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Association of a Type 2 Diabetes Genetic Risk Score with Insulin Secretion Modulated by Insulin Sensitivity among Chinese Hans

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Abstract

Type 2 diabetes (T2D) is characterized by insulin resistance and impaired insulin secretion. The present study aimed to identify the influence of insulin sensitivity on the genetic risk of impaired insulin secretion among a Chinese Han population. For 3,229 controls and 1,994 treatment naïve T2D, single nucleotide polymorphisms (SNPs) from 24 T2D-related genomic loci were genotyped and a genetic risk score (GRS) was constructed. Results showed that GRS was associated with insulin secretion and disposition indices in both controls and treatment naïve T2Ds. Upon stratifying the participants into tertiles by the Matsuda index, we observed an inhibitory relationship between the GRS and insulin secretion in low insulin sensitive but not in high insulin sensitive controls and treatment naïve T2Ds. Moreover, low insulin sensitive individuals exhibited more severe impairment in insulin secretion and beta cell response to insulin sensitivity with an increase in risk alleles. Our findings identified that the association of GRS with insulin secretion was strongly modulated by insulin sensitivity in both controls and T2Ds of Chinese Han. It indicates that insulin sensitization should be emphasized in prevention and treatment of T2D for beta cell protection.

Graphical Abstract

The present study aimed to identify the influence of insulin sensitivity on the genetic risk of impaired insulin secretion among a Chinese Han population. Results showed that GRS was associated with insulin secretion and disposition indices in both controls and treatment naïve type 2 diabetes (T2D) patients. Upon stratifying the participants into tertiles by the Matsuda index, we

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observed an inhibitory relationship between the GRS and insulin secretion in low insulin sensitive but not in high insulin sensitive controls and treatment naïve T2Ds. Low insulin sensitive individuals exhibited more severe impairment in insulin secretion and beta cell response to insulin sensitivity with an increase in risk alleles. It indicates that insulin sensitization should be emphasized in prevention and treatment of T2D for beta cell protection in Chinese Hans.

Keywords

Genetics of type 2 diabetes; Insulin secretion in vivo; Insulin sensitivity and resistance; Single nucleotide polymorphism

Introduction

The prevalence of diabetes in China has increased dramatically in recent decades. The Chinese National Diabetes and Metabolic Disorders Study (DMS) conducted in 2007–2008 reported a prevalence of diabetes in China of 9.7% among adults, and more than 90% of the affect individuals had type 2 diabetes (T2D)(1).

T2D is characterized by insulin resistance and impaired insulin secretion. The relative importance of these two components has been debated. Most studies have suggested that insulin resistance is the primary abnormality that induces beta cell dysfunction, whereas others proposed that defective beta cell function is a prerequisite for diabetes progression(2, 3). Despite this unsettled question, several studies have shown a hyperbolic relationship between insulin sensitivity and insulin secretion in the development of hyperglycemia(4). Moreover, ethnic discrepancies exist in the pathophysiology and clinical characteristics of T2D(5). In East Asians, T2D patients exhibit earlier beta cell dysfunction and less insulin resistance than Caucasian T2D patients, which suggests that the preservation of beta cell function should be especially emphasized in their management.

The pathogenesis of T2D is influenced by both the genetic makeup of an individual and the environment. Genome-wide association studies (GWAS) employing high-throughput technologies and primarily involving Caucasian patients have identified more than 120 T2D-related genomic loci, and most have been shown to significantly contribute to beta cell function(6). Interestingly, a previous study conducted in a non-diabetic Caucasian population using both oral and intravenous glucose tolerance tests revealed that an increase in risk allele summation for eight genetic loci, including *TCF7L2*, *CDKAL1*, *HHEX*, *SLC30A8*, *IGF2BP2*, *CDKN2A/2B*, *JAZF1*, and *WFS1*, was associated with a decline in insulin secretion in participants with low insulin sensitivity, whereas this was not seen in participants with high insulin sensitivity(7). The authors proposed that effective compensatory mechanisms could exist in individuals with high sensitivity that limited the inhibitory impact of the risk alleles on insulin secretion. However, whether insulin sensitivity can modulate the inhibitory effect of these genetic loci on insulin secretion in T2D patients has not been tested. In addition, these findings have not been replicated in a different population or ethnicity. Considering that the Chinese have vulnerable beta cell function, clarifying the influence of insulin sensitivity on the genetic determinants of insulin secretion is of clinical significance for both the prevention of T2D in non-diabetic controls

and the management of T2D and preservation of beta cell function in patients of Chinese ancestry.

In the present study, we examined the association of a genetic risk score (GRS) constructed using 24 single nucleotide polymorphisms (SNPs) in established T2D-related genomic loci with insulin secretion in both normoglycemic controls and treatment naïve T2D patients of Chinese ancestry from the DMS. Furthermore, we stratified the participants by insulin sensitivity and elucidated the influence of insulin sensitivity on the genetic risk in determinants of insulin secretion.

Materials and Methods

Study participants

All study participants were enrolled in the DMS(1). At enrollment, each participant completed a 75-g OGTT after overnight fasting. T2D cases were identified according to the 1999 WHO criteria of a fasting plasma glucose (FPG) ≥ 7.0 mmol/l, a 2-h plasma glucose ≥ 11.1 mmol/l, or a self-reported history of T2D. In total, there're 3,032 T2D patients and 3,229 normoglycemic individuals from the DMS with complete data sets for genotype, glucose measurements, and insulin measurements. To eliminate the potential effect of hypoglycemic treatments, we only included the treatment naïve T2D patients (n = 1,994) from the 3,032 T2D patients to conduct the analyses.

The study protocol was approved by the Ethics Committee of the China-Japan Friendship Hospital in Beijing, and the study was conducted in accordance with the Declaration of Helsinki II. Written informed consent was obtained from all participants prior to data collection.

Clinical measurements and laboratory methods

Body weight, height, waist circumference, and hip circumference were measured using standard methods. Body mass index (BMI) was calculated as weight/height² (kg/m²). Waist-hip-ratio (WHR) was calculated. Blood samples were obtained at 0 min, 30 min, and 2 h during the oral glucose tolerance test (OGTT) for measurement of plasma glucose and serum insulin concentrations. Serum insulin was measured by RIA.

The trapezoid method was used to calculate the glucose area under the curve (AUC) and insulin AUC during OGTT at 30 min and 120 min (GluAUC₃₀, GluAUC₁₂₀, InsAUC₃₀, and InsAUC₁₂₀)(8). The homeostasis model assessment for beta cell function (HOMA-B) and insulinogenic indices were calculated to estimate beta cell function. The homeostasis model assessment for insulin resistance (HOMA-IR) and Matsuda index (ISIm) were used to assess insulin sensitivity. Two disposition indices (DI), DI₃₀ and DI₁₂₀, were calculated as the measures of the beta cell response to insulin sensitivity. An oral DI was calculated. The formulae were as follows:

$$\text{HOMA-B} = \text{fasting serum insulin (mU/l)} \times 20 / [\text{FPG (mmol/l)} - 3.5](9)$$

$$\text{Insulinogenic index} = [\text{serum insulin at 30 min (mU/l)} - \text{fasting serum insulin (mU/l)}] / [\text{plasma glucose at 30 min (mmol/l)} - \text{FPG (mmol/l)}](10)$$

$$\text{HOMA-IR} = \text{fasting serum insulin (mU/l)} \times \text{FPG (mmol/l)} / 22.5(9)$$

$$\text{ISIm} = 10,000 / [\text{FPG (mg/dl)} \times \text{fasting serum insulin (mU/l)} \times \text{mean OGTT glucose (mg/dl)} \times \text{mean OGTT insulin (mU/l)}]^{1/2} (11)$$

$$\text{DI}_{30} = \text{ISIm} \times \text{InsAUC}_{30} / \text{GluAUC}_{30}(8)$$

$$\text{DI}_{120} = \text{ISIm} \times \text{InsAUC}_{120} / \text{GluAUC}_{120}(8)$$

$$\text{Oral DI} = \text{Insulinogenic index} / \text{HOMA-IR}(12)$$

Clinical characteristics of the study population

The clinical characteristics of the study population are shown in Table S1. The hypoglycemic treatment naïve T2Ds showed worse glucose tolerance than normoglycemic individuals, along with elevated fasting and 2-h OGTT serum insulin levels and a reduced 30-min insulin level (all $P < 1.00 \times 10^{-4}$). As expected, the treatment naïve T2Ds had greater beta cell dysfunction (assessed by insulinogenic index, HOMA-B, InsAUC₃₀/GluAUC₃₀, and InsAUC₁₂₀/GluAUC₁₂₀), lower insulin sensitivity (assessed by ISIm and HOMA-IR), and impaired beta cell response to insulin sensitivity (assessed by DI₃₀, DI₁₂₀, and oral DI; all $P < 1.00 \times 10^{-4}$).

Definition of high and low insulin sensitivity in controls and treatment naïve T2D patients

The normoglycemic controls were divided into tertiles according to the ISIm (group 1: ISIm < 6.917; group 2: 6.917 < ISIm < 10.142; group 3: ISIm > 10.142), and the treatment naïve T2D patients were as well (group 1: ISIm < 3.190; group 2: 3.190 < ISIm < 5.170; group 3: ISIm > 5.170). Groups 1 and 3 of controls and treatment naïve T2D patients were defined as participants with low and high insulin sensitivity, respectively.

Genotyping

Genomic DNA was isolated from peripheral blood samples using a DNA extraction kit (BioTeke Corporation, Beijing, China). Twenty-five T2D-related SNPs from 24 genomic loci validated by previous GWAS(13–25) were selected and genotyped successfully using the Illumina GoldenGate Indexing assay (Illumina Inc., San Diego, CA, USA) according to the manufacturer's instructions. The overall mean calling rate of the SNPs in the present population was 100%. The concordance rate based on 229 genotyping duplication was 100%. Only individuals with complete genotype data were included in the current study. Detailed information for the genotyped SNPs is provided in Table S2. The intronic SNPs in *FTO*, rs8050136 and rs9939609, located in the same linkage disequilibrium block. Thus, only rs8050136 was used to calculate the GRS in the analysis.

Statistical analysis

The Hardy-Weinberg equilibrium of each SNP among the study population was tested using a χ^2 test (Table S2). All of the SNPs adhered to Hardy-Weinberg equilibrium in controls of the study population ($P > 2.00 \times 10^{-3}$). The minor allele frequencies (MAFs) of the genotyped SNPs in the present study were close to those reported for a Han Chinese population from Beijing in the HapMap project (Table S2).

Prior to further analysis, non-Gaussian distributed quantitative traits were natural logarithmically transformed to normal distributions, and a GRS based on the genotyped 24 SNPs was constructed using the sum of the reported risk alleles for T2D in each participant (7, 26). Under an additive genetic assumption, a linear regression model was used to test the associations of T2D GRS with the metabolic indices when appropriate. Four multivariable models were tested: model 1, in which age and sex were adjusted as co-variables; model 2, in which age, sex, and BMI were adjusted; model 3, in which age, sex and ISIm were adjusted (except for HOMA-IR and ISIm); and model 4, in which age, sex, BMI, and ISIm were adjusted (except for HOMA-IR and ISIm). Interaction between the GRS and ISIm was assessed in models 3 and 4. Controls and treatment naïve T2Ds were divided into five groups by GRS respectively (controls: 19, 20~21, 22~23, 24~25, 26; treatment naïve T2Ds: 20, 21~22, 23~24, 25~26, 27), and each trait was compared among the GRS groups using ANOVA. In addition, a weighted GRS based on the SNPs' reported effective size on risk for T2D from GWAS of East Asians (Table S2)(27) were conducted, and were included in appropriate analyses (Table S3–S5).

Bonferroni correction was used to correct multiple comparisons. *P* values less than 3.33×10^{-3} (0.05/15) were considered statistically significant. Statistical analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC) and PLINK software (v1.05; <http://pngu.mgh.harvard.edu/purcell/plink>).

Power calculation

The present sample sizes of controls ($n = 3,229$) and treatment naïve T2D ($n = 1,994$) had 80% power to detect the associations between GRS and the insulin secretion-related indices of an effect size of 0.10 based on the five GRS groups using F test (one-way ANOVA) at $\alpha = 0.05$, respectively. Power calculation was performed using PASS software (version 11.0, NCSS).

Results

Association of T2D GRS with glycemia-related traits, insulin sensitivity, and insulin secretion in Chinese Hans

As shown in Table 1, a higher T2D GRS was found to be associated with increased fasting and 30-min OGTT glucose levels in controls, and this link was not greatly altered upon additional adjustment for BMI and/or ISIm.

A high GRS contributed to a reduced 30-min OGTT insulin level in controls and was related to the reduced fasting, 30-min, and 2-h OGTT insulin levels in treatment naïve T2D patients. The associations of GRS with the fasting and 2-h insulin level in T2D patients diminished after ISIm adjustment.

We identified that both normoglycemic and treatment naïve T2D individuals with a higher GRS tended to have impaired insulin secretion (assessed by insulinogenic index, $\text{InsAUC}_{30}/\text{GluAUC}_{30}$, $\text{InsAUC}_{120}/\text{GluAUC}_{120}$). Additionally, the higher GRS contributed to an impaired beta cell response to insulin sensitivity (assessed by oral DI, DI_{30} , and DI_{120}) in normoglycemic controls, whereas a higher GRS was associated with a reduced HOMA-B

and a better insulin sensitivity (assessed by ISIm) in treatment naïve T2D patients. The associations of GRS with insulinogenic index and HOMA-B in diabetes patients were attenuated to be non-significant after adjusted for ISIm.

After Bonferroni correction, the associations of the GRS with the 30-min OGTT glucose level and disposition indices (oral DI, DI_{30} , and DI_{120}) in controls remained significant, as did the associations of the GRS with 30-min OGTT insulin levels, $InsAUC_{30}/GluAUC_{30}$, $InsAUC_{120}/GluAUC_{120}$, and ISIm in treatment naïve T2D patients ($P < 3.33 \times 10^{-3}$).

Furthermore, we identified the interaction effects between the GRS and ISIm on the fasting insulin level in controls ($P = 4.40 \times 10^{-5}$) and treatment naïve T2D patients ($P = 1.45 \times 10^{-11}$), as well as on the 30-min OGTT insulin level ($P = 4.06 \times 10^{-2}$ in controls, $P = 4.69 \times 10^{-3}$ in treatment naïve T2D) and $InsAUC_{30}/GluAUC_{30}$ ($P = 4.18 \times 10^{-2}$ in controls, $P = 2.50 \times 10^{-2}$ in treatment naïve T2D). In addition, interaction effects between the GRS and $InsAUC_{120}/GluAUC_{120}$ ($P = 1.20 \times 10^{-2}$) in controls, as well as interaction effects between the GRS and HOMA-B ($P = 9.84 \times 10^{-3}$) and oral DI ($P = 2.28 \times 10^{-2}$) in treatment naïve T2Ds, were identified. The findings suggested an influence of ISIm on the association of GRS with insulin secretion.

When conducting a weighted T2D GRS based on the GWAS reported effective size in East Asians, the similar results were achieved (Table S3). Notably, the weighted GRS contributed to impaired insulin secretion, which was assessed by insulinogenic index, $InsAUC_{30}/GluAUC_{30}$, $InsAUC_{120}/GluAUC_{120}$, Oral DI, and DI_{30} , in controls and treatment naïve T2Ds.

Associations of T2D GRS with glycemia-related traits and insulin secretion after stratification by insulin sensitivity in Chinese Hans

Upon stratifying the participants into tertiles according to their insulin sensitivity (assessed by ISIm), associations were observed between the GRS and fasting and 30-min OGTT glucose levels in controls with low insulin sensitivity ($ISIm < 6.917$) but not in those with high insulin sensitivity ($ISIm > 10.142$) (Table 2). Similarly, treatment naïve T2D patients with low insulin sensitivity ($ISIm < 3.190$) showed the association of GRS with fasting glucose levels, which were not detected in high insulin sensitive patients ($ISIm > 5.170$) (Table 3). Additional adjustment for BMI and/or ISIm did not alter their associations significantly. Consequently, individuals with low insulin sensitivity exhibited significantly worse glycemic regulation with an increase in the risk alleles (Tables 4 and 5).

We further evaluated whether the associations between the GRS and insulin secretion were modulated by insulin sensitivity. A higher GRS was found to be related to a reduced 30-min OGTT insulin level after adjustment for ISIm in low insulin sensitive controls and was associated with reduced 30-min OGTT insulin levels in low insulin sensitive treatment naïve T2D patients (Tables 2 and 3).

Notably, associations of the GRS with the $InsAUC_{30}/GluAUC_{30}$, $InsAUC_{120}/GluAUC_{120}$, and insulin disposition indices DI_{30} and DI_{120} , were identified in low insulin sensitive individuals regardless of their glycemic status. In controls with low sensitivity, a higher GRS

contributed to the reduced insulinogenic index and oral DI, along with elevated HOMA-IR. In treatment naïve T2D patients with low sensitivity a higher GRS was associated with the reduced HOMA-B, and contributed to a reduced oral DI after adjusted for BMI or ISIm. In contrast, none of the associations were identified in the high sensitivity groups (Tables 2 and 3). Accordingly, after stratifying the individuals by GRS group, a decline in the insulin secretion parameters was observed in the controls and treatment naïve T2D patients with low insulin sensitivity rather than in those with high sensitivity (Tables 4 and 5).

After Bonferroni correction, the associations of the GRS with 30-min OGTT glucose level, insulinogenic index, $\text{InsAUC}_{120}/\text{GluAUC}_{120}$ and disposition indices (oral DI, DI_{30} , and DI_{120}) in controls with low sensitivity remained significant ($P < 3.33 \times 10^{-3}$).

Similar results were achieved in the comparisons using weighted T2D GRS among controls (Table S4). However, the insulin secretion parameters were not significant different in the treatment naïve T2D patients with low-insulin sensitivity and high-insulin sensitivity, except for $\text{InsAUC}_{120}/\text{GluAUC}_{120}$ and DI_{120} (Table S5).

Discussion

The present study identified associations between a T2D GRS and several glycemia-related and insulin secretion-related parameters, including the glucose and insulin levels during OGTT, insulinogenic index, $\text{InsAUC}_{30}/\text{GluAUC}_{30}$, $\text{InsAUC}_{120}/\text{GluAUC}_{120}$, and insulin disposition indices (oral DI, DI_{30} , and DI_{120}) in normoglycemic controls and/or treatment naïve T2D patients of Chinese ancestry. Importantly, stratification of the participants into tertiles by ISIm demonstrated an inhibitory effect of the GRS on insulin secretion in participants with low insulin sensitivity but not in high insulin sensitive individuals either in controls or treatment naïve T2D patients. To our best knowledge, this is the first study to investigate the influence of insulin sensitivity on the genetic risk of impaired insulin secretion in the Chinese, as well as in a T2D patient population.

In recent decades, multiple T2D-related genomic loci have been revealed by GWAS and the other genetic approaches(6). Among the genomic loci that could be replicated in different populations, a large proportion has been established to play an essential role in the progression of beta cell function decline, including *TCF7L2*, *FTO*, *CDKAL1*, *KCNQ1*, *WFS1*, etc.(28–32). Some of the genomic loci also were shown to contribute to insulin resistance, including *TCF7L2*, *FTO*, *KCNQ1*, *PPARG*, etc.(29, 33–35). In our previous study, 8 SNPs in or near *WFS1*, *CDKAL1*, *CDKN2A/2B*, *CDC123*, *HHEX*, *TCF7L2*, *KCNQ1*, and *MTNR1B* were associated with the risk for T2D(36). To elucidate the overall impact of these risk alleles, we constructed a GRS using the T2D susceptibility alleles, which has been proven to be useful for evaluating the risk of T2D in individuals(26, 36). In Caucasians, the GRS was proved to be related to insulin secretion in undiagnosed T2D patients(37). Using this GRS, we previously established that the overall contribution of risk alleles of these genetic variants significantly increased the accumulative incidence of T2D over a 7.5-year follow-up period in a Chinese population(36). In the present study, we hypothesized and demonstrated that the GRS was negatively related to insulin secretion in

both controls and T2D patients, suggesting a genetic determinant of beta cell function in Chinese individuals.

Epidemiology studies have described well the hyperbolic relationship between insulin sensitivity and insulin secretion in the development of hyperglycemia(4). However, the underlying mechanisms were not clarified. In non-diabetic Caucasians, it is established that the increase in risk allele summation for eight genetic loci was related to insulin secretion only in individuals with low insulin sensitivity, suggesting that insulin sensitivity could modulate this genetic effect(7). However, the findings were not replicated in another population, and it was not tested in T2D patients. Therefore, we speculated that the negative effects of these genetic risk alleles on insulin secretion could be modulated by insulin sensitivity in both controls and T2D patients of Chinese Han ancestry. The results in current study successfully prove our speculation by only demonstrating the associations of genetic risk and beta cell dysfunction in controls or in T2D patients with low insulin sensitivity. However, the biological mechanism needs further investigation.

The fact that the beta cells of East Asians are more vulnerable than those of Caucasians has been well accepted for decades. DECODE, DECODA, and DMS have established that the proportions of patients with impaired glucose tolerance and isolated post-prandial hyperglycemia, which are characterized by defects in insulin secretion, are considerably larger among East Asian patients with pre-diabetes and newly diagnosed diabetes of than among Caucasians(1, 38, 39). Moreover, T2D patients of East Asia generally experienced a rapid beta cell loss in the progression of diabetes(5). Therefore, the protection of beta cell function should be emphasized in the diabetes prevention and treatment strategy for both at-risk and diabetic populations among East Asians. Importantly, based on our observations, the association of the “harmful” genes with the decline in beta cell function could be modified by insulin sensitivity, which highlighted that insulin sensitizing could be a promising auxiliary strategy to protect beta cells in the Chinese, as well as East Asians. Moreover, insulin sensitivity is modifiable via both insulin sensitizer administration and multiple lifestyle interventions related to diet and physical activity.

In the present population, a significantly higher level of ISIm was observed in controls than in T2D patients. When respectively stratifying the two groups by ISIm, the ISIm values seem to be more comparable between controls with lowest insulin sensitivity and T2D patients with highest insulin sensitivity. However, the GRS was found to be only associated with insulin secretion in controls with the lowest sensitivity. Thus, we speculate that in this comparison the hyperglycemia and other metabolic features of T2D patients could override the influence of ISIm on the genes.

In addition, the results showed some inconsistent associations of metabolic traits with GRS between controls and T2D patients, which suggested that hyperglycemia might be a modifier of genetic risk besides ISIm. In fact, evidence showed that hyperglycemia could modulate the genetic risk of impaired insulin secretion. For example, the genetic variant rs560887 in *G6PC2* was shown to be associated with a decreased insulinogenic index and first-phase insulin secretion in normal glucose tolerance controls, which was not seen in individuals with pre-diabetes(40). In the present study, some of the metabolic traits were related to the

GRS either in controls or in diabetes patients. Thus, the exact effect of hyperglycemia on genetic risk needs further elucidation in the future.

The current study has the following strengths. Most importantly, it is the first study to elucidate that insulin sensitivity modulates the genetic inhibitory effect on insulin secretion in both controls and diabetes patients, as well as in Chinese. Second, participants of the study were recruited in the DMS, which is a large and representative population with high ethnic homogeneity for the normoglycemic or diabetic individuals in China mainland(1). Therefore, the results can be well generalized in China. Additionally, only treatment naïve T2Ds were included in the current study, which eliminated the potential effect of hypoglycemic treatments. Our findings indicate that the GRS contributes to the impaired insulin secretion only if the insulin sensitivity is low in Chinese patients regardless of their glycemic status. The findings have important clinical significance for the prevention and management of diabetes in Chinese and East Asian individuals.

However, our study also has several limitations. First, a future study applying an IVGTT and hyperinsulinemic–euglycemic clamp to precisely assess the insulin sensitivity and insulin secretion is needed to replicate the current findings in Chinese individuals. However, we performed the analyses by calculating the $\text{InsAUC}_{30}/\text{GluAUC}_{30}$ and $\text{InsAUC}_{120}/\text{GluAUC}_{120}$, which were previously proven to have a high correlation with the first-phase of insulin release and the second-phase and total insulin release during IVGTT, respectively(8). Second, it only includes previously identified T2D loci, and thus, the results do not consider uncovered T2D risk alleles across the genome. Nevertheless, 24 GWAS-validated genomic loci that have been well replicated in many populations were included to construct the GRS and were examined individually. In addition, more than 120 genomic loci have been identified to be associated with T2D risk during recent year. Thus, future studies are warranted to reveal the associations of insulin secretion and T2D GRS conducted using more genomic loci. Third, a GRS constructed by insulin secretion-related genetic risk alleles would be the most appropriate indicator for the genetic risk of beta cell dysfunction ideally. However, there was very limited information on the insulin secretion-related genetic variants. Therefore, T2D GRSs constructed by the amount of risk alleles or based on the weighted GRS based on their effective sizes for T2D risk were used in the present study instead, and similar results were achieved in both comparisons suggesting the associations were stable. The exploration of genetic variants related to insulin secretion is warranted in the future. Fourth, although it has been shown that the glycemic status can influence the associations of genes with metabolic traits, further studies are warranted to uncover the underlying mechanisms. Finally, longitudinal studies are required to evaluate the long term effect on beta cell function in controls and T2D patients, separately.

In conclusion, we identified that the GRS constructed from 24 T2D-related genetic variants predicted impaired insulin secretion only in controls and treatment naïve T2D patients of Chinese Han ancestry with low insulin sensitivity. Under certain glycemic conditions, only individuals whose insulin sensitivity was relatively low are susceptible to the inhibitory effect of the risk alleles. These findings suggest the protective role of high insulin sensitivity against the genetic risk for beta cell dysfunction independent of the presence of diabetes. In

this respect, it emphasizes good insulin sensitivity as a prerequisite for diabetes prevention and therapy to preserve beta cell function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Associations of T2D GRS with glycemic-related traits, insulin sensitivity, and insulin secretion parameters in DMS.

		Controls				Treatment naïve T2Ds			
		Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Fasting plasma glucose	β (SE)	0.0018(0.0007)	0.0017(0.0007)	0.0019(0.0007)	0.0018(0.0007)	0.0015(0.0023)	0.0018(0.0023)	0.0030(0.0022)	0.0029(0.0022)
	<i>P</i>	$P = 9.67 \times 10^{-3}$	$P = 1.69 \times 10^{-2}$	$P = 6.54 \times 10^{-3}$	$P = 8.88 \times 10^{-2}$	$P = 5.19 \times 10^{-1}$	$P = 4.26 \times 10^{-1}$	$P = 1.77 \times 10^{-1}$	$P = 1.98 \times 10^{-1}$
30-min OGTT plasma glucose	β (SE)	0.0039(0.0013)	0.0040(0.0013)	0.0040(0.0013)	0.0042(0.0013)	0.0018(0.0022)	0.0024(0.0022)	0.0034(0.0021)	0.0034(0.0021)
	<i>P</i>	$P = 2.90 \times 10^{-3}$	$P = 2.66 \times 10^{-3}$	$P = 1.78 \times 10^{-3}$	$P = 1.01 \times 10^{-3}$	$P = 3.92 \times 10^{-1}$	$P = 2.64 \times 10^{-1}$	$P = 1.02 \times 10^{-1}$	$P = 9.92 \times 10^{-2}$
2-h OGTT plasma glucose	β (SE)	0.0015(0.0013)	0.0011(0.0013)	0.0015(0.0013)	0.0012(0.0013)	0.0000(0.0029)	0.0006(0.0029)	0.0014(0.0029)	0.0015(0.0029)
	<i>P</i>	$P = 2.68 \times 10^{-1}$	$P = 4.25 \times 10^{-1}$	$P = 2.44 \times 10^{-1}$	$P = 3.52 \times 10^{-1}$	$P = 9.91 \times 10^{-1}$	$P = 8.30 \times 10^{-1}$	$P = 6.18 \times 10^{-1}$	$P = 5.99 \times 10^{-1}$
Fasting serum insulin	β (SE)	0.0034(0.0029)	0.0024(0.0028)	0.0040(0.0019)	0.0041(0.0019)	-0.0131(0.0046)	-0.0092(0.0044)	-0.0038(0.0029)	-0.0033(0.0029)
	<i>P</i>	$P = 2.33 \times 10^{-1}$	$P = 3.91 \times 10^{-1}$	$P = 3.65 \times 10^{-2}$	$P = 3.03 \times 10^{-2}$	$P = 4.43 \times 10^{-3}$	$P = 3.51 \times 10^{-2}$	$P = 1.84 \times 10^{-1}$	$P = 2.54 \times 10^{-1}$
30-min OGTT serum insulin	β (SE)	-0.0105(0.0045)	-0.0123(0.0044)	-0.0098(0.0031)	-0.0099(0.0031)	-0.0213(0.0064)	-0.0175(0.0062)	-0.0112(0.0050)	-0.0109(0.0050)
	<i>P</i>	$P = 1.87 \times 10^{-2}$	$P = 5.23 \times 10^{-3}$	$P = 1.82 \times 10^{-3}$	$P = 1.64 \times 10^{-3}$	$P = 8.43 \times 10^{-4}$	$P = 4.93 \times 10^{-3}$	$P = 2.65 \times 10^{-2}$	$P = 3.04 \times 10^{-2}$
2-h OGTT serum insulin	β (SE)	-0.0006(0.0046)	-0.0028(0.0046)	0.0001(0.0036)	-0.0005(0.0036)	-0.0166(0.0072)	-0.0115(0.0069)	-0.0057(0.0058)	-0.0046(0.0058)
	<i>P</i>	$P = 8.95 \times 10^{-1}$	$P = 5.47 \times 10^{-1}$	$P = 9.76 \times 10^{-1}$	$P = 8.87 \times 10^{-1}$	$P = 2.10 \times 10^{-2}$	$P = 9.82 \times 10^{-2}$	$P = 3.27 \times 10^{-1}$	$P = 4.24 \times 10^{-1}$
ISIm	β (SE)	-0.0008(0.0030)	0.0008(0.0029)	—	—	0.0152(0.0048)	0.0107(0.0045)	—	—
	<i>P</i>	$P = 7.90 \times 10^{-1}$	$P = 7.84 \times 10^{-1}$	—	—	$P = 1.52 \times 10^{-3}$	$P = 1.71 \times 10^{-2}$	—	—
HOMA-IR	β (SE)	0.0053(0.0030)	0.0041(0.0029)	—	—	-0.0116(0.0053)	-0.0073(0.0051)	—	—
	<i>P</i>	$P = 7.81 \times 10^{-2}$	$P = 1.61 \times 10^{-1}$	—	—	$P = 3.02 \times 10^{-2}$	$P = 1.50 \times 10^{-1}$	—	—
Insulinogenic index	β (SE)	-0.0200(0.0069)	-0.0225(0.0068)	-0.0193(0.0062)	-0.0203(0.0063)	-0.0283(0.0110)	-0.0258(0.0109)	-0.0192(0.0104)	-0.0196(0.0104)
	<i>P</i>	$P = 3.74 \times 10^{-3}$	$P = 1.04 \times 10^{-3}$	$P = 2.02 \times 10^{-3}$	$P = 1.20 \times 10^{-3}$	$P = 9.74 \times 10^{-3}$	$P = 1.84 \times 10^{-2}$	$P = 6.49 \times 10^{-2}$	$P = 5.97 \times 10^{-2}$
HOMA-B	β (SE)	-0.0020(0.0041)	-0.0024(0.0041)	-0.0017(0.0038)	-0.0012(0.0038)	-0.0162(0.0062)	-0.0134(0.0061)	-0.0105(0.0057)	-0.0099(0.0057)
	<i>P</i>	$P = 6.20 \times 10^{-1}$	$P = 5.64 \times 10^{-1}$	$P = 6.57 \times 10^{-1}$	$P = 7.54 \times 10^{-1}$	$P = 8.49 \times 10^{-3}$	$P = 2.79 \times 10^{-2}$	$P = 6.48 \times 10^{-2}$	$P = 8.42 \times 10^{-2}$
InsAUC ₃₀ /GluAUC ₃₀	β (SE)	-0.0114(0.0039)	-0.0130(0.0039)	-0.0107(0.0028)	-0.0109(0.0028)	-0.0215(0.0061)	-0.0182(0.0060)	-0.0130(0.0052)	-0.0127(0.0052)
	<i>P</i>	$P = 3.85 \times 10^{-3}$	$P = 8.08 \times 10^{-4}$	$P = 1.38 \times 10^{-4}$	$P = 1.09 \times 10^{-4}$	$P = 4.87 \times 10^{-4}$	$P = 2.63 \times 10^{-3}$	$P = 1.25 \times 10^{-2}$	$P = 1.50 \times 10^{-2}$
InsAUC ₁₂₀ /GluAUC ₁₂₀	β (SE)	-0.0107(0.0038)	-0.0125(0.0038)	-0.0100(0.0025)	-0.0104(0.0025)	-0.0212(0.0068)	-0.0175(0.0067)	-0.0121(0.0058)	-0.0116(0.0058)
	<i>P</i>	$P = 5.32 \times 10^{-3}$	$P = 8.64 \times 10^{-4}$	$P = 8.77 \times 10^{-5}$	$P = 4.93 \times 10^{-5}$	$P = 1.91 \times 10^{-3}$	$P = 9.09 \times 10^{-3}$	$P = 3.87 \times 10^{-2}$	$P = 4.74 \times 10^{-2}$
Oral DI	β (SE)	-0.0253(0.0069)	-0.0266(0.0069)	-0.0251(0.0069)	-0.0262(0.0069)	-0.0168(0.0117)	-0.0185(0.0117)	-0.0184(0.0117)	-0.0192(0.0117)
	<i>P</i>	$P = 5.32 \times 10^{-3}$	$P = 8.64 \times 10^{-4}$	$P = 8.77 \times 10^{-5}$	$P = 4.93 \times 10^{-5}$	$P = 1.91 \times 10^{-3}$	$P = 9.09 \times 10^{-3}$	$P = 3.87 \times 10^{-2}$	$P = 4.74 \times 10^{-2}$

		Controls				Treatment naïve T2Ds			
		Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
DI₃₀	<i>P</i>	<i>P</i> = <u>2.57×10⁻⁴</u>	<i>P</i> = <u>1.23×10⁻⁴</u>	<i>P</i> = <u>2.65×10⁻⁴</u>	<i>P</i> = <u>1.49×10⁻⁴</u>	<i>P</i> = 1.51×10 ⁻¹	<i>P</i> = 1.13×10 ⁻¹	<i>P</i> = 1.15×10 ⁻¹	<i>P</i> = 9.97×10 ⁻²
	β(SE)	-0.0122(0.0027)	-0.0123(0.0027)	-0.0122(0.0027)	-0.0123(0.0027)	-0.0063(0.0051)	-0.0075(0.0051)	-0.0092(0.0050)	-0.0094(0.0050)
DI₁₂₀	<i>P</i>	<i>P</i> = <u>4.67×10⁻⁶</u>	<i>P</i> = <u>4.65×10⁻⁶</u>	<i>P</i> = <u>4.57×10⁻⁶</u>	<i>P</i> = <u>4.33×10⁻⁶</u>	<i>P</i> = 2.17×10 ⁻¹	<i>P</i> = 1.41×10 ⁻¹	<i>P</i> = 6.45×10 ⁻²	<i>P</i> = 6.08×10 ⁻²
	β(SE)	-0.0115(0.0024)	-0.0117(0.0024)	-0.0115(0.0024)	-0.0117(0.0024)	-0.0060(0.0057)	-0.0068(0.0057)	-0.0083(0.0056)	-0.0083(0.0056)
	<i>P</i>	<i>P</i> = <u>1.16×10⁻⁶</u>	<i>P</i> = <u>7.06×10⁻⁷</u>	<i>P</i> = <u>1.19×10⁻⁶</u>	<i>P</i> = <u>7.50×10⁻⁷</u>	<i>P</i> = 2.93×10 ⁻¹	<i>P</i> = 2.35×10 ⁻¹	<i>P</i> = 1.42×10 ⁻¹	<i>P</i> = 1.44×10 ⁻¹

All non-Gaussian distributed quantitative traits were natural logarithmically transformed to normalize distributions. β coefficients and SEs were determined for the T2D GRS using multivariate linear regression under an additive assumption using the following models: Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, and BMI; Model 3, adjusted for age, sex, and ISIm (not applied for ISIm and HOMA-IR); Model 4, adjusted for age, sex, BMI, and ISIm (not applied for ISIm and HOMA-IR). *P* values < 0.05 are denoted in bold and underlined. AUC, area under curve; BMI, body mass index; DI, disposition index; DMS, the Chinese National Diabetes and Metabolic Disorders Study; GRS, genetic risk score; HOMA-B, the homeostasis model assessment for beta cell function; HOMA-IR, the homeostasis model assessment for insulin resistance; ISIm, Matsuda index; OGTT, oral glucose tolerance test; SE, standard error; T2D, type 2 diabetes.

Table 2

Associations of T2D GRS with glycemic-related traits, insulin sensitivity, and insulin secretion parameters in controls with low or high insulin sensitivity.

		Controls with low insulin sensitivity				Controls with high insulin sensitivity			
		Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Fasting plasma glucose	β (SE)	0.0028(0.0011)	0.0028(0.0011)	0.0027(0.0011)	0.0027(0.0011)	0.0007(0.0013)	0.0007(0.0013)	0.0008(0.0013)	0.0008(0.0013)
	<i>P</i>	<i>P</i> = <u>9.91×10⁻³</u>	<i>P</i> = <u>9.28×10⁻³</u>	<i>P</i> = <u>1.22×10⁻²</u>	<i>P</i> = <u>1.16×10⁻²</u>	<i>P</i> = 6.16×10 ⁻¹	<i>P</i> = 6.25×10 ⁻¹	<i>P</i> = 5.34×10 ⁻¹	<i>P</i> = 5.42×10 ⁻¹
30-min OGTT plasma glucose	β (SE)	0.0084(0.0021)	0.0086(0.0021)	0.0082(0.0021)	0.0084(0.0021)	0.0000(0.0024)	0.0002(0.0024)	0.0003(0.0024)	0.0005(0.0024)
	<i>P</i>	<i>P</i> = <u>7.22×10⁻⁵</u>	<i>P</i> = <u>4.51×10⁻⁵</u>	<i>P</i> = <u>9.90×10⁻⁵</u>	<i>P</i> = <u>6.51×10⁻⁵</u>	<i>P</i> = 9.89×10 ⁻¹	<i>P</i> = 9.36×10 ⁻¹	<i>P</i> = 8.91×10 ⁻¹	<i>P</i> = 8.27×10 ⁻¹
2-h OGTT plasma glucose	β (SE)	0.0040(0.0021)	0.0037(0.0021)	0.0038(0.0021)	0.0034(0.0021)	-0.0034(0.0024)	-0.0035(0.0024)	-0.0032(0.0024)	-0.0033(0.0024)
	<i>P</i>	<i>P</i> = 5.80×10 ⁻²	<i>P</i> = 8.34×10 ⁻²	<i>P</i> = 7.45×10 ⁻²	<i>P</i> = 1.08×10 ⁻¹	<i>P</i> = 1.54×10 ⁻¹	<i>P</i> = 1.45×10 ⁻¹	<i>P</i> = 1.78×10 ⁻¹	<i>P</i> = 1.69×10 ⁻¹
Fasting serum insulin	β (SE)	0.0055(0.0040)	0.0057(0.0040)	0.0032(0.0031)	0.0031(0.0031)	0.0020(0.0033)	0.0021(0.0033)	0.0034(0.0028)	0.0036(0.0028)
	<i>P</i>	<i>P</i> = 1.69×10 ⁻¹	<i>P</i> = 1.57×10 ⁻¹	<i>P</i> = 3.14×10 ⁻¹	<i>P</i> = 3.24×10 ⁻¹	<i>P</i> = 5.55×10 ⁻¹	<i>P</i> = 5.22×10 ⁻¹	<i>P</i> = 2.30×10 ⁻¹	<i>P</i> = 1.94×10 ⁻¹
30-min OGTT serum insulin	β (SE)	-0.0114(0.0060)	-0.0110(0.0060)	-0.0144(0.0051)	-0.0142(0.0051)	-0.0058(0.0060)	-0.0061(0.0060)	-0.0035(0.0052)	-0.0036(0.0052)
	<i>P</i>	<i>P</i> = 5.53×10 ⁻²	<i>P</i> = 6.66×10 ⁻²	<i>P</i> = <u>4.63×10⁻³</u>	<i>P</i> = <u>5.49×10⁻³</u>	<i>P</i> = 3.35×10 ⁻¹	<i>P</i> = 3.08×10 ⁻¹	<i>P</i> = 5.05×10 ⁻¹	<i>P</i> = 4.85×10 ⁻¹
2-h OGTT serum insulin	β (SE)	0.0020(0.0070)	0.0019(0.0070)	-0.0011(0.0062)	-0.0014(0.0063)	-0.0087(0.0062)	-0.0093(0.0062)	-0.0066(0.0056)	-0.0071(0.0056)
	<i>P</i>	<i>P</i> = 7.78×10 ⁻¹	<i>P</i> = 7.89×10 ⁻¹	<i>P</i> = 8.65×10 ⁻¹	<i>P</i> = 8.21×10 ⁻¹	<i>P</i> = 1.59×10 ⁻¹	<i>P</i> = 1.33×10 ⁻¹	<i>P</i> = 2.34×10 ⁻¹	<i>P</i> = 2.06×10 ⁻¹
ISIm	β (SE)	-0.0034(0.0031)	-0.0037(0.0031)	—	—	0.0018(0.0025)	0.0020(0.0025)	—	—
	<i>P</i>	<i>P</i> = 2.70×10 ⁻¹	<i>P</i> = 2.39×10 ⁻¹	—	—	<i>P</i> = 4.66×10 ⁻¹	<i>P</i> = 4.36×10 ⁻¹	—	—
HOMA-IR	β (SE)	0.0083(0.0040)	0.0085(0.0040)	—	—	0.0026(0.0034)	0.0028(0.0034)	—	—
	<i>P</i>	<i>P</i> = <u>4.06×10⁻²</u>	<i>P</i> = <u>3.61×10⁻²</u>	—	—	<i>P</i> = 4.33×10 ⁻¹	<i>P</i> = 4.08×10 ⁻¹	—	—
Insulinogenic index	β (SE)	-0.0315(0.0100)	-0.0317(0.0101)	-0.0341(0.0097)	-0.0344(0.0097)	-0.0068(0.0121)	-0.0076(0.0121)	-0.0047(0.0118)	-0.0055(0.0118)
	<i>P</i>	<i>P</i> = <u>1.74×10⁻³</u>	<i>P</i> = <u>1.66×10⁻³</u>	<i>P</i> = <u>4.55×10⁻⁴</u>	<i>P</i> = <u>4.17×10⁻⁴</u>	<i>P</i> = 5.76×10 ⁻¹	<i>P</i> = 5.30×10 ⁻¹	<i>P</i> = 6.89×10 ⁻¹	<i>P</i> = 6.44×10 ⁻¹
HOMA-B	β (SE)	-0.0024(0.0060)	-0.0023(0.0060)	-0.0045(0.0056)	-0.0046(0.0056)	0.0003(0.0073)	0.0006(0.0073)	0.0011(0.0072)	0.0015(0.0072)
	<i>P</i>	<i>P</i> = 6.85×10 ⁻¹	<i>P</i> = 7.06×10 ⁻¹	<i>P</i> = 4.17×10 ⁻¹	<i>P</i> = 4.13×10 ⁻¹	<i>P</i> = 9.63×10 ⁻¹	<i>P</i> = 9.34×10 ⁻¹	<i>P</i> = 8.74×10 ⁻¹	<i>P</i> = 8.35×10 ⁻¹
InsAUC ₃₀ /GluAUC ₃₀	β (SE)	-0.0151(0.0054)	-0.0148(0.0054)	-0.0178(0.0045)	-0.0178(0.0046)	-0.0044(0.0052)	-0.0048(0.0052)	-0.0025(0.0046)	-0.0028(0.0046)
	<i>P</i>	<i>P</i> = <u>5.32×10⁻³</u>	<i>P</i> = <u>6.26×10⁻³</u>	<i>P</i> = <u>9.24×10⁻⁵</u>	<i>P</i> = <u>1.01×10⁻⁴</u>	<i>P</i> = 3.97×10 ⁻¹	<i>P</i> = 3.59×10 ⁻¹	<i>P</i> = 5.82×10 ⁻¹	<i>P</i> = 5.48×10 ⁻¹
InsAUC ₁₂₀ /GluAUC ₁₂₀	β (SE)	-0.0153(0.0050)	-0.0152(0.0050)	-0.0182(0.0040)	-0.0183(0.0040)	-0.0049(0.0049)	-0.0054(0.0049)	-0.0029(0.0042)	-0.0033(0.0042)
	<i>P</i>	<i>P</i> = <u>2.24×10⁻³</u>	<i>P</i> = <u>2.46×10⁻³</u>	<i>P</i> = <u>4.83×10⁻⁶</u>	<i>P</i> = <u>4.65×10⁻⁶</u>	<i>P</i> = 3.15×10 ⁻¹	<i>P</i> = 2.67×10 ⁻¹	<i>P</i> = 4.82×10 ⁻¹	<i>P</i> = 4.27×10 ⁻¹
Oral DI	β (SE)	-0.0398(0.0109)	-0.0402(0.0110)	-0.0399(0.0109)	-0.0403(0.0110)	-0.0094(0.0129)	-0.0104(0.0130)	-0.0089(0.0129)	-0.0099(0.0129)
	<i>P</i>	<i>P</i> = <u>2.79×10⁻⁴</u>	<i>P</i> = <u>2.56×10⁻⁴</u>	<i>P</i> = <u>2.76×10⁻⁴</u>	<i>P</i> = <u>2.58×10⁻⁴</u>	<i>P</i> = 4.68×10 ⁻¹	<i>P</i> = 4.22×10 ⁻¹	<i>P</i> = 4.91×10 ⁻¹	<i>P</i> = 4.43×10 ⁻¹

	Controls with low insulin sensitivity				Controls with high insulin sensitivity			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
DI₃₀	β (SE)	-0.0185(0.0045)	-0.0185(0.0045)	-0.0184(0.0045)	-0.0026(0.0046)	-0.0028(0.0046)	-0.0026(0.0046)	-0.0029(0.0046)
	<i>P</i>	<i>P</i> = 4.62×10⁻⁵	<i>P</i> = 5.21×10⁻⁵	<i>P</i> = 5.16×10⁻⁵	<i>P</i> = 5.80×10 ⁻¹	<i>P</i> = 5.45×10 ⁻¹	<i>P</i> = 5.67×10 ⁻¹	<i>P</i> = 5.30×10 ⁻¹
DI₁₂₀	β (SE)	-0.0187(0.0039)	-0.0188(0.0040)	-0.0188(0.0039)	-0.0031(0.0042)	-0.0035(0.0042)	-0.0030(0.0042)	-0.0035(0.0042)
	<i>P</i>	<i>P</i> = 2.15×10⁻⁶	<i>P</i> = 2.17×10⁻⁶	<i>P</i> = 2.16×10⁻⁶	<i>P</i> = 4.65×10 ⁻¹	<i>P</i> = 4.10×10 ⁻¹	<i>P</i> = 4.67×10 ⁻¹	<i>P</i> = 4.10×10 ⁻¹

All non-Gaussian distributed quantitative traits were natural logarithmically transformed to normalize distributions. β coefficients and SEs were determined for the T2D GRS using multivariate linear regression under an additive assumption using the following models: Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, and BMI; Model 3, adjusted for age, sex, and ISIm (not applied for ISIm and HOMA-IR); Model 4, adjusted for age, sex, BMI, and ISIm (not applied for ISIm and HOMA-IR). *P*-values < 0.05 are denoted in bold and underlined. AUC, area under curve; BMI, body mass index; DI, disposition index; GRS, genetic risk score; HOMA-B, the homeostasis model assessment for beta cell function; HOMA-IR, the homeostasis model assessment for insulin resistance; ISIm, Matsuda index; OGTT, oral glucose tolerance test. SE, standard error; T2D, type 2 diabetes.

Table 3

Associations of T2D GRS with glycemic-related traits, insulin sensitivity, and insulin secretion parameters in treatment naïve T2D patients with low or high insulin sensitivity.

		Treatment naïve T2Ds with low insulin sensitivity				Treatment naïve T2Ds with high insulin sensitivity			
		Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Fasting plasma glucose	β (SE)	0.0087(0.0039)	0.0083(0.0039)	0.0090(0.0039)	0.0086(0.0039)	0.0041(0.0039)	0.0043(0.0039)	0.0046(0.0038)	0.0047(0.0038)
	<i>P</i>	<i>P</i> = <u>2.79×10⁻²</u>	<i>P</i> = <u>3.53×10⁻²</u>	<i>P</i> = <u>2.25×10⁻²</u>	<i>P</i> = <u>2.92×10⁻²</u>	<i>P</i> = 2.86×10 ⁻¹	<i>P</i> = 2.73×10 ⁻¹	<i>P</i> = 2.24×10 ⁻¹	<i>P</i> = 2.20×10 ⁻¹
30-min OGTT plasma glucose	β (SE)	0.0064(0.0034)	0.0062(0.0034)	0.0065(0.0034)	0.0064(0.0034)	0.0014(0.0037)	0.0015(0.0037)	0.0018(0.0037)	0.0018(0.0037)
	<i>P</i>	<i>P</i> = 6.42×10 ⁻²	<i>P</i> = 7.03×10 ⁻²	<i>P</i> = 5.88×10 ⁻²	<i>P</i> = 6.53×10 ⁻²	<i>P</i> = 6.99×10 ⁻¹	<i>P</i> = 6.85×10 ⁻¹	<i>P</i> = 6.19×10 ⁻¹	<i>P</i> = 6.17×10 ⁻¹
2-h OGTT plasma glucose	β (SE)	0.0084(0.0046)	0.0085(0.0046)	0.0082(0.0046)	0.0083(0.0046)	-0.0035(0.0053)	-0.0034(0.0053)	-0.0033(0.0053)	-0.0032(0.0053)
	<i>P</i>	<i>P</i> = 6.60×10 ⁻²	<i>P</i> = 6.42×10 ⁻²	<i>P</i> = 7.33×10 ⁻²	<i>P</i> = 7.00×10 ⁻²	<i>P</i> = 5.15×10 ⁻¹	<i>P</i> = 5.29×10 ⁻¹	<i>P</i> = 5.41×10 ⁻¹	<i>P</i> = 5.50×10 ⁻¹
Fasting serum insulin	β (SE)	-0.0047(0.0063)	-0.0032(0.0062)	0.0006(0.0042)	0.0009(0.0042)	-0.0018(0.0051)	-0.0016(0.0051)	0.0001(0.0040)	0.0001(0.0040)
	<i>P</i>	<i>P</i> = 4.56×10 ⁻¹	<i>P</i> = 6.11×10 ⁻¹	<i>P</i> = 8.96×10 ⁻¹	<i>P</i> = 8.33×10 ⁻¹	<i>P</i> = 7.27×10 ⁻¹	<i>P</i> = 7.57×10 ⁻¹	<i>P</i> = 9.80×10 ⁻¹	<i>P</i> = 9.88×10 ⁻¹
30-min OGTT serum insulin	β (SE)	-0.0189(0.0092)	-0.0181(0.0093)	-0.0142(0.0083)	-0.0144(0.0083)	-0.0129(0.0093)	-0.0127(0.0093)	-0.0105(0.0083)	-0.0106(0.0083)
	<i>P</i>	<i>P</i> = <u>4.15×10⁻²</u>	<i>P</i> = 5.13×10 ⁻²	<i>P</i> = 8.67×10 ⁻²	<i>P</i> = 8.30×10 ⁻²	<i>P</i> = 1.64×10 ⁻¹	<i>P</i> = 1.72×10 ⁻¹	<i>P</i> = 2.08×10 ⁻¹	<i>P</i> = 2.06×10 ⁻¹
2-h OGTT serum insulin	β (SE)	-0.0209(0.0110)	-0.0191(0.0110)	-0.0168(0.0104)	-0.0159(0.0104)	-0.0064(0.0095)	-0.0060(0.0095)	-0.0042(0.0087)	-0.0041(0.0088)
	<i>P</i>	<i>P</i> = 5.71×10 ⁻²	<i>P</i> = 8.21×10 ⁻²	<i>P</i> = 1.05×10 ⁻¹	<i>P</i> = 1.25×10 ⁻¹	<i>P</i> = 5.00×10 ⁻¹	<i>P</i> = 5.24×10 ⁻¹	<i>P</i> = 6.31×10 ⁻¹	<i>P</i> = 6.37×10 ⁻¹
ISIm	β (SE)	0.0054(0.0047)	0.0044(0.0047)	—	—	0.0028(0.0043)	0.0024(0.0043)	—	—
	<i>P</i>	<i>P</i> = 2.48×10 ⁻¹	<i>P</i> = 3.48×10 ⁻¹	—	—	<i>P</i> = 5.20×10 ⁻¹	<i>P</i> = 5.67×10 ⁻¹	—	—
HOMA-IR	β (SE)	0.0040(0.0073)	0.0051(0.0073)	—	—	0.0024(0.0059)	0.0027(0.0059)	—	—
	<i>P</i>	<i>P</i> = 5.81×10 ⁻¹	<i>P</i> = 4.79×10 ⁻¹	—	—	<i>P</i> = 6.92×10 ⁻¹	<i>P</i> = 6.51×10 ⁻¹	—	—
Insulinogenic index	β (SE)	-0.0342(0.0175)	-0.0342(0.0176)	-0.0291(0.0169)	-0.0301(0.0170)	-0.0075(0.0194)	-0.0074(0.0194)	-0.0049(0.0189)	-0.0051(0.0189)
	<i>P</i>	<i>P</i> = 5.11×10 ⁻²	<i>P</i> = 5.20×10 ⁻²	<i>P</i> = 8.60×10 ⁻²	<i>P</i> = 7.65×10 ⁻²	<i>P</i> = 6.98×10 ⁻¹	<i>P</i> = 7.03×10 ⁻¹	<i>P</i> = 7.95×10 ⁻¹	<i>P</i> = 7.88×10 ⁻¹
HOMA-B	β (SE)	-0.0207(0.0096)	-0.0186(0.0096)	-0.0162(0.0087)	-0.0151(0.0087)	-0.0129(0.0107)	-0.0130(0.0107)	-0.0123(0.0106)	-0.0125(0.0106)
	<i>P</i>	<i>P</i> = <u>3.16×10⁻²</u>	<i>P</i> = 5.23×10 ⁻²	<i>P</i> = 6.50×10 ⁻²	<i>P</i> = 8.42×10 ⁻²	<i>P</i> = 2.29×10 ⁻¹	<i>P</i> = 2.26×10 ⁻¹	<i>P</i> = 2.46×10 ⁻¹	<i>P</i> = 2.41×10 ⁻¹
InsulinAUC ₃₀ /glucoseAUC ₃₀	β (SE)	-0.0226(0.0095)	-0.0214(0.0095)	-0.0179(0.0085)	-0.0178(0.0085)	-0.0136(0.0092)	-0.0134(0.0092)	-0.0117(0.0086)	-0.0118(0.0086)
	<i>P</i>	<i>P</i> = <u>1.74×10⁻²</u>	<i>P</i> = <u>2.40×10⁻²</u>	<i>P</i> = <u>3.62×10⁻²</u>	<i>P</i> = <u>3.78×10⁻²</u>	<i>P</i> = 1.39×10 ⁻¹	<i>P</i> = 1.43×10 ⁻¹	<i>P</i> = 1.74×10 ⁻¹	<i>P</i> = 1.71×10 ⁻¹
InsulinAUC ₁₂₀ /glucoseAUC ₁₂₀	β (SE)	-0.0300(0.0110)	-0.0289(0.0110)	-0.0253(0.0102)	-0.0252(0.0103)	-0.0089(0.0096)	-0.0087(0.0096)	-0.0069(0.0089)	-0.0070(0.0090)
	<i>P</i>	<i>P</i> = <u>6.69×10⁻³</u>	<i>P</i> = <u>9.08×10⁻³</u>	<i>P</i> = <u>1.36×10⁻²</u>	<i>P</i> = <u>1.42×10⁻²</u>	<i>P</i> = 3.51×10 ⁻¹	<i>P</i> = 3.62×10 ⁻¹	<i>P</i> = 4.40×10 ⁻¹	<i>P</i> = 4.37×10 ⁻¹
Oral DI	β (SE)	-0.0382(0.0196)	-0.0393(0.0197)	-0.0387(0.0197)	-0.0396(0.0197)	-0.0099(0.0206)	-0.0101(0.0207)	-0.0096(0.0207)	-0.0098(0.0207)
	<i>P</i>	<i>P</i> = 0.0382	<i>P</i> = 0.0393	<i>P</i> = 0.0387	<i>P</i> = 0.0396	<i>P</i> = 0.0099	<i>P</i> = 0.0101	<i>P</i> = 0.0096	<i>P</i> = 0.0098

	Treatment naïve T2Ds with low insulin sensitivity				Treatment naïve T2Ds with high insulin sensitivity			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
DI₃₀	<i>P</i>	<i>P</i> = 5.20×10 ⁻²	<i>P</i> = 4.62×10⁻²	<i>P</i> = 4.49×10⁻²	<i>P</i> = 6.32×10 ⁻¹	<i>P</i> = 6.25×10 ⁻¹	<i>P</i> = 6.41×10 ⁻¹	<i>P</i> = 6.35×10 ⁻¹
	β(SE)	-0.0171(0.0085)	-0.0170(0.0085)	-0.0176(0.0085)	-0.0108(0.0086)	-0.0110(0.0086)	-0.0114(0.0086)	-0.0115(0.0086)
	<i>P</i>	<i>P</i> = 4.32×10⁻²	<i>P</i> = 4.51×10⁻²	<i>P</i> = 3.79×10⁻²	<i>P</i> = 2.11×10 ⁻¹	<i>P</i> = 2.03×10 ⁻¹	<i>P</i> = 1.83×10 ⁻¹	<i>P</i> = 1.80×10 ⁻¹
DI₁₂₀	β(SE)	-0.0245(0.0102)	-0.0245(0.0102)	-0.0251(0.0102)	-0.0062(0.0090)	-0.0063(0.0090)	-0.0066(0.0089)	-0.0067(0.0090)
	<i>P</i>	<i>P</i> = 1.66×10⁻²	<i>P</i> = 1.72×10⁻²	<i>P</i> = 1.45×10⁻²	<i>P</i> = 4.93×10 ⁻¹	<i>P</i> = 4.84×10 ⁻¹	<i>P</i> = 4.59×10 ⁻¹	<i>P</i> = 4.55×10 ⁻¹

All non-Gaussian distributed quantitative traits were natural logarithmically transformed to normalize distributions. β coefficients and SEs were determined for the T2D GRS using multivariate linear regression under an additive assumption using the following models: Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, and BMI; Model 3, adjusted for age, sex, and ISIm (not applied for ISIm and HOMA-IR); Model 4, adjusted for age, sex, BMI, and ISIm (not applied for ISIm and HOMA-IR). *P* values < 0.05 are denoted in bold and underlined. AUC, area under curve; BMI, body mass index; DI, disposition index; GRS, genetic risk score; HOMA-B, the homeostasis model assessment for beta cell function; HOMA-IR, the homeostasis model assessment for insulin resistance; ISIm, Matsuda index; OGTT, oral glucose tolerance test; SE, standard error; T2D, type 2 diabetes.

Table 4

Clinical characteristics of the controls with low and high insulin sensitivity in different GRS groups.

GRS	Controls with low insulin sensitivity								Controls with high insulin sensitivity									
	19	20–21	22–23	24–25	26	<i>P</i>	19	20–21	22–23	24–25	26	<i>P</i>	19	20–21	22–23	24–25	26	<i>P</i>
<i>n</i>	123	228	325	250	150	—	119	231	315	265	146	—	119	231	315	265	146	—
Male, <i>n</i> (%)	29(23.58)	69(30.26)	81(24.92)	56(22.40)	37(24.67)	3.63×10^{-1}	49(41.18)	91(39.39)	130(41.27)	117(44.15)	62(42.47)	8.73×10^{-1}	49(41.18)	91(39.39)	130(41.27)	117(44.15)	62(42.47)	8.73×10^{-1}
Age, year	49.00(45.00,57.00)	49.00(44.00,56.00)	50.00(45.00,56.00)	49.00(44.00,54.00)	50.00(44.00,55.00)	8.59×10^{-1}	50.00(44.00,56.00)	49.00(45.00,55.00)	50.00(45.00,56.00)	50.00(45.00,56.00)	49.50(44.00,57.00)	9.70×10^{-1}	50.00(44.00,56.00)	49.00(45.00,55.00)	50.00(45.00,56.00)	50.00(45.00,56.00)	49.50(44.00,57.00)	9.70×10^{-1}
BMI, kg/m ²	23.83(22.03,25.39)	23.99(22.04,25.22)	23.88(22.06,25.15)	23.83(22.37,25.66)	23.99(22.52,25.44)	9.03×10^{-1}	22.02(20.45,23.67)	22.13(20.55,23.95)	22.32(20.55,23.98)	22.32(20.38,23.91)	22.38(20.62,23.92)	7.33×10^{-1}	22.02(20.45,23.67)	22.13(20.55,23.95)	22.32(20.55,23.98)	22.32(20.38,23.91)	22.38(20.62,23.92)	7.33×10^{-1}
Waist circumference, cm	81.00(75.00,88.00)	81.50(76.50,87.00)	81.00(75.00,87.00)	80.50(75.00,86.00)	82.00(75.00,87.00)	7.21×10^{-1}	77.00(73.00,84.00)	78.00(73.00,83.00)	78.00(72.00,84.00)	77.00(72.00,83.00)	78.00(73.00,83.00)	9.82×10^{-1}	77.00(73.00,84.00)	78.00(73.00,83.00)	78.00(72.00,84.00)	77.00(72.00,83.00)	78.00(73.00,83.00)	9.82×10^{-1}
Fasting plasma glucose, mmol/l	5.20(4.80,5.42)	5.14(4.80,5.47)	5.15(4.86,5.49)	5.24(4.82,5.59)	5.29(4.93,5.60)	1.47×10^{-1}	4.89(4.52,5.23)	4.92(4.55,5.30)	4.90(4.52,5.30)	4.90(4.60,5.29)	4.90(4.56,5.29)	9.28×10^{-1}	4.89(4.52,5.23)	4.92(4.55,5.30)	4.90(4.52,5.30)	4.90(4.60,5.29)	4.90(4.56,5.29)	9.28×10^{-1}
30-min OGTT glucose, mmol/l	8.29(7.35,9.10)	8.45(7.39,9.58)	8.44(7.47,9.59)	8.53(7.50,9.69)	9.20(7.96,10.30)	8.84×10^{-5}	7.70(6.63,8.67)	7.79(6.90,8.89)	7.72(6.60,8.88)	7.80(6.67,8.81)	8.02(6.88,9.01)	4.45×10^{-1}	7.70(6.63,8.67)	7.79(6.90,8.89)	7.72(6.60,8.88)	7.80(6.67,8.81)	8.02(6.88,9.01)	4.45×10^{-1}
2-h OGTT glucose, mmol/l	6.11(5.25,6.65)	6.04(5.25,6.87)	6.27(5.41,6.90)	6.10(5.24,6.90)	6.28(5.36,7.02)	3.05×10^{-1}	5.64(4.89,6.40)	5.61(4.90,6.40)	5.63(4.78,6.50)	5.45(4.73,6.35)	5.55(4.68,6.30)	6.86×10^{-1}	5.64(4.89,6.40)	5.61(4.90,6.40)	5.63(4.78,6.50)	5.45(4.73,6.35)	5.55(4.68,6.30)	6.86×10^{-1}
Fasting serum insulin, mU/l	8.82(7.24,10.76)	8.85(7.46,10.87)	8.93(7.54,10.96)	9.17(7.22,11.83)	8.68(7.07,11.74)	5.70×10^{-1}	4.50(3.72,5.14)	4.47(3.71,5.07)	4.47(3.76,5.29)	4.49(3.78,5.36)	4.59(3.60,5.24)	8.97×10^{-1}	4.50(3.72,5.14)	4.47(3.71,5.07)	4.47(3.76,5.29)	4.49(3.78,5.36)	4.59(3.60,5.24)	8.97×10^{-1}
30-min OGTT insulin, mU/l	63.84(45.21,90.77)	58.51(42.32,81.93)	58.73(43.16,79.42)	54.83(39.69,78.92)	53.77(39.56,74.96)	3.84×10^{-1}	21.14(15.21,29.67)	19.57(14.51,28.83)	20.11(13.95,27.47)	19.03(13.92,26.63)	20.11(15.04,28.08)	4.29×10^{-1}	21.14(15.21,29.67)	19.57(14.51,28.83)	20.11(13.95,27.47)	19.03(13.92,26.63)	20.11(15.04,28.08)	4.29×10^{-1}
2-h OGTT insulin, mU/l	36.68(24.69,53.00)	38.09(25.90,56.16)	38.48(26.83,52.86)	39.09(28.58,58.07)	34.86(23.34,54.63)	1.51×10^{-1}	14.26(9.44,20.95)	14.55(9.73,19.80)	14.01(9.59,20.37)	14.33(9.26,18.96)	13.67(9.30,17.83)	5.48×10^{-1}	14.26(9.44,20.95)	14.55(9.73,19.80)	14.01(9.59,20.37)	14.33(9.26,18.96)	13.67(9.30,17.83)	5.48×10^{-1}
ISIm	5.47(4.47,6.19)	5.49(4.57,6.35)	5.54(4.56,6.27)	5.37(4.46,6.14)	5.41(4.56,6.20)	5.35×10^{-1}	12.66(11.21,14.71)	12.76(11.42,14.72)	12.92(11.39,15.11)	12.71(11.40,15.05)	12.80(11.51,15.03)	8.87×10^{-1}	12.66(11.21,14.71)	12.76(11.42,14.72)	12.92(11.39,15.11)	12.71(11.40,15.05)	12.80(11.51,15.03)	8.87×10^{-1}
HOMA-IR	2.06(1.65,2.44)	1.98(1.70,2.54)	2.04(1.69,2.57)	2.09(1.69,2.70)	2.08(1.65,2.83)	2.69×10^{-1}	0.96(0.80,1.12)	0.96(0.80,1.11)	0.97(0.82,1.15)	0.97(0.81,1.16)	1.00(0.81,1.15)	9.12×10^{-1}	0.96(0.80,1.12)	0.96(0.80,1.11)	0.97(0.82,1.15)	0.97(0.81,1.16)	1.00(0.81,1.15)	9.12×10^{-1}
Insulinogenic index	17.48(10.63,33.47)	16.47(9.23,25.17)	16.42(9.20,27.07)	14.16(8.07,24.32)	12.08(7.76,19.68)	5.72×10^{-3}	6.26(3.42,10.02)	5.41(3.20,9.38)	5.39(3.16,9.32)	5.64(2.78,10.25)	5.70(3.12,10.94)	8.75×10^{-1}	6.26(3.42,10.02)	5.41(3.20,9.38)	5.39(3.16,9.32)	5.64(2.78,10.25)	5.70(3.12,10.94)	8.75×10^{-1}
HOMA-B, %	109.23(84.81,146.67)	109.89(83.35,154.14)	110.88(82.31,154.09)	114.63(80.92,164.81)	100.80(77.18,144.41)	9.68×10^{-1}	64.29(50.12,96.75)	60.72(44.70,83.27)	62.28(45.26,98.10)	64.87(47.44,90.33)	62.86(46.03,87.78)	4.48×10^{-1}	64.29(50.12,96.75)	60.72(44.70,83.27)	62.28(45.26,98.10)	64.87(47.44,90.33)	62.86(46.03,87.78)	4.48×10^{-1}
InsAUC ₃₀ /GluAUC ₃₀	5.48(4.01,7.60)	5.14(3.80,6.83)	5.19(3.65,6.92)	4.79(3.54,6.65)	4.33(3.41,6.09)	6.91×10^{-2}	2.04(1.56,2.74)	1.89(1.45,2.69)	1.92(1.47,2.57)	1.94(1.44,2.60)	1.99(1.49,2.77)	5.48×10^{-1}	2.04(1.56,2.74)	1.89(1.45,2.69)	1.92(1.47,2.57)	1.94(1.44,2.60)	1.99(1.49,2.77)	5.48×10^{-1}
InsAUC ₁₂₀ /GluAUC ₁₂₀	6.84(5.39,9.95)	6.70(4.78,8.77)	6.49(4.82,8.98)	6.60(4.88,8.66)	5.75(4.53,7.68)	1.76×10^{-2}	2.70(1.96,3.49)	2.45(1.82,3.38)	2.46(1.91,3.28)	2.41(1.89,3.28)	2.48(1.86,3.38)	8.19×10^{-1}	2.70(1.96,3.49)	2.45(1.82,3.38)	2.46(1.91,3.28)	2.41(1.89,3.28)	2.48(1.86,3.38)	8.19×10^{-1}
Oral DI	8.47(4.79,17.63)	8.12(4.41,13.55)	7.60(4.09,13.47)	6.90(3.88,11.91)	5.58(3.41,9.73)	1.57×10^{-3}	6.50(3.54,10.89)	5.83(3.12,10.49)	5.57(3.00,11.32)	5.82(2.81,11.28)	5.80(3.13,12.08)	9.03×10^{-1}	6.50(3.54,10.89)	5.83(3.12,10.49)	5.57(3.00,11.32)	5.82(2.81,11.28)	5.80(3.13,12.08)	9.03×10^{-1}
DI ₃₀	28.06(21.58,36.95)	26.86(20.23,34.40)	26.54(19.80,35.94)	24.22(18.82,33.37)	23.40(18.72,31.41)	9.16×10^{-4}	26.39(20.90,34.09)	25.74(19.41,34.07)	25.11(19.91,33.16)	26.76(19.36,34.08)	27.06(19.31,33.21)	6.24×10^{-1}	26.39(20.90,34.09)	25.74(19.41,34.07)	25.11(19.91,33.16)	26.76(19.36,34.08)	27.06(19.31,33.21)	6.24×10^{-1}
DI ₁₂₀	36.18(30.44,46.99)	34.86(27.32,45.35)	33.67(26.81,43.45)	33.31(26.51,41.81)	30.61(24.86,38.66)	6.84×10^{-5}	34.32(25.73,41.82)	32.08(25.35,44.46)	31.94(25.84,40.96)	33.68(25.79,41.87)	32.61(24.22,42.55)	9.06×10^{-1}	34.32(25.73,41.82)	32.08(25.35,44.46)	31.94(25.84,40.96)	33.68(25.79,41.87)	32.61(24.22,42.55)	9.06×10^{-1}

Data are shown as median (interquartile range) or %. *P* values were calculated to assess the intergroup differences using χ^2 test or one-way ANOVA. *P* values < 0.05 are denoted in bold and underlined. AUC, area under curve; BMI, body mass index; DI, disposition index; GRS, genetic risk score; HOMA-B, the homeostasis model assessment for beta cell function; HOMA-IR, the homeostasis model assessment for insulin resistance; ISIm, Matsuda index; OGTT, oral glucose tolerance test; SE, standard error.

Table 5

Clinical characteristics of treatment naïve T2Ds with low and high insulin sensitivity in different GRS groups.

GRS	Treatment naïve T2Ds with low insulin sensitivity										Treatment naïve T2Ds with high insulin sensitivity							
	20	21–22	23–24	25–26	27	P	20	21–22	23–24	25–26	27	P	20	21–22	23–24	25–26	27	P
n	133	153	193	138	47	—	92	158	219	124	72	—	92	158	219	124	72	—
Male, n(%)	61(45.86)	56(36.60)	83(43.01)	51(36.96)	21(44.68)	4.00×10^{-1}	32(34.78)	72(45.57)	125(57.08)	66(53.23)	31(43.06)	3.30×10^{-3}	32(34.78)	72(45.57)	125(57.08)	66(53.23)	31(43.06)	3.30×10^{-3}
Age, year	54.00 (45.00, 64.00)	54.00 (46.00, 63.00)	54.00 (45.00, 62.00)	54.00 (46.00, 63.00)	51.00 (44.00, 65.00)	9.84×10^{-1}	54.00 (44.50, 61.00)	54.00 (46.00, 63.00)	55.00 (47.00, 63.00)	52.00 (45.50, 60.00)	52.50 (44.00, 62.00)	6.35×10^{-1}	54.00 (44.50, 61.00)	54.00 (46.00, 63.00)	55.00 (47.00, 63.00)	52.00 (45.50, 60.00)	52.50 (44.00, 62.00)	6.35×10^{-1}
BMI, kg/m ²	27.93 (25.71, 30.41)	27.53 (25.34, 30.31)	27.12 (24.80, 29.42)	27.83 (25.07, 29.78)	27.11 (24.98, 29.93)	4.08×10^{-1}	24.17 (22.43, 26.40)	24.44 (22.51, 26.70)	24.60 (22.68, 26.85)	24.06 (22.06, 26.17)	24.47 (21.91, 27.16)	5.59×10^{-1}	24.17 (22.43, 26.40)	24.44 (22.51, 26.70)	24.60 (22.68, 26.85)	24.06 (22.06, 26.17)	24.47 (21.91, 27.16)	5.59×10^{-1}
Waist circumference, cm	93.00 (87.00, 100.00)	92.00 (87.00, 99.00)	92.00 (84.00, 97.00)	92.00 (84.00, 98.00)	92.00 (87.00, 97.00)	1.83×10^{-1}	83.00 (78.00, 90.00)	86.00 (79.00, 91.00)	86.00 (80.00, 92.00)	83.50 (78.50, 92.00)	84.00 (79.50, 89.50)	3.46×10^{-1}	83.00 (78.00, 90.00)	86.00 (79.00, 91.00)	86.00 (80.00, 92.00)	83.50 (78.50, 92.00)	84.00 (79.50, 89.50)	3.46×10^{-1}
Fasting plasma glucose, mmol/l	7.27 (6.32, 8.61)	7.20 (6.26, 8.40)	7.25 (6.41, 9.15)	7.30 (6.27, 9.00)	8.03 (7.02, 9.48)	2.82×10^{-2}	6.34 (5.58, 7.21)	6.71 (5.70, 7.70)	6.85 (5.61, 7.80)	6.69 (5.69, 7.31)	6.78 (6.02, 7.75)	7.40×10^{-2}	6.34 (5.58, 7.21)	6.71 (5.70, 7.70)	6.85 (5.61, 7.80)	6.69 (5.69, 7.31)	6.78 (6.02, 7.75)	7.40×10^{-2}
30-min OGTT glucose, mmol/l	12.68 (11.50, 15.10)	12.73 (11.30, 14.53)	13.18 (11.46, 15.01)	13.14 (11.41, 15.38)	13.49 (12.19, 15.64)	1.43×10^{-1}	11.45 (9.72, 12.97)	11.21 (9.60, 12.94)	11.45 (9.73, 13.10)	10.81 (9.55, 12.75)	12.10 (10.15, 13.61)	5.02×10^{-1}	11.45 (9.72, 12.97)	11.21 (9.60, 12.94)	11.45 (9.73, 13.10)	10.81 (9.55, 12.75)	12.10 (10.15, 13.61)	5.02×10^{-1}
120-min OGTT glucose, mmol/l	13.08 (11.46, 16.32)	13.30 (11.57, 16.07)	14.02 (11.72, 17.50)	13.43 (12.10, 17.22)	14.17 (11.78, 18.40)	3.09×10^{-2}	12.39 (11.35, 14.11)	12.02 (10.91, 14.42)	12.10 (10.35, 14.50)	12.25 (10.57, 13.72)	12.22 (10.59, 14.44)	8.41×10^{-1}	12.39 (11.35, 14.11)	12.02 (10.91, 14.42)	12.10 (10.35, 14.50)	12.25 (10.57, 13.72)	12.22 (10.59, 14.44)	8.41×10^{-1}
Fasting serum insulin, mU/l	14.46 (11.74, 18.62)	14.65 (11.33, 20.55)	12.62 (10.83, 15.68)	14.14 (11.13, 19.18)	13.57 (12.14, 18.53)	3.62×10^{-4}	5.57 (4.86, 6.69)	5.30 (4.21, 6.71)	5.71 (4.67, 7.19)	5.29 (4.31, 6.44)	5.56 (4.43, 7.86)	5.04×10^{-1}	5.57 (4.86, 6.69)	5.30 (4.21, 6.71)	5.71 (4.67, 7.19)	5.29 (4.31, 6.44)	5.56 (4.43, 7.86)	5.04×10^{-1}
30-min OGTT insulin, mU/l	49.03 (32.19, 68.09)	51.61 (31.55, 82.73)	40.91 (28.19, 58.19)	41.62 (28.97, 68.27)	41.95 (22.86, 68.05)	2.22×10^{-3}	20.10 (12.97, 31.30)	14.52 (8.76, 23.15)	14.44 (9.77, 21.36)	16.53 (10.75, 24.51)	14.77 (9.59, 21.00)	2.03×10^{-3}	20.10 (12.97, 31.30)	14.52 (8.76, 23.15)	14.44 (9.77, 21.36)	16.53 (10.75, 24.51)	14.77 (9.59, 21.00)	2.03×10^{-3}
120-min OGTT insulin, mU/l	78.67 (44.43, 127.10)	85.56 (52.74, 132.38)	74.65 (43.59, 117.95)	70.29 (44.10, 131.86)	60.00 (33.36, 106.32)	2.00×10^{-1}	26.29 (18.68, 39.41)	22.29 (14.80, 36.06)	22.27 (12.77, 35.05)	24.42 (15.47, 36.05)	24.10 (17.06, 36.22)	2.51×10^{-2}	26.29 (18.68, 39.41)	22.29 (14.80, 36.06)	22.27 (12.77, 35.05)	24.42 (15.47, 36.05)	24.10 (17.06, 36.22)	2.51×10^{-2}
ISIm	2.32 (1.88, 2.68)	2.29 (1.60, 2.70)	2.52 (2.00, 2.85)	2.35 (1.75, 2.83)	2.20 (1.97, 2.68)	1.77×10^{-3}	6.50 (5.68, 8.06)	6.92 (5.89, 9.17)	6.67 (5.90, 8.65)	7.07 (6.18, 8.81)	6.61 (5.81, 8.34)	7.51×10^{-2}	6.50 (5.68, 8.06)	6.92 (5.89, 9.17)	6.67 (5.90, 8.65)	7.07 (6.18, 8.81)	6.61 (5.81, 8.34)	7.51×10^{-2}
HOMA-IR	4.96 (3.69, 6.46)	4.77 (3.43, 7.62)	4.41 (3.45, 6.03)	4.93 (3.88, 6.34)	5.21 (4.30, 6.96)	3.30×10^{-2}	1.58 (1.26, 2.01)	1.62 (1.34, 2.18)	1.71 (1.30, 2.16)	1.55 (1.22, 2.00)	1.73 (1.30, 2.19)	2.49×10^{-1}	1.58 (1.26, 2.01)	1.62 (1.34, 2.18)	1.71 (1.30, 2.16)	1.55 (1.22, 2.00)	1.73 (1.30, 2.19)	2.49×10^{-1}
Insulinogenic index	6.10 (3.18, 9.56)	6.77 (3.30, 10.94)	5.20 (2.79, 9.15)	4.97 (2.21, 9.59)	4.98 (1.45, 9.12)	1.73×10^{-2}	2.59 (1.21, 5.46)	2.03 (0.97, 3.86)	1.78 (0.89, 3.49)	2.37 (1.15, 5.77)	1.69 (1.10, 4.05)	3.58×10^{-2}	2.59 (1.21, 5.46)	2.03 (0.97, 3.86)	1.78 (0.89, 3.49)	2.37 (1.15, 5.77)	1.69 (1.10, 4.05)	3.58×10^{-2}
HOMA-B, %	84.12 (53.03, 109.91)	93.06 (58.22, 130.77)	70.64 (44.15, 101.79)	75.22 (48.31, 122.70)	61.71 (39.24, 93.26)	1.19×10^{-4}	42.41 (29.33, 58.46)	36.89 (23.04, 52.30)	35.87 (25.61, 53.00)	38.47 (24.03, 52.03)	32.64 (25.64, 50.69)	1.87×10^{-1}	42.41 (29.33, 58.46)	36.89 (23.04, 52.30)	35.87 (25.61, 53.00)	38.47 (24.03, 52.03)	32.64 (25.64, 50.69)	1.87×10^{-1}
InsAUC ₃₀ / GluAUC ₃₀	3.39 (2.28, 4.36)	3.72 (2.19, 5.31)	2.78 (1.79, 3.85)	3.01 (1.99, 4.40)	2.81 (1.55, 4.14)	3.99×10^{-4}	1.44 (1.08, 2.35)	1.18 (0.77, 1.74)	1.15 (0.76, 1.65)	1.27 (0.87, 1.92)	1.14 (0.77, 1.55)	3.48×10^{-3}	1.44 (1.08, 2.35)	1.18 (0.77, 1.74)	1.15 (0.76, 1.65)	1.27 (0.87, 1.92)	1.14 (0.77, 1.55)	3.48×10^{-3}
InsAUC ₁₂₀ / GluAUC ₁₂₀	4.95 (3.13, 7.15)	5.45 (3.39, 8.23)	4.54 (2.81, 6.18)	4.35 (2.58, 7.53)	4.19 (1.99, 6.75)	2.37×10^{-3}	2.13 (1.38, 3.07)	1.58 (1.12, 2.48)	1.68 (1.02, 2.35)	1.91 (1.20, 2.68)	1.65 (1.20, 2.51)	4.40×10^{-3}	2.13 (1.38, 3.07)	1.58 (1.12, 2.48)	1.68 (1.02, 2.35)	1.91 (1.20, 2.68)	1.65 (1.20, 2.51)	4.40×10^{-3}
Oral DI	1.18 (0.45, 2.36)	1.35 (0.54, 2.75)	1.21 (0.56, 2.29)	0.97 (0.41, 2.01)	0.97 (0.21, 1.78)	5.27×10^{-2}	1.60 (0.75, 4.30)	1.22 (0.57, 2.55)	1.14 (0.50, 2.56)	1.56 (0.83, 3.48)	1.19 (0.60, 2.57)	1.03×10^{-2}	1.60 (0.75, 4.30)	1.22 (0.57, 2.55)	1.14 (0.50, 2.56)	1.56 (0.83, 3.48)	1.19 (0.60, 2.57)	1.03×10^{-2}
DI ₃₀	7.04 (4.87, 9.36)	7.15 (4.99, 10.80)	6.86 (4.56, 9.04)	6.76 (4.44, 8.94)	5.85 (3.94, 8.85)	3.52×10^{-2}	10.01 (6.93, 15.65)	8.28 (6.30, 11.50)	8.69 (6.07, 12.34)	9.68 (6.69, 12.37)	8.28 (6.13, 10.39)	1.62×10^{-2}	10.01 (6.93, 15.65)	8.28 (6.30, 11.50)	8.69 (6.07, 12.34)	9.68 (6.69, 12.37)	8.28 (6.13, 10.39)	1.62×10^{-2}
DI ₁₂₀	11.30 (6.69, 17.21)	11.87 (7.27, 16.59)	10.08 (6.03, 15.69)	10.29 (5.99, 15.42)	8.34 (4.92, 12.94)	4.27×10^{-2}	13.77 (9.82, 20.13)	12.65 (9.16, 16.75)	12.17 (7.71, 16.53)	14.30 (9.86, 18.52)	12.47 (8.24, 16.39)	1.92×10^{-2}	13.77 (9.82, 20.13)	12.65 (9.16, 16.75)	12.17 (7.71, 16.53)	14.30 (9.86, 18.52)	12.47 (8.24, 16.39)	1.92×10^{-2}

Data are shown as median (interquartile range) or %. *P* values were calculated to assess the intergroup differences using χ^2 test or one-way ANOVA. *P* values < 0.05 are denoted in bold and underlined. AUC, area under curve; BMI, body mass index; DI, disposition index; GRS, genetic risk score; HOMA-B, the homeostasis model assessment for beta cell function; HOMA-IR, the homeostasis model assessment for insulin resistance; ISIm, Matsuda index; OGTT, oral glucose tolerance test; SE, standard error; T2D, type 2 diabetes.