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

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation

Published Version
doi:10.2337/db11-0973

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:11181022

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
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 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 × 10⁻⁶). 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, University of California, San Francisco, California; the 8Genetic and Molecular Epidemiology Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden; the 9Department of Preventive Medicine, Northwestern University, Chicago, Illinois; the 10Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom; the 11Department of Clinical Sciences, Addenbrooke’s Hospital, Cambridge, United Kingdom; the 12Integriertes Forschungs- und Behandlungszentrum (IFB) Adiposity Diseases, University of Leipzig, Leipzig, Germany; the 13Laboratory of Clinical Investigation, National Institute on Aging, Baltimore, Maryland; the 14Swiss Institute of Bioinformatics, Lausanne, Switzerland; the 15Community Health, University College London, London, United Kingdom; the 16Department of Genomic Epidemiology and Clinical Research Group, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; the 17Medical Department, University of Leipzig, Leipzig, Germany; the 18Integriertes Forschungs- und Behandlungszentrum (IFB) Adiposity Diseases, University of Leipzig, Leipzig, Germany; the 19Swiss Institute of Bioinformatics, Lausanne, Switzerland; the 20Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom; the 21Oxford Centre for Diabetes, Endocrinology, and Metabolism, University of Oxford, Oxford, United Kingdom; the 22Department of Preventive Medicine, Northwestern University, Chicago, Illinois; the 23Clinical Research Branch, National Institute on Aging, Baltimore, Maryland; the 24Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark; the 25Institute of Genetic Medicine, Johns Hopkins University, Baltimore, Maryland; the 26Human Genetics Center, The University of Texas Health Science Center at Houston, Houston, Texas; the 27National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland; the 28Department of Medicine III, Medical Faculty Carl Gustav Carus, University of Dresden, Dresden, Germany; the 29Department of Epidemiology and Public Health, University College London, London, United Kingdom; the 30Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom; the 31Laboratory of Clinical Investigation, National Institute on Aging, Baltimore, Maryland; the 32Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California; the 33Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; the 34Medical Research Council Lifecourse Epidemiology Unit, University of Southampton, Southampton, University of Michigan School of Public Health, Ann Arbor, Michigan; the 35Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland; the 36Swiss Institute of Bioinformatics, Lausanne, Switzerland; the 37Division of Preventive Medicine, Brigham and Women’s Hospital, Boston, Massachusetts; the 38Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts; the 39Human Genetics Center, The University of Texas Health Science Center at Houston, Houston, Texas; the 40National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland; the 41Department of Medical Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; the 42Measurement 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 TCFT7L2 and GCKR were associated with 2-h glucose levels, as were newly identified loci in ADC5Y, 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, ADC5Y, TCFT7L2, 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 analyses 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 was 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 of each SNP per 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 National Heart, Lung, and Blood Institute’s Framingham Heart Study, Boston, Massachusetts; the Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts; the Division of Endocrinology, Diabetes, and Metabolism, Cedars-Sinai Medical Center, Los Angeles, California; the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; the Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; the Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark; the Infection, Immu­nology and Public Health University, Southampton, Southampton, United Kingdom; the Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; the Folkhalsan Research Center, Helsinki, and Department of Social Services and Health Care, Jakobstad, Finland; the Diabetes and Endocrinology Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden; the Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; the Interdisciplinary Center for Clinical Research, University of Leipzig, Leipzig, Germany; the University of Eastern Finland, and Kuopio University Hospital, Kuopio, Finland; the Hospital Robert Debré, Paris, France; the Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington; the Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois (CHUV), and University of Lausanne, Lausanne, Switzerland; the Institute for Medical Informatics and Biometry, Medical Faculty Carl Gustav Carus, University of Dresden, Dresden, Germany; the Department of Epidemiology and Center for Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; the Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota; the Metabolic Disease Group, Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom; the Departments of Epidemiology, Medicine, and Health Services University, Washington, Seattle, Washington; the Group Health Research Institute, Group Health, Seattle, Washington; the Department of Biostatistics, University of Washington, Seattle, Washington; the Boston University Data Coordinating Center, Boston, Massachusetts; the Department of Medicine, Harvard Medical School, Boston, Massachusetts; the General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts; the Framingham Heart Study, Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington; the Division of Internal Medicine, CHUV, Lausanne, Switzerland; Brigham and Women’s Hospital, Boston, Massachusetts; the Harvard Medical School, Boston, Massachusetts; the Women’s Health Initiative, Boston, Massachusetts; the SNP panels, Diabetes Center, Gentofte, Denmark; the Genetics of Complex Traits, Peninsula College of Medicine and Dentistry, Exeter, United Kingdom; the Botnar Research Centre, University of Oxford, Oxford, United Kingdom; the Department of Genomics of Common Disease, School of Public Health, Imperial College London, London, United Kingdom; the Institute of Cellular Medicine, Newcastle University, Newcastle, United Kingdom; the Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California; the Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; the Institute of Biomedical Science, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; the Faculty of Health Sciences, University of Aarhus, Aarhus, Denmark; the University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Addenbrooke’s Hospital, Cambridge, United Kingdom; the Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts; the Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts; and the Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts.

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

Study descriptives are reported in Supplementary Table 1. Inactive individuals had a higher 2-h glucose (β = 0.22 mmol/L [95% CI 0.13–0.31], P = 1.63 × 10−6) and BMI (β = 0.73 kg/m² [0.51–0.95], P = 1.42 × 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 × 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 = 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 ≥ 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: α = 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 × 10−4; rs10423928 P = 1.9 × 10−4).

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>β (95% CI)</th>
<th>P</th>
<th>ρ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</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>
<td>43.2</td>
</tr>
<tr>
<td></td>
<td>ADCY5</td>
<td>rs2877116</td>
<td>C</td>
<td>46085</td>
<td>0.06 (0.04, 0.09)</td>
<td>1.53e-07</td>
<td>40.6</td>
</tr>
<tr>
<td></td>
<td>TCF7L2</td>
<td>rs12243326</td>
<td>C</td>
<td>45655</td>
<td>0.08 (0.05, 0.10)</td>
<td>5.82e-11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>VPS13C</td>
<td>rs17271305</td>
<td>G</td>
<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>
</tr>
<tr>
<td>B</td>
<td>GCKR</td>
<td>rs1260326</td>
<td>T</td>
<td>48705</td>
<td>-0.03 (-0.08, 0.01)</td>
<td>0.18</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ADCY5</td>
<td>rs2877116</td>
<td>C</td>
<td>48702</td>
<td>-0.01 (-0.06, 0.05)</td>
<td>0.81</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TCF7L2</td>
<td>rs12243326</td>
<td>C</td>
<td>48367</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>
</tr>
<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>
<tr>
<td>C</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>rs2877116</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>

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/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.
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>β (95% CI)</th>
<th>P</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>ADCY5</td>
<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>
</tr>
<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>

Perallele 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.
**ACKNOWLEDGMENTS**

A complete list of disclosures and acknowledgments is included in the Supplementary Data online.

I.B. owns stock in GlaxoSmithKline and Incyte. No other potential conflicts of interest relevant to this article were reported.

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.Ia., 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 and were involved in genotyping and performed statistical analyses. T.Y., T.S., G.K., D.M., and W.X. were involved in management of the project and/or involved studies and in the project design and performed statistical analyses. T.M.T., P.W.F., and I.P. were involved in management of the project and/or involved studies and in phenotyping. C.H.S. 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 and in the project design, data collection, and phenotyping. 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.

**REFERENCES**


24. Wong MY, Day NE, Luan JA, Chan KP, Wareham NJ. The detection of gene-environment interaction for continuous traits: should we deal with measurement error by bigger studies or better measurement? Int J Epidemiol 2003;32:51–57