

# Magnesium Intake and Risk of Type 2 Diabetes in Men and Women

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**OBJECTIVE** — To examine the association between magnesium intake and risk of type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — We followed 85,060 women and 42,872 men who had no history of diabetes, cardiovascular disease, or cancer at baseline. Magnesium intake was evaluated using a validated food frequency questionnaire every 2–4 years. After 18 years of follow-up in women and 12 years in men, we documented 4,085 and 1,333 incident cases of type 2 diabetes, respectively.

**RESULTS** — After adjusting for age, BMI, physical activity, family history of diabetes, smoking, alcohol consumption, and history of hypertension and hypercholesterolemia at baseline, the relative risk (RR) of type 2 diabetes was 0.66 (95% CI 0.60–0.73; *P* for trend <0.001) in women and 0.67 (0.56–0.80; *P* for trend <0.001) in men, comparing the highest with the lowest quintile of total magnesium intake. The RRs remained significant after additional adjustment for dietary variables, including glycemic load, polyunsaturated fat, *trans* fat, cereal fiber, and processed meat in the multivariate models. The inverse association persisted in subgroup analyses according to BMI, physical activity, and family history of diabetes.

**CONCLUSIONS** — Our findings suggest a significant inverse association between magnesium intake and diabetes risk. This study supports the dietary recommendation to increase consumption of major food sources of magnesium, such as whole grains, nuts, and green leafy vegetables.

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**T**ype 2 diabetes is on track to become one of the major global public health challenges of the 21st century (1). Primary prevention remains the major strategy to control this worldwide epidemic.

Modification of western diet and lifestyles is effective in preventing diabetes in high-risk populations (2). The western diet is characterized by high intake of sat-

urated and *trans* fats and refined grains and low intakes of whole grains, vegetables, and fiber, resulting in low micronutrient intake (3). Few studies have addressed the association between specific micronutrient components of western diets and diabetes risk.

Magnesium is an important component of many unprocessed foods, such as

whole grains, nuts, and green leafy vegetables, and it is largely lost during the processing of some foods (4). The over-processing of food and adoption of western diets have contributed to the substantially reduced magnesium intake in industrialized countries during the last century.

Hypomagnesemia is a common feature in patients with type 2 diabetes (5). Although diabetes can induce hypomagnesemia, magnesium deficiency has also been proposed as a risk factor for type 2 diabetes (6). Magnesium is a necessary cofactor for several enzymes that play an important role in glucose metabolism (7). Animal studies (8,9) have shown that magnesium deficiency has a negative effect on the post-receptor signaling of insulin. Some short-term metabolic studies (10,11) suggest that magnesium supplementation has a beneficial effect on insulin action and glucose metabolism.

In our previous analyses of dietary factors and diabetes based on limited follow-up (12–14), we found an inverse association between magnesium intake and risk of type 2 diabetes. However, these analyses did not fully control for other confounding factors and were limited in power to evaluate the association in subgroups. Two other prospective studies (15,16) have specifically evaluated this association, with contradictory results. The purpose of this analysis, with longer follow-up and more incident cases, was to prospectively evaluate the association between magnesium intake and risk of type 2 diabetes in two large cohorts of women and men.

## RESEARCH DESIGN AND METHODS

The characteristics of the Nurses' Health Study (NHS) and the Health Professionals' Follow-up Study (HPFS) have been described elsewhere (17,18). Briefly, the NHS was initiated in 1976, when 121,700 female registered nurses, aged 30–55 years, completed a mailed questionnaire on their medical history and lifestyle characteristics. Every 2 years, follow-up questionnaires have been sent to update information on potential risk factors and identify newly di-

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**Abbreviations:** ADA, American Diabetes Association; FFQ, food frequency questionnaire; HPFS, Health Professionals' Follow-up Study; NDDG, National Diabetes Data Group; NHS, Nurses' Health Study; MET, metabolic equivalent.

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

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agnosed cases of diabetes and other chronic diseases. The HPFS began in 1986 when 51,529 U.S. health professionals, aged 40–75 years, answered a detailed questionnaire on lifestyle and medical history. Similar to the NHS, this cohort has been followed through biennial questionnaires. In both cohorts, the response rate to the follow-up questionnaires has exceeded 90%.

Diet was first evaluated in 1980 in the NHS and in 1986 in the HPFS. Repeated dietary assessments have been carried out every 2–4 years. From participants who returned the baseline dietary questionnaire, we excluded those who had >10 blanks in food items or did not satisfy our a priori criteria of plausible daily caloric intake. For this analysis, we also excluded participants who at baseline reported history of diabetes, cardiovascular disease, or cancer. These exclusions left 85,060 women followed over 18 years (1980–1998) and 42,872 men followed over 12 years (1986–1998) for the present analysis.

### Magnesium intake

In the NHS, a 61-item semiquantitative food frequency questionnaire (FFQ) was used to collect dietary information in 1980. In 1984, the questionnaire was expanded to 131 items. Similar FFQs were used to update diet in subsequent follow-up in the NHS (1986, 1990, 1994, and 1998) and the HPFS (1986, 1990, 1994, and 1998). In the FFQ, a common unit or portion size for each food was specified and participants were asked how often they had consumed that amount on average during the previous year. The nine responses ranged from “never or less than once per month” to “six or more times per day.” Nutrient intake was computed by multiplying the frequency of consumption of each food by the nutrient content of the specified portions. Composition values for dietary magnesium and other nutrients were obtained from the Harvard University Food Composition Database (22 November 1993), derived from U.S. Department of Agriculture sources (19), and supplemented with manufacturer information. A detailed description of dietary questionnaires and their validity in these cohorts have been published elsewhere (20,21). Correlation coefficients between FFQ and dietary record for magnesium intake were 0.76 in women and 0.66 in men after

within-person variation was taken into account.

Use of specific brand and type of multivitamins was ascertained at baseline and updated every 2 years, asking current users about weekly number of multivitamins taken. This information was included in total magnesium intake computation. Questions on separate magnesium supplements were first asked in 1984 in the NHS and in 1986 in the HPFS, with information updated at least every 4 years. Although we did not have information on the exact magnesium content of these supplements, 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. In a separate analysis, we examined the association between magnesium supplement use and diabetes risk.

### Measurement of nondietary factors

In both cohorts, body weight was self-reported on baseline questionnaires and updated every 2 years. In validation studies, self-reported weights were highly correlated with measured weights (22). In the NHS, to be consistent with the baseline evaluation, we used the cumulative average of hours per week spent in moderate to vigorous activity. In the HPFS, we had detailed information on the hours per week spent in leisure-time physical activities since baseline and through follow-up. We calculated total weekly energy expenditure from physical activity expressed as metabolic equivalents (METs). The validity and reproducibility of the physical activity questionnaires have been previously documented in these cohorts (23,24). Every 2 years, we updated participants' smoking status (past, current, and number of cigarettes per day if smoking currently). Family history of diabetes (in first-degree relatives) was assessed on multiple occasions in both cohorts. We inquired about physician-diagnosed hypertension and high cholesterol every 2 years; these self-reports were highly accurate compared with medical records in a validation study (25).

### Ascertainment of diabetes

On each biennial questionnaire, we asked the participants if and when they had ever been diagnosed with diabetes. To confirm self-reported diagnoses, we mailed a sup-

plementary questionnaire regarding symptoms, diagnostic tests, and therapy. After excluding participants with type 1 and secondary diabetes, the diagnosis of type 2 diabetes was established when at least one of the following criteria was reported in the supplementary questionnaire: 1) at least one classic symptom of type 2 diabetes and elevated plasma glucose ( $\geq 140$  mg/dl [7.8 mmol/l] fasting or  $\geq 200$  mg/dl [11.1 mmol/l] random measure), 2) elevated plasma glucose concentrations on at least two different occasions in the absence of symptoms, or 3) treatment with hypoglycemic therapy (insulin or oral hypoglycemic agents). These criteria accord with those proposed by the National Diabetes Data Group (NDDG). The new guidelines from the American Diabetes Association (ADA) for diagnosing diabetes (fasting plasma glucose  $\geq 126$  mg/dl [7.0 mmol/l]) were announced in June 1997 (26) and have been incorporated into the confirmation and documentation of diabetes in subsequent follow-up in both cohorts.

The validity of the method for confirming type 2 diabetes by supplementary questionnaire using the NDDG criteria has been previously documented in these cohorts (27,28). To document the reliability of reports of diabetes in the most recent cycle (1996–1998), an additional validation study was carried out only in the NHS. In this study, we reviewed medical records in two separate groups: women who satisfied NDDG criteria by the supplementary questionnaire and women who satisfied only ADA criteria (fasting plasma glucose between 126 and 139 mg/dl). Medical record review confirmed the diagnosis of diabetes by NDDG criteria in 94 of 95 (98.9%) subjects for the former group. The number of women reporting that they met ADA but not NDDG criteria was small (<5% of cases in this cycle); medical record review confirmed the diagnosis of diabetes by ADA criteria in all but one person, thus confirming its validity using the new criteria.

### Statistical analysis

Person-time of follow-up for each participant was computed from the date of return of the baseline questionnaire (1980 for women and 1986 for men) to either the date of diabetes diagnosis, death, or the end of follow-up (January 1998 for HPFS or July 1998 for NHS), whichever occurred first.

Table 1—Age-adjusted dietary intakes and other potential risk factors for type 2 diabetes in men and women according to quintiles of magnesium intake at baseline (NHS: 1980; HPFS: 1986)

Quintile of magnesium intake	Women (NHS) (n = 8,502)*			Men (HPFS) (n = 42,872)*		
	1 (low)	3	5 (high)	1 (low)	3	5 (high)
Median intake (mg/day) (min-max)	217 (79–244)	290 (276–304)	377 (342–1,110)	268 (102–294)	348 (332–366)	458 (415–1,593)
Age (years)	44.9	46.3	47.2	52.0	53.4	54.4
BMI (kg/m <sup>2</sup> )†	24.7	24.1	24.0	25.7	25.6	25.0
Family history of diabetes (%)	18.9	18.2	18.8	17.3	17.2	17.4
Hypertension (%)	17.1	14.6	14.3	20.4	18.9	19.1
Hypercholesterolemia (%)	4.5	4.7	5.9	8.8	9.9	12.8
Current smoker (%)	27.0	28.8	31.0	13.2	9.3	7.3
Physical activity‡	3.5	3.9	4.4	16.3	21.8	27.7
Alcohol consumption (g/day)	5.9	6.7	6.9	11.7	11.7	10.7
Multivitamin use (%)	29.2	34.3	38.5	28.9	39.6	64.9
Magnesium supplement use (%)	2.1	3.2	4.5	0.3	2.5	13.8
Diet (adjusted for energy)						
Total calories (kcal/day)	1,541	1,594	1,540	1,962	2,021	1,974
Cholesterol (mg/day)	334	335	337	327	304	271
Total fat (% energy)	41.8	39.3	34.9	34.6	32.2	28.6
Saturated fat (% energy)	16.8	15.8	13.9	12.3	11.1	9.3
Polyunsaturated fat (% energy)	5.4	5.2	5.1	5.9	6.0	5.9
Trans fat (% energy)	2.5	2.3	1.9	1.5	1.3	0.9
Total fiber (g/day)	10.9	13.4	17.2	16.0	20.7	27.6
Cereal fiber (g/day)	2.1	2.5	2.8	4.2	5.7	8.7
Protein (% energy)	17.6	18.9	21.1	17.2	18.7	19.6
Glycemic load§	127	120	120	175	175	178
Coffee (cups/day)	1.0	2.4	3.3	1.1	1.5	1.4
Processed meat (serving/day)	0.20	0.17	0.11	0.24	0.18	0.10

Data are means, unless otherwise specified. \*Number of subjects at baseline; †BMI is calculated as weight in kilograms divided by the square of the height in meters; ‡physical activity as moderate/vigorous exercise in hours per week in women (NHS) and METs per week in men (HPFS); §glycemic load: sum of (glycemic index for individual food [white bread as reference = 1] × carbohydrate content of the food item) for each food; ||processed meats included sausages, salami, and bologna.

In the primary analysis, participants were divided into quintiles of total magnesium intake (including magnesium from multivitamins), and incidence rates were calculated as the number of events divided by total person-time in each quintile. The relative risks (RRs) were computed as the incidence rates of diabetes in each category of magnesium intake divided by the incidence rate in the lowest quintile of intake (reference group).

To reduce within-person variation and best represent the long-term effects of magnesium intake, we calculated the cumulative average intake of magnesium from all the dietary questionnaires available up to the start of each 2-year period (29). For example, for men, to model diabetes incidence in the 1988–1990 period, we used the 1986 magnesium intake and for the 1990–1992 period, we used the average of 1986 and 1990 intakes. We also conducted a secondary analysis using baseline magnesium intake only.

Cox proportional hazards models

stratified by age and time period were used in all multivariate analyses to estimate RRs. To control for multiple confounders, we adjusted for history of hypertension and hypercholesterolemia at baseline and biennially updated information on smoking status, BMI (in eight categories), level of physical activity, family history of diabetes (first-degree relatives), and alcohol intake (four categories). We also adjusted for several dietary variables (30), including glycemic load and intakes of cereal fiber, polyunsaturated fat, trans fat, and processed meat, all in quintiles. Finally, we performed stratified analyses according to levels of BMI, physical activity, and family history of diabetes.

All *P* values were two sided. Tests for trend were conducted using the median value for each quintile of magnesium intake analyzed as a continuous variable in the regression models. Likelihood ratio  $\chi^2$  was used to assess the significance of the interactions between magnesium intake and the variables used in the stratified

models. All analyses were done with SAS version 8.2 (SAS, Cary, NC).

**RESULTS**— At baseline, compared with those in the lowest quintile of magnesium intake, both women (in 1980) and men (in 1986) with higher intakes of magnesium tended to be leaner, more physically active, and more likely to take multivitamins and magnesium supplements (Table 1). Magnesium intake was positively associated with intakes of fiber and inversely associated with intakes of fat and processed meat. Averaged over the entire follow-up, the median intake (min-max) of magnesium was 290 mg/day (79–1,110 mg/day) in women and 349 mg/day (102–1,593 mg/day) in men.

During a follow-up of 18 years in the NHS (1,456,362 person-years) and 12 years in men (472,730 person-years), we documented 4,085 incident cases of type 2 diabetes in women and 1,333 in men. After adjusting for age and total energy intake (Table 2), we observed a significant

Table 2—RRs of type 2 diabetes in women and men according to quintiles of total magnesium intake

	Magnesium intake (quintiles)					P for trend
	1 (low)	2	3	4	5 (high)	
<b>NHS</b>						
Median magnesium intake (mg/day)	222	261	290	321	373	—
Number of cases	964	889	851	725	655	—
Person-years	291,818	290,406	290,060	292,336	291,177	—
Age- and energy intake-adjusted RR (95% CI)	1	0.81 (0.74–0.89)	0.74 (0.67–0.81)	0.60 (0.55–0.66)	0.55 (0.50–0.61)	<0.001
Age-, energy intake-, and BMI-adjusted RR (95% CI)	1	0.86 (0.79–0.95)	0.81 (0.74–0.90)	0.69 (0.63–0.76)	0.65 (0.59–0.72)	<0.001
Multivariate RR (95% CI)*	1	0.88 (0.80–0.96)	0.83 (0.76–0.91)	0.70 (0.64–0.78)	0.66 (0.60–0.73)	<0.001
Additional adjustment for dietary variables RR (95% CI)†	1	0.92 (0.84–1.01)	0.88 (0.80–0.98)	0.76 (0.69–0.85)	0.73 (0.65–0.82)	<0.001
<b>HPFS</b>						
Median magnesium intake (mg/day)	270	314	348.5	388	457	—
Number of cases	326	280	299	212	216	—
Person-years	93,702	94,991	93,768	95,344	94,925	—
Age- and energy intake-adjusted RR (95% CI)	1	0.80 (0.69–0.94)	0.84 (0.71–0.98)	0.56 (0.47–0.67)	0.56 (0.47–0.67)	<0.001
Age-, energy intake-, and BMI-adjusted RR (95% CI)	1	0.84 (0.72–0.99)	0.88 (0.76–1.04)	0.64 (0.54–0.76)	0.68 (0.57–0.81)	<0.001
Multivariate RR (95% CI)*	1	0.82 (0.70–0.97)	0.86 (0.73–1.01)	0.63 (0.53–0.75)	0.67 (0.56–0.80)	<0.001
Additional adjustment for dietary variables RR (95% CI)†	1	0.83 (0.70–0.98)	0.89 (0.75–1.05)	0.66 (0.55–0.80)	0.72 (0.58–0.89)	<0.001

\*Multivariate: energy (kcal/day), family history of diabetes (yes/no), BMI (8 categories): <22.0, 22.0–<23.0, 23.0–<25.0, 25.0–<28.0, 28.0–<30.0, 30.0–<33.0, 33.0–<36.0, and  $\geq 36.0$  kg/m<sup>2</sup>, physical activity (moderate/vigorous exercise [ $<1$ , 1, 2–3, 4–6,  $\geq 7$  h/week] in women and quintiles of METs per week in men, smoking status (never, past, and current smoking of 1–14, 15–24, and  $\geq 25$  cigarettes per day), alcohol consumption (four categories), hypertension (yes/no), and hypercholesterolemia (yes/no) at baseline; †dietary variables, including the same as above plus further adjustment for diet, including glycemic load and intakes of cereal fiber, polyunsaturated fats, *trans* fatty acid, and processed meat, all in quintiles.

inverse association between magnesium intake and risk of type 2 diabetes in both cohorts, with RRs (95% CIs) comparing the top versus bottom quintiles of 0.55 (0.50–0.61) and 0.56 (0.47–0.67) in women and men, respectively. After additional adjustment for BMI, the RRs were somewhat attenuated in both cohorts. However, the RRs were practically unchanged after further adjustment for other nondietary covariates. The RRs remained significant after the addition of dietary variables in the multivariate models. Further adjustment for caffeine slightly attenuated the association between magnesium intake and diabetes risk. The RRs (95% CIs) between extreme quintiles was 0.83 (0.73–0.95) in women and 0.76 (0.61–0.94) in men. Moreover, the adjustment for other minerals, such as calcium, potassium, and phosphorous, did not change the estimate of the association among women (RR comparing extreme quintiles 0.74 [0.63–0.88]), and the inverse association for magnesium

was stronger among men (0.62 [0.48–0.81]). Analyses with the single baseline diet assessment instead of updated cumulative average of repeated measurements yielded similar results: 0.79 (0.71–0.88) in women and 0.73 (0.60–0.90) in men. Excluding participants with a history of hypertension or hypercholesterolemia at baseline, using only symptomatic or non-symptomatic cases as an outcome, or modeling dietary rather than total magnesium intake did not materially change the results. Finally, the inclusion of diuretic use in the final model did not modify our results.

As shown in Table 3, the inverse association was persistent in subgroup analysis according to BMI, physical activity, and family history of diabetes. We did not identify any significant interactions between magnesium intake and these covariates. The inverse association was also similar between drinkers and nondrinkers and between participants with or without hypertension (data not shown).

Finally, we assessed the association between magnesium supplements and risk of type 2 diabetes. The proportion taking magnesium supplements in the entire follow-up period was 3.1% in women and 3.6% in men. There were relatively few cases in the supplement user group (111 in women and 52 in men). We found a significant inverse association in the age-adjusted model only in women (RR 0.82, 95% CI [0.68–0.99] in women and 1.01 [0.76–1.33] in men). However, in the multivariate models, we found no statistical association between use of magnesium supplements and diabetes risk in both women and men: 0.93 (0.77–1.12) and 1.07 (0.81–1.41), respectively. The use of multivitamins was not significantly associated with diabetes risk.

**CONCLUSIONS** — In these two large prospective studies, we observed a consistent inverse association between magnesium intake and risk of type 2 diabetes in men and women. This association was in-

Table 3—Multivariate RRs of type 2 diabetes according to quintiles of magnesium intake stratified by major risk factors\*

Variable	No cases‡	Quintiles of magnesium intake				P for trend
		2	3	4	5 (high)	
Women (NHS)						
BMI						
>27 kg/m <sup>2</sup>	3,147	0.90	0.81	0.74	0.71 (0.62–0.81)	<0.001
≤27 kg/m <sup>2</sup>	930	0.89	1.08	0.76	0.72 (0.56–0.92)	0.004
Physical activity†						
High	1,395	0.83	0.74	0.70	0.64 (0.52–0.78)	<0.001
Low	2,088	0.95	0.92	0.73	0.78 (0.66–0.92)	<0.001
Family history of diabetes						
Yes	1,813	0.92	0.95	0.79	0.77 (0.64–0.92)	0.001
No	2,272	0.91	0.83	0.74	0.69 (0.59–0.81)	<0.001
Men (HPFS)						
BMI						
>27 kg/m <sup>2</sup>	837	0.87	0.85	0.75	0.75 (0.57–0.98)	0.018
≤27 kg/m <sup>2</sup>	486	0.79	1.01	0.56	0.71 (0.50–0.99)	0.022
Physical activity†						
High	445	0.73	0.85	0.65	0.68 (0.47–0.99)	0.063
Low	710	0.89	0.86	0.62	0.71 (0.53–0.94)	0.002
Family history of diabetes						
Yes	472	0.73	0.67	0.68	0.62 (0.43–0.88)	0.013
No	856	0.89	1.04	0.64	0.78 (0.60–1.01)	0.012

\*The multivariate RRs are adjusting by all dietary and nondietary variables included in the most adjusted model in Table 2 (see footnote for the explanation of the adjustment). The variables used for stratification were not included in the model. The first quintile was used as the referent in all models; †used median values as cutoff points; ‡the number of cases do not match with Table 2 because of the presence of missing values removed in the stratified models.

dependent of other risk factors for type 2 diabetes, including several dietary factors. Moreover, the inverse association with magnesium intake was consistent across different subgroups defined by the main predictors of type 2 diabetes, such as BMI, physical activity, and family history of diabetes.

The prospective design reduces the possibility of recall and selection bias, and the high rate of follow-up reduces bias due to loss to follow-up. Another advantage is that diet was assessed multiple times during follow-up, which not only reduces measurement error (29), but also takes into account changes in eating behaviors.

Our study has several limitations. Given the size of these cohorts, screening for blood glucose was not feasible, thus some cases of diabetes may have been undiagnosed. However, our validation study showed that undiagnosed diabetes was rare in our cohort because the participants are health professionals (31). It is possible that participants with “unhealthy” diets are more likely to be screened for diabetes. However, the analysis using only symptomatic cases did not substantially change our results, arguing against

surveillance bias. On the other hand, the diagnostic criteria for type 2 diabetes were changed in 1997 such that lower plasma glucose levels would now be considered diagnostic. If these criteria were used since baseline, some noncases would have been reclassified as cases. However, this would bias the estimates toward the null.

The inverse association between magnesium intake and diabetes risk was observed in all multivariate models, including the main dietary and nondietary risk factors for diabetes. Moreover, the observed association was consistent within different subgroups, which further supports the idea that confounding by these factors was unlikely to explain our results. However, the effects of residual confounding cannot be completely ruled out in observational studies.

Besides earlier analyses within the NHS and HPFS (12–14), which were consistent with our present results, two other large prospective studies have specifically explored the association between magnesium intake and type 2 diabetes risk. Findings in older women (15) were very similar to our results, with an RR comparing extreme quintiles of 0.76 (95% CI 0.62–0.95) in a multivariate model, in-

cluding whole grain and cereal fiber. In the other study, Kao et al. (16) found an inverse association between serum magnesium levels and type 2 diabetes, but did not find a significant association between dietary magnesium and subsequent incidence of diabetes. Unlike our study, both of the other studies used only single baseline dietary assessment.

Several experimental studies suggest a protective role of magnesium intake against diabetes. Using a rat model of spontaneous type 2 diabetes, Balon et al. (32) demonstrated a significant reduction in the incidence of diabetes after 7 weeks of feeding with a magnesium-rich diet. In humans, some (11,33,34) but not all (35–37) experimental studies have shown benefits of magnesium supplements on glucose metabolism and/or insulin sensitivity. Some of the inconsistencies among these studies can be explained by differences in treatment periods, doses of magnesium, and parameters used to evaluate the effect. Moreover, most of these studies have been conducted on diabetic subjects, in whom the underlying insulin resistance could interfere with magnesium uptake at the cellular level (38). In one study (11), elderly nondiabetic subjects

participated in a double-blind, randomized, crossover study comparing magnesium supplements (4.5 g/day) versus placebo during 4 weeks. This study showed a beneficial effect on insulin response to glucose and insulin action. Whether long-term magnesium supplementation decreases the risk for type 2 diabetes in the general population is unclear, and the hypothesis merits testing in clinical trials. In our observational analysis, magnesium supplement use was not significantly associated with diabetes risk in multivariate models. However, the power of our study was limited by the low prevalence of magnesium supplement use in these cohorts.

Several mechanisms, including insulin secretion, binding, and action, have been proposed to explain the effect of intracellular or plasma magnesium on diabetes pathogenesis (6). Intracellular magnesium is a critical cofactor for several enzymes in carbohydrate metabolism, especially those involved in phosphorylation reactions such as tyrosine-kinase. In animal models (9), hypomagnesemia induced by low magnesium intake triggers severe insulin resistance, which was shown to be partially dependent on deficient tyrosine-kinase activity on the post-receptor pathway of insulin in muscle cells. In healthy humans, a study of short-term low magnesium diet (39) showed that it reduced serum and intracellular magnesium and produced insulin resistance, using a minimal model. Consistent with the effect of magnesium on insulin resistance, Fung et al. (40) found an inverse association between magnesium intake and fasting insulin level, a good marker of insulin resistance, in a cross-sectional sample of the NHS.

Higher magnesium intake is likely more beneficial among individuals with some degree of magnesium deficiency. However, there is no generally accepted test for magnesium status. Also, our subgroup analysis suggests that higher magnesium consumption is likely beneficial for all groups, regardless of their BMI, physical activity levels, and hypertension status.

In conclusion, these two large prospective cohorts provide strong and consistent evidence to support an inverse association between magnesium intake and diabetes risk. The effect of magnesium supplementation in general or high-risk populations requires further research,

ideally in randomized clinical trials. This study supports the dietary recommendation to increase consumption of major food sources of magnesium, such as whole grains, nuts, and green leafy vegetables.

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### References

- King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 21:1414–1431, 1998
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
- Popkin BM: The nutrition transition and obesity in the developing world. *J Nutr* 131:871S–873S, 2001
- Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A: Magnesium: an update on physiological, clinical and analytical aspects. *Clin Chim Acta* 294:1–26, 2000
- Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, Hutchinson RG, Metcalf PA: Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study: Atherosclerosis Risk in Communities Study. *J Clin Epidemiol* 48:927–940, 1995
- Tosiello L: Hypomagnesemia and diabetes mellitus: a review of clinical implications. *Arch Intern Med* 156:1143–1148, 1996
- Paolisso G, Scheen A, D'Onofrio F, Lefebvre P: Magnesium and glucose homeostasis. *Diabetologia* 33:511–514, 1990
- Dzurik R, Stefikova K, Spustova V, Fetkova N: The role of magnesium deficiency in insulin resistance: an in vitro study. *J Hypertens (Suppl. 9)*:S312–S313, 1991
- Suarez A, Pulido N, Casla A, Casanova B, Arrieta FJ, Rovira A: Impaired tyrosine-kinase activity of muscle insulin receptors from hypomagnesaemic rats. *Diabetologia* 38:1262–1270, 1995
- de Valk HW: Magnesium in diabetes mellitus. *Neth J Med* 54:139–146, 1999
- Paolisso G, Sgambato S, Gambardella A, Pizza G, Tesaro P, Varricchio M, D'Onofrio F: Daily magnesium supplements improve glucose handling in elderly subjects. *Am J Clin Nutr* 55:1161–1167, 1992
- Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC: Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 20:545–550, 1997
- Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC: Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA* 277:472–477, 1997
- Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE: Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 55:1018–1023, 1992
- Meyer KA, Kushi LH, Jacobs DR Jr, Slavin J, Sellers TA, Folsom AR: Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 71:921–930, 2000
- Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL: Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. *Arch Intern Med* 159:2151–2159, 1999
- van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB: Dietary fat and meat intake in relation to risk of type 2 diabetes in men. *Diabetes Care* 25:417–424, 2002
- Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB: Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA* 288:2554–2560, 2002
- US Department of Agriculture (USDA), Agricultural Research Service: USDA Nutrient Database for Standard Reference, release 13, SR13 [database online]. Available from <http://www.nal.usda.gov/fnic/foodcomp>. Accessed 11 July 2001
- Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE: Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 122:51–65, 1985
- Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC: Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 135:1114–1126, 1992
- Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC: Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1:466–473, 1990
- Chasan-Taber S, Rimm EB, Stampfer MJ,

- Spiegelman D, Colditz GA, Giovannucci E, Ascherio A, Willett WC: Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology* 7:81-86, 1996
24. Wolf AM, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Corsano KA, Rosner B, Kriska A, Willett WC: Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol* 23:991-999, 1994
  25. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE: Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 123:894-900, 1986
  26. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183-1197, 1997
  27. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH: A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 151:1141-1147, 1991
  28. Fung TT, Hu FB, Pereira MA, Liu S, Stampfer MJ, Colditz GA, Willett WC: Whole-grain intake and the risk of type 2 diabetes: a prospective study in men. *Am J Clin Nutr* 76:535-540, 2002
  29. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC: Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol* 149:531-540, 1999
  30. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC: Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 345:790-797, 2001
  31. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE: Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA* 289:1785-1791, 2003
  32. Balon TW, Gu JL, Tokuyama Y, Jasman AP, Nadler JL: Magnesium supplementation reduces development of diabetes in a rat model of spontaneous NIDDM. *Am J Physiol* 269:E745-E752, 1995
  33. Paolisso G, Sgambato S, Pizza G, Passariello N, Varricchio M, D'Onofrio F: Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. *Diabetes Care* 12:265-269, 1989
  34. Paolisso G, Scheen A, Cozzolino D, Di Maro G, Varricchio M, D'Onofrio F, Lefebvre PJ: Changes in glucose turnover parameters and improvement of glucose oxidation after 4-week magnesium administration in elderly noninsulin-dependent (type II) diabetic patients. *J Endocrinol Metab* 78:1510-1514, 1994
  35. Eibl NL, Kopp HP, Nowak HR, Schnack CJ, Hopmeier PG, Schernthaner G: Hypomagnesemia in type II diabetes: effect of a 3-month replacement therapy. *Diabetes Care* 18:188-192, 1995
  36. Lima Mde L, Cruz T, Pousada JC, Rodrigues LE, Barbosa K, Cangucu V: The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. *Diabetes Care* 21:682-686, 1998
  37. de Valk HW, Verkaaik R, van Rijn HJ, Geerdink RA, Struyvenberg A: Oral magnesium supplementation in insulin-requiring type 2 diabetic patients. *Diabet Med* 15:503-507, 1998
  38. Alzaid AA, Dinneen SF, Moyer TP, Rizza RA: Effects of insulin on plasma magnesium in noninsulin-dependent diabetes mellitus: evidence for insulin resistance. *J Endocrinol Metab* 80:1376-1381, 1995
  39. Nadler JL, Buchanan T, Natarajan R, Antonipillai I, Bergman R, Rude R: Magnesium deficiency produces insulin resistance and increased thromboxane synthesis. *Hypertension* 21:1024-1029, 1993
  40. Fung T, Manson J, Solomon C, Liu S, Willett W, Hu F: The association between magnesium intake and fasting insulin concentration in healthy middle-aged women. *J Am Coll Nutr*. In press