Lifestyle and metformin ameliorate insulin sensitivity independently of the genetic burden of established insulin resistance variants in Diabetes Prevention Program participants


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Tables= 2; Figure= 1

**Short Running Title:** Genetics of insulin resistance in DPP

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Abstract

Genome-wide association studies of glycemic traits have identified genetics variants that are associated with insulin resistance (IR) in the general population. It is unknown if people with genetic enrichment for these IR-variants respond differently to interventions that aim to improve insulin sensitivity. We built a genetic risk score based on 17 established IR-variants and their effect sizes (weighted IR-GRS) in 2,713 participants of the Diabetes Prevention Program (DPP) with genetic consent. We tested associations between the weighted IR-GRS and insulin sensitivity index (ISI) at baseline in all participants, and with change in ISI over 1-year of follow-up in DPP intervention (metformin and lifestyle) and control (placebo) arms. All models were adjusted for age, sex, ethnicity, and waist circumference at baseline (plus baseline ISI for 1-year ISI change models). A higher IR-GRS was associated with lower baseline ISI (β= -0.754 [SE=0.229] log-ISI per unit; P=0.001 in fully adjusted models). There was no differential effect of treatment for the association between IR-GRS on change in ISI; higher IR-GRS was associated with attenuation in ISI improvement over 1 year (β= -0.520 [SE=0.233]; P=0.03 in fully adjusted models; all treatment arms). Lifestyle intervention and metformin improved ISI, regardless of the genetic burden of IR-variants.
Introduction

Genome-wide association studies (GWAS) have yielded the identities of almost 100 common genetic variants associated with type 2 diabetes and glycemic traits. Though most of these variants are associated with beta-cell dysfunction, a concerted search for genetic associations with measures of insulin resistance (IR) has identified 19 single nucleotide polymorphisms (SNPs) that have reached genome-wide levels of significance for association with fasting insulin, as a proxy for IR, in large population-based studies. It is unknown whether these SNPs predict changes over time in IR in the context of interventions designed to ameliorate IR.

The Diabetes Prevention Program (DPP), a randomized controlled trial (RCT) of metformin and lifestyle versus placebo/control, showed large beneficial effects on IR. We constructed a genetic risk score (GRS) that was comprised of known IR-associated variants and tested if it was associated with IR at baseline in DPP participants and with change in IR over 1-year, accounting for potential interactions between the IR-GRS and treatment.

Methods:

Description of participants

The DPP study design and characteristics of the participants at baseline have been described in detail previously. In brief, the DPP was a US multicenter trial (27 centers) that tested intensive lifestyle modification and pharmacologic intervention to prevent progression to diabetes in glucose intolerant individuals. Enrolled participants had fasting plasma glucose between 95-125 mg/dL (5.3-6.9 mmol/L) and 2-hour plasma glucose between 140-199 mg/dL (7.8-11.0...
mmol/L) during a standard 75-gram oral glucose tolerance test (OGTT). A total of 3,234 participants were randomized to intensive lifestyle modification (goal >7% weight loss and >150 min/week of physical activity); metformin (850 mg twice daily); or placebo. The primary endpoint of the DPP was diabetes incidence. The diagnosis of diabetes was defined according to American Diabetes Association guidelines as a fasting glucose above ≥126 mg/dL or 2-h glucose ≥200 mg/dL during the OGTT, which were confirmed on a second test within 6 weeks.(10)

IRB approval was obtained at each clinical center and the coordinating center. The 2,713 participants included in this report provided written informed consent for the main study and for subsequent genetic investigations.

**Measurements at baseline and 1-year**

Demographics were collected at baseline; 95% of participants completed the 1-year follow-up. We derived glycemic regulation indices from validated equations based on glucose and insulin levels during the OGTT at baseline and 1-year follow-up. Participants did not take metformin/placebo on the morning of the OGTT. Methods for glucose and insulin assays are described elsewhere.(9) For our primary insulin sensitivity outcome, we calculated the insulin sensitivity index (ISI) as the reciprocal of HOMA insulin resistance (HOMA-IR), determined as 22.5/[(fasting insulin × fasting glucose)/18.01].(11) We estimated the insulin response by the insulinogenic index using the formula [(insulin at 30 min)-(insulin at 0 min)] / [(glucose at 30 min)-(glucose at 0 min)].(12) The oral disposition index was calculated using the formula [insulinogenic index/fastig insulin].(13) We also calculated the change in insulin sensitivity over time (ISI at 1-year – ISI at baseline). We chose 1-year because weight loss in intervention arms
was the most pronounced at that time point, and to evaluate ISI changes with the largest sample size for longitudinal analyses.

*Genotyping*

We extracted DNA from peripheral blood leukocytes. Genotyping was performed on the customized Metabochip (Illumina, San Diego, CA), containing ~200K SNPs chosen based on previous GWAS meta-analyses of 23 metabolic traits related to T2D, obesity and/or cardiovascular diseases. We excluded study participants with gender inconsistency or familial relatedness. We excluded SNPs with a call rate <95% or if they failed Hardy-Weinberg equilibrium ($P<1.0 \times 10^{-7}$) within each ethnic group. The overall genotyping success rate was >99.85%.

*Selection of the variants associated with insulin resistance (Table 1)*

We identified 19 variants that had been associated with fasting insulin (FI) at the accepted level of genome-wide significance ($P<5 \times 10^{-8}$) in GWAS previously published by MAGIC investigators. (5-7) We did not include *TCF7L2*, as the association of the T2D risk allele with lower FI is considered to be an artifact of ascertainment driven by the determination of this association in non-diabetic persons (i.e. carriers of the T2D risk allele have an associated reduction in beta-cell function that must be compensated by greater insulin sensitivity in order to remain diabetes-free, as observed at baseline in DPP participants and in other studies including non-diabetic population). (2) We built the GRS with and without *FTO*, as its effect on diabetes-related traits occurs mainly via its effect on adiposity; results were essentially the same, so we decided to present our main analyses using a IR-GRS including 17 SNPs primarily discovered as representing IR based on MAGIC reports (not including *FTO*).
Building the IR-GRS score

We computed the GRS based on the assumption of an additive genetic effect, and using published effect size on log-FI per risk allele (adjusted for age, sex, and BMI) based on MAGIC publicly available data (http://www.magicinvestigators.org/downloads/). Each subject was assigned an aggregate GRS based on the number of risk alleles × effect size for the respective 17 SNPs under investigation. We excluded 281 individuals with >3 missing SNPs. For participants with 1, 2, or 3 missing SNPs (total 120 individuals), we calculated their GRS by multiplying the GRS from the available SNPs by 34 and dividing by twice the number of successfully genotyped SNPs.

Statistical analyses

We present qualitative characteristics as frequency (percentage) and continuous variables as mean ± standard deviation (SD), if normally distributed, or as median with interquartile ranges (IQR), otherwise. We log-transformed ISI to achieve normal distribution. We used linear regression models to estimate the association of IR-GRS with baseline ISI and 1-year change in ISI, after adjusting for age, sex, ethnicity, and waist circumference (we included waist circumference because it is the anthropometric measure most strongly associated with outcomes in DPP(14) and based on our experience from previously conducted genetic analyses in DPP(15)). We further adjusted the 1-year change in ISI model for the baseline ISI, treatment group, and change in waist circumference. We used proportional hazards regression to estimate the effect of IR-GRS on the risk of developing diabetes, after adjusting for baseline covariates. We also checked for interaction effects between treatment and GRS. Furthermore, for easier interpretation
and illustration, we computed tertiles of IR-GRS and conducted the same analyses as with using GRS as a continuous variable; we presented participants baseline characteristics in each tertile and we assessed differences between tertiles groups using analysis of variance (ANOVA) for continuous variables with symmetric distributions, the non-parametric Kruskal-Wallis test for continuous variables with skewed distributions, and chi-square tests for categorical variables. We conducted sensitivity analyses in white participants only. All tests performed are two-sided and an alpha level of 0.05 was used to determine statistical significance. The Statistical Analysis Software (SAS) version 9.3 was used for all analyses (SAS Institute, Inc., Cary, NC).

Results:
The 2,713 DPP participants analyzed in this study were 50.7 ± 10.7 (mean ± SD) years old; 67% were women, and 45% were non-white. At baseline, BMI was 34.1 ± 6.7 (mean ± SD) kg/m² and waist circumference was 105.4 ± 14.6 cm (mean ± SD). Based on the selected 17 known IR genetic variants and their published effect size on FI (Table 1), the mean weighted IR-GRS was 0.34 ± 0.05 in the DPP population.

The baseline characteristics of DPP participants in each tertile of IR-GRS are shown in Table 2. Individuals in the lowest tertile of IR-GRS were less likely to be white and more likely to be African American than those in the highest tertile; they also had a higher BMI and waist circumference. A higher IR-GRS was associated with lower baseline insulin sensitivity ($\beta=-0.754$ log-ISI per GRS unit increase; SE=0.229; $P=0.001$) after adjustment for age, sex, ethnicity, and baseline waist circumference.
We evaluated the association between the IR-GRS and change in insulin sensitivity over the first year of the trial (Figure 1). The interaction between treatment arms (placebo/metformin/lifestyle) and the effect of IR-GRS on 1-year change in ISI was not significant ($P=0.98$), so we analyzed all participants together including treatment assignment as a covariate in the models. A higher IR-GRS was associated with attenuation or lack of improvement in insulin sensitivity over 1 year after adjustment for treatment arm, age, sex, ethnicity, and baseline ISI and waist ($\beta=-0.520$ change in log-ISI per GRS unit increase; SE=0.233; $P=0.03$); this association remained significant after we further adjusted for change in waist circumference over the first year ($\beta=-0.456$ change in log-ISI per GRS unit increase; SE=0.220; $P=0.04$). In subsidiary analyses of an IR-GRS that also included the $FTO$ risk variant at rs9939609, we found essentially the same results.

We also evaluated the association between IR-GRS and diabetes incidence over the course of the main trial (mean follow-up= 3.2 years). We found no significant association after adjusting for treatment arms, age, sex, ethnicity, and baseline waist circumference (HR=3.52 per GRS unit increase; 95% CI = (0.51, 24.52); $P=0.20$).

In our sensitivity analyses in white DPP participants only, the mean weighted IR-GRS was $0.35 \pm 0.04$. We found consistent associations with ISI in multivariable adjusted models: higher IR-GRS was associated with lower baseline insulin sensitivity ($\beta=-1.065$ log-ISI per GRS unit increase; SE=0.294; $P=0.0003$), and with attenuation or lack of improvement in insulin sensitivity over 1 year ($\beta=-0.800$ change in log-ISI per GRS unit increase; SE=0.299; $P=0.008$). We found no association of the IR-GRS with diabetes incidence.
Discussion

Lifestyle and metformin treatments during the DPP produced great improvement in insulin sensitivity, especially over the first year. This improvement in insulin sensitivity was associated with reduction of the risk of developing diabetes overall and in each treatment arm. This is concordant with other diabetes prevention RCTs showing that improvement in insulin sensitivity induced by lifestyle intervention is a strong predictor of risk reduction in diabetes. In the current report, we showed that DPP participants carrying a higher genetic burden for IR were indeed less insulin sensitive at baseline, and less likely to improve indices of insulin sensitivity at 1-year after taking into account adiposity and demographic characteristics. More importantly, we showed that lifestyle and metformin treatment improved insulin sensitivity independently of the genetic burden of the participants. Taken together, this means that among high-risk populations, a genetic risk score can predict who is likely to become more insulin resistant over time, but that treatment by either metformin or lifestyle modification can significantly improve their insulin sensitivity independent of their IR genetic burden.

A higher IR-GRS was associated with less improvement in ISI independent of waist circumference change over 1-year in our study; change in weight was correlated with change in IR, and both change in weight and change in ISI were independently correlated with diabetes incidence in each treatment arm. We have previously shown that a GRS derived from established T2D variants predict diabetes incidence in DPP participants, in contrast our IR-GRS was not associated with diabetes incidence in the current analyses. This may be because contributions of these genetic variants to diabetes risk in the DPP are below the level that can be
detected in this population; further, the majority of risk alleles at loci associated directly with FI are not associated with T2D in large population-based studies. (5-7) Our results are in keeping with the critical role of the beta cell in the pathogenesis of type 2 diabetes(18) and the greater predictive power of loci identified to be associated with beta-cell responses.(19) Indeed, in Framingham Heart Study and CARDIA population-based studies, a GRS based on T2D risk alleles representing IR pathways was not associated with diabetes incidence, while a similar score based on genes potentially affecting beta-cell function was significantly associated with diabetes over >25 years of follow-up.(19)

We observed a counterintuitive association of our IR-GRS with lower adiposity at baseline that is likely driven by the constraint on ascertainment induced by enrolling DPP participants within a narrow range of glycemia, as those with a greater degree of genetically-influenced IR must be protected by other features lest they develop diabetes and not be eligible for enrollment. We also noted a difference in the ethnic composition of each tertile of IR-GRS; putative ethnic differences in the genetic architecture of insulin secretion and sensitivity merit further exploration. Our sensitivity analyses in white participants gave similar results, but smaller samples size in other ethnic groups limited our ability to conduct analyses in each specific ethnicity represented in the DPP.

Our study is strengthened by its standardized measurements of anthropometry and of insulin sensitivity indices at baseline and over time, and that we assess genetics of IR in the context of interventions shown to improve insulin sensitivity that are clinically recommended. We acknowledge that the gold standard for IR measurement is the euglycemic-hyperinsulinemic
clamp, and that dynamic measurements obtained from multi-point OGTTs not available in DPP; our results might have been different if we had access to such measures. Power was limited by our sample size, especially in each treatment arm and for interaction testing. (20)

**Conclusion:** We demonstrated that a GRS informed by prior knowledge of established genetic determinants of IR in population-based studies was associated with IR at baseline and change in IR in DPP participants. Of high clinical importance, we showed that metformin and lifestyle improve insulin sensitivity independent of the IR genetic burden estimated based on current knowledge. Other genetic markers might predict intervention response, but these are challenging to detect with current methods and statistical approaches: thus novel approaches are necessary to reveal genetic predictors of response to diabetes preventive interventions to overcome the issue of limited power related to the relatively small sample size included in intervention trials.
**Author Contributions:** MFH wrote the manuscript, conceived analytic plans, and lead interpretation of results; WCK and JCF conceived the study design; CAC and KAJ conducted statistical analyses; all authors contributed to interpretation of results, edited and reviewed manuscript before submission. JCF is the guarantor of this work and, as such, had full access to all 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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views of the funding agencies. A complete list of Centers, investigators, and staff can be found in the Appendix.

**Disclosure Statement:** The authors have no relevant dualities of interest to declare.
References:


15. Hivert MF, Jablonski KA, Perreault L, et al. Updated genetic score based on 34 confirmed type 2 diabetes loci is associated with diabetes incidence and regression


Table 1: Frequencies of genetic variants associated with fasting insulin in previous MAGIC reports (European Descent) and in DPP participants – overall and by ethnic groups

<table>
<thead>
<tr>
<th>Putative genes</th>
<th>SNP</th>
<th>Risk allele based on MAGIC</th>
<th>Risk allele frequency MAGIC</th>
<th>Frequency DPP Overall</th>
<th>Frequency DPP Whites</th>
<th>Frequency DPP African Am</th>
<th>Frequency DPP Hispanic</th>
<th>Frequency DPP Asian/Pac Island</th>
<th>Frequency DPP American Indian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>COBLL1/GRB14</td>
<td>rs7607980</td>
<td>T</td>
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<td>88</td>
<td>85</td>
<td>89</td>
<td>98</td>
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<td>IRS1</td>
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<td>68</td>
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<td>8</td>
<td>12</td>
<td>22</td>
<td>6</td>
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<td>UHRF1BP1</td>
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<td>T</td>
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<td>67</td>
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<td>85</td>
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<td>66</td>
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<td>91</td>
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<td>39</td>
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<td>45</td>
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<td>53</td>
<td>43</td>
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</table>

Total number of DPP participants: 2713
IR-GRS mean (SD): 20.2 (2.8)
Table 2: Characteristics of Diabetes Prevention Program (DPP) participants at baseline by tertile of insulin resistance genetic risk score (IR-GRS)

<table>
<thead>
<tr>
<th></th>
<th>Tertile 1 (N=1070)</th>
<th>Tertile 2 (n=768)</th>
<th>Tertile 3 (n=875)</th>
<th>P-value</th>
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<td>IR-GRS</td>
<td>17.5 ± 1.5</td>
<td>20.5 ± 0.5</td>
<td>23.3 ± 1.4</td>
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<td>Demographic</td>
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<td>Age (years)</td>
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<td>50.5 ± 10.5</td>
<td>50.3 ± 11.0</td>
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<td>519 (48.5%)</td>
<td>433 (56.4%)</td>
<td>551 (63.0%)</td>
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<tr>
<td>% African Am</td>
<td>359 (33.6%)</td>
<td>139 (18.1%)</td>
<td>56 (6.4%)</td>
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<td>% Hispanic</td>
<td>148 (13.8%)</td>
<td>139 (18.1%)</td>
<td>171 (19.5%)</td>
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<td>% Asian</td>
<td>35 (3.3%)</td>
<td>39 (5.1%)</td>
<td>46 (5.3%)</td>
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<td>% American Indian</td>
<td>9 (0.8%)</td>
<td>18 (2.3%)</td>
<td>51 (5.8%)</td>
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<td>Sex</td>
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<td>% Male</td>
<td>346 (32.3%)</td>
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<td>% Female</td>
<td>724 (67.7%)</td>
<td>523 (68.1%)</td>
<td>580 (66.3%)</td>
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<td>Weight (kg)</td>
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<td>BMI (kg/m2)</td>
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<td>Waist (cm)</td>
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<td>104.8 ± 14.7</td>
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<td>Glycemic regulation</td>
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<tr>
<td>Fasting glucose (mg/dl)</td>
<td>106.7 ± 8.1</td>
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<td>106.6 ± 8.3</td>
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<td>[0.11 , 0.24]</td>
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<tr>
<td>HOMA IR</td>
<td>5.98</td>
<td>6.35</td>
<td>6.35</td>
<td>0.15</td>
</tr>
<tr>
<td>[4.24 , 8.81]</td>
<td>[4.37 , 9.07]</td>
<td>[4.22 , 9.06]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>124.8 ± 97.6</td>
<td>122.9 ± 87.5</td>
<td>127.1 ± 92.2</td>
<td>0.66</td>
</tr>
<tr>
<td>Proinsulin/Insulin ratio</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
<td>0.56</td>
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<tr>
<td>[0.13 , 0.24]</td>
<td>[0.13 , 0.23]</td>
<td>[0.13 , 0.24]</td>
<td></td>
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<tr>
<td>Oral disposition index</td>
<td>4.51</td>
<td>4.37</td>
<td>4.35</td>
<td>0.16</td>
</tr>
<tr>
<td>[3.06 , 6.78]</td>
<td>[2.91 , 6.38]</td>
<td>[2.95 , 6.47]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: BMI = body mass index; ISI = Insulin sensitivity index; HOMA-IR = homeostasis model for insulin resistance.

Data are mean±SD or median [IQR] for continuous variables and frequency (%) for categorical variables.
Figure 1: Change in insulin sensitivity index (ISI) over 1 year DPP participant in each arm according to tertile of genetic risk score for insulin resistance (IR-GRS)

Legend: all values are adjusted for baseline ISI, age, sex, ethnicity, and waist circumference at baseline. The Y-axis represents change in ISI (ln-transformed; with SE) over the first year of DPP. $P$-value for interaction treatment*IR-GRS per tertile = 0.97.
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