

1 **A polygenic score for type 2 diabetes risk is associated with both the acute and sustained**
2 **response to sulfonylureas**

3 Running Title: T2D risk score is associated with SU response

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21 ABSTRACT

22 There is a limited understanding of how genetic loci associated with glycemic traits and type 2
23 diabetes (T2D) influence the response to anti-diabetes medications. Polygenic scores provide
24 increasing power to detect patterns of disease predisposition that might benefit from a targeted
25 pharmacologic intervention. In the Study to Understand the Genetics of the Acute Response to
26 Metformin and Glipizide in Humans (SUGAR-MGH), we constructed weighted polygenic scores
27 using known genome-wide significant associations for T2D, fasting glucose (FG), and fasting
28 insulin (FI), comprised of 65, 43, and 13 single nucleotide polymorphisms, respectively. Multiple
29 linear regression tested for associations between scores and glycemic traits as well as
30 pharmacodynamic endpoints, adjusting for age, sex, race, and body mass index (BMI). A higher
31 T2D score was nominally associated with a shorter time to insulin peak, greater glucose area over
32 the curve, shorter time to glucose trough, and steeper slope to glucose trough after glipizide. In
33 replication, a higher T2D score was associated with a greater 1-year HbA1c reduction to
34 sulfonylureas in the Genetics of Diabetes Audit and Research, Tayside and Scotland (GoDARTS)
35 study ($p=0.02$). Our findings suggest that individuals with a higher genetic burden for T2D
36 experience a greater acute and sustained response to sulfonylureas.

37 Metformin and sulfonylureas are widely prescribed medications for the treatment of type
38 2 diabetes (T2D). Metformin is the recommended first-line agent for T2D, owing to its high
39 efficacy, low cost, and favorable side effect profile (1). Sulfonylureas are another commonly
40 employed agent due to their wide availability and glucose-lowering ability through stimulation of
41 insulin secretion from pancreatic β cells (2). Despite the recommendation that careful
42 consideration of patient factors should inform the choice of therapy (3), clinicians typically do not
43 account for the molecular target of each drug or integrate information about an individual's genetic
44 profile when prescribing a medication.

45 In the last decade, large-scale genome-wide association studies (GWAS) and high-
46 throughput sequencing studies have identified over 700 genetic signals influencing T2D risk and
47 glycemic traits (4-10). The expanding list of genetic variants has resulted in a better understanding
48 of the disease pathophysiology of T2D and the major processes that contribute to disease risk.
49 However, the impact of these genetic loci on the response to pharmacological interventions for
50 T2D has been less systematically studied.

51 With regards to metformin response, candidate gene studies have yielded initial findings
52 in transporter gene variants (*SLC22A1*, *SLC47A1*) but findings were not validated in subsequent
53 large-scale meta-analyses (11). GWAS and meta-analyses have revealed additional loci, including
54 single nucleotide polymorphisms (SNPs) in or near the gene encoding ataxia-telangiectasia
55 mutated kinase (*ATM*) (12) and in an intron SNP of the glucose transporter GLUT2 (*SLC2A2*)
56 (13). Pharmacogenetic studies of sulfonylurea response have been limited to candidate gene
57 studies, and no GWAS for sulfonylurea response has been published to date (14-17).

58 The impact of T2D-associated genetic variants on drug response has been investigated as
59 well. In particular, *TCF7L2*, the gene harboring common genetic variants with the largest effect

60 on T2D susceptibility discovered to date, has been associated with drug response to sulfonylureas
61 in those with established T2D (18) and in those at risk of T2D (19). For metformin, *TCF7L2* has
62 been associated with glycemic response in the early stages of disease (19, 20). Because individual
63 variants only have a modest effect, the field is now embracing the use of polygenic scores of
64 aggregated variants, which offer increasing power and capture a greater proportion of the variance
65 explaining a given trait (21).

66 As such, we examined whether polygenic scores derived from genome-wide significant
67 loci for glycemic traits and T2D are associated with glycemic traits and the response to metformin
68 and glipizide in the Study to Understand the Genetics of the Acute Response to Metformin and
69 Glipizide in Humans (SUGAR-MGH). We hypothesized that polygenic scores constructed based
70 on previously known genome-wide associations with fasting glucose (FG) and fasting insulin (FI)
71 would be associated with these glycemic traits in SUGAR-MGH. Furthermore, we expected that
72 a genetic predisposition to insulin secretion or action would influence the human response to
73 glipizide or metformin, respectively. For findings that reached significance, we sought replication
74 in the Genetics of Diabetes Audit and Research, Tayside and Scotland (GoDARTS) study, a
75 longitudinal cohort study of T2D.

76 RESEARCH DESIGN AND METHODS

77 **Study design and participants**

78 The study design of SUGAR-MGH has been previously described (22). Briefly, 1,000
79 participants were enrolled at three Boston academic medical centers between 2008-2015.
80 Participants were preferentially enrolled in the study if they had risk factors for T2D (i.e. metabolic
81 syndrome, obesity, polycystic ovarian syndrome, history of gestational diabetes, positive family
82 history) or lifestyle-controlled T2D. Some participants had previously unknown T2D, diagnosed

83 at the time of study entry. All participants were naïve to metformin and glipizide. Informed consent
84 was obtained from all study participants and the study protocol was approved by the Partners
85 Human Research Committee (Partners HealthCare, Boston, MA).

86 After an overnight fast of at least 8 hours, participants received a single dose of 5 mg
87 glipizide if their fasting blood glucose was >4.4 mmol/L (Visit 1). This threshold was chosen to
88 minimize the risk of hypoglycemia. Glucose and insulin levels were subsequently measured at
89 baseline, 30, 60, 90, 120, 180, and 240 minutes. The period of observation following glipizide
90 administration was terminated early if the participant developed neuroglycopenic symptoms, a
91 blood glucose ≤ 2.77 mmol/L with symptoms of hypoglycemia, blood glucose < 2.50 mmol/L with
92 or without symptoms of hypoglycemia, or at the discretion of study staff based on clinical
93 assessment. Subjects who did not meet the threshold to receive glipizide or terminated the glipizide
94 challenge early were excluded from analyses of glipizide response. Five days later, participants
95 received a two-day course of 500 mg metformin twice daily, followed by a 75-g oral glucose
96 tolerance test (OGTT) at Visit 2. Plasma glucose was measured by a hexokinase assay (Roche,
97 Indianapolis, IN) and insulin was determined using a radioimmunoassay (Beckman Coulter,
98 Fullerton, CA).

99 GoDARTS is a longitudinal case-control study that was established to study the genetics
100 of T2D. Over 18,000 participants were enrolled between December 1998 and August 2012, of
101 whom half were diagnosed with T2D and the remaining age- and sex-matched non-diabetic
102 controls were identified from general practice records in Tayside, Scotland. Details of the cohort
103 have been previously described (23). The GoDARTS study was approved by the Tayside
104 Committee for Medical Research Ethics. Written informed consent was obtained from each
105 participant.

106 For the replication analysis, we evaluated participants in GoDARTS who were diagnosed
107 with T2D and were either on a sulfonylurea as monotherapy or as an add-on to metformin. Subjects
108 with a history of insulin use, T2D diagnosed before 35 years of age, and with a baseline
109 hemoglobin A1c (HbA1c) <7% (53 mmol/mol) or >14% (130 mmol/mol) were excluded.

110 **Genotyping**

111 In SUGAR-MGH, DNA was extracted and genotyping was performed using the iPLEX-
112 GOLD Assay from Sequenom by allele-specific primer extension of amplified products with
113 detection by mass spectroscopy (24). Hardy-Weinberg equilibrium was tested within each self-
114 described ethnic group. SNPs with call rates <95% and samples with call rates <95% were
115 excluded.

116 Genotyping and quality control of the GoDARTS data have been described previously (12,
117 13). The SNPs included in the polygenic scores tested in this study were extracted from existing
118 GWAS data. Imputed SNPs had an imputation score >0.9.

119 **Polygenic score construction**

120 Polygenic scores were constructed for T2D, FG, and FI by summing the number of risk
121 alleles carried by each individual, weighted by the effect size estimates from well-established
122 genome-wide significant associations derived from the Meta-Analyses of Glucose and Insulin-
123 related traits Consortium (MAGIC) or Europeans in the DIAbetes Meta-ANalysis of Trans-Ethnic
124 association studies (DIAMANTE) Consortium (4, 6, 8). Due to the limited availability of SNPs on
125 our genotyping platform in SUGAR-MGH, we were able to include only a subset of the known
126 genome-wide significant loci for T2D and glycemic traits, resulting in a T2D polygenic score of
127 65 SNPs, FG score of 43 SNPs, and FI score of 13 SNPs. Supplemental Tables S1-3 list the genetic
128 variants, corresponding genes, and original GWAS references for each score. Effect alleles were

129 defined as T2D risk-raising, FG-raising, and FI-raising alleles. We utilized the 1000Genomes
130 database for global frequencies of the effect alleles because the individuals in SUGAR-MGH were
131 largely without overt T2D, and we wanted to avoid using a reference database that included
132 individuals from several T2D cohorts. If the lead SNP was not available, we utilized a proxy that
133 had an $r^2 > 0.8$ for Europeans. In GoDARTS, polygenic scores were created in the same manner.

134 **Statistical analyses**

135 In SUGAR-MGH, the area over the curve (AOC) for decreases in glucose during the
136 glipizide challenge was calculated by subtracting glucose area under the curve (AUC) by the
137 trapezoidal method from the baseline glucose value \times total time for the glipizide challenge. The
138 AUC for glucose and insulin following metformin administration was calculated by the trapezoidal
139 method, which accounted for baseline glucose and insulin values, respectively. Insulin resistance
140 by homeostasis model assessment (HOMA-IR) was calculated as previously described (25).
141 Missing data were not imputed.

142 The mean \pm standard deviation or median (interquartile range) are reported for continuous
143 normally or non-normally distributed traits, respectively. Assessment of normality was performed
144 using the Shapiro-Wilk test. Multiple linear regression with adjustments for age, sex, self-reported
145 race/ethnicity, and body mass index (BMI) were used to test the association between each
146 polygenic score and glycemic traits as well as pharmacodynamic endpoints. β coefficients are
147 presented as the incremental increase or decrease in the trait or endpoint per standard deviation of
148 the tested polygenic score. We assessed for both nominal significance ($p < 0.05$) and a more
149 stringent p -value of 0.008 for multiple comparisons (two drugs \times three polygenic scores).
150 Statistical analyses were performed using R 3.5.2 (26).

151 For the replication analyses in GoDARTS, multiple linear regression tested for the
152 association between polygenic score and the outcome of HbA1c reduction, defined as baseline
153 HbA1c (measured within 180 days prior to sulfonylurea initiation) minus on-treatment HbA1c at
154 one year. Additional covariates included baseline HbA1c, age at diagnosis of diabetes, sex, BMI,
155 average sulfonylurea dose, and mediation adherence as previously described (18).

156 **Data and Resource Availability**

157 The datasets analyzed during the current study are available from the corresponding author upon
158 reasonable request. Data from SUGAR-MGH are also available at [Clinicaltrials.gov](https://clinicaltrials.gov).

159 **RESULTS**

160 **Subject characteristics**

161 The baseline characteristics of the 1,000 participants in SUGAR-MGH are summarized in
162 Table 1. Approximately half of participants were female, the mean age was 47.2 years, and over
163 35% of participants came from ethnic minority populations. The mean BMI was 30.2 kg/m² and
164 mean fasting glucose was 5.16 mmol/L, consistent with a population at risk of requiring future
165 anti-diabetic agents. Only 26 participants had a diagnosis of T2D (not treated pharmacologically)
166 at the time of study entry. Of the 1,000 participants, 351 were either ineligible for the glipizide
167 challenge due to low fasting glucose or terminated the challenge early in accordance with study
168 protocol.

169 **Construction of polygenic scores for T2D, FG, and FI**

170 The distribution of all three polygenic scores is depicted in Figure 1. The mean T2D
171 polygenic score was 61.82 (range 44.49-80.93). The mean FG polygenic score was 48.92 (range
172 31.58-66.08). The mean FI polygenic score was 12.54 (range 5.11-22.74).

173 **Association between polygenic scores and baseline glycemetic traits**

174 Table 2 shows the associations between each polygenic score and either FG or FI at
175 baseline in SUGAR-MGH. The FG polygenic score was strongly associated with FG in our cohort
176 in multivariate analyses ($p<0.001$), with each standard deviation increase in score raising FG by
177 0.13 mmol/L. This association was present in stratified analyses of the non-Hispanic white
178 ($\beta=0.09$, $p=0.01$) and non-Hispanic black ($\beta=0.14$, $p=0.007$) individuals in SUGAR-MGH.
179 Likewise, a higher FI polygenic score was associated with higher FI ($p=0.04$); this finding was
180 also present in stratified analyses of non-Hispanic whites. A higher T2D polygenic score trended
181 toward significance ($p=0.05$) for the association with higher FG but was not associated with FI.

182 **Association between T2D score and the acute response to glipizide and metformin**

183 Table 3 summarizes the association between T2D polygenic score and select endpoints of
184 glipizide and metformin response. A higher T2D polygenic score was associated with a greater
185 glucose AOC, shorter time to glucose trough, steeper slope to glucose trough, and shorter time to
186 insulin peak following glipizide administration at nominal significance ($p<0.05$). When the more
187 stringent p -value of 0.008 was utilized to correct for multiple comparisons, the finding involving
188 the insulin-based endpoint remained significant. We tested and did not find a significant
189 association between T2D polygenic score and pharmacodynamic endpoints of metformin response
190 (change in FG, change in FI, change in HOMA-IR; Table 3).

191 Given that the T2D polygenic score was constructed using effect size estimates for
192 European ancestries and proxies were selected based on linkage disequilibrium in Europeans, we
193 performed stratified analyses for the non-Hispanic white and black participants separately. In the
194 non-Hispanic white subset of SUGAR-MGH (Supplemental Table S4), we observed that
195 individuals with a higher T2D polygenic score trended toward having a greater glucose AOC and
196 shorter time to insulin peak, though this did not reach our significance threshold after adjustment

197 for multiple testing. Similarly in the non-Hispanic black participants, a similar direction of
198 association was seen between a higher T2D polygenic score and shorter time to glucose trough
199 and insulin peak following glipizide (Supplemental Table S5). The relationship between higher
200 T2D polygenic score and steeper slope to glucose trough trended toward but did not reach
201 significance in both subgroups.

202 **Association between glycemic trait polygenic scores and the acute response to glipizide and** 203 **metformin**

204 Additionally, we observed associations between glycemic trait scores and endpoints of
205 glipizide response, reaching only nominal significance but not meeting the more stringent
206 significance threshold after adjustment for multiple testing. A higher FG polygenic score trended
207 toward a higher glucose AOC ($p=0.02$), with each standard deviation increase in score raising the
208 glucose AOC by 10.82 mmol/L*min (Supplemental Table S6). Moreover, each standard deviation
209 increase in FI polygenic score trended toward a 0.05 mmol/L higher glucose trough following
210 glipizide administration ($p=0.02$, Supplemental Table S7). No association was observed between
211 either glycemic trait polygenic score and select endpoints of metformin response (Supplemental
212 Tables S6-7).

213 **Replication in GoDARTS**

214 The baseline characteristics of the 2,228 individuals in GoDARTS who underwent
215 treatment with a sulfonylurea are summarized in Table 4. Approximately half of participants were
216 female, the mean age was 59.7 years, and the baseline HbA1c was 8.97% (75 mmol/mol). All
217 subjects were of European ancestry. To replicate our findings in SUGAR-MGH with respect to
218 sulfonylurea response, we constructed a weighted T2D polygenic score for each individual in
219 GoDARTS and tested for association with the HbA1c reduction over one year. The mean T2D

220 polygenic score was 74.92 (range 53.29-93.08) with a standard deviation of 5.90. In adjusted
221 analyses, for each standard deviation increase in T2D score, there was a 0.063% (0.07 mmol/mol)
222 greater HbA1c reduction in response to sulfonylurea therapy ($p=0.02$). Moreover, those in the top
223 decile of T2D polygenic score had a $0.27\% \pm 0.12\%$ greater HbA1c reduction compared to those
224 in the bottom decile ($p=0.03$).

225 DISCUSSION

226 In SUGAR-MGH, we built polygenic scores for elevated T2D risk, FG, and FI using
227 genome-wide significant variants discovered in GWAS for T2D and glycemic traits. We first
228 assessed whether the three polygenic scores were associated with glycemic traits, which would
229 indicate the generalizability of these scores to outcomes in this cohort. Subsequently we tested the
230 hypothesis that combining individual variants into a polygenic score may provide additional
231 information on patterns of T2D disease predisposition that may benefit from tailored
232 pharmacologic intervention.

233 We indeed demonstrated that sets of genome-wide significant genetic variants confirmed
234 to be associated with glycemic traits were associated with fasting glucose and insulin levels in
235 SUGAR-MGH. Our findings were consistent in direction with and stronger in significance than
236 previously reported findings in an interim analysis conducted for our design paper at two-thirds
237 study enrollment in SUGAR-MGH (22). Additionally, we examined whether a polygenic score for
238 T2D risk would be associated with the same glycemic traits in our cohort. We found that there was
239 a trend toward higher FG in those with a higher genetic burden for T2D, possibly related to the
240 overlap of 14 SNPs between the T2D and FG scores. No association was seen between T2D
241 polygenic score and FI, but this was not unexpected given that many of the genetic polymorphisms

242 in the T2D score were those that directly or indirectly affect pancreatic β -cell function rather than
243 insulin resistance.

244 We also tested the associations between each of the three polygenic scores and phenotypes
245 of glipizide and metformin response. Individuals with a higher genetic burden for T2D were found
246 to have a more robust response to glipizide, as indicated by a larger glucose AOC, representing a
247 greater cumulative drop in glucose over time. Additionally, a higher T2D score was associated
248 with a shorter time to glucose trough, steeper slope to glucose trough, and shorter time to insulin
249 peak, all consistent with an enhanced glipizide response. We note that these findings were all at
250 nominal significance ($p < 0.05$). Since the outcomes are correlated, we subsequently accounted for
251 multiple comparisons, after which only the insulin-based outcome remained statistically
252 significant. However, the presence of associations between T2D polygenic score and several
253 glipizide challenge endpoints provides evidence for a true impact on glipizide response. These
254 findings are additionally supported by the observation of a marginally higher glucose AOC in
255 individuals with a higher FG polygenic score, again indicative of a greater glipizide response.

256 Since many of the SNPs comprising the T2D polygenic score influence β -cell function, it
257 appears that treatment with glipizide, a sulfonylurea that stimulates insulin secretion from the β
258 cell, can overcome these genetic defects in the early stages of T2D pathogenesis. We speculate
259 that perhaps those with a higher risk of T2D may have overly sensitized β cells compared with
260 those with a lower polygenic score, resulting in an accentuated response to glipizide. This is similar
261 to what is observed in maturity-onset diabetes of the young (MODY) type 3, which is characterized
262 by *HNF1A* mutations causing decreased insulin secretion. Individuals with MODY3 demonstrate
263 a heightened sensitivity to sulfonylureas (27) but require insulin as the secretory defect progresses.
264 We hypothesize that individuals with a higher T2D risk score may behave in the same way,

265 whereby they initially have a sensitized β cell early in the disease course but may achieve β -cell
266 failure sooner.

267 Based on our findings, we sought replication in GoDARTS, a case-control study of T2D
268 with longitudinal clinical and genetic data available. For a subset of 2,228 individuals who
269 received a sulfonylurea, we tested whether a T2D polygenic score is associated with a clinical drug
270 response. We found that the mean T2D polygenic score was higher in GoDARTS than in SUGAR-
271 MGH, illustrating a higher burden of T2D risk variants. This was expected since GoDARTS
272 participants have established T2D requiring sulfonylurea therapy. Moreover, we observed that a
273 higher T2D score was again significantly associated with a greater sulfonylurea response, as
274 measured by HbA1c reduction at one year. Thus, we demonstrated that the T2D score was not
275 only associated with the physiologic response to an acute dose of glipizide, but also influenced the
276 sustained glycemic response to sulfonylureas. We acknowledge that a 0.063% greater reduction in
277 HbA1c per standard deviation increase in T2D score is clinically small; however, this difference
278 was as high as 0.27% when comparing the top and bottom deciles in T2D score. Therefore, the
279 clinical utility of the T2D polygenic score may be limited in most of the population, but becomes
280 more relevant in those at the extremes.

281 Interestingly, our findings appear to be in contrast with the candidate gene analysis of the
282 *TCF7L2* variant rs7903146 in GoDARTS, in which homozygotes for the T risk allele were less
283 likely to respond to sulfonylureas (18). We have previously postulated that this genotype may have
284 a differential effect in individuals with T2D who already have some degree of β -cell dysfunction
285 compared with those without overt T2D (19). One might expect that similarly those with a high
286 T2D score and a predisposition to β -cell failure would benefit from sulfonylureas early in the
287 disease course and have an attenuated response over time. However, our replication analyses in

288 GoDARTS suggest otherwise, in that the association between a higher T2D score and greater
289 response to sulfonylureas is observed even in those with established T2D and an average duration
290 of disease of 4.8 years. Whether this effect would be observed for those with an even longer
291 duration of T2D remains to be determined. If so, this could suggest that the T2D polygenic score
292 captures additional mechanisms that remain to be elucidated.

293 We also demonstrated that individuals with a higher FI polygenic score trended toward a
294 higher glucose trough, adjusted for baseline glucose, in response to glipizide. This finding might
295 suggest that for the same 5 mg dose of glipizide resulting in the same amount of insulin secretion,
296 individuals with a higher degree of insulin resistance respond worse and have a smaller glucose-
297 lowering response. Notably, this observation was present after adjustment for BMI but did not
298 meet the more stringent p -value for multiple comparisons. We also did not observe an effect on
299 other glipizide challenge endpoints.

300 With respect to metformin, we did not observe any significant associations between
301 polygenic score and phenotypic endpoints of metformin response. This is not surprising, especially
302 as T2D and FG polygenic scores comprising of predominantly β -cell function SNPs would not be
303 expected to associate with metformin response. Similarly in the Diabetes Prevention Program
304 (DPP), a pre-diabetic cohort, a genetic score of 34 T2D loci was associated with an increased risk
305 of progression to diabetes and a lower probability of regression to normoglycemia, but there was
306 no observed interaction effect of metformin on this association (28).

307 Prior pharmacogenetic studies of sulfonylurea response have been limited to candidate
308 gene studies (14-17), and few have examined individual T2D-associated genes (18, 19). Our study
309 is the first, to our knowledge, to show a significant association between an aggregate score of T2D
310 risk loci and drug response prospectively. One recently published study by Martono *et al.*

311 examined the added utility of genetic risk scores for insulin sensitivity, β -cell function, and T2D
312 for prediction of the initial response to metformin or sulfonylureas in a primary care population
313 with early T2D (29). They did not find an association between any of these scores and drug
314 response, as measured by 6-month HbA1c, adjusted for baseline HbA1c. However, the study
315 population was considerably smaller than ours (only 282 individuals initiating metformin and 89
316 individuals starting sulfonylureas) and may have been underpowered to detect significant effects.
317 We note that our study also utilized weighted polygenic scores and data from the most recent
318 GWAS for T2D (8).

319 Study strengths include the diverse population of our cohort, which allow for
320 generalizability of our findings. Furthermore, SUGAR-MGH was conducted under fasting
321 conditions, which limited the influence of dietary and lifestyle habits. While SUGAR-MGH had
322 the advantage of examining a physiologic response to an acute perturbation in a controlled
323 environment, the study design did not include an OGTT prior to metformin administration, which
324 would have provided a dynamic glucose challenge for assessing metformin response.

325 Another shortcoming is that we were only able to assess a fraction of the known genomic
326 loci for T2D and glycemic traits, due to the limited availability of SNPs on our genotyping
327 platform. Genome-wide genotyping is currently underway in SUGAR-MGH, which will permit
328 more extensive polygenic score construction in the future. This will include partitioned polygenic
329 scores, which group variants by a common biological process and can provide insight into disease
330 pathophysiology. The current study only analyzed restricted-to-significant polygenic scores, and
331 future studies examining global extended polygenic scores, generated from large numbers of
332 subthreshold significant variants, are needed as well. However, there appears to be limited
333 improvement in predictive performance between a restricted polygenic score comprising 199 SNPs

334 and a global polygenic score (21). These findings suggest that there may not be a significant step-
335 up in power with increasing the number of variants included in the polygenic score. Finally, we
336 note that the effect size estimates used in the polygenic score construction are for European
337 ancestry, which does not take into consideration that risk variants can have different effect sizes
338 in different populations. We also do not have ancestry information available on those individuals
339 who self-reported as “black” in our cohort. However, in our stratified analyses in non-Hispanic
340 white and black individuals (comprising 64% and 21% of SUGAR-MGH, respectively), we report
341 findings that trend in the same direction as our primary analyses concerning the impact of the T2D
342 polygenic score on glipizide response.

343 In summary, our findings suggest that there is some overlap between genes implicated in
344 the risk of developing T2D and those associated with the response to treatment with sulfonylureas.
345 We add to the growing body of literature on the potential utility of polygenic scores in
346 understanding the response to T2D pharmacotherapy. Our study provides preliminary evidence
347 that sulfonylureas could be more effective in T2D risk allele carriers, both in drug-naïve
348 individuals as well as those with established T2D. This finding is consistent with the recent results
349 reported by Dennis *et al.* in the ADOPT trial, showing that participants who cluster in the severely
350 insulin deficient diabetes phenotype (presumably enriched for beta-cell deleterious alleles)
351 experience a robust initial response to sulfonylureas, though it worsens over time (30). While
352 genetic variation has been shown to alter the response to therapy in T2D, further confirmatory
353 studies are necessary to clarify the role of polygenic scores in clinical decision-making.

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364 **Author Contributions.** J.H.L., L.S., V.K., and J.C.F. conceived and designed the experiments in
365 SUGAR-MGH. J.H.L., A.Y.D., E.R.P., and J.C.F. conceived and designed the replication analyses
366 in GoDARTS. V.K. and J.C.F. recruited participants in SUGAR-MGH. J.H.L., L.S., A.Y.D., and
367 V.K. analyzed the data. All authors took part in interpreting the data. J.H.L. and J.C.F. prepared
368 the manuscript. All authors read and edited the manuscript. J.C.F. is the guarantor of this work
369 and, as such, had full access to all the data in the study and takes responsibility for the integrity of
370 the data and the accuracy of the data analysis.

371 **Prior Presentation.** Portions of this study were previously presented in poster form at the 79th
372 Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7-11 June 2019.

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451 TABLES

452 **Table 1.** Demographic characteristics and baseline measurements of 1,000 participants in

453 SUGAR-MGH

	All participants (n=1,000)
Female (n, %)	539 (54%)
Age (years)	47.2 ± 16.2
BMI (kg/m ²), n=978	30.2 ± 7.1
Self-reported race/ethnicity (n, %)	
White, non-Hispanic	639 (64%)
Black, non-Hispanic	209 (21%)
Hispanic	69 (6.9%)
Asian, non-Hispanic	59 (5.9%)
Others	24 (2.4%)
Diagnosis of type 2 diabetes	26 (2.6%)
Fasting glucose (mmol/L)	5.16 ± 0.93
Fasting insulin (pmol/L), n=970	3.56 (3.03, 4.11)

454 Age, body mass index (BMI), and fasting glucose are shown as mean ± standard deviation.

455 Fasting insulin is presented as median (interquartile range).

456 **Table 2.** Association of polygenic scores with baseline glyceic traits in SUGAR-MGH

Polygenic score	Trait	β (95% CI)	<i>P</i>
Fasting glucose	Fasting glucose (mmol/L)	0.13 (0.07, 0.18)	<0.001
Fasting insulin	Ln fasting insulin (pmol/L)	0.05 (0.003, 0.10)	0.04
Type 2 diabetes	Fasting glucose (mmol/L)	0.05 (-2.1e-5, 0.10)	0.05
Type 2 diabetes	Ln fasting insulin (pmol/L)	0.009 (-0.04, 0.06)	0.71

457 Linear regression model was adjusted for age, sex, race/ethnicity, and body mass index (BMI). β

458 values are reported per standard deviation of polygenic score.

459 **Table 3.** Association of T2D polygenic score with glipizide and metformin endpoints in
 460 SUGAR-MGH

	N	β (95% CI)	P [§]
Glipizide endpoint*			
Glucose trough (mmol/L) [†]	639	-0.01 (-0.05, 0.02)	0.50
Glucose AOC (mmol/L*min)	633	10.05 (1.17, 18.93)	0.03
Time to glucose trough (min) [†]	639	-4.88 (-8.82, -0.94)	0.02
Slope to glucose trough (mmol/L/min) [†]	638	7.6e-4 (1.2e-4, 1.4e-3)	0.02
Ln peak insulin (pmol/L) [‡]	615	0.04 (-0.009, 0.09)	0.11
Time to insulin peak (min) [‡]	615	-5.83 (-9.91, -1.76)	0.005
Slope to insulin peak (pmol/L/min) [‡]	609	-0.11 (-0.33, 0.12)	0.35
Metformin endpoint			
Fasting glucose V2-V1 (mmol/L) [†]	924	-0.009 (-0.04, 0.02)	0.56
Glucose AUC (mmol/L*min)	900	6.79 (-3.20, 16.77)	0.18
Fasting insulin V2-V1 (pmol/L) [‡]	891	-3.11 (-6.74, 0.52)	0.09
Insulin AUC (pmol/L*min)	831	-66.27 (-2561.34, 1640.89)	0.67
Ln HOMA-IR V1 (mmol*pmol/L ²)	915	0.02 (-0.03, 0.08)	0.44
Ln HOMA-IR V2 (mmol*pmol/L ²)	914	-0.01 (-0.07, 0.05)	0.69
HOMA-IR V2-V1 (mmol*pmol/L ²)	914	-0.84 (-1.73, 0.04)	0.06

461 V1=visit 1, V2=visit 2, AOC=area over the curve, AUC=area under the curve. *351 individuals
 462 did not meet the threshold to receive glipizide or terminated the glipizide challenge early and
 463 were excluded from analyses of glipizide response. [†]Adjusted for baseline glucose. [‡]Adjusted for
 464 ln baseline insulin. Linear regression model was adjusted for age, sex, race/ethnicity, and body

465 mass index (BMI). §*P*-values of <0.008 are reported in bold and reflect significance after
466 adjustment for multiple testing.

467

468 **Table 4.** Demographic characteristics and baseline measurements of 2,228 participants in
 469 GoDARTS

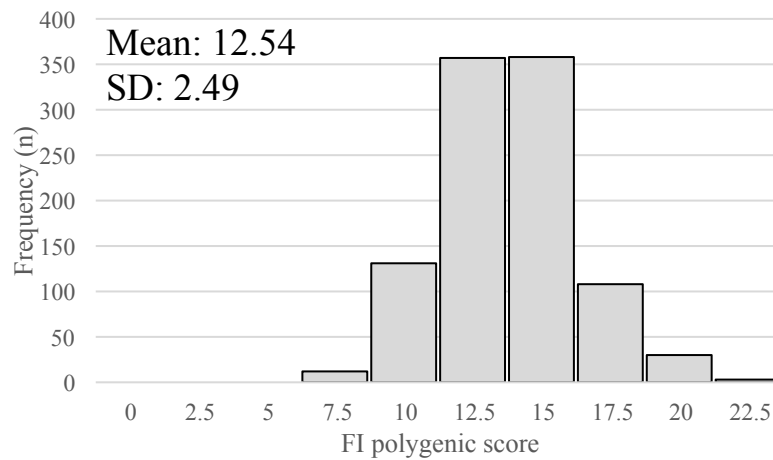
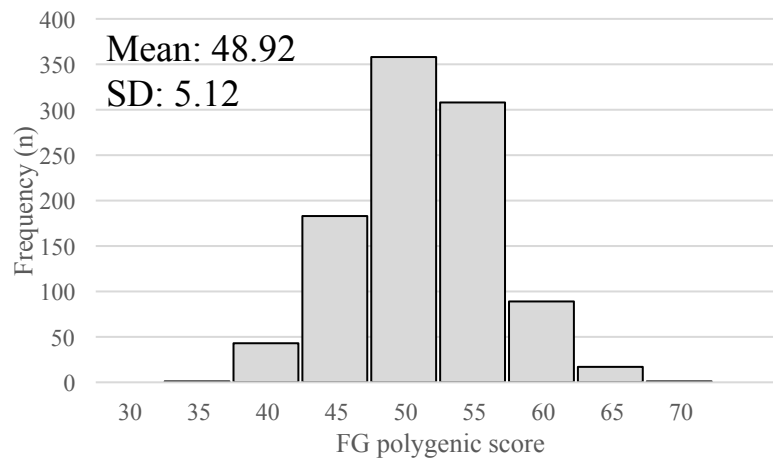
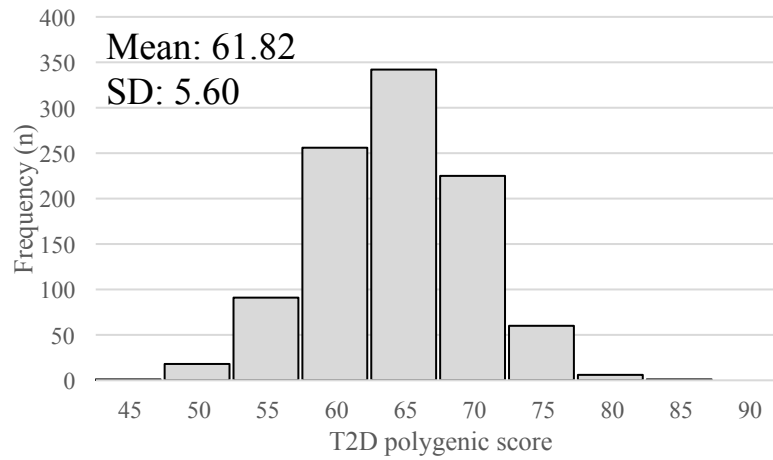
	All participants (n=2,228)
471	Age at diagnosis (years) 59.7 ± 10.3
472	Sex (% female) 45%
473	Duration of diabetes (years) 4.8 ± 4.4
474	Baseline BMI (kg/m ²)/
475	30.5 ± 5.4
476	Baseline HbA1c (%) 8.97 ± 1.47
	On-treatment HbA1c (%) 7.64 ± 1.40
	Average HbA1c reduction (%) 1.34 ± 1.69
	Sulfonylurea adherence (%) $86\% \pm 20\%$
	Sulfonylurea monotherapy (%) 44%

477 Age, BMI, and HbA1c values are presented as mean \pm standard deviation.

479 FIGURE LEGEND

480 **Figure 1.** Distribution of polygenic scores for (A) type 2 diabetes, (B) fasting glucose, (C)

481 fasting insulin across 1,000 individuals in SUGAR-MGH.



SUPPLEMENTAL MATERIAL

Supplemental Table S1. Genetic variants included in the T2D polygenic score.

SNP	Locus	CHR	POS	T2D raising allele	EAF	β	Reference
rs340879 ^a	<i>PROXI</i>	1	214156514	C	0.508	0.059	Morris et al. 2012
rs17106184	<i>FAF1</i>	1	50909985	G	0.921	0.063	Mahajan et al. 2014
rs340874	<i>PROXI</i>	1	214159256	C	0.376	0.068	Dupuis et al. 2010
rs10195252	<i>COBLL1</i>	2	165513091	T	0.603	0.06	Scott et al. 2012
rs1260326	<i>GCKR</i>	2	27730940	C	0.707	0.067	Saxena et al. 2010
rs2943641	<i>IRSI</i>	2	227093745	C	0.751	0.094	Rung et al. 2009
rs3923113	<i>GRB14</i>	2	165501849	A	0.615	0.056	Kooner et al. 2011
rs7578326	<i>IRSI</i>	2	227020653	A	0.714	0.079	Voight et al. 2010
rs7578597	<i>THADA</i>	2	43732823	T	0.863	0.12	Zeggini et al. 2008
rs7607980	<i>COBLL1</i>	2	165551201	T	0.893	0.084	Manning et al. 2012
rs243021	<i>BCL11A</i>	2	60584819	A	0.496	0.058	Voight et al. 2010
rs11708067	<i>ADCY5</i>	3	123065778	A	0.850	0.089	Dupuis et al. 2010
rs2877716 ^b	<i>ADCY5</i>	3	123094451	C	0.811	0.086	Morris et al. 2012
rs13094957 ^c	<i>UBE2E2</i>	3	23457080	T	0.745	0.071	Morris et al. 2012
rs1801282	<i>PPARG</i>	3	12393125	C	0.930	0.1	Altshuler et al. 2000
rs4402960	<i>IGF2BP2</i>	3	185511687	T	0.389	0.11	Morris et al. 2012
rs4607103	<i>ADAMTS9</i>	3	64711904	C	0.646	0.052	Zeggini et al. 2008
rs6795735	<i>ADAMTS9</i>	3	64705365	C	0.287	0.048	Zeggini et al. 2008
rs16861329	<i>ST6GAL1</i>	3	186666461	C	0.835	0.057	Kooner et al. 2011
rs6446482	<i>WFS1</i>	4	6295693	G	0.721	0.085	Morris et al. 2012
rs6813195	<i>TMEM154</i>	4	153520475	C	0.592	0.055	Mahajan et al. 2014
rs4457053	<i>ZBED3</i>	5	76424949	G	0.203	0.059	Voight et al. 2010
rs459193	<i>ANKRD55</i>	5	55806751	G	0.606	0.073	Morris et al. 2012
rs4865796	<i>ARL15</i>	5	53272664	A	0.760	0.051	Scott et al. 2012
rs10946398	<i>CDKAL1</i>	6	20661034	C	0.405	0.12	Zeggini et al. 2008
rs9368222	<i>CDKAL1</i>	6	20686996	A	0.269	0.14	Scott et al. 2012
rs17168486	<i>DGKB</i>	7	14898282	T	0.272	0.069	Morris et al. 2012
rs2191349	<i>DGKB</i>	7	15064309	T	0.572	0.066	Dupuis et al. 2010
rs4607517	<i>GCK</i>	7	44235668	A	0.143	0.055	Dupuis et al. 2010
rs972283	<i>KLF14</i>	7	130466854	G	0.693	0.012	Voight et al. 2010
rs3802177 ^d	<i>SLC30A8</i>	8	118185025	G	0.744	0.11	Morris et al. 2012
rs516946	<i>ANK1</i>	8	41519248	C	0.804	0.08	Morris et al. 2012
rs896854	<i>TP53INP1</i>	8	95960511	T	0.484	0.05	Voight et al. 2010
rs10811661	<i>CDKN2A/B</i>	9	22134094	T	0.824	0.16	Morris et al. 2012
rs2796441	<i>TLE1</i>	9	84308948	G	0.603	0.066	Morris et al. 2012
rs13292136	<i>TLE4</i>	9	81952128	C	0.898	0.085	Voight et al. 2010

rs1111875	<i>HHEX</i>	10	94462882	C	0.544	0.11	Morris et al. 2012
rs11257655	<i>CDC123</i>	10	12307894	T	0.301	0.09	Zeggini et al. 2008
rs12571751	<i>ZMIZ1</i>	10	80942631	A	0.535	0.07	Morris et al. 2012
rs7903146	<i>TCF7L2</i>	10	114758349	T	0.228	0.31	Morris et al. 2012
rs10830963	<i>MTNR1B</i>	11	92708710	G	0.260	0.099	Dupuis et al. 2010
rs1552224	<i>ARAP1</i>	11	72433098	A	0.900	0.1	Voight et al. 2010
rs163184	<i>KCNQ1</i>	11	2847069	G	0.373	0.081	Morris et al. 2012
rs2237892	<i>KCNQ1</i>	11	2839751	C	0.851	0.11	Yasuda et al. 2008
rs8181588 ^e	<i>KCNQ1</i>	11	2831541	T	0.807	0.19	Wheeler et al. 2017
rs231362	<i>KCNQ1</i>	11	2691471	G	0.729	0.055	Voight et al. 2010
rs757110	<i>KCNJ11</i>	11	17418477	C	0.274	0.068	Gloyn et al. 2003
rs10842994	<i>KLHDC5</i>	12	27965150	C	0.862	0.074	Morris et al. 2012
rs2261181	<i>HMG2</i>	12	66212318	T	0.156	0.11	Morris et al. 2012
rs7955901	<i>TSPAN8</i>	12	71433293	C	0.434	0.044	Morris et al. 2012
rs1531343	<i>HMG2</i>	12	66174894	C	0.213	0.1	Voight et al. 2010
rs7957197	<i>HNFI1A</i>	12	121460686	T	0.891	0.065	Voight et al. 2010
rs7961581	<i>TSPAN8</i>	12	71663102	C	0.238	0.038	Zeggini et al. 2008
rs1215451 ^f	<i>SPRY2</i>	13	80715893	G	0.771	0.083	Morris et al. 2012
rs12899811	<i>VPS33B</i>	15	91544076	G	0.636	0.042	Morris et al. 2012
rs2028299	<i>AP3S2</i>	15	90374257	C	0.270	0.063	Kooner et al. 2011
rs7178572	<i>HMG20A</i>	15	77747190	G	0.526	0.078	Kooner et al. 2011
rs8042680	<i>PRC1</i>	15	91521337	A	0.742	0.051	Voight et al. 2010
rs7202877	<i>CTRB2</i>	16	75247245	T	0.860	0.1	Morris et al. 2012
rs9939609	<i>FTO</i>	16	53820527	A	0.340	0.12	Frayling et al. 2007
rs11651052	<i>HNFI1B</i>	17	36102381	A	0.424	0.072	Morris et al. 2012
rs12970134	<i>MC4R</i>	18	57884750	A	0.207	0.052	Morris et al. 2012
rs12454712	<i>BCL2</i>	18	60845884	T	0.624	0.049	Saxena et al. 2012
rs3794991	<i>SUGPI</i>	19	19610596	T	0.088	0.079	Saxena et al. 2012
rs481282	<i>HNFA4</i>	20	42989267	A	0.255	0.05	Kooner et al. 2011

T2D=type 2 diabetes, SNP=single nucleotide polymorphism, CHR=chromosome, POS=position based on human genome 19, EAF=effect allele frequency based on global 1000Genomes. ^aproxy for rs2075423, ^bproxy for rs11717195, ^cproxy for rs1496653, ^dproxy for rs13266634, ^eproxy for rs2237896, ^fproxy for rs1359790.

Supplemental Table S2. Genetic variants included in the FG polygenic score

SNP	Locus	CHR	POS	FG raising allele	EAF	β	Reference
rs340874	<i>PROX1</i>	1	214159256	C	0.376	0.014	Dupuis et al. 2010
rs1260326	<i>GCKR</i>	2	27730940	C	0.707	0.029	Saxena et al. 2010
rs1371614	<i>DPYSL5</i>	2	27152874	T	0.268	0.016	Manning et al. 2012
rs552976	<i>G6PC2/ABCB11</i>	2	169791438	G	0.748	0.057	Soranzo et al. 2010
rs573225 ^a	<i>G6PC2</i>	2	169757541	A	0.855	0.063	Dupuis et al. 2010
rs11708067	<i>ADCY5</i>	3	123065778	A	0.850	0.023	Dupuis et al. 2010
rs10640 ^b	<i>AMT</i>	3	49454277	G	0.794	0.011	Scott et al. 2012
rs2877716 ^c	<i>ADCY5</i>	3	123094451	C	0.811	0.019	Morris et al. 2012
rs11920090	<i>SLC2A2</i>	3	170717521	T	0.816	0.027	Dupuis et al. 2010
rs4402960	<i>IGF2BP2</i>	3	185511687	T	0.389	0.012	Morris et al. 2012
rs8192675	<i>SLC2A2</i>	3	170724883	T	0.588	0.017	Wheeler et al. 2017
rs9368222	<i>CDKAL1</i>	6	20686996	A	0.269	0.014	Scott et al. 2012
rs10278336	<i>YKT6</i>	7	44245363	A	0.654	0.035	Morris et al. 2012
rs17168486	<i>DGKB</i>	7	14898282	T	0.272	0.031	Morris et al. 2012
rs2191349	<i>DGKB</i>	7	15064309	T	0.572	0.029	Dupuis et al. 2010
rs3824065	<i>YKT6</i>	7	44247258	C	0.655	0.034	Wheeler et al. 2017
rs4607517	<i>GCK</i>	7	44235668	A	0.143	0.064	Dupuis et al. 2012
rs6943153	<i>GRB10</i>	7	50791579	T	0.433	0.015	Scott et al. 2012
rs3802177 ^d	<i>SLC30A8</i>	8	118185025	G	0.744	0.028	Morris et al. 2012
rs4841132	<i>PPP1R3B</i>	8	9183596	A	0.093	0.03	Manning et al. 2012
rs983309	<i>PPP1R3B</i>	8	9177732	T	0.152	0.025	Scott et al. 2012
rs10758593	<i>GLIS3</i>	9	4292083	A	0.479	0.016	Morris et al. 2012
rs10811661	<i>CDKN2A/B</i>	9	22134094	T	0.824	0.024	Morris et al. 2012
rs16913693	<i>IKBKAP</i>	9	111680359	T	0.923	0.043	Scott et al. 2012
rs3829109	<i>DNLZ</i>	9	139256766	G	0.790	0.017	Scott et al. 2012
rs4918635 ^e	<i>ADRA2A</i>	10	113036224	C	0.718	0.031	Dupuis et al. 2010
rs7903146	<i>TCF7L2</i>	10	114758349	T	0.228	0.022	Morris et al. 2012
rs10501320	<i>MADD</i>	11	47293799	G	0.912	0.025	Strawbridge et al. 2011
rs10830963	<i>MTNR1B</i>	11	92708710	G	0.260	0.078	Dupuis et al. 2010
rs11605924	<i>CRY2</i>	11	45873091	A	0.674	0.022	Dupuis et al. 2010
rs1483121	<i>OR4SI</i>	11	48333360	G	0.959	0.029	Manning et al. 2012
rs1552224	<i>ARAP1</i>	11	72433098	A	0.900	0.02	Voight et al. 2010
rs174550	<i>FADS1</i>	11	61571478	T	0.702	0.02	Dupuis et al. 2010
rs174577	<i>FADS2</i>	11	61604814	C	0.608	0.02	Wheeler et al. 2017
rs7944584	<i>MADD</i>	11	47336320	A	0.878	0.025	Dupuis et al. 2010
rs10747083	<i>P2RX2</i>	12	133041618	A	0.760	0.014	Scott et al. 2012
rs2293941	<i>PDX1</i>	13	28491198	A	0.254	0.02	Manning et al. 2012
rs533873 ^f	<i>KL</i>	13	33555587	C	0.320	0.012	Scott et al. 2012

rs3783347	<i>WARS</i>	14	100839261	G	0.879	0.017	Scott et al. 2012
rs7163757 ^g	<i>C2CD4A</i>	15	62391608	C	0.505	0.02	Morris et al. 2012
rs2302593	<i>QPCTL</i>	19	46196634	C	0.576	0.014	Scott et al. 2012
rs6072275	<i>TOPI</i>	20	39743905	A	0.070	0.016	Scott et al. 2012
rs6113722	<i>FOXA2</i>	20	22557099	G	0.900	0.035	Scott et al. 2012

FG=fasting glucose, SNP=single nucleotide polymorphism, CHR=chromosome, POS=position based on human genome 19, EAF=effect allele frequency based on global 1000Genomes. ^aproxy for rs560887, ^bproxy for rs11715915, ^cproxy for rs11717195, ^dproxy for rs13266634, ^eproxy for rs10885122, ^fproxy for rs576674, ^gproxy for rs4502156.

Supplemental Table S3. Genetic variants included in the FI polygenic score

SNP	Locus	CHR	POS	FI raising allele	EAF	β	Reference
rs2820436	<i>LYPLAL1</i>	1	219640680	C	0.643	0.015	Scott et al. 2012
rs10195252	<i>COBLL1</i>	2	165513091	T	0.603	0.016	Scott et al. 2012
rs1260326	<i>GCKR</i>	2	27730940	C	0.707	0.019	Saxena et al. 2010
rs7578326	<i>IRSI</i>	2	227020653	A	0.714	0.023	Voight et al. 2010
rs9884482	<i>TET2</i>	4	106081636	C	0.350	0.016	Scott et al. 2012
rs459193	<i>C5orf67</i>	5	55806751	G	0.606	0.014	Morris et al. 2012
rs4865796	<i>ARL15</i>	5	53272664	A	0.760	0.015	Mahajan et al. 2014
rs2745353	<i>RSPO3</i>	6	127452935	T	0.552	0.014	Scott et al. 2012
rs1167800	<i>HIP1</i>	7	75176196	A	0.686	0.016	Scott et al. 2012
rs4841132	<i>PPP1R3B</i>	8	9183596	A	0.093	0.03	Manning et al. 2012
rs983309	<i>PPP1R3B</i>	8	9177732	T	0.152	0.029	Scott et al. 2012
rs7903146	<i>TCF7L2</i>	10	114758349	C	0.772	0.018	Morris et al. 2012
rs731839	<i>PEPD</i>	19	33899065	G	0.460	0.014	Scott et al. 2012

FI=fasting insulin, SNP=single nucleotide polymorphism, CHR=chromosome, POS=position based on human genome 19, EAF=effect allele frequency based on global 1000Genomes.

Supplemental Table S4. Association of T2D polygenic score with glipizide and metformin endpoints in 639 white, non-Hispanic participants in SUGAR-MGH

	N	β (95% CI)	P
Glipizide endpoint*			
Glucose trough (mmol/L) [†]	436	-0.03 (-0.08, 0.01)	0.18
Glucose AOC (mmol/L*min)	435	12.20 (1.27, 23.13)	0.03
Time to glucose trough (min) [†]	436	-2.30 (-6.85, 2.25)	0.32
Slope to glucose trough (mmol/L/min) [†]	436	5.7e-4 (-2.1e-4, 1.4e-3)	0.15
Ln peak insulin (pmol/L) [‡]	427	0.04 (-0.02, 0.09)	0.19
Time to insulin peak (min) [‡]	427	-5.17 (-9.70, -0.65)	0.03
Slope to insulin peak (pmol/L/min) [‡]	423	-0.10 (-0.40, 0.19)	0.50
Metformin endpoint			
Fasting glucose V2-V1 (mmol/L) [†]	590	-0.004 (-0.04, 0.03)	0.56
Glucose AUC (mmol/L*min)	582	14.15 (1.07, 27.24)	0.03
Fasting insulin V2-V1 (pmol/L) [‡]	577	-1.64 (-5.17, 1.89)	0.36
Insulin AUC (pmol/L*min)	542	-204.97 (-2123.85, 1713.90)	0.83
Ln HOMA-IR V1 (mmol*pmol/L ²)	586	0.05 (-0.02, 0.12)	0.14
Ln HOMA-IR V2 (mmol*pmol/L ²)	586	0.02 (-0.05, 0.09)	0.54
HOMA-IR V2-V1 (mmol*pmol/L ²)	586	-0.75 (-1.70, 0.20)	0.12

V1=visit 1, V2=visit 2, AOC=area over the curve, AUC=area under the curve. *191 individuals did not meet the threshold to receive glipizide or terminated the glipizide challenge early and were excluded from analyses of glipizide response. [†]Adjusted for baseline glucose. [‡]Adjusted for ln baseline insulin. Linear regression model was adjusted for age, sex, race/ethnicity, and body mass index (BMI). A *p*-value of <0.008 reflects statistical significance after adjustment for multiple testing.

Supplemental Table S5. Association of T2D polygenic score with glipizide and metformin endpoints in 209 black, non-Hispanic participants in SUGAR-MGH

	N	β (95% CI)	P
Glipizide endpoint*			
Glucose trough (mmol/L) [†]	115	0.003 (-0.10, 0.10)	0.96
Glucose AOC (mmol/L*min)	112	3.58 (-17.24, 24.40)	0.73
Time to glucose trough (min) [†]	115	-14.04 (-25.43, -2.65)	0.01
Slope to glucose trough (mmol/L/min) [†]	115	1.7e-3 (-8.3e-6, 0.003)	0.05
Ln peak insulin (pmol/L) [‡]	104	0.13 (-0.002, 0.25)	0.05
Time to insulin peak (min) [‡]	104	-14.60 (-27.34, -1.85)	0.02
Slope to insulin peak (pmol/L/min) [‡]	102	-0.05 (-0.88, -0.12)	0.01
Metformin endpoint			
Fasting glucose V2-V1 (mmol/L) [†]	192	-0.06 (-0.13, 0.02)	0.13
Glucose AUC (mmol/L*min)	183	-0.12 (-20.28, 20.04)	0.99
Fasting insulin V2-V1 (pmol/L) [‡]	180	-10.62 (-24.24, 2.99)	0.13
Insulin AUC (pmol/L*min)	169	-371.60 (-5059.66, 4316.37)	0.88
Ln HOMA-IR V1 (mmol*pmol/L ²)	190	0.008 (-0.13, 0.15)	0.91
Ln HOMA-IR V2 (mmol*pmol/L ²)	189	-0.07 (-0.23, 0.09)	0.41
HOMA-IR V2-V1 (mmol*pmol/L ²)	189	-2.21 (-5.31, 0.90)	0.16

V1=visit 1, V2=visit 2, AOC=area over the curve, AUC=area under the curve. *96 individuals did not meet the threshold to receive glipizide or terminated the glipizide challenge early and were excluded from analyses of glipizide response. [†]Adjusted for baseline glucose. [‡]Adjusted for ln baseline insulin. Linear regression model was adjusted for age, sex, race/ethnicity, and body mass index (BMI). A *p*-value of <0.008 reflects statistical significance after adjustment for multiple testing.

Supplemental Table S6. Association of FG polygenic score with glipizide and metformin endpoints in SUGAR-MGH

	N	β (95% CI)	P
Glipizide endpoint*			
Glucose trough (mmol/L) [†]	639	0.01 (-0.03, 0.05)	0.53
Glucose AOC (mmol/L*min)	633	10.82 (1.42, 20.22)	0.02
Time to glucose trough (min) [†]	639	3.12 (-1.09, 7.33)	0.15
Slope to glucose trough (mmol/L/min) [†]	638	-2.3e-4 (-9.2e-4, 4.6e-4)	0.51
Ln peak insulin (pmol/L) [‡]	615	-5.1e-4 (-0.05, 0.05)	0.98
Time to insulin peak (min) [‡]	615	4.05 (-0.26, 8.35)	0.07
Slope to insulin peak (pmol/L/min) [‡]	609	0.005 (-0.23, 0.24)	0.96
Metformin endpoint			
Fasting glucose V2-V1 (mmol/L) [†]	924	0.02 (-0.01, 0.05)	0.24
Glucose AUC (mmol/L*min)	900	4.22 (-5.79, 14.22)	0.41
Fasting insulin V2-V1 (pmol/L) [‡]	891	-3.11 (-6.77, 0.55)	0.10
Insulin AUC (pmol/L*min)	831	371.72 (-1742.16, 2485.60)	0.73
Ln HOMA-IR V1 (mmol*pmol/L ²)	915	0.03 (-0.02, 0.09)	0.27
Ln HOMA-IR V2 (mmol*pmol/L ²)	914	-0.004 (-0.06, 0.06)	0.90
HOMA-IR V2-V1 (mmol*pmol/L ²)	914	-0.85 (-1.75, 0.05)	0.06

V1=visit 1, V2=visit 2, AOC=area over the curve, AUC=area under the curve. *351 individuals did not meet the threshold to receive glipizide or terminated the glipizide challenge early and were excluded from analyses of glipizide response. [†]Adjusted for baseline glucose. [‡]Adjusted for ln baseline insulin. Linear regression model was adjusted for age, sex, race/ethnicity, and body mass index (BMI). A *p*-value of <0.008 reflects statistical significance after adjustment for multiple testing.

Supplemental Table S7. Association of FI polygenic score with glipizide and metformin endpoints in SUGAR-MGH

	N	β (95% CI)	P
Glipizide endpoint*			
Glucose trough (mmol/L) [†]	639	0.05 (0.007, 0.08)	0.02
Glucose AOC (mmol/L*min)	633	-0.78 (-9.93, 8.38)	0.87
Time to glucose trough (min) [†]	639	1.38 (-2.65, 5.40)	0.50
Slope to glucose trough (mmol/L/min) [†]	638	-3.8e-4 (-1.0e-3, 2.7e-4)	0.25
Ln peak insulin (pmol/L) [‡]	615	-0.004 (-0.05, 0.05)	0.87
Time to insulin peak (min) [‡]	615	1.63 (-2.62, 5.88)	0.45
Slope to insulin peak (pmol/L/min) [‡]	609	0.04 (-0.19, 0.27)	0.73
Metformin endpoint			
Fasting glucose V2-V1 (mmol/L) [†]	924	0.02 (-0.01, 0.05)	0.25
Glucose AUC (mmol/L*min)	900	-0.68 (-10.51, 9.14)	0.89
Fasting insulin V2-V1 (pmol/L) [‡]	891	-1.67 (-5.30, 1.96)	0.37
Insulin AUC (pmol/L*min)	831	968.00 (-1134.82, 3070.73)	0.37
Ln HOMA-IR V1 (mmol*pmol/L ²)	915	0.05 (-0.008, 0.10)	0.09
Ln HOMA-IR V2 (mmol*pmol/L ²)	914	0.01 (-0.05, 0.07)	0.68
HOMA-IR V2-V1 (mmol*pmol/L ²)	914	-0.59 (-1.47, 0.29)	0.19

V1=visit 1, V2=visit 2, AOC=area over the curve, AUC=area under the curve. *351 individuals did not meet the threshold to receive glipizide or terminated the glipizide challenge early and were excluded from analyses of glipizide response. [†]Adjusted for baseline glucose. [‡]Adjusted for ln baseline insulin. Linear regression model was adjusted for age, sex, race/ethnicity, and body mass index (BMI). A *p*-value of <0.008 reflects statistical significance after adjustment for multiple testing.