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Meta-Analysis Investigating Associations Between Healthy Diet and Fasting Glucose and Insulin Levels and Modification by Loci Associated With Glucose Homeostasis in Data From 15 Cohorts

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Whether loci that influence fasting glucose (FG) and fasting insulin (FI) levels, as identified by genome-wide association studies, modify associations of diet with FG or FI is unknown. We utilized data from 15 US and European cohort studies comprising 51,289 persons without diabetes to test whether genotype and diet interact to influence FG or FI concentration. We constructed a diet score using study-specific quartile rankings for intakes of whole grains, fish, fruits, vegetables, and nuts/seeds (favorable) and red/processed meats, sweets, sugared beverages, and fried potatoes (unfavorable). We used linear regression within studies, followed by inverse-variance-weighted meta-analysis, to quantify 1) associations of diet score with FG and FI levels and 2) interactions of diet score with 16 FG-associated loci and 2 FI-associated loci. Diet score (per unit increase) was inversely associated with FG ($\beta = -0.004$ mmol/L, 95% confidence interval: −0.005, −0.003) and FI ($\beta = -0.008$ ln-pmol/L, 95% confidence interval: −0.009, −0.007) levels after adjustment for demographic factors, lifestyle, and body mass index. Genotype variation at the studied loci did not modify these associations. Healthier diets were associated with lower FG and FI concentrations regardless of genotype at previously replicated FG- and FI-associated loci. Studies focusing on genomic regions that do not yield highly statistically significant associations from main-effect genome-wide association studies may be more fruitful in identifying diet-gene interactions.

diabetes; dietary pattern; gene-environment interaction; glucose; insulin

Abbrevations; ARIC, Atherosclerosis Risk in Communities; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; CHS, Cardiovascular Health Study; FG, fasting glucose; FG-GRS, FG-associated genetic risk score; FHS, Family Heart Study; FI, fasting insulin; Framingham, Framingham Generation 5 and Offspring Studies; GENDAI, Gene-Diet Attica Investigation on Childhood Obesity; GHRAS, Greek Health Randomized Aging Study; GLACIER, Gene-Lifestyle Interactions and Complex Traits in Elevated Disease Risk; GWAS, genome-wide association studies; Health ABC, Health, Aging and Body

Composition; InCHIANTI, Invecchiare in Chianti [Aging in the Chianti Area]; Malmö, Malmö Diet and Cancer Study (cardiovascular cohort); ln, natural log; MESA, Multi-Ethnic Study of Atherosclerosis; Rotterdam, Rotterdam Study; SD, standard deviation; SNP, single nucleotide polymorphism; THISEAS, The Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility; ULSAM, Uppsala Longitudinal Study of Adult Men; Young Finns, Young Finns Study.

Recent technological and methodological advances have led to multiple genome-wide association studies (GWAS) of complex human diseases such as type 2 diabetes (1, 2) and related quantitative traits (3). While results of these meta-analyses have identified multiple loci with modest effect estimates, much of the heritability of the phenotypic traits remains unexplained. Thus, the utility of using genotypes at these loci to improve clinical practice remains unknown. Nevertheless, clinical and lay public awareness of health-related genomic technologies is growing (4–6). This raises important clinical and public health questions: Do lifestyle choices, like adhering to a healthier diet, offset genetic risks (7–10)? Does genetic variation within populations necessitate individualized health-promoting dietary recommendations?

A "healthy diet" can be characterized using many different approaches. One popular approach is to create a composite score that ranks individuals on the basis of their intakes of foods or nutrients that have been favorably or unfavorably associated with diseases or risk factors (11–13). The resulting scores, or "dietary patterns," capture the highly complex nature of diet, where multiple foods and their nutrient constituents are consumed—none in isolation (14–16). Public health recommendations based on dietary patterns are also more easily understood than nutrient-based recommendations, since they can be placed in context with a person's behavior. Although there are many methods for characterizing dietary patterns, healthier diets share several common characteristics that are correspondingly reflected in dietary recommendations across countries. Diets associated with lower risk of type 2 diabetes and lower numbers of cardiometabolic risk factors (17, 18) comprise largely plant foods (e.g., whole grains, fruits, vegetables) and plant and marine sources of fat (e.g., nuts and seeds, fatty fish) in exchange for red and processed meats, foods high in sugar and salt, and highly refined grains.

The purpose of this study was to 1) evaluate associations of a dietary pattern score with fasting glucose (FG) and fasting insulin (FI) levels and 2) evaluate whether genotypes at known loci associated with FG and FI (3) modify the associations of dietary pattern with FG and FI, using data from multiple US and European cohort studies.

MATERIALS AND METHODS

Cohorts

The present work is a collaboration of investigators from US and European epidemiologic cohort studies included in the Nutrition Working Group of the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium (19). Table 1 provides descriptive information about the 15 studies included in this investigation (additional details have been published previously (19) and are given in Web Table 1 (available at http://aje.oxfordjournals.org/)). The analyses included the following cohort studies: the Atherosclerosis Risk in Communities (ARIC) Study, the Framingham Generation 5 and Offspring Studies (Framingham), the Rotterdam Study (Rotterdam), the Cardiovascular Health Study (CHS), the Gene-Diet Attica Investigation on Childhood Obesity (GENDAI), the Greek Health Randomized Aging Study (GHRAS), the Uppsala Longitudinal Study of Adult Men (ULSAM), Gene-Lifestyle Interactions and Complex Traits in Elevated Disease Risk (GLACIER), the Family Heart Study (FHS), the Health, Aging and Body Composition (Health ABC) Study, the Malmö Diet and Cancer Study (cardiovascular cohort) (Malmö), Invecchiare in Chianti [Aging in the Chianti Area] (InCHIANTI), the Multi-Ethnic Study of Atherosclerosis (MESA), the Young Finns Study (Young Finns), and the Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility (THISEAS). All persons studied were free of type 2 diabetes (defined by self-reported diabetes, pharmacologic treatment for diabetes, or FG concentrations $\geq$7 mmol/L) when FG and FI levels were measured, consented to genetic research, and provided written informed consent. All studies' examination protocols were approved by local institutional review boards, and the procedures followed in each were in accordance with the ethical standards of the responsible institutional or regional committee on human experimentation or with the Helsinki Declaration of 1975 as revised in 1983.

Diet score

Diet was assessed via food frequency questionnaire (in 13 of 15 cohorts), food records kept for 7 consecutive days (in ULSAM), or two 1-day dietary recalls (in GENDAI) (19) (see also Web Table 2). The diet score was based on intakes of 9 food groups defined consistently for all studies. Whole grains, fish, fruits, vegetables, and nuts/seeds were designated as favorable foods, whereas red and processed meats, sweets, sugared beverages, and fried potatoes were designated as unfavorable (additional details are given in Web Table 2). Intakes of foods/beverages were estimated in servings per day for all cohorts, with the exception of the ULSAM cohort, where grams per day were used. Intake of each food group was categorized into quartiles and assigned ascending values (0, 1, 2, 3) for favorable foods and descending values (3, 2, 1, 0) for unfavorable foods. These values were summed to generate a diet score (range, 0–27 points), with higher scores representing healthier diets.

We selected food groups for inclusion in the score based on 1) country-specific dietary guidelines; 2) results of investigations of the associations of specific dietary factors

Table 1. Characteristics of Participants From 15 Cohort Studies Included in a Meta-Analysis of the Influence of Diet and Genotype on Fasting Glucose and Insulin Concentrations, CHARGE Consortium

Cohort	First Author, Year (Reference No.)	Region	Maximum Sample Size (*n*)[a]	Mean Age, years (SD)	% Female	Mean Fasting Glucose Level, mmol/L (SD)	Mean Fasting Insulin Level, ln-pmol/L (SD)
ARIC Study	ARIC Investigators, 1989 (33)	United States	8,591	54.2 (5.7)	53.7	5.47 (0.50)	4.07 (0.66)
CHS	Fried, 1991 (34)	United States	2,745	72.3 (5.4)	62.3	5.53 (0.52)	4.44 (0.43)
FHS	Higgins, 1996 (35)	United States	3,187	51.4 (13.6)	53.6	5.22 (0.54)	4.10 (0.57)
Framingham	Feinleib, 1975 (36) and Splansky, 2007 (37)	United States	5,795	46.0 (11.5)	54.7	5.19 (0.48)	3.30 (0.41)
GENDAI	Papoutsakis, 2007 (38)	Mediterranean	1,087	11.2 (0.7)	53.2	4.75 (0.48)	3.69 (0.54)
GHRAS	Kanoni, 2008 (39)	Mediterranean	856	71.8 (5.7)	71.2	5.83 (1.63)	3.76 (0.56)[b]
GLACIER	Renström, 2011 (40)	Northern Europe	15,146	52.0 (8.8)	60.7	5.37 (0.62)	3.72 (0.64)[b]
Health ABC Study[b]	Houston, 2008 (41)	United States	1,281	74.8 (2.9)	50.2	5.16 (0.55)	3.81 (0.53)
InCHIANTI	Ferrucci, 2000 (42)	Mediterranean	1,071	67.7 (15.8)	56.3	4.84 (0.61)	4.18 (0.53)
Malmö	Berglund, 1993 (43)	Northern Europe	3,679	57.8 (6.0)	59.0	5.53 (0.52)	3.62 (0.53)
MESA	Bild, 2002 (44)	United States	2,271	62.4 (10.3)	51.9	4.85 (0.56)	3.48 (0.61)
Rotterdam	Hofman, 2011 (45)	Northern Europe	2,303	71.9 (6.6)	58.7	5.50 (0.53)	4.10 (0.52)
THISEAS	Theodoraki, 2010 (46)	Mediterranean	598	55.9 (13.6)	48.5	5.31 (0.64)	3.96 (0.58)[b]
ULSAM	Hedstrand, 1975 (47)	Northern Europe	933	71.0 (19.2)	0.0	5.37 (0.56)	4.31 (0.53)
Young Finns	Raitakari, 2008 (48)	Northern Europe	1,746	37.7 (5.0)	56.2	5.25 (0.48)	3.70 (0.77)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; CHS, Cardiovascular Health Study; FHS, Family Heart Study; Framingham, Framingham Generation 5 and Offspring Studies; GENDAI, Gene-Diet Attica Investigation on Childhood Obesity; GHRAS, Greek Health Randomized Aging Study; GLACIER, Gene-Lifestyle Interactions and Complex Traits in Elevated Disease Risk; Health ABC, Health, Aging and Body Composition; InCHIANTI, Invecchiare in Chianti [Aging in the Chianti Area]; Malmö, Malmö Diet and Cancer Study (cardiovascular cohort); MESA, Multi-Ethnic Study of Atherosclerosis; Rotterdam, Rotterdam Study; SD, standard deviation; SNP, single nucleotide polymorphism; THISEAS, The Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility; ULSAM, Uppsala Longitudinal Study of Adult Men; Young Finns, Young Finns Study.

[a] Maximum sample sizes for both outcomes are provided; exceptions include GHRAS, GLACIER, and THISEAS, where fewer observations were available for fasting insulin: 670, 917, and 258, respectively.

[b] Fasting glucose and fasting insulin levels were measured from baseline (year 1) samples; diet score variables were collected during year 2; and covariates (see Web Table 3) were measured at baseline (year 1).

and patterns with diabetes and its risk factors; 3) data availability in participating cohorts; 4) regional food usage patterns; and 5) food product consistency across cohorts. We also inspected correlations among these food groups and others not included in the final score in order to evaluate whether the consumption patterns (correlation matrices) were similar across cohorts. We did not include dairy foods in the score, despite the fact that dairy foods, particularly reduced-fat dairy foods, are endorsed by most national dietary guidelines. Evidence regarding beneficial effects of dairy food consumption (reduced-fat vs. whole-fat dairy foods) on the risk of impaired glucose control or type 2 diabetes is inconclusive (11, 20–23), and product composition (particularly in terms of fat percentage, fermentation/culturing processes, and amounts of added sugar—all important factors in this context) is highly variable across regions represented in the present work (criterion 5 above). When information about preparation was available, we excluded fried fish from the fish food group. We did not include baked, boiled, or mashed white potatoes in the total for vegetables, since high intake of white potatoes has been associated with greater risk of type 2 diabetes (24) and may reflect a Western animal-based diet in some cohorts. However, we also did not include white potatoes as an unfavorable food, since white potatoes represent an important component of a healthy Mediterranean-style diet in some cohorts. While some guidelines emphasize replacing animal sources of protein with plant sources of protein such as legumes, we did not include legumes in our diet score calculation because 1) intakes were low and 2) legumes are commonly consumed with meat products (e.g., pork and beans, meat chili), particularly in the United States, rather than as a meat substitute, as is more common in Mediterranean regions (11, 25). Lastly, we did not include poultry in the score because of the absence of compelling evidence linking poultry intake to glucose regulation or diabetes and the positive correlation between poultry and meat consumption in most cohorts.

Genetic loci

We selected the 16 loci associated with FG and the 2 loci associated with FI that met the criteria for genome-wide significance in a previous meta-analysis of GWAS (3) (allele frequencies and effect sizes are shown in Web Table 3, genotyping methods in Web Table 4). We also created an FG-associated genetic risk score (FG-GRS) by summing the number of risk alleles for each participant across the FG-associated single nucleotide polymorphisms (SNPs), theoretically ranging in most cohorts from 0 (no FG-raising alleles) to 32 (homozygous for the FG-raising allele at each of the 16 SNPs). In GENDAI and GHRAS, we calculated the FG-GRS for 14 of the 16 FG-associated SNPs, since neither rs11558471 (*SLC30A8*) nor rs4506565 (*TCF7L2*) was genotyped in these cohorts. In Malmö, we included persons with more than 60% of the SNPs genotyped and then imputed the missing genotypes (with the most common genotype). Results were similar when the 3 cohorts with missing genotype information were not included in FG-GRS-related analyses; thus, to preserve sample size, we included all 15 cohorts.

FG and FI concentrations and other characteristics

FG and FI concentrations were quantified for each cohort using enzymatic methods and radioimmunoassays, respectively (cohort-specific methods are shown in Web Table 4). We statistically analyzed FG values without transformation; because FI data were not normally distributed, FI values were natural log (ln)-transformed before statistical analysis. We present beta coefficients from regression analyses for (ln)FI. Measurement methods for other relevant covariates (listed below) are described in Web Table 5.

Statistical analyses

Cohort-specific analyses. For each cohort, we calculated associations between diet score and FG and FI concentrations using multivariable linear regression, with the diet score modeled as a continuous variable. Analyses were performed at each study center according to a standardized analytic plan. Model 1 adjusted for energy intake (kcal/day), age, sex, field center (in Health ABC, CHS, ARIC, FHS, InCHIANTI, and MESA), and population and/or family substructure (using principal components analysis for relevant cohorts, in CHS, FHS, Framingham, MESA, and Young Finns). Model 2 included further adjustment for smoking, physical activity, education, and alcohol consumption (defined within each cohort; described in Web Table 5). Model 3 further adjusted for body mass index (weight (kg)/height $(m)^2$). Regression coefficients from these models represent the predicted difference in FG (mmol/L) or FI (ln-pmol/L) concentration per 1-unit increase in diet score. For each cohort, we also assessed associations of the FG-GRS, the 16 FG-associated SNPs, and the 2 FI-associated SNPs with respective FG and FI outcomes, adjusting for age, sex, field center, and/or population substructure. An additive genetic model was used, consistent with the association pattern for these loci (3).

Our primary interaction tests of interest were between diet score and the FG-GRS (FG outcome) and the 2 FI-associated SNPs (FI outcome); interactions between diet score and the 16 individual SNPs making up the FG-GRS were secondary, exploratory analyses. To test these interactions, we included a diet score × FG-GRS (or SNP) cross-product term along with model 1 covariates. The resulting interaction regression coefficients represent the difference in the magnitude of the healthy diet association (per 1-unit increase in score) with FG (mmol/L) or FI (ln-pmol/L) concentration per copy of an FG- or FI-raising allele.

Meta-analyses. We used an inverse-variance-weighted meta-analysis with fixed effects, employing the rmeta package (version 2.16) in R 2.13.1 (http://www.R-project.org/), for diet score-outcome associations and METAL (http://www.sph.umich.edu/csg/abecasis/Metal/index.html) for SNP-outcome associations and diet score × SNP interactions. Heterogeneity was assessed by means of the I^2 index (26). Figures were generated with Stata 11.0 (Stata Corporation, College Station, Texas).

Sample sizes for the associations of diet score with FG concentration ranged from 48,787 to 51,289 (in models 3 and 1, respectively); and for FI, sample sizes ranged from

Table 2. Distribution of Diet Score and Food Group Components Across the 15 Cohort Studies Included in a Meta-Analysis of the Influence of Diet and Genotype on Fasting Glucose and Insulin Concentrations, CHARGE Consortium

Cohort	Diet Score[a]		Diet Score Favorable Food Groups, servings/day[b] (SD)					Diet Score Unfavorable Food Groups, servings/day[b] (SD)			
	Mean	Range	Whole Grains	Fish	Fruit	Vegetables	Nuts and Seeds	Red and Processed Meats	Desserts and Sweets	Sugar-sweetened Beverages	Fried Potatoes
ARIC Study	13.7	1–27	1.37 (1.25)	0.26 (0.28)	1.50 (1.25)	1.72 (1.15)	0.42 (0.58)	1.00 (0.72)	1.45 (1.37)	0.47 (0.88)	0.11 (0.16)
CHS	13.7	1–27	1.02 (0.65)	0.32 (0.30)	2.74 (1.47)	2.83 (1.49)	0.20 (0.25)	0.69 (0.58)	0.85 (0.39)	0.14 (0.26)	0.09 (0.14)
FHS	13.1	1–26	1.58 (1.55)	0.20 (0.22)	1.56 (1.38)	1.61 (1.27)	0.34 (0.57)	2.46 (1.21)	1.64 (1.44)	0.67 (1.1)	0.13 (0.2)
Framingham	13.2	1–26	1.17 (1.13)	0.27 (0.27)	1.26 (1.16)	2.80 (1.92)	0.37 (0.53)	0.77 (0.59)	1.41 (1.32)	0.48 (0.86)	0.10 (0.13)
GENDAI	9.5	1–20	0.41 (0.77)	0.21 (0.60)	1.21 (1.35)	1.08 (1.21)	NA	1.69 (1.36)	0.85 (0.85)	0.43 (0.62)	NA
GHRAS	11.0	2–19	1.06 (1.53)	0.33 (0.20)	2.15 (1.38)	1.53 (0.57)	NA	0.43 (0.34)	1.24 (1.09)	0.10 (0.17)	NA
GLACIER	11.9	0–24	2.71 (1.47)	0.17 (0.13)	1.59 (1.17)	1.61 (1.21)	NA	0.62 (0.31)	1.52 (1.34)	0.32 (0.49)	0.10 (0.13)
Health ABC Study[c]	15.7	3–27	1.01 (0.71)	0.16 (0.15)	1.88 (1.10)	2.00 (0.99)	0.32 (0.38)	0.71 (0.49)	1.40 (0.86)	0.05 (0.18)	0.07 (0.10)
InCHIANTI	10.6	2–20	0.20 (0.68)	0.22 (0.17)	2.83 (1.38)	2.58 (1.34)	0.02 (0.06)	1.03 (0.52)	2.41 (1.57)	0.08 (0.26)	NA
Malmö	13.7	1–26	1.92 (1.83)	0.55 (0.40)	2.02 (1.23)	2.50 (1.32)	0.07 (0.18)	1.45 (0.73)	3.30 (1.95)	0.29 (0.54)	0.18 (0.29)
MESA	13.6	1–27	0.69 (0.58)	0.15 (0.19)	1.89 (1.48)	2.23 (1.32)	0.35 (0.50)	0.53 (0.46)	1.37 (1.46)	0.41 (0.82)	0.11 (0.15)
Rotterdam	10.2	1–20	2.88 (1.50)	0.21 (0.18)	2.11 (1.16)	2.15 (0.94)	0.29 (0.51)	1.38 (0.63)	1.60 (1.13)	0.51 (0.66)	NA
THISEAS	11.9	0–26	1.37 (1.60)	0.50 (0.47)	1.66 (1.51)	3.53 (3.10)	0.59 (1.03)	1.20 (1.18)	0.94 (1.18)	0.34 (0.71)	0.26 (0.47)
ULSAM[d]	13.4	3–24	19.8 (13.3)	18.7 (13.7)	116.4 (99.2)	68.8 (53.9)	0.34 (5.27)	72.0 (27.9)	63.8 (53.5)	39.4 (88.2)	12.0 (16.6)
Young Finns	13.6	2–27	3.25 (1.88)	0.40 (0.32)	2.05 (2.10)	3.39 (2.26)	0.04 (0.08)	1.22 (0.78)	1.47 (1.26)	0.54 (0.90)	0.17 (0.19)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; CHS, Cardiovascular Health Study; FHS, Family Heart Study; Framingham, Framingham Generation 5 and Offspring Studies; GENDAI, Gene-Diet Attica Investigation on Childhood Obesity; GHRAS, Greek Health Randomized Aging Study; GLACIER, Gene-Lifestyle Interactions and Complex Traits in Elevated Disease Risk; Health ABC, Health, Aging and Body Composition; InCHIANTI, Invecchiare in Chianti [Aging in the Chianti Area]; Malmö, Malmö Diet and Cancer Study (cardiovascular cohort); MESA, Multi-Ethnic Study of Atherosclerosis; NA, not applicable; Rotterdam, Rotterdam Study; SD, standard deviation; SNP, single nucleotide polymorphism; THISEAS, The Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility; ULSAM, Uppsala Longitudinal Study of Adult Men; Young Finns, Young Finns Study.

[a] Summed quartile ranks of favorable food groups (0, 1, 2, and 3, for lowest to highest quartiles, respectively) and reversed quartile ranks of unfavorable food groups (3, 2, 1, and 0, for lowest to highest quartiles, respectively). The theoretical range is 0–27 points, with a high score representing the healthiest diet based on the selected parameters.

[b] Servings/day except for ULSAM (see footnote d).

[c] Fasting glucose and fasting insulin levels were measured from baseline (year 1) samples; diet score variables were collected during year 2; and covariates (see Web Table 3) were measured at baseline (year 1).

[d] In ULSAM, data were collected by 7-day food record and are characterized in g/day. See Web Table 1 for individual foods and beverages included within each food group.

Table 3. Associations of Healthy Diet Score With Fasting Glucose and Fasting Insulin Concentrations in a Meta-Analysis, CHARGE Consortium

	No. of Persons	β (SE)[a]	I^2, %	95% Confidence Interval
Fasting glucose, mmol/L				
Model 1[b]	51,289	−0.005 (0.0005)*	62.6	34.6, 78.6
Model 2[c]	48,902	−0.004 (0.0005)*	54.2	18, 74.5
Model 3[d]	48,787	−0.004 (0.0005)*	22.1	0, 57.8
Fasting insulin, ln-pmol/L				
Model 1	35,907	−0.010 (0.0006)*	71.3	51.7, 83
Model 2	34,415	−0.009 (0.0007)*	45.2	0, 70
Model 3	34,305	−0.008 (0.0005)*	12.3	0, 50.2

Abbreviations: CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; SE, standard error.

* $P < 0.0001$.

[a] Beta coefficient and standard error for the estimated difference in fasting glucose (mmol/L) or fasting insulin (ln-pmol/L) concentration per 1-unit increase in diet score.

[b] Model 1 adjusted for age, sex, energy intake, field center (in the Health, Aging and Body Composition Study, the Cardiovascular Health Study, the Atherosclerosis Risk in Communities Study, the Family Heart Study, Invecchiare in Chianti, and the Multi-Ethnic Study of Atherosclerosis), and population substructure (by principal components in the Cardiovascular Heath Study, the Family Heart Study, the Framingham Generation 5 and Offspring Studies, the Multi-Ethnic Study of Atherosclerosis, and the Young Finns Study).

[c] Model 2 adjusted for model 1 covariates plus highest attained educational level, smoking status, physical activity level, and alcohol intake (see Web Table 4 for cohort-specific definitions).

[d] Model 3 adjusted for the model 2 covariates plus body mass index.

34,305 to 35,907 (in models 3 and 1, respectively). Sample sizes for the interaction analyses for FG ranged from 48,872 for rs10830963 (*MTNR1B*) to 51,377 for rs2191349 (*KB/TMEM*), with sample sizes for the other 14 SNPs falling between those values. The sample size for interaction with the FG-GRS was 51,063. Sample sizes for the interaction analyses for FI were 35,739 for rs35767 (*IGF1*) and 35,991 for rs78094 (*GCKR*).

We defined the level of statistical significance on the basis of a Bonferroni correction: $P < 0.025$ for associations between the diet score and the two outcomes of interest; $P < 0.017$ for primary tests of interaction with the FG-GRS and the 2 FI-associated SNPs; and $P < 0.003$ for exploratory tests of interaction with each of the 16 individual FG-associated SNPs. Estimates of statistical power for various sample- and effect-size combinations are published elsewhere (19).

RESULTS

Mean values for the food groups comprising the diet score within each study are shown in Table 2. Variation in values followed expected regional differences in food consumption (19) but did not appear to relate to type of dietary assessment tool, age of the cohort, or chronologic years of dietary assessment.

Diet score was inversely associated with both FG and FI concentrations (Table 3); that is, healthier diets were associated with lower FG and FI concentrations. While the associations were not statistically significant within all cohorts, 12 of 15 cohorts showed inverse associations between diet score and FG (Figure 1), and all 15 cohorts showed inverse associations between diet score and FI (Figure 2). The meta-analyzed associations were robust; adjustment for demographic factors (model 1), lifestyle factors (model 2), and body mass index (model 3), a potential mediator of the relation between diet and health outcomes, had no material impact on the strength or magnitude of the effect estimates ($P < 0.0001$ for all) (Table 3). For each 5-unit change (approximately equal to the mean standard deviation (SD)) in diet score (pointing towards a healthier diet), FG concentrations were 0.03 mmol/L lower and FI concentrations were 0.05 ln-pmol/L lower (results were derived from model 3 regression coefficients; see Table 3 and Figures 3 and 4).

The previously published associations between 16 SNPs and FG and between 2 SNPs and FI were observed in the present collection of cohorts (10 of our 15 cohorts (or 53% of our sample size based on individuals) contributed to the original 54-cohort collaboration (3)) (Table 4). Effect sizes for FG ranged from a 0.01-mmol/L greater to a 0.08-mmol/L greater FG concentration per FG-raising allele, and the effect for FI was a 0.02-(ln)pmol/L increase per FI-raising allele, similar to values reported in the earlier meta-analysis (Table 4) (3). The FG-GRS was also significantly associated with FG concentrations in the present meta-analysis: For each additional FG-GRS unit (risk allele), FG concentrations were 0.03 mmol/L greater ($\beta = 0.03$ (standard error, 0.001), $P < 0.0001$; Table 4).

We observed no interactions between diet score and the FG-GRS, the 16 individual FG-associated SNPs, or the 2 FI-associated SNPs in our meta-analysis (Table 5; Web Figures 1–19). Within some cohorts, there were statistically

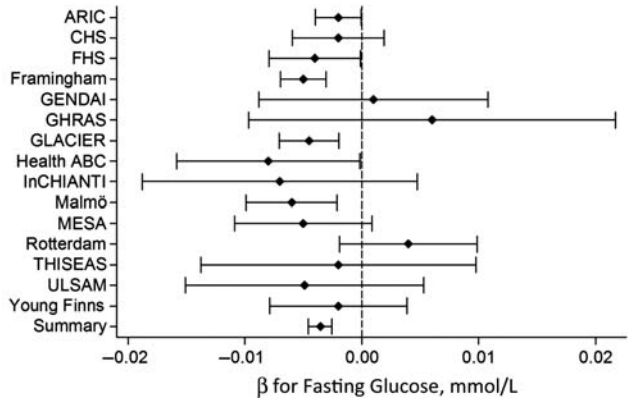

Figure 1. Associations between diet score and fasting glucose concentration in a meta-analysis of data from 15 cohort studies, CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium. Regression coefficients (β) for each of the 15 cohorts and the total association, summarized across all 15 cohorts, represent the difference in fasting glucose level (mmol/L) per 1-unit increase in diet score after adjustment for the model 3 covariates: energy intake, age, sex, field center (in Health ABC, CHS, ARIC, FHS, and InCHIANTI), population substructure (by principal components in CHS, FHS, Framingham, MESA, and Young Finns), smoking, physical activity level, highest attained educational level, alcohol consumption, and body mass index. Bars, 95% confidence interval. (ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study, FHS, Family Heart Study; Framingham, Framingham Generation 5 and Offspring Studies; GENDAI, Gene-Diet Attica Investigation on Childhood Obesity; GHRAS, Greek Health Randomized Aging Study; GLACIER, Gene-Lifestyle Interactions and Complex Traits in Elevated Disease Risk; Health ABC, Health, Aging and Body Composition Study; InCHIANTI, Invecchiare in Chianti [Aging in the Chianti Area]; Malmö, Malmö Diet and Cancer Study (cardiovascular cohort); MESA, Multi-Ethnic Study of Atherosclerosis; Rotterdam, Rotterdam Study; SNP, single nucleotide polymorphism; THISEAS, The Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility; ULSAM, Uppsala Longitudinal Study of Adult Men; Young Finns, Young Finns Study).

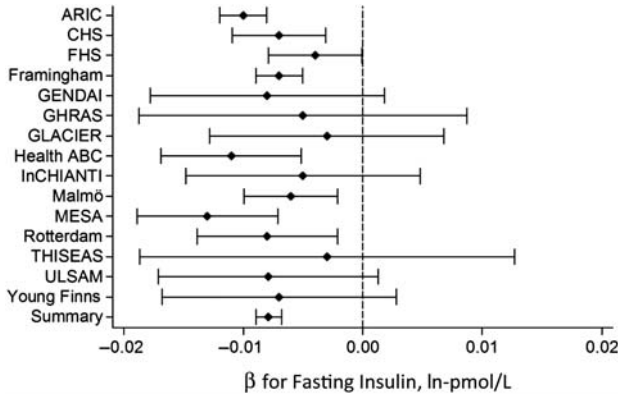

Figure 2. Associations between diet score and fasting insulin concentration in a meta-analysis of data from 15 cohort studies, CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium. Regression coefficients (β) for each of the 15 cohorts and the total association, summarized across all 15 cohorts, represent the difference in fasting insulin level (ln-pmol/L) per 1-unit increase in diet score after adjustment for the model 3 covariates: energy intake, age, sex, field center (in Health ABC, CHS, ARIC, FHS, and InCHIANTI), population substructure (by principal components in CHS, FHS, Framingham, MESA, and Young Finns), smoking, physical activity level, highest attained educational level, alcohol consumption, and body mass index. Bars, 95% confidence interval. (ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study, FHS, Family Heart Study; Framingham, Framingham Generation 5 and Offspring Studies; GENDAI, Gene-Diet Attica Investigation on Childhood Obesity; GHRAS, Greek Health Randomized Aging Study; GLACIER, Gene-Lifestyle Interactions and Complex Traits in Elevated Disease Risk; Health ABC, Health, Aging and Body Composition Study; InCHIANTI, Invecchiare in Chianti [Aging in the Chianti Area]; Malmö, Malmö Diet and Cancer Study (cardiovascular cohort); MESA, Multi-Ethnic Study of Atherosclerosis; Rotterdam, Rotterdam Study; SNP, single nucleotide polymorphism; THISEAS, The Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility; ULSAM, Uppsala Longitudinal Study of Adult Men; Young Finns, Young Finns Study).

significant interactions ($P < 0.05$), but these were inconsistent across cohorts with respect to loci (Web Figures 2–19) and were probably false-positive findings owing to the number of tests performed. Removing the youngest cohort (GENDAI, where the mean age was 11.2 years) did not change these conclusions. Inspection of the data according to the mean age of the cohorts (e.g., <70 years (10 cohorts) vs. ≥70 years (5 cohorts) at assessment) also revealed no consistent differences in the direction of interaction regression coefficients (Web Figures 1–19). Results from random-effects meta-analyses conducted on all of these data were not materially different from those of the fixed-effects meta-analysis (data not shown).

DISCUSSION

Using data from 15 well-characterized epidemiologic cohorts comprising US and European subjects without known diabetes, we observed favorable associations between adherence to a healthy diet, as reflected by the diet score, and FG and FI concentrations. These associations were not modified by genotype at loci previously shown to be reliably associated with glucose homeostasis, such that the association between a healthy diet and FG homeostasis was maintained independently of genotype at these loci. Thus, these data suggest that adhering to a healthy diet is important for everyone, regardless of genotype at these loci.

Although diet quality, as reflected by the diet score, did not modify the associations of the selected loci with FG and FI per se, a risk-allele carrier who adheres to a healthier diet would have lower FG and FI levels than a risk-allele carrier with a less healthy diet. Moreover, our data raise the possibility that modest differences in diet quality (towards a healthier diet) might offset the small genetic risk associated with common variants related to glucose homeostasis. For example, the average effect size across all 16 FG-raising alleles was approximately 0.03 mmol/L (a 0.03-mmol/L greater FG level) per allele, which compares in magnitude to an approximately 1.5-SD greater diet score (i.e., towards a healthier diet). More strikingly, the average 0.02-(ln)pmol/L

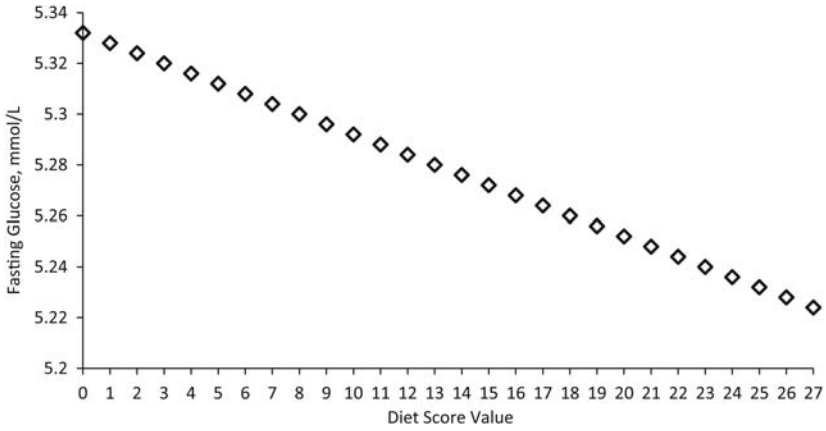

Figure 3. Predicted fasting glucose concentration according to diet score in a meta-analysis of data from 15 cohort studies, CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium. The graph shows predicted fasting glucose concentrations across the spectrum of possible diet score values (0–27), where a diet score of 13 is set to the across-cohorts mean fasting glucose level (5.28 mmol/L), fasting glucose concentrations are 0.004 mmol/L (the regression coefficient generated from model 3) lower per successively higher diet score value, and fasting glucose concentrations are 0.004 mmol/L higher per successively lower diet score value. The model 3 covariates included energy intake, age, sex, 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 Invecchiare in Chianti), population substructure (by principal components in the Cardiovascular Heath Study, the Family Heart Study, the Framingham Generation 5 and Offspring Studies, the Multi-Ethnic Study of Atherosclerosis, and the Young Finns Study), smoking, physical activity level, highest attained educational level, alcohol consumption, and body mass index.

greater FI level per FI-raising allele compares in magnitude to a ½-SD greater diet score.

Our observation that a healthy diet was cross-sectionally associated with lower FG and FI levels is consistent with previous studies of dietary pattern indexes and specific food groups comprising our healthy diet score (18, 19, 27–29). Our work demonstrates that dietary data can be coordinated sufficiently across studies from diverse regions to create a

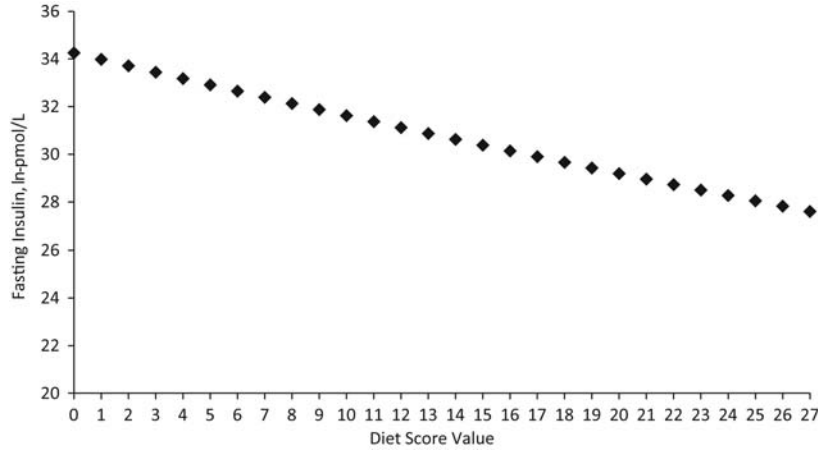

Figure 4. Predicted fasting insulin concentration according to diet score in a meta-analysis of data from 15 cohort studies, CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium. The graph shows predicted fasting insulin concentrations across the spectrum of possible diet score values (0–27), where a diet score of 13 is set to the across-cohorts mean fasting insulin level (3.43 ln-pmol/L), fasting insulin concentrations are 0.008 ln-pmol/L (the regression coefficient generated from model 3) lower per successively higher diet score value, and fasting insulin concentrations are 0.008 ln-pmol/L higher per successively lower diet score value. The plotted values are the result of exponentiating the ln-pmol/L estimates. The model 3 covariates included energy intake, age, sex, 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 Invecchiare in Chianti), population substructure (by principal components in the Cardiovascular Heath Study, the Family Heart Study, the Framingham Generation 5 and Offspring Studies, the Multi-Ethnic Study of Atherosclerosis, and the Young Finns Study), smoking, physical activity level, highest attained educational level, alcohol consumption, and body mass index.

Table 4. Associations[a] of Single Nucleotide Polymorphisms and Fasting Glucose Genetic Risk Score With Fasting Glucose and Fasting Insulin Concentrations in a Meta-Analysis, CHARGE Consortium

SNP	Chromosome	Nearest Gene	Effect Allele[b]	Other Allele	No. of Cohorts	Summary Association	
						β (SE)[c]	*P* Value
Fasting glucose-related loci							
rs340874	1	*PROX1*	C	T	15	0.0198 (0.0034)	8.31×10^{-09}
rs560887	2	*G6PC2*	C	T	15	0.0735 (0.0036)	3.05×10^{-90}
rs780094	2	*GCKR*	C	T	15	0.0298 (0.0034)	3.64×10^{-18}
rs11708067	3	*ADCY5*	C	T	15	0.0305 (0.0041)	1.28×10^{-13}
rs11920090	3	*SLC2A2*	T	A	15	0.0318 (0.0048)	4.88×10^{-11}
rs4607517	7	*GCK*	A	G	15	0.0612 (0.0045)	1.71×10^{-42}
rs2191349	7	*DGKB/TMEM195*	T	G	15	0.0248 (0.0033)	1.25×10^{-13}
rs11558471	8	*SLC30A8*	A	G	13[d]	0.0360 (0.0039)	2.88×10^{-20}
rs7034200	9	*GLIS3*	A	C	15	0.0180 (0.0033)	6.66×10^{-08}
rs10885122	10	*ADRA2A*	G	T	15	0.0200 (0.0053)	1.60×10^{-04}
rs4506565	10	*TCF7L2*	C	T	13[d]	0.0276 (0.0038)	4.79×10^{-13}
rs10830963	11	*MTNR1B*	G	C	15	0.0801 (0.0040)	2.80×10^{-91}
rs7944584	11	*MADD*	A	T	15	0.0249 (0.0038)	6.87×10^{-11}
rs11605924	11	*CRY2*	A	C	15	0.0239 (0.0034)	1.03×10^{-12}
rs174550	11	*FADS1*	T	C	15	0.0189 (0.0035)	8.52×10^{-08}
rs11071657	15	*FAM148B*	A	G	15	0.0071 (0.0035)	4.59×10^{-02}
FG-GRS					15	0.0283 (0.0009)	<0.0001
Fasting insulin-related loci							
rs780094	2	*GCKR*	C	T	15	0.0168 (0.0036)	3.70×10^{-06}
rs35767	12	*IGF1*	G	A	15	0.0153 (0.0048)	1.44×10^{-03}

Abbreviations: CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; FG-GRS, fasting glucose genetic risk score; SE, standard error; SNP, single nucleotide polymorphism.

[a] Adjusted for age, sex, field center (in the Health, Aging and Body Composition Study, the Cardiovascular Health Study, the Atherosclerosis Risk in Communities Study, the Family Heart Study, Invecchiare in Chianti, and the Multi-Ethnic Study of Atherosclerosis), and population substructure (by principal components in the Cardiovascular Heath Study, the Family Heart Study, the Framingham Generation 5 and Offspring Studies, the Multi-Ethnic Study of Atherosclerosis, and the Young Finns Study).

[b] Coded uniformly in all cohorts. Allele frequencies for each cohort can be found in Web Table 2.

[c] Beta coefficient and standard error for the estimated difference in fasting glucose (mmol/L) or fasting insulin (ln-pmol/L) concentration per 1-unit increase in the effect allele (the fasting glucose- or fasting insulin-raising allele), assuming an additive genetic model.

[d] SNP not genotyped in this cohort.

meaningful, predictive dietary score reflecting healthy food consumption.

We chose to test for interaction between diet and a select set of loci from a previous meta-analysis of GWAS for 3 main reasons: 1) the loci (or the functional SNPs these variants tag) from such studies are those with the strongest evidence of biologic relevance to glucose and insulin homeostasis; 2) these loci are the ones most likely to be used by medical practitioners (and consumers) for prognostic purposes (4–6); and 3) given the penalty for multiple testing and the probably small effect sizes for diet-gene interaction, an analysis focused on fewer SNPs would be more statistically powerful. Thus, we aimed to assess whether the effects of GWAS-identified loci altered the favorable associations of dietary factors with glucose and insulin homeostasis. Our finding of no interaction is important, as it suggests that the favorable influences attributed to dietary factors are likely to be conveyed regardless of genotype at the selected loci. Thus, from a public health viewpoint, population-based dietary recommendations are of benefit to everyone regardless of genetic variation, at least on the basis of the loci studied here. However, there may be other regions that do interact with diet that we overlooked in our focus on top-ranked GWAS loci, since, in order to reach the extremely low *P* values required for statistical significance, such loci necessarily show little heterogeneity in phenotypic effects (30). Future work focused on genome-wide interaction may uncover regions of the genome that influence biologic response to diet (30). A focus on a reduced number of loci remains important for preserving statistical power. However, other strategies that identify regions that are more likely to interact with environmental factors

Table 5. Meta-Analyzed Effect of Interactions Between Healthy Diet Score, Single Nucleotide Polymorphisms, and Fasting Glucose Genetic Risk Score on Fasting Glucose and Fasting Insulin Concentrations, CHARGE Consortium[a]

SNP	No. of Persons	Diet Score × SNP Interaction	
		β (SE)[b]	*P* Value
Fasting glucose-related loci			
rs340874	51,063	0.0010 (0.0008)	0.22
rs560887	51,117	0.0001 (0.0008)	0.91
rs780094	50,810	0.0007 (0.0008)	0.35
rs11708067	51,403	−0.0003 (0.0009)	0.77
rs11920090	50,828	0.0000 (0.0011)	0.99
rs4607517	51,172	0.0003 (0.0010)	0.76
rs2191349	51,377	−0.0009 (0.0008)	0.23
rs11558471	51,149	0.0002 (0.0009)	0.80
rs7034200	49,146	−0.0002 (0.0008)	0.83
rs10885122	51,126	0.0001 (0.0012)	0.93
rs4506565	51,145	0.0003 (0.0009)	0.77
rs10830963	48,872	−0.0003 (0.0009)	0.78
rs7944584	50,644	0.0006 (0.0009)	0.48
rs11605924	50,720	−0.0005 (0.0008)	0.56
rs174550	51,163	−0.0007 (0.0008)	0.40
rs11071657	51,273	0.0006 (0.0008)	0.44
FG-GRS	51,120	0.0001 (0.0002)	0.67
Fasting insulin-related loci			
rs780094	35,991	−0.0011 (0.0009)	0.25
rs35767	35,739	−0.0011 (0.0012)	0.38

Abbreviations: CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; FG-GRS, fasting glucose genetic risk score; SE, standard error; SNP, single nucleotide polymorphism.

[a] Results were adjusted for age, sex, energy intake, field center (in the Health, Aging and Body Composition Study, the Cardiovascular Health Study, the Atherosclerosis Risk in Communities Study, the Family Heart Study, Invecchiare in Chianti, and the Multi-Ethnic Study of Atherosclerosis), and population substructure (by principal components in the Cardiovascular Heath Study, the Family Heart Study, the Framingham Generation 5 and Offspring Studies, the Multi-Ethnic Study of Atherosclerosis, and the Young Finns Study).

[b] Beta coefficient and standard error for the estimated difference in fasting glucose (mmol/L) or fasting insulin (ln-pmol/L) concentration per 1-unit increase in the effect allele (the fasting glucose- or fasting insulin-raising allele), assuming an additive genetic model, interacting with a 1-point increase in the diet score.

show promise in helping to uncover gene-environment interactions while keeping penalties for multiple testing at a minimum (31).

Some caveats are warranted when interpreting the present data. First, we assumed that the dietary factors most relevant for glucose and insulin homeostasis were included in our diet score and that these factors were measured well. For the majority of our cohorts, we had evidence of successful estimation of dietary intake from conventional validation or reliability studies (described elsewhere (19)). Moreover, our observed associations between the healthy diet score and FG and FI levels are biologically plausible and consistent with other major studies on this topic, thus serving, to some degree, as evidence of construct validity. A second potential limitation of this study is that the global nature of our healthy diet score, which takes into account multiple food choices, may have overwhelmed the biologic influences of individual foods or food components. For example, we previously studied interactions between these same genetic loci and intake of whole-grain foods and observed evidence of interactions between whole grain intake and variation at the *GCKR* locus (19). In contrast, in the present study, we observed no evidence of interaction between the diet score and *GCKR* or any of the other studied loci, suggesting that the signal may be specific to whole grains (or a constituent) and that inclusion of other aspects of a healthy diet diluted this signal. Third, the magnitude of the association between the diet score and FG and FI was modest. Although this is consistent with most reports of associations between dietary factors (which are measured with known random error) and disease-related outcomes, results should be interpreted with consideration of their clinical relevance. Fourth, the selected loci explain only a small fraction of the variation in FG and FI levels (3). Fifth, while our study was uniquely large, it did not have sufficient power to detect very small interaction effects; however, such small interaction effects may be of limited clinical relevance. Lastly, observational studies are prone to residual confounding and causal inference is difficult, particularly in cross-sectional studies such as ours (32). Moreover, such data cannot inform us about the impact of *changing* dietary quality in the short term, a question that is of key importance in designing preventive interventions and that requires intervention studies to be adequately addressed.

Our meta-analysis of data from 15 cohort studies had several strengths. We were able to achieve a large sample size that far exceeded almost all previous studies of gene-diet interactions, while also using a standardized analytic plan and uniformly defined dietary exposures. Furthermore, we were able to take advantage of existing observational data which captured habitual dietary intake, perhaps most significant in the context of gene-environment interactions (32). Additionally, such studies possess information on important confounders, effect modifiers, or mediators of exposure-outcome relations which can be used in analyses. Much of the dietary data used in the current study came from long-standing, well-designed studies with appropriate assessments of data quality and a history of published nutritional epidemiologic research.

Determining whether genetic loci that have been reliably associated with complex disease traits modify associations attributed to protective lifestyle behaviors is important because the presence of such interactions might guide further research and targeted disease prevention. Determining that interactions do not exist between these loci and lifestyle behaviors is important, not least because direct-to-consumer personal genome profiling is now widely available, but data

concerning the utility of the information provided by these products and companies are not. Thus, studies such as ours may help dispel misunderstanding about the way common genetic variants affect disease risk and whether knowledge of one's genomic profile should motivate specific changes in lifestyle, as suggested by some personal genome product manufacturers (4). Based on the evidence reported here, we conclude that the importance of adhering to a healthy diet per se in maintaining glucose and insulin homeostasis is not influenced by one's genotypes at the loci we have studied. Although the present study suggests that the published variants for glucose and insulin traits do not interact with dietary patterns, it remains possible that future studies will discover novel loci that do interact with dietary factors. Future studies focusing on regions of the genome other than those that emerge as the most statistically significant main-effect signals from GWAS may be more fruitful in identifying diet-gene interactions.

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