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ASSOCIATIONS OF SERUM AND DIETARY MAGNESIUM WITH CARDIOVASCULAR DISEASE, HYPERTENSION, DIABETES, INSULIN, AND CAROTID ARTERIAL WALL THICKNESS: THE ARIC STUDY

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Abstract—The objective of this study was to examine the relationships of serum and dietary magnesium (Mg) with prevalent cardiovascular disease (CVD), hypertension, diabetes mellitus, fasting insulin, and average carotid intimal-medial wall thickness measured by B-mode ultrasound. A cross-sectional design was used. The setting was the Atherosclerosis Risk in Communities (ARIC) Study in four US communities. A total of 15,248 participants took part, male and female, black and white, aged 45–64 years. Fasting serum Mg, lipids, fasting glucose and insulin were measured; as was usual dietary intake by food frequency questionnaire and carotid intima-media thickness by standardized B-mode ultrasound methods. The results showed that serum Mg levels and dietary Mg intake were both lower in blacks than whites. Mean serum Mg levels were significantly lower in participants with prevalent CVD, hypertension, and diabetes than in those free of these diseases. In participants without CVD, serum Mg levels were also inversely associated with fasting serum insulin, glucose, systolic blood pressure and smoking. Dietary Mg intake was inversely associated with fasting serum insulin, plasma high density lipoprotein-cholesterol, systolic and diastolic blood pressure. Adjusted for age, race, body mass index, smoking, hypertension, Low density lipoprotein-cholesterol, and field center, mean carotid wall thickness increased in women by 0.0118 mm ($p = 0.006$) in diuretic users and 0.0048 mm ($p = 0.017$) in nonusers for each 0.1 mmol/l decrease in serum Mg level; the multivariate association in men was not significant. In conclusion, low serum and dietary Mg may be related to the etiologies of CVD, hypertension, diabetes, and atherosclerosis.

Atherosclerosis Blood pressure Cardiovascular disease Diabetes mellitus Dietary magnesium Glucose Insulin Serum magnesium Ultrasonography

INTRODUCTION

A role for magnesium (Mg) in cardiovascular disease (CVD) has been hypothesized for some time. Mg has been implicated in the negative correlation between CVD and hardness of drinking water [1], although the interpretation of this ecologic correlation remains.

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controversial. Tissue Mg deficiency is associated with greater CVD occurrence [2]. Dietary deficiency of Mg augments atherogenesis markedly in experimental animals fed a high cholesterol diet, while oral supplementation of Mg to similar animals lowers serum lipids and attenuates the atherosclerotic process [3]. Moreover, a recent systematic overview of all available randomized trials suggested that intravenous Mg therapy may reduce the incidence of serious ventricular arrhythmias and mortality in patients with acute myocardial infarction [4].

Hypertension and diabetes mellitus are also associated with hypomagnesemia, although it is unclear whether Mg has an etiologic role [5–9]. Associations with hypertension have been difficult to ascertain because hypertensives are commonly treated with diuretics, which increase urinary Mg excretion [10]. Low intracellular Mg and low Mg intake have been associated with elevated fasting insulin levels [11–15], and an elevated insulin level has been reported to be a risk factor for CVD, hypertension, and diabetes [16].

Few population-based epidemiologic studies have explored the associations of serum Mg levels and dietary Mg intake with disease, nor have studies adequately examined these associations in different race and sex subgroups. The present study examined the associations of serum and dietary Mg with prevalent CVD, hypertension, and diabetes, and with CVD risk factors in middle-aged adults. It also explored the association of serum Mg with ultrasound measurement of carotid wall thickness in participants free of CVD symptoms.

METHODS

Study participants and protocols

The Atherosclerosis Risk in Communities (ARIC) Study examined a cohort of 15,800 persons, aged 45–64 years between 1986 and 1990. Participants were selected by probability sampling from Forsyth County, NC, Jackson, MS, the northwestern suburbs of Minneapolis, MN, and Washington County, MD. Blacks were exclusively sampled in Jackson and oversampled in Forsyth County to assure that race-specific estimates could be made.

Of 15,800 ARIC participants, 55 were excluded because of age ineligibility or race other than black or white. Another 147 were excluded due to missing blood specimens, and 350 were excluded according to ARIC nutrition exclusion criteria (missing more than 10 items in the food frequency questionnaire, or total energy intake less than the sex-specific 1st percentile or greater than the 99th percentile). Of the 15,248 remaining participants an additional 2540 with prevalent CVD or missing CVD status were excluded from analyses restricted to CVD-free participants (leaving 12,708). Age-adjusted analyses of ultrasound data excluded an additional 1802 participants with missing wall thickness values. 1334 more were excluded from multivariate involving wall thickness, 994 because their medications had not been fully coded and 340 who were missing other covariates.

A home interview and clinic examination were performed. Procedures to measure alcohol intake, medication use, cigarette smoking, blood pressure, and body size were described elsewhere [17]. Quetelet's body mass index (BMI, kg/m^2) was computed. Prevalent CVD was defined for this analysis as a positive history of intermittent claudication, angina, or myocardial infarction (MI) by the Rose questionnaire [18], a physician diagnosis of MI, a Q-wave on the electrocardiogram (ECG), a history of coronary revascularization, or a positive response to the question "Has a doctor ever told you that you had a stroke?" Prevalent hypertension was defined as systolic blood pressure $\geqslant 140$ mmHg, a diastolic blood pressure $\geqslant 90$ mmHg, or the current use of antihypertensive medication. Prevalent diabetes mellitus was defined as a nonfasting glucose $\geqslant 11.1$ mmol/l, a fasting glucose $\geqslant 7.8$ mmol/l, a positive history of diabetes, or the current use of diabetes medication.

Measurements of serum Mg and other blood components

Subjects were asked to fast for 12 hr prior to the clinic examination. After informed consent, blood was drawn from the antecubital vein of seated participants using minimal trauma. Specimens were collected into vacuum tubes containing silicon (insulin and glucose) and EDTA (lipids). The tubes were centrifuged at 3000 ***g*** for 10 min at 4°C. After separation, aliquots were quickly frozen at -70°C until analysis performed within a few weeks. The measurement of serum Mg was based on the procedure of Gindler and Heth [19] and used the metallochromic dye, Calmagite [1-(1-hydroxy-4-methyl-2-phenylazo)-2-napthol-4-sulfonic acid]. The coefficient of variation, based on split specimens sent 1 week apart blindly to the laboratory, was

3%. Serum glucose was assessed by the hexokinase method. Serum insulin was assessed using a radioimmunoassay (125Insulin Kit; Cambridge Medical Diagnostics, Inc., Billerica, MA). Total cholesterol [20] and triglycerides [21] were measured by enzymatic methods, and low density lipoprotein (LDL)-cholesterol was calculated using the Friedwald equation [22]. High density lipoprotein (HDL)-cholesterol was measured after dextran–Mg precipitation [23].

Assessment of diet

Usual dietary intake over the last year was assessed using an interviewer-administered, modified version of the 61-item food frequency questionnaire developed by Willett *et al.* [24]. Dietary Mg intake was computed by multiplying the Mg content of the specified serving of each food item by the frequency of its daily consumption and summing over all items [24]. Because dietary Mg and total calorie intake were highly correlated ($r = 0.75$), dietary Mg in milligrams per 1000 kilocalories daily intake was used in this analysis.

B-mode ultrasound measurement

The standardized B-mode ultrasound methods used in the ARIC Study are based on the technique developed by Pignoli *et al.* [25]. Sonographers and ultrasound readers were trained and certified by the ARIC Ultrasound Reading Center [26]. The main feature of the ultrasound reading process is the measurement of the intima-media thickness of the far wall in one centimeter segments of the common carotid, the carotid bifurcation, and the internal carotid. The average of the intima-media thickness of these three segments on both the left and right sides was calculated. The rationale for this measure as an indicator of early atherosclerosis has been described [25].

Statistical methods

Race- and sex-specific distributions and mean $\pm$ SD values of serum and dietary Mg were computed for all eligible subjects. Analysis of covariance was used to compute race- and sex-specific, age- and BMI-adjusted means. Among participants without prevalent CVD, age- and BMI-adjusted, partial correlation coefficients were calculated between serum and dietary Mg and selected variables. When wall thickness measurements were missing for one or more of the six segments, they were imputed from the remaining measured segments from sex- and race-specific multivariate linear models, employing as predictors the visualized boundaries, BMI, and artery depth before calculating the average [27]. The imputation models were fit by the EM algorithm [28] using BMDP5V [29]. The imputed average intima-media thickness was used in the age-adjusted analysis of covariance. Multivariate regression analysis for unbalanced repeated measures models with unstructured covariance matrix was used to assess the relationship between carotid arterial wall thickness at the six sites and serum magnesium levels adjusted for average arterial depth and other covariates, with site interaction terms for all independent variables in the model [30]. Each regression coefficient we report for serum magnesium levels represents the estimated average effect for the six sites. Models were fitted using the SAS mixed procedure [31]. In order to be conservative in analysis involving ARIC's large sample size, results were considered statistically significant at $p \leqslant 0.01$. Statistical analysis was done using the SAS package [32].

RESULTS

Distributions of Mg in serum and diet

Serum Mg levels appeared to be approximately normally distributed among ARIC participants [Fig. 1(a)]. Mean levels were higher in whites than blacks ($p < 0.001$). The distributions of dietary Mg intake were slightly skewed to the right [Fig. 1(b)]. Mean dietary Mg intake per 1000 kcal was highest among white women and lowest among black men. Mean serum Mg was lower in diuretic users than nonusers (0.78 vs 0.79 mmol/l for blacks, 0.80 vs 0.83 mmol/l for whites, $p < 0.001$), while dietary Mg intake was higher in diuretic users than nonusers (158 vs 149 mg/1000 kcal for blacks, $p < 0.01$; 165 vs 164 mg/1000 kcal for whites, $p = 0.11$).

Mg and CVD, diabetes, and hypertension

Unadjusted race- and sex-specific mean values of serum and dietary Mg according to different prevalent diseases are presented in Table 1. Generally, serum Mg levels were lower in those with diabetes, hypertension, and/or CVD than in disease-free participants (without these three prevalent diseases). Participants with diabetes had the lowest values (0.73–0.81 mmol/l). Dietary Mg intake demonstrated an association in the opposite direction,

with generally high dietary Mg intake per 1000 kcal among diabetics.

Since age and BMI tended to be higher in participants with disease than those without, age- and BMI-adjusted mean serum Mg levels were calculated (Fig. 2). As with the unadjusted values, adjusted mean serum Mg levels were generally significantly lower among those with diabetes, hypertension, and/or CVD than among participants free of these diseases. Further adjustment for high serum creatinine levels ($\geqslant 1.5$ mg/dl), or exclusion of those with high serum creatinine, did not affect the results.

Mg and CVD risk factors

Table 2 shows age- and BMI-adjusted, partial correlation coefficients between serum and dietary Mg levels (mg/kcal energy intake) and selected variables among participants free of CVD. Generally, but with exceptions, serum Mg levels were correlated negatively ($p < 0.01$) with cigarette years of smoking, systolic blood pressure, plasma triglycerides, fasting glucose and insulin; and correlated positively with plasma LDL- and HDL-cholesterol levels. There were statistically significant inverse associations between dietary Mg intake and fast-

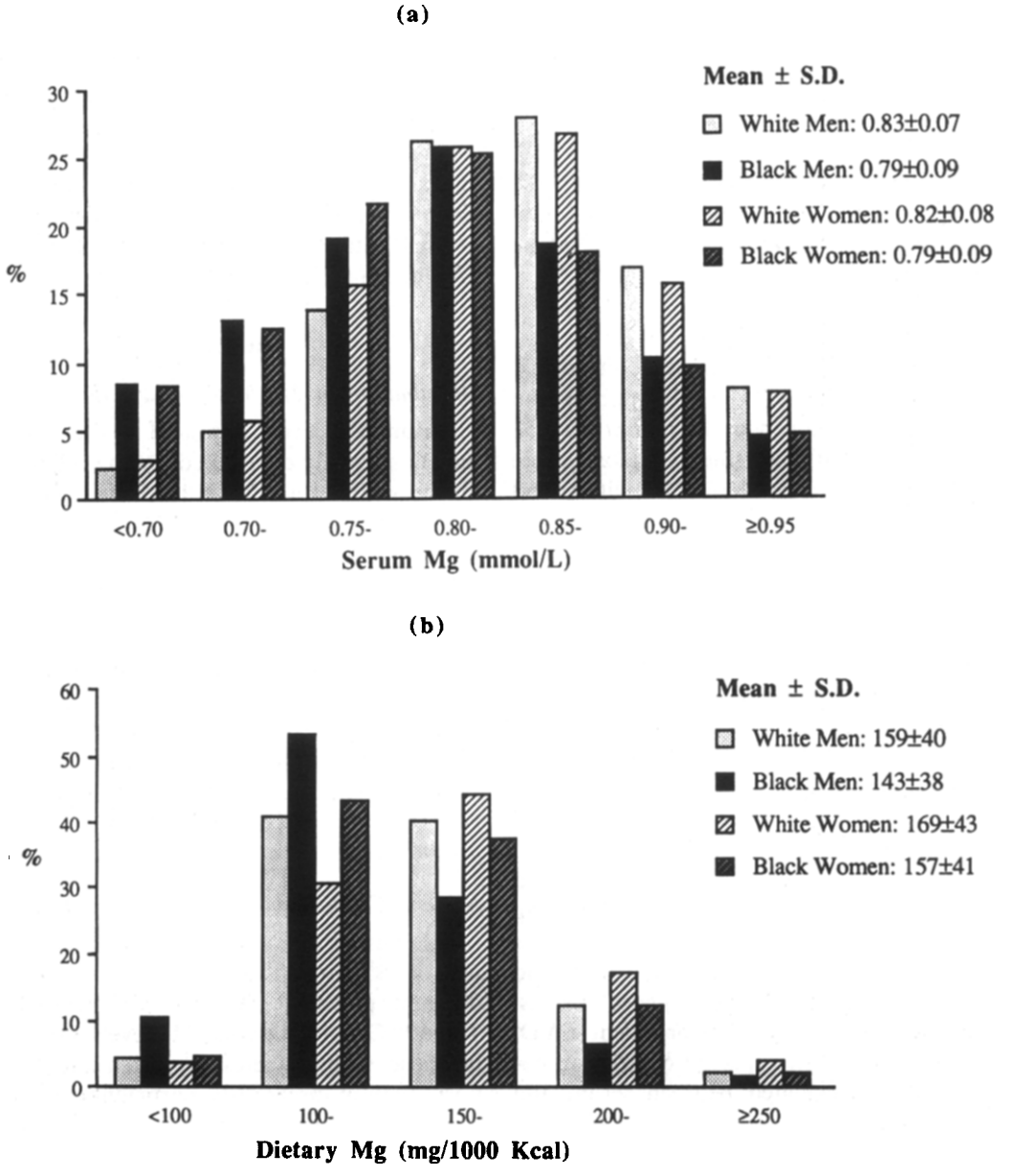


Fig. 1. Distributions of serum Mg level (a) and dietary Mg intake (b) by race and sex among ARIC study participants, 1986–90.

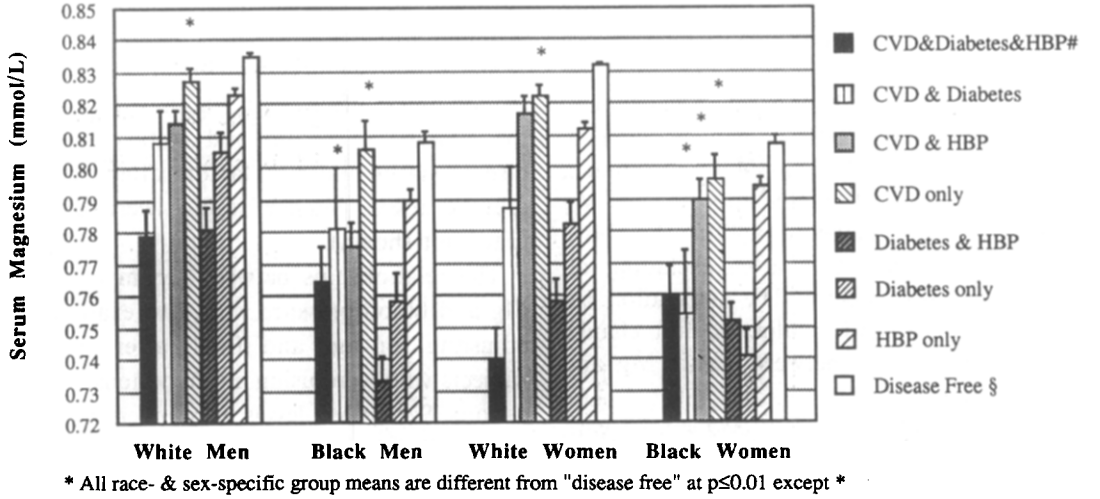
Table 1. Unadjusted mean levels of Mg in relation to prevalent diabetes, hypertension, and/or CVD

	White men		Black men		White women		Black women	
	n	Mean	*n*	Mean	*n*	Mean	*n*	Mean
Serum Mg (mmol/l)	(*n* = 5191)		(*n* = 1504)		(*n* = 5771)		(*n* = 2416)	
CVD & diabetes & hypertension	84	0.78	50	0.76	53	0.74	77	0.76
CVD & diabetes	55	0.81	16	0.78	37	0.79	14	0.75
CVD & hypertension	297	0.81	92	0.78	235	0.82	151	0.79
CVD only	469	0.83	66	0.81	438	0.82	96	0.79
Diabetes & hypertension	119	0.78	102	0.73	144	0.76	256	0.75
Diabetes only	145	0.80	67	0.76	137	0.78	93	0.74
Hypertension only	976	0.82	578	0.79	1066	0.81	888	0.79
Disease-free*	3046	0.84	533	0.81	3661	0.83	841	0.80
Dietary Mg (mg/1000kcal)								
CVD & diabetes & hypertension	84	169	50	167	53	167	77	171
CVD & diabetes	55	177	16	166	37	185	14	161
CVD & hypertension	297	160	92	145	135	162	151	160
CVD only	469	161	66	139	438	169	96	153
Diabetes & hypertension	119	168	102	156	144	175	256	167
Diabetes only	145	175	67	164	137	174	93	165
Hypertension only	976	158	578	139	1066	167	888	154
Disease-free*	3046	157	533	139	3661	170	841	155

SDs for serum Mg ranged 0.07–0.12 mmol/l; SDs for dietary Mg ranged 30–52 mg/1000 kcal.
*Free of CVD, diabetes, and hypertension.

ing insulin level, systolic and diastolic blood pressure, smoking (among white men), and alcohol intake (among whites), and a positive correlation with HDL-cholesterol. The correlation between serum Mg level and dietary Mg intake was less than 0.06 in all race- and sex-groups. Dietary Mg was correlated with several macro- and micronutrients: $r = 0.91$ for potassium, $r = 0.70$ for calcium, $r = 0.87$ for phosphorous, $r = 0.74$ for dietary fiber, $r = 0.57$ for saturated fat, and $r = 0.56$ for monounsaturated fat. Adjustment of serum Mg correlations for serum potassium, sodium, calcium, and creatinine yielded results similar to those in Table 2. Adjustment for dietary fiber, calcium, and sodium did not change the results, while further adjustment for dietary potassium eliminated most of the dietary Mg associations.

Analyses of covariance were performed to examine the independent associations of serum and dietary Mg with levels of fasting serum insulin, glucose, HDL-cholesterol, systolic and diastolic blood pressure. Selected interesting findings are shown in Figs 3 and 4. Age- and BMI-adjusted fasting serum insulin levels were inversely and curvilinearly associated with



* All race- & sex-specific group means are different from "disease free" at p≤0.01 except *

HBP = Hypertension

§ Participants free of CVD, diabetes, and hypertension

Fig. 2. Race- and sex-specific, age- and BMI-adjusted mean (SE) serum Mg level according to prevalent disease status.

Table 2. Race and sex-specific, age- and BMI-adjusted pearson partial correlation coefficients between serum/dietary Mg levels and selected variables among ARIC participants without CVD

Variables	White men ($n = 4308$)	Black men ($n = 1285$)	White women ($n = 5019$)	Black women ($n = 2088$)
Serum Mg (mmol/l)				
Smoking (cigarette years)	−0.06*	−0.07*	−0.04*	−0.05
Systolic BP	−0.06*	−0.08*	−0.06*	−0.04
Diastolic BP	−0.01	−0.04	−0.01	0.01
Triglycerides	−0.13*	−0.06	−0.15*	−0.12*
LDL-cholesterol	0.10*	0.06	0.08*	0.03
HDL-cholesterol	0.06*	−0.05	0.02	0.06*
Fasting glucose	−0.15*	−0.17*	−0.16*	−0.21*
Fasting insulin	−0.07*	−0.01	−0.03	0.00
Alcohol intake†	0.01	−0.10*	−0.02	−0.03
Dietary Mg (mg/1000 kcal)				
Smoking (cigarette years)	−0.05*	−0.06	−0.01	−0.01
Systolic BP	−0.01	−0.04	−0.06*	−0.07*
Diastolic BP	−0.03	−0.09*	−0.05*	0.07*
Triglycerides	−0.02	0.00	−0.04*	−0.01
LDL-cholesterol	0.00	0.02	−0.03	−0.01
HDL-cholesterol	0.05*	0.02	0.06*	0.06
Fasting glucose	0.05*	0.05	0.03	0.04
Fasting insulin	−0.06*	−0.03	−0.09*	−0.12*
Alcohol intake†	0.04*	−0.11*	−0.02	−0.02
Serum Mg	0.04*	0.06	0.01	−0.02

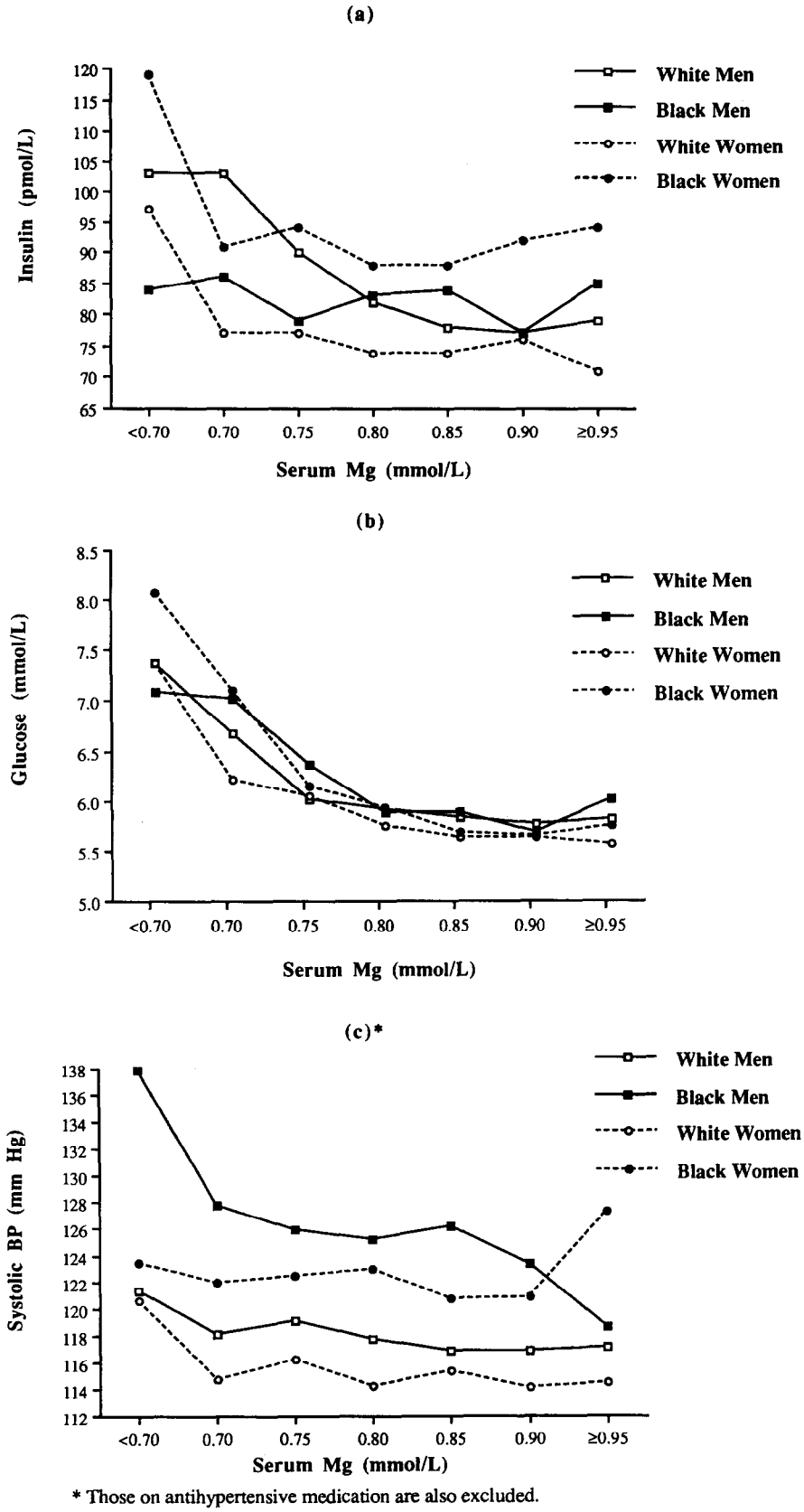
*$p \leq 0.01$.
†Alcohol intake: usual ethanol intake in grams per week.

serum Mg level, except in black men [Fig. 3(a)]. For example, the differences in adjusted insulin levels among those whose serum Mg was <0.7 mmol/l compared to those whose serum Mg was at approximately the mean level (0.8 to <0.85 mmol/l) were: white men, 20 pmol/l ($p = 0.002$); black men, 1 pmol/l ($p = 0.89$); white women, 23 pmol/l ($p < 0.001$); and black women, 31 pmol/l ($p < 0.001$). A similar association between glucose and serum Mg existed in all race, sex groups [Fig. 3(b)]. The differences in adjusted glucose levels among those whose serum Mg was <0.7 mmol/l compared to those whose level was 0.8 to <0.85 mmol/l were: white men, 1.46 mmol/l ($p < 0.001$); black men, 1.20 mmol/l ($p < 0.001$); white women, 1.63 mmol/l ($p < 0.001$); and black women, 2.13 mmol/l ($p < 0.001$). Since low serum Mg levels were seen in diabetes mellitus, the above analyses were performed after excluding all participants with diabetes. The association between serum Mg and insulin did not change appreciably, but that between serum Mg and glucose was attenuated.

The relationship of dietary Mg intake with age- and BMI-adjusted insulin and HDL-cholesterol levels are shown in Fig. 4(a and b). Dietary Mg intake was inversely related to fasting serum insulin and positively related to HDL-cholesterol, except among black men. For example, the differences in adjusted insulin levels among those whose dietary Mg intake was in the 1st quintile versus the 5th quintile were: white men, 13 pmol/l ($p < 0.001$); black men, 2 pmol/l ($p = 0.72$); white women, 12 pmol/l ($p < 0.001$); and black women, 27 pmol/l ($p < 0.001$). The differences in adjusted HDL-cholesterol levels for the 1st versus 5th quintile of dietary Mg intake were: white men, 0.06 mmol/l ($p = 0.001$); black men, 0.07 mmol/l ($p = 0.07$); white women, 0.09 mmol/l ($p < 0.001$); and black women, 0.10 mmol/l ($p = 0.002$).

Since diuretics may increase urinary Mg excretion and confound our findings, we repeated the analysis of serum and dietary Mg with disease status and risk factors after excluding diuretic users. Similar results were obtained (data not shown).

The relationships between serum or dietary Mg and blood pressure were also examined by adjusting for age and BMI, after excluding subjects who were using antihypertensive medications. Serum Mg levels were inversely related to systolic blood pressure except in black women in whom there was a U-shaped association [Fig. 3(c)]. Similar associations were also found between dietary Mg intake and systolic blood pressure, except in white men [Fig. 4(c)], and diastolic blood pressure (data not shown).



* Those on antihypertensive medication are also excluded.

Fig. 3. Race- and sex-specific, age- and BMI-adjusted mean fasting insulin (a), glucose (b), and systolic blood pressure (c) according to serum Mg level in participants without CVD.

Mg and carotid wall thickness

There was an inverse association between age-adjusted average carotid wall thickness and serum Mg level for women and for white men, but not black men (Fig. 5). Since diuretics may increase urinary excretion of Mg, we stratified on diuretic use and developed sex-specific multiple linear regression models. The relationship between carotid wall thickness and serum Mg levels was examined, adjusting for age, race, field center, smoking, LDL-cholesterol and BMI (Table 3). For each 0.1 mmol/l decrease in serum Mg level, mean carotid wall thickness increased 0.0059 mm in women not using diuretics ($p = 0.003$) and 0.0124 mm in women using diuretics ($p = 0.004$). To place these wall thicknesses in perspective, between the ages of 45–64, a 5 year increase was associated with a 0.043 mm increase in wall thickness among women not using diuretics. Further adjustment for prevalent hypertension changed these estimates of association for Mg only slightly. However, after adjustment for diabetes, only the association among women using diuretics remained statistically significant. The multivariate association in men was not significant in any model. Similar multiple linear regression analyses were performed between carotid wall thickness and dietary Mg intake; however, no appreciable association was evident (data not shown).

DISCUSSION

Serum Mg level and dietary Mg intake

Mg is the second most common intracellular electrolyte, after potassium, and the fourth most abundant cation in the body. Approximately 40% of the Mg contained in the adult human body resides in the muscles and soft tissues, about 1% in the extracellular fluid, and the remainder in the skeleton [33]. The plasma Mg level is maintained remarkably constant in healthy individuals by poorly understood hemostatic mechanisms [34]. Although the measurement of Mg in serum does not always reflect the overall status of Mg metabolism, it was well correlated with intracellular free Mg analyzed by ^{31}P-NMR spectroscopy ($r = 0.587$, $p < 0.05$) in 52 noninsulin-dependent diabetes mellitus patients and nondiabetic controls [35]. In a randomized, double-blind trial, participants with high normal blood pressure levels given oral Mg diglycine tablets (15 mmol or 340 mg of elemental Mg per day) had higher serum concentrations and urinary excretion of Mg at 3 and 6 months than those given placebo ($p < 0.01$) [36]. At present, serum Mg is still the most commonly used parameter for assessing disorders of Mg metabolism in clinical practice [37].

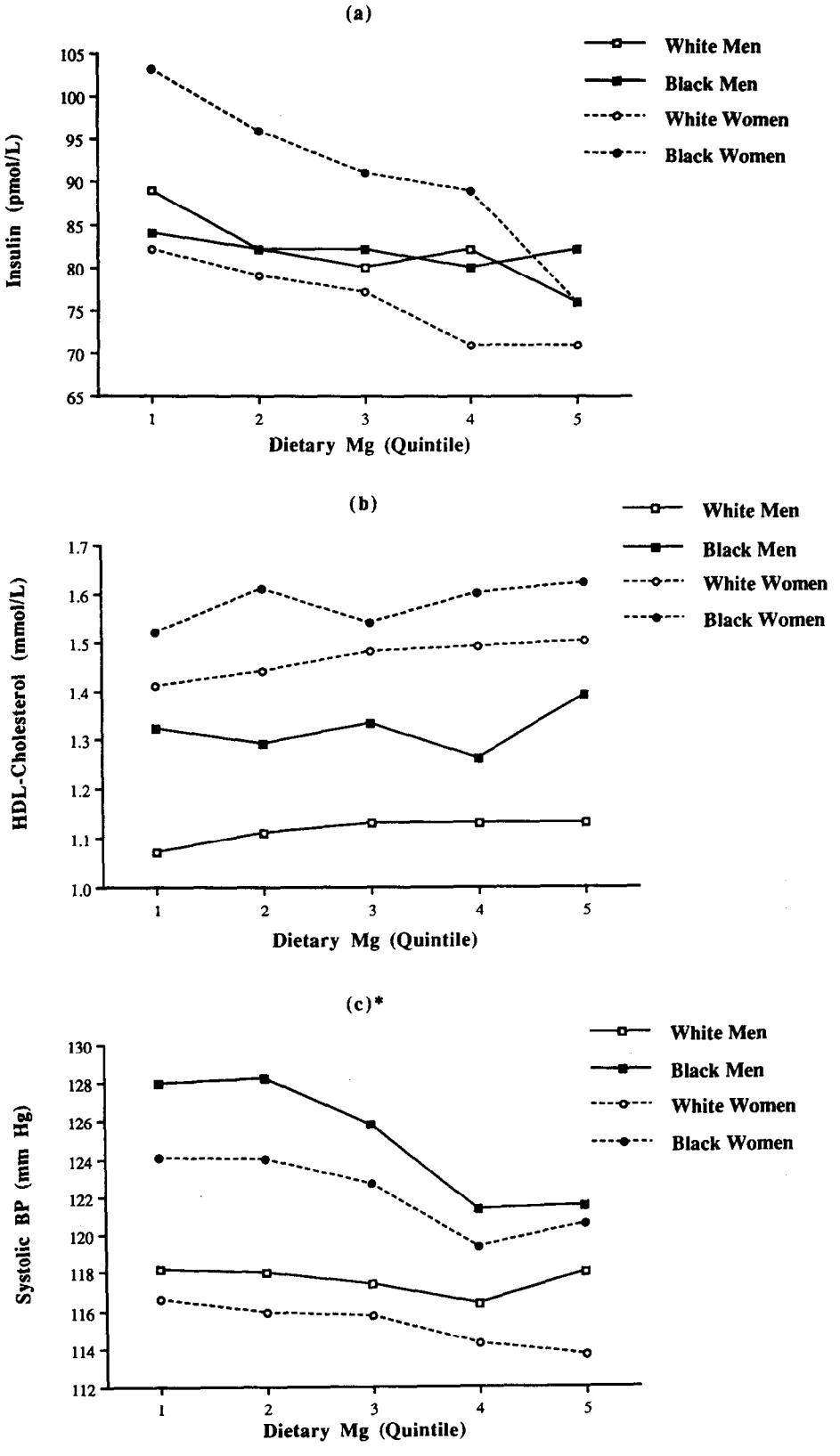
The major sources of Mg in the food supply are dairy products (20%); grain products (18%); vegetables (16%); meat, poultry, and fish (15%); and legumes, nuts, and soya products (13%) [38]. Drinking water may also contribute up to 27% to total Mg intake in areas where the water is hard and unsoftened [39].

Mg intake is highly correlated with several other macro- or micronutrients, especially dietary potassium ($r = 0.91$). Adjustment for dietary fat, fiber, and several dietary minerals did not change study results significantly. Although further adjustment for potassium eliminated most of the observed associations of dietary Mg with risk factors in Table 2, it is impossible to determine from the ARIC data whether dietary Mg or potassium is the important factor because of their high correlation.

In ARIC participants, serum Mg levels and dietary Mg intake were both lower in blacks than whites (Fig. 1). To our knowledge, these observations have not been reported previously. Part of the racial difference appeared to be a consequence of the higher prevalence of diabetes and hypertension in blacks, because among the "disease free" groups the black–white difference was smaller than overall, although still statistically significant (Table 1). Reduced serum Mg in blacks could result from a physiologic difference or from their lower Mg intake, although dietary and serum Mg were not significantly correlated in ARIC.

Association of Mg with CVD and lipids

The evidence for an association between hard water Mg and CVD is weak and not consistent from studies in one country to another [39, 40]. Data on coronary disease and serum Mg are also inconsistent [41, 42]. Stronger evidence for a CVD–Mg relationship is the lower Mg level found in the myocardium of victims of sudden coronary deaths, as compared with accident victims, in most [43–46] but not all [47] studies, although here an alternative explanation may be postinfarction Mg loss. In ARIC, mean serum Mg levels were significantly lower in those with prevalent CVD than in disease-free participants. Concomitant diabetes and/or hypertension explained a large part of this association (Fig. 2).



* Those on antihypertensive medication are also excluded.

Fig. 4. Race- and sex-specific, age- and BMI-adjusted mean fasting insulin (a), HDL-cholesterol (b), and systolic blood pressure (c) according to dietary Mg intake in participants without CVD.

Altura *et al.* [3, 48] reported that oral administration of Mg may lower serum cholesterol and triglycerides in experimental animals. They also reported that, in rabbits, hypercholesterolemia may cause the loss of Mg from soft tissues to the serum, thereby masking an underlying Mg deficiency [3]. However, a human study found no significant association between serum Mg and lipid levels [41]. In ARIC women and white men who were free of CVD, serum Mg was inversely related to serum triglycerides, while among whites, dietary Mg was positively related to HDL-cholesterol, independent of age and BMI [Table 2, Fig. 4(b)]. Serum Mg was also positively related to LDL-cholesterol (among whites only).

Association of Mg with hypertension and blood pressure

In ARIC participants free of CVD, hypertensives (especially those with diabetes) had lower serum Mg levels than disease-free people, independent of age and BMI. In contrast, dietary Mg intake among hypertensives with diabetes was somewhat higher than in disease-free participants. We also found a significantly inverse association between serum Mg level and systolic blood pressure, especially among black men, independent of age, BMI and use of antihypertensive medications, while black women showed a U-shaped association [Fig. 3(c)]. Similar associations were found between dietary Mg intake and systolic [Fig. 4(c)] and diastolic blood pressure.

Several studies that induced Mg deficiency in animal models found: (1) the greater the reduction in serum Mg concentration, the greater the reductions in lumen size of the microvasculature; and (2) an inverse correlation between serum Mg and arterial blood pressure. It has been suggested that the level of free, ionized Mg^{2+} in the extravascular fluid and at the cell membranes of vascular smooth muscle may play an important role in controlling vascular tone and contractility and in preventing the development of hypertension [49]. Furthermore, in a survey of 61 dietary variables in 615 men from the Honolulu Heart Program, dietary Mg emerged as the strongest correlate ($r = -0.12$) of blood pressure, stronger even than dietary potassium [50].

The influence of supplementation with oral Mg on blood pressure based on eight randomized, controlled trials has been inconsistent [36, 51–57]. Besides differences in study period and participants, different dosages of supplemental Mg might explain part of the inconsistency. Five of the eight trials used a 12.5–15 mmol/day dose of supplemental Mg which reflects levels that could potentially be attained by diet change alone [36, 51–54]. Four of these five trials failed to show any effect [36, 52–54]. Two trials using higher doses of Mg supplementation (20.6 or 25 mmol/day) showed

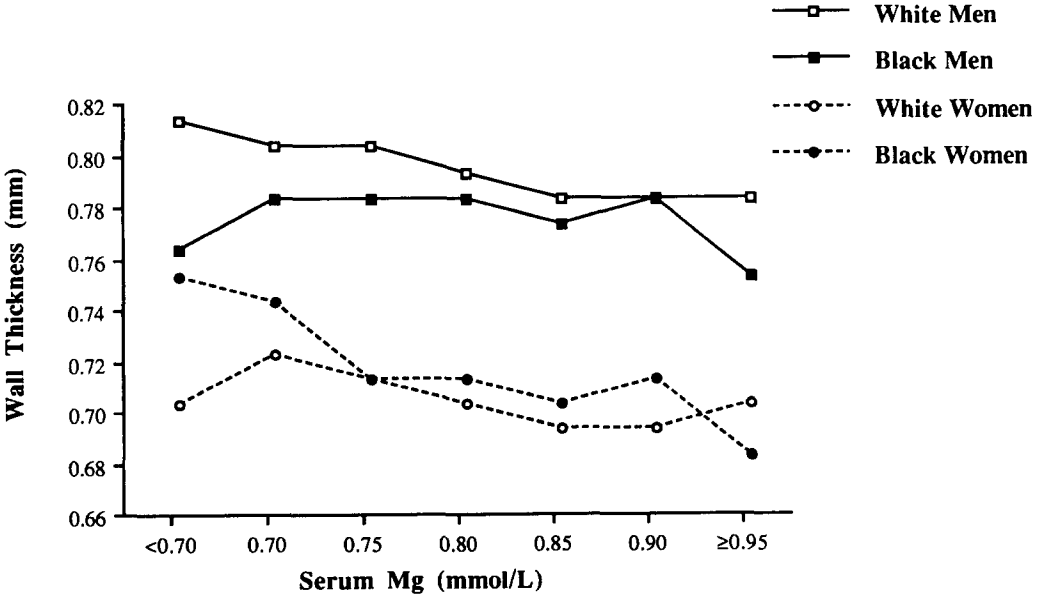


Fig. 5. Race- and sex-specific, age- and BMI-adjusted mean carotid arterial wall thickness according to serum Mg level in participants without CVD.

a significant reduction of blood pressure in patients with mild hypertension [55, 56]. A recently reported trial found a significant dose-dependent reduction in blood pressure in patients with mild hypertension by raising the Mg dose stepwise (15, 30, or 40 mmol/day) to pharmacological levels [57].

Association of Mg with diabetes mellitus, fasting glucose and insulin

A relationship between diabetes mellitus and Mg deficiency has been reported in both animals and humans [6–8]. McNair *et al.* [8] reported that, in insulin-treated diabetic patients, serum Mg correlated inversely with both fasting blood glucose and the urinary glucose excretion rate; urinary Mg excretion rate correlated directly with the same variables. Their data suggested that the net tubular reabsorption of Mg is decreased in diabetic patients in the presence of hyperglycemia, leading to hypermagnesuria and hypomagnesemia. Yajnik *et al.* [12] found a positive association between plasma Mg concentration and glucose disposal, and suggested that Mg is related to insulin sensitivity in adult onset diabetes. We did not examine urinary Mg excretion, but a high dietary Mg intake and low serum Mg level among diabetics suggests that urinary loss of Mg may be the major reason for the association (Table 1).

However, the inverse association of serum and dietary intake of Mg with fasting serum insulin levels suggests that Mg deficiency (perhaps secondary to hypermagnesuria) may also contribute to the etiology of diabetes. Numerous *in vitro* studies have pointed out the major role of Mg in insulin action [58–61]. It was suggested that Mg acts as a second messenger for insulin [58, 59]. In fact, cellular Mg deficiency is correlated with impaired function of many enzymes utilizing high energy phosphate bonds such as ATPase; these enzymes are involved in glucose metabolism and require Mg as a cofactor [11]. Several studies done in experimental animals or in diabetic or hypertensive patients, have suggested chronic Mg deficiency may contribute to insulin resistance [9, 12, 13, 62]. A population-based epidemiological study among young adults also reported that fasting insulin level was consistently and inversely related to dietary Mg intake, whereas the insulin association with dietary potassium was inconsistent [63].

In ARIC's middle-aged adults free of CVD, both serum and dietary Mg were inversely associated with fasting serum insulin levels, independent of age, BMI, and diabetes status [Figs 3(a) and 4(a)]. Serum Mg levels were also inversely associated with fasting glucose levels, independently of age and BMI [Fig. 3(b)], but the association was much weaker when diabetics were excluded.

Association of Mg with carotid atherosclerosis

Animal experiments indicate that Mg deficiency accelerates the atherosclerotic process [3]; and orally administered Mg suppresses the development of atherosclerotic lesions [3, 48, 64, 65]. Measurement of average carotid intima-media thickness by B-mode ultrasound, an indicator of atherosclerosis, enabled us to examine the relationship of serum Mg with early atherosclerosis in asymptomatic adults.

Serum Mg was significantly inversely associated with carotid wall thickness among women and white men, independent of age (Fig. 5). After adjusting for other CVD risk factors (race, BMI, smoking, LDL-cholesterol, hypertension, and diabetes) the association was still statistically significant in women but not in men (Table 3). The relationship of serum Mg to carotid wall thickness paralleled the Mg association with fasting insulin (significant in women and white men) [Fig. 3(a)], raising the possibility that elevated insulin may play a role in the relationship between Mg and atherosclerosis. Another ARIC analysis found that fasting

Table 3. Multiple regression analysis of carotid artery wall thickness (mm) on serum Mg (mmol/l) among diuretic users and nonusers without prevalent CVD

	Men		Women	
	β*	p	β*	p
	Diuretic nonusers			
	(n = 3707)		(n = 4241)	
Model 1	−0.0038	0.133	−0.0059	0.003
Model 2	−0.0026	0.299	−0.0048	0.017
Model 3	−0.0021	0.416	−0.0039	0.055
	Diuretic users			
	(n = 508)		(n = 1116)	
Model 1	−0.0005	0.949	−0.0124	0.004
Model 2	−0.0006	0.937	−0.0117	0.006
Model 3	0.0022	0.790	−0.0100	0.021

*Beta represents the difference in wall thickness (mm) per 0.1 mmol/l difference in serum Mg.

Model 1: adjusted for age, race, cigarette years of smoking, LDL-cholesterol, BMI, and field center.

Model 2: adjusted for age, race, cigarette years of smoking, LDL-cholesterol, BMI, field center, and hypertension.

Model 3: adjusted for age, race, cigarette years of smoking, LDL-cholesterol, BMI, field center, hypertension, and diabetes mellitus.

insulin level was positively associated with carotid wall thickness [66].

The associations of serum and dietary Mg with hypertension, diabetes, asymptomatic atherosclerosis, and CVD risk factors in these cross-sectional analyses cannot be inferred to be causal, as they may be biased due to nonresponse or misclassification of variables. They also cannot clarify whether low serum Mg contributes to the etiology of these conditions or is a result of the diseases and their treatment. While some race and gender inconsistencies remain to be explained, these data provide suggestive evidence of the role of Mg in chronic disease. While recommendations based upon data obtained from cross-sectional studies must be made cautiously, these results suggest that the clinical monitoring of Mg status among individuals with hypertension, diabetes, and CVD might be useful and foods rich in Mg (such as nuts, green vegetables, soyabeans, and whole grains) may provide protection against these chronic diseases. The benefit of oral Mg supplementation in the prevention and treatment of hypertension, diabetes, CVD, and atherosclerosis also warrants further study.

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