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Citation for published version:
MAGIC Investigators 2010, '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' Diabetes Care, vol. 33, no. 12, pp. 2684-91. DOI: 10.2337/dc10-1150

Digital Object Identifier (DOI):
10.2337/dc10-1150

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Diabetes Care

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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.

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-
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.
Whole-grain and genetic loci meta-analysis

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Regression coefficient (β [95% CI]) representing expected change in fasting glucose (mmol/l) per one-daily-serving–greater whole-grain intake</th>
<th>P</th>
<th>Regression coefficient (β [95% CI]) representing expected change in fasting insulin ([ln]pmol/l) per one-daily-serving–greater whole-grain intake</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: age, sex, energy intake, field center, or population structure*</td>
<td>-0.019 (-0.022 to -0.015)</td>
<td>&lt;0.0001</td>
<td>-0.021 (-0.025 to -0.017)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2: model 1 + education level, physical activity, alcohol intake, and smoking status†</td>
<td>-0.013 (-0.017 to -0.010)</td>
<td>&lt;0.0001</td>
<td>-0.022 (-0.026 to -0.017)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 3: model 2 + red or processed meat, fish, vegetables, fruit, coffee, nuts, and seeds‡</td>
<td>-0.012 (-0.016 to -0.008)</td>
<td>&lt;0.0001</td>
<td>-0.016 (-0.021 to -0.011)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 4: model 3 + BMI§</td>
<td>-0.009 (-0.013 to -0.005)</td>
<td>&lt;0.0001</td>
<td>-0.011 (-0.015 to -0.007)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

*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/m²).

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 x 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 I² index (21). Bonferroni correction was used to determine the level of statistical signifi-
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]: −0.020 to −0.015, P < 0.0001) (Fig. 1A; Table 2) and fasting insulin concentrations were 0.021 units lower (β [95% CI]: −0.025 to −0.017, P < 0.0001) (Fig. 1B, 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).

**RESULTS** — Table 1 summarizes the basic demographic characteristics of the 14 contributing cohorts. The mean self-reported daily whole-grain intake was instead of 0.019 units lower). Correlation with one daily whole-grain serving (that is, 0.010 units lower insulin in association with one copy of the insulin-raising C allele). For example, in individuals carrying the presence of the insulin-raising C allele. The strongest identified interaction was between whole-grain intake and rs780094 (in GCKR) in association with fasting insulin concentrations (βinteraction ± SE: 0.009 [In] 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.
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-phosphate, 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-

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).
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 \(\times\) environment interaction effects \(\text{(30)}\). 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 \(\text{(31)}\), 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 \(\text{(32)}\). Thus, loci that interact with other loci or with environmental factors may be less likely to rank highly in conventional GWAS 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 \(\times\) 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.

**Acknowledgments** — No potential conflicts of interest relevant to this article were reported.

**APPENDIX** — Full author list: the CHARGE Whole Grain Foods Study Group, in addition to the first 11 authors: Melissa Garcia, MPH12; Jennifer S. Anderson, MD, PhD14; Jack L. Follis, MS14; Luc Djousse, MD, DrPH15; Kenneth Mukamel, MD16; Constantina Papoutsakis, PhD17; Darius Mozaffarian, MD, DrPH17; M. Carola Zillikens, MD18; Stefania Bandinelli, MD19; Amanda J. Bennett, PhD20; Ingrid B. Borecki, PhD9; Mary F. Feitosa, PhD9; Luigi Ferrucci, MD, PhD12; Nita G. Forouhi, MD13; Christopher J. Groves, PhD21; Goran Hallmans, PhD22; Tamara Harris, MD12; Albert Hofman, PhD23; Denise K. Houston, PhD13; Frank B. Hu, PhD23; Ingegerd Johansson, PhD24; Stephen B. Kritchevsky, PhD15; Claudia Langenberg, MD, PhD16; Lenore Launer, PhD12; Yongmei Liu, PhD13; Ruth J. Loos, PhD18; Michael Nalls, PhD25; Marju Orho-Melander, PhD26; Frida Renstrom, PhD26; Kenneth Rice, PhD26; Ulf Riserus, PhD27; Olov Rolandsson, PhD28; Jerome I. Rotter, MD29; Georgi Saylor, BS33; Eric J. G. Sjöfrands, MD30; Per Sjögren, PhD26, Albert Smith, PhD31; Lauley Steinbringdottir, PhD32; André G. Uitterlinden, PhD38; Nicholas J. Wareham, PhD4; Inga Prokopenko, PhD33; James S. Pankow, PhD33; Cornelia M. van Duijn, PhD7; Jose C. Florez, MD, PhD33; Jacqueline C. M. Witten, PhD7; the MAGIC Investigators (complete author list can be found in the online appendix); Josée Dupuis, PhD35; George V. Dedousis, PhD3; Jose M. Ordovas, PhD30; Erik Ingelsson, PhD37; L. Adrienne Cupples, PhD9; David S. Siscovick, MD4; Paul W. Franks, PhD38; James B. Meigs, MD39.

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