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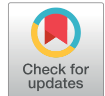

Investigating Gene–Diet Interactions Impacting the Association Between Macronutrient Intake and Glycemic Traits

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Few studies have demonstrated reproducible gene–diet interactions (GDIs) impacting metabolic disease risk factors, likely due in part to measurement error in dietary intake estimation and insufficient capture of rare genetic variation. We aimed to identify GDIs across the genetic frequency spectrum impacting the macronutrient–glycemia relationship in genetically and culturally diverse cohorts. We analyzed 33,187 participants free of diabetes from 10 National Heart, Lung, and Blood Institute Trans-Omics for Precision Medicine program cohorts with whole-genome sequencing, self-reported diet, and glycemic trait data. We fit cohort-specific, multivariable-adjusted linear mixed models for the effect of diet, modeled as an isocaloric substitution of carbohydrate for fat, and its interactions with common and rare variants genome-wide. In main effect meta-analyses, participants consuming more carbohydrate had modestly lower glycemic trait values (e.g., for glycated hemoglobin [HbA_{1c}], −0.013% HbA_{1c}/250 kcal substitution). In GDI meta-analyses, a common African ancestry–enriched variant (rs79762542) reached study-wide significance and replicated in the UK Biobank cohort, indicating a negative carbohydrate–HbA_{1c} association among major allele homozygotes only. Simulations

ARTICLE HIGHLIGHTS

- We aimed to identify genetic modifiers of the dietary macronutrient–glycemia relationship using whole-genome sequence data from 10 Trans-Omics for Precision Medicine program cohorts.
- Substitution models indicated a modest reduction in glycemia associated with an increase in dietary carbohydrate at the expense of fat.
- Genome-wide interaction analysis identified one African ancestry–enriched variant near the *FRAS1* gene that may interact with macronutrient intake to influence hemoglobin A_{1c}.
- Simulation-based power calculations accounting for measurement error suggested that substantially larger sample sizes may be necessary to discover further gene–macronutrient interactions.

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revealed that >150,000 samples may be necessary to identify similar macronutrient GDIs under realistic assumptions about effect size and measurement error. These results generate hypotheses for further exploration of modifiable metabolic disease risk in additional cohorts with African ancestry.

Diet is an established modifiable factor associated with risk of type 2 diabetes (T2D) and related cardiometabolic diseases (1). However, evidence is mixed regarding the ideal dietary macronutrient composition for risk reduction. Dietary interventions with differing proportions of energy from carbohydrates versus fat have shown varied

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efficacy for T2D risk reduction and substantial between-person heterogeneity in effects on cardiometabolic risk factors (2–4). Further, acute glycemic responses to meals with specific macronutrient composition are reproducible within individuals (5,6). Genetically different mouse strains have varying sensitivity of glycemic biomarkers to a high-fat diet (7) and to human-relevant dietary patterns (8). Retrospective analysis of human trials manipulating macronutrient intake has found genetic modifiers of glycemic response (9). Taken together, such studies suggest that genetics could be a key contributor to variability in the association between dietary macronutrient composition and glycemic health.

Gene–diet interaction (GDI) studies aim to identify genetic variants that modify the association between dietary behaviors and health. Furthermore, GDI studies support differential associations of dietary factors with glycemic traits according to genotypes, using both hypothesis-driven (10) and hypothesis-free (11,12) strategies. However, in general, discovery and replication of GDI with T2D risk has been poor, possibly due to measurement error in assessing habitual diet, low statistical power for interaction analysis, and biological and behavioral heterogeneity across populations (13). Additionally, to date, there has been little exploration of GDIs involving rare genetic variants, which affect a smaller proportion of the population but may have larger effect sizes (14).

Our primary aim was to discover novel putative genetic modifiers for the association between dietary macronutrient composition and glycemic traits. To this end, we performed a GDI analysis using common and rare genetic variants in >30,000 individuals with diverse ancestral backgrounds from the National Heart, Lung, and Blood Institute (NHLBI) Trans-Omics for Precision Medicine (TOPMed) program. We focused on modeling a dietary carbohydrate–fat exchange, which can be reasonably assessed via self-reported diet questionnaires and can be straightforwardly modified in the context of a healthful diet. Furthermore, the use of whole-genome sequencing (WGS) permitted the analysis of rare variants using set-based association tests. As a secondary aim, we sought to inform subsequent GDI research by exploring the impact of dietary exposure measurement error on statistical power in the context of realistic effect size estimates.

RESEARCH DESIGN AND METHODS

WGS

WGS was conducted through the NHLBI TOPMed program (Freeze 8 data release). Sequencing and alignment to the GRCh38 reference genome was performed at seven centers across the U.S.: Broad Institute of MIT and Harvard, Northwest Genomics Center, New York Genome Center, Illumina Genomic Services, Psomagen (formerly Macrogen), Baylor College of Medicine Human Genome Sequencing Center, and McDonnell Genome Institute at Washington University. Data harmonization and joint variant discovery and genotype calling were performed within the TOPMed Informatics Research Center at the University of Michigan. Sequence quality control filters were as follows: estimated DNA sample contamination <10% and at least 95% of the genome having coverage of at least 10 times. After genotyping, variants were further filtered for Mendelian inconsistency (based on a support vector machine classifier) and excess heterozygosity. Additional sample quality control was performed within the Data Coordinating Center at the University of Washington, including: matching sex as annotated and inferred from WGS, concordance of WGS genotypes with prior array-based "fingerprints," and agreement of inferred relatedness with expectations based on pedigrees. Additional details on the processing steps are available at: https://www.nhlbiwgs.org/topmed-whole-genome-sequencing-methods-freeze-8.

Global measures of ancestry and relatedness were calculated on the entire TOPMed Freeze 8 sample by the TOPMed Data Coordinating Center. Genetic principal components reflecting ancestry were calculated using the PC-AiR method (allowing for related individuals) (15), and kinship matrices were calculated using the PC-Relate method (accounting for principal components) (16), both from the GENESIS R package. A sparse genetic relationship matrix containing only relationships of degree four or closer was extracted for analysis. Samples were grouped into race/ethnicity categories based on cohort-reported values. Some individuals are represented in multiple studies in the TOPMed program (e.g., Jackson Heart Study and Atherosclerosis Risk in Communities [ARIC] study); in such cases, one individual from each duplicate pair was removed prior to analysis.

Harmonization of Glycemic Traits

Phenotypes were harmonized across the 10 studies based on a protocol developed within the TOPMed Diabetes Working Group. Glycemic traits, including fasting glucose (FG; millimoles per liter), fasting insulin (FI; picomoles per liter), and glycated hemoglobin (HbA_{1c}; percentage), were collected where available. Fasting (for FG and FI) was defined as at least 8 h without food or drink. FG measurements made in blood rather than plasma were adjusted by multiplying by a correction factor of 1.13. When multiple values were available for a given participant, blood draws were chosen to favor measurements made at study baselines and to maximize overlap with time points at which dietary data were collected. Participants were excluded if their glycemic trait blood draw was >1 year before or after diet measurement or if they had diabetes (defined as any of: taking antidiabetic medication, FG ≥7 mmol/L, or HbA_{1c} ≥6.5%). See Supplementary Fig. 1 for a participant inclusion flowchart. Further study-specific details are available in the Supplementary Methods. Phenotype data harmonization and all other post–genome-wide analyses and visualizations were conducted using R version 4.1.1 (17). Unless otherwise noted, all analyses including harmonization were

performed on the NHLBI BioData Catalyst cloud computing platform (18).

Harmonization of Dietary Data

Estimates of dietary intake were derived from self-reported diet questionnaires, either food frequency questionnaires, diet history, or 24-h recalls. Reported quantities of food and beverage consumption were converted into daily nutrient intake estimates via standard nutrient databases (see Supplementary Methods for study-specific details), with energy and macronutrients (carbohydrate, protein, and total fat) expressed in kilocalories per day. Participants were excluded if responses were deemed implausible, based on having total caloric intake <600 kcal/d or >4,800 kcal/d. Nutrient intake values were analyzed in units of kilocalories per day and Winsorized at 3 SDs from the mean within each cohort. Dietary fiber was represented in grams per day, and alcohol intake was reported as number of drinks per day. Diet questionnaires were completed at the same time point as blood draws for glycemic trait measurement, with the exception of a 3-year gap between diet and HbA_{1c} measurement in the ARIC study (see Supplementary Methods for details).

Genome-wide GDI Scans

For each cohort and glycemic trait, four genome-wide GDI scans were performed to identify diet-interacting loci: one for common variants and three gene-based aggregate tests for rare variants using different variant masks (described below). Mixed linear models were used to allow for random effects of kinship capturing close family relationships (degree four relatives or closer). The linear model setup was as follows:

$$FG/lnFI/HbA1c \sim g + CHO + g{*}CHO + \gamma + covariates$$

where g is the genotype at the variant of interest, CHO is dietary carbohydrate intake (kilocalories per day), and γ is a random effect governed by a sparse kinship matrix. General covariates included sex, age, age^2, five genetic principal components to capture genetic ancestry, cohort-reported race/ethnicity to capture potential confounding by ethnicity-related dietary behavior, and additional study-specific covariates (Supplementary Table 2). Dietary protein intake and total energy (also expressed in kilocalories per day) were included as covariates to set up an isocaloric substitution model in which increases in carbohydrate were implicitly exchanged for decreases in dietary fat. Dietary fiber (grams per day), alcohol intake (standard drinks per day), and BMI (kilograms per meter squared) were included as additional covariates to account for further lifestyle-related confounding. Though the inclusion of dietary fiber as a covariate impacts the interpretation of the carbohydrate term of interest, we found in preliminary analyses that its inclusion substantially decreased cross-study heterogeneity in parameter estimates, possibly due to a reduction in the confounding mentioned above. During null model fitting, heterogeneous variances were allowed within each cohort-reported race/ethnicity group (equivalent to including a random effect for this grouping variable). For variants on the X chromosome, male genotypes were coded as (0, 2).

Genome-wide interaction analysis was performed using the MAGEE package (19). Single-variant analysis (*glmm.gei* function) was conducted for variants with minor allele frequency (MAF) >1%. METAL (20) was used to perform fixed-effects meta-analysis across cohorts. Specifically, the 2-df joint meta-analysis patch was used (21), with genetic main effect and interaction *P* values derived downstream based on the resulting effect and SE estimates.

Gene-centric, set-based rare-variant analysis (*MAGEE* function) was conducted for variants with MAF <1%. Variant annotations derived from the WGSA v0.8 and WGSAParsr v6.3.8 were retrieved from the National Center for Biotechnology Information Database of Genotypes and Phenotypes (dbGaP). A genome-wide interaction meta-analysis was conducted for each of three variant masks: loss of function variants (VEP_ensembl_Consequence has terms *transcript_ablation*, *splice_acceptor_variant*, *splice_donor_variant*, *stop_gained*, *frameshift_variant*, *stop_lost*, *start_lost* or *transcript_amplification*), missense variants (VEP_ensembl_Consequence has the term *missense_variant*), and a broad coding and noncoding filter (containing high-confidence loss-of-function variants, missense variants, protein-altering variants, synonymous variants, variants overlapping enhancers, and variants overlapping promoters). *MAGEE* calculates three interaction *P* values: an adjusted variance component-like test, a burden test (assuming a consistent direction of effect for all variants), and a hybrid test (which combines the first two *P* values using the Fisher method). *P* values from the hybrid test were used in this study to balance the increased power of the burden test with the possibility that its assumption of homogeneous effect directions is violated. Meta-analysis was then performed using a fixed-effects strategy.

Linear mixed models without genotype terms, meant to understand the marginal dietary effects prior to considering genetic effects, were fit in R using analogous models to those with diet–genotype interaction terms. Diet–genetic principal component interaction terms were excluded from these models, and individuals in cohort-reported race/ethnicity groups with less than five members were excluded. Fixed-effect meta-analysis of the carbohydrate association (implicitly modeling an exchange with fat due to the additional dietary covariates) was conducted using the *meta* package.

Variant Follow-up

Sensitivity analysis was conducted to understand the impact of modeling choices on the interaction effect estimates derived in the genome-wide analysis. These linear mixed models were fit in R, with G × CHO interaction terms subject to fixed-effects meta-analysis using the *meta* package as with the models without genotype effects. Some of these involved subsets of the population: male and

female subsets were tested separately, as well as subsets without obesity (BMI <30 kg/m^2) and with and without prediabetes (defined as FG >5.6 mmol/L or HbA_{1c} $>5.7\%$ [39 mmol/mol]). Additional models included adjustment for smoking status (never/former/current, coded as 0/1/2 and analyzed as a continuous variable), the Alternative Healthy Eating Index 2010 (22) (a diet quality score), or a categorical coding of alcohol intake (none, modest [less than 1 drink per day for females or less than two drinks per day for males], or high), where available. These models with additional covariate adjustments also included adjustment for their interactions with genotype. Finally, a model including genotype interaction terms for other main dietary components and lifestyle confounders (total energy, protein, fiber, and alcohol) was included. This type of residual confounding by genotype–covariate interaction terms has been previously documented (23), but would have decreased statistical power if included in the genome-wide analysis, especially for lower-frequency variants.

Variant rs79762542 was investigated in greater depth as the only variant reaching study-wide significance. Based on its expression quantitative trait locus (eQTL) relationship impacting *FRAS1* gene expression in thyroid from the Genotype-Tissue Expression (GTEx) v8 data set (https://gtexportal.org/), we tested for colocalization of this signal with the carbohydrate interaction signal impacting HbA_{1c}. Interaction summary statistics were retrieved in a window of 1 Mb around the index variant rs79762542, and all thyroid-specific *cis*-eQTL summary statistics related to *FRAS1* were retrieved from GTEx. Colocalization was tested using the *coloc* package for R, assuming a single causal variant (*coloc.abf* function). Visualizations used the carbohydrate-to-fat ratio (simple ratio of kcalories from carbohydrate to kcalories from fat) as a summary variable to capture the modeled carbohydrate–fat exchange in a single variable for stratification. Tertiles of this ratio were defined in the entire pooled study cohort (with nonmissing HbA_{1c} values).

Replication Analysis in the UK Biobank

UK Biobank (UKB) is a large prospective cohort with both deep phenotyping and molecular data, including genome-wide genotyping, on $>500{,}000$ individuals aged 40–69 years living throughout the U.K. between 2006 and 2010 (24). Genotyping, imputation, and initial quality control on the genetic data set have been described previously (25). Analyses were conducted on genetic data release version 3, with imputation to a joint reference panel including the Haplotype Reference Consortium and the 1000 Genomes Project under UKB application 27892. This work was conducted under a Not Human Subjects Research determination (NHSR-4298 at the Broad Institute of MIT and Harvard).

Ancestry group labels, genetic principal components, and labels defining an unrelated subset of individuals were retrieved from the Pan-UKB project (https://pan.ukbb.broadinstitute.org/; data retrieved from UKB return of results number 2442). Only unrelated individuals were used for analysis, with additional removal of individuals who were pregnant or had diabetes at the study center visit. Two glycemic traits were available for testing in UKB: HbA_{1c} (provided in units of millimoles per mole and transformed after regression to units of HbA_{1c} percentage by dividing by 10.929) and glucose (collected as a random glucose measurement with subsequent removal of non-fasting individuals). Outliers for both traits (defined as more than 5 SDs from the mean) were removed. Dietary data came from one or more Oxford WebQ 24-h dietary assessments (26) completed at the study center or during online follow-up over the course of 2 years. Daily nutrient intake estimates (calculated centrally by the UKB) were averaged across all questionnaires for each individual and Winsorized at 3 SDs from the mean. After all exclusions, 178,352 individuals without diabetes had available genotype, biomarker, and dietary data.

Regression analysis in the UKB mirrored that of the primary analysis, replacing cohort-reported race/ethnicity with genetically defined ancestry groups as defined by the Pan-UKB project. Given the larger sample size available, gene–covariate interactions were included for dietary covariates (total energy, protein, fiber, and alcohol). When analyzing glucose, only the subset of individuals with reported fasting times of at least 8 h were included, reducing the sample size to 5,183. Due to the African-ancestry specificity of some of the top variants, a second replication analysis was performed in the African-ancestry subset of UKB.

Power Calculations

Interaction test power calculations were performed using the *ESPRESSO.GxE* R package, which uses a simulation-based approach to calculate empirical power estimates (given some sample size) and sample size requirements (to achieve 80% power). The following parameters were fixed for this analysis, chosen to mimic an analysis of HbA_{1c}: random seed = 1; significance threshold = 5×10^{-8}; phenotype mean = 5.5; phenotype SD = 0.5; phenotype reliability = 1; genetic main effect = 0.1; exposure mean = 0; exposure SD = 1; and exposure main effect = 0.2. The following parameters were varied: interaction effect {0.025, 0.0375, 0.05, 0.0625, 0.075, 0.0875, 0.1}, MAF {0.01, 0.05, 0.1, 0.5}, and exposure reliability {0.25, 0.5, 0.75, 1}. In this study, reliability is used to quantify the simulated measurement error of the phenotype and exposure and is equivalent to an intraclass correlation coefficient (ratio of between-subject variance to total [between-subject plus measurement error] variance).

To enable simulation-based power calculations for aggregate tests of rare variants while accounting for exposure measurement error, we developed an extension of the *ESPRESSO.GxE* package, called *ESPRESSO.GxE.RV*. In this extension, the basic structure of the simulations remains the same, but an additional parameter allows the user to specify a number of variants (M) to test in aggregate. Within

each simulation run, M variants are simulated, with some portion having equal interaction and main effects on the outcome (according to a user-specified causal variant fraction) and the rest generated randomly. The final *P* value from that simulation is calculated using the Fisher method on the full set of M *P* values. The following parameters were given different values for this set of simulations: interaction effect {0.025, 0.05, 0.075, 0.1, 0.125, 0.15, 0.175, 0.2} and MAF {0.0025, 0.005, 0.0075, 0.01}. Other parameters were specific to rare-variant tests: number of variants per aggregate test {1, 5, 10, 20} and causal fraction {0.1, 0.25, 0.5, 1}. Code for this extension of the package can be found on GitHub: https://github.com/kwesterman/ESPRESSO.GxE.RV.

To provide context for realistic GDI effect sizes despite few well-replicated examples of such interactions for glycemic traits in the literature, we retrieved results from variants reaching significance in a recent trans-ancestry genome-wide association studies for HbA_{1c} (27) and an estimated effect for the carbohydrate–HbA_{1c} relationship from a recent nutritional epidemiological analysis (28).

Data and Resource Availability

The TOPMed study data that support the findings of this study are available from the National Center for Biotechnology Information dbGaP, which were used under license for the current study and, therefore, are not publicly available. UKB data are available through a process described at: https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access. No applicable resources were generated or analyzed during the current study.

RESULTS

We analyzed data from 33,178 individuals without diabetes (based on FG, HbA_{1c}, or medication use) from 10 TOPMed program cohorts. Participants had diverse cohort-reported race/ethnicities, including: African American (*N* = 6,158), American Indian (*N* = 35), Asian (*N* = 124), White (*N* = 19,721), and Hispanic/Latino (*N* = 7,114). Dietary carbohydrate and fat as a percentage of total energy intake on average were 50.5% (SD 8.5%) and 32.2% (6.9%), respectively, in the full pooled sample, estimated using validated food frequency questionnaires or 24-h dietary recalls. Cohort-specific carbohydrate intake estimates (as percent of total energy [percent kilocalories]), glycemic trait values (FG, FI [or log-transformed (lnFI)], and HbA_{1c}), and additional population characteristics are presented in Supplementary Table 1 and Supplementary Fig. 2.

We first modeled the main association of macronutrient compositions with each of the glycemic traits. By adjusting for total energy and energy from protein, resulting regression estimates for carbohydrate represented a macronutrient exchange (increased 250 kcal from carbohydrate replacing an equivalent 250 kcal from fat; see *Research Design and Methods*). Meta-analysis of the individual cohorts indicated that a higher proportion of kcal from carbohydrate at the expense of fat was associated with lower FG (−0.030 mmol/L/250 kcal; $P = 2.2 \times 10^{-6}$), lnFI (−0.008 log[pmol/L]/250 kcal; *P* = 0.15), and HbA_{1c} (−0.012% [−0.13 mmol/mol] HbA_{1c}/250 kcal; *P* = 0.029). Forest plots of these results are shown in Supplementary Fig. 3.

Common Variant Interactions

We sought to identify macronutrient GDIs with the maximal sample available in TOPMed program cohorts to provide a baseline for discovery and evaluate our assumptions about expected effect sizes. Common variants (MAF >1%) were analyzed in a primary, single-variant analysis of gene–carbohydrate interactions, with the same regression adjustments as above. This GDI analysis produces interaction estimates for the difference in the macronutrient–glycemic trait association per alternate allele at the variant of interest. After genome-wide, cohort-specific analysis and cross-cohort meta-analysis, one variant reached a study-wide significance threshold of 1.67×10^{-8} (5×10^{-8}/3 glycemic traits). Two additional variants passed a standard genome-wide threshold of 5×10^{-8} (Table 1). We note that this threshold is liberal given the greater testing burden involved in the analysis of multiple ancestry groups (29). Of these three, none had evidence of a genetic main effect on the associated trait. Results are visualized in Supplementary Fig. 4 for all variants and shown in Supplementary Table 3 for variants with interaction $P < 10^{-5}$.

As the only variant reaching study-wide significance in the primary analysis, we looked deeper into the biological function of rs79762542 and the functional form of its interaction. Variant rs79762542 is observed on African-ancestry haplotypes and was discovered with respect to HbA_{1c}. The variant does not have known regulatory activity based on epigenomic assays in RegulomeDB, but there is evidence for a role in regulating expression of the nearby gene *FRAS1*, especially in thyroid, where this gene is most strongly expressed (GTEx project). Colocalization analysis did not support a shared causal signal between our interaction results and thyroid-specific eQTL signal (posterior probability of shared causal variant = 0.003%).

In genotype-stratified meta-analysis, HbA_{1c} showed a modest negative association with increasing carbohydrate relative to fat intake in major allele homozygotes (−0.033% [−0.36 mmol/mol] HbA_{1c}/250 kcal; *P* = 0.004) versus a positive association in minor allele carriers (0.10% [1.1 mmol/mol] HbA_{1c}/250 kcal; *P* = 0.42) that may not have reached significance due to the much lower sample size in this group (*N* = 1,055 across all studies) (Fig. 1*A*). This genetic effect modification was moderately consistent across cohorts, as visualized through stratification by genotype and carbohydrate/fat ratio (Fig. 1*B*; identical visualization in the African American race/ethnicity subset in Supplementary Fig. 5). Finally, with respect to the other glycemic traits in our analysis, interaction effects were directionally consistent but did not reach nominal significance (0.02 mmol/L/allele/250 kcal; *P* = 0.07 for FG and 0.003 log[pmol/L]/allele/250 kcal; *P* = 0.74 for lnFI).

Table 1—Top variants interacting with carbohydrate intake from the common-variant genome-wide interaction study

Trait	rsID	Chromosome	Position	Effect allele	Average EAF	Main effect estimate	Interaction estimate	$P_{interaction}$
HbA_{1c}	rs79762542	4	77979164	G	0.03	−0.013 (−0.038 to 0.012)	0.048 (0.031–0.064)	1.1×10^{-8}
FG	rs1288694	3	71275429	C	0.61	−0.003 (−0.011 to 0.004)	0.016 (0.01–0.022)	1.9×10^{-8}
lnFI	rs782681704	X	155084576	G	0.01	−0.049 (−0.209 to 0.11)	0.284 (0.182–0.385)	4.6×10^{-8}

Interaction estimates with 95% CIs are given in units of (trait units/allele/250 kcal carbohydrate). All variants passed a significance threshold of $P_{interaction} < 5 \times 10^{-8}$. EAF, effect allele frequency.

Lookups for the other two variants passing $P < 5 \times 10^{-8}$ revealed potential functional roles for these variants. Variant rs1288694 (common in multiple ancestries) impacted FG in our analysis. The variant is intronic to the *FOXP1* gene and may regulate splicing of the same gene (GTEx project). *FOXP1* has a demonstrated role in hepatic gluconeogenesis (30). Variant rs782681704 is observed on African-ancestry haplotypes and was discovered with respect to FI in our analysis. The variant is intronic to *BRCC3* and has likely regulatory activity (RegulomeDB score of 0.59), but does not have clear evidence as an eQTL for *BRCC3*.

We explored these three prioritized single-variant loci through sensitivity analysis (Supplementary Figs. 6 [rs79762542] and 7 [all three variants]). Interaction effects were robust in population subsets: only males, only females, and individuals without obesity. Exclusion of

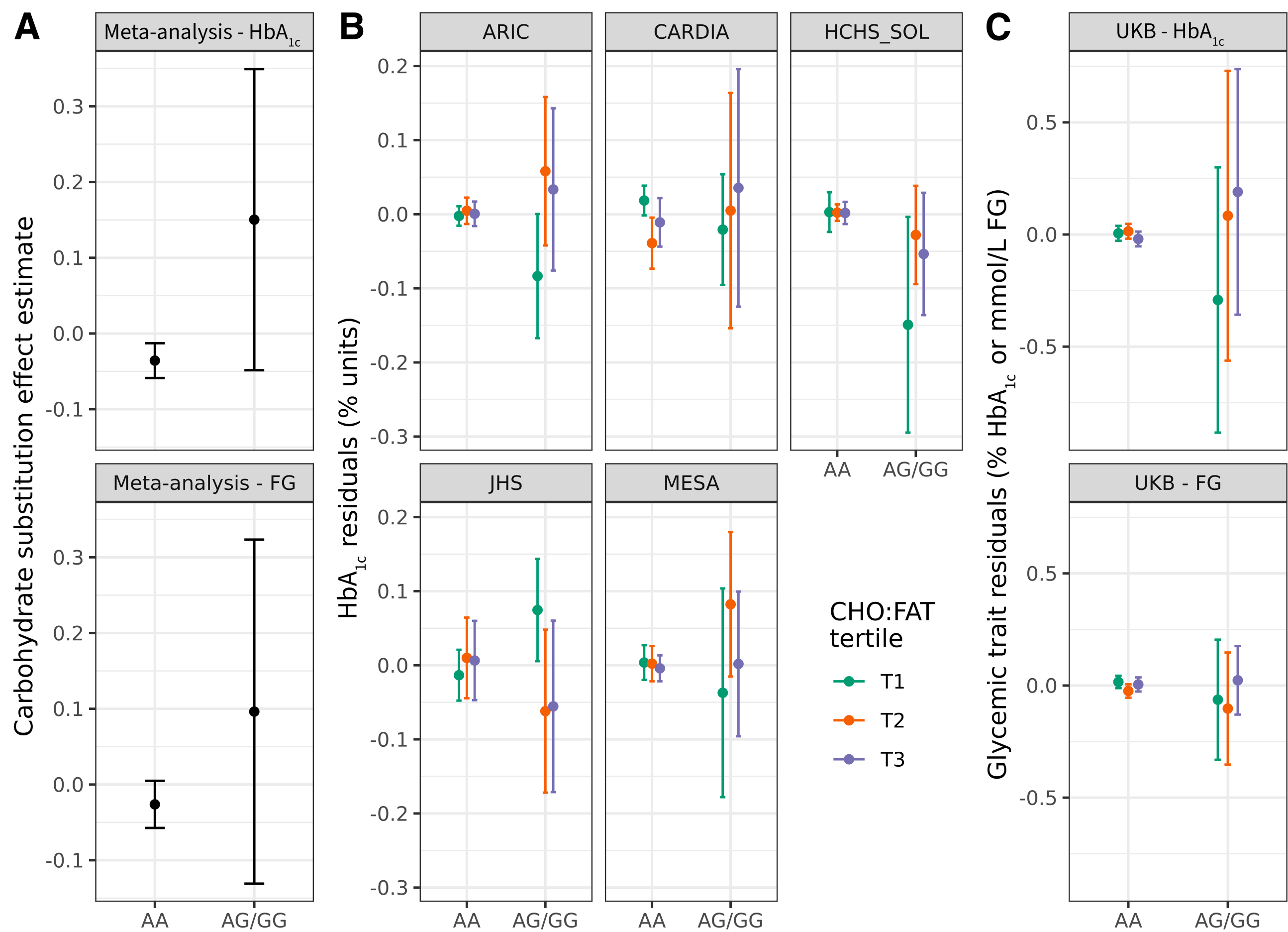

Figure 1—Exploration of the rs79762542 interaction and replication. *A*: Genotype-stratified dietary main effect estimates. *B*: Stratified plots (one for each cohort with HbA_{1c} available) display residualized HbA_{1c} within strata defined by both genotype at rs79762542 (none vs. any minor alleles) and tertile of carbohydrate/fat ratio. This ratio was defined in the pooled data set on a caloric basis and is used to provide a visual representation of the modeled macronutrient exchange. *C*: Similar stratified plots for the UKB replication cohort. For *B* and *C*, the *y*-axis displays residuals after regressing the relevant trait (HbA_{1c} or FG) on the set of covariates used in the replication analysis. Error bars indicate 95% CIs for the effect estimates (*A*) or mean residual values after stratification (*B* and *C*).

individuals either with or without prediabetes (beyond the predefined exclusion of individuals with diabetes) partially attenuated the interaction signal; this might be expected due to the removal of a substantial portion of the glycemic trait spectrum. Further, adjustment for either a diet quality score (Alternative Health Eating Index 2010) or smoking status (along with their genotype interactions) did not meaningfully impact estimates. Interaction estimates were also generally consistent in the African American race/ethnicity subset, indicating that the interactions for African ancestry–specific variants do not solely reflect population stratification.

Common Variant Replication

For the three prioritized single-variant loci, we tested for replication of these signals in the UKB [N = 178,352 with 24-h dietary assessment data (26) and glycemic biomarkers; see *Research Design and Methods*]. Of these, 5,183 individuals were included in FG analyses (based on fasting for at least 8 h prior to the associated blood draw). In the full multiancestry group (Supplementary Table 5), we saw nominal replication of the interaction at rs79762542 with respect to both HbA_{1c} (the discovery trait; P = 0.025) and FG (P = 0.013) (Fig. 1*C*). The interaction effect size with respect to HbA_{1c} (0.07% [0.77 mmol/mol] HbA_{1c}/allele/250 kcal) was of a similar magnitude to that from the primary meta-analysis (0.048% [0.52 mmol/mol] HbA_{1c}/allele/250 kcal). Because most of the prioritized variants were specific to African-ancestry individuals, we conducted a similar replication in just this subgroup of the UKB (Supplementary Table 6). This analysis revealed an even closer HbA_{1c} effect size to that of the meta-analysis despite a lack of significance (0.05% [0.55 mmol/mol] HbA_{1c}/allele/250 kcal; P = 0.29) and supported the rs79762542 interaction influencing FG (P = 0.046).

Rare Variant Interactions

Rare variants (MAF <1%) were analyzed in gene-centric, set-based tests, which help to overcome power limitations for low-MAF variants by aggregating signal across multiple variants annotated to the same gene. We used three variant aggregation strategies to define sets: selecting missense variants, loss-of-function variants, or a broader coding plus noncoding variant set annotated to each gene (see *Research Design and Methods*). No rare-variant interaction signals showed genome-wide significance ($P < 0.05$/28,111 total genes = 1.78×10^{-6}) (Supplementary Table 4 and Supplementary Fig. 8).

Since the set of rare variants used does not overlap with those from the common-variant tests, these gene-based tests can provide orthogonal evidence supporting common-variant signals while further clarifying potential effector genes. Each of the three prioritized single-variant findings were annotated to one or more genes based on proximity and/or eQTL data. None of these pairings showed supporting gene-based signals for the corresponding glycemic trait, though the single study-wide significant variant (rs79762542, discovered in relation to HbA_{1c}) showed a nominal corresponding signal from the gene-based test of *FRAS1* impacting FG (P = 0.028).

Power Calculations Incorporating Measurement Error

Given the modest discovery of GDIs despite the use of the maximal sample available within TOPMed cohorts and substantial harmonization effort, we sought to better understand the necessary power to detect expected GDI effects using literature-based anchors for context-specific expected effect sizes (Fig. 2*A*). Simulation-based power calculations for single-variant tests were conducted with added noise to account for the known random measurement error in dietary data. Assuming a conservative but realistic dietary measurement reliability of 0.5 (see *Research Design and Methods* for details), we established that a sample size of >150,000 would be required to detect a GDI effect of 0.025% (0.27 mmol/mol) HbA_{1c}/allele/SD carbohydrate at genome-wide significance for a variant with an MAF of 0.1 (Fig. 2*B* and *C*). As previously explored in the literature (31,32), power scaled approximately linearly with exposure measurement fidelity. If we alternatively assume perfect dietary exposure measurement, the associated sample size to detect the same effect was reduced to 80,000, indicating the importance of accounting for this measurement error. The necessary sample size, given realistic measurement reliabilities, increased even further for lower-frequency variants (e.g., 1.2 million for MAF = 1%).

We extended this simulation-based power calculation approach to test multiple variants jointly, mimicking the variant set-based test implemented for rare variants. Assuming similar measurement fidelity and effect sizes as for single variants and fixing the sample size to match the full sample used in this study (∼35,000), an aggregate test of 20 rare variants with a causal fraction of 50% and MAF of 0.25% had negligible power (Fig. 2*D*). Power increased somewhat but remained low when incorporating larger effect sizes (as are known to be present for rare-variant main effects on cardiometabolic traits) (33). For example, using an effect size of 0.1, approximately equal to the largest genetic main effect on HbA_{1c} reported by Wheeler et al. (27), power increased to 0.16. The full set of power simulation results is provided in Supplementary Tables 7 and 8 for single variants and set-based rare variants, respectively.

DISCUSSION

Our goal was to investigate genotype-related variability in the association of dietary macronutrient composition with glycemic traits. Importantly, this was based on a regression strategy modeling an isocaloric increase in dietary carbohydrate at the expense of fat (34). We conducted our comprehensive analyses in cohorts with racial/ethnic diversity with data for both common and rare variants from WGS. We examined multiple single variants with potential modifying roles for the relationship of carbohydrate intake with glycemic traits but did not find substantial evidence from

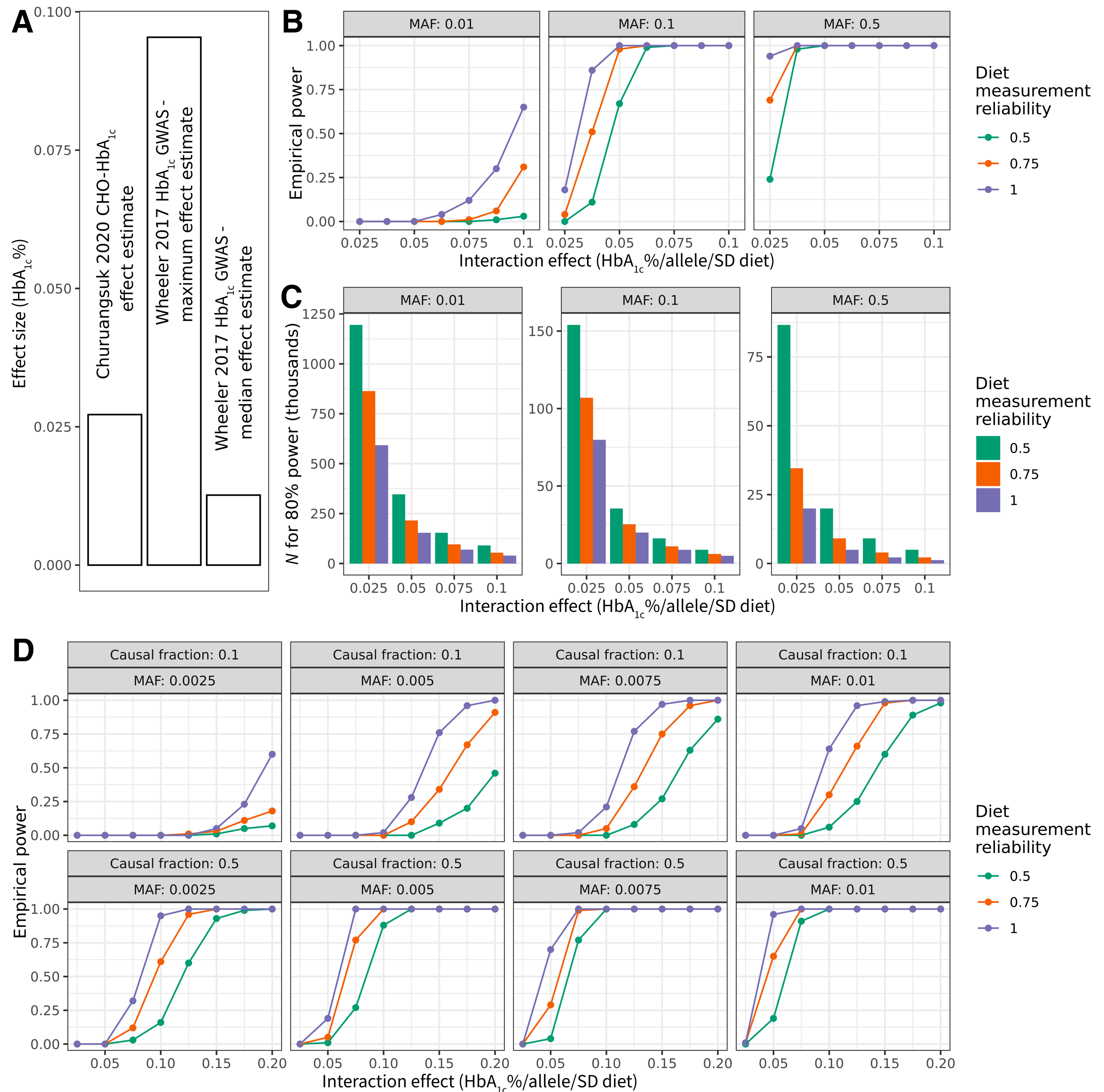

Figure 2—Power calculations for gene–environment interaction incorporating exposure measurement error. For all plots above, HbA_{1c} is used as a basis for parameter choices. *A*: Genetic and dietary effect sizes on HbA_{1c} for reference for potential interaction effects. Bars are annotated with the source study, either Churuangsuk et al. (28) or Wheeler et al. (27). *B*: Simulation-based empirical power estimates are shown as a function of the interaction effect (*x*-axis), MAF (panels left to right), and diet measurement reliability (colors). *C*: Bar plots show the estimated sample size needed to achieve 80% statistical power. Panels and colors are as in *B*. *D*: As in *A*, but modeling empirical power for simulated aggregate tests of 20 rare variants with a causal fraction of 0.1 or 0.5 (indicated in panel labels). Additional assumptions for these simulations (full details in *Research Design and Methods*): *N* = 35,000; phenotype mean of 5.5; phenotype SD of 0.5; exposure mean of 0; exposure SD of 1; genetic main effect of 0.01; and environmental main effect of 0.2.

gene-based tests for a role of rare variants in modifying this diet–glycemia relationship. Furthermore, our simulation-based power analysis highlighted the impact of dietary measurement error on statistical power for the GDI tests.

Dietary main effect models indicated that an increase in carbohydrate at the expense of dietary fat was associated with lower FG and HbA_{1c}. The impact of this macronutrient exchange on glucose homeostasis and diabetes risk is complex and likely depends on the respective macronutrient quality. Prior studies suggest null associations of total carbohydrate to total fat exchange on diabetes risk (35,36). However, an exchange of animal-sourced fat for carbohydrate or vegetable fat appears to have favorable associations with HbA_{1c} (37,38).

Our primary genome-wide common-variant interaction analysis yielded an interaction between a 250-kcal carbohydrate–fat substitution and HbA_{1c} with the African-ancestry rs79762542 variant, which was validated in the multiancestry UKB. Genotype-stratified analyses suggested that minor allele carriers generally had a small negative association between carbohydrate and HbA_{1c} (−0.033% [−0.36 mmol/mol] HbA_{1c}/250 kcal; P = 0.004) versus a larger but nonsignificant association in minor allele carriers, where the sample size was much lower (−0.10% [−1.1 mmol/mol] HbA_{1c}/250 kcal; P = 0.42). However, this precise pattern was not observed in all cohorts, possibly due to the low sample size of minor allele carriers in the populations studied. These results warrant further exploration in additional cohorts with African-ancestry individuals and dietary intervention studies to examine whether glycemic traits among minor allele carriers may benefit from higher-fat and lower-carbohydrate diet composition. This primary discovery was made with HbA_{1c} as an outcome, but our results from set-based rare variant analysis and the UKB replication suggest similar patterns with respect to other traits, such as FG.

Beyond GDI discovery, the genome-wide interaction study results provided an opportunity to inform and evaluate the effect size assumptions used in the power calculations. For example, the rs79762542 interaction had an effect size of 0.048% (0.52 mmol/mol) HbA_{1c}/allele/250 kcal carbohydrate, or 0.068% (0.74 mmol/mol) HbA_{1c}/allele/SD carbohydrate. This effect size is comparable to the relevant anchor for the power analysis [the referenced main effect association of carbohydrate with HbA_{1c} (28)].

This analysis leveraged WGS data along with multivariant set-based tests to better incorporate rare variants (MAF $<$0.01). While these variants do not contribute substantially to the overall population variance of glycemic or other traits, they tend to have larger effect sizes and thus may be important for the specific individuals carrying them (14). For example, phenylketonuria, a well-known inborn error of metabolism, acts through a rare-variant GDI in which severe adverse effects of phenylalanine intake are seen only in individuals with a particular genotype (39). In our study, despite helping to reinforce common-variant signals, the rare-variant analysis did not contribute additional findings after aggregation at the gene level. Substantially larger sample sizes will likely be necessary to uncover macronutrient GDIs involving rare variants.

We explored the statistical power for these interaction tests through simulations incorporating random dietary measurement error using available simulation-based power calculation software [ESPRESSO.GxE (40) for single variants] with additional extensions to allow for aggregate rare-variant tests. We estimated that substantially higher sample sizes (almost five times that used in this study) are required for sufficient power to detect macronutrient–gene interactions at expected effect sizes obtained from genetics and nutrition literature. This prompts two directions of further inquiry. First, it suggests the importance of complementary approaches that assess where there is any whole-genome contribution to the diet–glycemia association, at least in observational data sets. These whole-genome analyses trade resolution for statistical power (41) and have a precedent for GDIs in smaller study samples (42). Second, it reinforces the importance of collecting dietary intake data in the growing group of large-scale biobanks and cohorts. Improvements in study design, data collection methods, and analysis that can improve quality of dietary assessments are also warranted. For example, conducting rigorous validation studies of the data collection tools and approaches and ascertaining repeated dietary data can greatly improve the precision of these measurements on a population level. Advancements in objectively quantifying habitual diet from biospecimen samples are also underway and have potential to improve discovery for genetic analyses.

An important strength of this study is the breadth of ethnic and cultural diversity of the sample (increasing the likelihood that findings are robust) and of genetic variation (with WGS data enabling exploration of ancestry-specific genetic variation across the frequency spectrum). We also conducted a systematic investigation into the available statistical power while incorporating both realistic degrees of measurement error and evidence-based estimations of realistic effect sizes for gene–macronutrient interactions. However, the diversity of the included study sample also introduces heterogeneity that may be problematic. For example, the cohorts used different dietary assessment tools to capture habitual intake, leading to differences in the degree and direction of random and systematic measurement error. This is compounded by general, culturally driven differences in food intake across race/ethnicity groups. Furthermore, heterogeneity arises from the time of data collection; the perceptions of carbohydrate intake have trended as more and less healthful in recent decades, potentially resulting in differential confounding between diet and other health-related behaviors depending on the time of data collection (43). Future work can step beyond broad macronutrient categories by harmonizing intakes of specific foods or dietary patterns and analyzing macronutrient subtypes (e.g., added sugar and specific fatty acids). These approaches, combined with improved methods for detecting rare-variant gene–environment interactions, will help use the increasing volume of WGS data to discover new GDIs relevant for metabolic disease risk.

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