

Dietary Magnesium Intake and Risk of Cardiovascular Disease Among Women

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This study assessed the hypothesis that greater magnesium intake is associated with reduced risk for cardiovascular disease (CVD), including myocardial infarction (MI) and stroke, in a large prospective cohort of women. In 1993, a semi-quantitative food frequency questionnaire was used to assess magnesium intake in 39,876 female health professionals aged 39 to 89 years who had no history of CVD or cancer. During a median of 10 years of follow-up, 1,037 incident cases of CVD were identified, including 280 nonfatal MIs and 368 strokes. After adjustment for age and randomized treatment status, magnesium intake was not significantly associated with risk for incident CVD. Comparing the highest quintile of magnesium intake (median 433 mg/day) with the lowest quintile (median 255 mg/day), the relative risks were 0.87 (95% confidence interval [CI] 0.72 to 1.05, *p* for trend = 0.24) for total CVD, 0.88 (95% CI 0.70 to 1.12, *p* for trend = 0.34) for coronary heart disease (CHD), 1.03 (95% CI 0.72 to 1.49, *p* for trend = 0.96) for nonfatal MI, 1.11 (95% CI 0.61 to 2.00, *p* for trend = 0.95) for CVD death, and 0.87 (95% CI 0.64 to 1.18, *p* for trend = 0.55) for total stroke. Additional adjustment for other CVD risk factors did not materially change the observed null associations. In conclusion, the results do not support the hypothesis that magnesium intake reduces the development of CHD, although a modest inverse association with stroke cannot be ruled out. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96:1135–1141)

Magnesium is an essential mineral that has been favorably associated with many cardiovascular disease (CVD) risk factors.^{1–3} However, epidemiologic evidence regarding the role of dietary magnesium intake in the primary prevention of CVD is limited, especially for women. We used prospective data from the Women's Health Study to examine the relation of magnesium intake to the incidence of CVD, including stroke, in middle-aged and elderly American women. Using these results and those of previous studies, we also performed a random-effects meta-analysis to assess the consistency of magnesium-CVD associations.

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Methods

Study population: The Women's Health Study is a randomized, double-blind, placebo-controlled trial designed to evaluate the balance of benefits and risks of small-dose aspirin and vitamin E in the primary prevention of CVD and cancer.⁴ We randomized a total of 39,876 female health professionals aged 39 to 89 years who were free of coronary heart disease (CHD), stroke, and cancer (except for non-melanoma skin cancer). Of them, 98% provided detailed information about their diets at baseline, completing a 131-item semi-quantitative food frequency questionnaire (FFQ) in 1993.⁴ We excluded patients with >70 items left blank in their FFQs and with energy intakes outside the range of 2,514 kJ (600 kcal) to 14,665 kJ (3,500 kcal) and those with incomplete data on magnesium intake and other major lifestyle variables, which left 35,601 women for the analysis.

This study was conducted according to the ethical guidelines of Brigham and Women's Hospital. Written informed consent was obtained from all participants.

Assessment of magnesium intake: In the FFQ, participants were asked how often on average they had consumed individual foods of commonly used portion sizes during the previous year. Nine possible responses ranging from "never" to "6 or more times per day" were recorded. Nutrient intakes were computed by multiplying the frequency of consumption of each unit of food from the FFQ by the nutrient

Table 1

Age-adjusted (in 5-year categories) baseline characteristics according to quintiles (Q) of total and dietary magnesium intakes among 35,601 women in the Women's Health Study

Characteristic*	Dietary Magnesium				Total Magnesium			
	Q1 (n = 7,120)	Q3 (n = 7,120)	Q5 (n = 7,120)	p Value	Q1 (n = 7,118)	Q3 (n = 7,122)	Q5 (n = 7,120)	p Value
Median intake (mg/d)	252	319	399		255	328	433	
Mean age (yrs)	52.5	53.8	55.2	<0.0001	52.5	53.8	55.2	<0.0001
Mean body mass index (kg/m ²)	26.7	26.0	25.2	<0.0001	26.7	26.0	25.3	<0.0001
Alcohol consumption (g/d)	4.79	4.73	3.93	<0.0001	4.69	4.77	3.84	<0.0001
Current smoking	17.2%	12.9%	10.0%	<0.0001	17.3%	12.9%	9.55%	<0.0001
Vigorous exercise (\geq 4/wk)	5.65%	9.88%	18.4%	<0.0001	5.66%	10.2%	17.4%	<0.0001
Postmenopausal hormones (current user)	61.9%	57.0%	56.1%	<0.0001	62.9%	58.0%	53.5%	<0.0001
Multivitamin use (current user)	24.9%	29.3%	34.2%	<0.0001	17.2%	23.7%	54.2%	<0.0001
Parental history of MI at <60 yrs	14.7%	14.6%	14.5%	0.80	14.7%	14.9%	14.8%	0.92
Hypertension [†]	30.1%	25.4%	22.0%	<0.0001	29.9%	24.9%	22.7%	<0.0001
Hypercholesterolemia	29.8%	28.0%	29.1%	0.53	29.4%	28.8%	29.4%	0.92
Diabetes mellitus	2.00%	2.09%	3.23%	<0.0001	2.19%	2.38%	2.64%	0.004
Mean total calorie (kcal/day)	1,711	1,743	1,701	0.10	1,680	1,763	1,689	0.08
Mean total fat (g/day)	64.8	58.3	49.1	<0.0001	64.6	57.8	50.6	<0.0001
Mean protein (g/day)	74.0	81.9	86.3	<0.0001	74.5	82.3	85.4	<0.0001
Mean cholesterol (mg/day)	241	229	202	<0.0001	240	228	206	<0.0001
Mean fiber (g/day)	13.9	18.5	25.3	<0.0001	14.1	18.7	24.2	<0.0001
Mean glycemic load [†]	164	164	176	<0.0001	163	165	175	<0.0001

*All covariate values are according to quintiles of total magnesium intake. All the means of nutrients are energy adjusted.

[†] Glycemic load was defined as an indicator of blood glucose induced by an individual's total carbohydrate intake. Each unit of glycemic load represents the equivalent of 1-g carbohydrate from white bread.

content of the specified portion size according to food composition tables from the Harvard Food Composition Database.⁵ Data on the use of multivitamin supplements were taken into account to assess the intake of supplemental magnesium. Total magnesium represents the sum of magnesium intake from dietary and supplemental sources. Each nutrient was adjusted for total energy using the residual method.⁶ In populations of nurses and health professionals, this FFQ has demonstrated reasonably good validity as a measure of long-term average dietary intakes.⁵ Pearson's correlation coefficient between magnesium intake assessed by the FFQ and 2 weeks of diet records was 0.76.⁷

Outcomes: The primary end point for this analysis was incident CVD, which included nonfatal myocardial infarction (MI), stroke, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, and fatal CVD that occurred during follow-up. Diagnoses were confirmed by a committee of cardiologists and 1 neurologist. For MI, we used criteria proposed by the World Health Organization: symptoms plus either typical electrocardiographic changes or the elevation of cardiac enzymes.⁸ Reported percutaneous transluminal coronary angioplasty or coronary artery bypass graft was confirmed by hospital records. In the present study, CHD was defined to include nonfatal MI, fatal coronary events, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting. Cardiovascular deaths were confirmed through medical records, autopsy reports, and death certificates. A stroke was defined as a focal neuro-

logic deficit of vascular mechanism lasting >24 hours and confirmed by an end points committee. Stroke was classified according to the criteria established by the National Survey of Stroke into ischemic, hemorrhagic, and unknown types.⁹ Hemorrhagic stroke was further classified into intracerebral hemorrhage, subarachnoid hemorrhage, or intraventricular hemorrhage. Stroke classification was performed on the basis of medical records, reports of brain imaging, autopsy reports, and the judgment of the neurologist on the end points committee. The interobserver agreement of the classification of stroke and its subtypes in our study has been found to be excellent for the diagnosis of the 3 major subtypes.¹⁰

Data analysis: Each participant contributed follow-up time from the date of return of the baseline questionnaire to the date of the first diagnosis of a CVD end point, death, or end of the follow-up period, whichever came first. Participants were divided into quintiles according to their intakes of total magnesium from diet and supplements. We used Cox proportional-hazards models to estimate the relative risks (RRs) and 95% confidence intervals (CIs) of developing CVD. We adjusted for age (in years), randomized assignments (aspirin and vitamin E), total energy intake (quintiles), smoking (current, past, and never), exercise (rarely or never, <1 time/week, 1 to 3 times/week, and \geq 4 times/week), alcohol intake (rarely or never, 1 to 3 drinks/month, 1 to 6 drinks/week, and \geq 1 drink/day), the use of postmenopausal hormones (never, past, and current), body mass index (kilograms divided

Table 2
RR (95% CIs) of CVD according to total magnesium intake among 35,601 women in the Women's Health Study

Variable	Quintiles of Intake*					p Value for Linear Trend	p Value for Nonlinear Trend
	1 (Lowest) (n = 7,123)	2 (n = 7,122)	3 (n = 7,121)	4 (n = 7,122)	5 (Highest) (n = 7,122)		
Total magnesium intake*	255 (237–268)	296 (288–305)	328 (321–336)	365 (355–377)	433 (409–470)		
Cardiovascular disease							
No. of cases	208	180	221	195	233		
Multivariate model 1 [†]	1.00	0.80 (0.66–0.98)	0.94 (0.78–1.14)	0.79 (0.65–0.96)	0.87 (0.72–1.05)	0.24	0.14
Multivariate model 2 [‡]	1.00	0.87 (0.71–1.06)	1.04 (0.86–1.26)	0.89 (0.73–1.09)	1.00 (0.82–1.23)	0.85	0.40
CHD							
No. of cases	132	117	149	126	148		
Multivariate model 1 [†]	1.00	0.83 (0.64–1.06)	1.00 (0.79–1.27)	0.81 (0.63–1.03)	0.88 (0.70–1.12)	0.34	0.49
Multivariate model 2 [‡]	1.00	0.90 (0.70–1.16)	1.11 (0.88–1.41)	0.93 (0.72–1.19)	1.08 (0.84–1.38)	0.52	0.68
Nonfatal MI							
No. of cases	51	52	59	50	68		
Multivariate model 1 [†]	1.00	0.95 (0.64–1.39)	1.02 (0.70–1.48)	0.82 (0.56–1.22)	1.03 (0.72–1.49)	0.96	0.43
Multivariate model 2 [‡]	1.00	1.07 (0.72–1.57)	1.20 (0.82–1.76)	1.04 (0.70–1.54)	1.48 (1.01–2.18)	0.06	0.51
Stroke [§]							
No. of cases	77	63	72	69	87		
Multivariate model 1 [†]	1.00	0.76 (0.54–1.06)	0.82 (0.59–1.13)	0.74 (0.54–1.03)	0.87 (0.64–1.18)	0.55	0.09
Multivariate model 2 [‡]	1.00	0.81 (0.58–1.13)	0.90 (0.65–1.24)	0.81 (0.58–1.13)	0.90 (0.65–1.26)	0.68	0.27
CVD death							
No. of cases	18	19	34	20	29		
Multivariate model 1 [†]	1.00	0.95 (0.50–1.80)	1.57 (0.88–2.78)	0.86 (0.45–1.63)	1.11 (0.61–2.00)	0.95	0.61
Multivariate model 2 [‡]	1.00	1.09 (0.57–2.08)	1.83 (1.02–3.27)	0.99 (0.52–1.91)	1.32 (0.71–2.47)	0.60	0.41

* Total magnesium intake (milligrams per day) included the total amount of magnesium from both food and supplements.

[†] Multivariate model 1: adjusted for age (continuous) and randomized treatment assignment in the Women's Health Study.

[‡] Multivariate model 2: model 1 with additional adjustment for body mass index (quintiles), total energy intake (quintiles), smoking (current, past, and never), exercise (rarely or never, <1 time/week, 1 to 3 times/week, and ≥4 times/week), alcohol use (rarely or never, 1 to 3 drinks/month, 1 to 6 drinks/week, and ≥1 drink/day), postmenopausal hormone use (never, past, and current), multivitamin use (never, past, and current), history of diabetes (yes or no), history of hypertension (yes or no), history of hypercholesterolemia (yes or no), and parental history of MI at <60 years (yes or no).

[§] Total stroke included ischemic stroke, hemorrhagic stroke, and stroke of unknown type.

by height in square meters), the use of multivitamin supplements (never, past, and current), history of hypertension (yes or no), high cholesterol (yes or no), diabetes mellitus (yes or no), and parental history of MI at <60 years (yes or no). Tests of linear trend across increasing quintiles of magnesium intake were conducted by assigning the medians of intakes in quintiles (milligrams per day) treated as a continuous variable. To assess departure from linearity, we also included linear and quadratic terms (the median and the value squared) in the model to test nonlinear trend.

The same analytic approach was also used for analyses of dietary magnesium intake (from diet alone). All statistical analyses were conducted using SAS version 8.0 (SAS Institute Inc., Cary, North Carolina). All p values were 2 tailed.

To summarize evidence from previous cohort studies and maximize statistical power to test the hypothesis of magnesium-CVD associations, we performed a random-effects meta-analysis to calculate the pooled variance-weighted RRs for CHD and stroke comparing the highest category with the lowest category of magnesium intake (using Stata statistical software, version 7.0; StataCorp LP, College Station, Texas).¹¹

Results

In the present study, dietary sources accounted for about 96% of the total intake of magnesium. The median intake of magnesium was 326 mg/day for our cohort of middle-aged women, which is close to the recommended dietary allowance of 320 mg/day for adult women.¹² There was an approximately 1.7-fold difference in total magnesium intake between the highest and lowest quintiles of the study population (median 433 mg/day in the highest quintile vs 255 mg/day in the lowest quintile; Table 1). Women with greater magnesium intakes were older and leaner; were less likely to smoke cigarettes, drink alcohol, or take postmenopausal hormones; and were more likely to exercise and take multivitamin supplements than those with less intake. Women with large magnesium intakes also had less likelihood of having hypertension and a slightly greater proportion a history of diabetes (Table 1). Further, magnesium intake was positively correlated with dietary carbohydrate, protein, fiber, folate, and glycemic load and inversely associated with dietary intakes of all fatty acids and cholesterol (Table 1).

During a median of 10 years of follow-up (348,166 subject-years), we identified 1,037 incident cases of CVD: 672 CHD, 280 nonfatal MIs, 368 strokes, and 120 con-

Table 3

RRs of stroke subtypes according to quintiles of total magnesium intake in 35,601 middle-aged and older women in the Women's Health Study

Magnesium Intake*	Quintile Categories					p Value for Linear Trend	p Value for Nonlinear Trend
	1 (Lowest) (n = 7,123)	2 (n = 7,122)	3 (n = 7,121)	4 (n = 7,122)	5 (Highest) (n = 7,122)		
Median (range) (mg/day)	255 (237–268)	296 (288–305)	328 (321–336)	365 (355–377)	433 (409–470)		
Ischemic stroke							
No. of cases	64	46	54	54	64		
Multivariate model 1 [†]	1.00	0.66 (0.45–0.96)	0.73 (0.51–1.05)	0.69 (0.48–0.99)	0.75 (0.53–1.06)	0.24	0.07
Multivariate model 2 [‡]	1.00	0.72 (0.49–1.05)	0.81 (0.56–1.17)	0.77 (0.53–1.12)	0.83 (0.57–1.21)	0.53	0.18
Total hemorrhagic stroke							
No. of cases	12	15	12	12	19		
Multivariate model 1 [†]	1.00	1.18 (0.55–2.53)	0.91 (0.41–2.03)	0.87 (0.39–1.95)	1.31 (0.63–2.71)	0.58	0.43
Multivariate model 2 [‡]	1.00	1.20 (0.56–2.57)	0.93 (0.41–2.08)	0.85 (0.38–1.93)	1.07 (0.49–2.31)	0.94	0.69
Subarachnoid hemorrhage							
No. of cases	6	7	6	4	10		
Multivariate model 1 [†]	1.00	1.13 (0.38–3.37)	0.96 (0.31–2.98)	0.62 (0.18–2.22)	1.51 (0.54–4.19)	0.53	0.31
Multivariate model 2 [‡]	1.00	1.05 (0.35–3.14)	0.88 (0.28–2.76)	0.53 (0.14–1.91)	1.08 (0.36–3.20)	0.96	0.37
Intracerebral hemorrhage							
No. of cases	6	7	6	8	9		
Multivariate model 1 [†]	1.00	1.08 (0.36–3.21)	0.86 (0.28–2.68)	1.10 (0.38–3.18)	1.14 (0.40–3.23)	0.77	0.85
Multivariate model 2 [‡]	1.00	1.17 (0.39–3.51)	0.99 (0.31–3.09)	1.22 (0.41–3.62)	1.12 (0.37–3.38)	0.85	0.87

* Total magnesium intake included the total amount of magnesium from both food and supplements.

[†] Multivariate model 1: adjusted for age (continuous) and randomized treatment assignment in the Women's Health Study.[‡] Multivariate model 2: model 1 with additional adjustment for body mass index (quintiles), total energy intake (quintiles), smoking (current, past, and never), exercise (rarely or never, <1 time/week, 1 to 3 times/week, and ≥4 times/week), alcohol use (rarely or never, 1 to 3 drinks/month, 1 to 6 drinks/week, and ≥1 drink/day), postmenopausal hormone use (never, past, and current), multivitamin use (never, past, and current), history of diabetes (yes or no), history of hypertension (yes or no), history of hypercholesterolemia (yes or no), and parental history of MI at <60 years (yes/no).

firmed CVD deaths. After adjustment for age and randomized treatment assignment, greater magnesium intake was associated with a slightly lower risk for CVD, but the RR and the linear trend were nonsignificant (Table 2). Likewise, magnesium intake was not significantly associated with CHD, MI, total stroke, or CVD death. With further adjustment for known CVD risk factors, these RRs increased slightly but remained nonsignificant except for nonfatal MI, which had a marginally significant trend. This positive association between magnesium intake and nonfatal MI risk did not exist when additionally adjusted for dietary intake of folate, fiber and saturated fat.

Magnesium intake was not associated with total stroke in the age-adjusted or multivariate models (Table 2). We further examined magnesium intake in relation to risk for subtype of stroke. Of 368 incident stroke cases, we documented 282 ischemic, 70 hemorrhagic, and 16 unclassified strokes. Women with large intakes of magnesium seemed to have a modestly reduced risk for ischemic stroke compared with those in the lowest quintile in the age-adjusted analysis, but the trend over the quintiles was not significant (Table 3).

Additionally, all results were not appreciably changed when we performed the same analyses restricted to dietary magnesium intake (without supplements) (data not shown).

Diabetes, hypertension, hypercholesterolemia, and other high-risk conditions for CVD, such as cigarette smoking, may lead to changes in dietary magnesium intake and may thus bias the association between magnesium intake and CVD risk. To better control for information bias and con-

founding, we examined the association between magnesium intake and CVD risk in 3 subgroups of the cohort: (1) participants who reported no history of hypertension, hypercholesterolemia, or diabetes at baseline; (2) those with body mass indexes <25 kg/m²; and (3) those who had never smoked. Overall, there was no significant association between magnesium intake and CVD risk in these subgroups (data not shown).

Figure 1 summarizes the results of previous cohort studies on the association between magnesium intake and the risk for CVD. The random-effects pooled estimates of RRs comparing the highest category with the lowest category of magnesium intake were 0.86 (95% CI 0.67 to 1.10, p = 0.06 for between-study heterogeneity) for CHD, 0.80 (95% CI 0.68 to 0.95, p = 0.60 for heterogeneity) for total stroke, 0.84 (95% CI 0.65 to 1.08, p = 0.96 for heterogeneity) for ischemic stroke, and 0.87 (95% CI 0.60 to 1.28, p = 0.56 for heterogeneity) for hemorrhagic stroke.

Discussion

In this large prospective study of middle-aged and older American women, we found no significant association between magnesium intake and the incidence of total CVD, CHD, nonfatal MI, or stroke, although there was a suggestion of a lower risk for total stroke and ischemic stroke associated with larger intakes of magnesium.

Magnesium intake has long been believed to be protec-

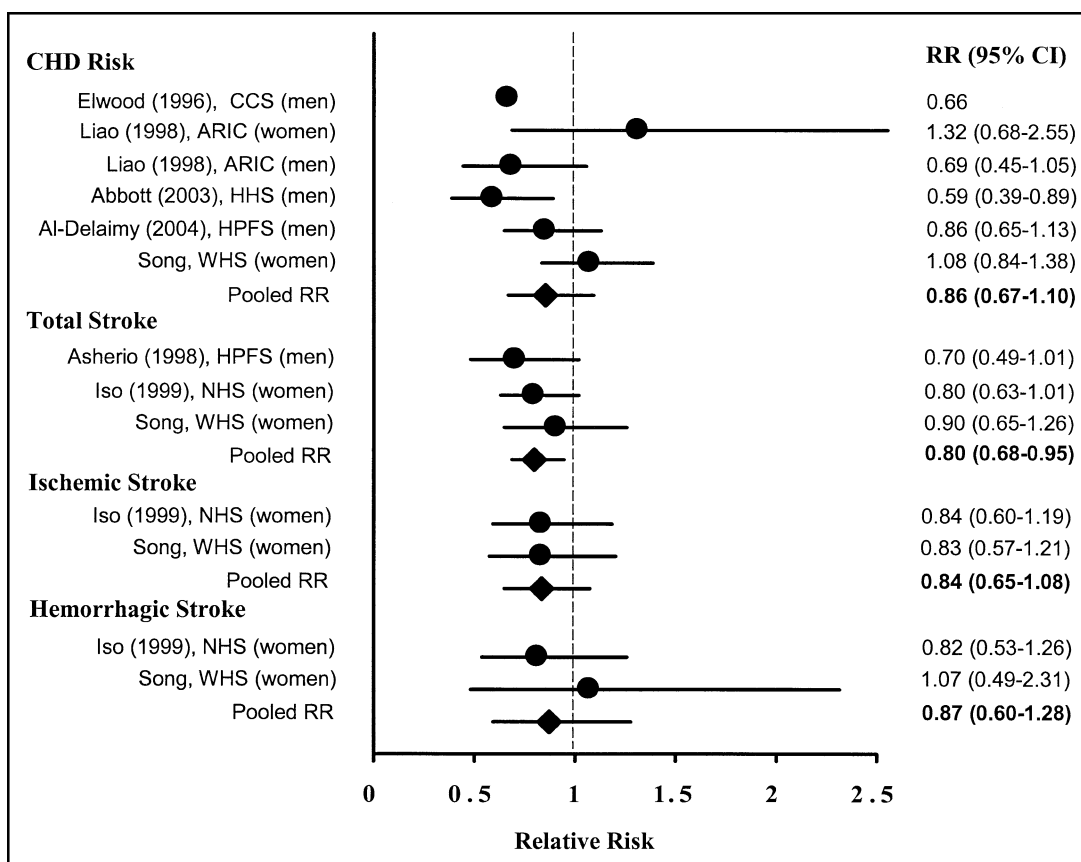


Figure 1. A meta-analysis of prospective studies regarding the association between dietary magnesium intake and incidence of CVD (CHD and stroke). Each circle indicates the multivariate-adjusted RR comparing the highest category of magnesium intake with the lowest category of intake in each study. The horizontal line represents the 95% CI. Studies are ordered by year of publication. The pooled RR and 95% CI are indicated by the diamonds. ARIC = Atherosclerosis Risk in Communities Study¹⁹; CCS = Caerphilly Cohort Study²²; HHS = Honolulu Heart Study²⁰; HPFS = Health Professionals Follow-Up Study^{21,28}; NHS = Nurses' Health Study²⁷; WHS = Women's Health Study (present study).

tive against CVD, mortality, or arrhythmias after CVD.² Abnormalities in intracellular magnesium homeostasis have been hypothesized to be a link between insulin resistance, type 2 diabetes mellitus, and CVD.^{1,13} Animal studies have shown that magnesium deficiency accelerates the atherosclerotic process and that magnesium supplementation suppresses the development of atherosclerosis.² Many small clinical trials have evaluated the efficacy of intravenous magnesium treatment in the secondary prevention of CVD, especially arrhythmias and mortality after acute MI,¹⁴ and early meta-analysis suggested a benefit.¹⁵ However, 2 recent large-scale trials showed no benefit of an acute intravenous infusion of magnesium on mortality from MI.^{16,17}

In contrast, the role of magnesium intake in the primary prevention of CVD is less well studied. Results from prospective studies of the relations between plasma levels or the dietary intake of magnesium and the incidence of CHD have been mixed. Two large cohort studies have reported a significant inverse association between serum magnesium levels and the risk for developing CHD^{18,19} or CHD mortality.¹⁸ However, caution needs to be exercised when interpreting these results, because it is questionable whether serum magnesium reflects body magnesium stores or intra-

cellular magnesium levels. Moreover, serum magnesium was not well correlated with dietary intake.¹⁹

Several cohort studies have prospectively examined the relation between dietary magnesium intake and the risk for developing CHD in men and yielded mixed results.¹⁹⁻²¹ In the Honolulu Heart Study of 7,172 men of Japanese ancestry living in Hawaii, an inverse association between magnesium intake assessed by 24-hour dietary recall and CHD incidence was evident in the first 15 years of follow-up and tended to be weakened with time.²⁰ During an average of 12 years of follow-up of 39,633 men in the Health Professionals' Follow-Up Study, dietary magnesium intake assessed by a 131-item FFQ was inversely associated with CHD, but the linear trend was substantially attenuated toward null after adjustment for standard CHD risk factors and dietary factors (transfatty acid, protein, cereal fiber, omega-3 fatty acid, and potassium).²¹ Similarly, the Atherosclerosis Risk in Communities Study observed a modest inverse association with risk for CHD in men but not in women over 4 to 7 years of follow-up.¹⁹ The null association in the present study is generally consistent with the findings from the Caerphilly cohort of 2,172 men²² and the cohort of women in the Atherosclerosis Risk in Communities Study.¹⁹ It is

also possible that negative findings from other cohort studies may not have been reported. Overall, the findings of cohort studies indicate that magnesium is unlikely to substantially decrease the risk for CHD, although a modest association cannot be ruled out.

Another area of controversy is the relation between magnesium intake and the development and progression of stroke. Magnesium may play a role in reducing cerebral ischemia.^{23–25} Some animal studies, although not all, have suggested potential neuroprotective effects by magnesium supplementation in rodent stroke models.²⁶ However, the relation between magnesium intake and the incidence of stroke is less well studied. In the 8-year Health Professionals' Follow-Up Study, with 328 documented strokes, dietary magnesium intake was inversely associated with risk for total stroke, especially in hypertensive men.²⁷ In the 14-year Nurses' Health Study, with 690 incident strokes (386 ischemic strokes and 193 hemorrhagic strokes), Iso et al²⁸ showed no significant associations between magnesium intake and total stroke and stroke subtype, although a modest effect of magnesium on ischemic stroke could not be excluded. Overall, the evidence is not convincing because of sparse data, and further investigation in prospective studies with sufficient cases of incident stroke is warranted.

The present study has several limitations. First, the misclassification of dietary intake could have led to an underestimation of the association between dietary magnesium intake and CVD risk in this study. Nevertheless, the FFQ that we used has been validated and can reasonably reflect long-term dietary intake.⁵ Using the same FFQ, we found that magnesium intake was associated with reduced risk for type 2 diabetes in our cohort, which further supports the validity of our dietary assessment.²⁹ Further, participants might change their diets after they develop some intermediate diseases, leading to a conservative estimate. However, excluding participants who were overweight, smoked, or had a history of hypertension, high cholesterol, and diabetes, which allows for reducing the possibility of bias from this source, yielded similar null associations. In addition, the intake of magnesium from supplements was negligible compared with total intake from diet and thus was unlikely to have influenced the results. We adjusted for possible confounders, but there is still the possibility of residual or unmeasured confounding. In addition, our cohort is a well-nourished population with relatively narrow range of magnesium intake and thus limits the power to detect a modest or moderate association. Finally, our null results are unlikely to be explained by recall or selection bias because of the prospective study design and high follow-up rate.

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