

ORIGINAL CONTRIBUTIONS

Liver and Biliary Tract

Long-Term Effect of Magnesium Consumption on the Risk of Symptomatic Gallstone Disease Among Men

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BACKGROUND: Magnesium deficiency can cause dyslipidemia and insulin hypersecretion, which may facilitate gallstone formation. However, the effect of long-term consumption of magnesium on the risk of gallstone disease is unknown.

METHODS: We prospectively studied magnesium consumption and risk of gallstone disease in a cohort of 42,705 U.S. men from 1986 to 2002. Magnesium consumption was assessed using a validated semiquantitative food frequency questionnaire. Newly diagnosed gallstone disease was ascertained biennially.

RESULTS: We documented 2,195 incident cases of symptomatic gallstones during 560,810 person-years of follow-up. The age-adjusted relative risks (RRs) for men with total magnesium intake and dietary magnesium, when the highest and lowest quintiles were compared, were 0.67 (95% confidence interval [CI] 0.59–0.77, *P* for trend <0.0001) and 0.67 (CI 0.59–0.76, *P* for trend <0.0001), respectively. After adjusting for multiple potential confounding variables, when extreme quintiles were compared, the multivariate RR of total magnesium intake (RR 0.72, CI 0.61–0.86, *P* for trend = 0.006) and dietary magnesium (RR 0.68, CI 0.57–0.82, *P* for trend = 0.0006) remained significant with a dose–response relationship.

CONCLUSIONS: Our findings suggest a protective role of magnesium consumption in the prevention of symptomatic gallstone disease among men.

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INTRODUCTION

Gallstone disease is very common in western countries and is increasingly a major cause of digestive morbidity (1). Among western populations, the majority of gallstones are cholesterol stones. Many factors have been associated with risk of cholesterol gallstones, but cholesterol-saturated bile is an important determinant of gallstone formation (2). High plasma triglyceride and low HDL-cholesterol levels are associated with a greater risk of cholesterol gallstones (2).

Magnesium is one of the most abundant minerals in cells with an essential role in fundamental biological functions, whose deficiency provokes various biochemical alterations in human systems (3–12). Magnesium intake is important in maintaining magnesium homeostasis (3), but the average in-

gestion of magnesium has diminished over the years (6). Magnesium is an important component of various unprocessed foods, such as fishes and whole grains, and it is largely lost during the processing of foods (3). Overprocessing of foods has contributed to the decline in magnesium intake in the United States and other industrialized countries.

A magnesium-deficient diet can elevate plasma triglyceride levels and lower plasma HDL-cholesterol levels (13–15), which may be associated with an increased incidence of gallstones (2). However, the effect of long-term magnesium consumption on the risk for gallstones in humans is unknown. In a large cohort of U.S. men, we examined long-term magnesium intake in relation to the occurrence of gallstone disease.

METHODS

Study Population

The Health Professionals Follow-up Study began in 1986 when 51,529 U.S. male dentists, veterinarians, optometrists, osteopathic physicians, and podiatrists who were 40–75 yr of age returned a questionnaire by mail regarding diet, medications, and medical history (16). Every 2 yr a follow-up questionnaire was sent to all surviving cohort members, up to six times per follow-up cycle for nonrespondents, to update information on exposures and to ascertain the occurrence of newly diagnosed illnesses, including gallstone disease. The follow-up rate for biennial questionnaires was greater than 94% in each 2-yr follow-up cycle. Diet was assessed every 4 yr. At baseline, we excluded men who reported a cholecystectomy or a diagnosis of gallstone disease, men with a reported daily energy intake outside the range of 800–4,200 kcal/day, and men with 70 or more blank food items on the dietary questionnaire. Men with a diagnosis of cancer were also excluded. After exclusions, the study population consisted of 42,705 men who were followed from 1986 to 2002. This study was approved by the institutional review board on the use of human subjects in research of the Brigham and Women's Hospital in Boston.

Assessment of Dietary Variables

Dietary information was derived from a 131-item semi-quantitative food frequency questionnaire (SFFQ) (16). Participants were asked to indicate the frequency, on average, of consuming a typical serving size of selected foods during the previous year. There were nine options for respondents to choose from, ranging from never or less than once per month to six or more times per day. Nutrient scores were computed by multiplying the frequency of consumption of each unit of food from the SFFQ by the nutrient content of the specified portion according to food-composition tables from the Harvard Food Composition Database and U.S. Department of Agriculture supplemented with manufacturers' data (17). Validity of the dietary data was documented by comparisons with multiple-week dietary records corrected for within-person variation in diet (16, 18). A full description of the SFFQ and the procedures used for calculating nutrient intake, as well as data on reproducibility and validity in this cohort, were reported previously (16, 18). All nutrients were adjusted for total energy intake using regression analysis. Data on the use of multivitamin supplements were taken into account to assess the intake of supplemental magnesium. Use of a specific brand and type of multivitamins was ascertained at baseline and updated every 2 yr. We estimated the content based on the most frequently used magnesium supplements on the market in the year of the questionnaires and used that amount for the calculation of total magnesium intake. Total magnesium represents the sum of magnesium intake from both dietary and supplemental sources.

Assessment of Nondietary Variables

Participants reported their body weight, cigarette smoking, use of medications, and leisure-time physical activity every

2 yr during the follow-up. The correlation coefficient between self-reported weight and measured weight was 0.96 (19). Physical activity was estimated by using the cumulative average number of hours per week on the basis of the reported time spent doing specific activities. Each activity was weighted by its intensity level. The validity of self-reported physical activity in this cohort was reported previously (20).

Ascertainment of End Points

The primary end point was incident symptomatic gallstones. In 1986 and on each follow-up questionnaire, participants were asked whether they had undergone a cholecystectomy or had been diagnosed as having gallstones by a physician. Participants were also asked whether the gallstone diagnosis had been confirmed by radiographic procedures or surgery and whether their gallstones were symptomatic. To verify self-reported symptomatic gallstone disease, a random sample of 441 self-reported diagnoses of cholecystectomy or gallstones were reviewed against medical records, and all but one of the 441 diagnoses was confirmed. Although the composition of the gallstones was not assessed, it is estimated that approximately 80% of gallstones in the study population are cholesterol stones (2).

Statistical Analysis

For each participant, follow-up time accrued from the month of return of the 1986 questionnaire and ended at the month of cholecystectomy, diagnosis of symptomatic gallstones, death, or the end of the study period, whichever occurred first. Men with asymptomatic gallstones or those whose gallstone diagnosis was not based on radiology or surgery, and men with diagnosed cancer were excluded from subsequent follow-up. Thus, the eligible population at risk comprised only those who remained free of gallstone disease and cancer at the beginning of each 2-yr follow-up interval. We divided participants into five categories (quintiles) according to their cumulative magnesium intake. Incidence rates were calculated by dividing the number of events by person-years of follow-up in each category. Age-adjusted relative risks (RRs) were calculated as the incidence rate of gallstone disease among men in different categories of magnesium intake compared with the incidence rate among men in the lowest intake category, with adjustment for age.

We analyzed total magnesium intake, including magnesium intake from supplements and dietary magnesium from food sources only in relation to the risk of gallstone disease. The incidence of gallstone disease was examined in relation to the cumulative average of exposure variables from all available questionnaires up to the start of each 2-yr follow-up interval to reduce within-subject variation and best represent long-term dietary intake (21). For example, magnesium intake from the 1986 questionnaire was related to the incidence of gallstone disease from 1986 to 1990, and the average magnesium intake from the 1986 and 1990 questionnaires was related to the incidence of gallstone disease from 1990 to 1994. Multivariate-adjusted RRs were computed using the Cox proportional hazards regression model (22). In

multivariate analyses, we simultaneously included intake of total energy and potential confounding covariates, including age, body mass index (calculated as weight in kilograms divided by the square of height in meters), weight change during the past 2 yr, cigarette smoking, physical activity, use of thiazide diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs), and intakes of alcohol, caffeine, dietary fiber, carbohydrate, protein, and saturated, polyunsaturated, and monounsaturated fats. Because diabetes mellitus is associated with magnesium consumption (12), and is a potential biologic mediator in the relationship between magnesium intake and risk of gallstone disease, we excluded the term representing history of diabetes mellitus from the multivariate model (23). Tests of linear trend across increasing categories were conducted by assigning the median value of exposure for each category and treating these as a single continuous variable (23). We evaluated potential effect modification in

stratified analyses. The likelihood ratio test was used to assess the significance of interaction terms. All RRs are presented with 95% confidence intervals (CI), and all reported *P* values are 2-sided. All analyses were performed with Statistical Analysis System software, release 9.1 (SAS Institute, Cary, NC).

RESULTS

In this cohort of men, magnesium from dietary sources (median 334 mg/day, mean [standard deviation] 341.5 [72.6] mg/day) accounted for approximately 98% of the total intake of magnesium (median 342 mg/day, mean [standard deviation] 352.8 [82.8] mg/day) in the entire follow-up period, which is close to the recommended dietary allowance of 350 mg/day for adult U.S. men (24). At baseline in 1986, men with a higher magnesium intake were less likely to be current

Table 1. Baseline Characteristics of 42,705 U.S. Men According to Quintiles of Total Magnesium Intake and Dietary Magnesium in 1986: The Health Professionals Follow-up Study

Characteristic*	Quintiles of Total Magnesium					<i>P</i> Value
	1 (Lowest)	2	3	4	5 (Highest)	
No. of participants	8,596	8,592	8,294	8,591	8,632	—
Mean age	52.4	52.5	52.6	52.8	52.9	<0.001
Mean body mass index (kg/m ²)	25.0	25.0	24.9	24.7	24.4	<0.001
Mean physical activity (METs)	15.5	18.0	20.4	22.1	26.0	<0.001
Current smoker (%)	2.3	2.1	1.7	1.6	1.3	<0.001
Use of thiazides (%)	1.4	1.5	1.5	1.4	1.5	0.98
Use of NSAIDs (%)	6.0	6.4	6.5	6.9	7.4	<0.001
Mean daily intake						
Carbohydrate (g)	224	226	233	239	253	<0.001
Protein (g)	85.0	90.3	92.5	94.8	97.4	<0.001
Alcohol (g)	11.5	11.4	11.5	12.1	11.0	0.53
Caffeine (mg)	203	242	254	260	261	<0.001
Saturated fat (g)	27.4	26.2	24.7	23.1	20.5	<0.001
Dietary fiber (g)	15.8	18.3	20.4	22.6	27.4	<0.001
Monounsaturated fat (g)	29.9	28.8	27.4	26.0	23.8	<0.001
Polyunsaturated fat (g)	13.1	13.3	13.2	13.2	13.1	0.52
Characteristic*	Quintiles of Dietary Magnesium					<i>P</i> Value
	1 (Lowest)	2	3	4	5 (Highest)	
No. of participants	8,642	8,387	8,619	8,464	8,593	—
Mean age	52.4	52.5	52.6	52.8	52.9	<0.001
Mean body mass index (kg/m ²)	25.0	25.0	25.0	24.8	24.4	<0.001
Mean physical activity (METs)	15.4	17.9	20.1	22.4	26.1	<0.001
Current smoker (%)	2.3	2.0	1.8	1.5	1.3	<0.001
Use of thiazides (%)	1.5	1.6	1.4	1.5	1.4	0.41
Use of NSAIDs (%)	6.3	6.5	6.7	6.7	7.2	<0.001
Mean daily intake						
Carbohydrate (g)	224	226	232	238	255	<0.001
Protein (g)	84.5	90.1	92.4	95.0	97.9	<0.001
Alcohol (g)	11.8	11.3	11.5	11.9	10.9	<0.001
Caffeine (mg)	198	237	252	261	271	<0.001
Saturated fat (g)	27.4	26.3	24.9	23.2	20.1	<0.001
Dietary fiber (g)	15.7	18.3	20.1	22.4	28.1	<0.001
Monounsaturated fat (g)	29.9	28.8	27.6	26.0	23.5	<0.001
Polyunsaturated fat (g)	13.1	13.3	13.3	13.2	13.1	0.78

*Values have been standardized for age of the cohort.

MET = metabolic equivalent tasks per week, defined as a multiple of metabolic equivalent of sitting at rest; NSAID = nonsteroidal anti-inflammatory drug.

Table 2. Adjusted Relative Risks (95% Confidence Interval) of Gallstone Disease According to Quintiles of Total Magnesium Intake, Dietary Magnesium, and Supplemental Magnesium Among U.S. Men in the Health Professionals Follow-up Study, 1986–2002

	Quintiles of Total Magnesium					<i>P</i> for Trend
	1 (Lowest)	2	3	4	5 (Highest)	
Median intake (mg/day)	262	307	342	382	454	–
Cases of GSD	502	468	385	438	402	–
Person-years	112,286	113,553	109,300	112,696	112,975	–
Model 1:	1.00	0.84	0.78	0.75	0.67	<0.0001
Age-adjusted		(0.73–0.95)	(0.69–0.89)	(0.66–0.86)	(0.59–0.77)	
Model 2:	1.00	0.86	0.82	0.80	0.72	0.006
Multivariate		(0.75–0.99)	(0.71–0.95)	(0.68–0.93)	(0.61–0.86)	
	Quintiles of Dietary Magnesium					
	1 (Lowest)	2	3	4	5 (Highest)	<i>P</i> for Trend
Median intake (mg/day)	260	301	334	370	431	–
Cases of GSD	522	451	414	408	400	–
Person-years	112,748	110,246	11,3975	111,266	112,576	–
Model 1:	1.00	0.82	0.76	0.68	0.67	<0.0001
Age-adjusted		(0.72–0.93)	(0.67–0.87)	(0.60–0.78)	(0.59–0.76)	
Model 2:	1.00	0.83	0.78	0.70	0.68	0.0006
Multivariate		(0.72–0.95)	(0.67–0.90)	(0.59–0.82)	(0.57–0.82)	
	Quintiles of Supplemental Magnesium*					
	1 (Lowest)	2	3	4	5 (Highest)	<i>P</i> for Trend
Median intake (mg/day)	1	2	3	13	84	–
Cases of GSD	137	106	137	133	146	–
Person-years	38,074	32,765	38,236	37,367	37,186	–
Model 1:	1.00	1.03	0.86	1.06	1.01	0.68
Age-adjusted		(0.81–1.33)	(0.65–1.15)	(0.82–1.37)	(0.78–1.30)	
Model 2:	1.00	1.02	0.84	1.08	1.06	0.80
Multivariate		(0.78–1.35)	(0.61–1.16)	(0.82–1.44)	(0.78–1.44)	

GSD = gallstone disease.

*Among men in the cohort who used magnesium supplements.

Model 2: Cox proportional hazards model included the following: age, body mass index, recent weight change during the past 2 yr, cigarette smoking, physical activity, thiazide diuretics, nonsteroidal anti-inflammatory drugs, and intakes of alcohol, caffeine, dietary fiber, carbohydrate, protein, and saturated, polyunsaturated, and monounsaturated fats, and total energy.

smokers, tended to be physically active and lighter, consumed less saturated and monounsaturated fats, but had higher intakes of protein, carbohydrate, caffeine, and fiber than men with a lower magnesium intake (Table 1).

During 560,810 person-years of follow-up from 1986 to 2002, we documented 2,195 incident cases of symptomatic gallstones, of which 1,297 cases required cholecystectomy. Because magnesium intake was associated both directly and inversely with several potential risk factors, we analyzed their relations with gallstone disease before and after adjustment for these variables.

The median total magnesium intake for the highest and lowest quintiles (quintile cutoff points: <288 mg/day, 288~323 mg/day, 324~359 mg/day, 360~409 mg/day, >409 mg/day) varied approximately 1.7-fold in this cohort (Table 2). Total magnesium intake was associated with a decreased risk of gallstone disease in the age-adjusted and multivariate analyses, and with a significant trend. The RR for men with total magnesium intake in the highest quintile

compared with men in the lowest quintile was 0.67 (95% CI 0.59–0.77, *P* for trend <0.0001) in age-adjusted analysis. The multivariate RR was slightly attenuated (RR 0.72, CI 0.61–0.86, *P* for trend = 0.006) when extreme quintiles were compared after adjusting for multiple potential confounding variables, including age, body mass index, recent weight change, cigarette smoking, physical activity, thiazide diuretics, NSAIDs, and intakes of alcohol, caffeine, dietary fiber, carbohydrate, protein, and saturated, polyunsaturated, and monounsaturated fats, and total energy (Table 2). The RR for men with dietary magnesium in the highest quintile compared with men in the lowest quintile was 0.67 (CI 0.59–0.76, *P* for trend <0.0001) in age-adjusted analysis. In multivariate analysis, when extreme quintiles were compared, the RR was 0.68 (CI 0.57–0.82, *P* for trend = 0.0006). We further analyzed dietary magnesium as a continuous variable in the multivariate model; for a 100-mg increase in dietary magnesium consumption, the multivariate RR was 0.86 (CI 0.78–0.94). Magnesium intake from supple-

Table 3. Adjusted Relative Risks* of Gallstone Disease, Stratified by Selected Gallstone Disease Risk Factors, According to Quintiles of Total Intake of Magnesium

Variables	Quintiles of Total Magnesium Intake					<i>P</i> for Trend
	1 (Lowest)	2	3	4	5 (Highest)	
Body mass index (kg/m ²)						
≥25	1.00	0.81 (0.68–0.96)	0.78 (0.65–0.94)	0.83 (0.68–1.01)	0.71 (0.57–0.89)	0.03
<25	1.00	0.98 (0.78–1.24)	0.88 (0.69–1.13)	0.77 (0.59–1.00)	0.71 (0.54–0.94)	0.07
Physical activity [†] (MET)						
High	1.00	0.85 (0.67–1.07)	0.75 (0.59–0.95)	0.77 (0.60–0.99)	0.69 (0.53–0.90)	0.17
Low	1.00	0.87 (0.73–1.04)	0.86 (0.71–1.03)	0.81 (0.66–0.99)	0.74 (0.59–0.94)	0.02
Age [‡]						
≥53	1.00	0.89 (0.75–1.06)	0.84 (0.70–1.01)	0.76 (0.62–0.92)	0.71 (0.57–0.88)	0.02
<53	1.00	0.85 (0.68–1.06)	0.79 (0.62–1.01)	0.94 (0.72–1.22)	0.77 (0.57–1.04)	0.18
Alcohol intake [†]						
High	1.00	0.83 (0.67–1.02)	0.81 (0.65–1.00)	0.77 (0.61–0.98)	0.72 (0.56–0.94)	0.04
Low	1.00	0.89 (0.74–1.07)	0.85 (0.69–1.04)	0.86 (0.69–1.06)	0.73 (0.57–0.92)	0.08
Weight change within past 2 yr						
>4 lbs	1.00	0.67 (0.45–0.98)	0.61 (0.40–0.92)	0.66 (0.43–1.02)	0.57 (0.35–0.93)	0.17
≤4 lbs	1.00	0.83 (0.68–1.01)	0.85 (0.69–1.04)	0.80 (0.64–0.99)	0.74 (0.58–0.94)	0.07

*The Cox proportional hazards model included the same covariates as in model 2 in Table 2. The variable used for stratification was excluded from the model.

[†]Median values were used as the cutoff point.

MET = metabolic equivalent tasks per week, defined as a multiple of metabolic equivalent of sitting at rest.

ments was not significantly associated with the risk of gallstone disease in age-adjusted (RR 1.01, CI 0.78–1.30, *P* for trend = 0.68) and multivariate (RR 1.06, CI 0.78–1.44, *P* for trend = 0.80) analyses. However, for a 100-mg increase in supplemental magnesium, the multivariate RR was 0.97 (CI 0.78–1.21). Because the CI for a 100-mg increase in supplemental magnesium included the RR for a comparable increment in dietary magnesium, the lack of significant association for supplemental magnesium could readily be due to low amounts of the latter. Intake of magnesium supplements represented only approximately 2% of total magnesium consumption in this cohort. Thus, the significant inverse association between total magnesium consumption and the risk of gallstone disease was mainly due to dietary magnesium.

To examine whether the inverse association with magnesium intake was modified by risk factors for gallstone disease, we repeated the multivariate analyses within subgroups of potential confounding variables (Table 3). We found no important change in association. The inverse associations between total magnesium intake and the risk of gallstone disease persisted in all subgroups, although they were not always statistically significant, which in part would be due to the reduced sample sizes in the subgroups.

Because diabetes mellitus is associated with magnesium intake (12), and is a potential biological mediator in the relationship between magnesium intake and risk of gallstone disease, we deliberately did not control for it. However, to

assess any residual effect we added this potential biologic mediator into the multivariate models. After adjustment for diabetes and other risk factors, the inverse association was little changed. The multivariate RR of gallstone disease for men in the highest quintile of total magnesium intake compared with men in the lowest quintile was 0.75 (CI 0.64–0.88, *P* for trend = 0.009).

To examine the possibility that latent gallstone disease might distort the relation between magnesium intake and risk of gallstone disease, we conducted an analysis excluding all cases that occurred during the first 4-yr follow-up period. Compared with men in the lowest quintile, men in the highest quintile had a multivariate RR of 0.73 (95% CI 0.60–0.90) for total magnesium intake and a multivariate RR of 0.69 (95% CI 0.56–0.85) for dietary magnesium (Table 4). To further examine the effect of latency in more detail, we used various lag times in the analysis (Table 4). The inverse associations became stronger with longer lag times. With a lag time of 12 yr, compared with men in the lowest quintile, men in the highest quintile had a multivariate RR of 0.46 (95% CI 0.31–0.69) for total magnesium intake and a multivariate RR of 0.51 (95% CI 0.34–0.77) for dietary magnesium.

We also addressed the possibility of bias by excluding cases with unremoved stones (*N* = 898) as these were presumably less symptomatic, limiting the analysis to cholecystectomy cases (*N* = 1,297). The age-adjusted RR for men in the highest quintile of total magnesium intake compared with men

Table 4. Relative Risks* of Gallstone Disease for High[†] Magnesium Consumption With Various Lag Times Between Baseline Diet Assessment and Start of Follow-Up Among U.S. Men in the Health Professionals Follow-up Study

Lag Time	No. of Cases	Follow-Up	Relative Risk (95% CI)	
			Total Magnesium	Dietary Magnesium
4 yr	1,592	1990–2002	0.73 (0.60–0.90)	0.69 (0.56–0.85)
8 yr	1,055	1994–2002	0.69 (0.54–0.88)	0.70 (0.54–0.90)
12 yr	415	1998–2002	0.46 (0.31–0.69)	0.51 (0.34–0.77)

*The multivariate model included the same covariates as in model 2 in Table 2.

[†]Quintile 5 was compared with quintile 1 in all analyses.

in the lowest quintile was 0.65 (95% CI 0.55–0.78), and the multivariate RR was 0.73 (95% CI 0.59–0.92).

DISCUSSION

In this large cohort study, we observed that a higher consumption of magnesium was associated with a reduced risk of gallstone disease with a dose–response relationship that was not accounted for by other potential risk factors including other measured dietary variables. The inverse association was also consistently present in the subgroups of potential confounding variables, which suggested an independent and homogeneous protective effect of magnesium consumption against gallstone disease.

The exact mechanism of magnesium intake in preventing gallstone disease is not clear and can be multi factorial. Hyperinsulinemia and insulin resistance are known to be positively associated with gallstone disease (25, 26). In experimental studies, magnesium is an important mediator of insulin action on the cellular level (3, 4, 27, 28). Magnesium deficiency can interfere with enzymatic reactions that use or produce adenosine triphosphate and tyrosine kinase activity, which is essential for insulin action, and can modify the enzymatic cascades that involve glucose metabolism, resulting in insulin resistance (29). Low magnesium consumption has been associated with high fasting insulin concentrations (30–32). Chronic hypersecretion of insulin, a feature of insulin resistance, may increase the cholesterol saturation index in the bile (33), and thus may facilitate gallstone formation. In animal and clinical studies, a magnesium-deficient diet can elevate plasma triglycerides and decrease plasma HDL-cholesterol levels (13, 34–37), and thus may increase the risk for gallstones (2). In experimental studies, dietary magnesium deficiency can stimulate generation of oxygen free radicals (38–40), which in turn may stimulate mucous glycoprotein secretion in the gallbladder (41, 42), and thereby promote the formation of gallstones.

Clinical and epidemiologic studies on the relationship between magnesium and gallstones are few and mixed. In a patient-control study using 24-h dietary recalls in Spain, patients with gallstones reported a lower intake of magnesium (43). In a nested case-control study in a cohort in Denmark, there was no association between gallstone disease and serum magnesium concentration in men (44). In a case-control

study, magnesium concentration in the bile was lower in patients with gallstones than in controls (45). The inconsistency may generally arise from lack of long-term dietary information, small sample size, and nonvalidated assessment of nutrients.

The prospective design of our study avoids the potential for differential reporting of magnesium intake by gallstone cases and noncases because all data on dietary intake were collected before the diagnosis of gallstone disease, which minimizes the possibility of selection and recall bias. In addition, consistently high follow-up rates in this cohort reduce the possibility that our results could be biased by nonresponding men.

Because information on nutrient intake was collected by self-report, the possibility of misclassification might be of concern. Random within-person variation could attenuate any true association of interest, but the SFFQ was designed to minimize this error by assessing average long-term dietary intake during the successive follow-up periods. The use of repeated measurements took into account possible changes in diet with time and reduced random variation. Because of the prospective design, any measurement errors would be expected to be unrelated to the gallstone disease end points. Any nondifferential misclassification would most likely bias the RRs toward the null and lead to an underestimation of the true effect. Thus, our estimate of the underlying association between magnesium consumption and risk of gallstone disease may be conservative.

Our results were restricted to men with cholecystectomy or diagnostically confirmed but unremoved symptomatic gallstones. Silent gallstones were not included because most would have been detected incidentally. The results might not be generalizable to all men with gallstones. However, the study focused on clinically relevant gallstone disease.

In this large study population, it was not possible to perform diagnostic screening procedures for the presence of gallstones. Because most gallstones are asymptomatic, it is likely that there was underascertainment of gallstones. It is not likely that the presence of asymptomatic gallstones at baseline was associated with the reporting of magnesium intake. Because RR estimation in follow-up cohort studies would not be biased by nondifferential underascertainment (23), our results are not likely biased due to asymptomatic gallstones.

Although we assessed and adjusted for a number of potential confounders in the analyses, we cannot exclude the

possibility of residual confounding, as in any observational study. It is possible that the inverse association was related to some unmeasured variable, such as socioeconomic status. However, because the population we studied is relatively homogeneous with respect to education and occupation, confounding by socioeconomic status was minimized.

To address the possibility of bias due to latent gallstone disease, we incorporated various lag periods of time between dietary assessment at baseline and subsequent development of gallstone disease. The inverse association persisted after various periods of follow-up were excluded. Additionally, in a subanalysis we restricted our outcomes to men with cholecystectomy and excluded men with unremoved gallstones who might be presumably less symptomatic. The inverse association still persisted after the exclusion.

In conclusion, our findings suggest a protective role of magnesium consumption in the prevention of symptomatic gallstone disease among men.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Magnesium is one of the most abundant minerals in cells, with an essential role in fundamental biological functions. In experiments, magnesium deficiency can cause dyslipidemia and insulin hypersecretion, which may affect bile lithogenicity.

What Is New Here

- A higher consumption of magnesium is associated with a reduced risk of gallstone disease with a dose-response relationship.

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CONFLICT OF INTEREST

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