Higher Magnesium Intake Is Associated with Lower Fasting Glucose and Insulin, with No Evidence of Interaction with Select Genetic Loci, in a Meta-Analysis of 15 CHARGE Consortium Studies[1–4]

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Abstract

Favorable associations between magnesium intake and glycemic traits, such as fasting glucose and insulin, are observed in observational and clinical studies, but whether genetic variation affects these associations is largely unknown. We

hypothesized that single nucleotide polymorphisms (SNPs) associated with either glycemic traits or magnesium metabolism affect the association between magnesium intake and fasting glucose and insulin. Fifteen studies from the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium provided data from up to 52,684 participants of European descent without known diabetes. In fixed-effects meta-analyses, we quantified *1*) cross-sectional associations of dietary magnesium intake with fasting glucose (mmol/L) and insulin (ln-pmol/L) and *2*) interactions between magnesium intake and SNPs related to fasting glucose (16 SNPs), insulin (2 SNPs), or magnesium (8 SNPs) on fasting glucose and insulin. After adjustment for age, sex, energy intake, BMI, and behavioral risk factors, magnesium (per 50-mg/d increment) was inversely associated with fasting glucose [$\beta = -0.009$ mmol/L (95% CI: -0.013, -0.005), $P < 0.0001$] and insulin [-0.020 ln-pmol/L (95% CI: -0.024, -0.017), $P < 0.0001$]. No magnesium-related SNP or interaction between any SNP and magnesium reached significance after correction for multiple testing. However, rs2274924 in magnesium transporter-encoding *TRPM6* showed a nominal association (uncorrected $P = 0.03$) with glucose, and rs11558471 in *SLC30A8* and rs3740393 near *CNNM2* showed a nominal interaction (uncorrected, both $P = 0.02$) with magnesium on glucose. Consistent with other studies, a higher magnesium intake was associated with lower fasting glucose and insulin. Nominal evidence of *TRPM6* influence and magnesium interaction with select loci suggests that further investigation is warranted. *J. Nutr.* 143: 345–353, 2013.

Introduction

Magnesium is an essential mineral found in many foods; rich sources include whole grains, green leafy vegetables, coffee, and legumes. Magnesium is a critical cofactor in >300 enzymatic reactions, including those related to energy metabolism (1). Evidence from cross-sectional and longitudinal observational studies suggests that diets higher in magnesium are associated with reduced risk of insulin resistance (2–8) and type 2 diabetes (9,10), whereas in intervention studies, supplemental magnesium improves measures of glucose and insulin metabolism in generally healthy adults (11,12), as well as in those with insulin resistance (13,14) and type 2 diabetes (15,16). However, little is known about potential interaction between magnesium intake and genetic variability on glycemic traits, in which genetic variants related to either magnesium transport and homeostasis or glucose and insulin metabolism may modify the pathways through which magnesium exerts its effects.

Single nucleotide polymorphisms (SNPs)[48] associated with modest elevation in fasting glucose (FG) and fasting insulin (FI)

concentrations have been identified through meta-analysis of genome-wide association studies (GWAS) (17). In addition, a GWAS meta-analysis of serum magnesium, a biomarker of magnesium status, identified 6 SNPs in genes linked to magnesium transport and homeostasis (18). Among these 6 SNPs, the C allele of rs4072037 in *MUC1*, which was associated with lower serum magnesium, was also associated with lower FG concentrations (18). Three studies have also investigated associations between magnesium-related loci in transient receptor potential cation channel, subfamily M, members 6 (*TRPM6*) or 7 (*TRPM7*) and diabetes or glycemic traits. One of these studies observed an association between carriers of the *TRPM6* rs2274924 variant and elevated total glycosylated hemoglobin and odds of gestational diabetes in 997 women after delivery (19). The loci studied in these 2 genes in the other 2 studies did not modify either disease (20,21) or glycemic traits (21); however, these were small studies and one included women only (20). The latter study (20) also examined interactions between magnesium intake and *TRPM6* and *TRPM7* loci on risk of type 2 diabetes, reporting increased odds of disease in women with a risk haplotype at rs3750425 and rs2274924 in *TRPM6* only when magnesium intake was <250 mg/d.

Despite plausible biological mechanisms underlying associations between magnesium and glycemic traits, such as magnesium's role as a cofactor for tyrosine kinase in the β subunit of the insulin receptor (22,23), the interaction between dietary magnesium and glycemia-related genetic variants on glucose and insulin has yet to be examined. Furthermore, genetic factors related to magnesium transport and homeostasis may modify associations between magnesium intake and glycemic traits. Examining interactions between dietary magnesium and these variants may enhance our understanding of type 2 diabetes etiology and pathogenesis. Therefore, we examined cross-sectional associations of dietary magnesium intake with FG and FI, associations of magnesium-related SNPs with FG and FI, and interactions between dietary magnesium intake and both magnesium-related and glycemia-related SNPs on FG and FI in meta-analyses of 15 cohort studies.

Methods

Participating cohorts. The sample for the cross-sectional meta-analyses included up to 52,684 participants of European descent from 15 cohort studies (**Table 1**) participating in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium Nutrition

[48] Abbreviations used: ARIC, Atherosclerosis Risk in Communities Study; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; CHS, Cardiovascular Health Study; FamHS, Family Heart Study; FG, fasting glucose; FHS, Framingham Heart Study; FI, fasting insulin; GENDAI, Gene-Diet Attica Investigation on Childhood Obesity; GHRAS, Greek Health Randomized Aging Study; GLACIER, Gene-Lifestyle interactions And Complex traits Involved in Elevated disease Risk; GWAS, genome-wide association study; HealthABC, Health, Aging, and Body Composition Study; InCHIANTI, Invecchiare in Chianti; MAGIC, Meta-Analyses of Glucose and Insulin-Related Traits Consortium; MESA, Multi-Ethnic Study of Atherosclerosis; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; SNP, single nucleotide polymorphism; ULSAM, Uppsala Longitudinal Study of Adult Men; YFS, Cardiovascular Risk in Young Finns Study.

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TABLE 1 Participant characteristics of 15 US and European cohort studies[1]

Cohort study (study acronym) (country)	n[2]	Age (y)	Sex (% women)	BMI (kg/m²)	Fasting glucose (mmol/L)	Fasting insulin[3] (pmol/L)	Dietary magnesium intake (mg/d)	Energy intake (kcal/d)	Alcohol intake (g/d)	Current smoker (%)	Completed high school (%)
Atherosclerosis Risk in Communities (ARIC) Study (USA)	8951	54 ± 5.7	53.7	27 ± 4.6 (n = 8586)	5.5 ± 0.50	58.6 ± 1.93 (16.1, 213)	260 ± 94.5	1640 ± 600	6.7 ± 1.0 (n = 8579)	24.4 (n = 8587)	84.1 (n = 8585)
Cardiovascular Health Study (CHS) (USA)	2745	72 ± 5.4	62.3	26 ± 4.3 (n = 2737)	5.5 ± 0.52	84.8 ± 1.54 (36.5, 197)	413 ± 145	2020 ± 650	5.8 ± 13 (n = 2740)	11.5 (n = 2744)	76.2 (n = 2739)
Family Heart Study (FamHS) (US)	3187 (3181)	51 ± 14	53.6	27 ± 5.3	5.2 ± 0.50	60.3 ± 1.82 (18.6, 196)	261 ± 95.8	1750 ± 620	6.4 ± 13	14.6	64.8
Framingham Heart Study (FHS) (USA)	5743 (5435)	49 ± 14	54.9	27 ± 5.2	5.3 ± 0.50	79.8 ± 1.47 (14.9, 544)	314 ± 115	1970 ± 660	11 ± 15	29.6	97.5
Gene-Diet Attica Investigation on Childhood Obesity (GENDAI) (Greece)	1087 (1064)	11 ± 0.70	53.2	20 ± 3.4	4.8 ± 0.48	40.0 ± 1.72 (13.8, 116)	225 ± 75.6	1890 ± 600	NA	NA	NA
Greek Health Randomized Aging Study (GHRAS) (Greece)	856 (670)	72 ± 7.5	71.2	30 ± 4.8	5.8 ± 1.6	43.1 ± 1.75 (14.4, 129)	237 ± 63.1	2160 ± 690	45 ± 90	14.5	64.0
Gene-Lifestyle interactions And Complex traits In Elevated disease Risk (GLACIER) (Sweden)	14,940 (892)	52 ± 8.8	60.7	26 ± 4.0	5.4 ± 0.62	41.3 ± 1.90 (11.8, 145)	291 ± 92.4	1720 ± 600	3.5 ± 4.5	21.6	79.1
Health, Aging, and Body Composition Study (Health ABC) (USA)	1281 (1256)	74 ± 2.8	50.2	26 ± 4.0	5.2 ± 0.55	45.1 ± 1.70 (15.9, 128)	294 ± 101	1810 ± 600	6.9 ± 14	6.10	89.1
Invecchiare in Chianti (Aging in the Chianti Area; InCHIANTI) (Italy)	1071 (1044)	68 ± 16	56.3	27 ± 4.1	4.8 ± 0.61	65.4 ± 1.70 (23.1, 185)	256 ± 74.6	2010 ± 600	15 ± 21	24.3	80.4
Malmö Diet and Cancer Study (Malmö) (Sweden)	4867 (4864)	58 ± 5.9	60.0	25 ± 3.8	5.5 ± 0.52	37.3 ± 1.70 (13.2, 106)	353 ± 91.3	2320 ± 670	10 ± 12	26.9	80.4
Multi-Ethnic Study of Atherosclerosis (MESA) (USA)	2145	63 ± 10	52.4	28 ± 5.0	4.9 ± 0.56	32.6 ± 1.84 (9.84, 108)	276 ± 113	1700 ± 720	8.8 ± 16	11.0	79.3
Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) (Sweden)	727	70 ± 0.20	51.2	27 ± 4.1	4.9 ± 0.51	50.4 ± 1.68 (18.2, 140)	317 ± 75.5	1890 ± 500	8.1 ± 7.9	10.6	44.7
Rotterdam Study (The Netherlands)	2340 (2273)	72 ± 6.6	58.0	27 ± 3.8	5.5 ± 0.53	62.8 ± 1.68 (22.7, 174)	314 ± 75.5	1990 ± 510	11 ± 14	15.8	90.3
Uppsala Longitudinal Study of Adult Men (ULSAM) (Sweden)	927 (919)	71 ± 0.60	0	26 ± 3.2	5.4 ± 0.56	73.7 ± 1.72 (25.6, 212)	286 ± 70.0	1750 ± 460	8.6 ± 13	20.2	41.0
Cardiovascular Risk in Young Finns Study (YFS) (Finland)	1788 (1783)	38 ± 5.0	54.1	26 ± 4.7	5.3 ± 0.75	40.5 ± 2.16 (8.94, 183)	480 ± 156	2410 ± 860	13 ± 20	18.3	84.6

[1] Values are mean ± SD or percentages (%). Alcohol intake originally quantified as drinks/wk in CHS and FamHS and as drinks/d in YFS. Conversion to grams per day was based on 1 drink containing 14 g alcohol. NA, not applicable.

[2] Maximum available observations, n, for interactions between magnesium intake and single nucleotide polymorphisms in glucose outcome analyses (n for insulin interaction analyses in parentheses). Sample sizes vary in some cohorts depending on availability of genotype information.

[3] Insulin was analyzed on the natural log scale and back-transformed to the geometric scale for presentation. Values are geometric mean ± SD (95% CI).

Working Group (24): the Atherosclerosis Risk In Communities (ARIC) Study; the Family Heart Study (FamHS); the Framingham Heart Study Offspring and Generation 3 (FHS); the Cardiovascular Health Study (CHS); the Gene-Diet Attica Investigation on Childhood Obesity (GENDAI); the Greek Health Randomized Aging Study (GHRAS); the Gene-Lifestyle interactions And Complex traits Involved in Elevated disease Risk (GLACIER); the Health, Aging, and Body Composition (Health ABC) Study; Invecchiare in Chianti (InCHIANTI); the Malmö Diet and Cancer Study cardiovascular cohort (Malmö); the Multi-Ethnic Study of Atherosclerosis (MESA); the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS); the Rotterdam Study (Rotterdam); the Uppsala Longitudinal Study of Adult Men (ULSAM); and the Cardiovascular Risk in Young Finns Study (YFS). Participants provided written informed consent, and the protocol was approved by local institutional review boards. Participants within each cohort were excluded from analyses if they had diabetes, defined as diagnosed or self-reported diabetes, and/or fasting glucose ≥7 mmol/L, and/or use of diabetes medications.

Dietary assessment. Dietary data were collected via FFQ in 11 cohorts and via dietary recall (1 cohort), food record (2 cohorts), or a combination of food diary and FFQ (1 cohort). Daily intakes of dietary magnesium (from food and beverage sources), kilocalories, fiber, caffeine, and alcohol were estimated for each participant (**Supplemental Table 1**). By using data from 2 of our cohorts (ARIC and FHS), we assessed the rank ordering of participants using magnesium values derived from food/beverage sources only versus food/beverage and supplemental sources. Unadjusted Spearman correlations between food/beverage magnesium and total (food/beverage and supplemental) magnesium intake were 0.93 and 0.92 in ARIC and FHS, respectively, and 0.84 and 0.83 in ARIC and FHS, respectively, after adjustment for energy intake. Ranks did not vary appreciably and supplemental sources contributed, on average, just 8–16 mg/d of magnesium intake above that derived from food/beverage sources. Only 6 of the 15 studies had supplement use information on <8000 participants. Given these considerations, and to maximize sample size, we considered magnesium intake from food/beverage sources only.

Genotyping, imputation, and SNP selection. SNPs were previously directly genotyped or imputed by participating cohorts before inclusion in this analysis (Supplemental Table 1). Of the 25 SNPs included in this meta-analysis, a previous GWAS meta-analysis in the Meta-Analyses of Glucose and Insulin-Related Traits Consortium (MAGIC)—which included data from CHS, FHS, InCHIANTI, and Rotterdam—identified 15 SNPs associated with FG, 1 with FI, and 1 with both FG and FI (17). Five SNPs were previously identified in another meta-analysis of GWAS of serum magnesium in MAGIC members, including ARIC, CHS, FHS, and Rotterdam (18). The remaining 3 SNPs associated with magnesium transport or homeostasis selected for this meta-analysis were based on the report by Song et al. (20). Not all SNPs were available in every cohort; total sample sizes for analyses vary accordingly (**Supplemental Table 2**).

FG and FI measurement. FG (mmol/L) and FI (pmol/L) were quantified in each cohort by using similar procedures (Supplemental Table 1). FI was natural log-transformed to reduce skewness before data analysis.

Covariate measurement. Cohort-specific assessment methods and definitions for BMI, educational level, smoking status, and physical activity are provided in Supplemental Table 1.

Cohort-specific analyses. Each cohort followed a uniform analysis plan to conduct the following analyses. First, main associations between magnesium intake and FG and FI were quantified with adjustment for age, sex, and energy intake (model 1); with additional adjustment for BMI (model 2); with additional adjustment for smoking, education, physical activity, and alcohol intake (model 3); and with additional adjustment for fiber and caffeine intake (model 4). Fiber and caffeine were considered as covariates to distinguish associations of magnesium with FG and FI from those due to nutrients contained in shared food

sources displaying similar associations with glycemic traits (e.g., whole grains and coffee). Second, to verify earlier reported associations with FG (16 SNPs) and FI (2 SNPs), and to investigate associations between magnesium-related SNPs (8 SNPs) and FG and FI, cohorts regressed FG and FI on SNPs of interest by using an additive genetic model (per additional outcome-raising allele) adjusted for age and sex and, where relevant, study field center and/or family or population substructure. Third, magnesium-SNP interactions were investigated by including a first-order interaction term (magnesium intake × SNP) in a model including magnesium intake, SNP, age, sex, and energy intake. Before meta-analysis, the β coefficients and SEs involving magnesium intake (per 1 mg/d) reported by each cohort were multiplied by 50 to estimate the association of a 50-mg/d increment in magnesium intake, because 1-mg/d estimates were exceedingly small. Fifty milligrams of magnesium reflects intake from ~2 ounces of espresso or 2 slices of whole-wheat bread. Assuming a hypothesis-consistent inverse association of magnesium with FG and FI, positive-interaction β coefficients indicate that the magnitude of the inverse association between magnesium intake and FG or FI is less in the presence of an FG- or FI-raising allele. That is, for individuals who carry 1 copy of an FG- or FI-raising allele, the lower FG or FI concentration observed in association with a 50-mg/d increment in magnesium intake would be diminished. Correspondingly, negative-interaction β coefficients indicate that the magnitude of the inverse association between magnesium intake and FG or FI is greater in the presence of an FG- or FI-raising allele. That is, for individuals who carry 1 copy of an FG- or FI-raising allele, the lower FG or FI concentration observed in association with a 50 mg/d higher magnesium intake would be stronger.

Meta-analyses. We conducted inverse variance–weighted, fixed-effects meta-analyses for *1)* main associations of magnesium intake on FG and FI by using STATA (version 12, Stata Corporation), *2)* main associations of SNPs with respective outcomes by using METAL (University of Michigan, Center for Statistical Genetics; www.sph.umich.edu/csg/abecasis/metal/), and *3)* interactions between SNPs and magnesium intake on respective outcomes by using METAL. The sample sizes for magnesium associations with FG ranged from 52,684 (model 1) to 48,588 (model 4), and with FI they ranged from 37,640 (model 1) to 34,137 (model 4). The sample sizes for interaction analyses on FG ranged from 29,280 (rs2274924) to 52,470 (rs4607517), and on FI they ranged from 28,851 (rs2274924) to 37,804 (rs780094). Heterogeneity across studies was tested by using Cochran's Q statistic and quantified by using the I^2 statistic (25). Approximately defined ranges for interpreting I^2 for low, moderate, substantial, and considerable heterogeneity are 0–40%, 30–60%, 50–90%, and 75–100%, respectively (26). To assess potential sources of heterogeneity, we conducted meta-regression of the main magnesium association and of the interaction analyses. [For the main associations of the 8 magnesium-related SNPs on FG or FI (Supplemental Table 2), because no (0%) to low (28%) heterogeneity was observed, meta-regressions were not conducted for these associations.] Meta-regression covariates included region (northern Europe vs. Mediterranean vs. United States), mean age of cohort (<60 vs. ≥60 y), mean magnesium intake of cohort (<300 vs. ≥300 mg/d), mean BMI of cohort (<27 vs. ≥27 kg/m^2), percentage of the cohort that was female, and sample size. We also conducted sensitivity analyses to assess the influence on the meta-analyzed estimate of any single cohort study by repeating analyses removing 1 cohort study at a time in the associations for magnesium, magnesium-related SNPs, and magnesium-SNP interactions. Random-effects meta-analyses were conducted secondarily; results were similar to those from the fixed-effects meta-analyses. Thus, we only present the results of the fixed-effects meta-analyses.

Power calculations for various magnitudes of association and sample sizes have been published elsewhere (24,27). Statistical significance was defined at an α level of 0.0015, based on Bonferroni correction for 34 total interaction tests.

Results

The demographic, dietary, and outcome characteristics of participants in the 15 cohort studies are provided in Table 1.

Mediterranean cohorts tended to have the lowest overall mean dietary magnesium intake and northern European cohorts the highest; the mean daily intake of dietary magnesium ranged from 224.7 mg/d in GENDAI (Greece) to 479.7 mg/d in YFS (Finland). Plots of mean intake across cohorts did not suggest that intake differed by either dietary assessment method or mean age (**Supplemental Figs. 1** and **2**).

Associations of magnesium intake with FG and FI. After adjustment for age, sex, alcohol, energy intake, BMI, smoking, education, and physical activity (model 3), magnesium intake was inversely associated with FG and FI concentrations. Per daily 50-mg increment of dietary magnesium, FG was 0.009 mmol/L lower [$\beta = -0.009$ mmol/L (95% CI: −0.013, −0.005), $P < 0.0001$] (**Table 2** and **Fig. 1**) and FI was −0.020 ln-pmol/L lower [$\beta = -0.020$ ln-pmol/L (95% CI: −0.024, −0.017), $P < 0.0001$] (**Table 2** and **Fig. 2**). After additional adjustment for caffeine and fiber intake (model 4), the association of magnesium with FG was attenuated [$\beta = -0.001$ mmol/L (95% CI: −0.006, 0.004), $P = 0.78$] (**Table 2**). However, magnesium intake remained significantly inversely associated with FI, although the magnitude of the association was mitigated [$\beta = -0.012$ ln-pmol/L (95% CI: −0.017, −0.007), $P < 0.0001$] (**Table 2**). Results of sensitivity analyses and meta-regressions did not substantively affect our conclusions, or reveal any clear sources of heterogeneity (results not shown).

Associations of SNPs with FG and FI. Meta-analyzed estimates of SNP associations with FG and FI are presented in Supplemental Table 2. The direction and magnitude of the associations of the 16 glucose- and 2 insulin-related SNPs on FG or FI, respectively, were consistent with those previously reported (17). The 8 SNPs related to magnesium homeostasis and transport showed no significant association with either FG or FI (Supplemental Table 2). A nominally significant inverse association with FG was observed per additional G allele at rs2274924 in *TRPM6* [$\beta = -0.013$ (95% CI: −0.024, −0.001) mmol/L, $P = 0.03$]. Results of sensitivity analyses and meta-regressions did not substantively affect our conclusions, or reveal any clear sources of heterogeneity (results not shown).

Magnesium-SNP interactions on FG and FI. Meta-analyzed estimates of interactions between magnesium intake and SNPs on FG and FI are presented in **Table 3** (with additional information in **Supplemental Figs. 3** and **4**). There was no significant interaction on either FG or FI, after correction for multiple testing (i.e., at $P < 0.0015$). Two nominally significant interactions were observed between SNPs and magnesium on FG. The first at rs11558471 in *SLC30A8* (previously associated with FG levels) suggested a stronger glucose-lowering association with higher magnesium intake in those with the A (risk) allele at this locus [interaction $\beta = -0.0045$ (95% CI: −0.0082, −0.0008) mmol/L per A allele and 50-mg/d increment in magnesium, $P = 0.02$]. The second at rs3740393 near *CNNM2* (previously associated with magnesium transport/homeostasis) suggested a weaker inverse association between magnesium intake and FG in those with the G (risk) allele at this locus [interaction $\beta = 0.0064$ (95% CI: 0.0009, 0.0119) mmol/L per G allele with 50 mg/d higher magnesium, $P = 0.02$]. Results of sensitivity analyses and meta-regressions did not substantively affect our conclusions, or reveal any clear sources of heterogeneity (results not shown).

Discussion

In this cross-sectional meta-analysis involving >50,000 participants free of diabetes in 15 cohort studies from the CHARGE Consortium, we observed inverse associations between magnesium intake and FG and FI concentrations, even after adjustment for BMI and other demographic and lifestyle factors known to influence diabetes risk. After further adjustment for fiber and caffeine intake, the inverse association of magnesium with FI remained significant, but not the association with FG. However, including these dietary components in the model may be an overadjustment, reflecting common food sources, thus leading to the observed mitigated associations. Our study is among the largest, to our knowledge, to investigate these tightly controlled measures of glucose homeostasis in generally healthy populations. Our findings support those of recent meta-analyses of studies on magnesium and incident type 2 diabetes, which estimated ~14% reduced risk of disease per daily 100-mg

TABLE 2 Meta-analyzed associations between magnesium intake and fasting glucose and fasting insulin in 15 cohort studies

Model[1]	Association[2] of fasting glucose (mmol/L) per 50-mg/d increment in magnesium intake				Association[2] of fasting insulin (ln-pmol/L) per 50-mg/d increment in magnesium intake			
	n[3]	β (95% CI)	P	I^2 (95% CI)	n[3]	β (95% CI)	P	I^2 (95% CI)
1	52,684	−0.016 (−0.019, −0.012)	<0.0001	50 (9, 72)	37,640	−0.028 (−0.032, −0.024)	<0.0001	80 (68, 88)
2	52,568	−0.013 (−0.017, −0.010)	<0.0001	20 (0, 56)	37,527	−0.023 (−0.026, −0.020)	<0.0001	81 (69, 88)
3	50,921	−0.009 (−0.013, −0.005)	<0.0001	30 (0, 62)	36,271	−0.020 (−0.024, −0.017)	<0.0001	75 (59, 85)
4	48,588	−0.001 (−0.006, 0.005)	0.78	30 (0, 65)	34,137	−0.012 (−0.017, −0.007)	<0.0001	46 (0, 73)

[1] Model 1 adjusted for age, sex, energy intake, study center (in Atherosclerosis Risk in Communities Study; Cardiovascular Health Study; Family Heart Study; Health, Aging, and Body Composition Study; Invecchiare in Chianti; Multi-Ethnic Study of Atherosclerosis), and family or population substructure (in Cardiovascular Health Study, Family Heart Study, Framingham Heart Study, Multi-Ethnic Study of Atherosclerosis, Cardiovascular Risk in Young Finns Study). Model 2 adjusted for model 1 with additional adjustment for BMI. Model 3 adjusted for model 2 with additional adjustment for smoking, education, physical activity, and alcohol intake. The Gene-Diet Attica Investigation on Childhood Obesity (child/adolescent cohort) did not adjust for smoking, education, or alcohol intake, because these variables are not applicable in this cohort. The Rotterdam Study did not adjust for physical activity, because this variable was not available in this cohort. Model 4 adjusted for model 3 with additional adjustment for fiber and caffeine. The Greek Health Randomized Aging Study, Prospective Investigation of the Vasculature in Uppsala Seniors, and Uppsala Longitudinal Study of Adult Men were excluded from model 4 analysis, because these cohorts did not have information on either fiber or caffeine intake.
[2] β coefficient and 95% CI shown as β (95% CI).
[3] The number of independent observations in each analysis.
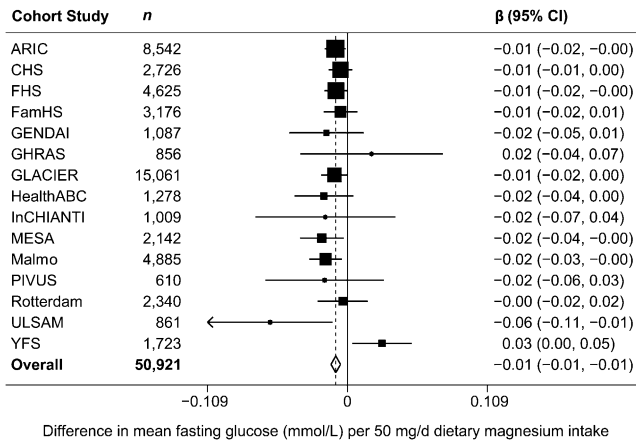
FIGURE 1 Forest plot of associations between dietary magnesium (50 mg/d) and fasting glucose (mmol/L) in 15 US and European cohort studies. The estimate from each cohort study, indicated by a filled square, was adjusted for age, sex, BMI, smoking, education, physical activity, alcohol intake, energy intake, study center (in ARIC, CHS, FamHS, HealthABC, InCHIANTI, MESA), and/or family or population substructure (in CHS, FamHS, FHS, MESA, YFS). GENDAI (child/adolescent cohort) did not adjust for smoking, education, or alcohol intake, because these variables were not applicable in this study. Rotterdam did not adjust for physical activity, because this variable was not available in the study. The size of the square is proportional to the weight of the cohort study in the overall fixed-effects estimate, and the horizontal line represents the 95% CI. The overall summary estimate and its 95% CI are indicated by the open diamond. ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; FamHS, Family Heart Study; FHS, Framingham Heart Study; GENDAI, Gene-Diet Attica Investigation on Childhood Obesity; GHRAS, Greek Health Randomized Aging Study, GLACIER, Gene-Lifestyle interactions And Complex traits Involved in Elevated disease Risk; HealthABC, Health, Aging, and Body Composition Study; InCHIANTI, Invecchiare in Chianti; MESA, Multi-Ethnic Study of Atherosclerosis; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; ULSAM, Uppsala Longitudinal Study of Adult Men; YFS, Cardiovascular Risk in Young Finns Study.

increment in magnesium intake (9,10). Previous prospective cohort studies investigating whole-grain (28) and coffee (29–33) consumption on type 2 diabetes risk have observed beneficial associations with higher consumption. From a reductionist viewpoint, it remains of interest whether the whole foods themselves or their key components (e.g., magnesium or fiber in whole grains, or magnesium, caffeine, or other polyphenols in coffee) exert health benefits. Our observations suggest that the association between magnesium intake and FI is at least partly independent of other dietary constituents found in magnesium-containing foods, such as whole grains and coffee, a phenomenon previously observed in at least 2 smaller observational studies (2,6). In prospective studies of magnesium intake and type 2 diabetes, associations of magnesium intake do not appear to be substantially affected after accounting for fiber intake (9). However, results of previous cross-sectional studies in adults free of diabetes are inconsistent with respect to magnesium's associations with FG, irrespective of adjustment for fiber intake (6,34,35). Because blood glucose is generally under tight homeostatic control in diabetes-free populations, such as those included here, our observations lend support to the hypothesis of magnesium's actions in insulin sensitivity and resistance with downstream, mitigating effects on diabetes pathogenesis (23).

Our findings on the associations of 16 glucose- and 2 insulin-related SNPs with FG and FI are in line with those previously reported (17). We also investigated 8 magnesium-related loci in relation to FG and FI, hypothesizing that if magnesium is causally related to these traits, genes that influence magnesium transport and homeostasis might be expected to affect FG and FI. However, we found no significant evidence that variation at these loci influences FG or FI. Our strongest, nominally significant association with FG was at rs2274924 ($P = 0.03$) in *TRPM6*, a gene encoding a magnesium-permeable epithelial channel with a critical role in magnesium reabsorption in the kidney. The missense mutation (A → G) at rs2274924 causes a Lys1584Glu amino acid change in exon 27 of the resulting channel protein. Nair et al. (19) recently reported that, in the presence of this polymorphism, the insulin signaling cascade is unable to activate the phosphorylation of the amino acid adjacent to the substituted amino acid resulting from the polymorphism, thereby rendering the variant TRPM6 channel insensitive to the activating effects of insulin. Furthermore, increased glycosylated hemoglobin and greater risk of gestational diabetes were observed in *GG* homozygotes compared to *AA* homozygotes in a cohort of 997 women (19). In contrast, rs2274924 was not associated with type 2 diabetes in 1 small case-control study in women (20). Consistent with other reports,
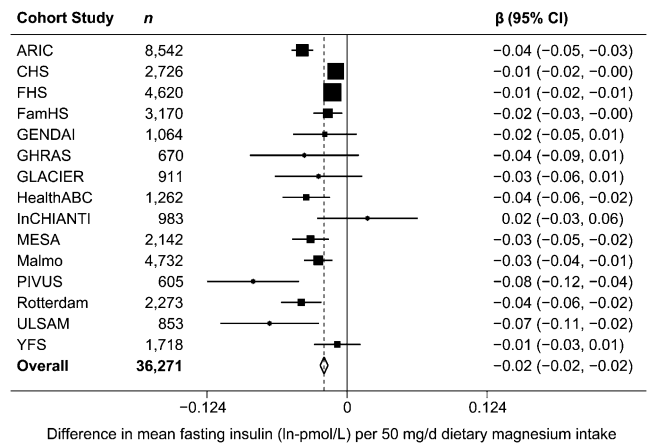
FIGURE 2 Forest plot of associations between dietary magnesium (50 mg/d) and fasting insulin (ln-pmol/L) in 15 US and European cohort studies. The estimate from each cohort study, indicated by a filled square, was adjusted for age, sex, BMI, smoking, education, physical activity, alcohol intake, energy intake, study center (in ARIC, CHS, FamHS, HealthABC, InCHIANTI, MESA), and/or family or population substructure (in CHS, FamHS, FHS, MESA, YFS). GENDAI (child/adolescent cohort) did not adjust for smoking, education, or alcohol intake, because these variables were not applicable in this study. Rotterdam did not adjust for physical activity, because this variable was not available in the study. The size of the square is proportional to the weight of the cohort study in the overall fixed-effects estimate, and the horizontal line represents the 95% CI. The overall summary estimate and its 95% CI are indicated by the open diamond. ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; FamHS, Family Heart Study; FHS, Framingham Heart Study; GENDAI, Gene-Diet Attica Investigation on Childhood Obesity; GHRAS, Greek Health Randomized Aging Study, GLACIER, Gene-Lifestyle interactions And Complex traits Involved in Elevated disease Risk; HealthABC, Health, Aging, and Body Composition Study; InCHIANTI, Invecchiare in Chianti; MESA, Multi-Ethnic Study of Atherosclerosis; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; ULSAM, Uppsala Longitudinal Study of Adult Men; YFS, Cardiovascular Risk in Young Finns Study.

TABLE 3 Meta-analyzed interactions between magnesium intake and SNPs on fasting glucose and fasting insulin in 15 cohort studies[1]

SNP	Nearest gene	Coded allele	Other allele	Coded allele frequency	Number of cohorts	Interaction[2] between 50-mg/d increment in magnesium intake × SNP on outcome			
						n^3	β (95% CI)	P	I^2 (95% CI)
Glucose-related SNPs						Outcome is fasting glucose (*mmol/L*)			
rs10830963	MTNR1B	G	C	0.28	15	51,257	0.0033 (−0.0006, 0.0072)	0.10	47 (4, 71)
rs10885122	ADRA2A	G	T	0.89	15	52,068	−0.0013 (−0.0064, 0.0038)	0.64	15 (0, 53)
rs11071657	C2CD4B	A	G	0.62	15	52,098	0.0023 (−0.0012, 0.0058)	0.21	0 (0, 35)
rs11558471	SLC30A8	A	G	0.69	13	50,329	−0.0045 (−0.0082, −0.0008)	0.02	5 (0, 37)
rs11605924	CRY2	A	C	0.48	15	52,264	0.0017 (−0.0016, 0.0050)	0.30	41 (0, 68)
rs11708067	ADCY5	A	G	0.78	14	50,829	−0.0006 (−0.0047, 0.0035)	0.78	12 (0, 51)
rs11920090	SLC2A2	T	A	0.86	14	51,441	−0.0019 (−0.0066, 0.0028)	0.43	35 (0, 65)
rs174550	FADS1	T	C	0.67	15	52,305	−0.0022 (−0.0055, 0.0011)	0.20	27 (0, 61)
rs2191349	DGKB-TMEM195	T	G	0.53	15	52,241	−0.0024 (−0.0057, 0.0009)	0.14	31 (0, 63)
rs340874	PROX1	C	T	0.53	14	51,449	−0.0004 (−0.0037, 0.0029)	0.81	12 (0, 50)
rs4506565	TCF7L2	T	A	0.29	13	49,253	−0.0001 (−0.0038, 0.0036)	0.97	54 (14, 75)
rs4607517	GCK	A	G	0.17	15	52,470	0.0020 (−0.0023, 0.0063)	0.35	0 (0, 22)
rs560887	G6PC2	C	T	0.71	15	51,479	0.0026 (−0.0009, 0.0061)	0.15	0 (0, 28)
rs7034200	GLIS3	A	C	0.48	15	52,016	0.0026 (−0.0007, 0.0059)	0.11	5 (0, 56)
rs780094	GCKR	C	T	0.39	15	52,442	0.0005 (−0.0028, 0.0038)	0.74	41 (0, 68)
rs7944584	MADD	A	T	0.73	15	51,263	0.0017 (−0.0020, 0.0054)	0.36	46 (2, 71)
Magnesium-related SNPs									
rs11144134	TRPM6	T	C	0.92	10	29,978	−0.0015 (−0.0091, 0.0061)	0.70	41 (0, 72)
rs2274924	TRPM6	A	G	0.84	10	29,280	0.0042 (−0.0013, 0.0097)	0.12	0 (0, 46)
rs3740393	CNNM2	G	C	0.85	11	30,904	0.0064 (0.0009, 0.0119)	0.02	38 (0, 70)
rs3750425	TRPM6	G	A	0.91	10	29,978	0.0052 (−0.0017, 0.0121)	0.14	0 (0, 2)
rs4072037	MUC1	C	T	0.45	11	30,905	−0.0028 (−0.0069, 0.0013)	0.17	31 (0, 66)
rs6746896	CNNM4	A	G	0.67	11	30,210	−0.0001 (−0.0042, 0.0040)	0.95	16 (0, 56)
rs8042919	TRPM7	G	A	0.90	11	30,905	−0.0049 (−0.0116, 0.0018)	0.15	4 (0, 62)
rs994430	CNNM3	A	T	0.60	11	30,905	−0.0004 (−0.0043, 0.0035)	0.84	0 (0, 54)
Insulin-related SNPs						Outcome is fasting insulin (*In-pmol/L*)			
rs35767	IGF1	G	A	0.84	15	37,485	0.0031 (−0.0020, 0.0082)	0.22	21 (0, 57)
rs780094	GCKR	C	T	0.58	15	37,804	−0.0028 (−0.0063, 0.0007)	0.12	36 (0, 66)
Magnesium-related SNPs									
rs11144134	TRPM6	T	C	0.92	10	29,549	−0.0004 (−0.0080, 0.0072)	0.94	6 (0, 65)
rs2274924	TRPM6	A	G	0.83	10	28,851	0.0041 (−0.0012, 0.0094)	0.13	0 (0, 60)
rs3740393	CNNM2	G	C	0.85	11	30,467	0.0013 (−0.0042, 0.0068)	0.64	0 (0, 49)
rs3750425	TRPM6	G	A	0.91	10	29,549	0.0046 (−0.0021, 0.0113)	0.17	0 (0, 58)
rs4072037	MUC1	C	T	0.45	11	30,468	−0.0003 (−0.0044, 0.0038)	0.88	27 (0, 64)
rs6746896	CNNM4	A	G	0.68	11	29,773	0.0009 (−0.0030, 0.0048)	0.65	6 (0, 63)
rs8042919	TRPM7	G	A	0.90	11	30,468	−0.0004 (−0.0071, 0.0063)	0.91	0 (0, 58)
rs994430	CNNM3	A	T	0.61	11	30,468	0.0004 (−0.0035, 0.0043)	0.84	7 (0, 63)

[1] Additive allele model, adjusted for age, sex, total energy intake, study center (in Atherosclerosis Risk in Communities Study; Cardiovascular Health Study; Family Heart Study; Health, Aging, and Body Composition Study; Invecchiare in Chianti; Multi-Ethnic Study of Atherosclerosis), and family or population substructure (in Cardiovascular Health Study, Family Heart Study, Framingham Heart Study, Multi-Ethnic Study of Atherosclerosis, Cardiovascular Risk in Young Finns Study). SNP, single nucleotide polymorphism.
[2] Interaction coefficient and 95% shown as β (95% CI).
[3] The number of independent observations in each interaction analysis.

we found no association of other previously studied *TRPM6* or *TRPM7* loci with either FG or FI (18,21). Taken together, it is unlikely that the most of the loci we studied implicated in magnesium transport and homeostasis are meaningfully affecting fasting measures of glucose or insulin, with the possible suggestive exception of *TRPM6* rs2274924 on glucose. Given recent evidence (19) and our cross-sectional approach, it is possible that this locus has deleterious downstream effects on intracellular magnesium and glucose handling secondary to the variant product's reduced sensitivity to insulin. Regardless of whether these loci are themselves playing a direct role does not preclude the involvement of magnesium-dependent pathways in the regulation of glucose and insulin homeostasis.

We observed no significant interactions between magnesium intake and loci on FG or FI, suggesting that magnesium's favorable associations with these traits are independent of genetic variation at the loci studied. Our strongest, albeit not significant, magnesium × SNP interaction on FG was at rs11558471 in *SLC30A8*, which we previously reported showed some evidence of interaction with total zinc intake on FG, although not below the multiple testing-corrected significance threshold in that study (P < 0.0025) (27). The interaction we report here with magnesium was in the same direction as that reported for zinc, which may reflect shared chemical properties of zinc and magnesium cations, or reflect similar affinity for these cations by the transmembrane transporter encoded by

SLC30A8. The second nominally significant interaction with magnesium intake on FG was at rs3740393 near *CNNM2*. The gene encodes a membrane protein required for renal magnesium handling; the G allele at this locus is associated with lower serum magnesium (18). If replicated in future studies, the interaction suggests that the magnitude of the inverse association between magnesium intake and FG is diminished in the presence of the serum magnesium–lowering G allele, versus the C allele. This interaction may plausibly indicate a higher dietary magnesium requirement in those with a propensity for lower serum magnesium to observe beneficial effects on fasting glucose.

To date, the only other study examining interactions between magnesium intake and loci in *TRPM6* and *TRPM7* was a small case-control study of type 2 diabetes in predominantly white, older women followed for 10 y. The authors reported that women who were carriers of 2 rare alleles from nonsynonymous SNPs in *TRPM6* (rs3750425 and rs2274924) had nearly 5 times the odds of type 2 diabetes when their magnesium intake was <250 mg/d (20). Despite our null interaction findings in relation to fasting glucose and insulin, we cannot rule out the possibility that in the presence of chronically low magnesium intake, these loci affect long-term risk of diabetes, which may not be reflected in the cross-sectional homeostatic measures analyzed in our study in individuals without known diabetes.

To our knowledge, this is one of the largest observational studies to investigate magnesium intake's associations with FG and FI, and it is the largest meta-analysis investigating interactions between magnesium intake and risk loci on FG and FI. In addition to following a uniform, a priori analysis plan in each cohort, we used cross-cohort exposure, covariate, and outcome definitions in a consortium-based meta-analytic context that minimizes the typical recall and publication bias associated with literature-based meta-analyses (36). The favorable inverse associations we report between magnesium intake and FG and FI are consistent with other studies investigating similar relationships.

The loci for this analysis were selected a priori from those identified and replicated in previous GWAS meta-analyses. Inherent to the GWAS method is that emergent loci have a homogenous effect both within and across populations; that is, these are areas of no environmental interaction, despite potentially widely varying environmental exposures, such as diet (37). Gene × environment approaches such as ours that rely on prior GWAS therefore must overcome the limitations inherent to both the homogeneity and the relatively small effect sizes conveyed by these loci to determine whether the variants modify the effects of an environmental exposure (37). Although the clinical importance of interactions even smaller than those detectable [due to power (24)] in analyses such as ours may be limited, they nevertheless remain of considerable mechanistic interest. Despite our hypothesis, the glycemia- and magnesium-related loci we investigated may yet be implicated in pathways through which magnesium acts to ultimately affect diabetes risk. Short-term magnesium supplementation (500 mg/d) in healthy adults has been shown to up- and downregulate >50 genes involved in inflammatory and metabolic pathways, and magnesium regulation, as well as genomic regions with unknown function (38). Furthermore, magnesium's interactions with loci to regulate insulin and glucose metabolism may be more evident in postchallenge measures of related traits, rather than the fasting traits used in our study (13,39,40). Therefore, our observations regarding the specific loci in the present study do not rule out the possibility that other genetic variants or genomic regions associated with glycemic traits interact with dietary magnesium.

In conclusion, our results indicate that higher dietary magnesium intake is inversely associated with FG and FI in individuals free of diabetes, generally irrespective of genetic variation at glycemia- and magnesium-related loci investigated. Nominal evidence for the influence of a *TRPM6* locus on FG and for magnesium interaction with loci in *SLC30A8* and *CNNM2* on FG indicate that future research, including GWAS, is necessary and may reveal genomic regions that more strongly influence associations between magnesium intake and traits related to glucose homeostasis (37).

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