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


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 55 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 × 10−8). All SNPs were associated with 2-h glucose (β = 0.06–0.12 mmol/allele, P ≤ 1.53 × 10−7), but no significant interactions were found with PA (P > 0.18) or BMI (P ≥ 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 1Medical Research Council Epidemiology Unit, Institute of Metabolic Science, Addenbrooke’s Hospital, Cambridge, United Kingdom; the 2Division of Preventive Medicine, Brigham and Women’s Hospital, Boston, Massachusetts; the 3Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland; the 4Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; the 5Hagedorn Research Institute, Gentofte, Denmark; the 6Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts; the 7Department of Medicine, Université de Sherbrooke, Sherbrooke, Québec, Canada; the 8Genetic and Molecular Epidemiology Unit, Department of Clinical Sciences, Lund University, Malmo, Sweden; the 9Gene–Environment and Clinical Research Group, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; the 10Department of Epidemiology, University of Leipzig, Leipzig, Germany; the 11Medical Department, University of Leipzig, Leipzig, Germany; the 12Institut für Genetik und Genomforschung, University of Leipzig, Leipzig, Germany; the 13Centre National de la Recherche Scientifique (CNRS)-UMR-S190, Institut Pasteur de Lille, Lille, France; the 14Centre for Statistical Genetics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan; the 15Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland; the 16Swiss Institute of Bioinformatics, Lausanne, Switzerland; the 17Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom; the 18Oxford Centre for Diabetes, Endocrinology, and Metabolism, University of Oxford, Oxford, United Kingdom; the 19Department of Preventive Medicine, Northwestern University, Chicago, Illinois; the 20Clinical Research Branch, National Institute on Aging, Baltimore, Maryland; the 21ReWalk Prevention and Research, Gilstrap University Hospital, Gilstrap, Denmark; the 22Institute of Genetic Medicine, Johns Hopkins University, Baltimore, Maryland; the 23Human Genetics Center, The University of Texas Health Science Center at Houston, Houston, Texas; the 24National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland; the 25Department of Medicine III, Medical Faculty Carl Gustav Carus, University of Dresden, Dresden, Germany; the 26Department of Epidemiology and Public Health, University College London, London, United Kingdom; the 27Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom; the 28Laboratory of Clinical Investigation, National Institute on Aging, Baltimore, Maryland; the 29Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California; the 30Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; the 31Medical 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 TCFTL2 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 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), and recent genome-wide association studies (10) identified PA as a modifier of type 2 diabetes risk variants.

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, TCFTL2, 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 descrip tives 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 studies 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% 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). Analysis from each study was performed with 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 10National Heart, Lung, and Blood Institute’s Framingham Heart Study, Framingham, Massachusetts; the 11Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts; the 12Division of Endocrinology, Diabetes, and Metabolism, Cedars-Sinai Medical Center, Los Angeles, California; the 13Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; the 14Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; the 15Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark; the 16Infection, Immunity, and Inflammation, University of Southampton, Southampton, United Kingdom; the 17Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; the 18Folkhälsoinstitutet Research Center, Helsinki, and Department of Social Services and Health Care, Jakobstad, Finland; the 19Diabetes and Endocrinology Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden; the 20Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; the 21Interdisciplinary Center for Clinical Research, University of Leipzig, Leipzig, Germany; the 22University of Eastern Finland, and Kuopio University Hospital, Kuopio, Finland; the 23Hôpital Robert Debré, Paris, France; the 24Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington; the 25Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois (CHUV), and University of Lausanne, Lausanne, Switzerland; the 26Institute for Medical Informatics and Biometry, Medical Faculty Carl Gustav Carus, University of Dresden, Dresden, Germany; the 27Department of Epidemiology and Cardiovascular Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; the 28Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota; the 29Metabolic Disease Group, Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom; the 30Departments of Epidemiology, Medicine, and Health Services Research, University of Washington, Seattle, Washington; the 31Group Health Research Institute, Group Health, Seattle, Washington; the 32Department of Biostatistics, University of Washington, Seattle, Washington; the 33Boston University Data Coordinating Center, Boston, Massachusetts; the 34Department of Medicine, Harvard Medical School, Boston, Massachusetts; the 60General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts; the 61Institute of Medicine, University of Cambridge, Cambridge, United Kingdom; the 62Department of Internal Medicine, CHUV, Lausanne, Switzerland; the 63Brigham and Women’s Hospital, Boston, Massachusetts; the 64Harvard Medical School, Boston, Massachusetts; the 65Cannon Diabetes Center, Genentech, South San Francisco, California; the 66Institute of Cellular Medicine, Newcastle University, Newcastle, United Kingdom; the 67Botnar Research Centre, University of Oxford, Oxford, United Kingdom; the 68Department of Genetics of Common Disease, School of Public Health, Imperial College London, London, United Kingdom; the 69Institute of Cellular Medicine, Newcastle University, Newcastle, United Kingdom; the 70Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California; the 71Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; the 72Institute of Biomedical Science, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; the 73Faculty of Health Sciences, University of Aarhus, Aarhus, Denmark; the 74University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Addenbrooke’s Hospital, Cambridge, United Kingdom; the 75Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts; the 76Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts; and the 77Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts.

Corresponding author: Robert A. Scott, robert.scott@mrc-epid.cam.ac.uk.

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R.A.S. and A.Y. contributed equally to this work.

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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 ($\beta$ 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 (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/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 $P = 1.9 \times 10^{-7}$).

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Gene</th>
<th>SNP</th>
<th>Effect allele</th>
<th>N</th>
<th>$\beta$ (95% CI)</th>
<th>P</th>
<th>$\rho$</th>
</tr>
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<tr>
<td>A SNP on 2h glucose</td>
<td>GCKR</td>
<td>rs1260326</td>
<td>T</td>
<td>45998</td>
<td>0.08 (0.06, 0.10)</td>
<td>9.20e-16</td>
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<td>ADCY5</td>
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<td>5.82e-11</td>
<td>0</td>
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<td>27913</td>
<td>0.08 (0.05, 0.11)</td>
<td>1.30e-08</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>GIPR</td>
<td>rs10423928</td>
<td>A</td>
<td>28700</td>
<td>0.12 (0.09, 0.15)</td>
<td>8.02e-14</td>
<td>69.4</td>
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<td>0</td>
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<tr>
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<td>rs2877716</td>
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<td>0.81</td>
<td>0</td>
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<td>rs12243326</td>
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<td>48362</td>
<td>0.01 (-0.04, 0.06)</td>
<td>0.39</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>VPS13C</td>
<td>rs17271305</td>
<td>G</td>
<td>30620</td>
<td>0.02 (-0.06, 0.10)</td>
<td>0.65</td>
<td>18.3</td>
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<tr>
<td></td>
<td>GIPR</td>
<td>rs10423928</td>
<td>A</td>
<td>32008</td>
<td>0.05 (-0.03, 0.13)</td>
<td>0.18</td>
<td>0</td>
</tr>
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<td>C SNP×BMI on 2h glucose</td>
<td>GCKR</td>
<td>rs1260326</td>
<td>T</td>
<td>53986</td>
<td>0.04 (0.00, 0.08)</td>
<td>0.04</td>
<td>24.2</td>
</tr>
<tr>
<td></td>
<td>ADCY5</td>
<td>rs2877716</td>
<td>C</td>
<td>54450</td>
<td>-0.03 (-0.07, 0.02)</td>
<td>0.22</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>TCF7L2</td>
<td>rs12243326</td>
<td>C</td>
<td>53517</td>
<td>-0.01 (-0.04, 0.03)</td>
<td>0.74</td>
<td>18.3</td>
</tr>
<tr>
<td></td>
<td>VPS13C</td>
<td>rs17271305</td>
<td>G</td>
<td>32828</td>
<td>0.03 (-0.02, 0.07)</td>
<td>0.27</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>GIPR</td>
<td>rs10423928</td>
<td>A</td>
<td>36498</td>
<td>0.06 (-0.02, 0.13)</td>
<td>0.13</td>
<td>31.8</td>
</tr>
</tbody>
</table>

$\beta$-coefficient

![Image](diabetes.diabetesjournals.org)
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

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Effect allele</th>
<th>N</th>
<th>(\beta) (95% CI)</th>
<th>(P)</th>
<th>(I^2)</th>
</tr>
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<tr>
<td>GCKR</td>
<td>rs1260326</td>
<td>T</td>
<td>39702</td>
<td>-0.02 (-0.08, 0.04)</td>
<td>0.51</td>
<td>7.9</td>
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<td>rs2877716</td>
<td>C</td>
<td>40184</td>
<td>-0.03 (-0.09, 0.03)</td>
<td>0.36</td>
<td>22.3</td>
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<tr>
<td>TCF7L2</td>
<td>rs12243326</td>
<td>C</td>
<td>39251</td>
<td>-0.11 (-0.17, -0.04)</td>
<td>0.002</td>
<td>14.1</td>
</tr>
<tr>
<td>VPS13C</td>
<td>rs17271305</td>
<td>G</td>
<td>18544</td>
<td>-0.03 (-0.12, 0.05)</td>
<td>0.45</td>
<td>9.1</td>
</tr>
<tr>
<td>GIPR</td>
<td>rs10423928</td>
<td>A</td>
<td>24600</td>
<td>-0.11 (-0.20, -0.03)</td>
<td>0.01</td>
<td>20</td>
</tr>
</tbody>
</table>

Per-allele difference in BMI (kg/m²)

FIG. 2. The SNP association with BMI is shown. The 2-h glucose–raising allele from Fig. 1A is shown as the effect allele.
GIPR rs10423928 is associated with lower BMI (−0.11 kg/m² 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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R.A.S., A.Y.C., N.G., A.K.M., M.-F.H., A.T., O.P., J.B.M., E.I., I.B., J.C.F., P.W.F., J.D., N.J.W., and C.La. wrote the manuscript. R.A.S. and A.Y.C. were involved in management of the project and/or involved studies and in the project design and performed statistical analyses. N.G., A.K.M., M.-F.H., D.S., A.Y., D.B., Z.K., D.M., L.J.R.-T., H.M.S., V.La., S.G., and T.M.T. performed statistical analyses. N.B.-N., C.L.-M., and K.R. were involved in management of the project and/or involved studies and in genotyping and performed statistical analyses. N.L.G., A.U.J., and I.P. were involved in genotyping and performed statistical analyses. T.T., S.B.e., S.R.B., S.B.r., N.F.D., U.E., R.J.F.L., J.S.P., D.S.S., E.I., R.M.W., O.P., J.C.F., and C.La. were involved in management of the project and/or involved studies and in the project design. E.B.o., G.M., M.O.G., and C.H.S. contributed to data collection and phenotyping, were involved in genotyping, and performed statistical analyses. L.L.B., S.J.B., H.C., M.R.E., A.J., P.K., G.L., M.A.M., A.R.W., and W.X. were involved in genotyping. A.T., M.A., O.D.C., J.S.E., J.G., F.B.H., P.M.-V., F.P., and A.S. contributed to data collection and phenotyping. P.S.C. and M.S. contributed to data collection and phenotyping and were involved in genotyping. D.E.A., E.B.r., Y.-D.I.C., S.P.S., D.J.C., N.G.F., T.H., A.H., T.J., C.L.e., V.L.y., M.M., K.E.N., F.R., D.R., P.S., G.W., D.R.W., M.B., and M.W. were involved in management of the project and/or involved studies. E.M.D., P.F., L.G., W.H.L.K., I.B., and P.W.F. were involved in management of the project and/or involved studies and in the project design, contributed to data collection and phenotyping, and were involved in genotyping C.S.F., G.H., I.J., P.E.H.S., G.H.W., J.W.H., K.A.J., A.A.S., C.C., B.M.P., J.I.R., L.F., and P.V. were involved in management of the project and/or involved studies and in data collection and phenotyping. B.I., M.K.i., 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, 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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