future studies should confirm this association and consider dietary trials of foods rich in magnesium (*e.g.*, fruits and vegetables) and magnesium supplementation in the general or at-risk populations.

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Supplementary Material

Supplementary Table S1

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