Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women[1–3]

Yiqing Song, Tricia Y Li, Rob M van Dam, JoAnn E Manson, and Frank B Hu

ABSTRACT

Background: Relations between magnesium intake and systemic inflammation and endothelial dysfunction are not well established.

Objective: The aim of the present study was to examine whether and to what extent magnesium intake is related to inflammatory and endothelial markers.

Design: We conducted a cross-sectional study of 657 women from the Nurses' Health Study cohort who were aged 43–69 y and free of cardiovascular disease, cancer, and diabetes mellitus when blood was drawn in 1989 and 1990. Plasma concentrations of C-reactive protein (CRP), interleukin 6 (IL-6), soluble tumor necrosis factor α receptor 2 (sTNF-R2), E-selectin, soluble intercellular adhesion molecule 1 (sICAM-1), and soluble vascular cell adhesion molecule 1 (sVCAM-1) were measured. Estimates from 2 semiquantitative food-frequency questionnaires, administered in 1986 and 1990, were averaged to assess dietary intakes.

Results: In age-adjusted linear regression analyses, magnesium intake was inversely associated with plasma concentrations of CRP (P for linear trend = 0.003), E-selectin ($P = 0.001$), and sICAM-1 ($P = 0.03$). After further adjustment for physical activity, smoking status, alcohol use, postmenopausal hormone use, and body mass index, dietary magnesium intake remained inversely associated with CRP and E-selectin. Multivariate-adjusted geometric means for women in the highest quintile of dietary magnesium intake were 24% lower for CRP (1.70 ± 0.18 compared with 1.30 ± 0.10 mg/dL; P for trend = 0.03) and 14% lower for E-selectin (48.5 ± 1.84 compared with 41.9 ± 1.58 ng/mL; P for trend = 0.01) than those for women in the lowest quintile.

Conclusion: Magnesium intake from diet is modestly and inversely associated with some but not all markers of systematic inflammation and endothelial dysfunction in apparently healthy women. *Am J Clin Nutr* 2007;85:1068–74.

KEY WORDS Magnesium intake, biomarkers, systemic inflammation, endothelial dysfunction, women

INTRODUCTION

Magnesium is an essential mineral with several dietary sources, including whole grains, green leafy vegetables, legumes, and nuts (1). National survey data indicate that dietary magnesium intake is inadequate in the US general population, particularly among adolescent girls, women, and the elderly (2, 3). Magnesium intake may be important in maintaining intracellular magnesium homeostasis, which has been hypothesized to be one of the common antecedents for the pathogenesis of insulin resistance, type 2 diabetes, hypertension, and cardiovascular disease (CVD) (4, 5). Cross-sectional studies have shown that magnesium intake correlates significantly with features of the metabolic syndrome (insulin resistance syndrome), including adiposity, hyperinsulinemia, insulin resistance, hypertriglyceridemia, low HDL cholesterol, and hypertension (6, 7). In prospective studies, dietary magnesium intake was inversely associated with the incidence of the metabolic syndrome (8) and its associated chronic diseases, including type 2 diabetes (9–11), CVD (12–14), hypertension (15, 16), and colorectal cancer (17, 18). However, the pathophysiologic mechanisms underlying these observed beneficial effects of magnesium intake are not fully understood.

Recognition is growing that, because they are common antecedents for the initiation of atherosclerosis and type 2 diabetes, systemic inflammation and endothelial dysfunction may be 2 integral components of the metabolic syndrome, (19, 20). Previous cross-sectional studies suggested an inverse association between magnesium intake and concentrations of high-sensitivity C-reactive protein (CRP) (7). This finding has led to the suggestion that the metabolic effects of magnesium intake may be due, at least in part, to magnesium's effects on systemic inflammation. It has as yet to be verified whether magnesium intake is related to other global inflammatory markers, such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α).

Several lines of experimental evidence have also suggested that magnesium intake may have beneficial effects on endothelial function (21–23). Endothelial dysfunction has been shown to be closely related to insulin resistance (20, 24) and to precede the onset of early atherosclerotic CVD and type 2 diabetes (25). Early endothelial dysfunction can readily be assessed by measuring circulating concentrations of endothelial soluble adhesion

[1] From the Division of Preventive Medicine (YS and JEM) and the Channing Laboratory (TYL, RMvD, and FBH), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, and the Departments of Nutrition (TYL, RMvD, and FBH) and Epidemiology (JEM and FBH), Harvard School of Public Health; Boston, MA.

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[3] Address reprint requests to Y Song, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, MA 02215. E-mail: ysong3@rics.bwh.harvard.edu.

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molecules. Because of limited data, it is unclear whether magnesium intake is inversely related to circulating concentrations of endothelial biomarkers.

We therefore conducted a cross-sectional analysis to investigate the relations between magnesium intake and plasma concentrations of inflammatory and endothelial biomarkers, including CRP, IL-6, soluble TNF-α receptor 2 (sTNF-R2), E-selectin, soluble intercellular adhesion molecule 1 (sICAM-1), and soluble vascular cell adhesion molecule 1 (sVCAM-1) in apparently healthy women.

SUBJECTS AND METHODS

Study population

The Nurses' Health Study (NHS) cohort was established in 1976 with 12 1700 female registered nurses residing in the United States. Every 2 y, follow-up questionnaires are sent to obtain updated information on potential risk factors and to identify newly diagnosed cases of chronic diseases. The present substudy included 657 women who were selected as control subjects for a nested case-control study of diabetes. These women did not have CVD, cancer, or diabetes mellitus at the time of blood drawing, and they had complete data on lifestyle and dietary information. The average age of the women at the time of blood drawing was 56 y (range: 43–69 y).

All participants gave written informed consent. The Brigham and Women's Hospital Institutional Review Board approved the study protocol.

Blood collection and assessment of biomarkers

Blood was collected in 1989 or 1990. Women who were willing to provide blood specimens were sent instructions and a phlebotomy kit. Blood specimens were returned by overnight mail on ice, and 97% arrived within 26 h of phlebotomy. On arrival, the samples were centrifuged (1200 $\times$ *g*, 15 min, room temperature) to separate plasma from buffy coat and red blood cells, and the samples were frozen in liquid nitrogen until they were analyzed. Quality-control samples were routinely frozen along with study samples to monitor plasma changes as a result of long-term storage and to monitor changes in assay variability. Study samples were analyzed in random order to further reduce systematic bias and interassay variation. All markers were measured in the Clinical Chemistry Laboratory at Children's Hospital (Boston, MA). CRP concentrations were measured with the use of a latex-enhanced turbidimetric assay on a Hitachi 911 (Denka Seiken, Tokyo, Japan). IL-6 concentrations were measured with the use of an ultrasensitive enzyme-linked immunosorbent assay (ELISA; R & D Systems (Minneapolis, MN) and sTNF-R2 by an ELISA kit with the use of immobilized monoclonal antibody to human TNF-R2 (Genzyme, Cambridge, MA). Concentrations of E-selectin, sICAM-1, and sVCAM-1 were measured with the use of a commercial ELISA (R&D Systems). The interassay CVs for the biomarkers were as follows: CRP, 3.4–3.8%; IL-6, 5.8–8.2%; sTNF-R2, 3.6–5.1%; E-selectin, 6.4–6.6%; sICAM-1, 6.1–10.1%; and sVCAM-1, 8.5–10.2%.

Assessment of dietary intake

In 1986 and 1990, a semiquantitative food-frequency questionnaire (SFFQ) was mailed to NHS participants. To minimize misclassification, usual dietary intakes assessed from the SFFQs administered in 1986 and 1990 were averaged for each participant to reflect long-term dietary intake during the time. In populations of nurses and health professionals, this SFFQ has shown reasonably good validity as a measure of long-term average dietary intakes (26). Pearson's correlation coefficient between magnesium intake assessed by SFFQ and 2 wk of diet records was 0.76 (15). The SFFQ included questions on 116 food items and specified serving sizes that were described with the use of natural portions or standard weight and volume measures of servings commonly consumed in this study population. For each food item, participants indicated the average frequency of their consumption during the past year in terms of the specified serving size by checking 1 of 9 frequency categories, which ranged from "almost never" to "$\geq$6 times/d." 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 (27).

On the baseline SFFQ, detailed information was also requested on the use of specific vitamins and minerals (including vitamins A, C, and E; iron; zinc; and calcium) and brands and types of multivitamins, as well as the dose and duration of use. Because the use of magnesium supplements was rare before 1990, no additional information was collected specifically on the use of magnesium supplements. Data on multivitamin preparations that provide the dose of magnesium in each preparation were taken into account to assess the 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 with the use of the residual method (28).

Assessment of other variables

Cigarette smoking and body weight were assessed in 1990. Body mass index (BMI; in kg/m^2) was calculated. Physical activity was assessed in the number of hours per week spent in common leisure-time physical activities, which was expressed as metabolic equivalent hours per week (MET-h/wk) (29). Alcohol intake was the mean (in g/d) of intakes in 1986 and 1990. Hormone therapy use was ascertained among postmenopausal women, who were classified as never, past, or current users in 1990.

Statistical analysis

We categorized total magnesium intake in quintiles. We used log-transformed plasma concentrations of biomarkers to achieve normal distributions. Age-adjusted Pearson's partial correlation coefficients were calculated to evaluate associations between these biomarkers and BMI. Multiple linear regression models (in PROC GLM) were used to control for potential confounding factors. Geometric means were computed by regressing the ln of plasma concentrations on magnesium intake and then taking an antilog of the resulting mean logarithmic value. We next calculated the exponential values of the means and the CIs for the markers. Multiple linear regressions were used to calculate regression coefficients for the relation between magnesium intake and biomarker concentrations. First, we adjusted only for age ($\leq$45, 45.1–50, 50.1–60, 60.1–65, or $>$65.1 y). In multivariate models, we further adjusted for smoking status (never, past, current 1–14 cigarettes/d, or current $\geq$15 cigarettes/d), physical

TABLE 1
Baseline characteristics according to quintile (Q) of total and dietary magnesium intakes in 657 apparently healthy women in the Nurses' Health Study[1]

	Total magnesium[2]				Dietary magnesium[2]			
Characteristic	Q1 (n = 132)	Q3 (n = 129)	Q5 (n = 131)	P for trend	Q1 (n = 131)	Q3 (n = 134)	Q5 (n = 132)	P for trend
Median intake (mg/d)	230	297	382		225	289	356	
Age (y)	54 ± 6.8	57 ± 6.5	59 ± 6.1	<0.001	54 ± 6.7	57 ± 6.5	59 ± 6.3	<0.001
BMI (kg/m^2)	27 ± 6.9	26 ± 5.3	26 ± 5.6	0.34	27 ± 6.9	26 ± 5.6	25 ± 4.9	0.05
Alcohol consumption (g/d)	5.0 ± 8.0	6.8 ± 13	4.6 ± 7.1	0.19	5.5 ± 8.8	6.6 ± 9.9	3.9 ± 6.3	0.15
Current smoker (%)	15	12	7	0.15	15	14	8	0.21
Physical activity (MET-h/wk)	9.6 ± 12	15 ± 14	19 ± 22	0.005	9.1 ± 11	17 ± 16	17 ± 19	0.001
Current postmenopausal hormone use (%)	35	47	40	0.67	39	38	37	0.45
Nutrient intakes[4]								
Energy intake (kcal/d)	1757 ± 536	1778 ± 490	1716 ± 474	0.39	1788 ± 543	1744 ± 484	1698 ± 493	0.12
Protein (g/d)	69 ± 11	76 ± 12	82 ± 16	<0.001	69 ± 11	75 ± 12	82 ± 16	<0.001
Carbohydrate (g/d)	193 ± 31	196 ± 34	212 ± 33	<0.001	193 ± 33	198 ± 32	213 ± 33	<0.001
Total fat (g/d)	61 ± 10	57 ± 9.0	50 ± 10	<0.001	61 ± 9.3	56 ± 8.9	50 ± 10	<0.001
trans Fat (g/d)	3.2 ± 1.0	2.7 ± 1.0	2.1 ± 0.8	<0.001	3.2 ± 1.03	2.7 ± 0.84	2.1 ± 0.8	<0.001
Fiber (g/d)	14 ± 3.6	18 ± 4.4	23 ± 7.5	<0.001	14 ± 3.4	18 ± 4.1	23 ± 7.3	<0.001
Glycemic load[5]	107 ± 20	103 ± 21	107 ± 22	0.09	107 ± 21	105 ± 21	107 ± 22	0.16

[1] MET, metabolic equivalent.
[2] All covariate values are according to the quintile of total and dietary magnesium intake. Total magnesium intake included the total amount of magnesium from both food and supplements; dietary magnesium accounted for 96% of the total amount of magnesium and did not include supplemental magnesium from any multivitamin.
[3] $\bar{x}$ ± SD (all such values).
[4] All the means of nutrients are energy adjusted.
[5] Defined as an indicator of blood glucose induced by a person's total carbohydrate intake. Each unit of glycemic load represents the equivalent of 1 g carbohydrate from white bread.

activity (<1.5, 1.5–5.9, 6.0–11.9, 12.0–20.9, or ≥21.0 MET-h/wk), alcohol intake (nondrinker, 0–4.9, 5.0–10.0, or >10.0 g/d), total calorie intake (continuous), menopausal status, and postmenopausal hormone use (never, past, or current). The final multivariate model also adjusted for BMI (<23, 23–24.9, 25–29.9, 30–34.9, or ≥35). Tests of linear trend across increasing quintiles of intake were conducted by assigning the medians of intakes in quintiles treated as a continuous variable. In addition, potential effect modifications were evaluated by subgroup analyses stratified by the prespecified factors, including BMI (<25 or ≥25), smoking status (never, past, or current smoker), alcohol intake (never, past, or current drinker), and postmenopausal hormone use (yes or no). The Wald test was used to assess the significance of multiplicative interaction terms.

The same analytic approach as above was used for analyses of dietary magnesium intake after excluding magnesium intake from supplements. All statistical analyses were conducted with the use of SAS software (version 9.1; SAS Institute, Cary, NC). All P values were two-tailed (α = 0.05).

RESULTS

In the present study, dietary sources accounted for ≈96% of the total intake of magnesium. There were ≈1.5-fold differences in total magnesium intake between the highest and lowest quintiles of the study population (medians: 382 mg/d in the highest quintile, 230 mg/d in the lowest). At baseline in 1990, women with a higher intake of magnesium were older, less likely to be current smokers, and more likely to be physically active than were women with lower magnesium intake (**Table 1**). High magnesium intake was also associated with a slightly lower BMI. Women in the highest quintile of magnesium intake had lower intakes of total and *trans* fat but higher intakes of dietary carbohydrate, protein, and fiber.

Almost all markers except sVCAM-1 were correlated with BMI; the partial correlation coefficients ranged from 0.13 to 0.47 (**Table 2**). Of inflammatory markers, CRP was the most strongly correlated with BMI (r = 0.47), followed by IL-6 and sTNF-R2. Of endothelial biomarkers, E-selectin was modestly correlated with all markers except sTNF-R2. sVCAM-1 was positively associated with sICAM-1, E-selectin, and sTNF-R2 but was not associated with CRP and IL-6.

Age-adjusted geometric mean plasma concentrations of CRP, E-selectin, and sICAM-1 trended toward significant decreases with increasing quintiles of magnesium intake (P for linear trend = 0.003 for CRP, 0.001 for E-selectin, and 0.03 for sICAM-1) (**Table 3**). Further adjustment for smoking status, alcohol use, exercise, total calorie intake, and postmenopausal hormone therapy did not materially attenuate these associations between magnesium intake and CRP and E-selectin. After additional adjustment for BMI, the inverse trends remained for CRP and E-selectin (P for trend = 0.03 and 0.01, respectively). CRP and E-selectin concentrations were 24% and 14% lower, respectively, in women in the highest quintile of dietary magnesium intake than in women in the lowest quintile (Table 3). Similarly inverse associations, albeit less pronounced, also persisted for total magnesium intake (data not shown).

Linear regression coefficients for the log-transformed biomarkers in relation to a 100 mg/d increase in dietary magnesium intake are shown in **Table 4**. Inverse associations were consistently observed between dietary magnesium and plasma concentrations of

TABLE 2
Age-adjusted Pearson's partial correlation coefficients for log-transformed markers[1]

Variables	CRP	IL-6	sTNF-R2	E-selectin	sICAM-1	sVCAM-1	BMI
CRP	—	0.32[2]	0.14[3]	0.22[2]	0.14[3]	0.04[4]	0.47[2]
IL-6	—	—	0.13[4]	0.24[2]	0.17[2]	0.12[4]	0.30[2]
sTNF-R2	—	—	—	0.10[4]	0.22[2]	0.26[2]	0.15[3]
E-selectin	—	—	—	—	0.37[2]	0.25[2]	0.28[2]
sICAM-1	—	—	—	—	—	0.39[2]	0.13[3]
sVCAM-1	—	—	—	—	—	—	0.09[4]
BMI	—	—	—	—	—	—	—

[1] CRP, C-reactive protein; IL-6, interleukin 6; sTNF-R2, soluble tumor necrosis factor α receptor 2; sICAM-1, soluble intercellular cell adhesion molecule 1; sVCAM-1, soluble vascular cell adhesion molecule 1.
[2–4] Significantly different from square root; [2]$P < 0.0001$, [3]$P < 0.001$, [4]$P \geq 0.05$.

CRP and E-selectin after adjustment for age, BMI, physical activity, smoking status, alcohol consumption, and use of hormone replacement therapy. We did not detect significant interactions of magnesium intake with BMI, waist circumference, current alcohol consumption status, smoking status, and physical activity for plasma concentrations of inflammatory and endothelial biomarkers (data not shown).

We also examined the associations between the main magnesium-rich foods and inflammatory and endothelial markers. Of the presented foods, whole grain was the main contributor to dietary magnesium, followed by green leafy vegetables, nuts, and legumes. However, the inverse associations were statistically significant only for green leafy vegetables and nuts with CRP and for green leafy vegetables with IL-6 (**Table 5**).

TABLE 3
Plasma concentrations of biomarkers of inflammation and endothelial dysfunction by quintile (Q) of dietary magnesium intake in 657 apparently healthy women in the Nurses' Health Study[1]

	Dietary magnesium intake					*P* for linear trend[2]
	Q1	Q2	Q3	Q4	Q5	
Median (mg/d)	225	262	289	316	356	
CRP (mg/dL)						
Age-adjusted	1.90 (1.50, 2.30)[3]	1.60 (1.30, 1.90)	1.50 (1.30, 1.90)	1.40 (1.20, 1.80)	1.20 (1.00, 1.50)	0.003
Model 1[4]	1.80 (1.50, 2.30)	1.50 (1.20, 1.90)	1.60 (1.30, 2.00)	1.40 (1.20, 1.80)	1.20 (1.00, 1.40)	0.003
Model 2[5]	1.70 (1.40, 2.10)	1.50 (1.30, 1.80)	1.50 (1.30, 1.80)	1.50 (1.30, 1.80)	1.30 (1.10, 1.50)	0.03
IL-6 (pg/mL)						
Age-adjusted	1.99 (1.77, 2.25)	1.92 (1.70, 2.17)	1.95 (1.74, 2.20)	1.68 (1.49, 1.89)	1.83 (1.62, 2.06)	0.14
Model 1[4]	1.96 (1.74, 2.22)	1.91 (1.69, 2.15)	1.99 (1.77, 2.25)	1.70 (1.51, 1.92)	1.81 (1.61, 2.05)	0.19
Model 2[5]	1.93 (1.71, 2.17)	1.91 (1.70, 2.15)	1.96 (1.74, 2.20)	1.72 (1.52, 1.93)	1.86 (1.65, 2.09)	0.40
sTNF-R2 (pg/mL)						
Age-adjusted	2246 (2079, 2427)	2414 (2236, 2605)	2490 (2309, 2685)	2236 (2070, 2415)	2253 (2087, 2433)	0.60
Model 1[4]	2236 (2068, 2417)	2433 (2254, 2627)	2496 (2313, 2692)	2257 (2089, 2438)	2220 (2055, 2398)	0.49
Model 2[5]	2205 (2041, 2383)	2435 (2256, 2627)	2475 (2295, 2668)	2277 (2109, 2459)	2249 (2083, 2427)	0.85
E-selectin (ng/mL)						
Age-adjusted	50.0 (46.3, 53.9)	44.7 (41.4, 48.1)	41.5 (38.5, 44.7)	43.3 (40.2, 46.7)	41.5 (38.5, 44.7)	0.001
Model 1[4]	49.2 (45.6, 53.0)	44.3 (41.1, 47.7)	42.1 (39.1, 45.3)	43.9 (40.8, 43.4)	41.3 (38.3, 44.5)	0.004
Model 2[5]	48.5 (45.0, 52.2)	44.6 (41.4, 47.9)	41.5 (38.6, 44.6)	44.3 (41.1, 47.7)	41.9 (38.9, 45.1)	0.01
sICAM-1 (ng/mL)						
Age-adjusted	257 (246, 269)	252 (241, 262)	250 (240, 260)	241 (231, 252)	243 (233, 254)	0.03
Model 1[4]	255 (245, 266)	249 (239, 259)	251 (241, 261)	244 (234, 254)	244 (234, 254)	0.11
Model 2[5]	254 (244, 265)	249 (239, 259)	251 (241, 261)	244 (234, 254)	246 (236, 256)	0.19
sVCAM-1 (ng/mL)						
Age-adjusted	542 (519, 567)	538 (515, 562)	538 (515, 562)	513 (491, 536)	519 (497, 543)	0.08
Model 1[4]	539 (515, 564)	540 (516, 564)	540 (517, 564)	515 (493, 539)	517 (495, 541)	0.09
Model 2[5]	539 (515, 564)	538 (515, 562)	541 (517, 515)	515 (492, 538)	519 (496, 543)	0.12

[1] CRP, C-reactive protein; IL-6, interleukin 6; sTNF-R2 soluble tumor necrosis factor α receptor 2; sICAM-1, soluble intercellular cell adhesion molecule 1; sVCAM-1, soluble vascular cell adhesion molecule. Magnesium intake from diet alone accounted for 96% of the total amount of magnesium; supplemental magnesium from any multivitamins was excluded for dietary magnesium.
[2] From multiple linear regression models for the relation between dietary magnesium intake and log-transformed biomarkers.
[3] Adjusted geometric $\bar{x}$; 95% CIs in parentheses (all such values).
[4] Multivariate model 1 was adjusted for age (≤45, 45.1–50, 50.1–60, 60.1–65, or >65.1 y), smoking status (never, past, current 1–14 cigarettes/d, or current ≥15 cigarettes/d), physical activity (<1.5, 1.5–5.9, 6.0–11.9, 12.0–20.9, or ≥21.0 metabolic equivalent h/wk), alcohol intake (none, 0–4.9, 5.0–10.0, or >10.0 g/d), total calorie intake (continuous), menopausal status, and postmenopausal hormone use (never, past, or current).
[5] Multivariate model 2 was model 1 with additional adjustment for BMI [(in kg/m^2) <23, 23–24.9, 25–29.9, 30–34.9, or ≥35].

TABLE 4
Linear regression coefficients for the relation between each increase of 100 mg/d in dietary magnesium intakes and log-transformed biomarkers of inflammation and endothelial dysfunction in 657 apparently healthy women in the Nurses' Health Study[1]

	Dietary magnesium intake[2]		
Biomarkers	Age-adjusted	Model 1[3]	Model 2[4]
CRP (mg/dL)	−0.20 ± 0.08 (0.009)	−0.21 ± 0.08 (0.006)	−0.14 ± 0.07 (0.04)
IL-6 (pg/mL)	−0.02 ± 0.05 (0.74)	−0.01 ± 0.05 (0.84)	0.01 ± 0.05 (0.83)
sTNF-R2 (pg/mL)	−0.03 ± 0.03 (0.03)	−0.03 ± 0.03 (0.03)	−0.02 ± 0.03 (0.50)
E-selectin (ng/mL)	−0.08 ± 0.03 (0.007)	−0.07 ± 0.03 (0.02)	−0.06 ± 0.03 (0.05)
sICAM-1 (ng/mL)	−0.02 ± 0.02 (0.33)	−0.008 ± 0.02 (0.62)	−0.003 ± 0.02 (0.83)
sVCAM-1 (ng/mL)	−0.03 ± 0.02 (0.14)	−0.02 ± 0.02 (0.17)	−0.02 ± 0.02 (0.21)

[1] All values are $\bar{x}$ ± SE; *P* values in parentheses. CRP, C-reactive protein; IL-6, interleukin 6; sTNF-R2, soluble tumor necrosis factor α receptor 2; sICAM-1, soluble intercellular cell adhesion molecule 1; sVCAM-1, soluble vascular cell adhesion molecule 1.

[2] *P* values are from the multiple linear regression models for the relation between dietary magnesium intake (per 100 mg/d increase) and log-transformed biomarkers.

[3] Multivariate model 1 was adjusted for age (≤45, 45.1–50, 50.1–60, 60.1–65, or >65.1 y), smoking status (never, past, current, 1–14 cigarettes/d, or current ≥15 cigarettes/d), exercise (<1.5, 1.5–5.9, 6.0–11.9, 12.0–20.9, or ≥21.0 metabolic equivalent h/wk), alcohol intake (none, 0–4.9, 5.0–10.0, or >10.0 g/d), total calorie intake (continuous), menopausal status, and postmenopausal hormone use (never, past, or current).

[4] Multivariate model 2 was model 1 with additional adjustment for BMI [(in kg/m^2) <23, 23–24.9, 25–29.9, 30–34.9, or ≥35].

DISCUSSION

In this study of apparently healthy women, higher magnesium intake was associated with lower concentrations of CRP and E-selectin independently of age, BMI, smoking status, physical activity, alcohol consumption, and postmenopausal hormone use. Such observational data are likely to reflect overall beneficial effects of magnesium intake from consumption of magnesium-rich foods such as whole grains, green leafy vegetables, legumes, and nuts on systemic inflammation and endothelial function.

Low-grade chronic inflammation, as reflected by elevated inflammatory markers, may be one of the common antecedents underlying the clustering of obesity, impaired glucose tolerance, dyslipidemia, and hypertension, that is known as the metabolic syndrome. Previous experimental studies showed that diet-induced magnesium deficiency led to elevated serum concentrations of inflammatory cytokines in rodent models (30–33). Epidemiologic data, although limited, have provided some cross-sectional evidence linking magnesium intake to systemic inflammation, as reflected by elevated concentrations of CRP. The inverse association between magnesium intake and CRP was first reported in a large population of 11 686 apparently healthy women in the Women's Health Study (7). In a large representative sample of US adults aged ≥20 y from the National Health and Nutrition Examination Survey 1999–2000 (34), persons who consumed less magnesium than the recommended daily allowance were 1.48–1.75 times more likely to have elevated CRP (≥3.0 mg/L) than were persons who consumed at least the recommended daily allowansce, after control for demographic and CVD risk factors. Those findings are also supported by one cross-sectional study of 371 nondiabetic, normotensive, obese Mexicans in which serum magnesium concentrations were found to be inversely associated with CRP concentrations (35). In the present study, we extended prior observations by assessing the correlation of magnesium intake with 3 biomarkers of systemic inflammation, including concentrations of CRP, IL-6, and

TABLE 5
Linear regression coefficients for concentrations of inflammatory and endothelial markers in relation to intakes of magnesium-rich food groups in 657 apparently healthy women in the Nurses' Health Study[1]

	Magnesium-rich foods[2]			
Biomarkers	Whole grain (per 100 g/d)	Green leafy vegetables (per 1 serving/d)	Legumes (per 1 serving/d)	Nuts (per 1 serving/d)
CRP	−0.33 ± 0.33 (0.32)	−0.29 ± 0.07 (<0.001)	−0.37 ± 0.26 (0.16)	−0.38 ± 0.18 (0.04)
IL-6	−0.23 ± 0.21 (0.29)	−0.11 ± 0.05 (0.02)	0.12 ± 0.17 (0.49)	−0.11 ± 0.12 (0.35)
sTNF-R2	0.02 ± 0.14 (0.87)	−0.05 ± 0.03 (0.09)	−0.10 ± 0.11 (0.36)	−0.03 ± 0.12 (0.70)
E-selectin	−0.14 ± 0.13 (0.31)	−0.03 ± 0.03 (0.35)	−0.17 ± 0.11 (0.10)	−0.11 ± 0.08 (0.14)
sICAM-1	−0.03 ± 0.07 (0.68)	−0.02 ± 0.02 (0.26)	0.02 ± 0.06 (0.73)	−0.03 ± 0.04 (0.43)
sVCAM-1	0.03 ± 0.08 (0.74)	−0.02 ± 0.02 (0.37)	−0.005 ± 0.06 (0.93)	−0.08 ± 0.05 (0.09)

[1] All values are $\bar{x}$ ± SE; *P* values in parentheses. CRP, C-reactive protein; IL-6, interleukin 6; sTNF-R2, soluble tumor necrosis factor α receptor 2; sICAM-1, soluble intercellular cell adhesion molecule 1; sVCAM-1, soluble vascular cell adhesion molecule 1.

[2] The multiple linear regression models were adjusted for age (≤45, 45.1–50, 50.1–60, 60.1–65, or >65.1 y), BMI [(in kg/m^2) <23, 23–24.9, 25–29.9, 30–34.9, or ≥35], smoking status (never, past, current 1–14 cigarettes/d, or current ≥15 cigarettes/d), exercise (<1.5, 1.5–5.9, 6.0–11.9, 12.0–20.9, or ≥21.0 metabolic equivalent h/wk), alcohol intake (none, 0–4.9, 5.0–10.0, or >10.0 g/d), total calorie intake (continuous), menopausal status, and postmenopausal hormone use (never, past, or current). Regression coefficients were based on per-unit increase per day: per 100-g increment in whole grain and per 1-serving increment in green leafy vegetables, nuts (without peanut butter), and legumes.

sTNF-R2. Although sTNF-R2, IL-6, and CRP may each serve as sensitive markers of an underlying global inflammatory state, our results showed a significant inverse association only between magnesium intake and CRP, a finding that may reflect the intrinsic biological properties of CRP as the principal downstream mediator of the acute-phase response, as well as the integrated effects of both TNF-α and IL-6 (36). However, our observations may also indicate that the CRP measurement is exceptionally stable and measured by robust, well-standardized immunoassays as compared with other inflammatory markers (36, 37).

In the present analysis, we also assessed the correlations between magnesium intake and the concentrations of 3 endothelial adhesion molecules, which are up-regulated in the early cascade of endothelial dysfunction. Elevated plasma concentrations of soluble forms of endothelial adhesion molecules, released from shedding or proteolytic cleavage from the endothelial cell surface, are considered useful indicators of endothelial dysfunction and activation (20, 25). E-selectin is expressed exclusively by endothelial cells, whereas ICAM-1 is constitutively expressed by several cells, including endothelium and leukocytes (25). VCAM-1 expression is found on activated endothelium and vascular smooth muscle cells. The specificity of soluble E-selection as a reflection of its membrane-bound form in the activated endothelium may make it a better surrogate than are concentrations of sICAM-1 and sVCAM-1. Our findings provide indirect evidence supporting the link between magnesium intake and endothelial dysfunction. One randomized, double-blind, placebo-controlled trial has shown that oral magnesium supplementation (30 mmol elemental magnesium/d) for 6 mo resulted in a significant improvement in endothelium-dependent brachial artery flow–mediated vasodilation in 50 patients with coronary artery disease (21), which indicates a direct effect of magnesium intake on endothelial function.

The underlying mechanisms by which magnesium intake influences systemic inflammation and endothelial dysfunction remain to be elucidated, although the most likely explanation is a causal link between magnesium homeostasis and insulin resistance (4, 5). Circulating concentrations of endothelial adhesion molecules and inflammatory cytokines are highly correlated with insulin resistance and its related metabolic abnormalities. It seems likely that the observed associations between magnesium intake and markers of inflammation and endothelial dysfunction may, at least in part, reflect the direct effect of magnesium intake on glucose and insulin homeostasis. Alternatively, magnesium may influence insulin resistance through a modulation of systemic inflammation and endothelial function. Increasing evidence points to systemic inflammation and endothelial dysfunction as 2 common and independent antecedents for the pathogenesis of insulin resistance (19, 20, 24). Thus, the associations we observed may reflect a direct role of magnesium in systemic inflammation and endothelial function.

The strengths of the present study include the large size and the relatively homogeneous nature of the cohort, which reduced confounding by several variables, such as access to medical care, educational attainment, and socioeconomic status. The assessment of multiple biomarkers with the use of robust and well-standardized assays, detailed diet assessment, and adjustment for principal risk factors all increased the validity of our results. Nonetheless, several limitations of the present study merit consideration. First, the cross-sectional design precludes inferences about the role of magnesium intake in causing inflammation and endothelial dysfunction. Second, biomarker concentrations were assessed only once, and dietary assessments are inevitably affected by some measurement errors. Nondifferential misclassification because of random measurement errors, especially for VCAM-1, may have attenuated the observed associations. Third, our evidence may be inadequate to support beneficial effects from magnesium independent of other highly correlated dietary nutrients, including fiber, calcium, and potassium. Because magnesium intake from supplements alone contributed a small proportion of total magnesium intake (<4%), our results largely reflect the associations for dietary magnesium intake. Thus, our results are more likely to support the potential benefits of high consumption of magnesium-rich foods such as whole grains, green leafy vegetables, legumes, and nuts. Although independent effects of magnesium intake on endothelial function are biologically plausible according to experimental evidence, any causal effects of magnesium intake on inflammation and endothelial function warrant further investigation. Fourth, because the present study population solely comprised female health professionals, most of whom were white, results from this study may not be generalizable to the general US population.

In conclusion, we found that, in apparently healthy women, dietary magnesium intake was inversely associated with plasma concentrations of CRP and E-selectin but not with those of IL-6, sTNF-R2, sICAM-1, or sVCAM-1. These data suggest that increasing the intake of magnesium from consumption of magnesium-rich foods such as whole grains, green leafy vegetables, legumes, and nuts may have potential beneficial effects on systemic inflammation and endothelial function. These observed associations, albeit generally modest, may represent a pathophysiologic mechanism for the pleiotropic effects of magnesium intake on the features of the metabolic syndrome and its associated chronic diseases. Clinical trials are warranted to separate out and establish the possible causal effects of magnesium supplements on chronic inflammation and endothelial function.

The study was conceived of and designed by YS and FBH. TYL, JEM, and FBH were responsible for acquisition of data. YS, TYL, RMvD, JEM, and FBH analyzed and interpreted the data. YS wrote the draft of the manuscript, and TYL, RMvD, JEM, and FBH critically reviewed the manuscript. YS, TYL, and FBH provided statistical expertise. JEM and FBH obtained funding and provided administrative, technical, and material support. JEM is listed as a coinventor on a pending patent held by Brigham and Women's Hospital that relates to the use of inflammatory biomarkers in diabetes prediction. None of the other coauthors had a personal or financial conflict of interest.

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