



# Magnesium Intake, Quality of Carbohydrates, and Risk of Type 2 Diabetes: Results From Three U.S. Cohorts

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Adela Hruby,<sup>1,2</sup> Marta Guasch-Ferré,<sup>2</sup>  
Shilpa N. Bhupathiraju,<sup>2,3</sup>  
JoAnn E. Manson,<sup>4,5</sup> Walter C. Willett,<sup>2,3,5</sup>  
Nicola M. McKeown,<sup>1</sup> and Frank B. Hu<sup>2,3,5</sup>

## OBJECTIVE

Magnesium intake is inversely associated with risk of type 2 diabetes in many observational studies, but few have assessed this association in the context of the carbohydrate quality of the diet. We hypothesized that higher magnesium intake is associated with lower risk of type 2 diabetes, especially in the context of a poor carbohydrate-quality diet characterized by low cereal fiber or high glycemic index (GI) or glycemic load (GL).

## RESEARCH DESIGN AND METHODS

In the Nurses' Health Study (NHS; 1984–2012,  $n = 69,176$ ), NHS2 (1991–2013,  $n = 91,471$ ), and the Health Professionals' Follow-Up Study (1986–2012,  $n = 42,096$ ), dietary intake was assessed from food frequency questionnaires every 4 years. Type 2 diabetes was ascertained by biennial and supplementary questionnaires. We calculated multivariate hazard ratios (HRs) of magnesium intake and incident diabetes, adjusted for age, BMI, family history of diabetes, physical activity, smoking, hypertension, hypercholesterolemia, GL, energy intake, alcohol, cereal fiber, polyunsaturated fats, trans fatty acids, and processed meat, and we considered the joint associations of magnesium and carbohydrate quality on diabetes risk.

## RESULTS

We documented 17,130 incident cases of type 2 diabetes over 28 years of follow-up. In pooled analyses across the three cohorts, those with the highest magnesium intake had 15% lower risk of type 2 diabetes compared with those with the lowest intake (pooled multivariate HR in quintile 5 vs. 1: 0.85 [95% CI 0.80–0.91],  $P < 0.0001$ ). Higher magnesium intake was more strongly associated with lower risk of type 2 diabetes among participants with high GI or low cereal fiber than among those with low GI or high cereal fiber (both  $P$  interaction  $< 0.001$ ).

## CONCLUSIONS

Higher magnesium intake is associated with lower risk of type 2 diabetes, especially in the context of lower carbohydrate-quality diets.

Considerable effort has been invested in identifying potentially protective effects of specific nutrients against type 2 diabetes, as well as the biological actions of these nutrients, both within and outside the context of a healthy diet. One such nutrient of interest is magnesium, recognized as a shortfall nutrient in the *Scientific Report of the 2015 Dietary Guidelines Advisory Committee* (1). Nearly 50% of the U.S. population has inadequate

<sup>1</sup>Nutritional Epidemiology Program, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA

<sup>2</sup>Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

<sup>3</sup>Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

<sup>4</sup>Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

<sup>5</sup>Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

Corresponding authors: Marta Guasch-Ferré, [mguasch@hsph.harvard.edu](mailto:mguasch@hsph.harvard.edu), and Adela Hruby, [adela.hruby@tufts.edu](mailto:adela.hruby@tufts.edu).

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A.H. and M.G.-F. contributed equally to this work.

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magnesium intake. Furthermore, hypomagnesemia may be present in up to a third of the general adult population; in those with prediabetes, insulin resistance, or diabetes, hypomagnesemia tends to be more pronounced (2), and low serum levels have been associated with increased risk of prediabetes and diabetes, likely via insulin resistance pathways (3).

Higher magnesium intake has been inversely associated with type 2 diabetes and related risk factors in previous studies. In short-term trials, supplemental magnesium intake exerts small beneficial effects on parameters of glucose and insulin metabolism (4). Prospective observational literature (5–9) supports an inverse association between magnesium intake and incident type 2 diabetes as well as precursor physiological states (i.e., insulin resistance and prediabetes), the latter suggesting potentially amplified roles of magnesium in the context of dietary factors related to these precursor states, such as carbohydrate load or unhealthy diets known to elevate type 2 diabetes risk (10–12). For example, inverse associations between magnesium and type 2 diabetes may be more pronounced in those with higher glycemic index (GI) or glycemic load (GL) diets, because higher GI and GL induce higher insulin demand, and magnesium is required for insulin signaling and action (13,14).

In a recent prospective analysis using data from three large U.S. cohorts, the Nurses' Health Studies (NHS and NHS2) and the Health Professionals Follow-up Study (HPFS), we observed that those with high GI or GL coupled with low cereal fiber intake had a higher risk of incident type 2 diabetes than those with a diet with high GI or GL and high cereal fiber (10). In 2004, we reported an inverse association in the NHS and HPFS between magnesium intake and incident type 2 diabetes through 1998 (5). In the present analysis, we extend follow-up in the NHS and HPFS by an additional 14 years through 2012, include the younger NHS2 cohort, and further extend the magnesium–type 2 diabetes literature by exploring magnesium in the context of carbohydrate quality of the underlying diet. Our primary hypothesis is that higher magnesium intake is associated with a lower risk of developing type 2 diabetes overall, and especially in the context of a poor diet as characterized by high GI or GL or low cereal fiber intake.

## RESEARCH DESIGN AND METHODS

### Study Population

We used data from three large longitudinal cohorts: the NHS (1984–2012), NHS2 (1991–2013), and HPFS (1986–2012). In brief, the NHS began in 1976 as a long-term investigation of the health effects of contraceptive methods of married female nurses, age 30–55 years (15). The NHS2 is a prospective cohort study of younger female nurses that began in 1989 when participants were age 25–42 years (15). The HPFS began in 1986 as a prospective cohort of male health professionals designed to evaluate associations of dietary factors with the incidence of chronic diseases (16). All three cohorts use validated biennial questionnaires to obtain updated information on participant medical history, lifestyle factors, and occurrence of chronic diseases. For the current study, baseline years were defined as 1984 in NHS, 1986 in HPFS, and 1991 in NHS2, when detailed information on diet was first collected via food frequency questionnaire (FFQ). We excluded participants with a history of type 1 or type 2 diabetes, cardiovascular disease, or cancer at baseline and those reporting implausible energy intake ( $<800$  or  $>4,200$  kcal/day for men and  $<500$  or  $>3,500$  kcal/day for women) or who left  $\geq 70$  FFQ items blank. The final sample size was 69,176 women from NHS, 91,471 women from NHS2, and 42,096 men from HPFS. The study protocols were approved by the institutional review board of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

### Exposure Assessment

A 126-item semiquantitative FFQ was used to assess diet in NHS in 1984 and in HPFS in 1986. A 133-item version was used to assess diet in NHS2 in 1991. Subsequently, FFQs were administered every 4 years to update dietary information in each cohort. Participants self-reported how often, on average, during the previous year they had consumed a common unit or portion size of foods and beverages (never to  $\geq 6$  times/day). Nutrient intakes were computed by multiplying the frequency of consumption of each food or beverage by the nutrient content of the specified portion, derived from the U.S. Department of Agriculture food composition database supplemented with information from manufacturers, and summing the contributions from

all items. Total magnesium intake included intake from foods and supplements. Supplemental intake was derived from questions on multivitamin/mineral and magnesium-specific preparations. GI values for individual food items on the FFQ were derived from available databases and publications (17,18). Average dietary GI was calculated by summing the product of the carbohydrate content per serving for each food item, multiplying it by the average number of reported daily servings of that food, and dividing it by the total daily carbohydrate content (19). Because the amount of carbohydrates in a diet varies, we derived a global dietary GL score by multiplying the amount of carbohydrates in the diet by the average GI. All foods and nutrients were energy adjusted using the residual method (20). The validity and reliability of the FFQs have been previously described (21–24). Previous validation studies in subsets of participants have shown that FFQ-derived estimates of energy-adjusted intakes of magnesium, fiber, and total carbohydrate are moderately to strongly correlated with diet record–derived reports (magnesium,  $r = 0.61$ – $0.73$ ; fiber,  $r = 0.63$ – $0.68$ ; total carbohydrate,  $r = 0.65$ – $0.73$ ) (22,24).

### Type 2 Diabetes Ascertainment

Incident type 2 diabetes was the primary end point of the current study. Participants who reported a diagnosis of type 2 diabetes on a biennial questionnaire were mailed a supplementary questionnaire regarding symptoms, diagnostic tests, and treatment. Using the criteria of the National Diabetes Data Group (25), a type 2 diabetes case was confirmed if at least one of the following was reported on the supplementary questionnaire: 1) one or more classic symptoms (i.e., excessive thirst, polyuria, weight loss, or hunger) and fasting plasma glucose concentrations  $\geq 7.8$  mmol/L or random plasma glucose  $\geq 11.1$  mmol/L, 2) elevated plasma glucose concentrations on two or more different occasions (fasting concentration  $\geq 7.8$  mmol/L, random concentration  $\geq 11.1$  mmol/L, and/or concentration  $\geq 11.1$  mmol/L after  $\geq 2$  h in an oral glucose tolerance test) in the absence of symptoms, or 3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). For cases identified after 1998, the criteria of the American Diabetes Association were applied, in which the

threshold for diagnosis of diabetes cases was lowered from a fasting plasma glucose concentration of 7.8 to 7.0 mmol/L (26). The present analysis includes only cases confirmed by the supplementary questionnaire, a method validated in two previous studies in which >97% of cases were confirmed by medical record review (27,28).

### Covariate Assessment

Using biennial follow-up questionnaires, participants provided updated information on their age, weight, smoking status, physical activity, menopausal status and use of postmenopausal hormone therapy (women), oral contraceptive use (women), and personal history of chronic diseases. Height was ascertained on the enrollment questionnaire. We calculated BMI as weight in kilograms divided by height in meters squared. Family history of diabetes in first-degree relatives was assessed in 1982 and 1988 in NHS; in 1989, 1997, 2001, and 2005 in NHS2; and in 1987 in HPFS.

### Statistical Analyses

Age-standardized baseline characteristics are presented by cohort as means (SE) or as percentages. In prospective analyses, intakes were cumulatively averaged from baseline to censoring events; updating of dietary information was stopped upon diagnosis of an outcome such as cancer or cardiovascular disease, because potential changes in diet after development of these conditions may confound the relationship between magnesium intake and diabetes. (Among the sensitivity analyses further described below, we also assessed cumulatively averaged dietary data irrespective of intermediate diagnoses.) Magnesium intake was divided into quintile categories based on the cumulative average; the median within each category was used to assess linear trends across intake categories.

Participant person-time was calculated from the return of the baseline questionnaire to the date of diagnosis of type 2 diabetes, death, date of loss to follow-up, or the cutoff date (30 June 2012 in NHS, 30 June 2013 in NHS2, and 31 December 2012 in HPFS), whichever occurred first. Cox proportional hazards regression models were used to estimate age- and multivariable-adjusted associations between magnesium intake and risk of type 2 diabetes. Models were adjusted for updated age (years) as the timescale, stratified by

calendar time in 2-year intervals, and total energy intake (kcal/day) (model 1). Model 2 was adjusted as for model 1, plus updated clinical and lifestyle risk factors, including BMI (eight categories: <22.0, 22.0 to <23.0, 23.0 to <25.0, 25.0 to <28.0, 28.0 to <30.0, 30.0 to <33.0, 33.0 to <36.0, and  $\geq 36.0$  kg/m<sup>2</sup>), family history of diabetes (yes/no), physical activity (<3, 3 to <9, 9 to <18, 18 to <27, and  $\geq 27$  metabolic-equivalent task hours [METs]/week), smoking status (never, past, and current smoking of 1–14, 15–24, and  $\geq 25$  cigarettes per day), alcohol consumption (0, 0.1–4.9, 5–14.9, and  $\geq 15$  g/day), hypertension (yes/no), and hypercholesterolemia (yes/no). Model 3 was further adjusted for dietary factors, including GL, intakes of cereal fiber, polyunsaturated fats, trans fatty acids, and processed meat, all in quintile categories. Additional adjustment of model 3 for updated oral contraceptive use and/or menopausal status in women did not substantively alter estimates and are therefore not presented.

We tested statistical interactions between magnesium and GI, GL, and cereal fiber intakes using continuous cross-product terms in models adjusted as for model 2 above, plus polyunsaturated fats, trans fatty acids, and processed meat. *P* for interaction was calculated using the  $-2$  log-likelihood test. To depict the joint associations of magnesium and cereal fiber, GI, and/or GL, we stratified by tertile categories of intake exposures and repeated analyses described above.

We conducted several sensitivity analyses. Although we had no a priori hypothesis regarding differential physiological use of dietary versus supplemental magnesium intake, we repeated analyses using dietary magnesium instead of total magnesium. We also examined the relationship between total magnesium intake and incident type 2 diabetes in those obtaining >0 mg/day magnesium intake from supplements (i.e., in supplement users) to assess whether estimates were different in supplement users. We additionally repeated analyses using a “simple update” approach, wherein the most recently reported diet is assessed against incident disease by the end of the subsequent interval (e.g., whether intake reported in 1988 was associated with type 2 diabetes status in 1992); a 4-year lag approach, wherein diet is cumulatively averaged, but time to an event begins 4 years

later (e.g., whether intake up to and including that reported in 1988 is associated with risk beginning in 1992); and, as mentioned above, cumulatively averaged dietary intake irrespective of intermediate diagnoses of cancer or cardiovascular disease. Finally, we tested the associations across prespecified strata of age (<60 vs.  $\geq 60$  years), BMI (<30 vs.  $\geq 30$  kg/m<sup>2</sup>), physical activity (<median vs. >median), family history of diabetes (yes vs. no), overall diet quality (<median vs. >median Alternative Health Eating Index score) (29), whole grain intake (<median vs. >median), and multivitamin supplement use (yes vs. no).

Owing to differences between the cohorts, including sex, age, follow-up time, and questionnaire differences, all analyses were performed separately in each cohort to achieve better control of confounding. The risk estimates from each multivariable-adjusted model from the three cohorts were meta-analyzed using a fixed-effect inverse variance-weighted approach (30). All statistical tests were two sided with an  $\alpha = 0.05$ . Analyses were conducted using SAS (version 9.4; SAS Institute Inc., Cary, NC).

### RESULTS

Baseline characteristics of 69,176 NHS, 91,471 NHS2, and 42,096 HPFS participants indicate that, as compared with those with the lowest magnesium intake, those with the highest intake were slightly older, had a slightly lower BMI, had higher levels of physical activity, and were less likely to be current smokers or to have hypertension (Table 1). They also tended to report higher intake of cereal fiber, whole grains, and multivitamins/supplements and lower intake of saturated fat, trans fat, and processed meat. Average total magnesium intake between the lowest and highest quintile categories differed by  $\sim 200$  mg/day. Total magnesium intake across follow-up was primarily derived from whole grains and cold cereals (average of 13–14% of intake across follow-up), followed by vegetables, dairy, and fruit (Supplementary Table 1). Plots of trends across time of magnesium intake indicate that intake on average tended to increase in all three cohorts (Supplementary Fig. 1). Both total and dietary magnesium intake were weakly to moderately correlated with other foods/nutrients of interest (Supplementary Table 2).

**Table 1—Age-standardized baseline characteristics of the study populations, according to extreme quintile categories of cumulative energy-adjusted total magnesium intake**

Characteristic*	Women (NHS, 1984)		Women (NHS2, 1991)		Men (HPFS, 1986)	
	Q1 (n = 13,982) 187–218 mg/day	Q5 (n = 13,853) 357–418 mg/day	Q1 (n = 18,066) 213–245 mg/day	Q5 (n = 18,388) 385–448 mg/day	Q1 (n = 8,407) 242–275 mg/day	Q5 (n = 8,408) 427–498 mg/day
Age (years)	48.2 (7.1)	51.9 (6.9)	35.6 (4.8)	36.5 (4.6)	53.4 (9.6)	53.6 (9.3)
BMI (kg/m <sup>2</sup> )	25.2 (5.1)	24.4 (4.2)	25.1 (6.1)	24.1 (4.7)	25.1 (5.2)	24.5 (4.8)
Caucasian (%)	97.7	97.7	95.4	96.6	94.8	94.6
Physical activity (METs/week)	10.7 (17.2)	18.7 (26.2)	14.8 (21.6)	28.0 (34.5)	16.0 (23.6)	27.5 (35.8)
Family history of diabetes (%)	28.4	27.9	39.8	37.4	19.7	20.4
Smoker (%)	25.5	23.1	14.2	10.4	13.1	7.3
Premenopausal (%)	46.7	45.5	96.2	96.1	—	—
Hypertension (%)	20.4	16.8	7.1	5.7	20.4	19.1
Hypercholesterolemia (%)	6.2	7.8	15.4	14.4	8.7	12.7
Total energy (kcal/day)	1,704 (541)	1,712 (527)	1,749 (565)	1,765 (542)	1,955 (632)	1,974 (625)
Alcohol (g/day)	6.8 (12.4)	6.5 (10.5)	2.4 (5.5)	3.1 (5.7)	11.7 (16.9)	10.9 (14.7)
GL†	102 (21.7)	99.1 (20.4)	125 (24.6)	124 (21.7)	123 (27.1)	130 (28.3)
GI	55.8 (3.2)	51.1 (4.1)	56.3 (2.9)	52.2 (3.4)	55.1 (3.3)	51.7 (3.8)
Cereal fiber (g/day)	3.2 (1.3)	5.5 (3.3)	4.1 (1.5)	7.5 (4.8)	4.1 (1.8)	8.5 (6.3)
Carbohydrates (g/day)	184 (34.4)	193 (32.0)	221 (37.4)	237 (34.4)	224 (43.5)	252 (45.3)
Whole grains (g/day)	7.2 (6.7)	22.9 (17.8)	10.2 (7.6)	32.5 (21.1)	9.9 (9.0)	36.9 (26.9)
Magnesium, total (mg/day)	200 (22.4)	399 (70.7)	226 (24.4)	427 (63.1)	256 (24.9)	475 (73.5)
Magnesium, dietary (mg/day)	200 (22.6)	367 (72.7)	226 (24.8)	373 (61.8)	255 (25.1)	435 (74.5)
PUFA (g/day)	12.0 (3.2)	11.5 (3.3)	11.5 (3.0)	10.8 (2.7)	13.1 (3.4)	13.2 (4.1)
SFA (g/day)	23.5 (4.7)	20.1 (4.5)	24.4 (5.1)	19.8 (4.6)	27.6 (5.9)	20.8 (5.9)
Trans fat (g/day)	3.9 (1.1)	2.7 (1.0)	4.0 (1.4)	2.6 (1.0)	3.5 (1.2)	2.1 (0.9)
Processed meat (servings/day)‡	0.19 (0.23)	0.10 (0.14)	0.16 (0.24)	0.07 (0.13)	0.24 (0.33)	0.10 (0.17)
Multivitamin/supplement use (%)	25.3	57.7	26.6	70.9	24.0	48.5

PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid. \*All characteristics, except for age, are age standardized and presented as mean (SD) or % . †GL is the sum of (the GI for an individual food [white bread as reference = 1] × the carbohydrate content of the food item) for each food. ‡Processed meats include sausages, salami, and bologna.

## Magnesium Intake and Risk of Type 2 Diabetes

Across up to 28 years of follow-up, we ascertained 17,130 incident cases of type 2 diabetes (7,620 in NHS, 6,080 in NHS2, and 3,430 in HPFS). In proportional hazards models adjusted for age and energy intake (model 1), total magnesium intake was strongly inversely associated with incident type 2 diabetes in a dose-response fashion in each cohort, with a 41% (NHS), 45% (NHS2), and 41% (HPFS) lower risk in the highest versus the lowest (reference) category of intake (all  $P$  trend <0.0001) (Table 2). These estimates were attenuated but remained significant after adjusting for BMI and other clinical and lifestyle risk factors (model 2) and dietary components (model 3). Pooling estimates of the fully adjusted model (model 3) from the three cohorts resulted in an overall 15% lower risk of incident type 2 diabetes (pooled hazard ratio [HR] for quintile 5 [Q5] vs. Q1: 0.85 [95% CI 0.80–0.91],  $P$  trend <0.0001) in

those with the highest total magnesium intake, compared with those with the lowest intake. Linear analyses supported this association, with each 50 mg/day of magnesium intake being associated with 4% lower risk of developing diabetes (pooled HR 0.96 [95% CI 0.95–0.98]).

Results of sensitivity analyses indicated consistent associations for dietary magnesium alone (pooled HR 0.83 [95% CI 0.77–0.89],  $P$  trend <0.0001) (Supplementary Table 3), in supplement users (pooled HR 0.86 [95% CI 0.81–0.91],  $P$  trend <0.0001) (Supplementary Table 4), when modeling intake in a simple update approach (pooled HR for total magnesium 0.90 [95% CI 0.85–0.95],  $P$  trend <0.0001), in a 4-year lag approach (pooled HR for total magnesium 0.90 [95% CI 0.84–0.95],  $P$  trend <0.01), and when modeling intake as the cumulative average irrespective of intermediate diagnoses such as cancer or cardiovascular disease (pooled HR for total magnesium 0.85 [95% CI 0.80–0.90],  $P$  trend <0.0001).

Analyses stratified by BMI, physical activity, family history of diabetes, overall diet quality (given by Alternative Health Eating Index score), and multivitamin supplement use suggested consistent associations across subgroups (all pooled  $P$  interaction >0.05). Although interactions suggested different associations by strata of age and whole grain intake, strata-specific pooled risk estimates did not indicate substantive differences (Supplementary Table 5).

## Joint Analyses of Magnesium Intake, Cereal Fiber Intake, GI, and Risk of Type 2 Diabetes

Joint analyses were initiated with testing of statistical interactions in line with hypotheses regarding the role of magnesium in the context of cereal fiber, GI, and GL. Interactions between magnesium and cereal fiber, and magnesium and GI, were statistically significant (both  $P$  interaction <0.0001) but were not significant between magnesium and GL ( $P$  interaction = 0.71). Joint analyses were thus

**Table 2—Risk of incident type 2 diabetes by quintile category of cumulative average total magnesium intake (mg/day) in three cohorts and pooled**

		HR (95%CI) per quintile category of cumulative average total magnesium intake (mg/day)*					P trend	HR (95% CI) per 50 mg/day
		Q1	Q2	Q3	Q4	Q5		
NHS	Median (mg/day)	229.0	269.5	298.5	332.0	390.0		
	Person-years	328,567	328,829	329,552	329,430	329,913		
	Cases	1,868	1,653	1,567	1,340	1,192		
	Model 1	1 (reference)	0.86 (0.80–0.92)	0.80 (0.75–0.86)	0.67 (0.63–0.72)	0.59 (0.55–0.64)	<0.0001	0.87 (0.85–0.88)
	Model 2	1 (reference)	0.91 (0.85–0.97)	0.88 (0.82–0.94)	0.77 (0.72–0.83)	0.70 (0.66–0.76)	<0.0001	0.91 (0.89–0.93)
	Model 3	1 (reference)	0.95 (0.88–1.01)	0.94 (0.87–1.01)	0.84 (0.78–0.91)	0.80 (0.73–0.88)	<0.0001	0.94 (0.92–0.97)
	NHS2	Median (mg/day)	248.7	291.5	323.5	360.0	424.7	
		Person-years	367,686	369,680	368,527	370,156	370,473	
		Cases	1,635	1,227	1,163	1,043	1,012	
		Model 1	1 (reference)	0.72 (0.67–0.78)	0.67 (0.62–0.72)	0.58 (0.54–0.63)	0.55 (0.51–0.60)	<0.0001
Model 2		1 (reference)	0.86 (0.80–0.93)	0.88 (0.82–0.94)	0.83 (0.77–0.90)	0.84 (0.77–0.91)	<0.0001	0.96 (0.95–0.98)
Model 3		1 (reference)	0.89 (0.82–0.96)	0.92 (0.85–1.00)	0.88 (0.81–0.97)	0.89 (0.81–0.99)	0.04	0.98 (0.96–1.00)
HPPS		Median (mg/day)	279.5	325.5	360.5	400.0	469.6	
		Person-years	170,136	170,180	171,130	170,069	170,776	
		Cases	832	777	692	602	527	
		Model 1	1 (reference)	0.90 (0.82–1.00)	0.82 (0.74–0.91)	0.68 (0.61–0.75)	0.59 (0.53–0.66)	<0.0001
	Model 2	1 (reference)	0.96 (0.86–1.06)	0.90 (0.81–1.00)	0.77 (0.69–0.85)	0.74 (0.66–0.82)	<0.0001	0.93 (0.91–0.95)
	Model 3	1 (reference)	0.99 (0.90–1.11)	0.97 (0.87–1.09)	0.87 (0.77–0.98)	0.88 (0.77–1.00)	0.02	0.97 (0.94–1.00)
	Model 1	1 (reference)	0.82 (0.78–0.86)	0.76 (0.72–0.79)	0.64 (0.61–0.67)	0.58 (0.55–0.61)	<0.0001	0.87 (0.86–0.88)
	Model 2	1 (reference)	0.90 (0.86–0.94)	0.88 (0.84–0.92)	0.79 (0.76–0.83)	0.76 (0.72–0.80)	<0.0001	0.94 (0.92–0.95)
	Model 3†	1 (reference)	0.94 (0.90–0.98)	0.94 (0.89–0.99)	0.86 (0.82–0.91)	0.85 (0.80–0.91)	<0.0001	0.96 (0.95–0.98)

\*Models were adjusted as follows. Model 1 was adjusted for updated age and energy intake. Model 2 was adjusted as for model 1, plus updated covariates, including BMI (eight categories: <22.0, 22.0 to <23.0, 23.0 to <25.0, 25.0 to <28.0, 28.0 to <30.0, 30.0 to <33.0, 33.0 to <36.0, and ≥36.0 kg/m<sup>2</sup>), family history of diabetes (yes/no), physical activity (<3, 3 to <9, 9 to <18, 18 to <27, and ≥27 METs/week), smoking status (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/day), alcohol consumption (0, 0.1–4.9, 5–14.9, and ≥15 g/day), hypertension (yes/no), and hypercholesterolemia (yes/no). Model 3 was further adjusted for GL<sub>1</sub> intakes of cereal fiber, polyunsaturated fats, trans fatty acids, and processed meat, all in quintiles. †Heterogeneity statistics, categorical: Cochran Q = 2.68, P value = 0.26, I<sup>2</sup> = 25%; continuous: Cochran Q = 3.00, P value = 0.22, I<sup>2</sup> = 33%.

conducted for magnesium with cereal fiber and GI. In models with exposures stratified into tertiles of low, medium, and high intake, higher magnesium intake was inversely associated with diabetes risk, with modestly stronger inverse associations observed in the context of lower carbohydrate quality (Figs. 1 and 2 and Supplementary Table 6). For example, in those with low cereal fiber intake, risk of diabetes in those with high magnesium intake compared with low intake was 0.84 (95% CI 0.79–0.91), representing a difference in relative risk of 16%. In those with high cereal fiber intake, risk of diabetes in those with low magnesium intake was 0.82 (95% CI 0.76–0.90), whereas risk in those with high magnesium intake was 0.71 (95% CI 0.67–0.75), representing a difference in relative risk of 11%.

## CONCLUSIONS

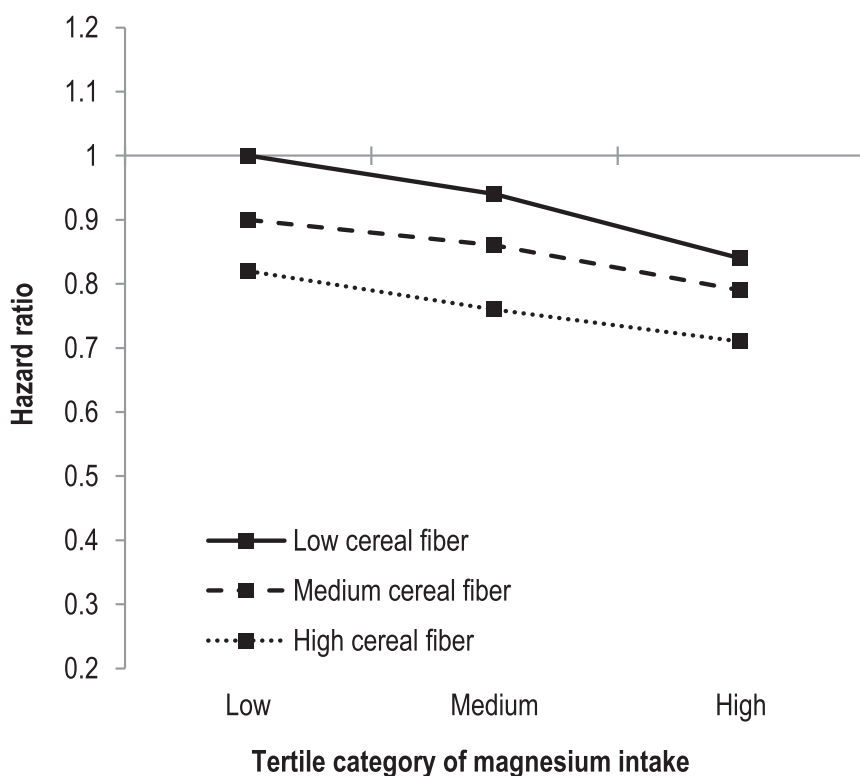
In the present analysis investigating magnesium intake and the risk of incident type 2 diabetes in three large U.S. cohorts across up to 28 years of follow-up, we observed that high magnesium intake was associated with 15% lower risk of

type 2 diabetes, as compared with those with low intake. The magnesium–diabetes relationship was modestly modified by the GI of the diet, as well as cereal fiber intake, wherein magnesium’s inverse associations with type 2 diabetes appeared stronger in the context of a low carbohydrate–quality diet, as characterized by low cereal fiber intake or high GI, than in the context of a high carbohydrate–quality diet, as characterized by high cereal fiber intake or low GI. Although higher magnesium intake was inversely related to risk irrespective of the carbohydrate quality of the diet, the strongest inverse association was observed in those reporting both the highest magnesium intake and the highest carbohydrate quality of the underlying diet.

Our results are consistent with a large body of observational literature on the beneficial role of magnesium on risk of type 2 diabetes (5,6,8,9). A recent meta-analysis of 25 prospective cohort studies indicated a linear dose–response relationship between magnesium intake and type 2 diabetes, such that risk was 8–13% lower per 100 mg/day increment in intake (9). Results from clinical trials of

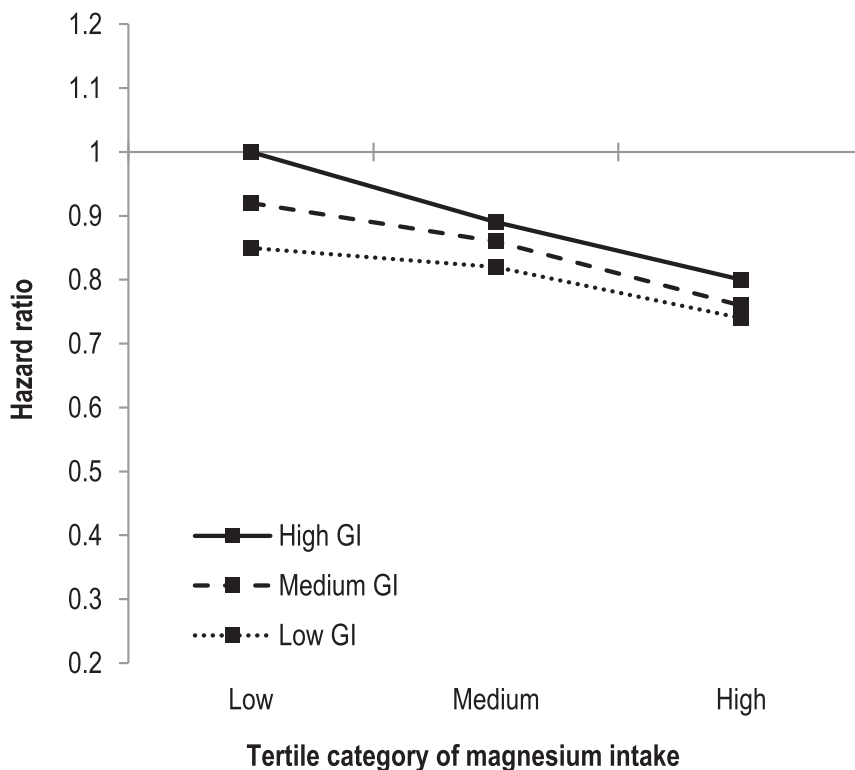
magnesium supplementation generally indicate beneficial effects of supplementation on markers of glucose and insulin in individuals with and without type 2 diabetes (4,31–33). A meta-analysis of nine supplementation trials in those with type 2 diabetes indicated that a median dose of 360 mg/day of magnesium significantly reduced fasting glucose levels by 0.56 mmol/L (95% CI –1.10 to –0.01) (32). A more recent meta-analysis of magnesium supplementation, not restricted to trials in those with prevalent disease, found reductions in insulin resistance and fasting glucose when trials were  $\geq 4$  months duration but did not find changes in HbA<sub>1c</sub> or insulin (4). However, meta-regression of these data indicated that insulin tended to decrease over longer trial durations, and further, of the 12 trials with HbA<sub>1c</sub> data, only 3 lasted at least 4 months (the rest were  $< 4$  months); thus, the authors noted that the trial durations may not be adequate to observe changes in HbA<sub>1c</sub> with supplementation durations of  $\leq 4$  months (4). Overall, data from both clinical and observational studies point to a role for magnesium intake in the prevention of type 2 diabetes.

It is interesting to note that some 40–50% of participants in the current study (i.e., those in the lowest two to three quartile categories) would be regarded as having inadequate intake based on the recommended dietary allowance of 320 mg/day for women and 420 mg/day for men (34). This estimate is consistent with estimates of intake in the U.S. population (1). The largest contributor of magnesium intake in the study population was whole grains and cold cereals, accounting for 12–14% of total intake, on average. Current U.S. dietary guidelines emphasize whole grains in lieu of refined grains as part of a healthy dietary pattern (35). Magnesium intake was also contributed by a number of other sources, including vegetables and leafy greens, fruits, and dairy, and even coffee intake contributed between 4 and 6% of total intake. Relatedly, there was lower risk with higher magnesium even in the presence of high cereal fiber, suggesting that magnesium from a variety of sources contributed to the lower risk we observed. Further, these data point to carbohydrate quality as just one aspect of a healthy diet and to the benefits of a varied diet in obtaining adequate intake for a ubiquitous nutrient such as magnesium. These points become



**Figure 1**—Joint associations of pooled HRs of magnesium and cereal fiber on risk of type 2 diabetes (pooled *P* interaction  $< 0.0001$ ). Tertile-specific point estimates are given for low, medium, and high magnesium intake, in tertile categories of low (solid line), medium (dashed line), and high (dotted line) cereal fiber intake. See Supplementary Table 6 for cohort-specific and pooled estimates.





**Figure 2**—Joint associations of pooled HRs of magnesium and GI on risk of type 2 diabetes (pooled *P* interaction <0.0001). Tertile-specific point estimates are given for low, medium, and high magnesium intake, in tertile categories of high (solid line), medium (dashed line), and low (dotted line) dietary GI. See Supplementary Table 6 for cohort-specific and pooled estimates.

more important in the context of popular dietary trends that severely restrict macronutrients, such as carbohydrates in low-carbohydrate diets, or exclude entire food groups, such as grains or dairy, which are important sources of shortfall nutrients like magnesium. Supplemental magnesium may be helpful, but it is not a panacea.

In the NHS and HPFS cohorts, we previously observed joint effects of dietary GI, GL, and cereal fiber; participants who habitually consumed diets with high GI or GL and low cereal fiber had nearly 50% higher risk for diabetes compared with those whose diets were high in cereal fiber and low in GI or GL (10). In the context of observational studies, habitual diet characterized by GI may be thought of as reflecting a given dietary pattern's carbohydrate quality, whereas GL reflects both quality and quantity of carbohydrates (36), which may be particularly relevant in populations where refined carbohydrates and sugars are dominant carbohydrate sources. Indeed, this may underlie observational reports that low-GI diets are associated with lower risk of diabetes-related risk factors (36–38) and risk of diabetes itself (10).

Because long-term consumption of a high-GI diet may increase demand on  $\beta$ -cells and potentially lead to  $\beta$ -cell exhaustion and failure, as well as increase circulating glucose and free fatty acids (17,39), there is strong biological plausibility for a role of magnesium in mitigating the effects of such a dietary pattern. Supporting the evidence from clinical trials and observational studies are *in vitro* and *in vivo* studies indicating that magnesium is integral to insulin secretion and sensitivity (13,14). For example, magnesium is essential for the autophosphorylation of the  $\beta$ -subunits of the insulin receptor, increasing the receptor's affinity for ATP, helping to drive insulin into cells (14). In addition, magnesium was shown to increase GLUT1 and GLUT4 expression in muscle in rodent diabetes models. Furthermore, insulin itself is a regulator of magnesium homeostasis, for example influencing renal reabsorption via stimulation of renal magnesium channels (14). Overall, the evidence points to low magnesium being not only a cause but a consequence of diabetes (14).

The present analysis benefited from three large, longitudinal cohorts, very

long follow-up, and repeated measures of intake. Although FFQs do not provide a precise picture of absolute intake, they rank individuals in terms of relative intake. The relative differences between high and low consumers in the current study were sufficient to reveal differential levels of risk between the groups and a plausible dose-response relationship. As in any observational study, ours is limited by the possibility of residual confounding or unaccounted-for confounding, the presence of which would affect the accuracy of our estimates. Although our study population was relatively homogeneous (predominantly Caucasian health professionals), limiting the generalizability of our findings, the roles of GI, cereal fiber, and magnesium in type 2 diabetes have been shown to be generally consistent across different race/ethnic groups and continents (9,10). We would therefore expect that our observations would hold across populations with similar dietary patterns and sources of magnesium.

In conclusion, magnesium intake was inversely associated with risk of type 2 diabetes, with modestly stronger inverse associations observed in the presence of lower carbohydrate-quality diets.

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**Author Contributions.** A.H. developed the hypotheses, interpreted the data, and drafted, reviewed, and edited the manuscript. M.G.-F. conducted the analyses, interpreted the data, and contributed to, reviewed, and edited the manuscript. S.N.B., J.E.M., W.C.W., and N.M.M. contributed to, reviewed, and edited the manuscript. F.B.H. developed the hypotheses and contributed to, reviewed, and edited the manuscript. A.H. and M.G.-F. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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