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Relations of dietary magnesium intake to biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women

Short Running Title: Dietary magnesium and inflammation in postmenopausal women

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Objective: Although magnesium (Mg) may favorably affect metabolic outcomes, few studies have investigated the role of Mg intake in systemic inflammation and endothelial dysfunction in humans.

Research Design and Methods: Among 3,713 postmenopausal women aged 50-79 y in the Women's Health Initiative Observational Study and free of cardiovascular disease, cancer, and diabetes at baseline, we measured plasma concentrations of high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), tumor necrosis factor α receptor 2 (TNF-α-R2), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), and E-selectin. Mg intake was assessed using a semi-quantitative food frequency questionnaire.

Results: After adjusting for age, ethnicity, clinical center, time of blood draw, smoking, alcohol, physical activity, energy intake, BMI, and diabetes status, Mg intake was inversely associated with hs-CRP (p-for-trend=0.003), IL-6 (p<.0001), TNF-α-R2 (p=0.0006), and sVCAM-1 (p=0.06). Similar findings remained after further adjustment for dietary fiber, fruit, vegetables, folate, and saturated and trans-fat intake. Multivariable-adjusted geometric means across increasing quintiles of Mg intake were 3.08, 2.63, 2.31, 2.53, 2.16 mg/L for hs-CRP (P=0.005), 2.91, 2.63, 2.45, 2.27, 2.26 pg/mL for IL-6 (p=0.0005), and 707, 681, 673, 671, 656 ng/mL for sVCAM-1 (P=0.04). An increase of 100 mg/d Mg was inversely associated with hs-CRP (-0.23 mg/L ± 0.07; p=0.002), IL-6 (-0.14 pg/mL± 0.05; p=0.004), TNF-α-R2 (-0.04 pg/mL ± 0.02; p=0.06), and sVCAM-1 (-0.04 ng/mL ± 0.02; p=0.07). No significant ethnic differences were observed.

Conclusions: High Mg intake is associated with lower concentrations of certain markers of systemic inflammation and endothelial dysfunction in postmenopausal women.

Magnesium (Mg) is a biologically active mineral that acts as a co-factor in hundreds of enzymatic reactions in the human body. In observational studies, Mg intake has been inversely associated with metabolic disease outcomes including hypertension (1), type 2 diabetes (2), cardiovascular disease (3), and colorectal cancer (4). The biological mechanism underlying these relations is not entirely clear, although experimental data in animals indicate that dietary Mg deficiency may promote an inflammatory response (5), ultimately leading to endothelial dysfunction and metabolic disease. Available data in humans also suggest that low Mg intake may be related to dyslipidemia (1) and insulin resistance (2). While Mg intake has been inversely associated with hs-CRP (1, 6) in white women, its associations with IL-6 and TNF-α (6, 7) have been inconsistent. Also, evidence regarding the relation of Mg intake to endothelial dysfunction as measured by elevated concentrations of adhesion molecules is limited (6, 8). Studies assessing dietary Mg intake in relation to inflammation and endothelial markers in minority populations are lacking, and it is not known if there are ethnic differences modifying this relation.

We therefore examined comprehensively the association between dietary Mg intake and circulating concentrations of biomarkers of systemic inflammation (hs-CRP, IL-6, and TNF-α-R2) and endothelial dysfunction (sICAM-1, sVCAM-1, and E-selectin) in an ethnically diverse cohort of postmenopausal women aged 50-79 years enrolled in the Women's Health Initiative Observational Study (WHI-OS), including whites, blacks, Hispanics, and Asians/Pacific Islanders.

RESEARCH DESIGN AND METHODS

A. Study Population: The Women's Health Initiative Observational Study (WHI-OS) is an ongoing national health study designed to examine demographic, lifestyle, dietary, and biological factors on health outcomes among postmenopausal women. Details on design and recruitment have been published elsewhere (9, 10). Briefly, a total of 93,676 women postmenopausal women aged 50-79 years were enrolled in the WHI-OS between September 1994 and December 1998 from 40 clinical centers nationwide. Eligible participants completed baseline demographic and dietary questionnaires, underwent physical examinations, and provided fasting blood samples. All WHI study procedures were approved by human subjects review at each clinical center, and all women signed informed consent before participating.

For the current study, we included all participants from a case-control study of type 2 diabetes nested within the WHI-OS (n=3,713), because all were free of cardiovascular disease, type 2 diabetes, and cancers at baseline. Details of this diabetes ancillary study have been published elsewhere (11, 12).

B. Baseline Measurements: Certified WHI trained staff measured height, weight, hip circumference, and blood pressure at the baseline visit. BMI (in kg/m^2) was calculated. Standardized questionnaires including information on age, ethnicity, education, income, occupation, medical and family history, smoking status, alcohol use, recreational physical activity, and medication and supplement use were administered. A semi-quantitative food frequency questionnaire (FFQ) used previously among similar populations (13, 14) was used to assess food and nutrient intake in the last three months. The nutrient database for the WHI FFQ was derived from the University of Minnesota Nutrition Coding Center nutrient database (Nutrition Coordinating Center,

Minneapolis, MN) (15). All dietary nutrient variables were adjusted for total energy intake using the residual method (16). The energy-adjusted correlation coefficient for dietary Mg intake comparing the FFQ to eight days of dietary intake (four 24-hour recalls and a 4-day food record) among the WHI postmenopausal female population was reported to be 0.7, indicating that the WHI FFQ reasonably captures short-term intake of dietary Mg in this population (17).

C. Blood Collection and Assessment of Biomarkers: Fasting blood specimens were collected from all participants at baseline according to a standardized protocol. Aliquots of serum, plasma, and buffy coat were frozen and shipped on dry ice to a central repository and stored at -70º C for future assays in outside laboratories. hs-CRP was measured on a chemistry analyzer (Hitachi 911; Roche Diagnostics, Indianapolis, Indiana) using an immunoturbidimetric assay with reagents and calibrators (Denka Seiken Co Ltd, Niigata, Japan). IL-6 was measured by an ultrasensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota). TNF-α-R2, sICAM-1, sVCAM-1, and E-selectin was measured by an enzyme-linked immunosorbent assay (R&D Systems). The coefficients of variation for each analyte were 1.61% for hs-CRP, 7.6% for IL-6, 3.5% for TNF-α-R2 (11), 6.7% for sICAM-1, 8.9% for sVCAM-1, and 6.5% for E-selectin (12).

D. Statistical Analysis: The distributions of hs-CRP, IL-6, TNF-α-R2, sICAM-1, sVCAM-1, and E-selectin were highly skewed, and thus log transformations were taken to achieve normal distributions. Multiple linear regression models (using PROC GLM) were used to compute geometric means of inflammatory and endothelial biomarkers across quintiles of dietary Mg after adjusting for confounding variables. Geometric means were calculated by regressing the natural logarithmic values of the plasma concentration of inflammatory and endothelial biomarkers on dietary Mg intake and taking the antilog of the resulting mean logarithmic value. Tests of linear trend across increasing quintiles of dietary Mg intake were conducted by using the median value of each quintile as a continuous variable in the model. Regression coefficients for the change in inflammatory and endothelial biomarkers for an increase of 100 mg/d of dietary Mg stratified by ethnicity were also calculated using linear regression models. All multivariable models were adjusted for matching factors [age, ethnicity (White, African American, Hispanic/Latino, Asian/Pacific Islander) clinical center, and time of blood draw], smoking status (never, past, and current), alcohol (never, past, and current drinkers), physical activity measured by expenditure of energy from recreational activity (continuous), total energy intake (continuous), BMI (continuous), and type 2 diabetes case-control status (cases and controls). To specifically address the independent association of Mg intake, the final multivariate models were further adjusted for dietary fiber intake and other dietary factors such as fruit (continuous), vegetable (continuous), folate (continuous), trans fat (continuous), and saturated fat intake (continuous). Variance inflation factors were examined for all models to check for multicollinearity issues. To further assess potential effect modification, subgroup analyses with pre-specified factors including ethnicity (White, African American, Hispanic/Latino, and Asian/Pacific Islander), BMI (<25 and ≥ 25 kg/m^2), smoking status, [never smokers and ever smokers (current and past smokers)], alcohol intake (nondrinkers and current drinkers), and dietary fiber intake [low fiber intake (<21 g/day) and high fiber intake (≥ 21 g/day)] were conducted. The Wald test was used to assess the significance of multiplicative interaction terms.

To account for measurement error, we further conducted a deattenuation analysis using a regression coefficient relating the dietary Mg measurement from the baseline food frequency questionnaire to eight days of food records obtained from 113 women in the WHI (17) (18).

All p-values were two-tailed, and p-values less than 0.05 were considered to indicate statistical significance unless otherwise specified. All statistical analyses were conducted using SAS software (version 9.1; SAS Institute, Cary, North Carolina).

RESULTS

Characteristics of participants are summarized in Table 1. On average, African Americans had a higher BMI, higher smoking rate, higher dietary fat intake, and lower intake of dietary fiber and total Mg than women in other ethnic groups. Asian/Pacific Islanders had lower concentrations of hs-CRP, TNF-α-R2 and E-selectin compared with other ethnic groups, while African Americans had higher concentrations of hs-CRP and IL-6.

Higher dietary Mg intake was significantly associated with lower concentrations of inflammatory biomarkers including hs-CRP (P for linear trend=0.003), IL-6 (P for linear trend <.0001), and TNF-α-R2 (P for linear trend=0.0006) (Table 2). Further adjustment for dietary fiber intake attenuated but did not alter the linear trends for hs-CRP (P for linear trend=0.009), IL-6 (P for linear trend=0.0005), and TNF-α-R2 (P for linear trend=0.10) in relation to Mg intake. After additionally controlling for fruit and vegetable, folate, and saturated and trans fat intake, dietary Mg intake remained significantly associated with hs-CRP and IL-6. Multivariable adjusted geometric means across increasing quintiles of dietary Mg were 3.08, 2.63, 2.31, 2.53, 2.16 mg/L for hs-CRP (P for linear trend=0.005) and 2.91, 2.63, 2.45, 2.27, 2.26 pg/mL for IL-6 (P for linear trend=0.0005).

Similarly, we observed significant trends of an inverse association of dietary Mg intake with concentrations of sVCAM-1 (P for linear trend=0.06) and E-selectin (P for linear trend=0.0007) (Table 2). After further adjustment for dietary fiber intake, the inverse association with sVCAM-1 remained strong (P for linear trend=0.05) and the association with E-selectin was diminished. After additional adjustment for dietary factors, only sVCAM-1 remained significantly associated with dietary Mg intake; multivariable adjusted geometric means of sVCAM-1 across increasing quintiles of dietary Mg were 707, 681, 673, 671, 656 ng/mL (P for linear trend=0.04). Tests of variance inflation indicated no serious multicollinearity issues in the models (Variance inflation factor < 5 for all models).

Assuming a linear relation, an increment per each 100 mg/day in dietary Mg intake was inversely associated with hs-CRP ($\beta = -0.23 \pm 0.07$; p=0.002) and IL-6 ($\beta = -0.14 \pm 0.05$; p=0.004) (Model 3) (Table 3). After correction for measurement error, the association was strengthened for both hs-CRP ($\beta = -0.31 \pm 0.10$) and IL-6 ($\beta = -0.19 \pm 0.07$). There was a suggestion that the association of dietary Mg with hs-CRP concentration varied by ethnicity, with strong associations among White and African American women but no associations among Hispanic and Asian-Pacific Islander women (p for interaction=0.05). Inverse associations of dietary Mg with IL-6 concentration were observed in each ethnicity, without statistical evidence of heterogeneity (p for interaction=0.77). Compared with normal weight women (BMI < 25), concentrations of hs-CRP and IL-6 were significantly higher among overweight women (BMI ≥ 25), and inverse correlations with dietary Mg were more pronounced (Figure 1a-b). Similarly, in subgroup analyses stratified by smoking

status (Figure 1c-d), concentrations of hs-CRP and IL-6 were higher and demonstrated a stronger inverse association among ever smokers than never smokers (P for trend among ever smokers: hs-CRP: p=0.01.; IL-6: p=0.0008). Tests of interaction were also significant for alcohol intake (IL-6: p=0.04; E-selectin: p=0.008) and dietary fiber intake (TNF-α-R2: p=0.05).

CONCLUSIONS

In this large, ethnically diverse cohort of postmenopausal women, dietary Mg intake was inversely associated with plasma concentrations of hs-CRP, IL-6, TNF-α-R2, sVCAM-1, and E-selectin independent of known risk factors for metabolic outcomes. Adjustment for dietary fiber intake attenuated but did not significantly alter these associations except in the case of E-selectin. After further adjustment for fruit and vegetable intake, folate intake, and saturated and trans fat intake, these inverse trends remained significant for hs-CRP, IL-6, and sVCAM-1, suggesting that dietary Mg may influence concentrations of these biomarkers independently of other dietary factors associated with inflammation

Our findings support the notion that Mg intake improves systemic inflammation and endothelial dysfunction and may play a role in the prevention of type 2 diabetes and metabolic syndrome, a longstanding relation with causality yet to be confirmed. These data are consistent with a considerable body of experimental evidence in animals suggesting that acute Mg deficiency leads to an inflammatory response (5). Observational data in humans provide additional support for this relation. To date, several cross-sectional studies have reported a link between both low dietary Mg intake (1, 6) and serum Mg concentrations (19) and elevated hs-CRP in Caucasian populations. Fiber intake and dietary patterns high in Mg were also inversely associated with hs-CRP concentrations in the Nurses' Health Study (8) and in NHANES 1999-2000 (20). However, the relation of Mg intake to IL-6 and TNF-α is less clear. No association was reported between dietary Mg intake and TNF-α-R2 or IL-6 in the Nurses' Health Study (6). However, a "Western" dietary pattern, lower in Mg containing foods, was found to be associated with elevated IL-6 and other markers of inflammation and endothelial dysfunction (8). Our findings provide evidence that hs-CRP and IL-6 may serve as sensitive markers of inflammation that may directly benefit from increased Mg intake through dietary sources.

CRP is an acute phase reactant secreted by the liver in response to inflammatory cytokines including IL-6 and TNF-α and is an independent predictor of cardiovascular disease (21) and type 2 diabetes (11). IL-6 and TNF-α are proinflammatory cytokines secreted by macrophages and T-cells to stimulate an immune response to trauma. Low plasma Mg concentrations and the subsequent disruption in intracellular Mg homeostasis may play a role in activating the inflammatory response (22). However, because hs-CRP is a more sensitive and robust marker of systemic inflammation than other inflammatory markers (23), it may be more readily detected. Our findings also suggest that IL-6 may also be sensitive to fluctuations in dietary intake of Mg. Although TNF-α-R2, a cell surface receptor believed to modulate the action of TNF-α, was inversely associated with dietary Mg intake before adjustment for dietary fiber intake, this relation was attenuated after adjustment suggesting that the inverse association with TNF-α-R2 is most likely driven by the independent effects of dietary fiber.

With regard to endothelial dysfunction, we observed that dietary Mg was inversely associated with plasma concentrations of sVCAM-1 independently of

other dietary factors. sVCAM-1 and sICAM-1 are cellular adhesion molecules belonging to the immunoglobulin family and are primarily involved in the attachment and transendothelial migration of leukocytes in response to inflammatory cytokines (24). We observed no association between dietary Mg intake and plasma concentrations of sICAM-1, a finding consistent with a cross-sectional study in the Nurses' Health Study (6). However, we observed a modest association with sVCAM-1 that remained significant even after adjusting for dietary factors associated with endothelial dysfunction and cardiovascular disease. Although the biological explanation for the variability in results across markers is not clear, these findings further support the link between low Mg intake and elevated concentrations of certain markers of endothelial dysfunction. E-selectin is a cellular adhesion molecule found primarily on the surface of stimulated endothelial cells and mediates the initial rolling of leukocytes along the endothelium (25). In the current study, we observed an inverse association of dietary Mg intake with E-selectin which disappeared after accounting for dietary factors associated with inflammation.

In this multiethnic cohort of women, we observed notable ethnic variation in strengths of association across ethnicity. To our knowledge, no previous work has examined potential ethnic differences in the relation of Mg to systemic inflammation and endothelial dysfunction. Our findings of possible interactions in the current study should be interpreted with caution (i.e. hypothesis-generating) because ethnicity-specific sample sizes were small and the differences could partially be due to residual confounding from demographic and lifestyle factors. More importantly, the generally consistent patterns across the four ethnic groups provide additional evidence to support the notion that increased Mg intake may have beneficial effects on alleviating systemic inflammation and endothelial dysfunction. We also observed stronger associations of dietary Mg intake with hs-CRP and IL-6 concentrations among subgroups with the highest concentrations of these inflammatory markers, i.e. overweight women and smokers. Similar findings among these high-risk subgroups were reported in the Women's Health Study (1), suggesting that Mg intake may be most beneficial among women who are predisposed to systemic inflammation.

There are several limitations that merit consideration. First, the measurement of dietary Mg intake may be inaccurate because of self-report inconsistencies; however, Mg intake assessed by our FFQ has a correlation of 0.7 when validated against dietary records (17). Furthermore, in analyses that corrected for measurement error, the relation between Mg intake and biomarkers was strengthened. Second, dietary Mg intake is highly correlated with several nutrients including dietary fiber, potassium, and folate, and is found in high concentrations in foods such as whole grains, nuts, and fruits and vegetables. Therefore, parsing out the independent effects of dietary Mg is a challenge. In the current study, we sought to examine the independent effects of dietary Mg through adjustment for dietary fiber as well as fruit and vegetable intake, folate intake, and saturated and trans fat intake in multivariable adjusted models to control for potential confounding. Our findings suggest that dietary Mg is associated with several markers of inflammation and endothelial dysfunction independent of these dietary factors, although we could not completely exclude the possibility of residual confounding. This coupled with the cross-sectional design does limit our ability to make causal inferences regarding the effect of Mg intake on markers of inflammation and endothelial dysfunction.

In conclusion, we found that dietary intake of Mg was independently and inversely

associated with plasma concentrations of hs-CRP, IL-6 and sVCAM-1 in postmenopausal women. These findings are consistent with previous studies mostly in whites and support the notion that diets high in Mg-rich foods including whole grains, nuts, and leafy green vegetables should be encouraged for metabolic disease prevention.

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Figure 1. Multivariable adjusted means of hs-CRP (mg/L) and IL-6 (pg/mL) across increasing quintiles of dietary Mg stratified by BMI [BMI <25 (n = 1,047); BMI ≥ 25 (n = 2,666)] (A and B) and smoking status [Never smokers (n= 1,959); Ever Smokers (including past and current smokers, n=1,707)] (C and D). Models adjusted for matching factors [age, race/ ethnicity, clinical center, time of blood draw], smoking, alcohol, total energy expenditure/week, total energy intake, BMI, type 2 diabetes status, dietary fiber intake, fruit & vegetable intake, folate intake, trans and saturated fat intake (Model 3). Tests of linear trend conducted by using the median value of each quintile as a continuous variable in the model.

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Table 1. Baseline Characteristics according to ethnicity among post-menopausal women in the Women's Health Initiative Observational Study (n=3,713)

	Race/Ethnicity			
	White	African American	Hispanic/Latino	Asian/Pacific Islander
n	1,922	1,123	423	245
Mean age (years)	64 ± 6.9	61.0 ± 6.7	60 ± 6.8	64 ± 7.6
Mean BMI (kg/m^2)	29 ± 6.7	31 ± 7.1	29 ± 5.8	25 ± 4.5
Current Smoker (%)	6	12	5	4
Current Drinker (%)	69	51	51	40
Total Energy Expenditure from Recreational Physical Activity (METs/week)	12 ± 13.3	11 ± 13.5	11 ± 14.9	14 ± 14.4
Current Postmenopausal hormone use (%)	43	31	42	50
Nutrient Intakes				
Carbohydrate (% of energy)	52 ± 9.4	52 ± 9.9	53 ± 10.1	56 ± 8.5
Protein (% of energy)	17 ± 3.3	16 ± 3.5	16 ± 3.6	16 ± 3.1
Fat (% of energy)	31 ± 8.5	33 ± 8.5	31 ± 9.6	29 ± 7.6
Dietary fiber (g/day)	17 ± 7.0	14 ± 7.1	16 ± 7.8	15 ± 6.5
Total Mg intake (mg/day)[*]	335 ± 198	261 ± 170	279 ± 191	277 ± 152
Dietary Mg intake (mg/day)[†]	263 ± 100	222 ± 140	229 ± 127	219 ± 96
Markers of Inflammation				
Hs-CRP (mg/L)	5.01 ± 7.2	5.91 ± 15.4	4.66 ± 5.5	2.11 ± 3.95
IL-6 (pg/mL)	3.26 ± 5.0	3.68 ± 4.58	3.14 ± 3.67	2.87 ± 6.24
TNF-α-R2 (pg/mL)	2785 ± 871	2423 ± 819	2517 ± 767	2292 ± 688
Markers of Endothelial Dysfunction				
sICAM-1 (ng/mL)	328 ± 94	270 ± 106	319 ±103	255 ± 79
sVCAM-1 (ng/mL)	819 ± 278	639 ± 224	738 ± 301	690 ± 243
E-selectin (ng/mL)	47.0 ± 28.1	45.4 ± 24.5	48.7 ± 28.1	40.2 ± 23.5

Data are means ±SD unless otherwise indicated. [*]Total Mg intake includes intake from dietary and supplemental sources. [†]Dietary Mg includes intake from diet alone.

Table 2. Mean plasma concentrations of biomarkers of inflammation by quintile (Q) of dietary Mg intake among post-menopausal women in the Women's Health Initiative Observational Study (n= 3,713)

	Dietary Mg					
	Q1	Q2	Q3	Q4	Q5	P for linear trend
Median (mg/d)	168.5	204.4	233.2	263.1	310.2	
Hs-CRP (mg/L)						
Model 1*	2.89 (2.59, 3.23)†	2.58 (2.31, 2.87)	2.31 (2.07, 2.58)	2.60 (2.31, 2.92)	2.29 (2.03, 2.58)	0.003
Model 2‡	2.99 (2.61, 3.41)	2.61 (2.33, 2.92)	2.32 (2.07, 2.59)	2.57 (2.28, 2.90)	2.23 (1.96, 2.55)	0.009
Model 3§	3.08 (2.67, 3.55)	2.63 (2.34, 2.94)	2.31 (2.07, 2.59)	2.53 (2.24, 2.86)	2.16 (1.87, 2.50)	0.005
IL-6 (pg/mL)						
Model 1*	2.91 (2.70, 3.13)	2.63 (2.45, 2.83)	2.46 (2.28, 2.64)	2.28 (2.11, 2.46)	2.27 (2.10, 2.46)	<.0001
Model 2‡	2.86 (2.62, 3.13)	2.62 (2.43, 2.82)	2.45 (2.28, 2.64)	2.29 (2.11, 2.48)	2.30 (2.11, 2.51)	0.0005
Model 3§	2.91 (2.64, 3.19)	2.63 (2.44, 2.84)	2.45 (2.27, 2.64)	2.27 (2.09, 2.46)	2.26 (2.05, 2.49)	0.0005
TNF-α- R2 (pg/mL)						
Model 1*	2461 (2392, 2532)	2506 (2437, 2577)	2426 (2357, 2497)	2424 (2352, 2498)	2338 (2267, 2411)	0.0006
Model 2‡	2429 (2347, 2514)	2493 (2422, 2566)	2423 (2354, 2494)	2434 (2360, 2510)	2361 (2282, 2443)	0.10
Model 3§	2422 (2335, 2513)	2493 (2421, 2567)	2422 (2353, 2493)	2433 (2358, 2511)	2358 (2270, 2448)	0.15
sICAM-1 (ng/mL)						
Model 1*	300 (291, 310)	303 (293, 313)	300 (290, 311)	303 (292, 314)	293 (282, 304)	0.31
Model 2‡	303 (291, 316)	304 (294, 315)	300 (290, 311)	302 (291, 314)	291 (279, 303)	0.13
Model 3§	301 (288, 315)	304 (293, 315)	300 (290, 311)	302 (291, 314)	292 (278, 305)	0.29
sVCAM-1 (ng/mL)						
Model 1*	695 (673, 718)	677 (655, 699)	673 (651, 695)	675 (652, 699)	665 (642, 689)	0.06
Model 2[4]	703 (676, 731)	680 (657, 703)	673 (651, 696)	673 (650, 697)	660 (634, 686)	0.05
Model 3§	707 (678, 738)	681 (658, 704)	673 (651, 696)	671 (648, 696)	656 (628, 685)	0.04
E-selectin (ng/mL)						
Model 1*	45.5 (43.2, 47.8)	42.5 (40.4, 44.7)	40.8 (38.8, 43.0)	40.8 (38.7, 43.1)	40.7 (38.5, 43.0)	0.0007
Model 2‡	43.9 (41.2, 46.7)	41.9 (39.8, 44.1)	40.7 (38.6, 42.9)	41.3 (39.1, 43.6)	41.8 (39.4, 44.5)	0.43
Model 3§	43.8 (41.0, 46.8)	41.9 (39.7, 44.2)	40.7 (38.7, 42.9)	41.4 (39.1, 43.8)	42.1 (39.4, 45.1)	0.62

†Adjusted geometric means, 95% CI in parentheses. *Model 1 adjusted for matching factors [age, race/ ethnicity, clinical center, time of blood draw], smoking, alcohol, total energy expenditure from recreational physical activity /week), total energy intake, BMI, case-control status. ‡Model 2 adjusted for variables in Model 1 + dietary fiber intake. §Model 3 adjusted for variables in Model 2 + fruit and vegetable intake, folate intake, and total saturated and trans fat intake.

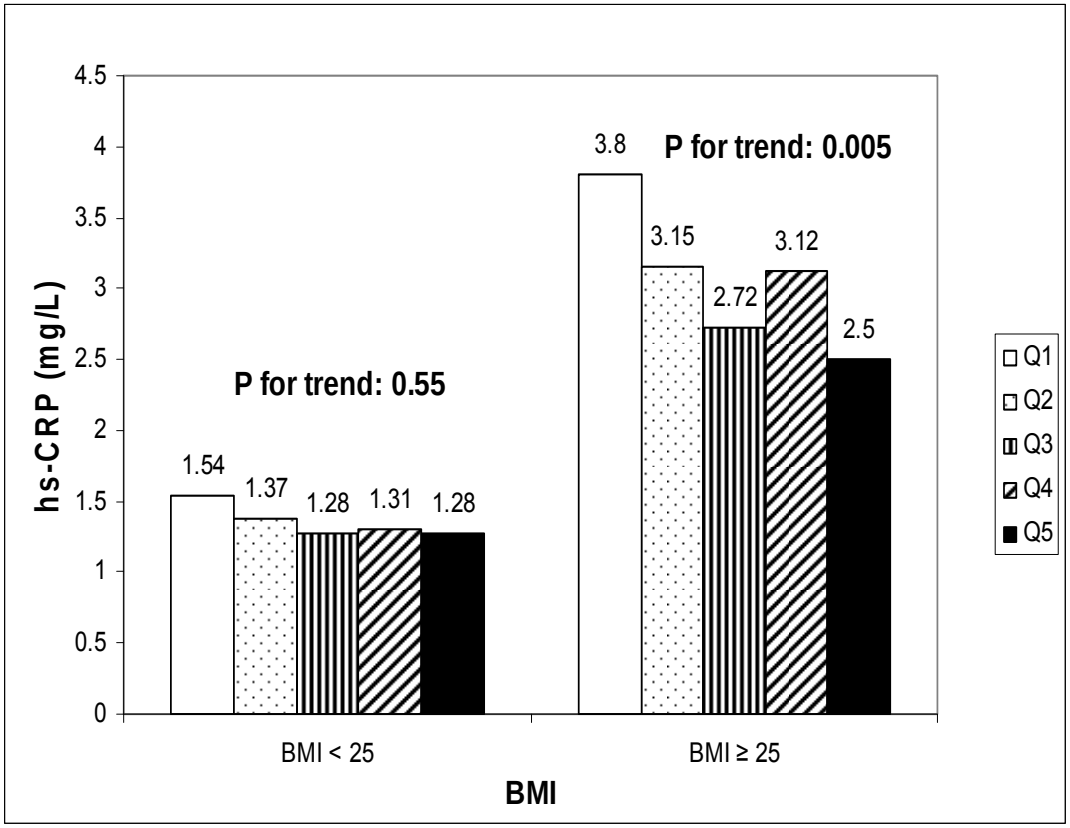
Table 3. Linear regression coefficients for the relation between each increase of 100 mg/d in dietary Mg intake and log-transformed biomarkers of inflammation and endothelial dysfunction among post-menopausal women in the Women's Health Initiative Observational Study (n=3,713)

		Dietary Mg		
Ethnicity	Biomarkers	Model 1[*]	Model 2[†]	Model 3[‡]
All (n=3,713)	CRP (mg/L)	-0.12 ± 0.04[§] (0.004)[‖]	-0.17 ± 0.06 (0.006)	-0.23 ± 0.07 (0.002)
	IL-6 (pg/mL)	-0.15 ± 0.03 (<.0001)	-0.12 ± 0.04 (0.005)	-0.14 ± 0.05 (0.004)
	sTNF-R2 (pg/mL)	-0.04 ± 0.01 (0.0004)	-0.04 ± 0.02 (0.02)	-0.04 ± 0.02 (0.06)
	sICAM-1 (ng/mL)	-0.01 ± 0.01 (0.30)	-0.04 ± 0.02 (0.05)	-0.03 ± 0.02 (0.15)
	sVCAM-1 (ng/mL)	-0.02 ± 0.01 (0.13)[‡]	-0.04 ± 0.02 (0.05)	-0.04 ± 0.02 (0.07)
	E-selectin (ng/mL)	-0.07 ± 0.02 (0.0005)	-0.02 ± 0.03 (0.47)	-0.01 ± 0.03 (0.71)
White (n=1,922)	CRP (mg/L)	-0.07 ± 0.05 (0.13)	-0.16 ± 0.07 (0.03)	-0.27 ± 0.09 (0.004)
	IL-6 (pg/mL)	-0.14 ± 0.04 (0.0001)	-0.09 ± 0.05 (0.08)	-0.19 ± 0.07 (0.006)
	sTNF-R2 (pg/mL)	-0.06 ± 0.01 (<.0001)	-0.05 ± 0.02 (0.03)	-0.04 ± 0.03 (0.13)
	sICAM-1 (ng/mL)	-0.03 ± 0.01 (0.01)	-0.02 ± 0.02 (0.37)	-0.02 ± 0.02 (0.41)
	sVCAM-1 (ng/mL)	-0.03 ± 0.02 (0.07)	-0.02 ± 0.02 (0.38)	-0.03 ± 0.03 (0.30)
	E-selectin (ng/mL)	-0.09 ± 0.03 (0.0003)	-0.04 ± 0.04 (0.25)	-0.03 ± 0.05 (0.48)
African American (n=1,123)	CRP (mg/L)	-0.17 ± 0.07 (0.02)	-0.21 ± 0.11 (0.06)	-0.34 ± 0.14 (0.01)
	IL-6 (pg/mL)	-0.18 ± 0.05 (0.0006)	-0.11 ± 0.08 (0.16)	-0.17 ± 0.10 (0.08)
	sTNF-R2 (pg/mL)	-0.02 ± 0.02 (0.37)	-0.007 ± 0.03 (0.83)	-0.008 ± 0.04 (0.83)
	sICAM-1 (ng/mL)	0.009 ± 0.04 (0.79)	-0.08 ± 0.05 (0.12)	-0.08 ± 0.07 (0.21)
	sVCAM-1 (ng/mL)	-0.02 ± 0.02 (0.50)	-0.04 ± 0.04 (0.24)	-0.03 ± 0.04 (0.42)
	E-selectin (ng/mL)	-0.05 ± 0.03 (0.13)	-0.01 ± 0.05 (0.80)	-0.02 ± 0.06 (0.79)
Hispanic (n=423)	CRP (mg/L)	-0.12 ± 0.10 (0.25)	-0.16 ± 0.16 (0.34)	0.07 ± 0.20 (0.73)
	IL-6 (pg/mL)	-0.07 ± 0.08 (0.43)	-0.16 ± 0.13 (0.21)	-0.03 ± 0.16 (0.87)
	sTNF-R2 (pg/mL)	-0.04 ± 0.03 (0.19)	-0.09 ± 0.05 (0.05)	-0.09 ± 0.06 (0.12)
	sICAM-1 (ng/mL)	-0.04 ± 0.03 (0.20)	-0.06 ± 0.05 (0.22)	0.01 ± 0.06 (0.85)
	sVCAM-1 (ng/mL)	-0.01 ± 0.04 (0.71)	-0.10 ± 0.06 (0.12)	-0.14 ± 0.08 (0.07)
	E-selectin (ng/mL)	-0.07 ± 0.06 (0.22)	-0.05 ± 0.09 (0.55)	-0.07 ± 0.11 (0.51)
Asian/ Pacific Islander (n=245)	CRP (mg/L)	-0.14 ± 0.34 (0.68)	-0.04 ± 0.52 (0.94)	0.23 ± 0.65 (0.72)
	IL-6 (pg/mL)	-0.36 ± 0.14 (0.01)	-0.33 ± 0.21 (0.12)	-0.48 ± 0.27 (0.07)
	sTNF-R2 (pg/mL)	0.04 ± 0.05 (0.39)	0.001 ± 0.07 (0.98)	0.02 ± 0.09 (0.81)
	sICAM-1 (ng/mL)	0.08 ± 0.05 (0.11)	0.03 ± 0.08 (0.73)	0.12 ± 0.09 (0.19)
	sVCAM-1 (ng/mL)	0.02 ± 0.06 (0.71)	-0.06 ± 0.09 (0.48)	-0.07 ± 0.11 (0.52)
	E-selectin (ng/mL)	0.09 ± 0.09 (0.30)	0.22 ± 0.13 (0.09)	0.44 ± 0.16 (0.008)

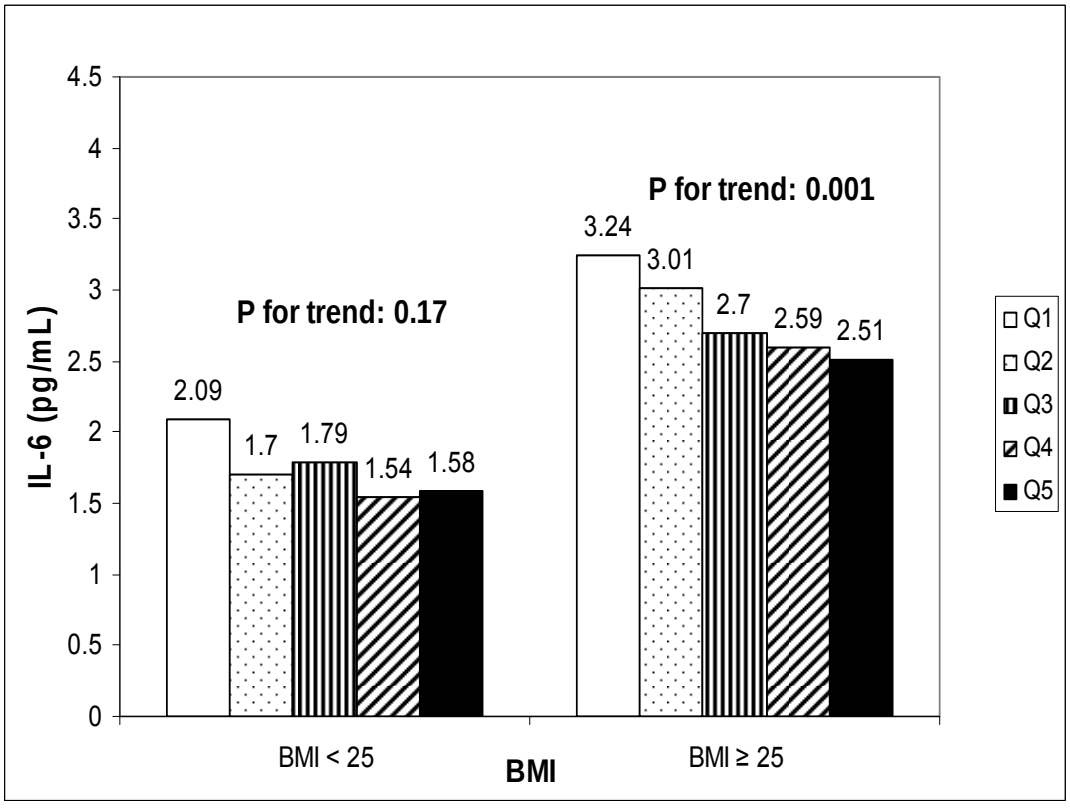
[§]All values are means ± SE (p-values); [‖]P-values are from multiple linear regression models for the relation between dietary Mg intake (per 100 mg/d increase) and log-transformed biomarkers. [*]Model 1 adjusted for matching factors [age, race/ ethnicity, clinical center, time of blood draw], smoking, alcohol, total energy expenditure/week, total energy intake, BMI, case-control status. [†]Model 2 adjusted for variables in Model 1 + dietary fiber. [‡]Model 3 adjusted for variables in Model 2 + fruit, vegetable, folate intake, total saturated and trans fat intake.

Figure 1.

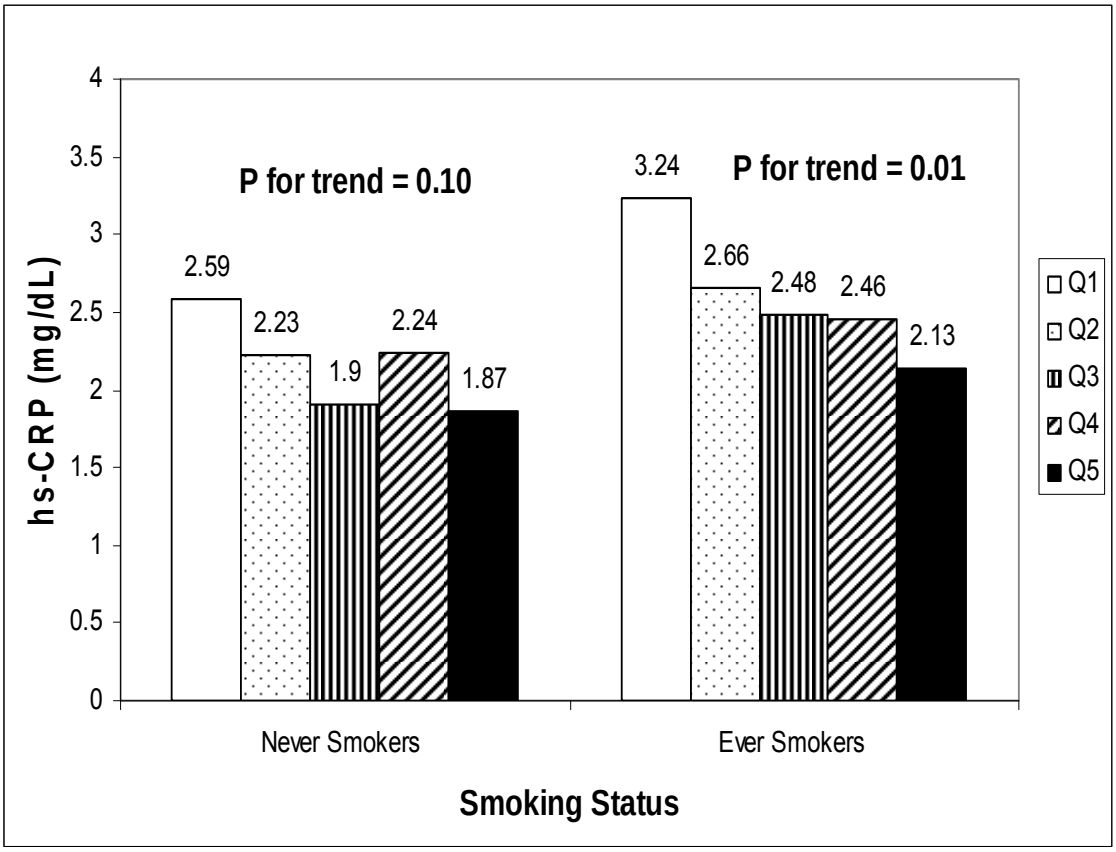
A.


hs-CRP (mg/L)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
P for trend: 0.55
P for trend: 0.005
1.54
1.37
1.28
1.31
1.28
3.8
3.15
2.72
3.12
2.5
BMI < 25
BMI ≥ 25
BMI
Q1
Q2
Q3
Q4
Q5

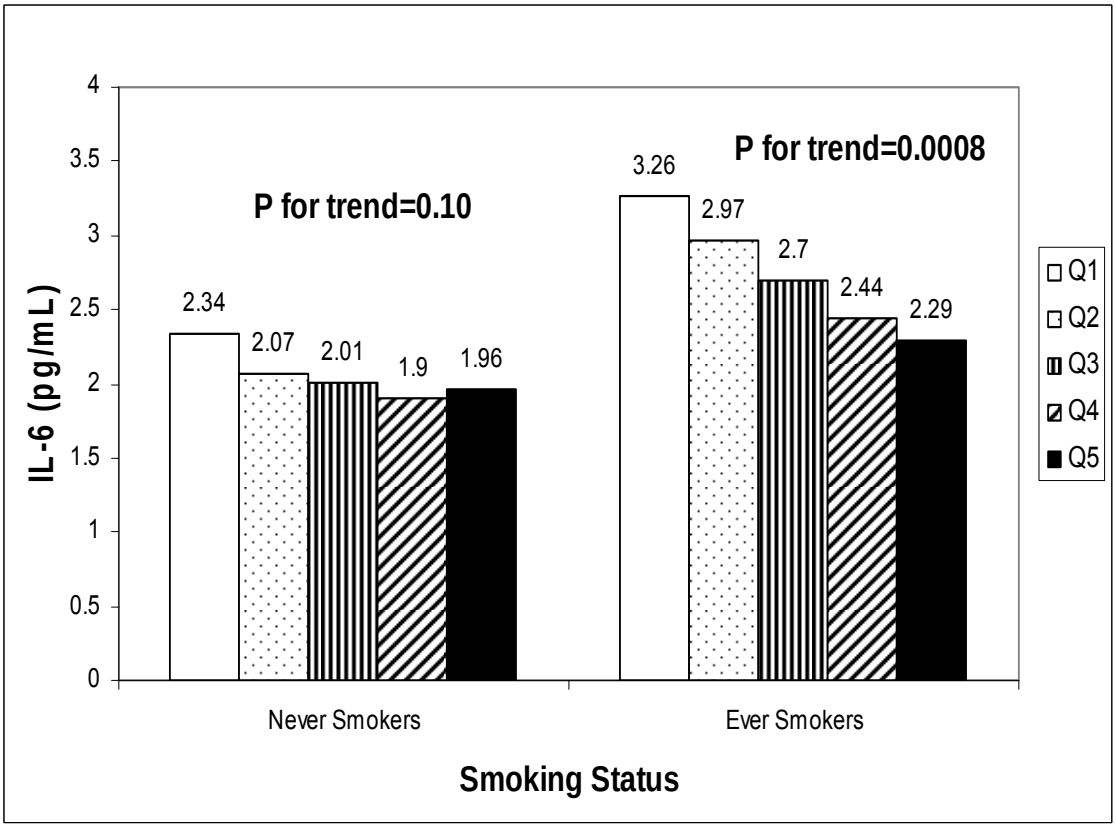
B.


IL-6 (pg/mL)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
P for trend: 0.17
P for trend: 0.001
2.09
1.7
1.79
1.54
1.58
3.24
3.01
2.7
2.59
2.51
BMI < 25
BMI ≥ 25
BMI
Q1
Q2
Q3
Q4
Q5

C.


hs-CRP (mg/dL)
4
3.5
3
2.5
2
1.5
1
0.5
0
P for trend = 0.10
P for trend = 0.01
2.59
2.23
1.9
2.24
1.87
3.24
2.66
2.48
2.46
2.13
Q1
Q2
Q3
Q4
Q5
Never Smokers
Ever Smokers
Smoking Status

D.


IL-6 (pg/mL)
4
3.5
3
2.5
2
1.5
1
0.5
0
P for trend=0.10
P for trend=0.0008
2.34
2.07
2.01
1.9
1.96
3.26
2.97
2.7
2.44
2.29
Q1
Q2
Q3
Q4
Q5
Never Smokers
Ever Smokers
Smoking Status