

Magnesium Intake, C-Reactive Protein, and the Prevalence of Metabolic Syndrome in Middle-Aged and Older U.S. Women

YIQING SONG, MD^{1,2,3}
PAUL M. RIDKER, MD, MPH^{1,4}
JOANN E. MANSON, MD, DRPH^{1,2}

NANCY R. COOK, SCD^{1,2}
JULIE E. BURING, SCD^{1,2,5}
SIMIN LIU, MD, SCD^{1,2}

OBJECTIVE — The aim of this study was to examine whether and to what extent magnesium intake is related to systemic inflammation and the metabolic syndrome.

RESEARCH DESIGN AND METHODS — We performed a cross-sectional analysis on data from 11,686 women ≥ 45 years of age participating in the Women's Health Study who were initially free of cardiovascular disease and cancer and had no use of postmenopausal hormones.

RESULTS — In age- and BMI-adjusted analyses, magnesium intake was inversely associated with plasma C-reactive protein (CRP) concentrations; CRP concentrations were 12% lower in the highest intake quintile than in the lowest (P for trend < 0.0001). This association was not appreciably altered by further adjustment for other potential confounding variables including dietary factors; the mean CRP concentrations for ascending quintiles of magnesium intake were 1.50, 1.39, 1.35, 1.34, and 1.31 mg/l (P for trend = 0.0003). This inverse association was stronger for women with a BMI ≥ 25 kg/m² ($P < 0.0001$ for interaction) and those who were current or past smokers ($P = 0.0009$ for interaction). After adjustment for confounding lifestyle and dietary factors, women in the highest quintile of magnesium intake had 27% lower risk of the metabolic syndrome (defined according to the National Cholesterol Education Program criteria) compared with those in the lowest quintile of intake (odds ratio 0.73 [95% CI 0.60–0.88], P for trend = 0.0008).

CONCLUSIONS — Our results suggest that magnesium intake is inversely associated with systemic inflammation and the prevalence of the metabolic syndrome in middle-aged and older women.

Diabetes Care 28:1438–1444, 2005

From the ¹Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; the ²Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; the ³Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; the ⁴Center for Cardiovascular Disease Prevention and the Donald Reynolds Center for Cardiovascular Research, Division of Cardiovascular Diseases, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and the ⁵Department of Ambulatory Care and Prevention, Harvard Medical School, Boston, Massachusetts.

Address correspondence and reprint requests to Yiqing Song, MD, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave. East, Boston, MA 02215. E-mail: ysong@hsph.harvard.edu.

Received for publication 16 January 2005 and accepted in revised form 16 February 2005.

P.M.R. has received grant/research support from AstraZeneca, Bristol-Myers Squibb, and Novartis.

Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; SFFQ, semiquantitative food frequency questionnaire; WHS, Women's Health Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

© 2005 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Magnesium is an essential mineral with several dietary sources including whole grains, green leafy vegetables, legumes, and nuts (1). As a critical cofactor for hundreds of enzymes and a direct antagonist of intracellular calcium, intracellular magnesium homeostasis has been hypothesized to be a link between insulin resistance, type 2 diabetes, hypertension, and cardiovascular disease (CVD) (2,3). Growing evidence from both experimental and observational studies suggests that magnesium intake from either diet or supplements may favorably affect a cluster of chronic metabolic disorders, including insulin resistance (4,5), type 2 diabetes (5–7), CVD (8,9), and hypertension (10,11). The beneficial effects of magnesium intake have been explained by several mechanisms, including improvement of glucose and insulin homeostasis (12,13), lipid metabolism (14,15), and vascular or myocardial contractility (2,16); antiarrhythmic effects (2,17); anticoagulant or antiplatelet effects (2,3,17); and increased endothelium-dependent vasodilation (2,16). Systemic inflammation, as measured by plasma C-reactive protein (CRP) concentrations, is widely believed to be one of the common mechanisms underlying the development of these metabolic-related disorders (18). Magnesium intake may protect against diabetes and CVD in part through reducing low-grade inflammation. However, it remains uncertain whether and to what extent magnesium intake is related to systemic inflammation. Furthermore, there is little evidence on whether magnesium intake is associated with the presence of metabolic syndrome.

We therefore conducted a cross-sectional analysis to investigate the relationship between magnesium intake and plasma CRP concentrations and the prevalence of metabolic syndrome in a large cohort of middle-aged and older U.S.

women in the Women's Health Study (WHS).

RESEARCH DESIGN AND METHODS

The WHS is a randomized, double-blind, placebo-controlled trial designed to evaluate the balance of benefits and risks of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer (19). We randomized a total of 39,876 female health professionals ≥ 45 years of age who were free of coronary heart disease, stroke, and cancer (except for nonmelanoma skin cancer) at baseline (19). Of them, 98% provided detailed information on their diet by completing a 131-item semiquantitative food frequency questionnaire (SFFQ) in 1993 (20). We excluded from the analyses women with unreliable dietary data (≥ 70 items left blank in their questionnaire or energy intake < 600 kcal or $> 3,500$ kcal) and women with missing data for total magnesium intake. To minimize the effects of postmenopausal hormone therapy on systemic inflammation and the metabolic syndrome, we further excluded women who were current or ever postmenopausal hormone users, leaving 11,686 women for the analysis. Of these, 9,887 were free of diabetes at study entry and contributed complete data for all five components of the metabolic syndrome. The study protocol was approved by the Brigham and Women's Hospital institutional review board, and the protocol adhered to the guidelines put forth in the Helsinki declaration and Belmont Accord for the duration of the study.

Assessment of magnesium intake

In the SFFQ, participants were asked how often on average they had consumed individual foods of a commonly used portion size during the previous year. Nine possible responses ranging from "never" to "six or more times per day" were recorded. Nutrient intakes were computed by multiplying the frequency of consumption of each unit of food from the SFFQ by the nutrient content of the specified portion size according to food composition tables from the Harvard Food Composition Database (21). Data on use of multivitamin supplements were taken into account to assess intake of supplemental magnesium. Total magnesium represents the sum of magnesium intake from both dietary and supplemental sources. Each nutrient was adjusted for

total energy using the residual method (22). In populations of nurses and health professionals, this SFFQ has demonstrated reasonably good validity as a measure of long-term average dietary intakes (23). The Pearson correlation coefficient between magnesium intake assessed by SFFQ and 2 weeks of diet records was 0.76 (10).

Definition of the metabolic syndrome

The metabolic syndrome was defined according to the diagnostic criteria proposed by the Adult Treatment Program III of the National Cholesterol Education Program, as previously described (24). Women with three or more of the following conditions were typically defined as having the metabolic syndrome: 1) triglycerides ≥ 150 mg/dl, 2) HDL cholesterol < 50 mg/dl, 3) blood pressure $\geq 135/85$ mmHg, 4) obesity as defined by a waist circumference > 88 cm (35 inch), and 5) abnormal glucose metabolism as defined by a fasting glucose ≥ 110 mg/dl. In the WHS, however, waist circumference was not reported until year 6 of follow-up. To assess the robustness of our definition for obesity using waist data, we repeated our analyses using a BMI cut point of 30 kg/m² or using a value of BMI that corresponded to the same percentile cut point for BMI as did a waist circumference of 88 cm. Because fasting glucose levels were not available, we instead used the diagnosis of incident type 2 diabetes during an average of 8.8 years follow-up as an alternative measure of baseline abnormal glucose metabolism. The validity of self-reported diabetes has been confirmed by a validation study, as previously reported (25).

Biochemical measurements

Blood samples for the WHS were stored in liquid nitrogen and were thawed before assay. CRP was measured by a validated high-sensitivity assay (Denka Seiken, Nigata, Japan), as previously reported (26). Total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels were measured with direct measurement assays (Roche Diagnostics, Indianapolis, IN). This laboratory is certified for the measurement of lipids and is a core facility for ongoing standardization programs regarding the measurement of CRP. All samples were handled identically and analyzed in random order to reduce sys-

temic bias and interassay variation. Blinded quality control specimens were analyzed simultaneously with the study sample. The average intraassay coefficient of variation (CV) for CRP was 7.8% (26), and the interassay CVs were 2.5–5.1% (27).

Data analysis

We first categorized total magnesium intake into quintiles and then calculated the median plasma concentrations of CRP according to each quintile of intake. We then calculated geometric means of plasma concentrations of CRP because it was not normally distributed. Geometric means were computed by regressing the natural logarithm of plasma CRP concentrations on magnesium intake and then taking an antilog of the resulting mean logarithmic value. Multiple linear regression models were used to control for potential confounding factors. The initial model was adjusted for age (continuous) and BMI (continuous). In multivariate models, we further adjusted for smoking status (current, past, and never), exercise (rarely/never, less than one time per week, one to three times per week, and four or more times per week), alcohol intake (rarely/never, one to three drinks per month, one to six drinks per week, and one or more drinks per day), total calorie intake (continuous), multivitamin use (never, past, and current), history of diabetes (yes/no), history of hypertension (yes/no), history of high cholesterol (yes/no), and parental history of myocardial infarction before 60 years of age (yes/no). The final multivariate model added dietary factors, including intakes of total fat, cholesterol, glycemic load, and folate (all categorized as quintiles). Tests of linear trend across increasing quintiles of intake were conducted by assigning the medians of intakes in quintiles treated as continuous variables. Furthermore, potential effect modifications were evaluated by subgroup analyses stratified by the pre-specified factors, including BMI ($<$ or ≥ 25 kg/m²), smoking status (never, past, or current), history of hypertension (yes/no), high cholesterol (yes/no), and diabetes (yes/no). To eliminate possible residual confounding, the number of cigarettes smoked per day (< 15 , ≥ 15 to < 25 , and ≥ 25) was adjusted in the subgroup analysis for current smokers, and BMI (continuous) remained in the models for both subgroups stratified by BMI ($<$

or ≥ 25 kg/m²). Wald test was used to assess the significance of interaction terms.

We further sought evidence that magnesium intake might be associated with the components of the metabolic syndrome. We performed an analysis limited to the 9,887 study participants who had completed data on characteristics of the metabolic syndrome at study entry. First, we classified all participants as having none, one, two, three, four, or five components of the metabolic syndrome. We then compared the distribution of magnesium intake among individuals with or without each of the individual components of the syndrome as defined above. We also used logistic regression analysis to assess for evidence of association between magnesium intake and the metabolic syndrome. The odds ratios (OR) and 95% CIs for the prevalence of the metabolic syndrome were calculated. The logistic model adjusted for the same covariates as those in the CRP analyses, except for BMI, history of hypertension, high cholesterol, and diabetes, which were either used for defining the metabolic syndrome or highly correlated with the syndrome components.

The same analytic approach as above was used for analyses of dietary magnesium intake after excluding all magnesium supplements. All statistical analyses were conducted using SAS (version 8.0; SAS Institute, Cary, NC). All *P* values were two tailed ($\alpha = 0.05$).

RESULTS— In the present study, dietary sources accounted for ~96% of 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 10th Recommended Dietary Allowances of 320 mg/day for adult women (28). There was an ~1.5-fold difference in total magnesium intake between the highest and lowest quintiles of the study population (median: 422 mg/day in the highest quintile vs. 252 mg/day in the lowest).

At baseline in 1993, women with high intake of magnesium were slightly older, were less likely to be current smokers or have a history of hypertension, and were more likely to exercise, use multivitamins, or have a history of high cholesterol or diabetes than women with low magnesium intake. High magnesium intake was also associated with a slightly lower BMI

(Table 1). Women in the highest quintile of magnesium intake had a lower intake of total fat and cholesterol, but a higher intake of dietary carbohydrate, protein, fiber, and high-glycemic load foods.

Magnesium intake was inversely associated with plasma CRP concentrations (Table 2). In age- and BMI-adjusted analyses, the geometric mean CRP concentrations for increasing quintiles of total magnesium intake were 1.49, 1.37, 1.35, 1.34, and 1.33 mg/l (*P* for trend = 0.0004). After additional adjustment for smoking status, alcohol use, exercise, total calorie intake, multivitamin use, history of diabetes, hypertension, and high cholesterol, as well as parental history of myocardial infarction before 60 years of age, the mean CRP concentrations for ascending quintiles of magnesium intake were 1.46, 1.37, 1.35, 1.36, and 1.34 mg/l (*P* for trend = 0.02). Moreover, this association was more evident after additional adjustment for dietary factors, including total fat, cholesterol, glycemic load, and folate (*P* for trend = 0.0003). Although dietary fiber intake is highly correlated with magnesium intake (correlation coefficient = 0.62), further adjustment for fiber intake did not attenuate the association between magnesium intake and CRP concentrations. The inverse trend remained significant (the mean CRP for quintiles of total magnesium intake was 1.48, 1.38, 1.35, 1.34, and 1.33 mg/l; *P* for trend = 0.02).

As shown in Fig. 1, a significant inverse association between magnesium intake and plasma CRP concentrations was more apparent in overweight women with a BMI of ≥ 25 kg/m² (*P* for trend = 0.002) than those with a BMI ≤ 25 kg/m² (*P* for trend = 0.03). Likewise, this inverse association was pronounced among women who ever smoked (*P* for trend = 0.05 for current smokers and *P* for trend < 0.0001 for past smokers) but not among those who never smoked (*P* for trend = 0.49). Tests of interaction were significant for smoking status (*P* = 0.0009) and overweight (*P* < 0.0001). In contrast, the inverse association between magnesium intake and CRP concentrations persisted across all subgroups stratified by history of hypertension or high cholesterol or diabetes without significant interactions (data not shown).

Table 3 displays the prevalence of individual metabolic syndrome components for 9,887 women free of diabetes at

baseline according to quintiles of magnesium intake. The prevalence of each of the six components was lower in women in the highest quintile of magnesium intake than in women in the lowest quintile. All these associations reached statistical significance except for hypertriglyceridemia. When the waist circumference (> 88 cm) was used for defining central obesity, the proportion of women with three or more characteristics of the metabolic syndrome was 24%. The prevalence of the metabolic syndrome was 7% lower in the highest relative to the lowest categories of magnesium intake (Table 3). Only 17% of participants were classified as having metabolic syndrome when a BMI cut point of 30 kg/m² was used as the obesity criterion.

We also observed significant decreases in prevalent risk of the metabolic syndrome across the quintiles of baseline magnesium intake in logistic models (Table 4). The multivariate-adjusted ORs for prevalent metabolic syndrome from the lowest quintiles to the highest quintiles of magnesium intake were 1.00 (referent), 0.91 (95% CI 0.78–1.06), 0.84 (0.72–0.99), 0.81 (0.68–0.96), and 0.73 (0.60–0.88) (*P* for trend = 0.0008). Further adjustment for dietary fiber or plasma CRP concentrations did not markedly change this inverse association. When obesity was defined using either a BMI cut point of 30 kg/m² or a value of BMI (≥ 25.69 kg/m²) that corresponded to the same percentile cut point for BMI as did a waist circumference of 88 cm, results were almost similar.

Additionally, results were not appreciably changed when we performed the same analyses restricted to dietary magnesium intake (without supplements). As magnesium intake from supplements alone contributed a small proportion of total magnesium intake ($< 4\%$), limited variation of supplemental magnesium intake did not allow us to have sufficient statistical power to perform a separate analysis of magnesium supplements.

CONCLUSIONS— In this large cohort of middle-aged and older U.S. female health professionals, we found a significant inverse association between magnesium intake and plasma concentrations of CRP. This inverse association appeared to be more pronounced among women who were overweight and those who ever smoked. We also found that magnesium

Table 1—Baseline characteristics according to quintiles of total magnesium intake among 11,686 women in the WHS

Variable	Quintile of magnesium intake (mg/day)					P value
	1 (lowest)	2	3	4	5 (highest)	
n	2,336	2,339	2,337	2,337	2,337	
Median intake (mg/day)	252	293	324	359	422	
Age (years)	51 ± 6.5	52 ± 6.7	52 ± 7.1	53 ± 7.3	53 ± 7.7	<0.0001
BMI (kg/m ²)	27 ± 5.8	27 ± 5.4	26 ± 5.1	26 ± 5.0	25 ± 4.8	<0.0001
Smoking (%)						<0.0001
Current	15	12	12	10	8.7	
Never	55	56	52	53	52	
Past	30	32	36	37	39	
Vigorous exercise (%)						<0.0001
Rarely/never	50	41	36	33	28	
<1/week	22	23	22	19	17	
1–3/week	23	28	33	35	38	
≥4/week	5.6	8.0	10	13	16	
Alcohol consumption (%)						<0.0001
Rarely never	50	44	41	40	45	
1–3 drinks/month	14	13	13	14	14	
1–6 drinks/week	26	33	36	36	31	
≥1 drink/day	9.6	10	10	10	8.7	
Current user of multivitamins (%)	16	18	22	29	49	<0.0001
Parental history of myocardial infarction before age 60 years (%)	16	14	14	14	15	0.41
History of hypertension (%)*	25	22	22	23	21	0.01
History of high cholesterol (%)†	23	22	24	25	27	0.0002
History of diabetes (%)	2.3	1.8	2.7	3.1	3.3	0.01
Dietary variables						
Total calorie (kcal/day)	1,690 ± 555	1,771 ± 533	1,782 ± 537	1,788 ± 527	1,719 ± 525	0.18
Total fat (g/day)	65 ± 12	61 ± 10	58 ± 9.8	55 ± 10	51 ± 11	<0.0001
Total carbohydrate (g/day)	210 ± 36	213 ± 31	219 ± 30	226 ± 31	237 ± 35	<0.0001
Protein (g/day)	75 ± 14	80 ± 12	82 ± 13	84 ± 14	85 ± 15	<0.0001
Cholesterol (mg/day)	240 ± 75	235 ± 66	228 ± 65	219 ± 66	205 ± 73	<0.0001
Folate (mg/day)	298 ± 163	348 ± 168	386 ± 174	440 ± 194	593 ± 241	<0.0001
Fiber (g/day)	14 ± 3.3	17 ± 3.4	18 ± 3.8	20 ± 4.6	24 ± 7.0	<0.0001
Glycemic load‡	164 ± 33	162 ± 28	164 ± 27	168 ± 28	175 ± 30	<0.0001

Data are means ± SD unless otherwise indicated. All nutrient variables are energy adjusted. *History of hypertension was defined as a diagnosis of physician or self-reported blood pressure >140/90 mmHg. †History of high cholesterol was defined as having either any history of cholesterol-lowering medication use, a physician diagnosis of high cholesterol, or a self-reported cholesterol ≥240 mg/dl. ‡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.

intake was inversely associated with the prevalence of metabolic syndrome. These results suggest that a beneficial effect of magnesium intake on type 2 diabetes and CVD may be related to its roles in systemic inflammation and/or the development of the metabolic syndrome.

Although an inverse association between serum magnesium concentrations and CRP concentrations was observed in a cross-sectional study of 371 nondiabetic, nonhypertensive obese Mexicans (29), few studies have specifically examined the association between magnesium intake and systemic inflammation. As an acute-phase reactant reflecting low-grade

inflammation, CRP levels have been recognized as an important risk factor for type 2 diabetes, hypertension, and CVD (18). Therefore, it is plausible that the beneficial effects of magnesium on these chronic diseases are partially mediated by improvement in low-grade inflammatory state.

Another finding of our study is that the potential effects of magnesium intake on CRP concentrations were greater among women who were overweight or ever-smokers. This result parallels our previous finding that magnesium intake is associated with lower fasting insulin concentrations among overweight women

(5). Obesity and smoking status have been recognized as important predictors of high concentrations of plasma CRP. The extent to which magnesium intake influences insulin sensitivity or proinflammatory status may be magnified among overweight people or ever-smokers who are prone to chronic inflammation.

Growing evidence also suggests that CRP is a marker for the presence of metabolic syndrome (24,30–32). Metabolic syndrome comprises a constellation of metabolic abnormalities including visceral obesity, glucose intolerance, hypertension, and dyslipidemia (33,34). The evidence that magnesium favorably af-

Table 2—Plasma CRP (mg/l) according to quintiles of total magnesium intake in 11,686 initially apparently healthy women from the WHS

Magnesium intake	Quintile of magnesium intake					P for trend
	1 (lowest)	2	3	4	5 (highest)	
n	2,336	2,339	2,337	2,337	2,337	
Median intake range (mg/day)	252 (113–276)	293 (276–309)	324 (309–341)	359 (341–384)	422 (384–1138)	
Plasma CRP (mg/l)						
Crude	1.67 (0.67–3.80)	1.49 (0.59–3.37)	1.39 (0.56–3.28)	1.33 (0.54–3.15)	1.23 (0.52–2.96)	<0.0001
Model 1*	1.49 (1.43–1.56)	1.37 (1.32–1.43)	1.35 (1.29–1.41)	1.34 (1.29–1.40)	1.33 (1.28–1.39)	0.0004
Model 2†	1.46 (1.40–1.52)	1.37 (1.32–1.43)	1.35 (1.30–1.41)	1.36 (1.30–1.41)	1.34 (1.29–1.40)	0.02
Model 3‡	1.50 (1.43–1.57)	1.39 (1.34–1.45)	1.35 (1.30–1.41)	1.34 (1.28–1.39)	1.31 (1.25–1.37)	0.0003
Model 4§	1.48 (1.41–1.55)	1.38 (1.33–1.45)	1.35 (1.30–1.41)	1.34 (1.29–1.40)	1.33 (1.27–1.40)	0.02

*Data are expressed as geometric mean (95% CI) unless otherwise indicated. *Model 1 adjusted for age and BMI. †Model 2 additionally adjusted for smoking, exercise, total calories, alcohol use, multivitamin use, history of diabetes, history of hypertension, history of high cholesterol, and parental history of myocardial infarction before 60 years. ‡Model 3 included all covariates in model 2 and dietary intakes of total fat, cholesterol, folate, and glycemic load. §Model 4 additionally adjusted for dietary fiber.

fects metabolic abnormalities such as insulin resistance, hypertension, and dyslipidemia, though not entirely consistent, has led us to hypothesize that magnesium intake is related to a lower risk of metabolic syndrome. Our findings provide some evidence for this hypothesis. This notion is also supported by a small cross-sectional study in which lower serum magnesium concentrations were strongly related to higher prevalences of dyslipidemia and hypertension, as well as the metabolic syndrome (35).

Our study strengths include the large size and the relatively homogeneous nature of our cohort, which reduced confounding by several variables, such as access to medical care, educational attain-

ment, and socioeconomic status. The large number of serum samples assessed, detailed diet assessment, and adjustment for major risk factors all increase the validity of our results.

Nonetheless, several limitations in the present study merit consideration. First, the cross-sectional design precludes any causal inferences about the role of magnesium intake. Second, blood samples were assessed once only and dietary assessments were done using SFFQ. Measurement errors might have biased the results toward the null. Third, our evidence may be inadequate to support beneficial effects from magnesium independent of other highly correlated dietary nutrients, including fiber, calcium, and potassium.

Nevertheless, consistency of our observed associations for magnesium may not be fully explained by other healthy lifestyle factors. More importantly, there is biological plausibility for the direct impact of magnesium intake on metabolic risk factors based on experimental evidence. Fourth, the lack of information on fasting glucose or insulin levels at baseline did not allow for a strict National Cholesterol Education Program definition for the metabolic syndrome. Because we used the diagnosis of incident diabetes during 8.8 years of follow-up as a surrogate for abnormal baseline glucose metabolism, misclassification of the metabolic syndrome may have biased our estimates. However, the findings of the present study were not

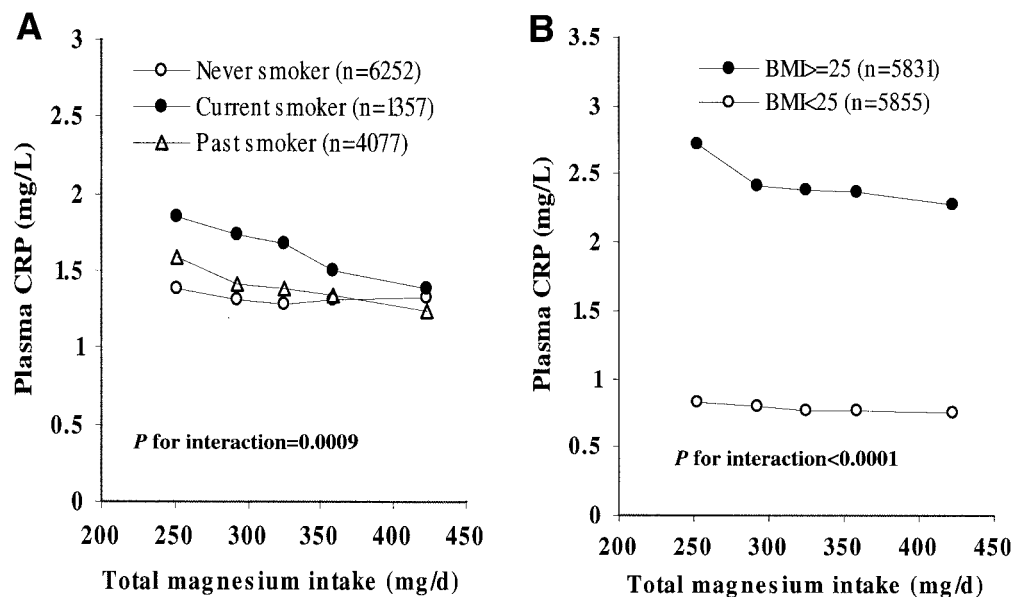


Figure 1—Adjusted geometric mean of plasma CRP (mg/l) by quintiles (Q1–Q5) of total magnesium intake in 11,686 apparently healthy women stratified by smoking status (A) and overweight (B). Analyses were adjusted for age, BMI, smoking, exercise, total calories, alcohol use, multivitamin use, history of diabetes, history of hypertension, history of high cholesterol, parental history of myocardial infarction before 60 years of age, and dietary intakes of total fat, cholesterol, folate, and glycemic load. Further adjustment for cigarettes smoked was made for the subgroup of current smokers, and BMI variable was controlled in the models for both subgroups stratified by BMI.

Table 3—Baseline characteristics of metabolic syndrome components among 9,887 initially apparently healthy women free of diabetes in the WHS

Magnesium intake	Quintile categories					P for trend
	1 (lowest)	2	3	4	5 (highest)	
n	1,977	1,978	1,976	1,978	1,978	
Median intake (range) (mg/day)	253 (116–277)	294 (277–309)	325 (309–341)	359 (341–383)	423 (383–837)	
Metabolic abnormalities*						
Abdominal obesity (%)						
Waist circumference >88 cm	48	45	41	41	36	<0.0001
BMI \geq 30 kg/m ²	22	21	16	16	12	<0.0001
Low HDL cholesterol†	55	51	48	47	47	<0.0001
Hypertriglyceridemia‡	29	27	26	26	27	0.14
High blood pressure§	33	31	31	30	27	<0.0001
Abnormal glucose metabolism	5.0	4.4	3.7	3.7	3.3	0.005
Metabolic syndrome components (%)#						
\geq 1 component	77	74	71	71	69	<0.0001
\geq 2 components	51	49	45	43	41	<0.0001
\geq 3 components	28	26	24	23	21	<0.0001
\geq 4 components	11	9.5	9.0	8.4	6.9	<0.0001
5 components	1.8	1.2	1.1	1.1	1.1	0.07

*The metabolic abnormalities were defined following the National Cholesterol Education Program Adult Treatment Program III guidelines. †HDL cholesterol <50 mg/dl; ‡triglycerides \geq 150 mg/dl; §blood pressure \geq 135/85 mmHg; ||the diagnosis of incident type 2 diabetes during follow-up was used as an indicator of baseline abnormal glucose metabolism; #central obesity was defined using waist circumference (>88 cm).

altered after removing those with incident diabetes. Therefore, we believe it unlikely that this decision affected validity because magnesium intake was consistently related to several other metabolic

components, including central obesity, dyslipidemia, and hypertension. Finally, because our study population included solely female health professionals who were mostly white,

results from the present study may not be generalizable to those in the general U.S. population.

In conclusion, we found that magnesium intake was inversely associated with

Table 4—Relative risk of metabolic syndrome (three or more components) according to quintiles of magnesium intake in 9,887 initially apparently healthy women free of diabetes in the WHS

Metabolic syndrome (waist >88 cm for obesity)	Quintile categories					P for trend
	1 (lowest)	2	3	4	5 (highest)	
Age, calorie-adjusted	1.00	0.85 (0.74–0.98)	0.74 (0.64–0.86)	0.68 (0.59–0.79)	0.61 (0.52–0.71)	<0.0001
Model 1*	1.00	0.91 (0.78–1.05)	0.82 (0.71–0.96)	0.78 (0.67–0.90)	0.69 (0.59–0.81)	<0.0001
Model 2†	1.00	0.91 (0.78–1.06)	0.84 (0.72–0.99)	0.81 (0.68–0.96)	0.73 (0.60–0.88)	0.0008
Model 3‡	1.00	0.91 (0.78–1.07)	0.85 (0.72–1.01)	0.84 (0.70–1.01)	0.77 (0.63–0.95)	0.02
Model 4§	1.00	0.92 (0.79–1.08)	0.87 (0.74–1.03)	0.83 (0.70–0.99)	0.75 (0.61–0.91)	0.002
Metabolic syndrome (BMI \geq 30 kg/m ² for obesity)						
Age, calorie-adjusted	1.00	0.83 (0.71–0.97)	0.73 (0.62–0.86)	0.64 (0.54–0.76)	0.54 (0.45–0.64)	<0.0001
Model 1*	1.00	0.89 (0.75–1.04)	0.82 (0.69–0.97)	0.74 (0.62–0.87)	0.61 (0.51–0.73)	<0.0001
Model 2†	1.00	0.90 (0.76–1.06)	0.86 (0.72–1.03)	0.80 (0.66–0.97)	0.67 (0.54–0.83)	0.0003
Model 3‡	1.00	0.89 (0.75–1.06)	0.84 (0.70–1.02)	0.78 (0.63–0.96)	0.65 (0.52–0.83)	0.0004
Model 4§	1.00	0.91 (0.76–1.08)	0.90 (0.74–1.08)	0.90 (0.74–1.08)	0.81 (0.66–0.99)	0.0006

Data are median (range). *Model 1 adjusted for age, smoking, exercise, total calories, alcohol use, multivitamin use, and parental history of myocardial infarction before 60 years. †Model 2 additionally adjusted for dietary intakes of total fat, cholesterol, folate, and glycemic load. ‡Model 3 adjusted for all covariates in model 2 and dietary fiber. §Model 4 adjusted for all covariates in model 2 and plasma CRP concentrations.

plasma concentrations of CRP and the prevalence of metabolic syndrome. These data support the potential benefits in primary prevention of type 2 diabetes, hypertension, and CVD by vegetables, whole grains, legumes, and nuts that are rich in magnesium, although future large clinical trials to confirm the efficacy of magnesium supplements are clearly warranted.

Acknowledgments—This study was supported by grant DK66401 (National Institute of Diabetes and Digestive and Kidney Diseases) from the National Institutes of Health.

Y.S. is supported by a scholarship from the Carson Family Scholarship Program in the Harvard School of Public Health.

We are indebted to the 39,876 dedicated and committed participants of the WHS. We acknowledge the contributions of the entire staff of the WHS.

P.M.R. is listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory markers in cardiovascular disease and diabetes.

References

- Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A: Magnesium: an update on physiological, clinical and analytical aspects. *Clin Chim Acta* 294:1–26, 2000
- Barbagallo M, Dominguez LJ, Galioto A, Ferlisi A, Cani C, Malfa L, Pineo A, Busardo A, Paolisso G: Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. *Mol Aspects Med* 24:39–52, 2003
- Paolisso G, Barbagallo M: Hypertension, diabetes mellitus, and insulin resistance: the role of intracellular magnesium. *Am J Hypertens* 10:346–355, 1997
- Fung TT, Manson JE, Solomon CG, Liu S, Willett WC, Hu FB: The association between magnesium intake and fasting insulin concentration in healthy middle-aged women. *J Am Coll Nutr* 22:533–538, 2003
- Song Y, Manson JE, Buring JE, Liu S: Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care* 27:59–65, 2004
- Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC: Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 20:545–550, 1997
- Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE: Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 55:1018–1023, 1992
- Abbott RD, Ando F, Masaki KH, Tung KH, Rodriguez BL, Petrovitch H, Yano K, Curb JD: Dietary magnesium intake and the future risk of coronary heart disease (the Honolulu Heart Program). *Am J Cardiol* 92:665–669, 2003
- Al-Delaimy WK, Rimm EB, Willett WC, Stampfer MJ, Hu FB: Magnesium intake and risk of coronary heart disease among men. *J Am Coll Nutr* 23:63–70, 2004
- Ascherio A, Hennekens C, Willett WC, Sacks F, Rosner B, Manson J, Witteman J, Stampfer MJ: Prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertension* 27:1065–1072, 1996
- Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, Sacks F, Stampfer MJ: A prospective study of nutritional factors and hypertension among US men. *Circulation* 86:1475–1484, 1992
- Nadler JL, Buchanan T, Natarajan R, Antomipillai I, Bergman R, Rude R: Magnesium deficiency produces insulin resistance and increased thromboxan synthesis. *Hypertension* 21:1024–1029, 1993
- Paolisso G, Ravusin E: Intracellular magnesium and insulin resistance: results in Pima Indians and Caucasians. *J Clin Endocrinol Metab* 80:1382–1385, 1995
- Altura BM, Altura BT: Magnesium and cardiovascular biology: an important link between cardiovascular risk factors and atherogenesis. *Cell Mol Biol Res* 41:347–359, 1995
- Rasmussen HS, Aurup P, Goldstein K, McNair P, Mortensen PB, Larsen OG, Lawaetz H: Influence of magnesium substitution therapy on blood lipid composition in patients with ischemic heart disease: a double-blind, placebo controlled study. *Arch Intern Med* 149:1050–1053, 1989
- Touyz RM: Role of magnesium in the pathogenesis of hypertension. *Mol Aspects Med* 24:107–136, 2003
- Chakraborti S, Chakraborti T, Mandal M, Mandal A, Das S, Ghosh S: Protective role of magnesium in cardiovascular diseases: a review. *Mol Cell Biochem* 238:163–179, 2002
- Bassuk SS, Rifai N, Ridker PM: High-sensitivity C-reactive protein. *Curr Probl Cardiol* 29:439–493, 2004
- Buring JE, Hennekens CH: The Women's Health Study: summary of the study design. *J Myocard Ischemia* 4:27–29, 1992
- Liu S, Buring JE, Sesso HD, Rimm EB, Willett WC, Manson JE: A prospective study of dietary fiber intake and risk of cardiovascular disease among women. *J Am Coll Cardiol* 39:49–56, 2002
- Watt BK, Merrill AL: *Composition of Foods: Raw, Processed, Prepared, 1963–1992: Agriculture Handbook no. 8*. Washington, DC, U.S. Department of Agriculture, 1993
- Willett WC, Stampfer MJ: Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 124:17–27, 1986
- Willett WC: *Nutritional Epidemiology*. New York, Oxford University Press, 1998
- Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. *Circulation* 107:391–397, 2003
- Song Y, Manson JE, Buring JE, Liu S: A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the Women's Health Study. *Diabetes Care* 27:2108–2115, 2004
- Ridker PM, Rifai N, Rose L, Buring JE, Cook NR: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 347:1557–1565, 2002
- Rifai N, Ridker PM: Population distributions of C-reactive protein in apparently healthy men and women in the United States: implication for clinical interpretation. *Clin Chem* 49:666–669, 2003
- Council NR: *Recommended Dietary Allowances*. 10th ed. Washington, DC, National Academy of Sciences Press, 1989
- Guerrero-Romero F, Rodriguez-Moran M: Relationship between serum magnesium levels and C-reactive protein concentration, in non-diabetic, non-hypertensive obese subjects. *Int J Obes Relat Metab Disord* 26:469–474, 2002
- Frohlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, Mucic R, Brenner H, Koenig W: Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care* 23:1835–1839, 2000
- Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW: C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 110:380–385, 2004
- Laaksonen DE, Niskanen L, Nyyssonen K, Punnonen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT: C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. *Diabetologia* 47:1403–1410, 2004
- Wilson PW, Grundy SM: The metabolic syndrome: practical guide to origins and treatment: part I. *Circulation* 108:1422–1424, 2003
- Wilson PW, Grundy SM: The metabolic syndrome: a practical guide to origins and treatment: part II. *Circulation* 108:1537–1540, 2003
- Guerrero-Romero F, Rodriguez-Moran M: Low serum magnesium levels and metabolic syndrome. *Acta Diabetol* 39:209–213, 2002