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ARTICLE

Impaired pancreatic beta cell compensatory function is the main cause of type 2 diabetes in individuals with high genetic risk: a 9 year prospective cohort study in the Chinese population

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Abstract
Aims/hypothesis We aimed to evaluate the combined effects of type 2 diabetes risk variants on predicting deterioration of blood glucose and progression of beta cell function and insulin sensitivity in a 9 year prospective cohort from the Chinese population.
Methods We constructed a weighted genetic risk score (GRS) model based on 40 variants associated with type 2 diabetes validated in an established cross-sectional Chinese population ($n = 6,822$). The weighted scores were categorised into tertiles to assess the predictive capacity for incidence of type 2 diabetes and impaired glucose regulation (IGR), as well as for changes in Stumvoll first- and second-phase insulin secretion indices and Gutt's insulin sensitivity index (ISI) in a community-based 9 year prospective cohort ($n = 2,495$), including 2,192 individuals with normal glucose tolerance and 303 with IGR at baseline, through logistic, Cox and multiple linear regression tests.
Results Weighted GRS predicted the incidence of type 2 diabetes and IGR in logistic regression (OR 1.236, 95% CI 1.100, 1.389, $p = 0.0004$) as well as in the Cox model (HR 1.129, 95% CI 1.026, 1.242, $p = 0.0128$) after adjusting for age, sex, BMI, smoking and alcohol status at baseline. Moreover, we observed that weighted GRS was able to predict deterioration in beta cell function ($\beta = -0.0480$, $p = 9.66 \times 10^{-5}$ and $\beta = -0.0303$, $p = 3.32 \times 10^{-5}$ for first- and second-phase insulin secretion, respectively), but not insulin sensitivity ($p = 0.3815$), during the 9 year follow-up period.
Conclusions/interpretation The weighted GRS predicted blood glucose deterioration arising from change in beta cell function in the Chinese population. Individuals in the intermediate- or high-weighted GRS group exhibited progressive deterioration of beta cell function.

Keywords Beta cell function · Prospective study · Weighted genetic risk score

Jing Yan, Danfeng Peng and Feng Jiang contributed equally to this work.

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Abbreviations

GRS	Genetic risk score
IGR	Impaired glucose regulation
ISI	Insulin sensitivity index
NGT	Normal glucose tolerance
SNP	Single nucleotide polymorphism

Introduction

Type 2 diabetes is a complex disease caused by both genetic and environmental factors [1]. Currently, genome-wide

association studies (GWASs) have identified more than 90 loci for type 2 diabetes susceptibility [2, 3]. Because a single variant confers modest risk, combining multiple loci as a genetic risk score (GRS) is useful for predicting incident type 2 diabetes in prospective studies in European ancestry [4, 5].

However, the mechanism underlying the predictive capacity of GRS for deterioration in beta cell function and insulin sensitivity contributing to type 2 diabetes remains unknown. Several cross-sectional studies suggest that the majority of type 2 diabetes single nucleotide polymorphisms (SNPs) are associated with beta cell function, whereas a limited number of SNPs are associated with insulin resistance [6, 7]. We selected 40 well-replicated SNPs associated with type 2 diabetes in the Chinese population and constructed a model to explore the predictive capacity of weighted GRS for incidence of type 2 diabetes and impaired glucose regulation (IGR), as well as progressive deterioration of both beta cell function and insulin action, in a 9 year prospective study in the Chinese population.

Methods

Individuals There were two different populations analysed in the current study. The cross-sectional population, including 3,410 individuals with type 2 diabetes and 3,412 individuals with normal glucose tolerance (NGT), was used to construct a weighted-GRS model appropriate to the Chinese population. The clinical characteristics of the 6,822 individuals are presented in electronic supplementary material (ESM) Table 1.

The community-based prospective cohort ($n = 2,495$) was used to investigate the predictive capacity of the weighted GRS model for deterioration in blood glucose and progression of beta cell dysfunction as well as changes in insulin sensitivity during the 9 year follow-up period.

The study commenced in 1998–1999 with the enrolment of 5,994 individuals of Chinese ancestry. Individuals were examined at baseline and invited to participate in another two follow-up examinations in 2002–2003 and 2010–2012. Individuals with known type 2 diabetes at the baseline examination or without a sample for genotyping were excluded. Ultimately, 2,495 individuals (including 2,192 with NGT and 303 with IGR) were analysed at baseline.

In total, 2,032 individuals participated in the first follow-up, and 1,179 completed the second follow-up. A 'positive event' indicating blood glucose deterioration was defined as an 'incident progressing from NGT to IGR or type 2 diabetes, and IGR to type 2 diabetes'. Individuals who had 'positive events' or completed the second follow-up were considered to have 'censored data'. Of 2,495 individuals at baseline, 1,306 individuals had 'censored data' and 1,189 individuals were lost to follow-up. Individual characteristics at baseline are presented in ESM Table 2.

Type 2 diabetes and IGR were diagnosed according to the 1999 World Health Organization definition. All individuals provided written informed consent, and the studies were approved by the Institutional Review Board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital.

Anthropometric and biochemical measurements All individuals completed a standard medical questionnaire and a detailed clinical investigation. Briefly, anthropometric variables such as height, weight, waist circumference and blood pressure were measured. OGTTs were performed for each individual at baseline and two follow-up visits to measure fasting and postprandial 2 h plasma glucose levels. Fasting and 2 h serum insulin levels for each individual were also measured at baseline and the second follow-up visit. Insulin sensitivity and beta cell function were assessed by HOMA for insulin sensitivity index (ISI) and beta cell function (β) [8] as well as computations proposed by Stumvoll et al [9] and Gutt et al [10], thus generating HOMA-ISI, HOMA-β, Stumvoll first- and second-phase insulin secretion indices and Gutt-ISI.

SNP selection, genotyping and GRS computation We genotyped 89 SNPs reported to be associated with type 2 diabetes using the MassARRAY Compact Analyzer (Sequenom, San Diego, CA, USA). From the results, we identified 40 SNPs that were significantly associated with diabetes risk in the Chinese population (ESM Table 3). None of the SNPs failed quality-control analyses, with call rates of >95% and concordance rates of >99%.

Considering the varying effect size, the weighted GRS was calculated based on the 40 SNPs. We first created a weighted score, which was calculated by multiplying each participant's allele score (0, 1, 2) by the SNP's relative effect size (β coefficient) obtained from our cross-sectional study. Then, the value of the weighted score was rescaled by dividing all values by the sum of the β coefficients and then multiplying by the total number of SNPs, thus obtaining the final weighted GRS [11]. For missing data, only individuals for whom data were missing for ≥4 of the 40 SNPs were excluded. The weighted GRSs of the remaining individuals with missing data were standardised to those of individuals with complete data. The calculation formula was as follows: standardised weighted GRS = [(weighted GRS based on non-missing genotypes) / (number of non-missing genotypes)] × (the total number of the SNPs).

Statistical analysis Data are presented as the means with SDs, *n* (%), ORs or HRs with 95% CIs. Quantitative traits with a skewed distribution were logarithmically transformed to approximate univariate normality. Genotype distributions between case and control individuals were compared using logistic regression under a log additive model in PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/) [12]. We

categorised individuals into three groups according to the weighted GRS to calculate the HRs for incidence of type 2 diabetes and IGR using a Cox proportional hazards model. Weighted GRS was categorised into tertiles, and a multiple linear regression was applied to test the associations of weighted GRS with quantitative traits. All analyses were adjusted for covariates such as age, sex and BMI. The statistical analyses were performed using SAS software (version 8.0; SAS Institute, Cary, NC, USA). A two-tailed p value <0.05 was considered statistically significant.

Results

Over an average follow-up of 9.0 (SD 2.8) years, 260 individuals developed type 2 diabetes and 326 individuals developed IGR. The incidence of type 2 diabetes was 17.3 per 1,000 person-years. Individuals were stratified according to the weighted GRS:

- Low risk (L), weighted GRS < 43.0
- Intermediate risk (I), 43.0 ≤ weighted GRS < 46.7
- High risk (H), weighted GRS ≥ 46.7.

Logistic regression revealed that the weighted GRS was a significant predictor of incident blood glucose deterioration after adjusting for age, sex, BMI, smoking and alcohol status at baseline (OR 1.236, 95% CI 1.100, 1.389, $p = 0.0004$). Then, we used a Cox proportional hazards model for time to incident 'positive events', and the result was similar after adjusting for the same covariates (HR 1.129, 95% CI 1.026, 1.242, $p = 0.0128$). Moreover, cumulative incidence of type 2 diabetes and IGR increased significantly across the tertiles of weighted GRS (Fig. 1a). There was a significant difference in incidence among the three groups at the end of follow-up ($p = 0.0016$).

In the 1,179 individuals who completed the second follow-up, we investigated the effects of weighted GRS on progression of beta cell function and insulin sensitivity over the 9 year follow-up. Insulin sensitivity, as assessed by Gutt-ISI, decreased significantly from baseline to the end of the study in all three groups (by 34.1% in the L-weighted GRS group, 33.7% in the I-weighted GRS group and 33.8% in the H-weighted GRS group). We identified no significant difference in insulin sensitivity among the three groups at baseline or the end of the study ($p = 0.8494$ and $p = 0.7262$, respectively). In contrast, although the three groups exhibited the same beta cell function indicated by Stumvoll first- and second-phase insulin secretion indices at baseline ($p = 0.4621$ and $p = 0.8112$, respectively), the two indices in the H-weighted GRS group were significantly reduced compared with the L-weighted GRS group ($p = 0.0001$ and $p = 4.17 \times 10^{-5}$, respectively) at the end of the follow-up. Multiple linear regression revealed that the weighted GRS was nominally associated with Stumvoll first- and second-phase insulin

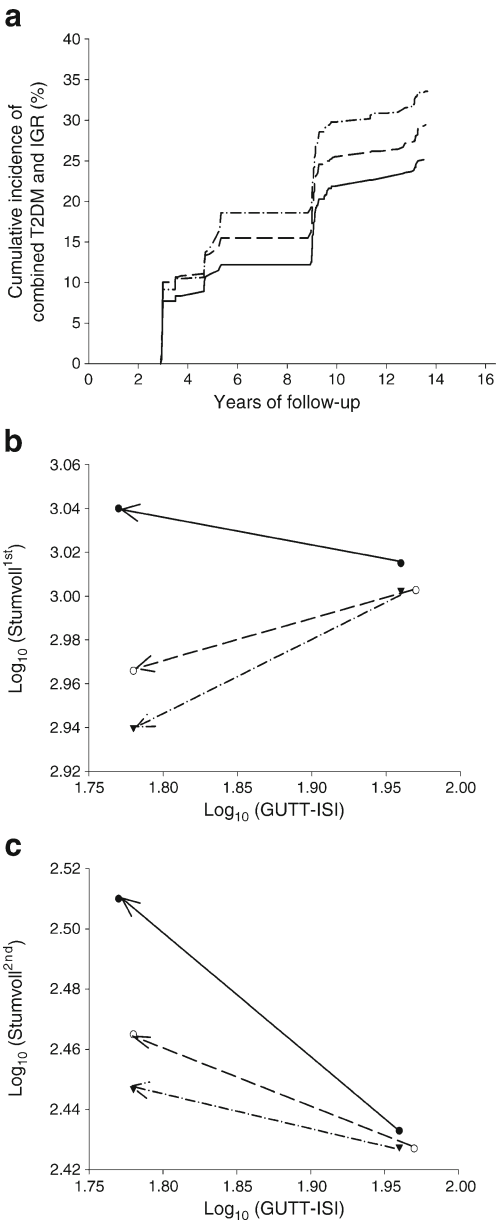

Fig. 1 Incidence of combined type 2 diabetes and IGR as well as trajectories of Gutt-ISI and Stumvoll first- and second-phase insulin secretion indices during the 9 year follow-up. (**a**) Cumulative incidence of time to detect type 2 diabetes and IGR, stratified by tertile of weighted GRS. Solid line, lowest tertile; dashed line, middle tertile; dashed–dotted line, highest tertile. (**b**) Vector plot of log-transformed Gutt-ISI and log-transformed Stumvoll first-phase insulin secretion index over time (baseline and the second follow-up), stratified by tertile of weighted GRS. (**c**) Vector plot of log-transformed Gutt-ISI and log-transformed Stumvoll second-phase insulin secretion index over time (baseline and the second follow-up), stratified by tertile of weighted GRS. Data in (**b**) and (**c**) are shown as means of log-transformed Gutt-ISI, Stumvoll first- and second-phase insulin secretion index. Black circle/solid line, lowest tertile; white circle/dashed line, middle tertile; black triangle/dashed–dotted line, highest tertile. Stumvoll$^{1st/2nd}$, Stumvoll first-/second-phase insulin secretion index; T2DM, type 2 diabetes mellitus

secretion indices at the second follow-up after adjustment for baseline sex, age, BMI and Stumvoll first- or second-phase insulin secretion index (Table 1, $p = 9.66 \times 10^{-5}$ and $p = 3.32 \times 10^{-5}$, respectively). Furthermore, the vector plot of beta cell function and insulin sensitivity revealed that only individuals in the L-weighted GRS group had elevated first- and second-phase insulin secretion, which compensated for impaired insulin sensitivity during the 9 year follow-up. However, individuals in the other two groups had decreased first-phase insulin secretion accompanied by increased second-phase secretion to partly offset the initial low levels (Fig. 1b, c).

Discussion

In the current study, we constructed a weighted-GRS model based on 40 replicated SNPs and demonstrated that combining genetic information with a weighted GRS was predictive of blood glucose deterioration (the OR for incidence of type 2 diabetes and IGR was 1.236 per level of weighted GRS) as well as progression of beta cell dysfunction over a 9 year follow-up period.

Previously, several prospective studies demonstrated that GRS predicted incident type 2 diabetes in white populations [4, 5], but few studies elucidated the underlying mechanism. One cross-sectional study in the Chinese population indicated that GRS was associated with HOMA-β in control individuals ($\beta = -0.029$, $p = 0.0422$) [13]. Furthermore, the phenomenon that Chinese populations are moderately susceptible to type 2 diabetes may due to their poor beta cell function. The incidence of type 2 diabetes was increased in Chinese individuals compared with whites when the two populations shared the same BMI [14]. In our study, weighted GRS predicted progression of beta cell dysfunction ($p = 0.0045$, $p = 9.66 \times 10^{-5}$ and $p = 3.32 \times 10^{-5}$ for HOMA-β, and Stumvoll first- and second-phase insulin secretion index, respectively). Although all three groups had progressive impairment in insulin sensitivity, only individuals in the L-weighted GRS group had a better reserve and secretory function of beta cells to compensate for elevated insulin resistance. Individuals in the other two groups exhibited impaired beta cell compensatory function, implied by decreased first-phase insulin secretion during the follow-up test, as well as a lower increase in second-phase secretion, compared with the L-weighted GRS group. In contrast, the weighted GRS had no predictive capacity for deterioration in insulin sensitivity ($p = 0.0506$ and $p = 0.3815$ for HOMA-ISI and Gutt-ISI, respectively), which is likely to be mainly affected by ageing.

In addition, we used the weights from published European studies of 71 SNPs associated with type 2 diabetes to construct a weighted-GRS European model as a comparison. The OR for incidence of type 2 diabetes and IGR was 1.146 per level of weighted GRS European (95% CI 1.020, 1.288, $p = 0.0219$). However, there was no significant predictive capacity of weighted GRS European in the Cox proportional hazards model ($p = 0.0948$). Furthermore, the predictive capacity of weighted GRS European for change in first- and second-phase insulin secretion was weakened ($p = 0.0239$ and $p = 0.0438$ for Stumvoll first- and second-phase insulin secretion indices, respectively [ESM Table 4]) compared with the weighted GRS model established in the current study. Our results highlight that ethnic differences play an important role in the genetics of type 2 diabetes.

There were limitations to our study. Participant loss to follow-up was relatively high in the current study, which may be due to migration of the community population as Shanghai becomes increasingly urbanised. Individuals lost to follow-up exhibited worse insulin sensitivity, mainly characterised by older age, higher fasting and 2 h insulin

Table 1 Association between weighted GRS and beta cell function and insulin sensitivity at the end of the 9 year follow-up

Variable	Weighted GRS			β (SE)	*p* value
	L ($n = 392$)	I ($n = 406$)	H ($n = 381$)		
HOMA-ISI	0.257 (0.175, 0.436)	0.285 (0.192, 0.474)	0.289 (0.207, 0.594)	0.0268 (0.0136)	0.0506
HOMA-β	152.150 (89.700, 228.316)	133.250 (70.504, 193.862)	132.151 (57.354, 194.978)	−0.0429 (0.0151)	0.0045
Gutt-ISI	59.029 (43.185, 81.381)	60.766 (44.379, 80.855)	61.048 (44.561, 86.517)	0.0069 (0.0079)	0.3815
Stumvoll first-phase insulin secretion index	1,137.180 (766.448, 1,553.440)	1,032.370 (647.391, 1,357.920)	945.200 (537.085, 1,292.280)	−0.0480 (0.0123)	9.66×10^{-5}
Stumvoll second-phase insulin secretion index	327.847 (242.886, 416.468)	291.862 (208.844, 369.962)	270.867 (186.964, 357.569)	−0.0303 (0.0073)	3.32×10^{-5}

Data are presented as median (interquartile range) or *n*

The *p* value of each variable was adjusted for sex, age, BMI and the value of the variable at baseline in the multiple linear regression analysis

levels compared with individuals with censored data. As individuals lost were prone to type 2 diabetes or IGR, the cumulative incidence of type 2 diabetes and IGR calculated in our study may be underestimated. However, there was no obvious difference in the proportions of lost individuals vs those with censored data in the three weighted GRS groups (L, I and H) ($p = 0.0890$), suggesting that loss was random. Therefore, we speculated that the effects of loss to follow-up on our finding that weighted GRS can predict deterioration of blood glucose and beta cell function would be limited.

In conclusion, our study demonstrated that weighted GRS predicted blood glucose deterioration through its effect on beta cell function in a Chinese population during 9 years of follow-up. Further studies should test the predictive capacity of weighted GRS in multi-ethnic populations and seek to target its clinical utility.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement JY, DP and FJ acquired and analysed the data, and wrote the manuscript. RZ, TW, DY, MC and SW analysed the data and revised the manuscript critically for important intellectual content. YB and XH contributed to the design of the study and revised the manuscript critically for important intellectual content. CH and WJ contributed to the conception and design of the study, wrote and revised the manuscript critically for important intellectual content. All authors read and approved the final version to be published. CH and WJ are the guarantors of this work.

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