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Higher Genetic Risk for Type 2 Diabetes Is Associated With a Faster Decline of β-Cell Function in an East Asian Population

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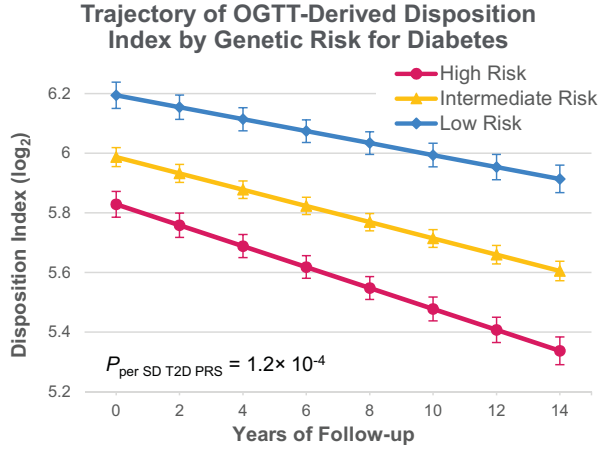

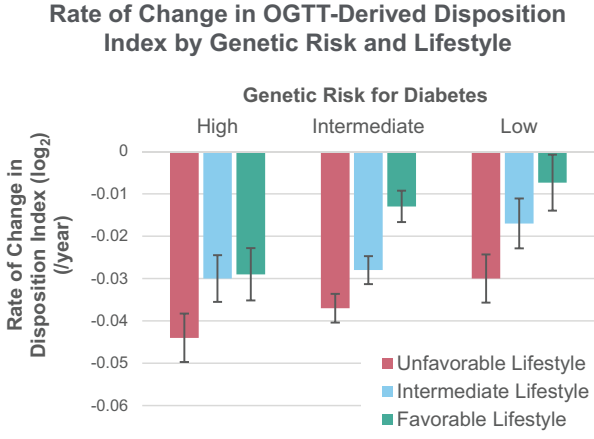

- In this 14-year prospective cohort study with biennial 2-h 75-g oral glucose tolerance tests (OGTTs) based in Korea (N=6,311), individuals with a higher genetic risk for type 2 diabetes (T2D) exhibited not only a lower OGTT-derived disposition index (DI) at baseline but also a notably faster rate of its decline during follow-up.
- Healthy lifestyle was associated with an attenuated rate of decline of OGTT-derived DI across all genetic risk groups, and this information could be used to enable a focused lifestyle intervention.

PRS, polygenic risk score

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Progressive β-cell dysfunction plays an important role in type 2 diabetes (T2D) development and its treatment.
- **What is the specific question we wanted to answer?**
  Is the genetic risk of T2D, in the form of polygenic risk score, associated with the progressive decline in β-cell function?
- **What did we find?**
  In this 14-year prospective cohort study using biennial oral glucose tolerance tests, having a higher polygenic risk for diabetes was associated with a lower disposition index at baseline, as well as a faster rate of its decline over time. Healthy lifestyle attenuated the deterioration regardless of genetic risk.
- **What are the implications of our findings?**
  Genetic information could be used to identify individuals at risk for a rapid decline in β-cell function.

Higher Genetic Risk for Type 2 Diabetes Is Associated With a Faster Decline of β-Cell Function in an East Asian Population

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OBJECTIVE

While most genetic variants of type 2 diabetes (T2D) are suggested to be associated with β-cell dysfunction cross sectionally, their association with the longitudinal change of β-cell function remains largely unknown.

RESEARCH DESIGN AND METHODS

We analyzed data from 6,311 participants without T2D at baseline (mean [SD] age 51.6 [8.7] years) from a community-based prospective cohort in Korea. Participants underwent biennial 2-h 75-g oral glucose tolerance tests (OGTTs) during 14 years of follow-up, and the OGTT-derived disposition index (DI) was used as a marker for β-cell function. Genetic risk was quantified using the genome-wide polygenic risk score (PRS) and was stratified into low (1st quintile), intermediate (2nd–4th quintiles), and high (5th quintile) genetic risk. Lifestyle was assessed according to Life's Essential 8.

RESULTS

During a mean follow-up of 10.9 years, 374 (29.6%), 851 (22.5%), and 188 (14.9%) participants developed T2D in the high, intermediate, and low genetic risk groups, respectively. Compared with the low genetic risk group, participants in the high genetic risk group had a 25% lower DI at baseline. Furthermore, in longitudinal analysis, we observed a 1.83-fold faster decline in $\log_2$-transformed DI per year (−0.034 vs. −0.019, $P = 2.1 \times 10^{-3}$; per 1-SD increase in T2D PRS, $P = 1.2 \times 10^{-4}$). Healthy lifestyle attenuated the rate of decline in DI across all genetic risk groups.

CONCLUSIONS

Individuals with a higher genetic risk for T2D exhibited not only a lower OGTT-derived β-cell function at baseline but also a notably more rapid decline during follow-up. This information could be used to enable a focused precision prevention with lifestyle intervention.

More than half a billion people are living with diabetes worldwide, and there are twice as many individuals at risk for developing diabetes (1). Attempts to understand diabetes pathophysiology has led to global collaborations to find genetic risk factors of type 2 diabetes (T2D) (2). Recent genome-wide association studies (GWAS) have discovered hundreds of genetic loci, candidate genes, and pathways that help us to better understand the disease. Moreover, these genetic variants could also aid in the implementation of

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more precise predictions, as they are associated with an individual's risk of developing T2D when combined into polygenic scores (3).

Many T2D genetic risk variants have been reported to be associated with insulin secretory response and insulin sensitivity obtained from oral glucose tolerance tests (OGTTs) or intravenous glucose tolerance tests (IVGTTs) (4). However, the cross-sectional nature of association studies does not provide information about whether these variants are responsible for differences in trajectories in β-cell function over time. Prediction of the trajectory of β-cell function would be of greater clinical utility to facilitate the identification of people at risk for rapid deterioration in β-cell function and assist in patient management. In the Metabolic Syndrome in Men (METSIM) study, the genetic risk score for T2D, comprising 76 variants, was associated with change in disposition index (DI) (5). However, the study was conducted exclusively in European men and had only a single follow-up after 4.6 years. Whether this association between genetic risk and the progressive β-cell dysfunction could be observed in a long-term prospective cohort study involving multiple measurements of β-cell function is largely unknown.

In this study, we evaluated the association of genetic risk and the trajectory of β-cell function in a large-scale, community-based cohort in Korea specifically designed to investigate environmental and genetic risk factors of T2D. We report results of 6,311 participants without T2D at baseline whose genetic risk was assessed using a genome-wide polygenic scoring method (6) and whose biennial trajectory of β-cell function derived from OGTT was followed for 14 years. We also investigated the interplay among genetic risk, lifestyle, and the trajectory of β-cell function.

RESEARCH DESIGN AND METHODS

Study Population

The Ansan-Ansung Cohort Study is a prospective, community-based cohort study in South Korea that has been previously described in detail (7). The study is part of the Korean Genome and Epidemiology Study, which aimed to investigate trends and the genetic and environmental etiology of chronic complex disorders, including diabetes. Participants aged 40–69 years residing either in the urban Ansan or the rural Ansung community were enrolled in the study. The baseline survey was done between 2001 and 2002, and the follow-up examination was performed every 2 years. Data from 2001 to 2016 were included for analysis in this study. The overall study flow is described in Supplementary Fig. 1. The study protocol was approved by the ethics committee of the Korean Center for Disease Control and the institutional review board of Seoul National University Hospital (1801-095-916). All participants provided written informed consent.

Procedures

Details of the procedures were described previously (7). Briefly, anthropometric parameters and blood pressure were measured by standard methods. Fasting plasma glucose (FPG), fasting insulin, total cholesterol, triglycerides, HDL cholesterol, and HbA_{1c} were measured in a central laboratory following an overnight 12-h fast. LDL cholesterol was calculated using Friedewald formula (8). Each participant underwent a 2-h 75-g OGTT at study enrollment, and the test was repeated every 2 years. Plasma samples were taken at 0, 60, and 120 min during the OGTT to measure plasma glucose and insulin concentrations. Participants who had been previously diagnosed with diabetes or reported taking diabetes medication were exempt from undergoing OGTT. Definition of diabetes was based on the American Diabetes Association diagnostic criteria using FPG, 2-h glucose, and HbA_{1c} (9). Among the 8,840 participants with genotype data in the Ansan-Ansung Cohort Study, 7,523 did not have T2D at baseline, and 6,311 with at least two points of OGTT data during follow-up were included in the current study.

Pancreatic β-cell secretory response was estimated by 60-min insulinogenic index (IGI_{60}), which was calculated based on plasma insulin and glucose levels at 0 and 60 min during the OGTT. The IGI_{60} was calculated using the following equation:

$$\frac{\text{insulin}_{60\text{min}} - \text{insulin}_{0\text{min}}\ [\mu\text{U/mL}]}{\text{glucose}_{60\text{min}} - \text{glucose}_{0\text{min}}\ [\text{mmol/L}]}$$

Insulin sensitivity was evaluated using the composite (Matsuda) insulin sensitivity index (ISI) and was calculated using values from 0, 60, and 120 of the OGTT as follows:

$$\frac{10,000}{\sqrt{(fasting\ glucose) \times (fasting\ insulin) \times (mean\ glucose) \times (mean\ insulin)}}$$

To reflect β-cell function while accounting for insulin sensitivity, we estimated the OGTT-derived DI by multiplying IGI_{60} by the composite ISI.

Genotype Data and Calculation of the Polygenic Risk Score

Participants were genotyped using the Affymetrix Genome-Wide Human SNP Array 5.0 as previously described (7). Genotype imputation was done using the TransOmics for Precision Medicine (TOPMed) Imputation Server with the TOPMed r2 reference panel (10). Principal component analysis indicated that participants clustered closely with the East Asian population within the 1000G Phase 3 reference data set (Supplementary Fig. 2) (11). Unrelated participants with high-quality genotyping data were used to derive an individual-level genome-wide polygenic risk score (PRS). The primary analysis, which investigated the association with the trajectory of OGTT-derived indices, was conducted using a T2D PRS calculated via a Bayesian regression method (PRS-CSx) (6). Briefly, the PRS-CSx integrates GWAS summary statistics from multiple populations, enabling a more accurate effect size estimation by sharing information between summary statistics. This is particularly useful in non-European populations, as existing GWAS have been conducted predominantly in individuals of European descent and the PRS derived from GWAS of the European population has limited transferability to non-European populations. We used the European and East Asian ancestry-specific summary statistics from the Type 2 Diabetes Global Genomics Initiative (T2DGGI) consortium to derive the effect size for the 1,015,552 HapMap3 variants (2,12). An individual-level PRS was calculated using Plink software and standardized to have a mean of 0 and SD of 1 (13).

In our secondary analysis, we tested for an association between the trajectory of OGTT-derived indices and the genetic risk score (GRS) restricted to significant variants, as well as the cluster-specific partitioned polygenic score (pPS),

using the index variants from the T2DGGI consortium (2). Briefly, T2D-related genetic variants were grouped into eight clusters based on their association with 32 cardiometabolic traits: β-cell dysfunction with a positive association with proinsulin (β-cell +PI), β-cell dysfunction with a negative association with proinsulin (β-cell −PI), residual glycemic, body fat, metabolic syndrome, obesity, lipodystrophy, and liver and lipid metabolism. Index variants with a low minor allele frequency (<1%) or poor imputation quality (r^2 <0.7) were excluded from the analysis. From the 1,289 genome-wide–significant index variants, a total of 824 variants were included in the analysis (detailed number of variants per cluster shown in Supplementary Table 1). Each of these index variants was tested for association with baseline and the rate of change in composite ISI, IGI_{60}, and DI in an additive model with a Bonferroni-corrected significance threshold of $P < 6.7 \times 10^{-5}$ (0.05/824).

Assessment of Lifestyle Factors

To assess the lifestyle factors of the participants, we considered five behavioral components of lifestyle according to Life's Essential 8: *1*) no current smoking, *2*) not overweight, *3*) healthy diet, *4*) regular physical activity, and *5*) adequate sleep duration (14). We used lifestyle information that was self-reported at baseline. Missing rates were below 5% for each factor, and missing data were imputed as median and mode values for continuous and categorical variables, respectively. No current smoking and BMI <23 kg/m^2 were classified as low risk (15). For diet, we evaluated its quality using the healthy plant-based diet index (hPDI) that was described previously (16,17). Diet information was obtained from a validated, semiquantitative food frequency questionnaire based on 106 items, which was further classified into 17 food groups (18). The hPDI score was higher in people with increased consumption of whole grains, fruits, vegetables, nuts, legumes, and tea/coffee and with less consumption of refined grains, potatoes, sugar-sweetened beverages, sweets, desserts, salty food, animal fat, dairy eggs, fish, and meat. Having an hPDI score >48 was defined as having a healthy diet based on previous results (16). Regular physical activity was defined as at least 150 min/week of moderate activity or 75 min/week of vigorous activity. Adequate sleep duration was defined as ≥7 h and <9 h per day (19). Participants were categorized as having a favorable lifestyle (at least four healthy lifestyle components), intermediate lifestyle (three healthy lifestyle components), and unfavorable lifestyle (two or fewer healthy lifestyle components).

Statistical Analysis

Data are presented as counts and percentages for categorical variables and mean (SD) for continuous variables. We normalized variables with non-Gaussian distribution by logarithmic transformation. Proportions were compared using the χ^2 test for categorical variables, and means were compared using Student *t* test or ANCOVA for continuous variables. Test for trend was performed using generalized linear regression and Cochran-Armitage test for continuous and categorical variables, respectively. Participants were grouped as having high genetic risk (i.e., highest quintile of T2D PRS), intermediate risk (quintiles 2–4), and low risk (lowest quintile). We conducted a longitudinal analysis of $\log_2$-transformed IGI_{60}, composite ISI, and DI using linear mixed models to estimate the average levels of the parameters over time within genetic risk groups from baseline up to 14 years of follow-up (20). The fixed effects were time, group, and group by time, and individual was included as a random effect. The primary analysis included adjustment for age at enrollment, sex, and the first 10 principal components of ancestry. OGTT data were used until the diagnosis of diabetes, as treatment for diabetes could significantly alter OGTT results. Data points with negative IGI_{60} values were excluded during logarithmic normalization (11% of total data points). For the Cox regression analysis to calculate the risk for T2D for each genetic risk group, T2D PRS was constructed using European and East Asian ancestry-specific T2D GWAS that does not include the Ansan-Ansung cohort to avoid overfitting (21,22). Statistical analysis was performed with Python version 2.7.5 and R version 4.2.2 software using the computing server at the Genomic Medicine Institute Research Service Center.

Data and Resource Availability

The Ansan-Ansung Cohort Study data are available from the Korean National Institute of Health (https://biobank.nih.go.kr). The data sets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

RESULTS

Population Characteristics and Incidence of Diabetes

Baseline characteristics of the 6,311 Ansan-Ansung cohort participants are shown in Table 1. Participants with a higher genetic risk for T2D had a stronger family history of diabetes, higher fasting glucose, higher 2-h glucose, and higher HbA_{1c} levels. It is important to note that the participants included in the analysis had normal fasting glycemia, even in the high genetic risk group (84.5 mg/dL, 95% CI 84.0–85.0). Participants with a higher genetic risk were younger at baseline probably because those who already developed diabetes at baseline were excluded from the analysis (23). Fasting insulin, systolic blood pressure, and cholesterol profile did not differ across genetic risk groups. During a mean follow-up of 10.9 years, 188 participants (14.9%), 851 participants (22.5%), and 374 participants (29.6%) developed T2D in the low, intermediate, and high genetic risk groups, respectively. Having a higher genetic risk for diabetes was associated with a higher risk for diabetes, with an adjusted hazard ratio of 2.54 (95% CI 2.12–3.04) in the high genetic risk group and 1.88 (1.60–2.22) in the intermediate genetic risk group compared with the low genetic risk group (Supplementary Fig. 3).

Genetic Risk for T2D Is Associated With Lower Baseline β-Cell Function

Comparison across genetic risk groups at baseline revealed that a higher genetic risk for diabetes was associated with impaired insulin sensitivity (lower composite ISI), decreased β-cell secretory response (lower IGI_{60}), and impaired β-cell function relative to insulin sensitivity (lower DI) (Fig. 1). We observed a significantly lower composite ISI at baseline per 1-SD increase in T2D PRS ($\beta_{ISI} = -0.042$, $P_{SD} = 6.2 \times 10^{-5}$), with a 3% decrease and an 8% decrease in the intermediate and high genetic risk groups compared with the low genetic risk group, respectively ($P_{trend} = 1.9 \times 10^{-4}$). Also, there was a significantly lower IGI_{60} at baseline per 1-SD increase in T2D PRS ($\beta_{IGI60} = -0.107$, $P_{SD} = 1.6 \times 10^{-5}$), with a 12% decrease and a 19% decrease in the intermediate and high genetic risk groups, respectively,

Table 1—Baseline characteristics of study participants by genetic risk for diabetes

Genetic risk for diabetes	Low risk (n = 1,262)	Intermediate risk (n = 3,787)	High risk (n = 1,262)	P*	Statistically significant post hoc analysis comparisons ($P < 0.05$)†
Age (years)	51.9 (8.7)	51.7 (8.7)	50.8 (8.6)	0.003	b, c
Male sex	613 (48.6)	1,771 (46.8)	586 (46.4)	0.159	
BMI (kg/m^2)	24.4 (3.0)	24.4 (3.0)	24.6 (3.0)	0.266	
Waist circumference (cm)	82.1 (8.8)	82.1 (8.6)	82.1 (8.5)	0.988	
Systolic blood pressure (mmHg)	120 (18)	120 (18)	121 (17)	0.535	
Diastolic blood pressure (mmHg)	80 (11)	80 (11)	80 (11)	0.628	
FPG (mg/dL)	81.5 (8.0)	82.6 (8.2)	84.5 (9.0)	<0.001	a, b, c
2-h glucose (mg/dL)	110 (28)	115 (30)	119 (31)	<0.001	a, b, c
HbA_{1c} (%)	5.49 (0.33)	5.54 (0.34)	5.59 (0.34)	<0.001	a, b, c
Fasting insulin (pmol/L)‡	6.3 (1.9)	6.4 (1.9)	6.6 (1.8)	0.101	
IGI_{60}‡	7.6 (3.7)	6.7 (3.5)	6.2 (3.3)	<0.001	a, b
Composite ISI‡	10.0 (1.8)	9.7 (1.8)	9.2 (1.7)	<0.001	b, c
DI‡	70.9 (3.4)	61.1 (3.2)	53.6 (3.1)	<0.001	a, b, c
Total cholesterol (mmol/L)‡	186 (1.2)	187 (1.2)	188 (1.2)	0.285	
Triglycerides (mmol/L)‡	135 (1.6)	136 (1.6)	139 (1.6)	0.092	
HDL cholesterol (mmol/L)‡	44.2 (1.2)	44.0 (1.2)	43.7 (1.2)	0.175	
LDL cholesterol (mmol/L)‡	110 (1.4)	111 (1.3)	111 (1.3)	0.364	
Hypertension	335 (26.5)	985 (26.0)	347 (27.5)	0.580	
Family history of diabetes	102 (8.1)	367 (9.7)	162 (12.8)	<0.001	b, c
Lifestyle factors§					
No current smoking	945 (74.9)	2,869 (75.8)	956 (75.8)	0.81	
Not overweight	417 (33.0)	1,215 (32.1)	385 (30.5)	0.381	
Regular physical activity	732 (58.0)	2,306 (60.9)	750 (59.4)	0.172	
Healthy diet	851 (67.4)	2,592 (68.4)	864 (68.5)	0.786	
Adequate sleep	629 (49.8)	1,870 (49.4)	651 (51.6)	0.398	
Healthy lifestyle category				0.85	
Favorable (≥4 healthy lifestyle factors)	351 (27.8)	1,080 (28.5)	351 (27.8)		
Intermediate (3 healthy lifestyle factors)	448 (35.5)	1,368 (36.1)	469 (37.2)		
Unfavorable (≤2 healthy lifestyle factors)	463 (36.7)	1,339 (35.4)	442 (35.0)		

Data are unadjusted mean (SD), geometric mean (geometric SD), or n (%). *P values for the difference between genetic risk groups were calculated using ANOVA and the χ^2 test for continuous and categorical variables, respectively. †a, Low genetic risk vs. intermediate genetic risk; b, low genetic risk vs. high genetic risk; c, intermediate genetic risk vs. high genetic risk. ‡Variable was log-transformed before statistical analysis and shown as the geometric mean (geometric SD). §Refers to behavioral lifestyle factors adapted from the lifestyle components of Life's Essential 8.

compared with the low genetic risk group ($P_{trend} = 4.3 \times 10^{-5}$). The trend was more prominent for DI ($\beta_{DI} = -0.134$, $P_{SD} = 1.0 \times 10^{-8}$), with a 14% decrease and a 25% decrease at baseline in the intermediate and high genetic risk groups, respectively ($P_{trend} = 2.6 \times 10^{-8}$). These data suggest that insulin secretory defects may coexist with decreased insulin sensitivity in people with a high genetic risk for diabetes, even in the normoglycemic state. Among the 824 index variants known to be associated with T2D, an intronic variant of *CDKAL1* (rs7766070) was significantly associated with the baseline IGI_{60} and DI but not with baseline ISI ($\beta_{IGI60} = -0.168$, $P = 2.3 \times 10^{-6}$; $\beta_{DI} = -0.137$, $P = 4.65 \times 10^{-5}$) after Bonferroni correction (Supplementary Table 2).

Genetic Risk for T2D Is Associated With Progressive β-Cell Dysfunction

There was a total of 33,718 OGTT data points (mean 5.34 per person) available for analysis across the mean follow-up of 10.9 years. Higher T2D PRS was associated not only with a lower composite ISI, IGI_{60}, and DI at baseline but also with a faster decline in DI with a smaller compensatory increase in IGI_{60} over time (Fig. 2 and Supplementary Table 3). The rate of decline of the $\log_2$-transformed composite ISI was not significantly different among genetic risk groups during follow-up (P_{SD} = 0.70). Regarding IGI_{60}, the low genetic risk group had the highest rate of increase in IGI_{60} ($\beta_{IGI60} = 0.016$, $P = 9.2 \times 10^{-6}$),

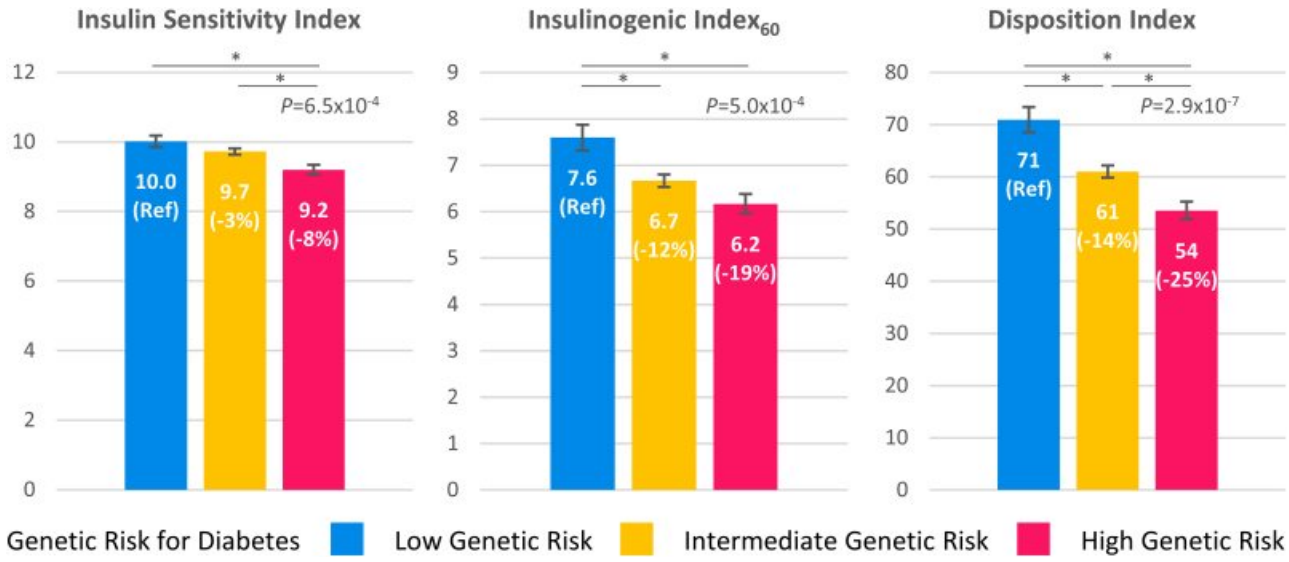

Figure 1—Baseline composite ISI, IGI_{60}, and DI by genetic risk for T2D. Variables were log-transformed before statistical analysis and shown as the geometric mean. *P* values show comparisons between groups performed by ANCOVA, adjusted by baseline age, sex, and the first 10 principal components of ancestry. Error bars indicate the SE of the mean. $*P < 0.05$ at post hoc analysis. Ref, reference.

whereas no significant increase was observed in the high genetic risk group ($\beta_{IGI60} = 1.1 \times 10^{-3}$, $P = 0.765$). After 10 years, there was an additional 3.7% decrease in IGI_{60} per 1-SD increase in T2D PRS ($P_{SD} = 9.1 \times 10^{-4}$).

The trajectory of DI, which adjusts the β-cell secretory response by insulin sensitivity, demonstrated a more pronounced divergence among the genetic risk groups (Fig. 2). The log_2-transformed DI decreased in all genetic risk groups during follow-up, with a 1.83-fold faster decline in the high genetic risk group compared with the low genetic risk group (−0.034 vs. −0.019, $P = 0.0021$). After 14 years of follow-up, there was a 17% decrease compared with baseline in the low genetic risk group, while there was a 28% decrease in the high genetic risk group. Per 1-SD increase in T2D PRS was associated with an additional 4.1% decrease in DI after 10 years ($P_{SD} = 1.2 \times 10^{-4}$). This translates into a doubling of the baseline difference of DI (log_2-transformed) between the high and low genetic risk groups after 32 years. The significant change per 1-SD increase in T2D PRS and the trend of a faster decline of DI remained consistent after additional adjustment for T2D clinical risk factors, such as fasting glucose, BMI, family history of T2D, hypertension, and regular physical activity (24) (Supplementary Table 4). Analysis of extremes showed further deviation in the trajectory of DI, with a 1.95-fold faster decline in the highest decile group compared with the lowest decile group (−0.036 vs. −0.018, $P = 0.011$) (Supplementary Table 5).

Among the 824 lead T2D variants, an intronic variant of *SGSM1* (rs7291042) was associated with a faster rate of decline in log_2-transformed DI ($\beta_{DI} = -0.0104$, $P = 5.3 \times 10^{-6}$). An intergenic variant near *FOXA2* (rs2181063) and an intronic variant of *LAMC1* (rs4129858) was associated with the rate of change in log_2-transformed ISI ($\beta_{ISI} = -4.0 \times 10^{-3}$, $P = 5.1 \times 10^{-5}$; $\beta_{ISI} = -4.2 \times 10^{-3}$, $P = 1.2 \times 10^{-5}$, respectively) (Supplementary Table 6).

Comparison With GRS and Cluster-Specific Polygenic Scores

As calculating PRS using >1 million genome-wide variants requires a high level of computational expertise, we further investigated whether a simpler T2D GRS, computed with only the 824 genome-wide significant index single nucleotide variants, was also associated with the changes in β-cell function. A 1-SD increase in T2D GRS was significantly associated with the rate of change in DI ($\beta_{DI} = -6.3 \times 10^{-3}$, $P_{SD} = 4.5 \times 10^{-5}$) to a similar degree to that of T2D PRS calculated with PRS-CSx (Supplementary Tables 7 and 8). Among the eight cluster-specific pPSs, a 1-SD increase in β-cell +PI, β-cell −PI, residual glycemic, body fat, and metabolic syndrome pPS was significantly associated with a lower DI at baseline (Supplementary Table 8). However, only the residual glycemic pPS was associated with the faster decline in DI ($\beta_{DI} = -4.8 \times 10^{-4}$, $P_{SD} = 2.0 \times 10^{-3}$) (Supplementary Table 9). In terms of insulin sensitivity, the baseline composite ISI was significantly associated with the pPS for the residual glycemic, obesity, and lipodystrophy clusters (Supplementary Table 8). Notably, the pPS for the obesity cluster showed a significant association with a faster decline in composite ISI over time ($\beta_{ISI} = -1.9 \times 10^{-3}$, $P_{SD} = 4.5 \times 10^{-3}$) (Supplementary Table 9).

Healthy Lifestyle Attenuates Rate of Progressive β-Cell Dysfunction

As lifestyle modification is the mainstay in the management of people at risk for developing diabetes, we investigated the interaction of lifestyle, genetic risk, and the trajectory of β-cell function. An unfavorable lifestyle was associated with a 2.40-fold faster rate of decline in log_2-transformed DI compared with a favorable lifestyle (−0.035 vs. −0.015, $P = 2.9 \times 10^{-5}$) (Supplementary Table 10). Across all genetic risk groups, adherence to a healthy lifestyle was associated with a slower decline in DI (Fig. 3). Having an unfavorable lifestyle, compared with a favorable lifestyle, was associated with a 1.51-fold faster decline in log_2-transformed DI in the high genetic risk group (−0.044 vs. −0.029, $P = 0.080$) (Supplementary Table 11). This translates to a 10% less decline in DI after 10 years in people with a favorable lifestyle compared with those with an unfavorable lifestyle in the high genetic risk group. The attenuated decline

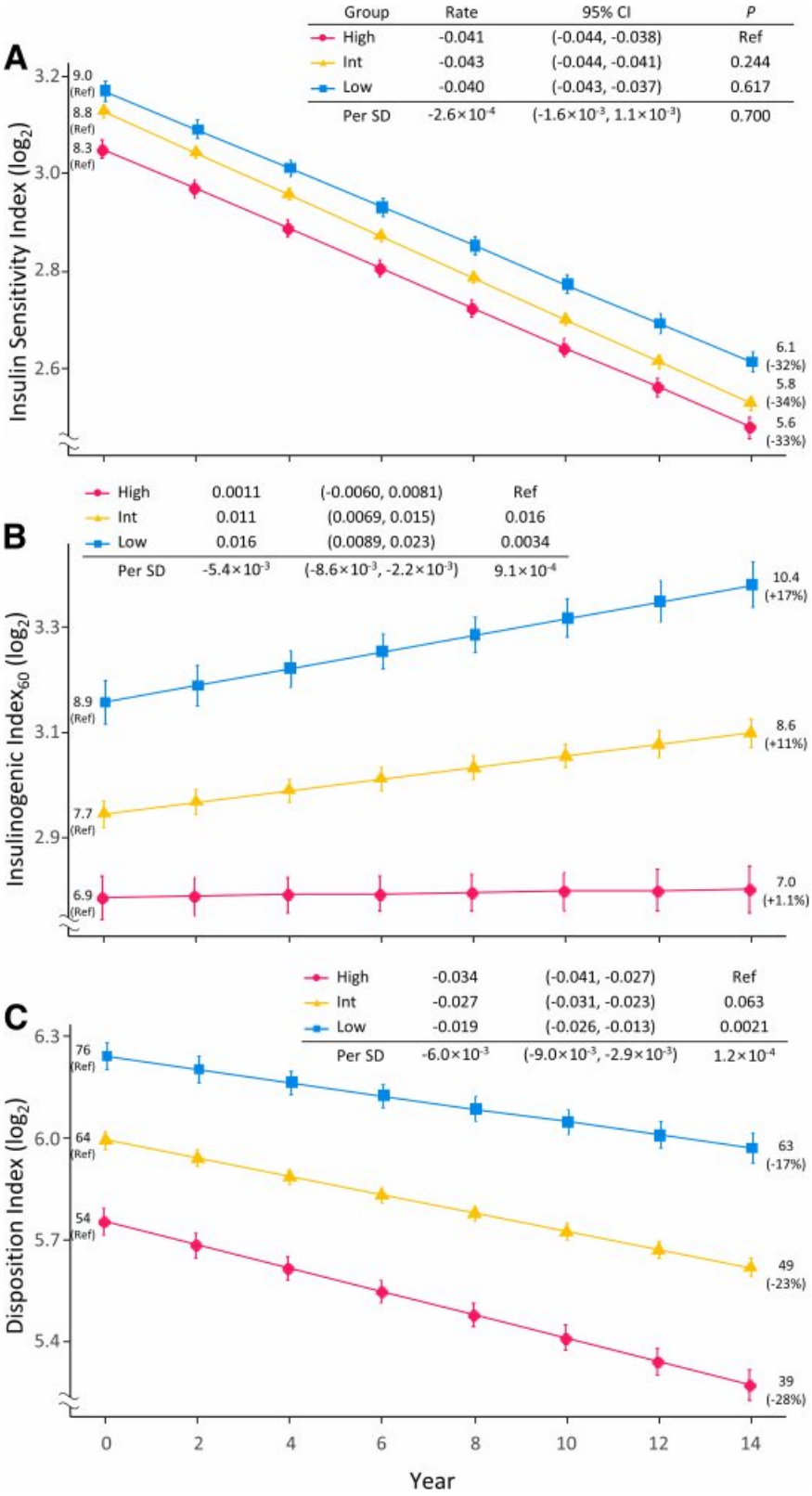

Figure 2—Trajectories of composite ISI (*A*), IGI_{60} (*B*), and DI (*C*) by genetic risk for T2D. Data are adjusted for baseline age, sex, and the first 10 principal components of ancestry. The average level of the parameter is plotted from baseline to year 14 at 2-year intervals. Back-transformed levels at baseline and at year 14 are shown with the percentage of change from baseline in the parenthesis. The average rate of change per year of log_2-transformed parameter and its 95% CI by genetic risk group and per 1-SD increase in T2D PRS are presented in each panel. Comparison of the rate of change of index by genetic risk group was performed, with the high genetic risk group as reference (Ref). Error bars indicate the SE of the mean. High, high genetic risk group; Int, intermediate genetic risk group; Low, low genetic risk group.

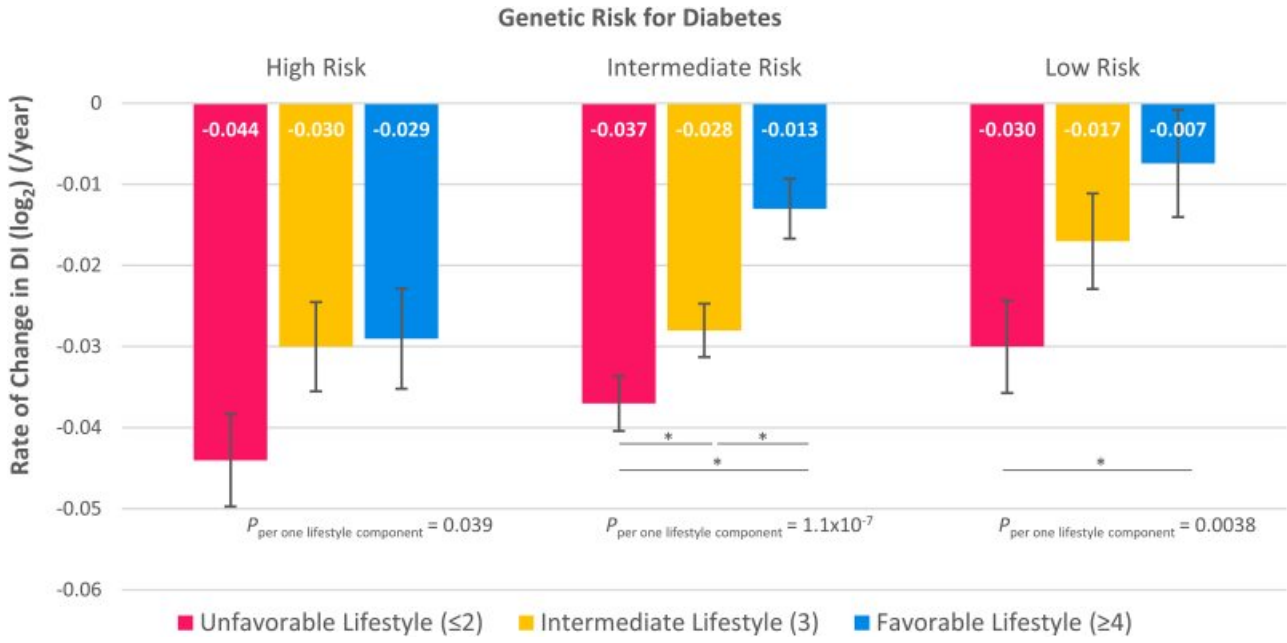

Figure 3—Rate of change in DI by genetic risk for T2D and lifestyle. The rate of change in $\log_2$-transformed DI by genetic risk for T2D and lifestyle is shown. Lifestyle factors were no current smoking, not overweight, regular physical activity, healthy diet, and adequate sleep duration. Data are adjusted for baseline age, sex, and the first 10 principal components of ancestry. *P* values for the decrease in the rate of decline in DI per one additional component of healthy lifestyle are presented. Error bars indicate the SE of the mean. *$P < 0.05$ at post hoc analysis.

in DI after 10 years in people with a favorable lifestyle compared with those with an unfavorable lifestyle was 15% ($P = 2.4 \times 10^{-6}$) and 14% ($P = 0.011$) in the intermediate and low genetic risk groups, respectively. There was a significantly slower rate of decline in DI per each increment in healthy lifestyle component, which was consistent across all genetic risk groups (Fig. 3 and Supplementary Table 11). This translates to a 4.4% less decline in DI after 10 years per one additional healthy lifestyle component in people with high genetic risk ($P = 0.039$), which is similar to having a lower genetic risk by 1-SD decrease (4.1% less decline) in T2D PRS.

CONCLUSIONS

In this study, we investigated the association of genetic risk for T2D assessed by genome-wide polygenic score and the trajectory of OGTT-derived β-cell function for as long as 14 years in a prospective cohort specifically designed to study the genetic and environmental risk factors for diabetes. Having a higher genetic risk for diabetes was associated with a lower composite ISI, IGI_{60}, and DI at baseline. Moreover, it was associated with a similar decline in composite ISI but a significantly less compensatory increase in IGI_{60}, resulting in a faster decline in DI. A healthy lifestyle was associated with an attenuation in the rate of decline in DI across all genetic risk groups.

The results from our study support three notable conclusions. First, the genome-wide polygenic score, derived from individual's genetic information, reflects the pathophysiology of T2D in terms of β-cell function and insulin sensitivity. During the development of diabetes, insulin sensitivity typically declines, and there is an insufficient compensatory increase in insulin secretion (7,25–27). Our findings demonstrate that the PRS was robustly associated with baseline β-cell dysfunction and impaired insulin sensitivity. This aligns with previous cross-sectional studies that reported the association between genetic variants of diabetes and both β-cell dysfunction and insulin sensitivity (4). Our results expand this notion and clearly demonstrate that a genetic predisposition to T2D is associated with a progressive decline in β-cell function adjusted for insulin sensitivity in a longitudinal cohort that was followed with biennial OGTTs. Intriguingly, the PRS showed a stronger association with, and a greater degree of change in, the trajectory of insulin secretory function compared with insulin sensitivity. This might be attributed to the fact that among the known T2D-related variants, a larger number of variants are suggested to be associated with β-cell dysfunction than insulin sensitivity (28).

Second, the genetic risk assessed by PRS could be used to predict the clinical course of an individual's β-cell function. We have quantitatively demonstrated that people with a higher genetic risk for T2D follow a steeper course to the development of diabetes, even after adjusting for clinical risk factors. Specifically, there was an additional 4.1% decrease in DI after 10 years for each SD increase in T2D PRS. Furthermore, after 32 years, the baseline difference of $\log_2$-transformed DI between the low and high genetic risk groups is projected to have doubled. This finding underscores the clinical utility of T2D PRS in predicting T2D and identifying individuals at risk for a rapid decline in β-cell function. Given the ongoing nature of β-cell dysfunction even after the diagnosis of diabetes (29,30), our results could be extrapolated to predicting the clinical course following the diagnosis of diabetes, which requires further validation. People with a high genetic risk for diabetes could have a shorter time to treatment failure of oral medication, leading to earlier initiation of insulin therapy because of rapid deterioration of β-cell function. Also, the accelerated decline of β-cell function

in people with a high genetic risk for diabetes may result in an increased risk for diabetes-related complications (31,32).

Third, our results show that healthy lifestyle may ameliorate the decline in β-cell function across all genetic risk groups. These data align with previous studies reporting the interplay between gene and environment in the risk for T2D (33–35). Results from our study suggest that PRS could be used to prioritize individuals at high risk of rapid deterioration of β-cell function and emphasize lifestyle modifications. Our analysis implies that improving one lifestyle component at a time can prevent a decline of β-cell function by 4.4% after 10 years in the high genetic risk group. This information could motivate people, especially those at high genetic risk, to actively engage in lifestyle interventions.

The strength of this study is that we evaluated β-cell function and insulin sensitivity using estimates derived from 2-h 75-g OGTTs in a large prospective cohort. We repeatedly measured these parameters every 2 years for up to 14 years, with an average of 5.34 measurements per person. We adjusted for various clinical factors and evaluated comprehensive lifestyle factors to evaluate the gene-environment interactions. We have also demonstrated that the T2D GRS constructed with just the index single nucleotide variants could also be used to identify people at risk for rapid β-cell deterioration, which would be more practical in its application in the current clinical settings.

Our study has certain limitations. First, it was conducted in a single community-based prospective cohort of East Asian ancestry, which limits generalizability. Additional studies are required to replicate our findings in a variety of populations. Second, we used a β-cell index derived from OGTTs and not IVGTTs. While indices derived from OGTTs have been shown to correlate well with those derived from IVGTTs in cross-sectional analyses, this relationship is less apparent for ISI in longitudinal settings (36). Also, we used IGI_{60} as the index of pancreatic β-cell secretory response because glucose and insulin at 30 min were not available. However, IGI_{60} is an acceptable measure of early insulin secretion as it correlates well with IGI_{30} and using OGTT-derived β-cell indices is a more feasible approach than IVGTT-derived measures in a large prospective cohort setting such as ours (28,37).

In conclusion, after quantifying genetic risk using a genome-wide polygenic score among 6,311 participants in a prospective cohort, having a higher genetic risk for T2D was associated with a faster rate of decline in β-cell function. Healthy lifestyle, assessed by five independent components, was associated with a decreased rate of decline in β-cell function across all genetic risk groups. Genetic information could be used to identify those at risk for faster decline of β-cell function, enabling a focus on lifestyle intervention.

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