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Journal

Diabetes, 61(5)

ISSN

0012-1797

Authors

Scott, Robert A
Chu, Audrey Y
Grarup, Niels
et al.

Publication Date

2012-05-01

DOI

10.2337/db11-0973

Peer reviewed

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

Robert A. Scott,[1] Audrey Y. Chu,[2,3] Niels Grarup,[4,5] Alisa K. Manning,[6] Marie-France Hivert,[7] Dmitry Shungin,[8,9,10] Anke Tönjes,[11,12] Ajay Yesupriya,[13] Daniel Barnes,[1] Nabila Bouatia-Naji,[14,15] Nicole L. Glazer,[16] Anne U. Jackson,[17] Zoltán Kutalik,[18,19] Vasiliki Lagou,[20,21] Diana Marek,[18,19] Laura J. Rasmussen-Torvik,[22] Heather M. Stringham,[17] Toshiko Tanaka,[23] Mette Aadahl,[24] Dan E. Arking,[25] Sven Bergmann,[18,19] Eric Boerwinkle,[26] Lori L. Bonnycastle,[27] Stefan R. Bornstein,[28] Eric Brunner,[29] Suzannah J. Bumpstead,[30] Soren Brage,[1] Olga D. Carlson,[31] Han Chen,[6] Yii-Der Ida Chen,[32] Peter S. Chines,[27] Francis S. Collins,[27] David J. Couper,[33] Elaine M. Dennison,[34] Nicole F. Dowling,[13] Josephine S. Egan,[31] Ulf Ekelund,[1] Michael R. Erdos,[27] Nita G. Forouhi,[1] Caroline S. Fox,[35,36] Mark O. Goodarzi,[32,37] Jürgen Grässler,[28] Stefan Gustafsson,[38] Göran Hallmans,[39] Torben Hansen,[4,5,40] Aroon Hingorani,[29] John W. Holloway,[41] Frank B. Hu,[42] Bo Isomaa,[43] Karen A. Jameson,[34] Ingegerd Johansson,[10] Anna Jonsson,[44] Torben Jørgensen,[24,45] Mika Kivimaki,[29] Peter Kovacs,[46] Meena Kumari,[29] Johanna Kuusisto,[47] Markku Laakso,[47] Cécile Lecoeur,[14,15] Claire Lévy-Marchal,[15,48] Guo Li,[49] Ruth J.F. Loos,[1] Valeri Lyssenko,[44] Michael Marmot,[29] Pedro Marques-Vidal,[50] Mario A. Morken,[27] Gabriele Müller,[51] Kari E. North,[52] James S. Pankow,[53] Felicity Payne,[54] Inga Prokopenko,[20,21] Bruce M. Psaty,[55,56] Frida Renström,[8,42] Ken Rice,[57] Jerome I. Rotter,[32] Denis Rybin,[58] Camilla H. Sandholt,[4,5] Avan A. Sayer,[34] Peter Shrader,[59,60] Peter E.H. Schwarz,[28] David S. Siscovick,[61] Alena Stančáková,[47] Michael Stumvoll,[11,12] Tanya M. Teslovich,[17] Gérard Waeber,[62] Gordon H. Williams,[63,64] Daniel R. Witte,[65] Andrew R. Wood,[66] Weijia Xie,[66] Michael Boehnke,[17] Cyrus Cooper,[34,67] Luigi Ferrucci,[23] Philippe Froguel,[14,15,68] Leif Groop,[44] W.H. Linda Kao,[3] Peter Vollenweider,[62] Mark Walker,[69] Richard M. Watanabe,[70,71] Oluf Pedersen,[4,5,72,73] James B. Meigs,[59,60] Erik Ingelsson,[38] Inês Barroso,[54,74] Jose C. Florez,[59,75,76,77] Paul W. Franks,[8,9,42] Josée Dupuis,[6,35] Nicholas J. Wareham,[1] and Claudia Langenberg[1]

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) × BMI and SNP × 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 (β = 0.22 mmol/L [95% CI 0.13–0.31], $P = 1.63 \times 10^{-6}$). All SNPs were associated with 2-h glucose (β = 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

From the [1]Medical Research Council Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, United Kingdom; the [2]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts; the [3]Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland; the [4]Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; the [5]Hagedorn Research Institute, Gentofte, Denmark; the [6]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts; the [7]Department of Medicine, Universite de Sherbrooke, Sherbrooke, Québec, Canada; the [8]Genetic and Molecular Epidemiology Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden; the [9]Genetic Epidemiology and Clinical Research Group, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; the [10]Department of Odontology, Umeå University, Umeå, Sweden; the [11]Medical Department, University of Leipzig, Leipzig, Germany; the [12]Integriertes Forschungs- und Behandlungszentrum (IFB) Adiposity Diseases, University of Leipzig, Leipzig, Germany; the [13]Office of Public Health Genomics, Centers for Disease Control and Prevention, Atlanta, Georgia; the [14]Centre National de la Recherche Scientifique (CNRS)-UMR-8199, Institut Pasteur de Lille, Lille, France; the [15]University Lille Nord de France, Lille, France; the [16]Department of Medicine–Preventive Medicine and Epidemiology, Boston University, Boston, Massachusetts; the [17]Center for Statistical Genetics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan; the [18]Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland; the [19]Swiss Institute of Bioinformatics, Lausanne, Switzerland; the [20]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom; the [21]Oxford Centre for Diabetes, Endocrinology, and Metabolism, University of Oxford, Oxford, United Kingdom; the [22]Department of Preventive Medicine, Northwestern University, Chicago, Illinois; the [23]Clinical Research Branch, National Institute on Aging, Baltimore, Maryland; the [24]Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark; the [25]Institute of Genetic Medicine, Johns Hopkins University, Baltimore, Maryland; the [26]Human Genetics Center, The University of Texas Health Science Center at Houston, Houston, Texas; the [27]National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland; the [28]Department of Medicine III, Medical Faculty Carl Gustav Carus, University of Dresden, Dresden, Germany; the [29]Department of Epidemiology and Public Health, University College London, London, United Kingdom; the [30]Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom; the [31]Laboratory of Clinical Investigation, National Institute on Aging, Baltimore, Maryland; the [32]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California; the [33]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; the [34]Medical Research Council Lifecourse Epidemiology Unit, University of Southampton, Southampton,

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 $\geq$ 7 mmol/L, and individuals with a BMI <18.5 kg/m^2 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 categoric, 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

United Kingdom; the [35]National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts; the [36]Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; the [37]Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, Los Angeles, California; the [38]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; the [39]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; the [40]Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark; [41]Infection, Inflammation and Immunity, University of Southampton, Southhampton, United Kingdom; the [42]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; the [43]Folkhälsan Research Center, Helsinki, and Department of Social Services and Health Care, Jakobstad, Finland; the [44]Diabetes and Endocrinology Unit, Department of Clinical Sciences, Lund Univeristy, Malmö, Sweden; the [45]Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; the [46]Interdisciplinary Center for Clinical Research, University of Leipzig, Leipzig, Germany; the [47]University of Eastern Finland, and Kuopio University Hospital, Kuopio, Finland; the [48]INSERM CIC EC 05, Hôpital Robert Debré, Paris, France; the [49]Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington; the [50]Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois (CHUV), and University of Lausanne, Lausanne, Switzerland; the [51]Institute for Medical Informatics and Biometry, Medical Faculty Carl Gustav Carus, University of Dresden, Dresden, Germany; the [52]Department of Epidemiology and Carolina Center for Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; the [53]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota; the [54]Metabolic Disease Group, Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom; the [55]Departments of Epidemiology, Medicine, and Health Services, University of Washington, Seattle, Washington; the [56]Group Health Research Institute, Group Health, Seattle, Washington; the [57]Department of Biostatistics, University of Washington, Seattle, Washington; the [58]Boston University Data Coordinating Center, Boston, Massachusetts; the [59]Department of Medicine, Harvard Medical School, Boston, Massachusetts; the

[60]General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts; the [61]Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington; the [62]Department of Internal Medicine, CHUV, Lausanne, Switzerland; [63]Brigham and Women's Hospital, Boston, Massachusetts; the [64]Harvard Medical School, Boston, Massachusetts; the [65]Steno Diabetes Center, Gentofte, Denmark; [66]Genetics of Complex Traits, Peninsula College of Medicine and Dentistry, Exeter, United Kingdom; the [67]Botnar Research Centre, University of Oxford, Oxford, United Kingdom; the [68]Department of Genomics of Common Disease, School of Public Health, Imperial College London, London, United Kingdom; the [69]Institute of Cellular Medicine, Newcastle University, Newcastle, United Kingdom; the [70]Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California; the [71]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; the [72]Institute of Biomedical Science, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; the [73]Faculty of Health Sciences, University of Aarhus, Aarhus, Denmark; the [74]University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge, United Kingdom; the [75]Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts; the [76]Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts; and the [77]Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts.

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/m^2 [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/m^2 = 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 (SNPxPA $P \geq 0.18$ 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 (SNPxPA $P \geq 0.1$ for interaction). Figure 1C shows the difference in SNP effect on 2-h glucose per 10 kg/m^2. 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/m^2 group (Supplementary Fig. 1), although few individuals at >35 kg/m^2 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/m^2 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
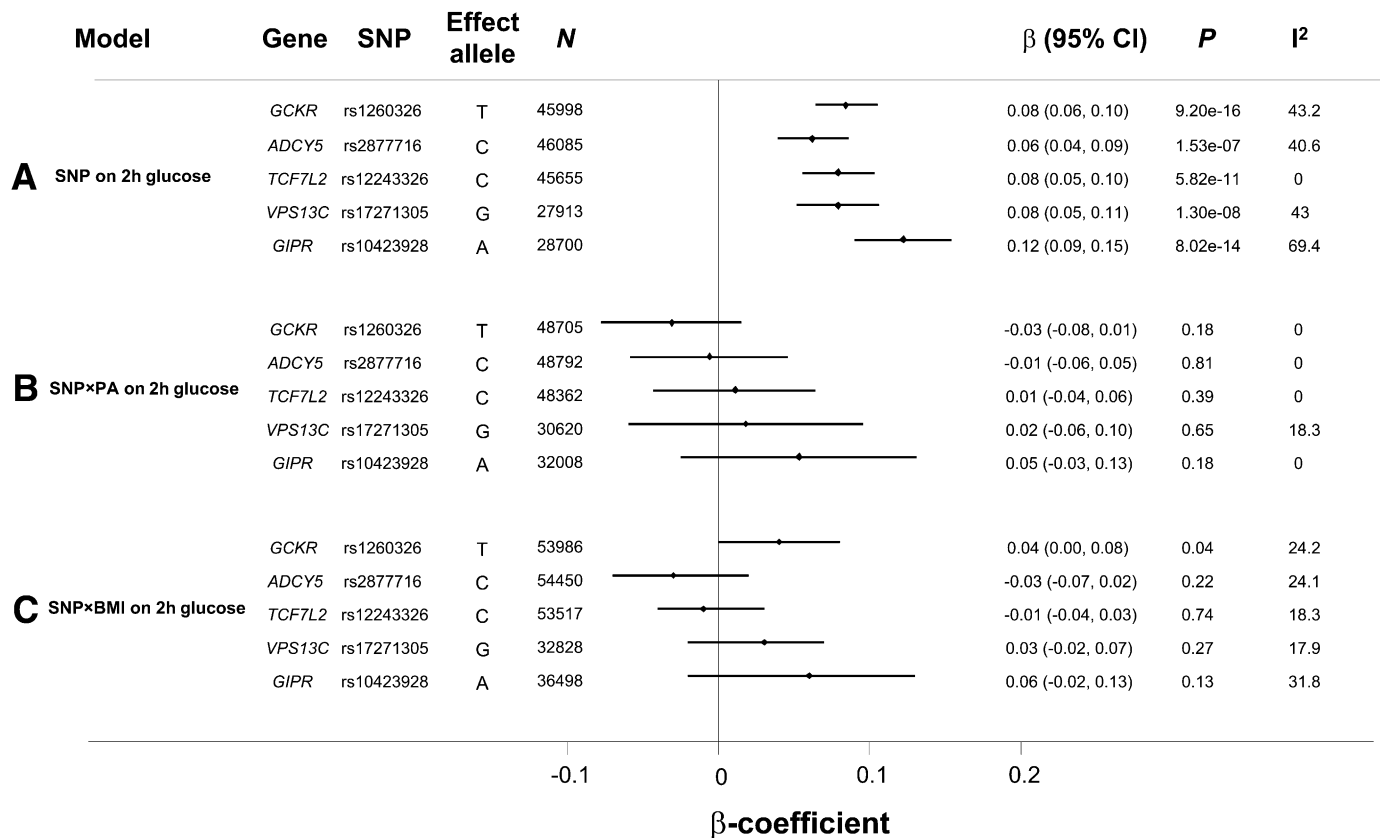

Model		Gene	SNP	Effect allele	N		β (95% CI)	P	I²
A	SNP on 2h glucose	GCKR	rs1260326	T	45998		0.08 (0.06, 0.10)	9.20e-16	43.2
		ADCY5	rs2877716	C	46085		0.06 (0.04, 0.09)	1.53e-07	40.6
		TCF7L2	rs12243326	C	45655		0.08 (0.05, 0.10)	5.82e-11	0
		VPS13C	rs17271305	G	27913		0.08 (0.05, 0.11)	1.30e-08	43
		GIPR	rs10423928	A	28700		0.12 (0.09, 0.15)	8.02e-14	69.4
B	SNP×PA on 2h glucose	GCKR	rs1260326	T	48705		-0.03 (-0.08, 0.01)	0.18	0
		ADCY5	rs2877716	C	48792		-0.01 (-0.06, 0.05)	0.81	0
		TCF7L2	rs12243326	C	48362		0.01 (-0.04, 0.06)	0.39	0
		VPS13C	rs17271305	G	30620		0.02 (-0.06, 0.10)	0.65	18.3
		GIPR	rs10423928	A	32008		0.05 (-0.03, 0.13)	0.18	0
C	SNP×BMI on 2h glucose	GCKR	rs1260326	T	53986		0.04 (0.00, 0.08)	0.04	24.2
		ADCY5	rs2877716	C	54450		-0.03 (-0.07, 0.02)	0.22	24.1
		TCF7L2	rs12243326	C	53517		-0.01 (-0.04, 0.03)	0.74	18.3
		VPS13C	rs17271305	G	32828		0.03 (-0.02, 0.07)	0.27	17.9
		GIPR	rs10423928	A	36498		0.06 (-0.02, 0.13)	0.13	31.8

β-coefficient

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/m^2 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.
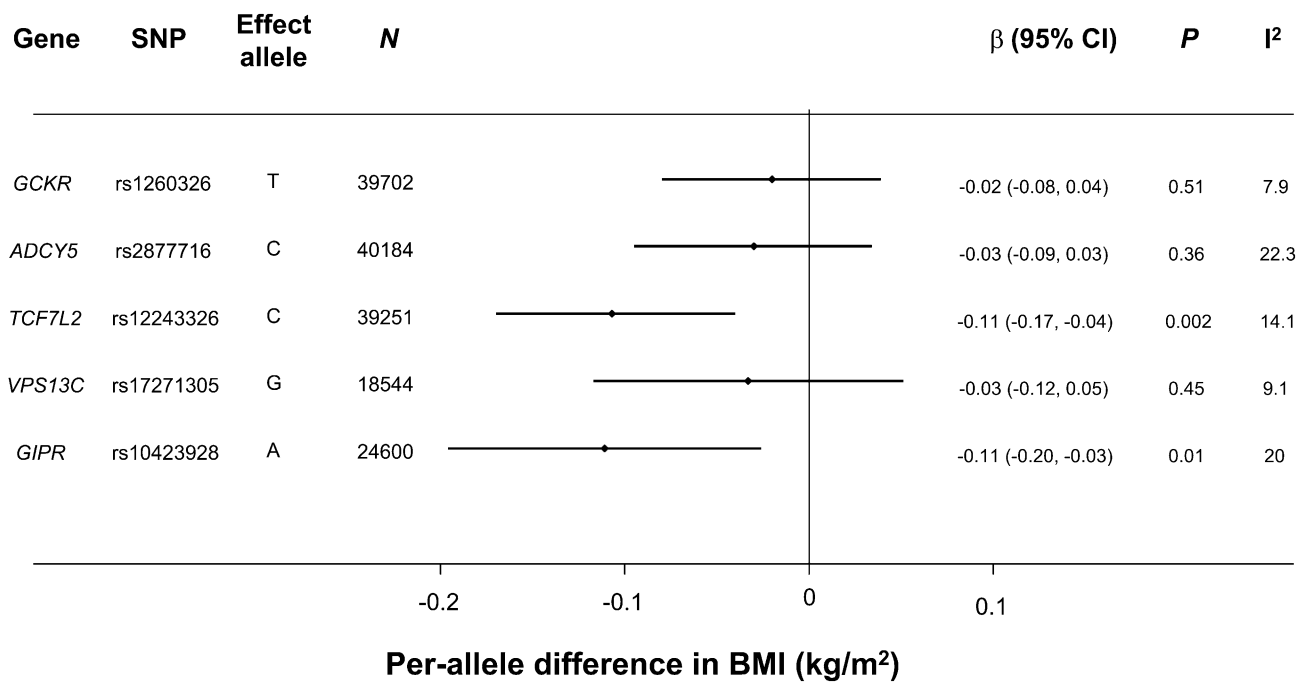
Gene	SNP	Effect allele	N	β (95% CI)	P	I²
GCKR	rs1260326	T	39702	-0.02 (-0.08, 0.04)	0.51	7.9
ADCY5	rs2877716	C	40184	-0.03 (-0.09, 0.03)	0.36	22.3
TCF7L2	rs12243326	C	39251	-0.11 (-0.17, -0.04)	0.002	14.1
VPS13C	rs17271305	G	18544	-0.03 (-0.12, 0.05)	0.45	9.1
GIPR	rs10423928	A	24600	-0.11 (-0.20, -0.03)	0.01	20

Per-allele difference in BMI (kg/m²)

FIG. 2. The SNP association with BMI is shown. The 2-h glucose–raising allele from Fig. 1*A* 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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