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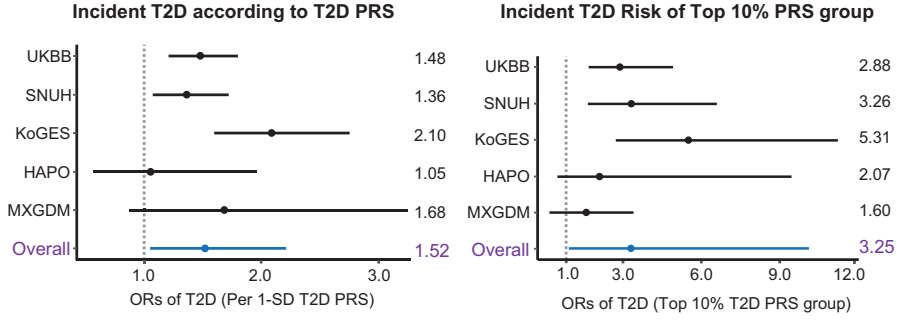
- **Women with a history of gestational diabetes mellitus (GDM) are at increased risk of developing incident type 2 diabetes (T2D).**
- **We analyzed data from five GDM cohorts (UK Biobank (UKBB), Seoul National University Hospital (SNUH), Korean Genome and Epidemiology Study (KoGES), Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) and Mexican GDM (MXGDM)) representing four different ancestries (N=1,895).**
- **Genome-wide T2D polygenic risk score (PRS) is associated with increased risk of incident T2D (Odds Ratio (OR)=1.52).**
- **There was a significant association when we compared top 10 % PRS group to all other remainders (OR=3.25).**



T2D polygenic risk score was associated with the onset of T2D in women with a history of GDM

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ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Women with a history of gestational diabetes mellitus (GDM) are at an increased risk of developing type 2 diabetes (T2D), at least partially because of a higher genetic risk.
- **What is the specific question(s) we wanted to answer?**
  We incorporated genome-wide T2D polygenic risk score into a clinical risk model to test if it improved the predictive accuracy for T2D in women with previous GDM across with diverse ancestral backgrounds and clinical settings.
- **What did we find?**
  T2D polygenic risk score was associated with incident T2D and improved the predictive accuracy.
- **What are the implications of our findings?**
  Genetic information in women with a history of GDM could be used to identify those who are at high risk of future development of T2D.

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OBJECTIVE

Women with a history of gestational diabetes mellitus (GDM) are at increased risk of developing type 2 diabetes (T2D). It remains unclear whether genetic information improves prediction of incident T2D in these women.

RESEARCH DESIGN AND METHODS

Using five independent cohorts representing four different ancestries (n = 1,895), we investigated whether a genome-wide T2D polygenic risk score (PRS) is associated with increased risk of incident T2D. We also calculated the area under the receiver operating characteristics curve (AUROC) and continuous net reclassification improvement (NRI) following the incorporation of T2D PRS into clinical risk models to assess the diagnostic utility.

RESULTS

Among 1,895 women with previous history of GDM, 363 (19.2%) developed T2D in a range of 2 to 30 years. T2D PRS was higher in those who developed T2D (−0.08 vs. 0.31, $P = 2.3 \times 10^{-11}$) and was associated with an increased risk of incident T2D (odds ratio 1.52 per 1-SD increase, 95% CI 1.05–2.21, P = 0.03). In a model that includes age, family history of diabetes, systolic blood pressure, and BMI, the incorporation of PRS led to an increase in AUROC for T2D from 0.71 to 0.74 and an intermediate improvement of NRI (0.32, 95% CI 0.15–0.49, $P = 3.0 \times 10^{-4}$). Although there was variation, a similar trend was observed across study cohorts.

CONCLUSIONS

In cohorts of GDM women with diverse ancestry, T2D PRS was significantly associated with future development of T2D. A significant but small improvement was observed in AUROC when T2D PRS was integrated into clinical risk models to predict incident T2D.

Gestational diabetes mellitus (GDM) is defined as abnormal glucose tolerance first recognized during pregnancy (1). Beyond the adverse pregnancy outcomes associated with GDM, such as an increased rate of macrosomia and related birth injuries, women with a history of GDM are at increased risk of developing type 2 diabetes (T2D). As many as 20–40% of women with GDM progress to T2D within 10 years after parturition (2,3). Several risk factors, including severity of hyperglycemia during pregnancy, prepregnancy BMI, and family history of diabetes, are known to be associated with the

development of T2D (2). While there have been efforts to predict the onset of T2D using these traditional clinical risk factors, these approaches still have shortcomings. This is largely because the women diagnosed with GDM are relatively young, and do not exhibit the typical risk factors or endophenotypes associated with T2D as prominently as other at-risk individuals (1,4). This led to a modest prediction accuracy of clinical models, typically around an area under the receiver operating characteristic curve (AUROC) of 0.7 in previous studies (4). Therefore, predicting which women with GDM will progress to T2D remains challenging.

In recent years, the success of genome-wide association studies (GWAS) has expanded the number of genetic variants associated with T2D to over 600 (5). However, these common variants individually confer only a small relative risk and explain a limited portion of the heritability of diabetes (6). Previous studies also indicated that integrating this genetic information as individual-level polygenic risk score (PRS) has potential to improve the current T2D prediction model, based on clinical risk factors (7,8). Recent advances in PRS methods have expanded their scope to encompass the entire genome, comprising millions of variants rather than just a limited number of significant variants and reducing error introduced by noise using shrinkage priors. This has resulted in greater predictive efficacy compared with previous efforts and facilitated risk stratification by identifying individuals with high genetic risk for T2D in the general population, with most studies focusing on Europeans (9,10). The applicability of these advancements to women with a history of GDM, who are considered at high risk for T2D, warrants further study, particularly in the context of diverse ancestral backgrounds.

In this study, we investigated the utility of genome-wide genetic information on T2D prediction in women with a history of GDM from five cohorts representing four different ancestral backgrounds. We first quantified the association between genome-wide T2D PRS and incident T2D while evaluating their potential for risk stratification. Next, we evaluated whether incorporating T2D PRS into a clinical risk model could improve the predictive accuracy for incident T2D. Exploring the role of PRS in this context will serve as a valuable example to assess whether genetic information could advance the implementation of precision medicine (11).

RESEARCH DESIGN AND METHODS

Study Cohorts

Five independent cohorts that represent four different ancestries were used in this study. Three were longitudinal cohorts designed to specifically follow women with a history of GDM, and two were population-based cohorts where GDM women were selected retrospectively. The screening process to identify eligible women with GDM is depicted in Supplementary Fig. 1. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki as revised in 2013.

UK Biobank

UK Biobank (UKBB) cohort is a prospective population-based cohort that enrolled half a million people aged 37 to 73 years from across England, Scotland, and Wales between 2007 and 2010 (12). Participants with a history of GDM and their incident T2D events were defined using a previously validated algorithm (13). This algorithm screens the participants with GDM using self-reported medical history and medication records entered via touchscreen or through verbal interview with study nurse.

Seoul National University Hospital

Seoul National University Hospital (SNUH) GDM cohort is a hospital-based prospective study that enrolled women with GDM between 1996 and 2003 in Korea (14). For the diagnosis of GDM, a 50-g 1-h oral glucose tolerance test (OGTT) during 24–28 weeks' gestation was used for screening, warranting a diagnostic 100-g OGTT if the result was $\geq$140 mg/dL (15). Among the 357 participants, a total of 13 (3.6%) were diagnosed with GDM before week 24. The thresholds for the diagnosis were based on the National Diabetes Data Group (NDDG) criteria (14). T2D was diagnosed based on the American Diabetes Association (ADA) criteria (16).

Korean Genome and Epidemiology Study

Korean Genome and Epidemiology Study (KoGES) is a collection of prospective population-based cohort studies in Korea (17). We exclusively focused on the Health Examinee cohort, as it comprises the largest number of participants with longitudinal follow-up. Participants with a history of GDM were identified based on self-reported medical history. Incident T2D events were captured based on self-reported medical history and laboratory data (fasting glucose and HbA_{1c}).

Hyperglycemia and Adverse Pregnancy Outcomes Study

Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study is a prospective observational study that recruited approximately 25,000 pregnant women aged 18 years or older from nine countries (18). The participants with a history of GDM were identified based on the International Association of the Diabetes and Pregnancy Study Groups criteria, and T2D diagnosis was made using the ADA criteria (18,19). In this study, we exclusively included non-Hispanic European, East Asian, and South Asian participants because of the limited sample size for other ancestries (Hispanic, African American, etc.).

Mexican GDM Study

Mexican GDM (MXGDM) cohort is a hospital-based prospective cohort that recruited Mexican women at four different health institutions in Mexico City (20). Pregnant women aged 18 years or older and beyond 20 gestational weeks were eligible for the study. GDM was diagnosed with a two-step approach, including a diagnostic 100-g OGTT using Carpenter-Coustan criteria (21). T2D events were identified based on 75-g 2-h OGTT according to the ADA criteria (16). Women who did not finish the diagnostic OGTT or who were diagnosed with a subclinical metabolic disease were excluded.

Genetic Data and PRS

Detailed information on computing PRS is provided in Supplementary Table 1. Briefly, we constructed T2D PRS representing a weighted average of the effects of variants across the genome: genome-wide PRS using the PRS–continuous shrinkage priors method (22). We determined the weights for the T2D PRS using the independent training sets, external ancestry-specific GWAS summary statistics, and linkage disequilibrium (LD) reference panels from prior publications to avoid any overfitting.

UKBB

The participants in the UKBB were genotyped on the Affymetrix UK Biobank Lung Exome Variant Evaluation Axiom array or the Affymetrix UK Biobank

Axiom array and imputed using the UK10K reference panel (12). PRS was calculated based on the summary statistics of the Diabetes Genetic Replication and Meta-analysis (DIAGRAM) consortium and the UKBB LD reference panel (22,23).

SNUH

The participants in the SNUH cohort were genotyped using the Affymetrix Axiom Biobank Plus Genotyping Array and imputed using the TOPMed reference panel (14). PRS was calculated based on summary statistics obtained from the Biobank Japan (BBJ) and 1000 Genomes Project Phase 3 (1000GP3) LD reference panel (22,24,25).

KoGES

The participants in the KoGES cohort were genotyped using the Korea Biobank Array, which is optimized for the Korean population (26). Single nucleotide polymorphism genotype data were imputed using the East Asian 1000GP3 LD reference panel, and PRS was calculated based on summary statistics from BBJ and 1000GP3 LD reference panel (22,24,25).

HAPO

The participants of the HAPO study were genotyped using the Multi-Ethnic Genotyping Array. Imputation was carried out separately based on each ancestry, using the respective ancestral population from the 1000GP3 reference panel (25,27). PRS was calculated using summary statistics from BBJ for East Asian participants, and those from the DIAGRAM and the Diabetes Meta-analysis of Trans-Ethnic Association Studies (DIAMANTE) consortium for their corresponding non-Hispanic European and South Asian participants, along with 1000GP3 LD reference panels (22–24,28).

MXGDM

The participants in the MXGDM cohort were genotyped using Illumina Global Screening Array v3.0 and imputed using the TOPMed r2 reference panel (29). PRS was calculated using European GWAS summary statistics from the DIAMANTE consortium and the UKBB LD reference panel (22,30).

Statistical Analysis

We obtained clinical information, including age at GDM diagnosis, a family history of diabetes, BMI, systolic blood pressure (SBP), and fasting plasma glucose (FPG). For the SNUH and MXGDM cohorts, we used SBP and FPG measurements taken during pregnancy and prepregnancy BMI. For the HAPO cohort, we used measurements of SBP, FPG, and BMI taken during 24–32 weeks' gestation. However, for the UKBB and KoGES, which were population based and lacked specific pregnancy-related data, we used BMI, SBP, and FPG recorded at baseline enrollment of the cohort. The FPG data from the UKBB were excluded because of their unavailability. For participants without an exact age of GDM diagnosis, we used the age at their most recent pregnancy, if available. Otherwise, participants with any missing variables (diagnosis date of GDM, family history of diabetes, BMI, SBP, and FPG) were excluded from the analysis. Participants who had T2D prior to the GDM diagnosis were also excluded. For the population-based cohorts (UKBB and KoGES), we excluded individuals with pregestational diabetes if their age at T2D diagnosis was earlier than their age at GDM diagnosis. The SNUH and MXGDM cohorts were established for GDM research purposes, and women with pregestational diabetes were excluded during enrollment. HAPO study excluded participants from the study if their glucose level during pregnancy was diagnostic of diabetes (20). Baseline characteristics are presented as *n* (percent) for categorical variables, mean (SD) for normally distributed variables, and median (Q1, Q3) for nonnormally distributed variables.

We standardized T2D PRS within each cohort to have a mean of zero and SD of one. To analyze the association between T2D PRS and risk of incident T2D, odds ratios (OR) were calculated for 1-SD increment of PRS using logistic regression in each cohort. Among the first 10 genetic principal components (PCs), which reflects ancestry information and population structure, those showing a statistically significant association with incident T2D were adjusted for in the logistic model investigating the association between T2D PRS and incident T2D. As part of risk stratification, we compared participants whose PRS ranked in the top 10% and 25% to all the other remaining participants to evaluate the risk of incident T2D in the high genetic risk group (Fig. 1*B* and Supplementary Table 4).

We also conducted a time-to-event analysis using a Kaplan-Meier curve and Cox proportional hazards regression model to assess the risk of incident T2D based on the T2D PRS (Fig. 2*B* and Supplementary Fig. 3). The hazard ratios (HR) for incident T2D were calculated for each PRS with 1-SD increment in T2D PRS. The duration of follow-up for each participant was calculated as years from the date of GDM diagnosis to either the onset of T2D or end of follow-up, whichever came first. We incorporated significant genetic PCs and compared participants whose T2D PRS ranked in the top 10% and 25% to all other remaining participants. Since the HAPO cohort lacked a precise date of T2D diagnosis, it was excluded from the time-to-event analysis (Fig. 2*B* and Supplementary Table 4).

For the clinical implications of T2D PRS, we assessed the effect of PRS on incident T2D prediction by calculating the AUROC, continuous net reclassification improvement (NRI), and NRI quadrants using three logistic regression models as follows (Supplementary Tables 5–11). Model 1 was adjusted for age at GDM diagnosis and family history of diabetes. Model 2 included two additional clinical risk factors: BMI and SBP. Model 3, considered the strongest prediction model, incorporated FPG into model 2. We categorized the NRI as strong if the value exceeded 0.6, intermediate if between 0.2 and 0.6, and weak if below 0.2 (31). As T2D PRS was nonsignificantly associated with a decreased risk of incident T2D in European subgroup of the HAPO study because of a limited sample size, we analyzed both AUROC and NRI, with and without this subgroup, to assess the potential overestimation when including this subgroup (Supplementary Table 3).

Genotype quality control and statistical analysis were performed using PLINK 1.90 and R 4.2.1.

Data and Resource Availability Statement

The data sets generated during and/or analyzed in the study are available from the corresponding author upon reasonable request.

RESULTS

Population Characteristics

A total of 1,895 participants with a history of GDM across five GDM cohorts

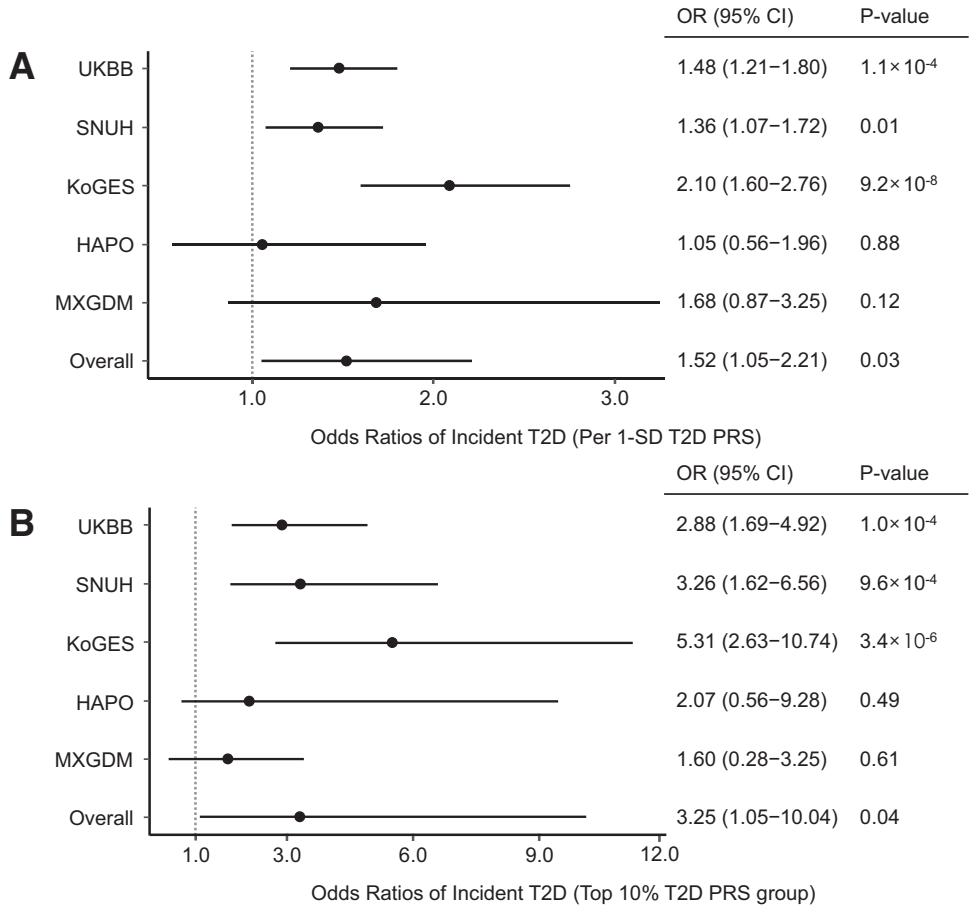

Figure 1—Risk of incident T2D according to genetic risk. ORs of T2D PRS in each group are shown. ORs were calculated for a 1-SD increment of T2D PRS using a logistic regression model. The model was adjusted for the statistically significant first 10 PCs that reflected ancestry. *A*: We compared participants with incident T2D to participants without incident T2D. *B*: We compared participants whose T2D PRS ranked in the top 10% to all other remaining participants.

were included in the analysis. The baseline characteristics of each cohort are displayed in Table 1. The proportion of participants who were diagnosed with incident T2D varied from 8.8% (HAPO) to 28.3% (SNUH) across the cohorts in a range of 2 (MXGDM) to 30 years (UKBB) of median follow-up. The mean age at GDM diagnosis was lowest in the KoGES cohort (26.9 years) and highest in the MXGDM cohort (34.8 years). The range of mean BMI spanned from 22.8 (SNUH) to 29.1 kg/m^2 (UKBB) across the five cohorts. Detailed characteristics according to the development of T2D are presented in Supplementary Table 2. Generally, individuals who developed T2D exhibited a stronger family history of diabetes (e.g., UKBB 50.8% vs. 42.0% and SNUH 50.5% vs. 37.1%). In addition, the mean BMI was also higher in participants who developed incident T2D (e.g., UKBB 33.1 vs. 28.2 kg/m^2 and SNUH 24.0 vs. 22.2 kg/m^2).

T2D PRS Based on GDM and T2D Status

We first compared the genome-wide T2D PRS in UKBB based on whether the participant had GDM and/or T2D (Supplementary Fig. 2). The highest average T2D PRS was observed in women with a history of GDM who later developed T2D (0.63, 95% CI −1.26–2.52). This was followed by women who developed T2D without a prior history of GDM (0.48, 95% CI −1.33–2.29), those who did not develop T2D after a GDM pregnancy (0.17, 95% CI −1.72–2.07), and finally, those without a history of either GDM or T2D (−0.19, 95% CI −2.04–1.65). The result was similar in the KoGES cohort.

Next, for those who had a history of GDM, we computed standardized T2D PRS within each study cohort. Across cohorts, the mean T2D PRS of participants who progressed to T2D was significantly higher compared with those who did not, except for the non-Hispanic European subgroup of HAPO, where no statistically significant difference was observed. When meta-analyzed, standardized mean T2D PRS was significantly higher in those who developed T2D (0.31, 95% CI −1.67–2.30) compared with those who did not (−0.08, 95% CI −2.00–1.85, $P = 2.7 \times 10^{-11}$) (Supplementary Table 3).

T2D PRS and Risk of T2D After GDM

We further investigated whether T2D PRS is an independent predictor of T2D after GDM pregnancy. T2D PRS was significantly associated with incident T2D, with an overall OR of 1.52 per SD (95% CI 1.05–2.21, $P = 0.03$) (Fig. 1*A*). The strongest association was observed in the KoGES cohort (OR 2.10, 95% CI 1.60–2.76, $P = 9.2 \times 10^{-8}$), where the participants' age at GDM diagnosis was relatively lower and had a median of 28 years of follow-up. When we compared participants whose T2D PRS ranked in the top 10% to the rest, there was a significantly increased risk of incident T2D (OR 3.25, 95% CI 1.05–10.04,

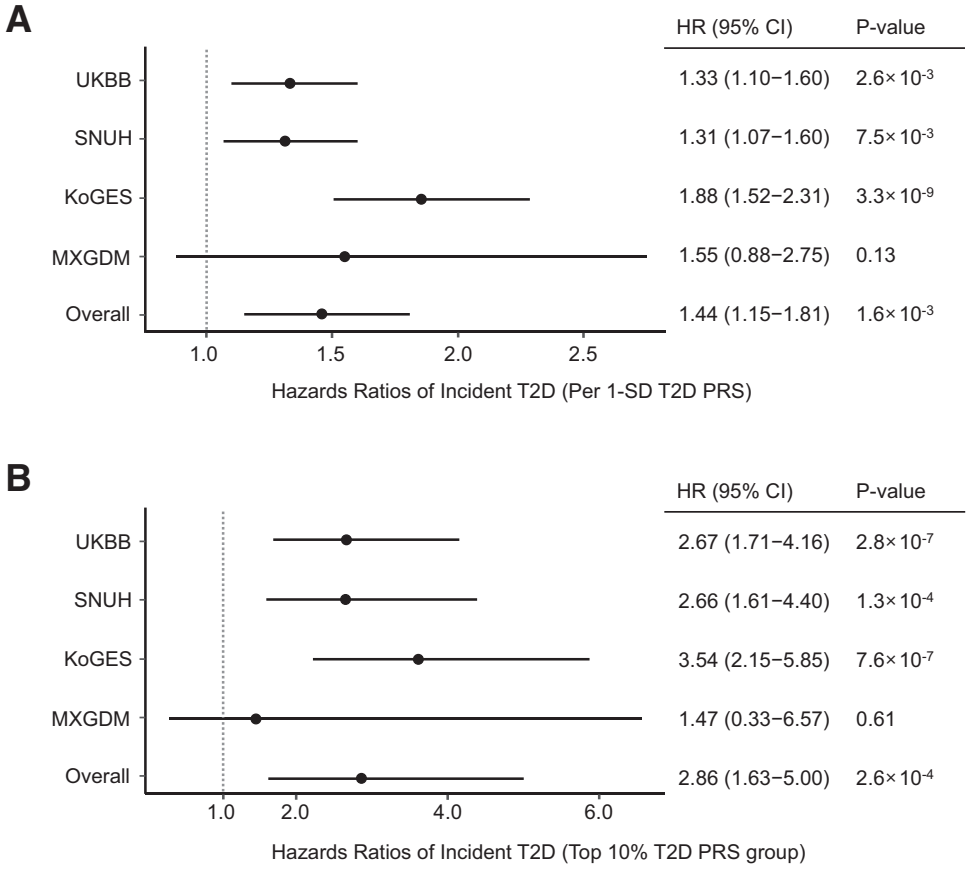

Figure 2—Risk of incident T2D according to genetic risk and follow-up time. HRs of T2D PRS in each group are shown. HRs were calculated for a 1-SD increment of T2D PRS using Cox proportional hazards regression model regarding follow-up time. The model was adjusted for the statistically significant first 10 PCs that reflected ancestry. *A*: We compared participants with incident T2D to participants without incident T2D. *B*: We compared participants whose T2D PRS ranked in the top 10% to all other remaining participants.

P = 0.04) (Fig. 1*B*). Participants in the KoGES cohort whose T2D PRS ranked in the top 10% had as much as a 5.31-fold increase in odds compared with the remaining participants.

The trend was consistent across all four cohorts in the time-to-event analysis, except for the HAPO study, where age at diagnosis for both GDM and T2D was not available. T2D PRS was significantly associated with incident T2D, with an overall HR of 1.44 per SD (95% CI 1.15–1.81, $P = 1.6 \times 10^{-3}$) (Fig. 2*A*). Individuals whose T2D PRS was in the top 10% had 2.86 times (95% CI 1.63–5.00, $P = 2.6 \times 10^{-4}$) higher risk of developing T2D compared with all other participants (Fig. 2*B*). Similarly, individuals whose T2D PRS was in the top 25% had 1.66 times (95% CI 1.06–2.59, P = 0.03) higher risk of developing T2D (Supplementary Table 4).

Clinical Implication of T2D PRS

When T2D PRS was integrated into clinical models, there was an improvement in predictive ability, as evidenced by the increase in AUROC. In model 1, which included only age at GDM and family history of diabetes, the incorporation of T2D PRS improved the AUROC by 0.07, from 0.61 (95% CI 0.58–0.64) to 0.68 (95% CI 0.65–0.71). The non-Hispanic European subgroup of the HAPO cohort was excluded from this and subsequent models because the T2D PRS was nonsignificantly associated with a decreased risk of incident T2D and could potentially overestimate the AUROC when meta-analyzed (Supplementary Table 5). The result including the non-Hispanic European subgroup of HAPO was similar, as shown in Supplementary Table 6. Model 2 includes two additional variables, SBP and BMI, both of which can be easily obtained through physical examination. Incorporating T2D PRS into model 2 resulted in a 0.03 increase in AUROC, from 0.71 (95% CI 0.68–0.74) to 0.74 (95% CI 0.71–0.77) (Table 2). The KoGES cohort exhibited the highest incremental AUROC (0.06). In model 3, which also includes FPG, a key component in the diagnosis of T2D, the meta-analyzed AUROC was 0.79 (95% CI 0.75–0.82). Upon integrating T2D PRS, there was still a minimal increase in the AUROC, rising by 0.01 to 0.80 (95% CI 0.76–0.84) (Supplementary Table 5). Incorporating T2D PRS into model 1 resulted in an intermediate improvement of NRI (0.29, 95% CI 0.16–0.42, $P = 2.0 \times 10^{-5}$) (Supplementary Tables 7–9). The overall NRI was at an intermediate to weak level but also statistically significant in model 2 (0.32, 95% CI 0.15–0.49, $P = 3.0 \times 10^{-4}$) and model 3 (0.18, 95% CI 0.03–0.33, P = 0.02) (Supplementary Tables 7, 10, and 11).

CONCLUSIONS

In this study, we have shown that genome-wide T2D PRS is associated with incident T2D in women with a history of

Table 1—Baseline characteristics of study participants

Cohort	UKBB	SNUH	KoGES	HAPO	MXGDM
No. of participants	683	357	370	418	67
Incident T2D events, *n* (%)	124 (18.2)	101 (28.3)	87 (23.5)	37 (8.8)	14 (20.9)
Mean age at GDM, years (SD)	32.0 (5.5)	31.5 (4.1)	26.9 (3.9)	32.5 (5.0)	34.8 (4.3)
Family history of diabetes, *n* (%)	298 (43.6)*	146 (40.9)	135 (36.5)*	113 (27.0)	51 (76.1)
Mean BMI, kg/m^2 (SD)	29.1 (6.2)*	22.8 (3.2)†	23.8 (3.3)*	28.7 (4.5)	28.8 (5.9)
Mean SBP, mmHg (SD)	135.5 (18.6)*	111.3 (13.1)	119.3 (13.7)*	108.3 (10.1)	113.2 (12.9)
Mean FPG, mmol/L (SD)	—	5.2 (1.0)	5.7 (1.8)*	4.9 (0.4)	6.4 (2.1)
Median follow-up time, years (Q1, Q3)	30.0 (23.0, 40.0)	4.0 (2.3, 6.4)	28.0 (22.0, 34.8)	—	2.0 (2.0, 3.0)
Ancestry	Non-Hispanic EUR	EAS	EAS	EUR (228), EAS (147), SAS (43)	Hispanic
Cohort type	Population-based	Hospital-based	Population-based	Hospital-based	Hospital-based
Baseline data collection time	2007 – 2010	1996 – 2003	2004 – 2013	1999 – 2003	2010
Diagnostic criteria for GDM	Eastwood et al. (13)	NDDG	Self-report survey	IADPSG	Carpenter-Coustan

SBP, systolic blood pressure; EUR, European; EAS, East Asian; SAS, South Asian. *Refers to the values measured at baseline enrollment, not during pregnancy. †Refers to the pregestational values, not during pregnancy.

GDM across five independent cohorts. Participants who developed T2D had significantly higher T2D PRS compared with those who did not, and a 1-SD increase in T2D PRS was associated with a 1.44-fold increased hazard of incident T2D. Having a T2D PRS in the top 10% was associated with a 2.86-fold increased hazard of developing T2D following a diagnosis of GDM. This suggests that the T2D PRS could be useful in risk stratification and in identifying individuals at high risk. We also demonstrated that the T2D PRS had clinical implications for predicting incident T2D. Incorporation of T2D PRS improved the prediction accuracy of clinical models, leading to a small but significant increase in AUROC. Furthermore, there was a weak to intermediate improvement in NRI in each model when T2D PRS was added. Although there was variation, we observed a similar trend across study cohorts with diverse ancestral backgrounds, and varying diagnostic criteria and clinical settings. Our study is noteworthy for validating the utility of genome-wide T2D PRS using the latest methodologies in predicting incident cases of T2D after GDM pregnancy.

This study presents three notable findings. First, our study revealed that women with a history of GDM are enriched with genetic risk factors for T2D, and T2D PRS composed of these risk factors is significantly associated with the risk of developing T2D. Considering that as many as 50% of women with a history of GDM progress to T2D after 40 years, our findings underscore the significance of genetic risk factors in predicting the risk of progression to T2D (32,33). Moreover, our time-to-event analysis indicates that those with a high T2D PRS are likely to have earlier onset of T2D.

Secondly, our results highlight the potential of T2D PRS for risk stratification. Following childbirth, more than 90% of GDM women revert to normoglycemia. It is recommended that all women with a history of GDM undergo an OGTT between 4 and 12 weeks postpartum, and, if the results are normal, they should be tested every 1–3 years (34). However, it is important to note that the attendance rate for these postpartum visits is low (35). Our results suggest that T2D PRS could be effective in stratifying women with GDM and identifying those at particularly high risk of developing T2D. We demonstrated that those in the top 10% of T2D PRS have an HR of up to 2.86 for progressing to T2D compared with the remaining 90% of women with GDM. These women should be prioritized for screening for T2D and intensive lifestyle modification, as it has been demonstrated that lifestyle interventions, including weight management, are effective in reducing the risk of T2D after GDM pregnancy (36,37).

Finally, our study underscores both the strengths and limitations of using a genome-wide T2D PRS for predicting T2D development in women with a history of GDM. Previous studies showed that incorporating T2D PRS improved the prediction accuracy of incident T2D after GDM pregnancy, yielding a 0.03–0.04 increase

Table 2—AUROC curves of model 2

Cohort	AUROC curve without PRS (95% CI)	AUROC curve with PRS (95% CI)
UKBB	0.75 (0.71–0.80)	0.76 (0.72–0.81)
SNUH	0.67 (0.61–0.73)	0.69 (0.63–0.76)
KoGES	0.70 (0.64–0.76)	0.76 (0.71–0.82)
HAPO	0.71 (0.59–0.81)	0.75 (0.61–0.85)
MXGDM	0.73 (0.58–0.88)	0.76 (0.62–0.90)
Overall	0.71 (0.67–0.75)	0.74 (0.70–0.78)

Model 2 was adjusted for age at GDM diagnosis, family history of diabetes, BMI, and SBP. Non-Hispanic European subgroup of the HAPO study cohort was excluded.

in the AUROC. However, most of the studies included only a limited sample size and specific ancestral backgrounds, and the methods to construct PRS were outdated (2,38). We showed that adding a T2D PRS into model 1 and 2 improved the AUROC by 0.06 and 0.03, respectively. However, it could be argued that these improvements may not be clinically meaningful (31). Model 1 considers age at diagnosis of GDM and family history of diabetes, while model 2 also includes SBP and BMI, both of which are simple but important predictors of T2D. Previous studies showed that adding fasting glucose and HbA_{1c} to clinical models nearly maximizes predictive accuracy, as these glycemic measures are directly involved in T2D diagnosis (6,39). It is worth noting that these glycemic measures taken early after a GDM pregnancy might have less accuracy, as these women are typically younger and may not fully exhibit the metabolic derangements that precede diabetes onset.

There are several limitations in our study. First, the non-Hispanic European subgroup of the HAPO cohort consists of participants from various geographic locations (U.K., U.S., etc.). This could have affected the accuracy of ancestry-specific PRS analysis. Additionally, participants with OGTT values higher than predefined thresholds during pregnancy were excluded from the HAPO study (20). Limiting the participants to those with milder hyperglycemia might have contributed to the lack of significant differences in T2D PRS between those who progressed to T2D and those who did not in the non-Hispanic European subgroup. Secondly, we used the BMI and SBP measured at baseline enrollment for the UKBB and KoGES cohort, rather than during pregnancy or early postpartum period. This could potentially diminish the influence of T2D PRS on the prediction of incident T2D, because clinical variables measured when participants are older might induce a higher predictive power of the clinical model. Furthermore, there is a limitation and conflicting view regarding the utility of NRI, as a positive NRI index does not always indicate clinical utility (40). We were unable to perform the AUROC and NRI analyses in model 3 for the UKBB cohort because of the absence of FPG data. Lastly, we used European GWAS summary statistics and LD panel for the MXGDM cohort. Despite these limitations, consistent ORs and incremental AUROC were observed across the study cohorts.

In conclusion, using five cohorts with diverse ancestry and clinical setting, we showed that there is a significant association between the T2D PRS and incident T2D in women with a history of GDM. Moreover, the incorporation of T2D PRS into clinical risk models slightly but significantly enhanced the accuracy in predicting the future development of T2D. Genetic information on women with previous GDM pregnancies could be used to identify those who are at high risk of future development of T2D and provide an opportunity for tailored prevention.

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