Interactions of Dietary Whole-Grain Intake With Fasting Glucose– and Insulin-Related Genetic Loci in Individuals of European Descent

A meta-analysis of 14 cohort studies

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OBJECTIVE — Whole-grain foods are touted for multiple health benefits, including enhancing insulin sensitivity and reducing type 2 diabetes risk. Recent genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) associated with fasting glucose and insulin concentrations in individuals free of diabetes. We tested the hypothesis that whole-grain food intake and genetic variation interact to influence concentrations of fasting glucose and insulin.

RESEARCH DESIGN AND METHODS — Via meta-analysis of data from 14 cohorts comprising ~48,000 participants of European descent, we studied interactions of whole-grain intake with loci previously associated in GWAS with fasting glucose (16 loci) and/or insulin (2 loci) concentrations. For tests of interaction, we considered a P value <0.0028 (0.05 of 18 tests) as statistically significant.

RESULTS — Greater whole-grain food intake was associated with lower fasting glucose and insulin concentrations independent of demographics, other dietary and lifestyle factors, and BMI (β [95% CI] per 1-serving-greater whole-grain intake: −0.009 mmol/l glucose [−0.013 to −0.005], $P < 0.0001$ and −0.011 pmol/l [ln] insulin [−0.015 to −0.007], $P = 0.0003$). No interactions met our multiple testing–adjusted statistical significance threshold. The strongest SNP interaction with whole-grain intake was rs780094 (*GCKR*) for fasting insulin ($P = 0.006$), where greater whole-grain intake was associated with a smaller reduction in fasting insulin concentrations in those with the insulin-raising allele.

CONCLUSIONS — Our results support the favorable association of whole-grain intake with fasting glucose and insulin and suggest a potential interaction between variation in *GCKR* and whole-grain intake in influencing fasting insulin concentrations.

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Diet modification is among the premier targets for the prevention of many chronic diseases and has proven particularly effective for prevention and management of type 2 diabetes. For example, improvement in dietary quality, in conjunction with other lifestyle modifications like increased physical activity, was shown to be more effective than pharmacological treatment in prevention of diabetes in individuals at high risk (1). Further, lifestyle modification may mitigate the risk associated with the strongest known diabetes risk loci (2). While the existence of environmental influences on genetic risk (and vice versa, gene × environment interaction) is generally accepted, few examples have been empirically demonstrated and replicated using population-based or trial data (3).

Measures of carbohydrate source, quality, or quantity, like whole-grain intake, fiber intake, glycemic index, and glycemic load, are of particular interest in relation to glucose metabolism and diabetes risk (4). Carbohydrate quality and whole-grain intake have been tested in recent nested diabetes case-control studies of diet × gene interaction (5–7). Findings from these studies, while intriguing, need replication in studies of larger sample size and uniform design to more thoroughly elucidate the relationships among diet, genetic factors, and diabetes risk (8,9).

Polymorphic regions in the human genome associated with risk of diabetes (10,11) and related quantitative traits (12) have been identified and replicated in populations of European ancestry. Information on personal genetic risk is al-

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Table 1—*Participant characteristics in 14 participating cohorts*

	*N**	Age (years)	Sex (% women)	Fasting glucose (mmol/l)	Fasting insulin (pmol/l)†	Whole-grain intake (servings/day)‡	Energy intake (kcal/day)	BMI (kg/m^2)
Health, Aging, and Body Composition Study (Health ABC) (U.S.)	1,249	74.8 ± 2.9	51.0%	5.1 ± 0.6	44.7 (43.4–46.1)	0.96 (0.99)	1,807 ± 599	26.2 ± 4.0
Cardiovascular Health Study (CHS) (U.S.)§¶	2,765 (2,753)	72.3 ± 5.4	62.0%	5.5 ± 0.5	84.8 (83.5–86.2)	0.94 (1.13)	1,807 ± 641	26.0 ± 4.3
Framingham Heart Study (FHS) (U.S.)§¶	5,835	46.1 ± 12	54.7%	5.2 ± 0.5	27.0 (26.7–27.3)	0.92 (1.08)	1,982 ± 662	26.7 ± 5.0
Atherosclerosis Risk in Communities (ARIC) Study (U.S.)§¶	7,201	54.2 ± 5.7	53.7%	5.5 ± 0.5	58.9 (58.0–59.9)	1.01 (1.44)	1,644 ± 603	26.7 ± 4.7
Family Heart Study (FamHS) (U.S.)¶	2,094 (2,089)	50.1 0.5	55.5%	5.2 ± 0.5	58.3 (56.8–59.7)	1.14 (1.64)	1,733 ± 603	27.3 ± 5.1
The Age, Gene/Environment Susceptibility-Reykjavik Study (AGES) (Iceland)§	2,819	76.4 ± 5.5	59.7%	5.5 ± 0.5	55.1 (53.9–56.4)	1.79 (1.07)	NA	26.9 ± 4.3
Fenland (U.K.)¶	720	45.0 ± 7.3	56.1%	4.9 ± 0.5	38.5 (37.3–39.7)	1.28 (1.15)	1,949 ± 702	27.0 ± 4.9
Malmö Diet and Cancer Study (Malmö) (Sweden)	4,924 (4,765)	57.5 ± 5.9	59.0%	5.5 ± 0.5	37.4 (36.8–38.0)	1.49 (2.02)	2,324 ± 672	25.4 ± 3.8
Uppsala Longitudinal Study of Adult Men (ULSAM) (Sweden)¶	942 (932)	71.0 ± 0.6	0%	5.4 ± 0.6	64.5 (62.3–66.8)	2.04 (1.48)	1,749 ± 462	26.0 ± 3.2
Gene-Lifestyle interactions And Complex traits In Elevated disease Risk (GLACIER) (Sweden)	14,913 (891)	52.2 ± 8.7	59.9%	5.4 ± 0.6	41.0 (39.3–42.8)	1.66 (2.09)	1,823 ± 549	25.8 ± 4.0
Rotterdam Study (the Netherlands)§¶	2,304	65.4 ± 6.6	58.7%	5.5 ± 0.5	63.4 (62.1–64.8)	3.50 (3.00)	1,991 ± 505	26.6 ± 3.8
Invecchiare in Chianti (Aging in the Chianti Area; InCHIANTI) (Italy)¶	1,071 (1,044)	67.7 ± 16	56.3%	4.8 ± 0.6	56.3 (54.4–58.1)	0.00 (2.22)	2,014 ± 601	27.0 ± 4.1
Gene-Diet Attica Investigation on Childhood Obesity (GENDAI) (Greece)¶	1,087 (1,064)	11.2 ± 0.7	53.2%	4.8 ± 0.5	40.0 (38.7–41.3)	0.00 (0.50)	1,891 ± 595	20.0 ± 3.4
Greek Health Randomized Aging Study (GHRAS) (Greece)¶	865 (670)	71.8 ± 7.5	71.2%	5.8 ± 1.6	43.1 (41.3–45.0)	0.00 (2.00)	2,156 ± 693	29.7 ± 4.8

Data are means ± SD, median (interquartile range)‡, or geometric mean (95% CI). *Maximum available observations for interactions between whole-grain intake and SNPs in glucose analyses; values vary in some cohorts depending on availability of genotype information (in parentheses, where sample size for insulin analyses differs from glucose analyses). †Insulin was analyzed on the natural log scale and back transformed to the geometric scale for presentation. Presented values are means (95% CI). §Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium cohorts. ¶Meta-Analyses of Glucose and Insulin-Related Traits Consortium cohorts. NA, not available.

ready being disseminated to individuals within the general population and touted for its potential contribution to personalized medicine (13–15), although the underlying clinical utility has yet to be demonstrated (16,17). Given the potential for individual genetic risk to be empirically quantified and rapidly communicated, it is of interest to both clinicians and the general public to discover if modifiable characteristics like diet can mitigate risk in individuals empirically defined as "high risk" on the basis of genotype.

The aims of the current cross-sectional investigation were accomplished through a multicohort collaboration (18,19) including ~48,000 individuals of European descent originating from 14 cohort studies conducted in North America and northern and southern Europe. Our hypotheses were that *1*) whole-grain food intake is inversely associated with fasting glucose and insulin concentrations and 2) single nucleotide polymorphisms (SNPs), previously identified as predictive of fasting glucose (16 SNPs) and fasting insulin (2 SNPs) concentrations (12), and whole-grain intake interact to influence these traits in individuals without diabetes.

RESEARCH DESIGN AND METHODS

— Participants from each of the 14 cohorts (Table 1; supplemental Table S1 in the online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc10-11150/DC1) were excluded if diabetes was present at the time of glucose and insulin measurement (defined by self-reported diabetes, pharmacologic treatment for diabetes, or fasting glucose concentrations ≥7 mmol/l), if consent to genetic research was not provided, or diet and genotype information did not meet cohort-specific quality-control standards (supplemental Tables S2 and S3). Participants provided written informed consent, and protocols were approved by local institutional review boards.

Characterization of whole-grain intake

Daily servings of whole-grain foods were estimated in each cohort as the sum of daily servings of whole-grain items included on food frequency questionnaires (FFQs) (11 cohorts), a lifestyle questionnaire (1 cohort), reported during multiple 24-h recalls (1 cohort), or recorded in 7-day dietary diaries (1 cohort). Breakfast cereals containing ≥25% whole grain or bran by weight were considered whole

Table 2—*Meta-analyzed association between daily whole-grain intake and fasting glucose and fasting insulin in 14 cohorts*

	n	Regression coefficient (β [95% CI] representing expected change in fasting glucose [mmol/l] per one-daily-serving–greater whole-grain intake)	*P*	*n*	Regression coefficient (β [95% CI] representing expected change in fasting insulin [{ln}pmol/l] per one-daily-serving–greater whole-grain intake)	*P*
Model 1: age, sex, energy intake, field center, or population structure*	48,723	−0.019 (−0.022 to −0.015)	<0.0001	34,201	−0.021 (−0.025 to −0.017)	<0.0001
Model 2: model 1 + education level, physical activity, alcohol intake, and smoking status†	48,207	−0.013 (−0.017 to −0.010)	<0.0001	34,108	−0.022 (−0.026 to −0.017)	<0.0001
Model 3: model 2 + red or processed meat, fish, vegetables, fruit, coffee, nuts, and seeds‡	46,985	−0.012 (−0.016 to −0.008)	<0.0001	33,993	−0.016 (−0.021 to −0.011)	<0.0001
Model 4: model 3 + BMI§	46,928	−0.009 (−0.013 to −0.005)	<0.0001	33,937	−0.011 (−0.015 to −0.007)	0.0003

*Energy intake was not estimated in the Age, Gene/Environment Susceptibility-Reykjavik Study cohort. Field center was included as a covariate in the Health, Aging, and Body Composition Study; the Cardiovascular Health Study, the Atherosclerosis Risk in Communities Study, the Family Heart Study, and the Invecchiare in Chianti (Aging in the Chianti Area) Study. Principal components were used to adjust for population structure in the Framingham Heart Study and the Family Heart Study. †Education level and physical activity were defined uniquely by cohort. Smoking status was characterized as current, former, or never in 12 cohorts and as current or not current in 3 cohorts (Framingham Heart Study; Age, Gene/Environment Susceptibility-Reykjavik Study; Uppsala Longitudinal Study of Adult Men). Education level, smoking status, and alcohol intake were not adjusted in the Gene-Diet Attica Investigation on Childhood Obesity cohort (fifth and sixth graders). ‡Most cohorts included each of dietary covariates listed in the table as servings per day or grams per day; exceptions are noted in the online supplement. §BMI was modeled as a continuous variable in all cohorts (kg/m^2).

grain when brand name information and corresponding industry-provided ingredients were available (20). In cohorts where food reference portions were given alongside frequency options (i.e., semiquantitative FFQ), the reference portion was assigned as one serving. In cohorts where food items were quantified in daily grams, uniform weights were assigned as one serving on a food-by-food basis. (details in supplemental Table S2).

Genotyping, fasting glucose, and insulin quantification: assessment of other relevant variables

Cohort-specific methods for genotyping, fasting glucose and insulin quantification, and assessment of other participant characteristics, as well as allele frequencies at each locus are described in supplemental Tables S3, S4, and S5. The SNPs used in the present analysis were associated ($P < 5 \times 10^{-8}$) with fasting glucose and/or fasting insulin in a previous meta-analysis of genome-wide association studies with independent replication (12); 15 SNPs were associated with only fasting glucose, 1 SNP with only fasting insulin, and 1 SNP with both fasting glucose and insulin (listed in Table 3). Fasting glucose and insulin were quantified by enzymatic methods and radioimmunoassay, respectively.

Statistical analysis

Glucose was analyzed without transformation and insulin was natural log transformed before analysis. β-Coefficients from regression analyses are presented for (ln)insulin. For descriptive purposes, cohort mean insulin concentrations were back transformed and presented as geometric means with 95% CIs.

Cohort-specific analyses

Each cohort provided β-coefficients and SEs for the following linear regression models: *1*) association between daily servings of whole-grain foods and fasting glucose or fasting insulin concentrations, *2*) interactions between daily servings of whole-grain foods and 16 SNPs for fasting glucose concentrations, and *3*) interactions between daily servings of whole-grain foods and 2 SNPs for fasting insulin concentrations. To evaluate associations of whole-grain intake with fasting glucose and insulin concentrations, we used the following four linear regression models (listed in Table 2 and defined in supplemental Table S6; linear mixed-effects models were used to account for familial correlation among participants in the Framingham Heart Study and the Family Heart Study): model 1, age (years, continuous), sex, energy intake (kcal/day, continuous) plus field center (in the Health, Aging, and Body Composition Study; the Cardiovascular Health Study; the Atherosclerosis Risk in Communities Study; the Family Heart Study, and the Invecchiare in Chianti [Aging in the Chianti Area] Study) and population substructure (by principal components in Framingham Heart Study and Family Health Study); model 2, model 1 plus lifestyle characteristics; model 3, model 2 plus select dietary factors; and model 4, model 3 plus BMI. For the interaction analyses, we used model 1 covariates. In accordance with an additive model where the SNPs were uniformly modeled for the glucose- or insulin-raising allele, the interaction regression coefficients represent the difference in the magnitude of the whole-grain association (per one daily serving) with glucose (mmol/l) or (ln) insulin (pmol/l) per copy of the glucose- or insulin-raising allele.

Meta-analyses

We used an inverse variance–weighted meta-analysis with fixed effects to estimate summary effects (METAL software [http://www.sph.umich.edu/csg/abecasis/metal/index.html] for whole-grain × SNP interaction tests; and Stata 11.0, Stata Corporation, College Station, TX, for whole-grain outcome associations) and assessed heterogeneity by the I^2 index (21). Bonferroni correction was used to determine the level of statistical signifi-

Table 3—*Meta-analyzed interactions between daily whole-grain intake and genotype for select SNPs for fasting glucose and fasting insulin in 14 cohorts**

SNP	Nearest gene	Glucose- or insulin-raising allele/other allele	Number of cohorts	*n*	Regression coefficient for interaction between daily servings of whole grains × SNP for fasting glucose (mmol/l) β	SE	*P*	I^2 (95% uncertainty interval) (%)
Glucose-related SNP								
rs340874	*PROX1*	C/T	13	43,527	−0.0011	0.0030	0.71	0 (0–57)
rs780094	*GCKR*	C/T	14	48,303	0.0040	0.0027	0.13	0 (0–55)
rs560887	*G6PC2*	C/T	13	43,488	−0.0001	0.0032	0.98	0 (0–57)
rs11708067	*ADCY5*	A/G	13	43,555	0.0039	0.0036	0.28	24 (0–61)
rs11920090	*SLC2A2*	T/A	13	43,451	0.0006	0.0043	0.89	0 (0–57)
rs2191349	*DGKB/TMEM195*	T/G	13	43,561	−0.0044	0.0029	0.13	0 (0–57)
rs4607517	*GCK*	A/G	14	48,323	0.0002	0.0035	0.95	0 (0–55)
rs11558471	*SLC30A8*	A/G	10	40,776	−0.0007	0.0034	0.84	0 (0–62)
rs7034200	*GLIS3*	A/C	13	43,362	0.0015	0.0029	0.60	0 (0–57)
rs10885122	*ADRA2A*	G/T	13	43,391	0.0082	0.0044	0.06	0 (0–57)
rs4506565	*TCF7L2*	T/A	12	45,911	0.0004	0.0030	0.88	51 (6–75)
rs11605924	*CRY2*	A/C	13	43,567	−0.0016	0.0029	0.58	0 (0–57)
rs7944584	*MADD*	A/T	13	43,361	0.0049	0.0033	0.14	0 (0–57)
rs174550	*FADS1*	T/C	14	48,162	−0.0027	0.0028	0.34	32 (0–64)
rs10830963	*MTNR1B*	G/C	13	43,433	0.0028	0.0035	0.42	32 (0–65)
rs11071657	*C2CD4B*	A/G	13	42,500	0.0035	0.0031	0.26	0 (0–57)
Insulin-related SNP					Regression coefficient for interaction between daily servings of whole grains × SNP for fasting insulin [(ln)pmol/l]			
rs780094	*GCKR*	C/T	14	33,784	0.0091	0.003	0.006	1 (0–36)
rs35767	*IGF1*	G/A	13	29,078	0.0022	0.005	0.69	0 (0–57)

*Regression coefficient for interaction between daily servings of whole grains × SNP for fasting glucose (mmol/l) and fasting insulin [(ln)pmol/l], adjusted for age, sex, energy intake (not in the Age, Gene/Environment Susceptibility-Reykjavik Study), and field center (Health, Aging, and Body Composition Study; the Cardiovascular Health Study; the Atherosclerosis Risk in Communities Study; and the Invecchiare in Chianti [Aging in the Chianti Area] Study) and population structure by principal components in the Framingham Heart Study and the Family Heart Study.

cance; with 16 tests for glucose and 2 for insulin, we used $\alpha = 0.05/18 = 0.0028$.

The sample sizes for the whole-grain associations with fasting glucose ranged from 48,723 to 46,928 in models 1 and 4, respectively, and for fasting insulin, samples ranged from 34,201 to 33,937 in models 1 and 4, respectively. The sample sizes for the whole-grain × SNP interaction analyses for fasting glucose ranged from 40,776 for rs11558471 to 48,323 for rs4607517 and rs174550, with samples sizes for the other 13 SNPs between those values. The sample sizes for the whole-grain × SNP interaction analyses for fasting insulin was 29,078 for rs35767 and 33,784 for rs780094. Post hoc estimates of study power are provided in supplemental Fig. S1.

RESULTS — Table 1 summarizes the basic demographic characteristics of the 14 contributing cohorts. The mean self-reported daily whole-grain intake was lowest in Mediterranean regions and highest in northern European regions. Variation did not appear to correspond to measurement method (FFQ vs. 24-h recalls versus dietary records) (supplemental Fig. S2).

Associations of whole-grain intake with fasting glucose and insulin concentrations

With adjustment for sex, age, and energy intake, greater whole-grain intake was associated with lower fasting glucose and insulin concentrations. For each one-daily-serving–greater intake of whole-grain foods, fasting glucose concentrations were 0.019 units lower (β [95% CI]: −0.019 mmol/l [−0.022 to −0.015], $P < 0.0001$) (Fig. 1*A*; Table 2) and fasting insulin concentrations were 0.021 units lower (β [95% CI]: −0.021 [ln] pmol/l [−0.025 to −0.017], $P < 0.0001$) (Fig. 1*B*; Table 2). Results from models 2–4 were similar (Table 2), showing only slight attenuation in the regression estimates (Table 2; see also supplemental Figs. S3 and S4 and supplemental Table S7).

Interactions of whole-grain intake and SNPs with respect to fasting glucose and insulin concentrations. The strongest identified interaction was between whole-grain intake and rs780094 (in *GCKR*) in association with fasting insulin concentrations ($\beta_{interaction} \pm$ SE: 0.009 [ln] pmol/l ± 0.003, $P = 0.006$). Translated, this interaction regression coefficient indicates that greater whole-grain intake had a weaker insulin-lowering effect in the presence of the insulin-raising C allele. For example, in individuals carrying one copy of the insulin-raising C allele, the lower insulin concentration observed in association with greater whole-grain intake would be reduced by 0.009 units (that is, 0.010 units lower insulin in association with one daily whole-grain serving instead of 0.019 units lower). Correspondingly, in individuals carrying two

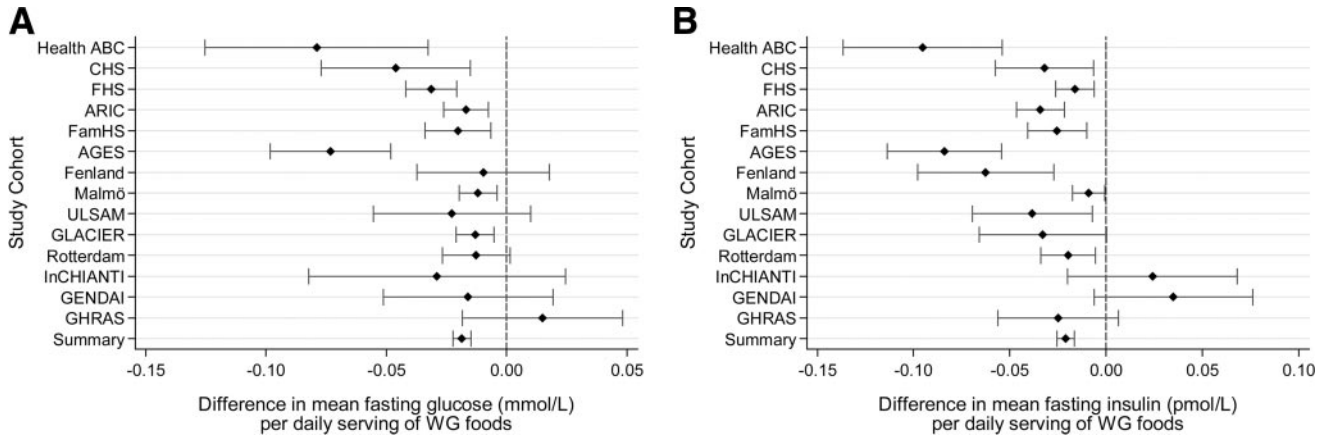

Figure 1—*Associations between daily whole-grain intake* (A) *and fasting glucose* (B) *and fasting insulin in 14 cohorts. A: Regression coefficient (β [95% CI]) representing expected change in fasting glucose (mmol/l) per one-daily-serving–greater whole-grain intake. B: Regression coefficient (β [95% CI]) representing expected change in fasting insulin [(ln)pmol/l] per one-daily-serving–greater whole-grain intake. Data are adjusted for model one covariates: age, sex, energy intake, field center, or population structure (Note: energy intake was not estimated in the AGES cohort; field center was included as a covariate in Health ABC, CHS, ARIC, FamHS, and InCHIANTI; population structure by principal components in FHS and FamHS).*

copies of the insulin-raising C allele, the lower insulin concentration observed in association with greater whole-grain intake would be reduced by 0.018 units (that is, 0.001 units lower insulin in association with one daily whole-grain serving instead of 0.019 units lower). After correction for multiple hypothesis testing, none of the interactions between whole-grain intake and the preselected SNPs (including rs780094) met our a priori cut point for significance ($P < 0.0028$) (Table 3 and supplemental Figs. S5 and S6).

CONCLUSIONS — Understanding how a potentially modifiable dietary characteristic like whole-grain food intake influences genetic effects on metabolic homeostasis may help elucidate the therapeutic potential of personalized medicine. We have performed a meta-analysis evaluating interactions between whole-grain food intake, an easily modifiable dietary characteristic with known associations with fasting glucose, insulin and diabetes risk, and loci previously identified as significantly and reproducibly associated with concentrations of fasting glucose and insulin (12). This is, to our knowledge, the largest and most comprehensive study of gene × lifestyle interactions conducted to date. In over 48,000 European individuals, we observed robust associations of whole-grain intake with fasting glucose and fasting insulin concentrations, firmly supporting observations previously made in other, smaller studies (22–25). The most promising interaction we identified was between whole grains and variation in *GCKR* (rs780094) in association with fasting insulin, where the inverse association between whole-grain intake and fasting insulin concentrations was weakened in the presence of the insulin-raising allele. However, for the majority of loci studied, the inverse association of whole-grain intake with fasting glucose or fasting insulin was present regardless of allelic variation at these loci.

Current findings in the context of gene × environment interaction investigations

The polymorphic locus rs780094 lies near a splice site in intron 18 of the *GCKR* gene whose product is a regulatory protein that inhibits glucokinase, a key regulatory step in glucose metabolism that is influenced by dietary composition (26). The locus was originally identified in the Diabetes Genetics Initiative GWAS for triglyceride levels (27). Later, the triglyceride-raising T allele was associated with lower fasting glucose and insulin concentrations (28) and confirmed in a meta-analysis of several GWAS (12). Fine mapping of the region for association with triglyceride levels pinpointed a Pro446Leu missense variant in *GCKR* (28) that is less responsive to regulation by concentrations of fructose-6-phospate, resulting in increased liver glucokinase activity, enhanced glycolysis, and elevated liver malonyl-CoA. The consequence of this metabolic shift manifests in lower fasting glucose and elevated triglyceride concentrations (29). The mechanism by which whole-grain food intake improves insulin resistance may involve glucokinase, and our results suggest that allelic variation at *GCKR* could diminish the beneficial effects of whole-grain foods on insulin homeostasis, possibly via the strong effect of *GCKR* variant on both triglyceride and glucose levels.

No other studied interaction met our Bonferroni-corrected cut point for statistical significance. Aside from the possibility that there really is no interaction between whole grains and these loci, the null results could still reflect insufficient statistical power or misclassification in the quantification of whole-grain intake. It is also possible that latent interactions might be observable in acute diet intake settings, that is, after a whole-grain–enriched meal where postmeal measures of insulin sensitivity are obtained.

Previous studies have evaluated interactions between diabetogenic loci and whole-grain intake or other proxies of carbohydrate intake or overall dietary quality. Three nested case-control studies previously investigated interactions of whole-grain intake (6), glycemic index/glycemic load (5), or a Western dietary pattern (7) with *TCF7L2* SNPs (rs7903146 (6) and rs12255372 (5,6) or a genetic risk score that included a *TCF7L2* marker among 10 risk loci (7). All three studies reported significant interactions ($P < 0.05$) between the *TCF7L2* variants and the respective dietary factors on diabetes incidence. Unlike these studies, we found no evidence of interaction between whole-grain food intake and the rs4506565 variant (an-

other *TCF7L2* marker highly correlated [r^2 0.68–0.917] with rs7903146 in Europeans) with respect to either fasting glucose or fasting insulin concentrations. We cannot exclude interactions between whole-grain intake and *TCF7L2* variants on diabetes risk, as the mechanisms of interaction may differ in persons with established diabetes. On the other hand, these previous studies were relatively small and did not apply conservative corrections for multiple testing, raising the possibility of false-positive findings.

Strengths and limitations of the present work

The strengths of our study include its large sample size, clearly defined a priori hypotheses, control for multiple testing, comparable whole-grain definitions across cohorts, and inclusion of well-characterized cohorts with diverse underlying dietary patterns (i.e., unique correlation structure of foods), which reduces the potential for confounding by other foods correlated with whole-grain intake. However, studies such as ours also have some inherent limitations. For example, measurement error in epidemiological studies can seriously impact the ability to detect small gene × environment interaction effects (30). The study-specific interaction regression coefficients covered a wide range (i.e., we observed small regression coefficients and large within-study variances), suggesting that some random errors may have reduced study power. Thus, even though our study is large in relative terms, it may still lack power to detect small interaction effects. On the other hand, if too small to be detected by our analysis, such small interactions might have relatively limited population or clinical relevance. The role of measurement error in dietary assessment has been long debated (31), and it is possible that the influence of genetic factors on these outcomes may vary according to whole-grain intake in more well-controlled clinical settings. Furthermore, even though sequential adjustment for putative confounding factors had little impact on the effect sizes across models, we cannot exclude the possibility that residual confounding explains some of our findings. It may also be that because we used an overly conservative method for adjusting for multiple testing, some of our findings may be falsely negative.

Genome-wide scans typically rank the most significant effects highest. The statistical significance of a genotype-phenotype association is diminished in the presence of interaction (32). Thus, loci that interact with other loci or with environmental factors may be less likely to rank highly in conventional GWASs compared with those that have strong main effects that are not modified by other exposures. Thus, by examining only the top main effects from GWAS in the present study, we may have overlooked numerous valid gene × whole-grain interaction effects elsewhere in the genome. Furthermore, because it is unknown whether the SNPs studied here are the causal variants, it is possible that stronger effects attributable to rarer SNPs could underlie some of the examined loci. It is worth noting that for some SNPs, we observed a high degree of heterogeneity in interaction effects across cohorts, suggesting the possibility of multidimensional interactions, which could not be examined in the present study.

Results of this large, comprehensive investigation of gene-diet interaction, suggest that the association of whole-grain intake with fasting insulin may be modified by *GCKR* rs780094. While intriguing, the test of interaction did not meet our conservative Bonferroni-corrected cut point for statistical significance and requires confirmation in other studies. Our results do show that whole-grain food intake is similarly and inversely associated with fasting insulin and glucose irrespective of genetic variation at the other loci studied. Our work coincides with the dawn of a new age in genetic and nutritional research. Investigations such as ours contribute to a better understanding of how diet therapy may (or may not) be individualized to a person's genetic background. However, to fully realize this potential, studies will require more precisely measured exposures (such as nutritional biomarkers of whole-grain intake) and should include experimental settings where diet is manipulated in people of contrasting genetic risk profiles.

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