TITLE

Higher magnesium intake reduces risk of impaired glucose and insulin metabolism, and progression from prediabetes to diabetes in middle-aged Americans

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RUNNING TITLE

Magnesium intake and impaired metabolic states

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ABSTRACT (WORD COUNT = 269)

Objective: To assess 7-yr associations between magnesium intake and incident prediabetes and/or insulin resistance (IR), and progression from these states to type 2 diabetes.

Research Design and Methods: In 2,582 community-dwelling participants 26–81 yrs old at baseline, magnesium intake and risk of incident "metabolic impairment," defined as impaired fasting glucose (≥5.6–<7.0 mmol/L), impaired glucose tolerance (2-hr postload glucose ≥7.8–<11.1 mmol/L), IR, *or* hyperinsulinemia (≥90th percentile of HOMA-IR or fasting insulin, respectively), was estimated among those with normal baseline status, and risk of incident diabetes was estimated among those with baseline metabolic impairment. In participants without incident diabetes, we examined magnesium intake in relation to 7-yr changes in fasting and postload glucose and insulin, IR, and insulin sensitivity.

Results: After adjusting for age, sex, and energy intake, compared to those with the lowest magnesium intake, those with the highest intake had 37% lower risk of incident metabolic impairment (*P* trend=0.02), while in those with baseline metabolic impairment, higher intake was associated with 32% lower risk of incident diabetes (*P* trend=0.05). In the combined population, the risk in those with the highest intake was 53% (*P* trend=0.0004) of those with the lowest intake. Adjusting for risk factors and dietary fiber attenuated associations in the baseline normal population, but did not substantially affect associations in the metabolically impaired. Higher magnesium intake tended to associate with lower follow-up fasting glucose and IR, but not fasting insulin, postload values, or insulin sensitivity.

Conclusions: Magnesium intake may be particularly beneficial in offsetting risk of developing diabetes among those at high risk. Magnesium's long-term associations with non-steady state (dynamic) measures deserve further research.

INTRODUCTION

Prediabetes and diabetes affected an estimated 45% of US adults in 2010 (1). Diabetes significantly raises risk of heart disease and stroke morbidity and mortality, and is the leading cause of adult blindness and kidney failure. An estimated $245 billion in indirect and direct medical costs are attributable annually to diabetes (2). Diet modification is recommended as an important prevention strategy at any stage of progression from health to overt type 2 diabetes (3). Prospective studies (4–6) have shown that individuals with higher magnesium intake are 10–47% less likely to develop type 2 diabetes. However, only 50% of Americans one year or older achieve the Recommended Dietary Allowance (RDA) for magnesium, which is 400–420 mg/day for adult men, and 300–310 mg/day for adult women (7,8).

A body of clinical evidence (9–14) supports a role for magnesium supplementation in glucose and insulin metabolism. A meta-analysis of nine magnesium supplement trials in those with type 2 diabetes found that a median magnesium dose of 360 mg/d was associated with significantly lower post-intervention fasting glucose (FG) in treatment groups, suggesting improved glucose control (12). A recent small randomized, placebo-controlled trial in obese, non-diabetic, insulin resistant individuals demonstrated that 365 mg/d of magnesium for 6 months significantly lowered FG, fasting insulin (FI), and insulin resistance (IR), and improved insulin sensitivity (13). Three-month supplementation with magnesium in individuals with other risk factors, such as mild hypertension or hypomagnesaemia, has been found to improve insulin sensitivity and pancreatic beta-cell function (9–11), while low-magnesium diets given to otherwise healthy individuals have been shown to impair insulin sensitivity after just 3 weeks (14).

Few prospective studies have evaluated magnesium intake in relation to various stages of progression of disordered glucose and insulin metabolism, i.e., from normal to impaired states including prediabetes and insulin resistance, over the long term (i.e., >5 years), even though these states are significant risk factors for diabetes as well as cardiovascular disease (15–17). In addition, few studies have examined magnesium's associations with long-term progression from baseline impaired states to type 2 diabetes (4,18). One study of magnesium intake in US adults estimated that the optimal magnesium intake level in relation to insulin sensitivity measured 5 years later was at least 325 mg/d (18); and another study in US adults reported lower long-term IR with higher magnesium intake (4).

In the present analysis, we evaluated the prospective association between magnesium intake and incidence of metabolic impairment, defined as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), IR, or hyperinsulinemia, in otherwise healthy individuals, and to incident diabetes in those with baseline metabolic impairment, to assess whether magnesium intake may have differing associations at varying stages of underlying metabolic impairment.

METHODS

Study Sample

The National Heart, Lung, and Blood Institute's Framingham Heart Study (FHS) Offspring cohort is a community-based, longitudinal study of cardiovascular disease that began in 1971 whose participants are among the offspring of the Original FHS cohort (19). In the fifth examination cycle (1991–1995) of the Offspring cohort, 3,799 participants underwent a standard medical examination, including laboratory and anthropometric measurements, as well as dietary assessment. Participants were followed from baseline at the fifth through seventh (1998–2001) examinations. Individuals were excluded if they had a history of diabetes or were identified as having diabetes at the baseline examination (n=400); if they had invalid dietary data at baseline (n=326); if they were missing necessary covariates (n=109); if they were not present at the final follow-up examination (n=329, 135 of whom were lost-to-follow-up owing to death); or if they had invalid or missing dietary data over follow-up (n=53). The final sample size for the primary analysis was 2,582 participants.

A 2-hour 75-g oral glucose tolerance test (OGTT) was administered to all participants at exam 5 and in a subset of participants at exam 7 who had undergone OGTT at exam 5, based on glucose tolerance at exam 5 (sex block-randomly selected from 5 quintile strata of fasting glucose). A total of 863 participants had follow-up OGTT measures available for the present analysis.

The original data collection protocols were approved by the Institutional Review Board at Boston University Medical Center, and written informed consent was obtained from all participants. The present study protocol was reviewed by the Tufts Medical Center and Tufts University Health Sciences Institutional Review Board.

Dietary Assessment

The Harvard semi-quantitative, 126-item food frequency questionnaire (FFQ) was used to assess dietary intake at each exam (20). The FFQ included a list of foods together with a standard serving size and 9 consumption frequency categories ranging from "never, or less than once per month" to "6+ per day." Participants were asked to report consumption of each food item over the previous year. Invalid FFQs were defined as those which estimated daily caloric intake as <600 kcal/d, or ≥4,000 kcal/d for women, ≥4,200 kcal/d for men, or those which had ≥12 blank items. The exposure of interest, total magnesium intake, included both dietary and non-dietary (i.e., supplemental) sources. Magnesium intake from non-dietary sources contributed approximately 5% of total intake.

The relative validity of the FFQ for energy-adjusted magnesium intake has been previously reported (20–22), and shows reasonable correlation with estimates from dietary records (r = 0.67–0.71) (20). All nutrients were adjusted for total energy using the residual method (23).

To account for long-term dietary exposure and to reduce within-person variability, intake of nutrients are presented as mean intake obtained from the dietary data of the fifth (baseline), sixth, and/or seventh examinations. For those with incident type 2 diabetes, intake of nutrients and energy were averaged across dietary data from the fifth examination up to but not including the examination at which diabetes incidence was ascertained. For those without incident diabetes, intake was averaged across all exams (5, 6, and/or 7) for which dietary data was available.

Outcome Measures and Definitions

Fasting plasma glucose (FG) and 2-hr OGTT glucose were measured in fresh specimens with a hexokinase reagent kit (A-Gent glucose test; Abbot, South Pasadena, CA). At baseline (exam 5), fasting plasma insulin (FI) and 2-hr OGTT insulin were measured using Coat-A-Count total

insulin radioimmunoassay (RIA) (Diagnostic Products Corp., Los Angeles, CA) while at exam 7, FI and 2-hr OGTT insulin were measured using a different assay, the human-specific insulin RIA (Linco Research Inc., St. Charles, MO). Owing to the different assays used to measure insulin at exams 5 and 7, a calibration study was conducted using FI in frozen plasma from 87 participants. These samples from exam 5 were re-analyzed approximately 9 years later using the human-specific insulin RIA assay and a regression equation was derived to calibrate total insulin RIA measures at exam 5 to human-specific RIA-equivalent values. The calibrated measures were used in the present analysis.

We defined metabolic impairment or type 2 diabetes based in part on impaired glucose criteria from the American Diabetes Association (ADA) (24), in addition to impaired insulin criteria (**Supplemental Table S1**): participants were classified as having type 2 diabetes if they had a diagnosis of type 2 diabetes, reported use of an oral hypoglycemic drug or insulin, or had FG ≥7.0 mmol/L (≥126 mg/dL) or 2-hr OGTT glucose ≥11.1 mmol/l (≥200 mg/dL). Metabolic impairment was defined has having one or more of the following: IFG, IGT, IR, or hyperinsulinemia, per criteria that follow. Participants were classified as having normal fasting glucose (NFG) if they had FG <5.6 mmol/L (<100 mg/dL). IFG was classified as FG ≥5.6–<7.0 mmol/L (≥100–<126 mg/dL). Normal glucose tolerance (NGT) was classified as 2-hr OGTT glucose <7.8 mmol/L (<140 mg/dL). IGT was classified as 2-hr OGTT glucose ≥7.8–<11.1 mmol/L (≥140–<200 mg/dL). HOMA-IR, a measure of hepatic IR, was calculated as FI (μU/mL) × FG (mmol/L) / 22.5 (25). IR was defined as HOMA-IR ≥90th percentile. Hyperinsulinemia was defined as FI ≥90th percentile. Gutt's Insulin Sensitivity Index$_{0,120}$ (ISI), a measure of peripheral tissue insulin sensitivity, was calculated as ISI = (m/mean plasma glucose)/log(mean serum insulin), where the glucose uptake rate in peripheral tissues (m) =

(75000 mg + [FG (mg/dL) – 2-hr OGTT glucose (mg/dL)] × 0.19 × weight (kg)] / 120 min; mean plasma glucose = mean of FG (mmol/L) and 2-hr OGTT glucose (mmol/L); and mean serum insulin = mean of serum FI (μU/L) and 2-hr OGTT serum insulin (μU/L) (26).

Covariates

Potential confounders of the relationship between diet and progression to metabolic impairment or diabetes were considered as covariates. Covariates were assessed at baseline as follows: age (y), BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference (cm) was measured at the umbilicus with the participant standing. Parental history of diabetes was based on self-reported history in one or both natural parents. Blood pressure (BP) was measured twice by a physician and averaged to calculate the systolic and diastolic BP (mmHg). Hypertension (yes/no) was defined as BP ≥130/85 mmHg or undergoing treatment for hypertension. Information on regular smoking during the year prior to the examination (yes/no) was assessed via questionnaire. Physical activity was quantified as a continuous score based on activity levels as well as intensities of these activities, as previously described (27).

Statistical Analyses

We generated energy-adjusted quintile categories of averaged magnesium intake. Participant characteristics adjusted for age, sex, and energy (in the case of foods and nutrients) are presented across quintile categories. Tests for linear trend across increasing categories of intake were performed by assigning the median value of intake within each category and treating these as a continuous variable.

Because we sought to characterize magnesium's associations with progression from normal to metabolic impairment, we assessed the association of magnesium intake with: 1)

incident metabolic impairment (defined as having IFG, IGT, IR, *or* hyperinsulinemia), among participants with normal status (NFG, NGT, no IR, *and* normoinsulinemia) at baseline; and 2) incident type 2 diabetes among participants who had baseline metabolic impairment, as defined above. Because there were few cases of incident diabetes among those with normal baseline status (n=25), these cases were incorporated into our definition of incident metabolic impairment. In secondary, sensitivity analyses, we redefined metabolic impairment by use of the ADA prediabetes criteria of IFG and IGT *only*, as these are frequently used in other clinical and research contexts. This redefinition also allowed us to examine whether excluding IR and hyperinsulinemia from the definition of metabolic impairment impacts magnesium's associations with incident disorder. Relative risks (RR) and 95% confidence intervals (95%CI) across quintile categories of magnesium intake were estimated from multivariable logistic regression analyses for incident metabolic impairment or diabetes. *P* for trend was estimated using the median value in each category of intake.

In secondary analyses in participants without incident diabetes, we assessed the association between magnesium intake and change in continuous measures of FG, FI, HOMA-IR, 2-hr OGTT glucose and insulin, and ISI over an average 7-y period. Change was modeled in each case as the final measure adjusted for the baseline measure. For these continuous outcomes, we estimated least squares adjusted means of values in each quintile category of energy-adjusted magnesium intake. *P* for trend was estimated using the median value in each category of intake. Natural-logged values were used for FI, HOMA-IR, and 2-hr OGTT insulin, which were back-transformed to geometric means for presentation.

For all outcomes, the initial analysis was adjusted for age, sex, and energy intake (model 1). Model 2 was adjusted as for model 1, plus parental history of diabetes, BMI, physical

activity, smoking status, alcohol intake, and hypertension. In model 3, we further adjusted for dietary fiber. Additional adjustment for caffeine did not change the results and therefore we do not include those results. Dietary fiber and caffeine were initially chosen because they represent surrogates of non-magnesium constituents of commonly consumed magnesium-containing foods (i.e., whole grains and coffee), which themselves have been associated with lower risk of type 2 diabetes (6,28–30). Adjusting for these dietary variables allows us to at least partially distinguish the associations of magnesium from the associations of the foods themselves, their constituents (e.g., phytochemicals), or from health behaviors associated with these nutrients (e.g., higher fiber may also be a surrogate for a healthy lifestyle).

In post-hoc analyses, we modeled energy-adjusted dietary magnesium intake, adjusted for magnesium from supplements, to assess whether dietary intake specifically accounted for the observed associations. The results of dietary magnesium paralleled those of total magnesium, and without an *a priori* hypothesis regarding the mechanism of magnesium from dietary versus supplemental sources, we present the results from the original analyses of total magnesium intake described above.

Finally, we separately tested for statistical interaction between magnesium and age, sex, and BMI in the final models using cross-product terms. No interaction was statistically significant (all $P > 0.1$). Substituting waist circumference for BMI, or including waist circumference or change in weight between baseline and follow-up, did not substantively alter results.

All analyses were conducted in SAS (version 9.3, SAS Institute, Cary, North Carolina). Statistical significance was set at the 0.05 level. All tests were two-tailed.

RESULTS

Baseline clinical and dietary characteristics of 2,582 participants are presented across quartile categories of energy-adjusted magnesium intake in **Table 1**. The average age of the population was 54 y, 55% were women, 42% were overweight, and 21% were obese. Average magnesium intake was 308 mg/d, which parallels intake reported in other US adult populations (31). Approximately 50% of women and 75% of men reported magnesium intake below the RDA. In analyses of trend from lowest to highest quartile category of magnesium intake, those in the highest category were more likely to be female, older, and have lower BMI. They were less likely to have hypertension or to have smoked regularly in the prior year. Intake of energy and most other nutrients increased along with increasing magnesium intake, except for alcohol. Baseline characteristics of almost all glucose and insulin parameters tended to be lower in participants with higher magnesium intake. Magnesium intake was moderately correlated with dietary fiber (r=0.67, P <0.001), but not with caffeine (r=0.03, P=0.08).

Incident Metabolic Impairment among Those with Normal Status at Baseline

Among the 1,654 (64.1%) participants without metabolic impairment at baseline, there were 307 (18.6%) cases of incident metabolic impairment, of which 25 were cases of incident diabetes over an average 6.9 y follow-up. Risk of incident metabolic impairment and diabetes in those with normal status at baseline, according to magnesium intake, are presented in **Table 2**. In the basic model, adjusted for age, sex, and energy intake, higher magnesium intake was associated with 37% lower risk of incident metabolic impairment (Q1 (reference) vs. Q5 RR [95%CI] 0.63 [0.45–0.87], P trend = 0.02), which was attenuated after adjusting for risk factors (P trend = 0.08), and further attenuated after adjusting for dietary fiber (P trend = 0.26).

Incident Type 2 Diabetes among Metabolically Impaired at Baseline

Among the 928 (35.9%) participants impaired at baseline, there were 154 (16.6%) cases of incident diabetes over an average 6.9 y follow-up. After adjusting for age, sex, and energy intake, higher magnesium intake was associated with 32% lower risk of incident diabetes (0.68 [0.41–1.12], *P* trend = 0.05) (**Table 2**). The trend was attenuated after adjusting for risk factors (*P* trend = 0.18), but further adjusting for fiber intake de-attenuated the estimate such that the final estimate was 38% lower risk in the highest compared to the lowest category of magnesium intake (0.62 [0.35–1.10)], *P* trend = 0.05).

In the total study population, there were 179 (6.9%) incident cases of diabetes over an average 6.9 y follow-up. In fully adjusted models, higher magnesium intake was associated with 51% lower risk of incident diabetes (0.49 [0.27–0.88], *P* trend = 0.01) (**Table 2**).

Secondary Analyses

In secondary analyses, IR and hyperinsulinemia were excluded from the working definition of baseline or incident metabolic impairment and, as such, more closely aligned with ADA prediabetes criteria (IGT and/or IFG). Prevalence of baseline metabolic impairment, as a percentage of the total sample, decreased from 35.9% to 31.4%, and incident metabolic impairment, as a percentage of those who were normal at baseline, also decreased from 18.6% to 17.2%.

Results of these analyses were similar to those using the primary definition. Among those with normal status at baseline when impairment was defined by IGT and/or IFG, higher magnesium intake was not associated with risk of incident metabolic impairment after adjusting for age, sex, and energy intake (*P* trend = 0.12) (**Table 3**). However, among those initially impaired at baseline, trends for lower risk of incident diabetes across increasing quintile categories of magnesium showed associations similar to those observed when the definition of

metabolic impairment included insulin-based criteria: in the fully adjusted model, those with the highest magnesium intake had 44% lower risk of developing diabetes compared to the lowest magnesium intake [RR 0.56 (0.32–0.99], *P* trend = 0.02).

Linear Outcomes in the Total Sample

Adjusted means of various measures of glucose and insulin homeostasis and metabolism after approximately 7-yrs of follow-up in those without incident diabetes are presented in **Table 4**. In basic models adjusted for age, sex, energy intake, and the corresponding baseline measure, there were significant inverse trends with higher magnesium intake and subsequent FG (Q1 vs. Q5: 5.42 vs. 5.32 mmol/L, *P* trend = 0.003) and HOMA-IR (3.08 vs. 2.89, *P* trend = 0.05). However, all trends were attenuated after additionally adjusting the risk factor model (model 2) for dietary fiber (model 3).

DISCUSSION

Our results support previously reported longitudinal associations between higher magnesium intake and lower risk of type 2 diabetes (5,6). Across 7 years of follow-up, higher magnesium intake appeared to partially offset risk of developing metabolic impairment in those with normal baseline glucose and insulin homeostasis. In addition, in those with baseline metabolic impairment, magnesium intake was also associated with lower risk of type 2 diabetes. Interestingly, magnesium's associations with incident impairment were stronger when the definition of metabolic impairment included hyperinsulinemia and IR, than when they included hyperglycemia or impaired glycemic response alone. This is intriguing, since elevated insulin or insulin resistance are etiological predecessors of chronically elevated fasting glucose concentrations (15), perhaps indicating that magnesium intake is more important to maintaining long-term healthy insulin metabolism. This is supported by our observation that those with the highest magnesium intake had, on average, 6% lower HOMA-IR after 7 yrs than those with the lowest magnesium intake, after adjusting for risk factors. However, as our results indicate, once metabolic impairment had taken hold, magnesium intake seemed to be associated with lower risk of type 2 diabetes, regardless of whether baseline metabolic impairment was defined by both glucose and insulin criteria, or glucose criteria alone.

Our observation of lower risk of type 2 diabetes with higher magnesium intake is one that is fairly well-established in the magnesium literature (4–6,32,33). In addition, several clinical studies of magnesium supplementation in those with and without diabetes indicate that magnesium supplementation can improve glycemic control, insulin sensitivity, and beta-cell function (9–11,13,34). However, the duration of these clinical studies have been relatively short (≤6 months) and most of the observational studies of magnesium intake in relation to insulin

homeostasis or metabolism have been cross-sectional (33,35–37). As such, there is a relative dearth of knowledge on the long-term impact of magnesium intake on insulin metabolism.

Our results related to HOMA-IR are consistent with another study in younger American adults (18–30 y at baseline) evaluating magnesium intake against repeated measures of HOMA-IR over 20 y, in which a significant inverse association was observed between insulin resistance and magnesium intake, after adjusting for risk factors similar to those adjusted for in the present analysis (4). While our follow-up was shorter, our population was older, and we excluded those with incident diabetes in our analyses, we nevertheless also observed an inverse trend between higher magnesium intake and long-term HOMA-IR. However, this association did not persist after adjustment for dietary fiber. One other prospective study examined magnesium intake and insulin sensitivity in 1,036 US adults (56.4% women) participating in the Insulin Resistance Atherosclerosis Study (IRAS) (18). In that study, a threshold effect of magnesium intake (at 325 mg/d) was observed in relation to insulin sensitivity, derived from intravenous glucose tolerance test (18). Progressively poorer 5-yr insulin sensitivity was observed below that threshold, with no evidence for improvement of sensitivity above that threshold.

Magnesium's associations with insulin sensitivity are supported by experimental evidence in animals fed magnesium-deficient diets, in which insulin sensitivity of peripheral tissue decreases via reduced autophosphorylation of tyrosine kinase, a component of the beta subunit of the insulin receptor for which magnesium is a co-factor (38). In addition, hypomagnesaemia is thought to deleteriously impact the proliferation and mass of beta-cells, thus affecting insulin production (39,40). Insulin itself may also be a regulating magnesium metabolism, as prolonged high concentrations of circulating insulin, such as those known to

occur in insulin resistance, induce increases in renal magnesium excretion, thus perpetuating a deleterious cycle (40).

While we observed that higher magnesium intake was inversely associated with long-term changes in fasting glucose and IR in those without incident diabetes (attenuated after adjustment for fiber intake), we did not observe significant trends of magnesium intake with fasting insulin, glucose clearance or insulin metabolism (as post-OGTT measures), or insulin sensitivity (as ISI), although we had >80% power to observe, for example, the observed difference in 2-hr glucose between extreme quintiles. However, our findings are consistent with a recent 6-month trial in non-diabetic, insulin resistant individuals which demonstrated that treatment with 365 mg/d of magnesium results in significantly lowered FG, HOMA-IR, and improved insulin sensitivity (Matsuda index, but not Gutt's ISI)—with no effect on 2-hr glucose or insulin, and only marginal effects on FI (13). It may be that Gutt's ISI, measured both in the trial and in the present analysis with null associations, is measuring peripheral insulin resistance, where as other insulin-related measures, such as HOMA-IR or the Matsuda index, reflect hepatic insulin resistance (13).

We included fiber as a potential confounder owing to the body of literature on fiber's protective effects against diabetes (6), and to shared dietary sources of magnesium and fiber, such as whole grains and vegetables. Interestingly, including fiber in our models (model 3) had differential effects on magnesium's diabetes-risk-lowering associations, depending on whether the population was initially normal or impaired. In those with normal baseline status, fiber attenuated the observed associations of magnesium on risk of metabolic impairment, suggesting that magnesium intake is not acting independently of the effects of fiber in those who are initially healthy. However, in those with impaired baseline status, fiber de-attenuated the association of

magnesium, suggesting that higher magnesium intake may be more important to those with existing metabolic impairment, irrespective of fiber intake. This may, in part, be related to deficient magnesium status generally observed in those with metabolic impairment (39). Of note is that there was no interaction between magnesium intake and fiber, or between magnesium intake and impairment status. Fiber intake was only approximately 0.5 g/d higher, and magnesium intake approximately 8 mg/d higher, on average, in those with normal vs. impaired status at baseline.

Our study has several strengths. We benefitted from a large sample in a well-characterized community-based cohort with repeated dietary measures (up to 3) for estimation of magnesium intake over 7 years. Incident metabolic impairment and diabetes were classified based on fasting and postload measures, rather than relying on self-report alone. This study also has several limitations. First, different insulin assays were used at baseline and final exams. Although we calibrated fasting values at exam 5 to those at exam 7, no calibration was possible for postload insulin. Therefore, the null findings observed between magnesium intake and fasting and postload insulin and ISI may be a partial result of this. Second, higher magnesium intake may also be reflective of better health consciousness, a confounder which we may have inadequately controlled for despite adjusting for fiber intake, cigarette smoking status, and physical activity, which may serve as surrogate markers of a healthy lifestyle. While residual confounding of lifestyle factors may remain an issue, the attenuation by fiber intake of our estimates may also represent an over-adjustment of the model, owing to magnesium and fiber's shared food sources (namely, whole grains). Finally, the generalizability of our findings may be limited, as ours was a relatively homogenous, middle-aged Caucasian population.

In conclusion, higher magnesium intake may lower risk of progressing to diabetes among those with the highest risk of doing so—namely, those with insulin resistance or prediabetes. These findings support a role for higher magnesium intake in those at high risk of developing diabetes, and the need for large, randomized trials to confirm these observations.

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Table 1—*Characteristics of study population free of type 2 diabetes at baseline*

	Quintile category of energy-adjusted averaged magnesium intake					
	1	**2**	**3**	**4**	**5**	
n	516	517	516	517	516	
Median, mg/d	236	272	299	332	395	
Range, mg/d	101–258	258–286	286–314	314–356	356–651	
Characteristic*						***P* linear trend**
Age, y	53.0 (0.4)	53.6 (0.4)	53.5 (0.4)	54.0 (0.4)	55.2 (0.4)	0.003
Sex, % female	44 (2)	52 (2)	53 (2)	59 (2)	68 (2)	<0.001
BMI, kg/m^2	27.7 (0.2)	27.1 (0.2)	26.9 (0.2)	26.7 (0.2)	26.6 (0.2)	0.003
Current smoker, %	23 (2)	19 (2)	22 (2)	18 (2)	10 (2)	<0.001
Waist circumference, cm	93.1 (0.5)	91.2 (0.5)	91.2 (0.5)	90.5 (0.5)	90.3 (0.5)	0.002
Hypertensive, %	49 (2)	45 (2)	41 (2)	41 (2)	41 (2)	0.02
Physical activity score	34.8 (0.3)	34.9 (0.3)	34.4 (0.3)	35.1 (0.3)	34.9 (0.3)	0.37
Dietary Characteristics						
Magnesium, total, mg/d	227.0 (2.2)	270.7 (2.2)	291.8 (2.2)	324.2 (2.2)	395.7 (2.1)	<0.001
from diet	224.3 (2.0)	268.5 (2.0)	286.4 (2.0)	313.2 (2.0)	359.4 (2.0)	<0.001
from supplement	2.7 (1.4)	2.2 (1.4)	5.4 (1.4)	11.0 (1.3)	36.3 (1.4)	<0.001
Alcohol, g/d	10.6 (0.7)	11.0 (0.7)	11.2 (0.7)	11.4 (0.7)	9.4 (0.7)	0.23
Fiber, g/d	13.7 (0.2)	16.4 (0.2)	17.4 (0.2)	19.1 (0.2)	22.8 (0.2)	<0.001
Caffeine, mg/d	253.0 (9.7)	281.2 (9.6)	298.9 (9.6)	335.5 (9.6)	302.5 (9.7)	<0.001
Energy, kcal/d	1959 (26)	1741 (26)	1792 (26)	1822 (26)	2020 (26)	<0.001
Glucose and Insulin Characteristics						
Fasting glucose, mmol/L	5.28 (0.02)	5.27 (0.02)	5.26 (0.02)	5.22 (0.02)	5.19 (0.02)	0.01
Fasting insulin, pmol/L †	208.5 (1.0)	200.3 (1.0)	200.3 (1.0)	196.4 (1.0)	192.5 (1.0)	<0.001
HOMA-IR †	7.03 (1.01)	6.75 (1.01)	6.69 (1.01)	6.55 (1.01)	6.36 (1.01)	<0.001
2-hr OGTT glucose, mmol/L	6.07 (0.07)	5.89 (0.07)	5.73 (0.07)	5.73 (0.07)	5.75 (0.07)	<0.001
2-hr OGTT insulin, pmol/L †	595.9 (1.0)	550.0 (1.0)	523.2 (1.0)	523.2 (1.0)	507.8 (1.0)	<0.001
Gutt's ISI	25.4 (0.3)	26.2 (0.3)	26.9 (0.3)	26.8 (0.3)	27.1 (0.3)	<0.001
NFG, %	71 (2)	70 (2)	74 (2)	76 (2)	77 (2)	0.02
NGT, %	85 (1)	88 (1)	90 (1)	90 (1)	88 (1)	0.08

Fasting insulin >90th percentile, %	16 (1)	8 (1)	11 (1)	7 (1)	8 (1)	<0.001
HOMA-IR >90th percentile, %	15 (1)	8 (1)	11 (1)	7 (1)	7 (1)	<0.001

* Characteristics are age- and sex-adjusted, except for age and sex, which are mutually adjusted. Dietary characteristics, except energy, are further adjusted for energy. Data are mean (SE), unless otherwise indicated. HOMA-IR, homeostasis model assessment of insulin resistance; ISI, Gutt's Insulin Sensitivity Index$_{0-120}$; NFG, normal fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.
† Analyzed in the natural-log scale and back-transformed to geometric mean (geometric SE) for presentation.
‡ Normal fasting glucose defined as fasting plasma glucose <5.6 mmol/L (<100 mg/dL). Normal glucose tolerance defined as 2-hr OGTT glucose <7.8 mmol/L (<140 mg/dL).

Table 2—*Relative risk of progression from normal to metabolically impaired (IFG, IGT, insulin resistant, or hyperinsulinemic) and metabolically impaired to type 2 diabetes, by quintile categories of energy-adjusted magnesium intake.**

	Quintile category of energy-adjusted averaged magnesium intake†					
Median intake, mg/d	**1** 235	**2** 272	**3** 298	**4** 332	**5** 395	*P* linear trend
Incident metabolic impairment (or type 2 diabetes) among unimpaired at baseline						
Total, *n*	298	319	325	356	356	1654
Cases, *n*	71	56	59	72	49	307
Model 1‡	1 *(Ref)*	0.79 (0.58–1.08)	0.81 (0.60–1.10)	0.93 (0.70–1.24)	0.63 (0.45–0.87)	0.02
Model 2	1 *(Ref)*	0.78 (0.57–1.07)	0.87 (0.64–1.17)	0.95 (0.72–1.26)	0.68 (0.49–0.94)	0.08
Model 3	1 *(Ref)*	0.79 (0.57–1.08)	0.88 (0.64–1.22)	0.97 (0.71–1.33)	0.70 (0.47–1.06)	0.26
Incident type 2 diabetes among metabolically impaired at baseline						
Total, *n*	218	198	191	161	160	928
Cases, *n*	39	40	31	24	20	154
Model 1‡	1 *(Ref)*	1.15 (0.77–1.71)	0.92 (0.60–1.41)	0.83 (0.52–1.32)	0.68 (0.41–1.12)	0.05
Model 2	1 *(Ref)*	1.22 (0.83–1.80)	1.00 (0.66–1.53)	0.94 (0.59–1.49)	0.77 (0.47–1.27)	0.18
Model 3	1 *(Ref)*	1.14 (0.77–1.70)	0.90 (0.58–1.41)	0.82 (0.49–1.36)	0.62 (0.35–1.10)	0.05
Incident type 2 diabetes in total population						
Total, *n*	516	517	516	517	516	2582
Cases, *n*	49	46	33	29	22	179
Model 1‡	1 *(Ref)*	0.98 (0.66–1.44)	0.70 (0.46–1.07)	0.62 (0.40–0.97)	0.47 (0.28–0.76)	0.0004
Model 2	1 *(Ref)*	1.02 (0.70–1.50)	0.84 (0.55–1.27)	0.75 (0.49–1.16)	0.59 (0.36–0.96)	0.01
Model 3	1 *(Ref)*	0.97 (0.66–1.43)	0.77 (0.49–1.20)	0.68 (0.42–1.09)	0.49 (0.27–0.88)	0.01

* Baseline “normal” defined as FG <5.6 mmol/L (<100 mg/dL), 2-hr OGTT glucose <7.8 mmol/L (<126 mg/dL), HOMA-IR <90th percentile, *and* FI <90th percentile. Baseline and incident “metabolic impairment” defined as FG ≥5.6 and <7.0 mmol/L (≥100–<125 mg/dL) *or* 2-hr OGTT glucose ≥7.8 and <11 mmol/L (≥140–<199 mg/dL) *or* HOMA-IR ≥90th percentile *or* FI ≥90th percentile. Type 2 diabetes defined as FG ≥7.0 mmol/L (≥126 mg/dL), 2-hr OGTT ≥11 mmol/L (≥200 mg/dL), or use of insulin or oral hypoglycemics. FG, fasting plasma glucose; FI, fasting plasma insulin; HOMA-IR, homeostasis model assessment of insulin resistance; OGTT, oral glucose tolerance test.

† As median value in each quintile of energy-adjusted magnesium intake (mg/d).

‡ Model 1 adjusted for age, sex, and energy intake. Model 2 was adjusted as for model 1, plus parental history of diabetes, BMI, physical activity score, smoking status, alcohol intake, and hypertension. Model 3 adjusted as for model 2, plus dietary fiber.

Table 3—*Relative risk of progression from normal to metabolically impaired (IFG or IGT) or metabolically impaired to type 2 diabetes by ADA Criteria, by quintile categories of energy-adjusted magnesium intake.**

	Quintile category of energy-adjusted averaged magnesium intake†					
	1	**2**	**3**	**4**	**5**	
Median intake, mg/d	235	272	298	332	395	*P* linear trend
Incident metabolic impairment among unimpaired at baseline						
Total, *n*	333	337	355	372	374	1771
Cases, *n*	72	50	58	75	49	304
Model 1‡	1 *(Ref)*	0.75 (0.54–1.04)	0.81 (0.59–1.11)	1.04 (0.78–1.38)	0.67 (0.48–0.93)	0.12
Model 2	1 *(Ref)*	0.77 (0.55–1.06)	0.85 (0.63–1.15)	1.07 (0.81–1.41)	0.74 (0.53–1.02)	0.33
Model 3	1 *(Ref)*	0.78 (0.56–1.08)	0.87 (0.63–1.21)	1.11 (0.82–1.51)	0.78 (0.52–1.18)	0.71
Incident type 2 diabetes among metabolically impaired at baseline						
Total, *n*	183	180	161	145	142	811
Cases, *n*	38	39	30	21	19	147
Model 1‡	1 *(Ref)*	1.06 (0.71–1.57)	0.91 (0.59–1.39)	0.70 (0.43–1.14)	0.63 (0.38–1.05)	0.02
Model 2	1 *(Ref)*	1.12 (0.76–1.67)	1.03 (0.67–1.57)	0.84 (0.52–1.35)	0.71 (0.43–1.18)	0.09
Model 3	1 *(Ref)*	1.05 (0.70–1.56)	0.93 (0.60–1.44)	0.73 (0.43–1.22)	0.56 (0.32–0.99)	0.02

* Baseline “normal” defined as FG <5.6 mmol/L (<100 mg/dL) *and* 2-hr OGTT glucose <7.8 mmol/L (<126 mg/dL). Baseline and incident “metabolic impairment” defined as FG ≥5.6 and <7.0 mmol/L (≥100–<125 mg/dL) *or* 2-hr OGTT glucose ≥7.8 and <11 mmol/L (≥140–<199 mg/dL). Type 2 diabetes defined as FG ≥7.0 mmol/L (≥126 mg/dL), 2-hr OGTT ≥11 mmol/L (≥200 mg/dL), or use of insulin or oral hypoglycemics. ADA, American Diabetes Association; FG, fasting plasma glucose; OGTT, oral glucose tolerance test.

† As median value in each quintile of energy-adjusted magnesium intake (mg/d).

‡ Model 1 adjusted for age, sex, and energy intake. Model 2 was adjusted as for model 1, plus parental history of diabetes, BMI, physical activity score, smoking status, alcohol intake, and hypertension. Model 3 adjusted as for model 2, plus dietary fiber.

Table 4—*Adjusted means of measures of glucose and insulin by quintile categories of energy-adjusted magnesium intake over 7-yrs of follow-up in participants without incident type 2 diabetes*

	Quintile category of energy-adjusted averaged magnesium intake†					
Median,	**1**	**2**	**3**	**4**	**5**	
mg/d	236	272	299	332	395	*P* linear trend
Fasting glucose (mmol/L), *n*=2312						
Model 1*	5.42 (0.02)	5.38 (0.02)	5.38 (0.02)	5.39 (0.02)	5.32 (0.02)	0.003
2	5.40 (0.02)	5.38 (0.02)	5.38 (0.02)	5.39 (0.02)	5.33 (0.02)	0.02
3	5.40 (0.02)	5.38 (0.02)	5.38 (0.02)	5.40 (0.02)	5.34 (0.02)	0.17
Fasting insulin (pmol/L), *n*=2185 †						
Model 1*	89.14 (1.02)	88.11 (1.02)	86.99 (1.02)	88.16 (1.02)	85.20 (1.02)	0.13
2	88.79 (1.02)	88.18 (1.02)	87.21 (1.02)	88.18 (1.02)	85.23 (1.02)	0.15
3	88.30 (1.02)	88.00 (1.02)	87.17 (1.02)	88.32 (1.02)	85.74 (1.02)	0.41
HOMA-IR, *n*=2185 †						
Model 1*	3.09 (1.02)	3.01 (1.02)	2.98 (1.02)	3.02 (1.02)	2.89 (1.02)	0.04
2	3.07 (1.02)	3.02 (1.02)	2.99 (1.02)	3.02 (1.02)	2.89 (1.02)	0.05
3	3.05 (1.02)	3.01 (1.02)	2.98 (1.02)	3.03 (1.02)	2.91 (1.02)	0.26
2-hr OGTT glucose (mmol/L), *n*=863						
Model 1*	6.75 (0.11)	6.35 (0.12)	6.63 (0.11)	6.75 (0.11)	6.43 (0.11)	0.27
2	6.69 (0.11)	6.36 (0.12)	6.61 (0.11)	6.78 (0.11)	6.46 (0.11)	0.64
3	6.64 (0.12)	6.34 (0.12)	6.61 (0.11)	6.80 (0.11)	6.51 (0.12)	0.79
2-hr OGTT insulin (pmol/L), *n*=837 †						
Model 1*	383.84 (1.05)	347.90 (1.05)	368.35 (1.04)	381.10 (1.04)	338.50 (1.04)	0.14
2	380.67 (1.05)	348.71 (1.05)	365.32 (1.04)	387.28 (1.04)	337.95 (1.04)	0.19
3	378.40 (1.05)	348.08 (1.05)	365.11 (1.04)	387.75 (1.04)	340.08 (1.05)	0.40
Gutt's ISI, *n*=837						
Model 1*	22.47 (0.40)	23.69 (0.41)	22.87 (0.39)	22.41 (0.39)	23.58 (0.38)	0.26
2	22.67 (0.40)	23.69 (0.40)	22.94 (0.38)	22.26 (0.39)	23.49 (0.38)	0.57
3	22.80 (0.44)	23.73 (0.41)	22.96 (0.38)	22.23 (0.39)	23.34 (0.42)	0.95

* Model 1 adjusted for corresponding baseline measure, age, sex, and energy intake. Model 2 was adjusted as for model 1, plus parental history of diabetes, BMI, physical activity score, smoking status, alcohol intake, and hypertension. Model 3 adjusted as for model 2, plus dietary fiber.
HOMA-IR, homeostasis model assessment of insulin resistance; ISI, Gutt's Insulin Sensitivity Index$_{0-120}$; OGTT, oral glucose tolerance test.
† Analyzed in the natural-log scale and back-transformed to geometric mean (geometric SE) for presentation.

ONLINE SUPPLEMENTAL MATERIAL

Supplemental Table S1—*Criteria underlying definitions of metabolic impairment*

	Defining criteria		
Indicator	**Normal**	**Impaired**	**Type 2 diabetes***
Fasting glucose	<5.6 mmol/L (<100 mg/dL)	≥5.6 but <7.0 mmol/L (100–<126 mg/dL)	≥7.0 mmol/L (≥126 mg/dL)
2-hr OGTT glucose	<7.8 mmol/L (<140 mg/dL)	≥7.8 but <11.1 mmol/L (140–<200 mg/dL)	≥11.1 mmol/L (≥200 mg/dL)
Fasting insulin	<90th percentile†	≥90th percentile	--
HOMA-IR	<90th percentile‡	≥90th percentile	--

* Or by reported diagnosis of type 2 diabetes, or reported use of an oral hypoglycemic drug or insulin. HOMA-IR, homeostasis model assessment of insulin resistance; OGTT, oral glucose tolerance test.
† In this sample, baseline cut-point of 41.0; incident cut-point of 25.0.
‡ In this sample, baseline cut-point of 10.1; incident cut-point of 6.7.