Dietary Magnesium Intake in Relation to Plasma Insulin Levels and Risk of Type 2 Diabetes in Women

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OBJECTIVE — Higher intake of magnesium appears to improve glucose and insulin homeostasis; however, there are sparse prospective data on the association between magnesium intake and incidence of type 2 diabetes.

RESEARCH DESIGN AND METHODS — In the Women's Health Study, a cohort of 39,345 U.S. women aged ≥45 years with no previous history of cardiovascular disease, cancer, or type 2 diabetes completed validated semiquantitative food frequency questionnaires in 1993 and were followed for an average of 6 years. We used Cox proportional hazard models to estimate multivariate relative risks (RRs) of type 2 diabetes across quintiles of magnesium intake compared with the lowest quintile. In a sample of 349 apparently healthy women from this study, we measured plasma fasting insulin levels to examine their relation to magnesium intake.

RESULTS — During 222,523 person-years of follow-up, we documented 918 confirmed incident cases of type 2 diabetes. There was a significant inverse association between magnesium intake and risk of type 2 diabetes, independent of age and BMI ($P = 0.007$ for trend). After further adjustment for physical activity, alcohol intake, smoking, family history of diabetes, and total calorie intake, the multivariate-adjusted RRs of diabetes from the lowest to highest quintiles of magnesium intake were attenuated at 1.0, 1.06, 0.81, 0.86, and 0.89 ($P = 0.05$ for trend). Among women with BMI ≥25 kg/m^2, the inverse trend was significant; multivariate-adjusted RRs were 1.0, 0.96, 0.76, 0.84, and 0.78 ($P = 0.02$ for trend). Multivariate-adjusted geometric mean insulin levels for overweight women in the lowest quartile of magnesium intake was 53.5 compared with 41.5 pmol/l among those at the highest quartile ($P = 0.03$ for trend).

CONCLUSIONS — These findings support a protective role of higher intake of magnesium in reducing the risk of developing type 2 diabetes, especially in overweight women.

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Magnesium is a cofactor in several enzymes critical for carbohydrate metabolism (1) and is believed to play a role in glucose homeostasis, insulin action, and the development of type 2 diabetes (1,2). Hypomagnesemia has been shown to occur frequently among patients with diabetes, especially those with poor metabolic control (2). Several cross-sectional studies have also observed an inverse association between plasma or erythrocyte magnesium levels and fasting insulin levels in diabetic patients and apparently healthy individuals (3,4). Accumulating evidence also suggests an inverse association between serum or plasma magnesium levels and risk of type 2 diabetes, indicating a potential role of magnesium status in the pathogenesis of type 2 diabetes (3,5,6).

Magnesium intake is believed to be important in maintaining magnesium homeostasis (1). Experimental studies have shown that magnesium supplementation improves insulin-mediated glucose disposal and insulin secretion (1,7). Some metabolic studies and clinical trials suggested that magnesium supplementation might improve insulin action among nondiabetic participants or patients with type 2 diabetes (5,8), but others have shown no effect (9–11). Also, the direct impact of magnesium intake on risk of type 2 diabetes has been controversial and only sparse prospective data are available (6,12). We therefore prospectively investigated whether total magnesium intake from food and supplements is related to risk of developing type 2 diabetes in a large cohort of U.S. women from the Women's Health Study (WHS). We also conducted a cross-sectional study to examine the relation between magnesium and fasting insulin levels in a subsample of apparently healthy women randomly selected from the WHS.

RESEARCH DESIGN AND METHODS

— The WHS is a randomized, double-blind, placebo-controlled trial designed to evaluate the balance of benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer (13). We randomized a total of 39,876 female health professionals aged ≥45 years who were free of coronary heart disease, stroke, and cancer (other than nonmelanoma skin cancer). Of them, 98% provided detailed information about their diet, completing a 131-item semiquantitative food frequency questionnaire (SFFQ) in 1993 (13). We excluded subjects with >70 items left blank in their SFFQ, with energy intake outside the

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Abbreviations: SFFQ, semiquantitative food frequency questionnaire; WHS, Women's Health Study.

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

See accompanying editorial, p. 270.

range of 2,514 kJ (600 kcal) and 14,665 kJ (3,500 kcal), and with reported diabetes at baseline, which left 38,025 women for the analysis.

The study protocol was approved by the Brigham and Women's Hospital institutional review board, and the protocol adhered to the guidelines put forth in the Helsinki Declaration and Belmont Accord for the duration of the study.

Assessment of magnesium intake

For each food, a commonly used unit or portion size was specified, and each participant was asked how often she had consumed that amount, on average, during the previous year. Nine possible responses ranging from "never" to "six or more times per day" were recorded. Nutrient intakes were computed by multiplying the frequency of consumption of each unit of food from the SFFQ by the nutrient content of the specified portion size according to food composition tables from the Harvard Food Composition Database (14). Data on use of multivitamin supplements were taken into account to assess intake of supplemental magnesium. Total magnesium represents the sum of magnesium intake from both dietary and supplemental sources. Each nutrient was adjusted for total energy using the residual method (15). In populations of nurses and health professionals, this SFFQ has demonstrated reasonably good validity as a measure of long-term average dietary intakes (16). The Pearson correlation coefficient between magnesium intake assessed by SFFQ and 2 weeks of diet records was 0.76 in women (17).

Ascertainment of incident type 2 diabetes

Women with a history of diabetes were excluded at baseline. Thereafter, all of the participants were asked annually whether and when they had been diagnosed with type 2 diabetes since completing the previous questionnaire at baseline. We mailed a supplemental questionnaire inquiring about the onset of disease, symptoms, diagnostic tests, and hypoglycemic treatment to all respondents reporting a diagnosis of type 2 diabetes and confirmed type 2 diabetes according to the guidelines proposed by the American Diabetes Association (18). If a participant was receiving treatment with hypoglycemic medications (insulin or oral hypoglycemic agents), a confirmed diagnosis was presumed. In a validation study of our diagnostic algorithm for type 2 diabetes from 1999 to 2000, 97.5% (78 of 80) of self-reported cases were confirmed by medical records (19).

Assessment of fasting insulin levels

In our cross-sectional analysis, we included 349 randomly selected women who had served as control subjects in a previous case-control study nested in the WHS (20). This subsample comprised healthy, nondiabetic, middle-aged women who remained free of diabetes during the 4-year period subsequent to assessment of baseline clinical and biochemical parameters. Baseline fasting specimens from these women were assayed for insulin levels. Double antibody systems (Linco Research, St. Louis, MO), with <0.2% cross-reactivity between insulin and its precursors, were used to measure specific concentrations of plasma insulin. All samples were handled identically and analyzed in random order to reduce systematic bias and interassay variation. Blinded quality control specimens were analyzed simultaneously with the study sample. The average intra-assay coefficient of variation for insulin levels was 14.7% (20).

Data analysis

We calculated the incidence rates of type 2 diabetes for each quintile of baseline magnesium intake by dividing the number of incident cases by the person-years of follow-up from 1993 to 2001. After testing the proportional hazard assumption, we used Cox proportional hazard models to estimate the rate ratios (described as relative risks [RRs]) and 95% CIs of developing type 2 diabetes for each quintile of magnesium intake compared with the lowest quintile. The initial model was adjusted for age, and the model was then adjusted for age and BMI (continuous). In multivariate models, we adjusted for age (continuous), BMI (continuous), smoking status (current, past, and never), exercise (rarely/never, <1 time/week, 1–3 times/week, and ≥4 times/week), alcohol intake (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), family history of diabetes (yes or no), and total energy intake (five categories). We also examined the confounding effects of some important dietary factors, such as glycemic load, dietary fiber, and total fat intake. In stratified analyses, we assessed the potential effect modification by BMI (< or ≥25 kg/m^2). The likelihood ratio test was used to assess the significance of interaction terms between magnesium intake and BMI. Tests of linear trend across increasing quintiles of magnesium intake were conducted by assigning the medians of intakes in quintiles (milligrams per day) treated as a continuous variable. Because participants with a history of hypertension or with elevated cholesterol levels might have changed their dietary intake, we also carried out similar analyses excluding these women at baseline.

In our cross-sectional analysis in 349 apparently healthy nondiabetic women, we calculated medians and geometric means of plasma levels of insulin because they were not distributed normally. We categorized magnesium intake into quartiles and then calculated the median plasma insulin levels according to quartiles of magnesium intake. Geometric means were computed by regressing the natural logarithm of plasma levels of insulin on magnesium intake and then taking an antilog of the resulting mean logarithmic value. Multiple linear regression models were used to control for the same potential confounding factors included in the Cox hazard model. Tests of linear trend across increasing quartiles of magnesium intake were conducted by assigning the medians of intakes in quartiles (milligrams per day) treated as a continuous variable. Finally, to explore the possible modifying effect of BMI on the relation of magnesium intake with fasting insulin levels, we repeated similar analyses stratified by BMI (< or ≥25 kg/m^2). All statistical analyses were conducted using SAS (version 8.0; SAS, Cary, NC).

RESULTS — In the present study, dietary sources accounted for ~96% of total intake of magnesium. The median intake of magnesium was 326 mg/day for our cohort of middle-aged women, which is close to the 10th Recommended Dietary Allowances of 320 mg/day for adult women (21). There was an ~1.5-fold difference in total magnesium intake between the highest and lowest quintiles of the study population (median 433 mg/day in the highest quintile vs. 255 mg/day in the lowest).

At baseline in 1993, women with a high intake of magnesium were older, less likely to be current smokers, or to have a history of hypertension, and were more likely to exercise, use postmenopausal

Table 1—*Baseline characteristics among 38,025 women according to quintiles of total magnesium intake in the WHS*

Variable	Quintile of magnesium intake (mg/day)				
	1 (lowest)	2	3	4	5 (highest)
Median intake (mg/day)	255	296	328	365	433
Age (years)	52.5 ± 6.5	53.3 ± 6.8	53.9 ± 6.9	54.4 ± 7.1	55.3 ± 7.4
Smoking (%)					
Current	17.4	14.5	13.0	10.7	9.4
Never	52.3	51.0	49.7	51.2	51.1
Past	30.3	34.5	37.3	38.0	39.5
Exercise (%)					
Rarely/never	51.0	41.2	35.8	33.0	28.7
<1/week	20.8	22.5	21.2	18.5	16.6
1–3/week	22.5	29.0	32.7	35.7	37.3
≥4/week	5.7	7.4	10.3	12.8	17.5
Alcohol consumption (%)					
Rarely/never	49.4	43.2	41.1	41.0	45.3
1–3 drinks/month	13.1	12.9	12.9	13.7	13.5
1–6 drinks/week	27.4	32.7	34.8	34.5	32.0
≥1 drink/day	10.1	11.2	11.2	10.8	9.2
Postmenopausal (%)	48.6	51.2	54.5	57.3	61.0
Postmenopausal hormone use (%)					
Never	53.6	50.7	47.6	45.2	41.2
Past	10.1	9.4	9.7	10.5	10.7
Current	36.3	39.8	42.6	44.2	48.2
Mean BMI (kg/m^2)	26.6	26.2	25.8	25.5	25.2
Multivitamin use (%)	17.3	20.5	23.5	31.1	54.3
Magnesium supplement (%)	2.3	5.2	8.9	18.8	54.8
History of hypertension (%)*	27.8	25.2	24.3	24.1	23.8
History of high cholesterol (%)*	25.2	25.3	26.4	27.3	29.0
Parental history of diabetes (%)*	25.5	24.8	24.7	24.0	24.6
Total energy (kcal)	1,682 ± 556	1,737 ± 526	1,764 ± 531	1,765 ± 527	1,683 ± 521
Carbohydrate (g)	210 ± 36.6	214 ± 31.1	220 ± 30.3	228 ± 31.6	238 ± 35.1
Total fat (g)	64.5 ± 11.7	60.9 ± 10.2	57.8 ± 9.9	54.3 ± 10.3	50.6 ± 11.3
Cholesterol (mg)	240 ± 75.1	234 ± 68.1	228 ± 65.3	218 ± 66.8	205 ± 74.7
Proteins (g)	74.7 ± 13.8	79.6 ± 12.7	82.2 ± 13.1	83.8 ± 13.8	85.1 ± 15.4
Fiber (g)	14.1 ± 3.4	16.9 ± 3.5	18.7 ± 3.9	20.9 ± 4.7	24.3 ± 7.4
Dietary GI†	77.7 ± 4.5	75.8 ± 4.1	74.8 ± 4.1	74.1 ± 4.4	73.3 ± 4.8

Data are mean ± SD, unless otherwise indicated. All covariate values are according to the quintiles of total magnesium intake. All the means of nutrients are energy adjusted. *History of hypertension is defined as a diagnosis by physician or self-reported blood pressure >140/90 mmHg, and history of high cholesterol and family history of diabetes were self-reported. †Dietary GI is defined as glycemic index, an indicator of blood glucose induced by a specified food, which compares the plasma glucose response to this food with the response induced by the same amount of a carbohydrate source, in this case, white bread.

hormones, use supplements of multivitamins including magnesium, or have a history of high cholesterol than women with low magnesium intake. High magnesium intake was also associated with a slightly lower BMI (Table 1). Women in the highest quintile of magnesium intake had a lower intake of total fat and cholesterol intake but a higher intake of dietary carbohydrates, protein, and fiber.

During an average of 6 years of follow-up (222,523 person-years), we documented 918 confirmed incident cases of type 2 diabetes. The age-adjusted RRs of type 2 diabetes were 1.0, 0.92, 0.68, 0.64, and 0.62 ($P < 0.001$ for trend) from the lowest to the highest quintiles of total magnesium intake (Table 2). After controlling for BMI, the linear trend was substantially attenuated but remained statistically significant. As compared with the lowest quintile of total magnesium intake, the age- and BMI-adjusted RRs of type 2 diabetes across increasing quintiles were 1.0, 1.02, 0.77, 0.80, and 0.82 ($P = 0.007$ for trend). After further adjustment for family history of diabetes, physical activity, smoking, alcohol intake, and total energy intake, the multivariate-adjusted RRs were 1.0, 1.06, 0.81, 0.86, and 0.89 ($P = 0.05$ for trend). Similar results were observed for dietary magnesium intake, albeit with less significance for linear trend in the multivariate model ($P = 0.09$ for trend).

The association between magnesium intake and risk of type 2 diabetes was appreciably modified by BMI (Table 3). We found a significantly inverse association between magnesium intake and the incidence of type 2 diabetes only in women with a BMI of ≥25 kg/m^2. The multivariate-adjusted RRs were 1.0, 0.96, 0.76, 0.84, and 0.78 for increasing quintiles ($P = 0.02$ for trend). Similarly, restricting

Table 2—*RRs of type 2 diabetes according to quintiles of total and dietary intake of magnesium in the WHS*

	Quintile					
	1 (lowest)	2	3	4	5 (highest)	*P* for trend
Total magnesium intake						
Median intake (mg/day)	255	296	328	365	433	—
Cases	230	217	162	155	154	—
Person-years	44,291	44,482	44,586	44,634	44,530	—
Age adjusted	1.00	0.92 (0.77–1.11)	0.68 (0.55–0.83)	0.64 (0.52–0.78)	0.62 (0.51–0.77)	<0.001
Age and BMI adjusted	1.00	1.02 (0.84–1.23)	0.77 (0.63–0.95)	0.80 (0.65–0.99)	0.82 (0.67–1.02)	0.007
Multivariate model	1.00	1.06 (0.88–1.28)	0.81 (0.66–1.00)	0.86 (0.70–1.06)	0.89 (0.71–1.10)	0.05
Dietary magnesium intake						
Median intake (mg/day)	252	291	319	349	399	—
Cases	229	204	185	155	145	—
Person-years	44,283	44,428	44,545	44,655	44,612	—
Age adjusted	1.00	0.87 (0.72–1.06)	0.78 (0.64–0.94)	0.64 (0.52–0.79)	0.59 (0.48–0.73)	<0.001
Age and BMI adjusted	1.00	0.97 (0.80–1.18)	0.91 (0.74–1.11)	0.79 (0.64–0.97)	0.82 (0.66–1.02)	0.01
Multivariate model	1.00	1.00 (0.83–1.22)	0.96 (0.79–1.18)	0.84 (0.68–1.04)	0.88 (0.71–1.10)	0.09

Data are RRs (95% CI). The multivariate model was adjusted for age (continuous), smoking (current, past, and never), BMI (continuous), exercise (rarely/never, <1 time/week, 1–3 times/week, and ≥4 times/week), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), family history of diabetes (yes or no), and total calories (quintiles).

the analysis to women who had no history of hypertension or history of high cholesterol levels did not materially change the observed associations. There were statistically significant interactions between magnesium intake and BMI on risk of type 2 diabetes (test for interaction: $P = 0.01$ for total magnesium intake and $P = 0.02$ for dietary intake).

There was a consistent relation between the median plasma fasting insulin levels and magnesium intake in our cross-sectional study (Table 4). These 349 healthy women with an average age of 55.3 years had a mean BMI of 25.7 kg/m^2 at baseline, and their lifestyle and dietary characteristics were similar to the entire WHS cohort (data not shown). After adjustment for age, BMI, family history of diabetes, physical activity, smoking, alcohol intake, and total energy intake, the linear trend for the multivariate-adjusted geometric mean insulin levels was borderline significant (Table 4). As shown in Fig. 1, a significant inverse association between magnesium intake and fasting insulin levels was apparent only in women with BMI ≥25 kg/m^2 ($P = 0.03$ for trend) but not in women with BMI <25 kg/m^2 ($P = 0.22$ for trend). From the lowest to the highest quartiles of magnesium intake, the multivariate-adjusted geometric mean plasma insulin levels were 53.5 and 41.5 pmol/l in overweight women and 34.8 and 33.0 pmol/l in women with BMI <25 kg/m^2.

CONCLUSIONS — In this prospective study, we found a modest inverse association between magnesium intake and risk of developing type 2 diabetes among middle-aged women. This inverse association appeared to be significant among women who were overweight (BMI ≥25 kg/m^2). Also, our cross-sectional study showed a consistently inverse association between magnesium intake and plasma levels of fasting insulin in overweight women.

The prospective design and high follow-up rates in our study minimized the

Table 3—*Multivariate RR of type 2 diabetes according to quintile of magnesium intake among two subgroups stratified by BMI in the WHS*

	Quintile					
	1 (lowest)	2	3	4	5 (highest)	*P* for trend
Total magnesium intake						
Median intake (mg/day)	255	296	328	365	433	—
BMI <25 kg/m^2	1.00	2.00 (1.07–3.72)	1.36 (0.70–2.65)	1.09 (0.55–2.18)	1.85 (0.99–3.46)	0.28
BMI ≥25 kg/m^2	1.00	0.96 (0.79–1.18)	0.76 (0.61–0.94)	0.84 (0.67–1.05)	0.78 (0.62–0.99)	0.02
Dietary magnesium						
Median intake (mg/day)	252	291	319	349	399	—
BMI <25 kg/m^2	1.00	1.78 (0.94–3.35)	1.61 (0.85–3.08)	1.11 (0.56–2.23)	1.77 (0.95–3.32)	0.29
BMI ≥25 kg/m^2	1.00	0.93 (0.76–1.14)	0.87 (0.71–1.08)	0.81 (0.65–1.01)	0.77 (0.61–0.98)	0.02

Data are RRs (95% CI). Multivariate RR was adjusted for age (continuous), smoking (current, past, and never), exercise (rarely/never, <1 time/week, 1–3 times/week, and ≥4 times/week), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), family history of diabetes (yes or no), and total calories (quintiles), as well as further adjustment for BMI (three categories).

Table 4—*Plasma fasting insulin level according to quartiles of magnesium intake in 349 apparently healthy women from the WHS*

Fasting insulin levels (pmol/l)	Quartile of intake 1 (lowest)	2	3	4 (highest)	*P* for trend
Total magnesium intake					
Median intake (mg/day)	259	307	356	425	—
Crude [median (interquartile range)]	42.6 (29.9–59.3)	47.4 (32.7–72.6)	37.2 (26.0–57.0)	36.4 (27.8–52.3)	0.004
Age adjusted	44.3 (39.9–50.1)	49.0 (43.6–54.8)	38.5 (34.3–43.1)	37.3 (33.3–41.9)	0.005
Age and BMI adjusted	43.4 (39.3–47.8)	47.0 (42.7–51.8)	39.6 (36.0–43.7)	38.9 (35.3–42.8)	0.03
Multivariate adjusted	42.1 (37.7–47.0)	45.2 (40.4–50.5)	39.3 (35.1–43.9)	38.5 (34.5–43.0)	0.08
Dietary magnesium intake					
Median intake (mg/day)	255	301	339	387	—
Crude [median (interquartile range)]	44.0 (28.8–63.1)	43.5 (30.6–64.6)	37.2 (29.5–57.4)	36.6 (26.0–50.3)	0.003
Age adjusted	44.7 (39.8–50.2)	47.5 (42.3–53.2)	40.9 (36.4–45.8)	36.2 (32.3–40.7)	0.004
Age and BMI adjusted	43.8 (39.2–48.9)	46.5 (42.2–51.2)	40.9 (37.1–45.0)	38.1 (34.5–42.0)	0.02
Multivariate adjusted	42.5 (38.1–47.5)	45.2 (40.4–50.4)	40.0 (35.9–44.7)	37.8 (33.9–42.0)	0.05

Data are expressed as geometric mean (95% CI, unless noted otherwise). All covariate values are according to the quartiles of magnesium intake. The multivariate linear model was adjusted for age (continuous), smoking (current, past, and never), BMI (continuous), exercise (rarely/never, <1 time/week, 1–3 times/week, and ≥4 times/week), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), family history of diabetes (yes or no), and total calories (quintiles).

possibility of selection and recall bias. As our SFFQ was designed to assess long-term average dietary intakes and any measurement errors from SFFQ were unlikely to be related to end points, misclassification of nutrient measurement should be nondifferential and tend to attenuate our observed associations. Thus, our estimate of the underlying association between magnesium intake and risk of incident type 2 diabetes may be somewhat conservative. It is also unlikely that our results are influenced by misdiagnosis of type 2 diabetes because of a high accuracy of self-reported diabetes compared with medical records in our validation study. In addition, since we have adjusted for the major risk factors for type 2 diabetes, confounding effects from those factors should be minimized.

Nevertheless, some limitations of the present study merit consideration. First, our evidence may be inadequate to support the beneficial effects from magnesium independent of dietary nutrients, including fiber, calcium, and potassium. These factors are highly correlated so that it is unlikely to completely separate the independent effect of magnesium from them. Yet, consistency of our observed associations for magnesium may not be fully explained by other dietary factors. More importantly, there is clear evidence from animal models and metabolic studies supporting the direct impact of magnesium intake on insulin resistance and type 2 diabetes. Second, we cannot completely exclude the possibilities of residual confounding from unmeasured factors. Excluding participants who had a history of hypertension or high cholesterol levels, which allows for better control of residual confounding from healthy lifestyle and dietary factors, revealed a similar inverse association between magnesium intake and type 2 diabetes risk in our secondary analysis. Finally, in our cross-sectional analysis, it is unlikely that measurement errors for plasma insulin levels would be related to baseline measurements of nutrients. Thus, the strong

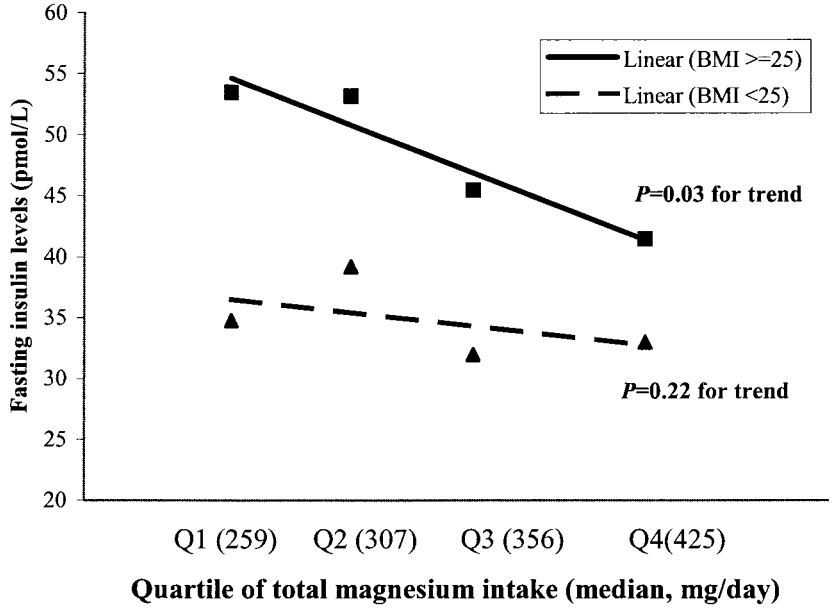

Figure 1—*Adjusted geometric mean fasting insulin levels (pmol/l) by quartiles (Q1–Q4) of magnesium intake in 349 apparently healthy women in two BMI categories, <25 kg/m^2 and ≥25 kg/m^2. Potential confounding factors were adjusted for, including age (continuous), smoking (current, past, and never), exercise (rarely/never, <1 time/week, 1–3 times/week, and ≥4 times/week), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), family history of diabetes (yes or no), and total calories (quintiles). Median magnesium intake for each quartile is in parentheses.*

correlation observed between magnesium intake and fasting insulin levels cannot be explained by potential correlated errors.

Our finding of an inverse association between magnesium intake and incident type 2 diabetes risk is consistent with previous reports from several prospective studies, including the Nurses' Health Study (12,22), the Iowa Women's Health Study (23), and the Health Professionals Follow-up Study (24). In contrast, such an association was not found in the Atherosclerosis Risk In Communities study (6). In our study, the inverse association between magnesium intake and risk of type 2 diabetes was most apparent among overweight women. In overweight women, those in the highest quintile of magnesium intake had a 22% lower risk of developing diabetes than those in the lowest quintile. In the Nurses' Health Study, a significant trend from the lowest quintile to the highest quintile of magnesium intake for the risk of type 2 diabetes was evident for women with a BMI of ≥29 kg/m^2 (P for trend = 0.008) (12).

Another finding of our study is that BMI modified the relation of magnesium intake with fasting insulin levels among healthy women. The linear trend between magnesium intake and fasting insulin levels was evident only among overweight women. Obesity-related insulin resistance and metabolic disorders have been recognized as important risk factors for type 2 diabetes. The extent to which magnesium intake influences insulin sensitivity may differ among women with different body weight. We speculated that the potential beneficial effects of high intake of magnesium might be greater among overweight people who are prone to insulin resistance. On the other hand, there is a concern that dietary underreporting by overweight people may lead to an artifactual inverse association between magnesium intake and diabetes risk. However, in general, under- or overreporting of individual foods has similar errors in all nutrients. Errors in measuring individual nutrients are therefore strongly correlated with errors in measuring total energy intake (16). Furthermore, there is no evidence of under- or overreporting of macronutrients expressed as a percentage of energy because adjustment for energy intake reduces extraneous between-person variation due to general under- or overreporting of food intake. In our analyses, only energy-adjusted nutrient intakes were used, including magnesium intake. Moreover, adjustment for BMI for our main and subgroup analyses did not eliminate the significantly inverse association between magnesium and type 2 diabetes. More importantly, the results from our cross-sectional analysis of the relations of magnesium intake with fasting insulin levels corroborate our findings from prospective data and, furthermore, suggest that the protective role of magnesium intake in relation to type 2 diabetes may be largely due to improvement of insulin resistance. Experimental studies have shown an adverse effect of magnesium deficiency on glucose-induced insulin secretion and insulin-mediated glucose uptake (25,26). Conversely, magnesium supplementation was shown to prevent fructose-induced insulin resistance (27) and delay the onset of spontaneous type 2 diabetes in rat models (7). Some but not all metabolic studies (5,8) and clinical trials have suggested that magnesium supplementation improves insulin-induced glucose uptake in both healthy elderly or diabetic participants.

However, the underlying cellular or molecular mechanisms by which magnesium intake influence insulin resistance is still not well understood. Abnormalities in intracellular magnesium homeostasis have been hypothesized to be the link between insulin resistance, type 2 diabetes, and cardiovascular disease (2). First, magnesium functions as a cofactor for enzymes in glucose metabolism utilizing high-energy phosphate bonds (1). Second, intracellular magnesium levels may be important for maintaining insulin sensitivity in skeletal muscle or adipose tissue (2,5). Diminished levels of magnesium may decrease tyrosine kinase activity at insulin receptors (25) and increase intracellular calcium levels (2), leading to an impairment of insulin signaling. Third, intracellular magnesium levels may influence glucose-stimulated insulin secretion in pancreatic β-cells through altered cellular ion metabolism (2) or other pathways linked to oxidative stress and free radical formation (28).

In conclusion, our findings suggest that higher intake of magnesium may reduce the incidence of type 2 diabetes among middle-aged women, especially among those who are overweight. Our results support the potential benefits of diet modification for prevention of type 2 diabetes by consuming foods rich in fruits, green leafy vegetables, whole grains, and nuts, which are also the primary food sources of magnesium.

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