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No Interactions Between Previously Associated 2-Hour Glucose Gene Variants and Physical Activity or BMI on 2-Hour Glucose Levels

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Gene–lifestyle interactions have been suggested to contribute to the development of type 2 diabetes. Glucose levels 2 h after a standard 75-g glucose challenge are used to diagnose diabetes and are associated with both genetic and lifestyle factors. However, whether these factors interact to determine 2-h glucose levels is unknown. We meta-analyzed single nucleotide polymorphism (SNP) \times BMI and SNP \times physical activity (PA) interaction regression models for five SNPs previously associated with 2-h glucose levels from up to 22 studies comprising 54,884 individuals without diabetes. PA levels were dichotomized, with individuals below the first quintile classified as inactive (20%) and the remainder as active (80%). BMI was considered a continuous

trait. Inactive individuals had higher 2-h glucose levels than active individuals ($\beta = 0.22$ mmol/L [95% CI 0.13–0.31], $P = 1.63 \times 10^{-6}$). All SNPs were associated with 2-h glucose ($\beta = 0.06$ – 0.12 mmol/allele, $P \leq 1.53 \times 10^{-7}$), but no significant interactions were found with PA ($P > 0.18$) or BMI ($P \geq 0.04$). In this large study of gene–lifestyle interaction, we observed no interactions between genetic and lifestyle factors, both of which were associated with 2-h glucose. It is perhaps unlikely that top loci from genome-wide association studies will exhibit strong subgroup-specific effects, and may not, therefore, make the best candidates for the study of interactions. *Diabetes* 61:1291–1296, 2012

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Glucose levels 2 h after a 75-g glucose challenge are used to diagnose diabetes and are associated with cardiovascular morbidity and mortality even below the diabetic threshold (1). A large number of type 2 diabetes-associated genetic variants have now been identified (2), and recent genome-wide meta-analyses identified five loci that were associated with postchallenge glucose at genome-wide levels of significance (3). Previously identified single nucleotide polymorphisms (SNPs) in *TCF7L2* and *GCKR* were associated with 2-h glucose levels, as were newly identified loci in *ADCY5*, *GIPR*, and *VPS13C*. Risk alleles at each of these loci conferred elevated 2-h glucose levels with effect sizes ranging from 0.07 to 0.11 mmol/L per allele (3), although with some heterogeneity.

Age, BMI, and physical inactivity are all associated with glycemia and are key risk factors for type 2 diabetes (4–6). Glucose levels at 2 h appear more susceptible to age- and lifestyle-mediated increases than fasting glucose levels. For example, physical activity (PA) levels have been shown to be inversely associated with 2-h glucose but not with fasting glucose (7,8). Differences in 2-h glucose between individuals at either end of the PA spectrum are appreciable, with the most active individuals having a mean 2-h glucose level ~1 mmol/L lower than those with low PA levels (7). Furthermore, lifestyle intervention trials including prescribed PA have been effective in decreasing the incidence of diabetes in individuals with impaired glucose tolerance at baseline (9,10). However, it is unclear whether these responses to PA are homogenous among those with genetically conferred elevations in 2-h glucose levels or whether genetic effects are similar across lifestyle strata. Identification of gene-lifestyle interactions will offer valuable insight into the etiologic processes leading to disease and the biologic pathways by which lifestyle modification can reduce the risk of diabetes.

Although gene-lifestyle interactions are suggested as being important in the etiology of type 2 diabetes, few consistently replicated examples have been identified (11) and methodologic difficulties limit the opportunity for literature-based meta-analyses (12). The association of 2-h glucose with lifestyle and genetic factors makes it a good trait for the study of gene-lifestyle interaction. Furthermore, the heterogeneity observed in the association between SNPs and 2-h glucose (3) is potentially attributable to factors such as gene-lifestyle interaction. Therefore, we investigated the presence of gene-lifestyle interactions at these five 2-h glucose-associated loci (in or near *GCKR*, *ADCY5*, *TCF7L2*, *VPS13C*, and *GIPR*) by meta-analyzing SNP×PA and SNP×BMI interactions on 2-h glucose in up to 54,884 individuals from 22 studies.

RESEARCH DESIGN AND METHODS

Participating cohort characteristics. We meta-analyzed results from up to 22 Meta-Analyses of Glucose and Insulin Related Traits Consortium (MAGIC) studies (3) comprising up to 54,884 individuals. Study descriptives are detailed in Supplementary Table 1. Participants with known diabetes, those with fasting glucose ≥ 7 mmol/L, and individuals with a BMI < 18.5 kg/m² were excluded. All data were cross-sectional except for Atherosclerosis Risk in Communities Study (ARIC) where PA data were available at the visit ~3 years before 2-h glucose measurement.

Lifestyle exposure classification. Study-specific details of the measurement of PA are in Supplementary Table 1. Where a quantitative measure of PA was available, individuals below the first quintile were classified as inactive and the remainder as active (i.e., 20% inactive and 80% active). In studies where PA data were categorical, the proportion of inactive individuals was dependent on the questionnaire used and reported in Supplementary Table 1. Inactive individuals were coded as 0 and active individuals as 1 in the analyses. BMI was treated as a continuous variable in the primary analyses.

Genotyping and statistical analysis. Genotyping methods are reported in Supplementary Table 1 and have been described in detail previously (3). Analysts from each study performed study-level analyses and submitted summary statistics to the meta-analysis group. We ran linear regression models testing the association of each SNP with 2-h glucose, adjusted for age, sex, fasting glucose, BMI, and PA (as a dichotomous variable), and any necessary study-specific variables. We also examined the association of each SNP with BMI, adjusted for

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age and sex. Given our exclusion of individuals on the basis of glycemia, we sought replication of BMI associations by lookup of those SNPs in previous Genetic Investigation of ANthropometric Traits (GIANT) meta-analyses (13). To investigate SNP×PA and SNP×BMI interactions, each study included interaction terms (e.g., SNP×PA) in the models and reported the estimated interaction effect and standard error. The interaction effect estimates were combined using inverse variance-weighted meta-analysis. Studies with genotypes extracted from genome-wide SNP arrays reported interaction terms with robust standard errors and are included in the meta-analysis as such. Additive genetic models were applied.

We performed meta-analyses using a fixed-effects, inverse-variance weighted approach via the *metan* command in Stata SE-11.1 software (StataCorp LP, College Station, TX) to study SNP main effects on 2-h glucose or BMI. To study interaction between SNPs and PA or BMI, as well as the association between PA and BMI with 2-h glucose, we used random effects meta-analyses to account for potential heterogeneity introduced by factors such as PA differences among studies (Supplementary Table 1).

RESULTS

Study descriptives are reported in Supplementary Table 1. Inactive individuals had a higher 2-h glucose ($\beta = 0.22$ mmol/L [95% CI 0.13–0.31], $P = 1.63 \times 10^{-6}$) and BMI ($\beta = 0.73$ kg/m² [0.51–0.95], $P = 1.42 \times 10^{-10}$) than active individuals. Higher BMI was also associated with higher 2-h glucose levels (β per 1 kg/m² = 0.086 mmol/L [0.08–0.10], $P = 1.04 \times 10^{-47}$). SNP effects were consistent with those reported previously in overlapping studies (Fig. 1A) (3).

SNP×PA and SNP×BMI interactions on 2-h glucose. Figure 1B shows the absence of any difference in SNP effect on 2-h glucose between inactive and active individuals (SNP×PA $P \geq 0.18$ for interaction). Likewise, we did not

observe any significant interaction effects when analyses were limited to those studies showing association between PA and 2-h glucose (SNP×PA $P \geq 0.1$ for interaction). Figure 1C shows the difference in SNP effect on 2-h glucose per 10 kg/m². Again, no statistically significant interaction effects were observed after correction for multiple testing (five tests for each hypothesis: $\alpha = 0.01$), although rs1260326 in *GCKR* reached nominal levels of statistical significance (albeit with very small interaction effects). BMI-stratified results for rs1260326 showed that SNP effects were largest in the 30 to 34.9 kg/m² group (Supplementary Fig. 1), although few individuals at >35 kg/m² makes the smaller effect in this stratum difficult to interpret.

Association of SNPs with BMI. As can be seen from Fig. 2, *TCF7L2* rs12243326 and *GIPR* rs10423928 were both associated with BMI: the alleles associated with increased 2-h glucose were associated with lower BMI. The *TCF7L2* and *GIPR* SNPs were both associated with a 0.11 kg/m² lower BMI per allele (95% CI –0.17 to –0.04 and –0.20 to –0.03, respectively; Fig. 2). These findings were directionally consistent with those from previous meta-analyses by the GIANT consortium (13) (rs12243326 $P = 5.7 \times 10^{-4}$; rs10423928 $P = 1.9 \times 10^{-6}$).

DISCUSSION

Each of the gene variants investigated in the current study was robustly associated with 2-h glucose levels, as reported previously in overlapping studies (3). However, we observed

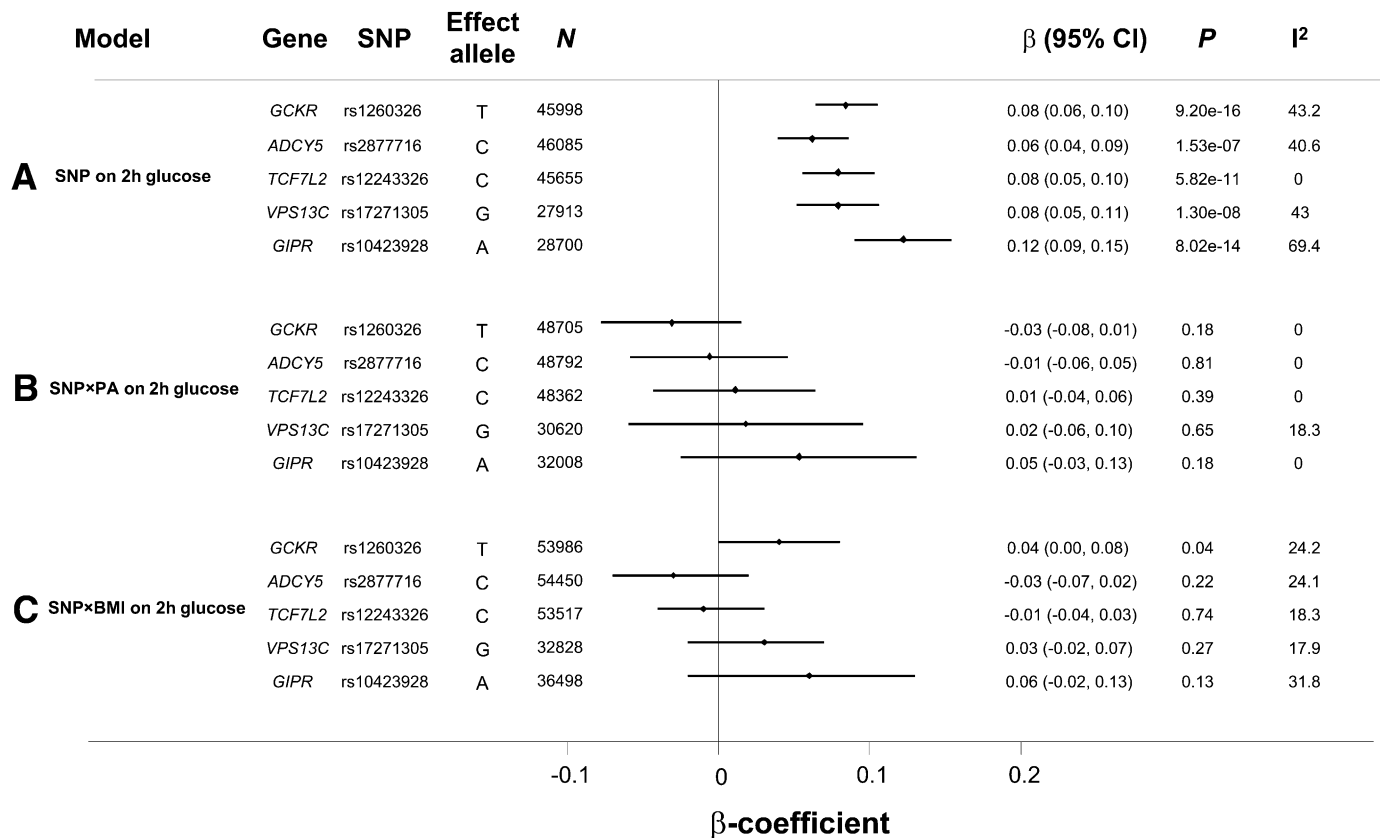


FIG. 1. A: Effect of SNP is shown on 2-h glucose. The β -coefficient is the magnitude of the observed association. B: Shows the SNP×PA interaction effect in which the β -coefficient is the difference in SNP association effect between inactive and active individuals. Inactive individuals were coded as 0 and active individuals a 1; therefore, a value of 0 for the interaction coefficient reflects equivalent SNP effect in inactive and active strata, whereas a positive value reflects a larger SNP effect in active individuals. C: The SNP×BMI interaction is shown. Here, the β -coefficient is the difference in SNP effect per 10 kg/m² difference in BMI. A positive value reflects a larger SNP effect in those with higher BMI. The 2-h glucose-raising allele in A is always the effect allele.

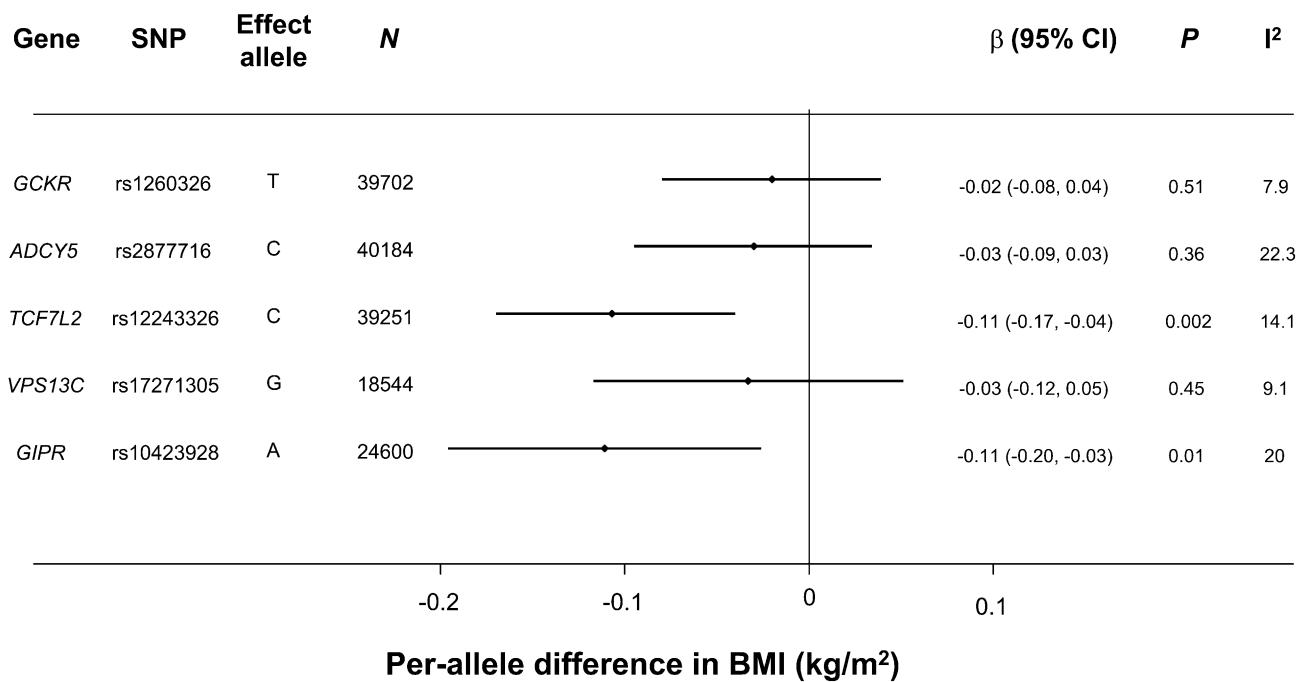


FIG. 2. The SNP association with BMI is shown. The 2-h glucose-raising allele from Fig. 1A is shown as the effect allele.

no difference in effect of the gene variants studied among PA groups or with increasing BMI.

Previous studies have reported gene-lifestyle interactions, although often based on small sample sizes without independent replication (11). In light of the small effect sizes of most complex disease-associated SNPs, large sample sizes are important to investigate interactions (14). However, despite the large sample size in the current study, no significant interactions were observed between 2-h glucose-associated SNPs and established lifestyle correlates. Notably, however, in 6 of the 10 interaction meta-analyses we performed (i.e., 5 SNPs and interaction with PA or BMI), at least 1 individual study would have shown a significant interaction had it been studied in isolation. However, had we considered studies individually, for ~200 tests of interaction we would have observed only nine interactions at $P < 0.05$, spread among a range of studies. We suggest that these associations reflect type I errors. Such a finding further supports our use of large sample sizes or independent replication to reduce the potential for type I error.

Although the variety of subjective measures and dichotomous classification of PA is an important limitation of the current study, inactive individuals had a higher 2-h glucose and a higher BMI than active individuals, suggesting the validity of our PA classification. Another factor may contribute to the absence of interactions: the SNPs we selected arose as top SNPs associated with 2-h glucose levels from a genome-wide meta-analysis (3). Although heterogeneity of associations was observed for *ADCY5*, *TCF7L2*, and *GIPR* (3), these SNPs had the strongest association P values in the genome by virtue of their effect size relative to the variation in effect size among samples. One may not, therefore, expect significant variation in genetic effect between subgroups of the population. A similar approach to ours was recently used to investigate interactions between breast cancer-associated genes and risk-altering lifestyle exposures and also failed to detect significant interactions between them (15), although there was a suggestion that a physically

active lifestyle attenuated genetic predisposition to obesity (16).

Although it has been suggested that the search for interactions should be informed by biologic plausibility (11), experience from the study of genetic main effects, where hypothesis-generating discovery approaches revolutionized the field (2), suggests that such an approach, not limited to those SNPs with extremely significant main effects, may be valuable in detecting gene-lifestyle interactions. Such approaches have been proposed and efforts are underway, but whether current analytic methods will yield success in the genome-wide search for gene-lifestyle interactions remains unclear.

Data from large-scale trials, such as the Finnish Diabetes Prevention Study (DPS) and Diabetes Prevention Program (DPP), have shown suggestions of differential response to intervention by genotype (17–22), although not always reaching statistical significance for interaction (17–19). However, lifestyle interventions in such studies often contain numerous lifestyle modifications, making interpretation of any interaction difficult, whereas large-scale genotype-stratified lifestyle intervention trials are not feasible. Therefore, prospective nested approaches will likely offer the most efficient approach for the study of gene-lifestyle interaction (23), allowing standardized measures of lifestyle at baseline and also the opportunity to study large numbers of individuals. Refined and standardized lifestyle exposure measurement will also represent a valuable alternative to straightforward increases in sample size (24).

Variants in *TCF7L2* have previously been associated with diabetes (2,17) and a number of related traits (3,25). The diabetogenic, glucose-raising allele was previously associated with lower BMI, although not conclusively (26), and principally in individuals with diabetes (27,28). Here, we replicate this association in a larger sample size of participants without diabetes, where the glucose-raising allele at rs12243326 was associated with a 0.11 kg/m²-lower BMI (Fig. 2). Similarly, we report that the glucose-raising allele at

GIPR rs10423928 is associated with lower BMI (-0.11 kg/m^2 per allele). Lookup results from the GIANT consortium suggest that these associations are unlikely to arise from ascertainment bias.

Although the association with BMI highlights a genetic predisposition on BMI and the risk of confusing gene–gene and gene–environment interactions, the small proportion of variance in BMI explained by such SNPs is likely to limit the effect of this concern in our study. Because BMI is a major risk factor for diabetes and has a strong positive association with 2-h glucose, it seems counterintuitive that 2-h glucose-raising alleles at *TCF7L2* and *GIPR* are associated with lower BMI and highlights the etiologic complexity of type 2 diabetes.

In conclusion, in our study of up to 54,884 individuals from 22 studies, we found no evidence of gene–lifestyle interaction among the variants studied. This was despite the clear association of 2-h glucose with PA, BMI, and genetic exposures. Although the descriptive epidemiology of diabetes suggests an influence of gene–lifestyle interaction in its etiology, our study finds no evidence to that effect for SNPs known to be associated with 2-h glucose. Further, our study supports the use of large-scale analyses to robustly investigate gene–lifestyle interaction. In future, hypothesis-generating approaches may offer a valuable opportunity to detect gene–lifestyle interactions in type 2 diabetes and related traits.

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involved in management of the project and/or involved studies and in data collection and phenotyping. B.I., M.Ki., J.K., M.L., and J.B.M. were involved in management of the project and/or involved studies and in the project design, data collection, and phenotyping. M.Ku. was involved in management of the project and/or involved studies and in the project design, data collection, and phenotyping, and genotyping. J.D. was involved in management of the project and/or involved studies, in project design, and in genotyping, and performed statistical analyses. N.J.W. was involved in management of the project and/or involved studies, in project design, and in data collection and phenotyping. R.A.S. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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