Genome-Wide Polygenic Risk Scores and prediction of Gestational Diabetes in South Asian Women

Amel Lamri[1,2], Shihong Mao[2], Dipika Desai[2], Milan Gupta[2], Guillaume Paré[2,3], Sonia S Anand[1,2,4]

1. Department of Medicine, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada
2. Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada
3. Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada
4. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

Corresponding Author: Dr. Sonia S Anand,

McMaster University, MDCL 3202,

1280 Main St W, Hamilton,

Ontario L8S 4K1, Canada.

Tel.: +1-905-525-9140, ext. 21523;

Fax: +1-905-528-2814.

e-mail: anands@mcmaster.ca

Keywords: Genome-wide polygenic risk score; gestational diabetes, type 2 diabetes, South Asian, heritability.

Word Count: 4431

ABBREVIATIONS

1KG	1000 Genomes
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence Interval
DIAGRAM	DIAbetes Genetics Replication and Meta-analysis
GDM	Gestational Diabetes
PRS	Polygenic Risk Scores
GraBLD	Gradient Boosted and LD adjusted
GRM	Genomic Relationship Matrix
GREML	Genomic relatedness matrix residual maximum likelihood
GRS	Genetic Risk Score
GWAMA	Genome-Wide Association Meta-Analysis
GWAS	Genome-Wide Association Study
LD	Linkage Disequilibrium
LDMS	LD and MAF stratified
MAF	Minor Allele frequency
MAGIC	Meta-Analyses of Glucose and Insulin-related traits Consortium
MS	MAF stratified
OR	Odds Ratio
PCA	Principal Component analysis
P+T	Pruning and Thresholding
ROC	Receiver Operating Characteristic
SC	Single component
SE	Standard Error
SNP	Single Nucleotide polymorphism
START	South Asian Birth Cohort
T2D	Type 2 Diabetes
UKB	UK Biobank

ABSTRACT

Gestational diabetes Mellitus (GDM) affects 1 in 7 births and is associated with numerous adverse health outcomes for both mother and child. GDM is suspected to share a large common genetic background with type 2 diabetes (T2D). In this study, we first sought to build and characterize different GDM genome-wide polygenic risk scores (PRSs) using whole genome genotypes from the South Asian Birth Cohort (START) and data from the DIAGRAM consortium. The second aim of this study was to estimate the heritability of GDM.

GDM PRSs were derived for 832 South Asian women participating in the START study using three methods (Pruning and thresholding (P+T), LDpred, and the gradient boosted and LD adjusted (GraBLD) methods). Summary statistics were derived from Mahajan et al., 2014 and Scott et al., 2017, two large genome-wide association meta-analysis performed in ethnically diverse and European participants respectively. Linkage disequilibrium (LD) between variants was assessed using the START and 1000 Genomes (1KG) data. Both weighted and unweighted PRSs were derived. Association with GDM was tested using logistic regression. Heritability of GDM was estimated using the GRMEL approach. Results were replicated in South Asian and European women from the UK Biobank (UKB) study.

The best P+T GraBLD and LDpred PRSs were all based on data from Mahajan *et al*., but differed with respect to their source of LD. The best PRS was highly associated with incident GDM in START (AUC= 0.62, OR: 1.60 [95%CI: 1.44–1.69]) and in South Asian (AUC=0.65) and British (AUC=0.58) women from UKB. Heritability of GDM approximated 0.83 [95%CI: 0.38 - 1] in START and 0.17 [95%CI: 0.03 – 0.31] in South Asian women from UKB.

Our results highlight the importance of combining whole genome data, summary statistics from large multi-ethnic genome-wide meta-analysis in order to derive an optimal PRSs and to estimate the heritability of GDM in South Asian women.

INTRODUCTION

Gestational diabetes Mellitus (GDM) is defined as dysglycemia due to elevated blood glucose levels first identified during pregnancy, and is specifically defined based on glucose response to an oral glucose challenge test in pregnancy. GDM has been associated with numerous adverse health outcomes affecting mother and child, both during and after pregnancy [1,2] and because of its increasing prevalence (~ 1 in 7 births), GDM has become a major health concern worldwide [3].

Although GDM is thought to have a strong genetic component, no studies have estimated the heritability of GDM to our knowledge. Nevertheless, since GDM and T2D have similar risk factors and share common pathophysiological pathways, the heritability of GDM is thought to be similar to that of T2D.

Numerous genome-wide association studies (GWAS) and genome-wide association meta-analysis (GWAMA) of glucose related traits and T2D have been conducted in non-gravid populations, and summary statistics from large consortia (e.g., MAGIC and DIAGRAM) are publicly available [4-13]. By contrast, few studies of genetic determinants of GDM have been conducted or published. For instance, only two studies sought to identify genes associated with dysglycemia, GDM and diabetes during pregnancy by GWAS [14,15]. Top signals from these studies were located within/near *CDKAL1*, *MTNR1B, GCKR*, *PCSK1*, *PPP1R3B* and *G6PC2*, which were previously known for their association with glucose metabolism and T2D [14,15]. In addition, other T2D associated loci (e.g., *TCF7L2*, *PPARG*, *CDKN2A/B*, *KCNQ1*, *GCK*, etc.) were also significantly associated with GDM when tested separately [16-39], or combined as genetic risk scores (GRS) [33,34,40-42].

GRSs and polygenic risk scores (PRSs) are used to capture genetic information at one or more loci. Most of published studies interested in complex traits/diseases and using GRSs typically

combine data for a small number of single nucleotide polymorphisms (SNPs), and the predictive power of these GRSs is sub-optimal [43]. However, with the increased availability of whole genome genotypes and publicly available data from large consortia, GRSs with a larger number of variants are being used, and the predictive value of these genome-wide polygenic risk scores (PRSs) has substantially improved [44,45].

PRSs can be derived using different approaches, however, these require requires both summary statistics from an external GWAS and a genetic data for a reference panel for between-variants linkage disequilibrium LD (LD) calculations. Pruning and thresholding (P+T) is a commonly used heuristic approach to derive PRSs in which variants are filtered based on an empirically determined P-value threshold. Linked variants are further clustered in different groups and SNPs with the highest significance (lowest P values) in each group are prioritized and included in the PRS while variants of less significance within the group are pruned out [46]. Other programs have been shown to improve the predictive value of the score by allowing the inclusion of a larger number of independent as well as linked variants into the score using different approaches. For instance, LDpred another commonly used method, estimates the mean weight of each variant, assuming a prior knowledge of the genetic architecture of the trait (fraction causal) and using a Bayesian approach [47]. More recently, we developed the gradient boosted and LD adjusted (GraBLD), a new PRS building approach which applies principles of machine-learning to estimate of SNP weights (gradient boosted regression trees), and regional LD adjustment [48].

The first objective of this study was to determine the optimal gene score and investigate the association of genetic variants combined in PRSs with GDM in South Asian women participating to the South Asian Birth Cohort (START). We considered several parameters: 1) two different sources of GWAS summary statistics (Mahajan *et al.*, 2014 [5] *vs.* Scott *et al.*, 2017 [6]); 2) two templates for LD calculation (1000 Genomes phase 3 [49] *vs.* START genotypes); 3)

different minimal values of the number of samples in each SNP's analysis in the consortia; 4) weighted *vs.* unweighted GWPRSs; 5) three methods to derive the PRSs; Pruning and Thresholding (P+T),. LDpred and GraBLD and; 6) different P-value thresholds (for P+T and LDpred PRSs only). The second objective was to estimate the heritability of GDM from: 1) whole genome data, and 2) SNPs in the top P+T PRS. Our results were further validated in a subset of South Asian and European Women who participated in the UK Biobank study [50].

METHODS

Study Design and participants

The South Asian Birth Cohort (START) study: START is a prospective cohort designed to evaluate the environmental and genetic determinants of cardiometabolic traits of South Asian pregnant women and their offspring living in Ontario, Canada. The rationale and study design are described elsewhere [51]. In brief, 1,012 South Asian (people who originate from the Indian subcontinent) pregnant women, between the ages of 18 and 40 years old, were recruited during their second trimester of pregnancy from the Peel Region of Ontario, Canada through physician referrals between July 11, 2011 and Nov. 10, 2015. All START participants signed an informed consent including genetic consent, and the study was approved by local ethics committees (Hamilton Integrated Research Ethics Bard, William Osler Health System, and Trillium Health Partners). A detailed description of the maternal measurements has been published previously [52].

UK Biobank: The UK Biobank is a large population-based study which includes over 500,000 participants living in the United Kingdom [50]. Men and Women aged 40 - 69 years were recruited between 2006 and 2010 and extensive phenotypic and genotypic data about the participants was collected, including ethnicity and a question regarding past history of GDM. Details of this

study are available online (https://www.ukbiobank.ac.uk) [50]. Data from UK Biobank were used in order to validate the results from the START study.

Derived variables

START Study: GDM status was determined using the South Asian specific cutoffs as defined in the Born in Bradford study (fasting glucose level of 5.2 mmol/L or higher, or a 2-hour post load level of 7.2 mmol/L or higher) [53]. Self-reported GDM status was used if these measures were unavailable. Participants with a history of T2D prior to pregnancy were excluded. Using these criteria, 832 START participants with known GDM status (301 cases and 531 controls) and available genotypes were included in the analysis. The South Asian ethnicity/ancestry of participants was validated using genetic data.

UK Biobank: Participants in the UK Biobank completed questionnaires at several time points (questionnaire of initial assessment visit, 2006-2010; questionnaire of first repeat assessment visit, 2012-2013; questionnaire of imaging visit, 2014 onwards). For the purpose of our study, GDM cases were defined as women who reported having had diabetes during pregnancy only collected at any time point using questionnaires. The control group was comprised of women who: 1) had at least one child (self-reported, live births only) 2) had never been diagnosed with diabetes or GDM in all assessments. The ethnicity/ancestry of participants was validated using genetic data.

DNA extraction, Genotyping, Imputation and Filtering and SNP extraction:

START: DNA was extracted and genotyped from a total of 867 samples (START mothers) using the Illumina Human CoreExome-24 and Infinium CoreExome-24 arrays (Illumina, San-Digeo, CA, USA). Data was cleaned using standard quality control (QC) procedures [54] and 837 women samples passed the QC. Genotypes were subsequently phased using SHAPEIT v2.12 [55], and imputed with the IMPUTE v2.3.2 software [56], using the 1000 Genomes (phase 3) data

as a reference panel [49]. Variants with an info score ≥ 0.7 were kept for analysis. Addition data manipulation and SNP selection criteria for the building of the PRSs are detailed in Supplementary Information and Supplementary Figure 1.

UK Biobank: A total of ~500,000 participants from the UK biobank were genotyped using the UK BiLEVE or UK Biobank Affymetrix Axiom arrays. Detailed QC, phasing and imputation procedures have previously been described [57]. As a result, 3,169 and 220,703 unrelated South Asian and European (from Great Britain) women respectively passed QC. Among these, 2,386 and 184,869 participants had available GDM status respectively, and were used to replicate our results from the START study. Genotypes for > 98% of SNPs included in our top START GDM PRSs were available (info score ≥ 0.6) and were extracted for the replication.

Consortium data

Summary statistics (P-value, effect size) from the following two DIAGRAM sources were used in order to build the PRSs:

1) *Mahajan et al., Nature Genetics, 2014*

   This trans-ethnic GWAMA included 12,171 T2D cases and 56,862 controls of European ancestry; 6,952 cases and 11,865 controls of East Asian ancestry; 5,561 cases and 14,458 controls South Asian ancestry and 1,804 cases and 779 controls of Mexican and Mexican American ancestry [5]. This study was selected for its multi-ethnic composition and its inclusion of South Asian participants.

2) Scott et al., Diabetes, 2017

This study combines data from 18 GWAS, for a total of 26,676 T2D cases and 132,532 controls of European ancestry [6]. This study was selected for its large sample size and its relatively homogenous samples (100% white Caucasians).

Summary statistics of these studies were downloaded from DIAGRAM's main website (http://www.diagram-consortium.org).

Templates for LD calculation

LD calculations used to build the PRSs were derived from the following two genotyping datasets: 1) START study (LD source hereafter referred to as LD_{START}); and 2) the 1000 Genomes consortium (LD source hereafter referred to as LD_{1KG}). Genotypes of 1000 Genomes participants were downloaded from the project's data portal (http://www.internationalgenome.org), and a subset of participants was created in order to match the proportion of the ethnicities represented in each consortium study.

Pruning and thresholding PRSs

Both weighted and unweighted PRSs were built using GNU Parallel [58] and PLINK v1.9 (https://www.cog-genomics.org/plink2). 64 different clump P-value cutoffs ranging from 5×10^{-8} to 1 were tested in order to identify the optimal index variant's significance threshold. All other parameters were set to default. A diagram of the different P+T PRSs built is show in Supplementary Figure 2.

LDpred

LDpred PRSs were derived using the LDpred software v0.9.9 (https://github.com/bvilhjal/ldpred) [47]. The fractions of causal variants assumed a prior were

similar to the P value thresholds used for the P+T PRSs. Since the number of SNPs was different between the PRSs, The LD radius was adjusted accordingly in each model using the recommended formula (N SNP/3000). All other parameters were kept on their default setting. A diagram of the different P+T PRSs built is show in Supplementary Figure 2.

GraBLD

GraBLD PRSs were built using several functions available in the GraBLD R package (https://github.com/GMELab/GraBLD) [48]. Data of all the women participating in the START study were used for the calibration. All parameters were set to default.

Association analysis

The association of each PRS with GDM was assessed using a univariate logistic regression model, and areas under the receiver-operating characteristic (ROC) curves (AUCs, c-statistics) were compared in order to determine the PRS with the highest predictive value of GDM. Continuous PRSs were also divided into quartiles in order to compare the participants with highest PRS values to the other groups. Statistical significance of the difference between the predictive values of two PRSs was tested using the DeLong's test for two correlated ROC curves. Analyses were performed using GNU Parallel [58] and R v3.3 [59].

Heritability

The proportion of the variance of GDM explained by: 1) whole genome data; 2) SNPs included in our top PRS was estimated by genomic relatedness matrix residual maximum likelihood (GREML) analysis using the GCTA software [60-63]. Both single-component (GREML-SC) [61] and multicomponent (GRMEL-MS and GREML-LDMS-I) GREML models were tested [63]. Minor allele frequency (MAF) stratified GREML (GRMEL-MS) models included 2 genomic relationship matrices (GRMs) created based on the minor allele frequency (MAF) of the SNPs

(bin1: MAF≤ 0.01; bin2: MAF>0.01). In our individual LD and MAF stratified GREML (GREML-LDMS-I) models, SNPs were grouped by their MAFs and by and their individual levels of LD (2 LD bins × 2 MAF bins, LD cutoffs based on medians), resulting in 4 GRMs in total [61,63]. Models were either unadjusted or adjusted for the first 5 PCA axes.

RESULTS:

Population characteristics:

Error! Reference source not found. shows the characteristics of START and UK Biobank women included in the analyses. Because of major differences in recruitment strategies, inclusion criteria and study protocols, selected participants from the UK biobank were of older age, weight, and BMI compared to START participants. Furthermore, the proportion of participants with GDM was significantly lower in South Asian women from the UK Biobank and even more so in European women of the same study.

Minimum sample size per SNP in consortium data:

In the two DIAGRAM studies from which we extracted summary statistics, the number of participants tested for association with T2D was different for each SNPs and ranged between 25 – 110,219 and 4,731 – 158,186 in Mahajan *et al.* and Scott *et al* respectively (Supplementary Figure 3, Supplementary Table 1).

We derived several PRSs for which the list of variants was restricted to SNPs tested in at least 0, 85, 90, 95 and 98% of the maximum sample size in the consortium GWAMA of interest. The number of SNPs used in the PRS and the percentage of SNP loss for each one of these thresholds are shown in Supplementary Table 1. The percentage of variants lost after this filtering was the most substantial in PRSs based on Mahajan *et al.*, with only 346,290 polymorphisms remaining when keeping variants tested in ≥ 95% samples (Supplementary Table 1).

For both Mahajan *et al.* and Scott *et al.* based PRSs, the optimal minimum percent of participants to keep varied depending on the method used (P+T, LDpred or GraBLD), the source of LD estimates (LD_{START} or LD_{1KG}) and the consortium P-value threshold (Figure 1, Figure 2, Supplementary Figure 3 and Table 2).

With an AUC of 0.62, the best GraBLD PRS included 1,305,596 SNPs and was derived using weights from Mahajan *et al.* ($W_{Mahajan}$); LD from START (LD_{START}); SNPs tested in ≥ 90% of the samples in the consortium data ($N_{90\%}$). This top GraBLD PRS will hereafter be referred to as GraBLD_PRS_1_$W_{Mahajan}$_LD_{START}_$N_{90\%}$. The best P+T was comprised of 9,274 SNPs, showed an AUC of 0.62 and was derived using the following parameters: Weights from Mahajan *et al.* ($W_{Mahajan}$); LD from 1KG (LD_{1KG}); SNPs tested in ≥ 85% of the maximum sample size ($N_{85\%}$) and a maximum P-value of 0.016 in its reference consortium GWAMA ($P_{0.016}$). This top P+T PRS will be referred to as PT_PRS_1_$W_{Mahajan}$_LD_{1KG}_$N_{85\%min}$_$P_{0.016}$. Finally, with an AUC of 0.62 as well, the best LDpred PRS included 1,290,525 SNPs and was derived using weights from Mahajan *et al.* ($W_{Mahajan}$); LD from 1KG (LD_{1KG}); SNPs tested in ≥ 85% of the samples in the consortium data ($N_{85\%}$). This top LDpred PRS will hereafter be referred to as LDpred_PRS_1_$W_{Mahajan}$_LD_{1KG}_$N_{85\%}$. Detailed characteristics and rankings of the best PRSs are shown in Supplementary Table 2

Pruning and Threshold PRSs

AUCs of unweighted P+T PRSs were similar to AUCs for their weighted counterpart at very low P-value thresholds (clump P ≤ 0.004). Interestingly, the inclusion of variants with association P-values that are less significant than the usual GWAS significance threshold (5×10^{-8}) always resulted in a considerable increase in the predictive value of the scores. Optimal AUCs were reached at clump P-values ranging from 0.016 - 0.20 depending on the source of LD or the consortium used (Figure 1, Supplementary figure 2 and Table 2). Passed these

maximal points, the difference between weighted and unweighted PRSs gradually increased, with the weighted PRSs performing better than their unweighted counterparts (Figure 1, Supplementary figure 2).

LDpred PRSs:

Similarly to P+T PRSs, the increase in the fraction of causal SNPs (from P values of 5×10^{-8} to P = 0.0005 corresponding to 0.5 and 7.5 % of consortium SNPs in Mahajan *et al.* and Scott *et al.* respectively) highly improved the predictive value of the PRSs (Figure 2). The increase in the fraction causal passed this point was not associated with a significant change in the AUC of LDpred PRSs (Figure 2).

GraBLD vs. P+T vs LDpred PRSs: As previously mentioned, whether the performance of a PRS derived using a given method was better than that of its different counterparts (other two methods) largely depended on the consortium data, the source of LD, the minimum % of participants, and the maximum clump P-value cutoffs used. Nevertheless, when comparing the best PRS derided from each method, no significant difference was observed between GraBLD, LDpred and P+T derived top PRS (AUCs=0.62, Table 2, $P_{difference} = 0.95$). When comparing P+T to LDpred only, AUCs were higher and more stable as higher P-value threshold were tested with LDpred PRS than P+T PRS (Figure 3).

Mahajan et al. vs. Scott et al. PRSs: The predictive value of most Mahajan-based P+T PRSs were higher than that of their Scott-based counterparts (Figure 4). For GraBLD and LDpred PRSs, all Mahajan based PRSs had higher AUCs than Scott based PRSs (Figure 4, data not shown). Finally, the best Mahajan-based PRS always outperformed the top Scott-based PRSs for all three methods (Table 2, Supplementary Table 2)

***LD from 1000 Genomes vs. START*:** AUCs of the best LD_{START} PRSs were not significantly different from AUCs of their LD_{1KG} counterpart for P+T, LDpred and GraBLD PRSs (Figure 5, Table 2).

Association with GDM:

The association results of the top PRSs (GraBLD_PRS_1_$W_{Mahajan}$_LD_{START}_$N_{90\%}$, PT_PRS_1_$W_{Mahajan}$_LD_{1KG}_$N_{85\%}$_$P_{0.016}$ and LDpred_PRS_1_$W_{Mahajan}$_LD_{1KG}_$N_{85\%}$) with GDM (univariate models) are shown in Table 2 (continuous PRSs) and Table **Error! Reference source not found.** (categorical PRSs). The odds of developing GDM was 2 to 2.5 folds higher in participants with the highest PRSs (top 25%) compared to the rest (75%) of the study population, depending on the type of PRS used. When analyzing participants with high or low PRSs values only, our results show that participants with the highest PRS values (top 25%) had between 3 and 3.4 folds increase in their risk of GDM compared to the participants with the lowest PRS values (bottom 25%). these results were similar in both UK Biobank South Asian and European replication dataset (Table3).

Heritability

In order to better characterize the genetic architecture of GDM, the total heritability as well as the proportion of the variance covered by the currently available GWAS data were estimated using different models. Heritability of GDM derived from whole genome data ($h^2_{WG_SNPs)}$ and from SNPs used to derive the top P+T PRS ($h^2_{Top_PT_PRS_SNPs}$) were estimated for the South Asian women from the START and UK biobank studies. Results are shown in Table 4. Estimates with the smallest standard errors were observed when using 1 or 2 GRMs, while the increase in the number of GRMs included in the models (4 or above) resulted in a loss of precision. Hence, even though GRMEL-LDMS-I is considered as one of the best approaches to estimate h[263], results using this method are not further discussed. The proportion of the variance

in GDM explained by whole genome data was close to 0.83 [95%CI: 0.38 - 1] in South Asian women from the START study ($h^2_{WG_SNPs\ in\ START}$: 0.80 – 0.87 depending on the number of components and the adjustments, Table 4). By contrast, $h^2_{WG_SNPs}$ estimated in the UK biobank replication dataset were lower ($h^2_{WG_SNPs\ in\ UKB}$ = 0.17 [95% CI: 0.03 – 0.31]). As expected, heritability estimated from the restricted list of SNPs used in our top PRS was smaller than the heritability estimated from whole genome data especially in START ($h^2_{Top_PT_PRS_SNPs\ in\ START}$ = 0.17 [95%CI: 0.04 – 0.30]), and the 9,274 SNPs in the top PT PRS explained ~ 20% of the total genetic variance of the phenotype (Table 4). In South Asian women from UKB, SNPs in the top PRS explained ~ 30% of the total h^2 estimate

DISCUSSION

In this study, we built several thousands of GDM PRSs using whole genome genotypes, large consortium data and 3 different methods. Our best PRS was built using the LDpred method, with weights extracted from Mahajan *et al.* and LD calculated using 1KG genotypes. This PRS was also significantly associated with GDM in South Asian women from the START study, an observation that was successfully replicated in South Asian and European women from the UK biobank. Participants with the highest PRS values had an increased risk of GDM when compared to the other groups. Heritability estimates were higher in the START study than in the UK Biobank dataset.

In order to build our PRSs, we used summary statistics from two large GWAMAs. One of the major advantages in using data from Mahajan *et al.* was that ~20% of its participants originated from the South Asian sub-continent. This study also had a large maximum number of cases and controls, but many of the SNPs included in the meta-analysis were tested in a much smaller sample (Supplementary figure 3, Supplementary Table 1). On the other hand, no South Asian participants were included in the GWAMA performed by Scott *et al.* but the average number

of samples tested for each SNP was larger than for Mahajan*'s*. Our results show that Mahajan-based PRSs consistently outperformed their Scott-based counterparts in spite of a lower genome coverage and smaller average number of participants per SNP. This highlights the importance of using consortium data of the same ethnic group than the study at hand whenever possible. However, since Mahajan *et al.*'s summary statistics are derived for T2D and from a blend of participants of different ethnicities, we expect that our top PRSs could be further improved if built based on summary statistics derived from a large GDM GWAMA in South Asians only. In general, efforts should be made to produce more large genetic studies in non-European populations.

Our results from the START study suggest that the heritability of GDM in South Asian women living in Canada is high, and should range between 0.34 and 1 ($h^2_{WG_SNPs\ in\ START}$ ~ 0.83 [95%CI: 0.34 – 1]). This is in line with the recent estimations of T2D SNP-based heritability, which approximates 0.54 [95%CI: 0.47 - 0.61] [64]. However, because of the large standard errors and small number of GRMs included in our models, h^2_{GW} estimates described in this study should be interpreted with caution [63,61]. Heritability estimates derived from UK Biobank genotypes we describe were much smaller than those estimated for the START study. This is most likely due to major differences in study design, recruitment strategies and phenotyping of GDM between the two studies, which resulted in a considerable difference in the proportion of participants with GDM (~36 % in START *vs.* 2% in UK Biobank). As previously described, the diagnosis of GDM in START was based on plasma glucose levels measurements performed during pregnancy in response to an oral glucose challenge, and used South Asian-specific diagnosis cutoffs. However, in UK Biobank participants, GDM status was retrospectively self-reported, which most likely resulted in an increased number of misclassifications and a reduced number of reported GDM cases. In an effort to refine the phenotype, our control group was restricted to women without GDM who went through at least one live birth. Nevertheless, the lack of

sensitivity and specificity of the GDM phenotype likely remains an issue in UKB, which could explain the low heritability estimates observed in this study. Furthermore, since heritability is also influenced by the environment, it is possible that part of the difference in heritability observed between START and UK Biobank is due to differences in the respective North American and European lifestyles and environments. Our heritability results also provide an insight on the genetic architecture of GDM by showing that a relatively large proportion (~20 – 30%) of the genetic variance of GDM is captured by a very small number of SNPs (< 10.000 SNPs). Nevertheless, a large proportion of the heritability remains unexplained by variants tested in Mahajan *et al*., and the causes of this missing heritability should be investigated in future studies.

A significant conclusion derived from this study is that, whatever the consortium or the method used, restricting the list of SNPs to GWAS significant variants (P value $\leq 5\times10^{-8}$) drastically reduces the predictive value of the PRSs. Unfortunately, many studies still rely on this threshold to select their loci of interest and derive their risk scores. We recommend the use of higher P-value thresholds (> 0.01 in our case) whenever possible in order to increase the predictive value of the PRS. In the same line of idea, and based on our results, h^2 estimates derived from a restricted list of SNPs are smaller than h^2 derived from whole genome data These results are to be expected and are a consequence of the reduced number of SNPs included in the models, and hence, a poorer tagging and lower coverage [61]. This reflects the importance of using whole genome data not only when building PRSs but when also for the estimation of SNP-based heritability.

Based on our results, weighted PRSs perform similarly, or better than their unweighted counterparts. For P+T PRSs, the predictive value of the unweighted PRSs are especially lower than for weighted PRS at high P-value cutoffs. Hence, we recommend the use weighted PRSs

whenever possible. If unweighted PRSs are used, P-value cutoffs should be set between 0.01 and 0.1.

When comparing the three methods used, the top GraBLD and P+T and LDpred PRSs showed similar results. Nevertheless, since more parameters were involved, the identification of the optimal P+T and LDpred PRS required the test of several thousand predictors (n = 2,560 and 1280 respectively), while a similar result was achieved by testing 40 GraBLD models only. When testing different P value cutoffs, the results of LDpred-derived PRS were somewhat more stable as the threshold increased than for P+T. While this may lead one to slightly favor the use of LDpred or GraBLD for the building of PRSs, an advantage of the P+T is it produces similar results by using fewer SNPs.

In the absence of available summary statistics of large GDM GWAMAs, we used data from T2D studies to build our PRSs. Several reports suggested that T2D and GDM share a common genetic background. Our results show that a T2D PRSs can be highly predictive of GDM in South Asian women, hence confirming the hypothesis of a common genetic background between these two complex disorders. However, GDM probably also has unique genetic signals which are not captured by T2D studies and *vice versa*. In addition, the effect size of the genetic variant could be different for each one of these conditions. This issue could have reduced the general predictive value of our PRSs, but does not affect the conclusions of our model comparisons since as all the PRSs were subject to it.

In conclusion, our results show that combining whole genome data, summary statistics from a large multi-ethnic genome-wide meta-analysis, and using the appropriate methodology, play a crucial for the building of a highly predictive PRSs and the estimation of heritability of GDM in South Asian women.

ACKNOWLEDGEMENTS

The authors thank the UK Biobank for making their data available. The South Asian Birth Cohort (START) study data were collected as part of a bilateral program funded by the Indian Council of Medical Research / Canadian Institutes of Health Research (Project grant number: 298104, Foundation Scheme grant number: FDN-143255, Study grant numbers: INC 109205). This study was also supported by Heart and Stroke Foundation of Canada (grant NA7283. Sonia Anand is supported by a Tier 1 Canada Research Chair in Ethnic Diversity and Cardiovascular Disease, and a Heart and Stroke Foundation/Michael G. DeGroote Chair in Population Health Research at McMaster University. Guillaume paré is supported by a Canada Research Chair.

REFERENCES

1 Melchior H, Kurch-Bek D & M., M. The Prevalence of Gestational Diabetes: A Population-Based Analysis of a Nationwide Screening Program. *Dtsch Aerzteblatt Int.* (2017).

2 Farrar, D. *et al.* Hyperglycaemia and risk of adverse perinatal outcomes: systematic review and meta-analysis. *BMJ* **354**, i4694, doi:10.1136/bmj.i4694 (2016).

3 International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation. . (2017).

4 Morris, A. P. *et al.* Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet* **44**, 981-990, doi:10.1038/ng.2383 (2012).

5 Mahajan, A. *et al.* Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. *Nat Genet* **46**, 234-244, doi:10.1038/ng.2897 (2014).

6 Scott, R. A. *et al.* An Expanded Genome-Wide Association Study of Type 2 Diabetes in Europeans. *Diabetes* **66**, 2888-2902, doi:10.2337/db16-1253 (2017).

7 Wheeler, E. *et al.* Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis. *PLoS Med* **14**, e1002383, doi:10.1371/journal.pmed.1002383 (2017).

8 Prokopenko, I. *et al.* A central role for GRB10 in regulation of islet function in man. *PLoS Genet* **10**, e1004235, doi:10.1371/journal.pgen.1004235 (2014).

9 Manning, A. K. *et al.* A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance. *Nat Genet* **44**, 659-669, doi:10.1038/ng.2274 (2012).

10 Strawbridge, R. J. *et al.* Genome-wide association identifies nine common variants associated with fasting proinsulin levels and provides new insights into the pathophysiology of type 2 diabetes. *Diabetes* **60**, 2624-2634, doi:10.2337/db11-0415 (2011).

11 Dupuis, J. *et al.* New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet* **42**, 105-116, doi:10.1038/ng.520 (2010).

12 Saxena, R. *et al.* Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. *Nat Genet* **42**, 142-148, doi:10.1038/ng.521 (2010).

13 Soranzo, N. *et al.* Common variants at 10 genomic loci influence hemoglobin A(1)(C) levels via glycemic and nonglycemic pathways. *Diabetes* **59**, 3229-3239, doi:10.2337/db10-0502 (2010).

14 Kwak, S. H. *et al.* A genome-wide association study of gestational diabetes mellitus in Korean women. *Diabetes* **61**, 531-541, doi:10.2337/db11-1034 (2012).

15 Hayes, M. G. *et al.* Identification of HKDC1 and BACE2 as genes influencing glycemic traits during pregnancy through genome-wide association studies. *Diabetes* **62**, 3282-3291, doi:10.2337/db12-1692 (2013).

16 Tarnowski, M. *et al.* GCK, GCKR, FADS1, DGKB/TMEM195 and CDKAL1 Gene Polymorphisms in Women with Gestational Diabetes. *Can J Diabetes* **41**, 372-379, doi:10.1016/j.jcjd.2016.11.009 (2017).

17 Anghebem-Oliveira, M. I. *et al.* Type 2 diabetes-associated genetic variants of FTO, LEPR, PPARg, and TCF7L2 in gestational diabetes in a Brazilian population. *Arch Endocrinol Metab* **61**, 238-248, doi:10.1590/2359-3997000000258 (2017).

18 de Melo, S. F. *et al.* Polymorphisms in FTO and TCF7L2 genes of Euro-Brazilian women with gestational diabetes. *Clin Biochem* **48**, 1064-1067, doi:10.1016/j.clinbiochem.2015.06.013 (2015).

19 Kasuga, Y. *et al.* Association of common polymorphisms with gestational diabetes mellitus in Japanese women: A case-control study. *Endocr J* **64**, 463-475, doi:10.1507/endocrj.EJ16-0431 (2017).

20 Kanthimathi, S. *et al.* Association of recently identified type 2 diabetes gene variants with Gestational Diabetes in Asian Indian population. *Mol Genet Genomics* **292**, 585-591, doi:10.1007/s00438-017-1292-6 (2017).

21 Tarnowski, M., Malinowski, D., Safranow, K., Dziedziejko, V. & Pawlik, A. CDC123/CAMK1D gene rs12779790 polymorphism and rs10811661 polymorphism upstream of the CDKN2A/2B gene in women with gestational diabetes. *J Perinatol* **37**, 345-348, doi:10.1038/jp.2016.249 (2017).

22 Wang, X. *et al.* Association study of the miRNA-binding site polymorphisms of CDKN2A/B genes with gestational diabetes mellitus susceptibility. *Acta Diabetol* **52**, 951-958, doi:10.1007/s00592-015-0768-2 (2015).

23 Wang, Y. *et al.* Association of six single nucleotide polymorphisms with gestational diabetes mellitus in a Chinese population. *PLoS One* **6**, e26953, doi:10.1371/journal.pone.0026953 (2011).

24 Lauenborg, J. *et al.* Common type 2 diabetes risk gene variants associate with gestational diabetes. *J Clin Endocrinol Metab* **94**, 145-150, doi:10.1210/jc.2008-1336 (2009).

25 Fatima, S. S., Chaudhry, B., Khan, T. A. & Farooq, S. KCNQ1 rs2237895 polymorphism is associated with Gestational Diabetes in Pakistani Women. *Pak J Med Sci* **32**, 1380-1385, doi:10.12669/pjms.326.11052 (2016).

26 Kanthimathi, S. *et al.* Hexokinase Domain Containing 1 (HKDC1) Gene Variants and their Association with Gestational Diabetes Mellitus in a South Indian Population. *Ann Hum Genet* **80**, 241-245, doi:10.1111/ahg.12155 (2016).

27 Al-Hakeem, M. M. Implication of SH2B1 gene polymorphism studies in gestational diabetes mellitus in Saudi pregnant women. *Saudi J Biol Sci* **21**, 610-615, doi:10.1016/j.sjbs.2014.07.007 (2014).

28 Kwak, S. H. *et al.* Polymorphisms in KCNQ1 are associated with gestational diabetes in a Korean population. *Horm Res Paediatr* **74**, 333-338, doi:10.1159/000313918 (2010).

29 Shin, H. D. *et al.* Association of KCNQ1 polymorphisms with the gestational diabetes mellitus in Korean women. *J Clin Endocrinol Metab* **95**, 445-449, doi:10.1210/jc.2009-1393 (2010).

30 Cho, Y. M. *et al.* Type 2 diabetes-associated genetic variants discovered in the recent genome-wide association studies are related to gestational diabetes mellitus in the Korean population. *Diabetologia* **52**, 253-261, doi:10.1007/s00125-008-1196-4 (2009).

31 Reyes-Lopez, R., Perez-Luque, E. & Malacara, J. M. Metabolic, hormonal characteristics and genetic variants of TCF7L2 associated with development of gestational diabetes mellitus in Mexican women. *Diabetes Metab Res Rev* **30**, 701-706, doi:10.1002/dmrr.2538 (2014).

32 Lin, P. C., Chou, P. L. & Wung, S. F. Geographic diversity in genotype frequencies and meta-analysis of the association between rs1801282 polymorphisms and gestational diabetes mellitus. *Diabetes Res Clin Pract* **143**, 15-23, doi:10.1016/j.diabres.2018.05.050 (2018).

33 Ding, M. *et al.* Genetic variants of gestational diabetes mellitus: a study of 112 SNPs among 8722 women in two independent populations. *Diabetologia* **61**, 1758-1768, doi:10.1007/s00125-018-4637-8 (2018).

34 Ekelund, M. *et al.* Genetic prediction of postpartum diabetes in women with gestational diabetes mellitus. *Diabetes Res Clin Pract* **97**, 394-398, doi:10.1016/j.diabres.2012.04.020 (2012).

35 Frigeri, H. R. *et al.* The polymorphism rs2268574 in Glucokinase gene is associated with gestational Diabetes mellitus. *Clin Biochem* **47**, 499-500, doi:10.1016/j.clinbiochem.2014.01.024 (2014).

36 Pagan, A. *et al.* A gene variant in the transcription factor 7-like 2 (TCF7L2) is associated with an increased risk of gestational diabetes mellitus. *Eur J Obstet Gynecol Reprod Biol* **180**, 77-82, doi:10.1016/j.ejogrb.2014.06.024 (2014).

37 Shaat, N. *et al.* A variant in the transcription factor 7-like 2 (TCF7L2) gene is associated with an increased risk of gestational diabetes mellitus. *Diabetologia* **50**, 972-979, doi:10.1007/s00125-007-0623-2 (2007).

38 Watanabe, R. M. *et al.* Transcription factor 7-like 2 (TCF7L2) is associated with gestational diabetes mellitus and interacts with adiposity to alter insulin secretion in Mexican Americans. *Diabetes* **56**, 1481-1485, doi:10.2337/db06-1682 (2007).

39 Papadopoulou, A. *et al.* Gestational diabetes mellitus is associated with TCF7L2 gene polymorphisms independent of HLA-DQB1*0602 genotypes and islet cell autoantibodies. *Diabet Med* **28**, 1018-1027, doi:10.1111/j.1464-5491.2011.03359.x (2011).

40 Kawai, V. K. *et al.* A genetic risk score that includes common type 2 diabetes risk variants is associated with gestational diabetes. *Clin Endocrinol (Oxf)* **87**, 149-155, doi:10.1111/cen.13356 (2017).

41 Kwak, S. H. *et al.* Prediction of type 2 diabetes in women with a history of gestational diabetes using a genetic risk score. *Diabetologia* **56**, 2556-2563, doi:10.1007/s00125-013-3059-x (2013).

42 Cormier, H. *et al.* An explained variance-based genetic risk score associated with gestational diabetes antecedent and with progression to pre-diabetes and type 2 diabetes: a cohort study. *BJOG* **122**, 411-419, doi:10.1111/1471-0528.12937 (2015).

43 Ripatti, S. *et al.* A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet* **376**, 1393-1400, doi:10.1016/S0140-6736(10)61267-6 (2010).

44 Abraham, G. *et al.* Genomic prediction of coronary heart disease. *Eur Heart J* **37**, 3267-3278, doi:10.1093/eurheartj/ehw450 (2016).

45 Khera, A. V. *et al.* Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* **50**, 1219-1224, doi:10.1038/s41588-018-0183-z (2018).

46 International Schizophrenia, C. *et al.* Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748-752, doi:10.1038/nature08185 (2009).

47 Vilhjalmsson, B. J. *et al.* Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *Am J Hum Genet* **97**, 576-592, doi:10.1016/j.ajhg.2015.09.001 (2015).

48 Pare, G., Mao, S. & Deng, W. Q. A machine-learning heuristic to improve gene score prediction of polygenic traits. *Sci Rep* **7**, 12665, doi:10.1038/s41598-017-13056-1 (2017).

49 Consortium, T. G. P. *et al.* A global reference for human genetic variation. *Nature* **526**, 68-74, doi:10.1038/nature15393 (2015).

50 Sudlow, C. *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* **12**, e1001779, doi:10.1371/journal.pmed.1001779 (2015).

51 Anand, S. S. *et al.* Rationale and design of South Asian Birth Cohort (START): a Canada-India collaborative study. *BMC Public Health* **13**, 79, doi:10.1186/1471-2458-13-79 (2013).

52 Anand, S. S. *et al.* Causes and consequences of gestational diabetes in South Asians living in Canada: results from a prospective cohort study. *CMAJ Open* **5**, E604-E611, doi:10.9778/cmajo.20170027 (2017).

53 Farrar, D. *et al.* Association between hyperglycaemia and adverse perinatal outcomes in south Asian and white British women: analysis of data from the Born in Bradford cohort. *Lancet Diabetes Endocrinol* **3**, 795-804, doi:10.1016/S2213-8587(15)00255-7 (2015).

54 Anderson, C. A. *et al.* Data quality control in genetic case-control association studies. *Nat Protoc* **5**, 1564-1573, doi:10.1038/nprot.2010.116 (2010).

55 Delaneau, O., Marchini, J., Genomes Project, C. & Genomes Project, C. Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. *Nat Commun* **5**, 3934, doi:10.1038/ncomms4934 (2014).

56 Howie, B. N., Donnelly, P. & Marchini, J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* **5**, e1000529, doi:10.1371/journal.pgen.1000529 (2009).

57 Bycroft, C. *et al.* Genome-wide genetic data on ~500,000 UK Biobank participants. *BioRxiv* (2017).

58 Tange, O. GNU Parallel - The Command-Line Power Tool. *;login: The USENIX Magazine* **36**, 42-47 (2011).

59 R: A language and environment for statistical computing v. 3.3 (R Foundation for Statistical Computing, Vienna, Austria, 2016).

60 Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet* **88**, 76-82, doi:10.1016/j.ajhg.2010.11.011 (2011).

61 Yang, J. *et al.* Common SNPs explain a large proportion of the heritability for human height. *Nat Genet* **42**, 565-569, doi:10.1038/ng.608 (2010).

62 Yang, J. *et al.* Genetic variance estimation with imputed variants finds negligible missing heritability for human height and body mass index. *Nat Genet* **47**, 1114-1120, doi:10.1038/ng.3390 (2015).

63 Evans, L. M. *et al.* Comparison of methods that use whole genome data to estimate the heritability and genetic architecture of complex traits. *Nat Genet* **50**, 737-745, doi:10.1038/s41588-018-0108-x (2018).

64 Speed, D. *et al.* Reevaluation of SNP heritability in complex human traits. *Nat Genet* **49**, 986-992, doi:10.1038/ng.3865 (2017).

	START*	UK Biobank – SAW	UK Biobank – Brit-EUR-W
Number of Participants with GDM data	832	2,386	184,869
GDM, n (%)	301 (36.2%)	52 (2.2 %)	627 (0.43 %)
Age, yr	30.2 (4.0)	53.0 (8.1)‡	57.6 (7.8)‡
Height, cm	162.3 (6.2)¥	156.8 (5.9)‡	162.5 (6.1)‡
Weight, kg	62.6 (12.0) ¥	67.7 (12.5)‡	71.0 (13.2)‡
BMI, kg/m^2	23.8 (4.4)	27.5 (4.9) ‡	26.9 (4.9)‡
Family history of diabetes, n (%)	334 (40.2)	1,556 (49.1)	25656 (17.57)

Table 1: Characteristics of women participants from the START and UK Biobank studies with available GDM and Genotype data. *South Asian Women with GDM status. Data are mean (SD) unless otherwise indicated. ¥ pre-pregnancy values, ‡ Values from baseline data. Abbreviations: BMI, Body mass index; GDM, gestational diabetes; SA-W, South Asian women, Brit-EUR-W, Europeans women from Great Britain; START, South Asian Birth Cohort.

			START				UK Biobank SAW				UK Biobank Brit-EUR-W			
PRS Type	Consortium	LD source	Beta	SE	P-value	AUC	Beta	SE	P-value	AUC	Beta	SE	P-value	AUC
P+T	**Mahajan et al, 2014**	**1KG**	**0.445**	**0.08**	**8.7×10^{-9}**	**0.62**	**0.423**	**0.14**	**0.003**	**0.61**	**0.303**	**0.04**	**4.63×10^{-14}**	**0.58**
		START	0.448	0.08	6.55×10^{-9}	0.62	0.512	0.14	0.0003	0.64	**0.291**	0.04	3.84×10^{-13}	0.58
	Scott et al, 2017	1KG	0.370	0.07	7.86×10^{-7}	0.60	0.280	0.14	0.05	0.57	**0.296**	0.04	1.45×10^{-13}	0.58
		START	0.351	0.07	2.98×10^{-6}	0.60	0.300	0.14	0.03	0.59	**0.270**	0.04	1.88×10^{-11}	0.57
GraBLD	**Mahajan et al, 2014**	1KG	0.465	0.08	1.8×10^{-9}	0.62	0.520	0.14	0.0003	0.64	**0.343**	0.04	1.14×10^{-17}	0.59
		START	**0.470**	**0.08**	**1.32×10^{-9}**	**0.62**	**0.510**	**0.14**	**0.0005**	**0.63**	**0.351**	**0.04**	**1.86×10^{-18}**	**0.59**
	Scott et al, 2017	1KG	0.317	0.07	1.61×10^{-5}	0.59	0.388	0.14	0.006	0.61	**0.344**	0.04	8.08×10^{-18}	0.59
		START	0.342	0.07	3.93×10^{-6}	0.59	0.387	0.14	0.006	0.61	**0.348**	0.04	4.15×10^{-18}	0.59
LDpred	**Mahajan et al, 2014**	**1KG**	**0.461**	**0.07**	**2.18×10^{-9}**	**0.65**	**0.527**	**0.14**	**0.0002**	**0.65**	**0.305**	**0.04**	**2.63×10^{14}**	**0.58**
		START	**0.470**	0.08	1.32×10^{-9}	0.62	0.44	0.14	0.002	0.61	0.278	0.04	3.32×10^{-2}	0.57
	Scott et al, 2017	**1KG**	**0.347**	**0.07**	**4.05×10^{-6}**	**0.59**	**0.382**	**0.14**	**0.006**	**0.61**				
		START	0.281	0.07	0.00015	0.57	0.225	0.13	0.10	0.55	0.323	0.04	1.90×10^{-16}	0.59

Table 2: Characteristics and GDM association results of the top weighted P+T and GraBLD PRSs in South Asian women from the START and UK Biobank studies. Results are from univariate association tests with GDM. The top 2 PRSs are shown in bold. Abbreviations: 1KG, 1000Genomes; AUC area under the curve; GraBLD, Gradient Boosted and LD adjusted; LD, Linkage Disequilibrium; NA, Non applicable; P+T, pruning and thresholding; PRS, Polygenic Risk Score; SAW, South Asian Women; Brit-EUR-W, European women from Great Britain; SE, Standard Error; START, South Asian Birth Cohort.

			START			UK Biobank - SA			UK Biobank – Brit EUR		
High PRS definition	Reference group	PRS type	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Top 25%	Remaining 75%	GraBLD	2.51	1.82 - 3.47	1.75×10^{-8}	2.66	1.51 - 4.63	0.0006	1.75	1.48 – 2.05	2.07e-11
		P+T	2.08	1.51 – 2.87	7.44×10^{-6}	1.80	0.99 – 3.17	0.05	1.65	1.40 – 1.94	2.41e-09
		LDpred	2.00	1.45 – 2.76	2.11×10^{-5}	2.61	1-16 – 3.60	0.01	1.72	1.46 – 2.02	7.66e-11
Top 25%	Lowest 25%	GraBLD	3.40	2.25 - 5.17	7.30×10^{-9}	5.30	2.17 - 15.88	0.0008	2.11	1.69 – 2.66	1.09e-10
		P+T	3.09	2.10 – 4.74	1.47×10^{-7}	4.21	1.67 – 12.82	0.005	2.22	1.76 - 2.82	3.08e-11
		LDpred	3.06	2.02 – 4.69	1.77×10^{-7}	3.59	1.53 – 9.84	0.006	2.08	1.66 – 2.62	3.09e-10

Table 3: Association results of Top PRS (categories) with GDM in South Asian women from the START and UK Biobank studies.

GraBLD PRS used: PRS1_GraBLD_$W_{Mahajan}$_LD_{START}_$N_{90\%}$,. P+T PRS used: PRS2_$PT_{Mahajan}$_LD_{1KG}_$N_{85\%}$_$P_{0.016}$. Abbreviations: CI, confidence interval; Brit EUR, European participants from Great Britain; PRS, Genome-wide Polygenic Risk Score; GraBLD, Gradient Boosted and LD adjusted; OR, Odds ratio; P+T, Pruning and thresholding; SA, South Asians; START, South Asian Birth Cohort. .

			START				UK Biobank - SA			
			Unadjusted		Adjusted		Unadjusted		Adjusted	
	Method	N of GRMs	h^2	SE [95%CI]	h^2	SE (CI)	h^2	SE (CI)	h^2	SE (CI)
Whole genome data	GREML-SC	1	0.83	0.45 [0.38 – 1.00]	0.87	0.51 [0.36 – 1.00]	0.17	0.14 [0.03 – 0.31]	0.15	0.16 [0 – 0.31]
	GREML- MS	2	0.80	0.46 [0.34 -1.00]	0.85	0.51 [0.33 – 1.00]	0.11	0.15 [0 – 0.26]	0.12	0.17 [0 – 0.29]
	GREML- LDMS-I	4	1	0.65 [0.34 -1.00]	0.95	0.73 [0.22 – 1.00]	0.23	0.25 [0 – 0.48]	0.26	0.27 [0 – 0.53]
SNPs in top PRS	GREML-SC	1	0.17	0.13 [0.04 – 0.30]	0.16	0.13 [0.02 – 0.29]	0.07	0.05 [0.02 – 0.11]	0.06	0.05 [0.01 – 0.11]
	GREML- MS	2	0.17	0.13 [0.04 – 0.30]	0.15	0.13 [0.02 – 0.28]	0.07	0.05 [0.02 – 0.12]	0.06	0.04 [0.02 – 0.10]
	GREMEL- LDMS-I	4	NA	NA	NA	NA	0.08	0.05 [0.03 – 0.13]	0.07	0.04 [0.02 – 0.12]

Table 4: Heritability estimates for GDM in South Asian women from the START and UK Biobank studies.

Top PRS: Mahajan 2014, LD_{1KG},). Adjusted models also include the first 5 eigenvectors from PCA. Abbreviations: 1KG, 1000 Genomes; AUC area under the curve; CI, confidence interval; GREML, genomic relatedness matrix residual maximum likelihood ; GREML-SC, single component GREML; GREML-MS, MAF stratified GREML, GREMEL- LDMS-I, LD and MAF stratified GREML (at SNP individual level) ; GRM, genomic relationship matrix; NA, not available; PCA, Principal component Analysis; P+T, Pruning and thresholding; SAW, South Asian women; Brit-EUR-W, European women from Great Britain; SE, Standard Error; SNP, Single Nucleotide Polymorphism; SAS, South Asians; START, South Asian Birth Cohort.

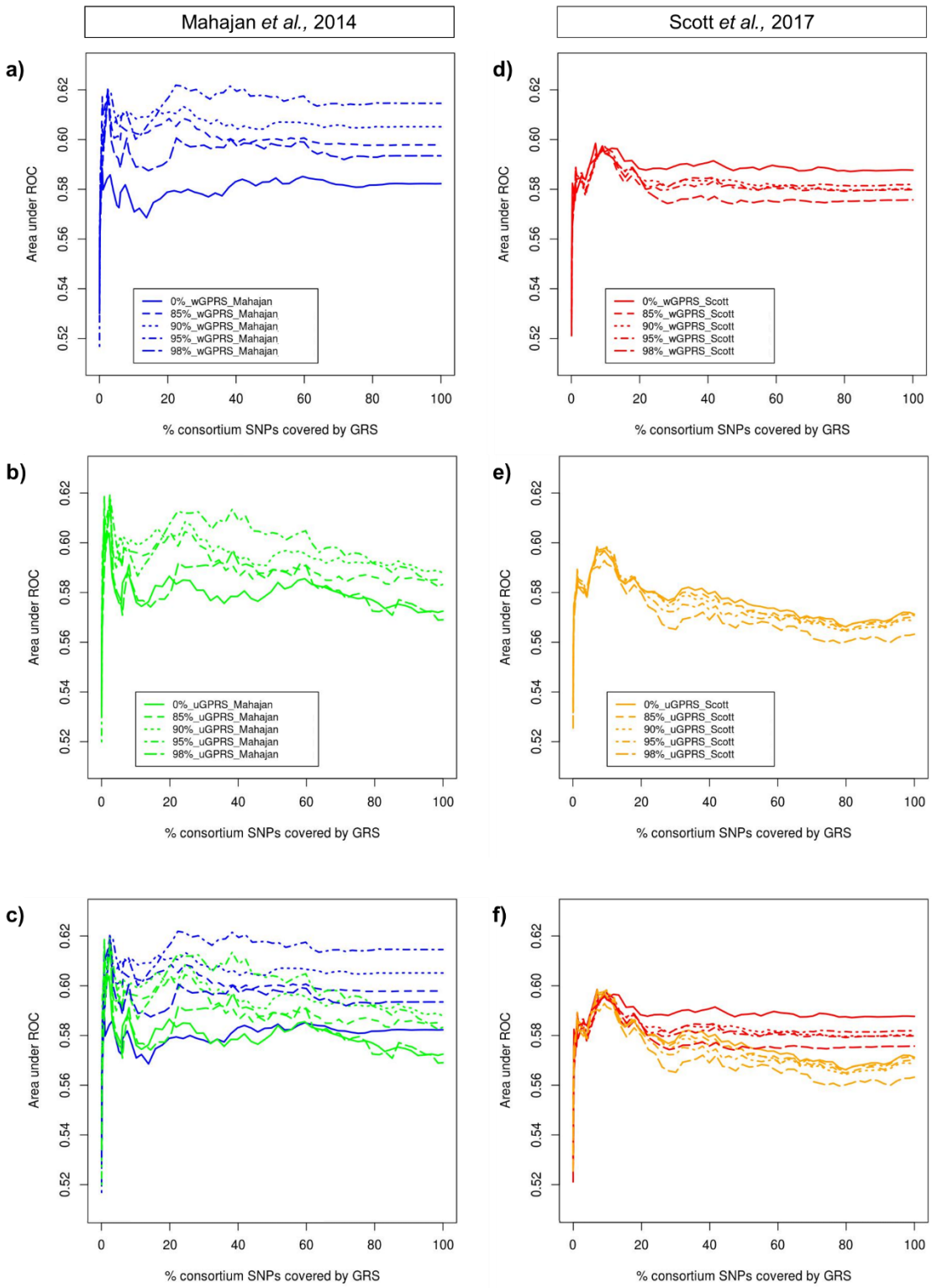

Figure 1: AUCs of the different weighted and unweighted LDSTART P+T PRSs based on Mahajan et al. and Scott et al. Results from association tests with GDM. Abbreviations: 0 85 90 95 and 98%, PRS including a subset of SNPs tested in at least 0 85 90 95 and 98% of the total samples of the consortium study respectively; AUC area under the curve; PRS, Genome-wide Polygenic Risk Score; LD, Linkage disequilibrium; P+T, Pruning and thresholding; SNP, Single Nucleotide Polymorphism; START, South Asian Birth Cohort; ROC, receiver operating characteristic; uPRS, unweighted PRS; wPRS, weighted PRS.

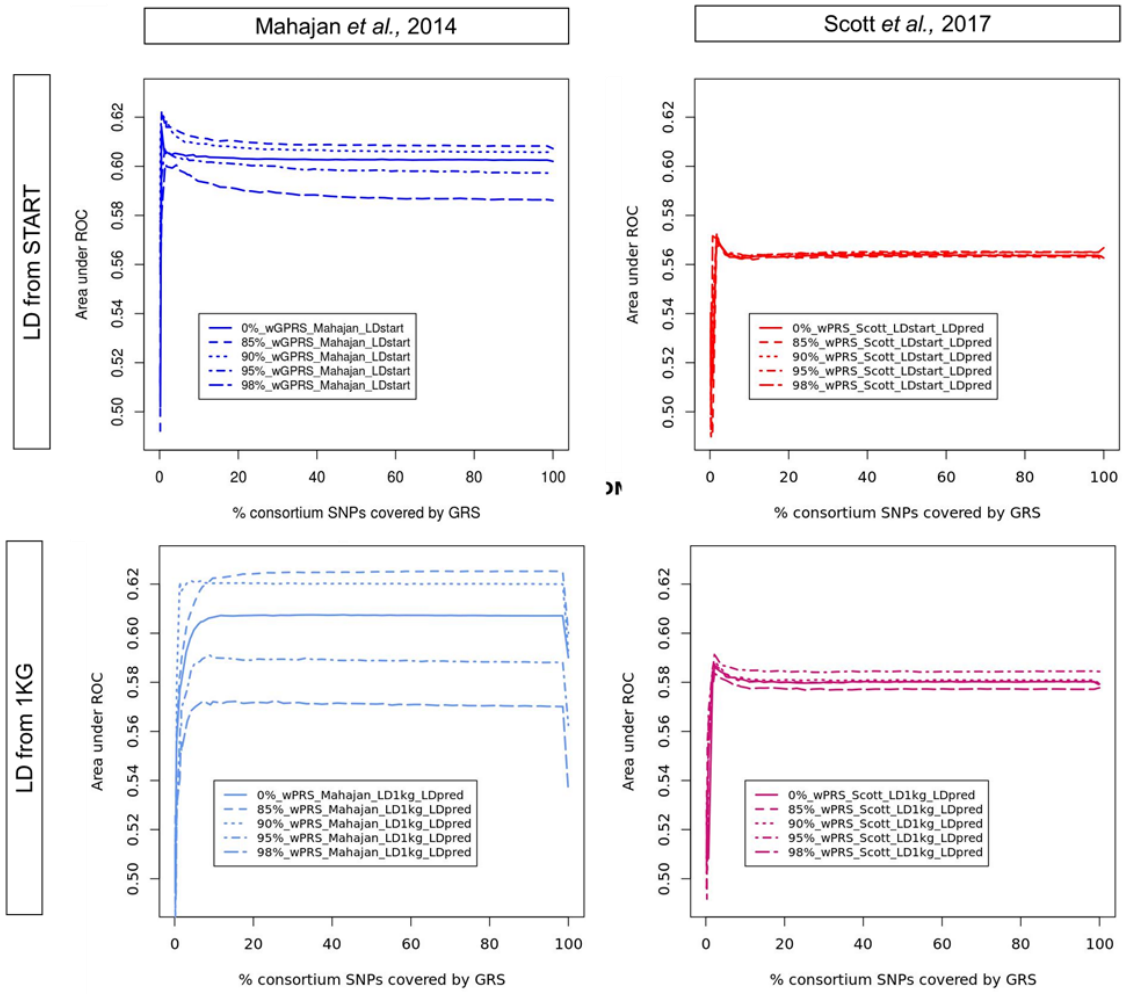

Figure 2: AUCs of the different LDpred PRSs based on Mahajan *et al.* and Scott *et al.* Results from association tests with GDM. Abbreviations: 0 85 90 95 and 98%, PRS including a subset of SNPs tested in at least 0 85 90 95 and 98% of the total samples of the consortium study respectively; 1KG, 1000 Genomes; AUC area under the curve; PRS, Polygenic Risk Score; LD, Linkage disequilibrium; SNP, Single Nucleotide Polymorphism; ROC, receiver operating characteristic; wPRS, weighted PRS.

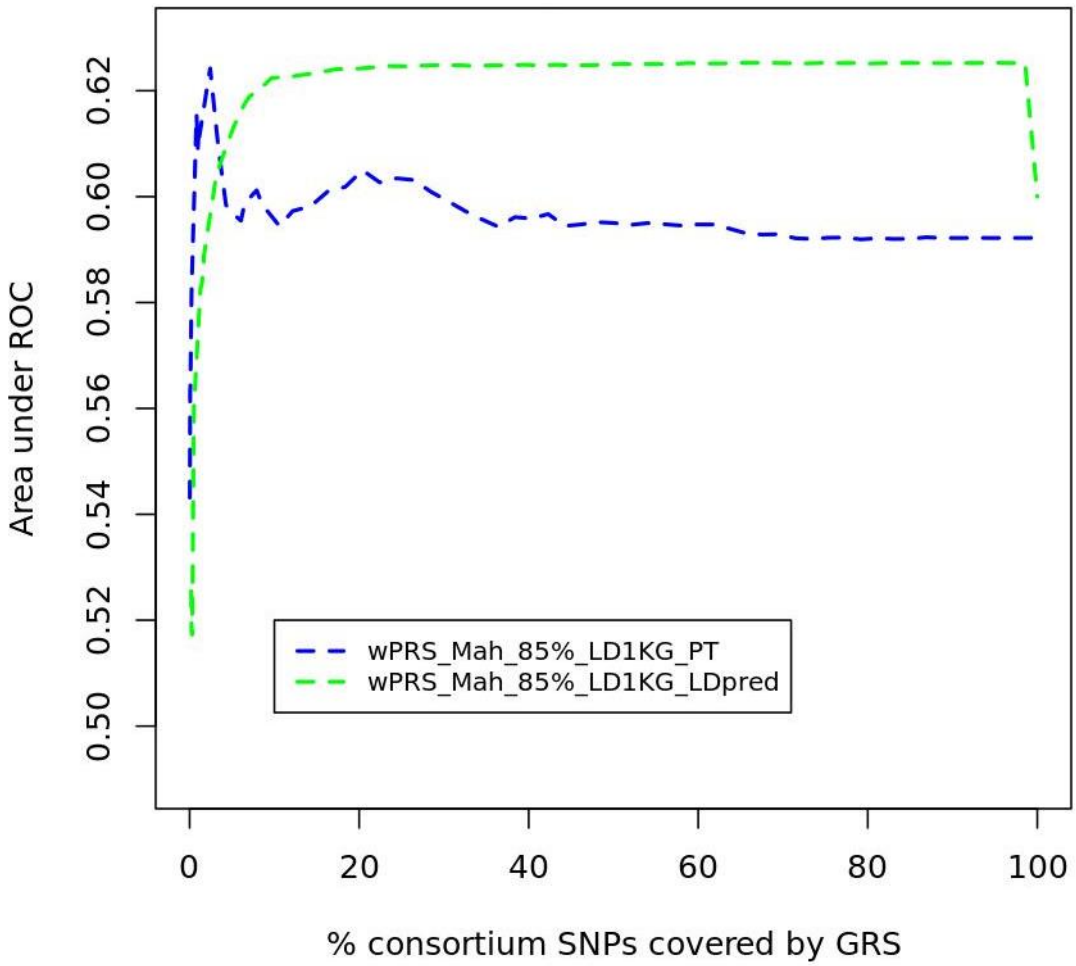

Figure 3; AUCs of the Mahajan *et al.* LD_{1KG} $N_{85\%}$ P+T and LDpred PRSs in START. Abbreviations: 85 %, PRS including a subset of SNPs tested in at least 85 % of the total samples of the consortium study respectively; 1KG, 1000 Genomes; AUC area under the curve; PRS, Polygenic Risk Score; LD, Linkage disequilibrium; P+T, Pruning and thresholding; START, South Asian Birth Cohort; ROC, receiver operating characteristic; wPRS, weighted PRS

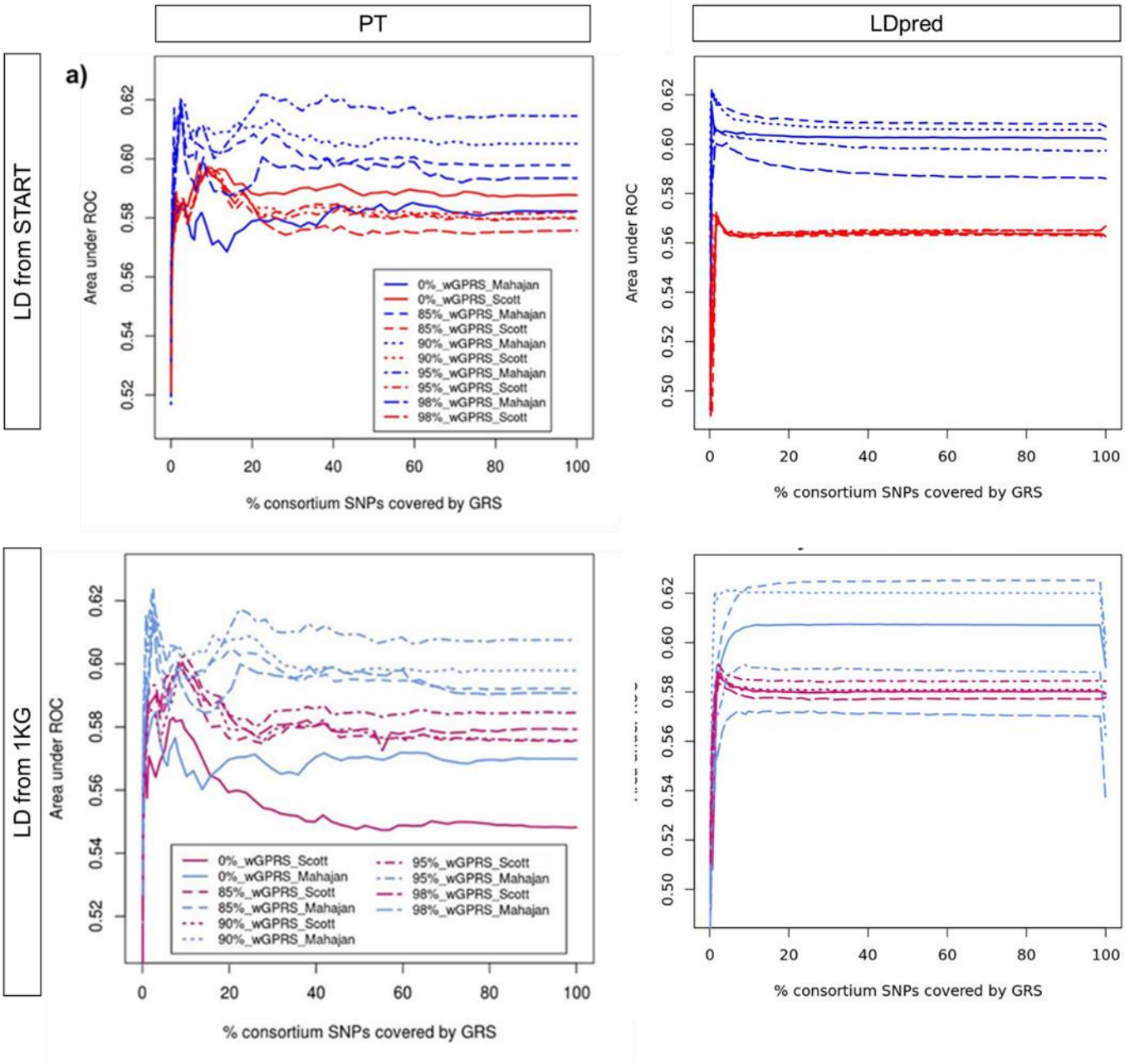

Figure 4 : AUCs of the different weighted P+T and LDpred PRSs based on Mahajan *et al*. and Scott *et al.* Results from association tests with GDM.**a)** LD from START **b)** LD from 1000 Genomes. Abbreviations: 0 85 90 95 and 98%, PRS including a subset of SNPs tested in at least 0 85 90 95 and 98% of the total samples of the consortium study respectively; 1KG, 1000 Genomes; AUC area under the curve; PRS, Genome-wide Polygenic Risk Score; LD, Linkage disequilibrium; P+T, Pruning and thresholding; SNP, Single Nucleotide Polymorphism; START, South Asian Birth Cohort; ROC, receiver operating characteristic; uPRS, wPRS, weighted PRS.

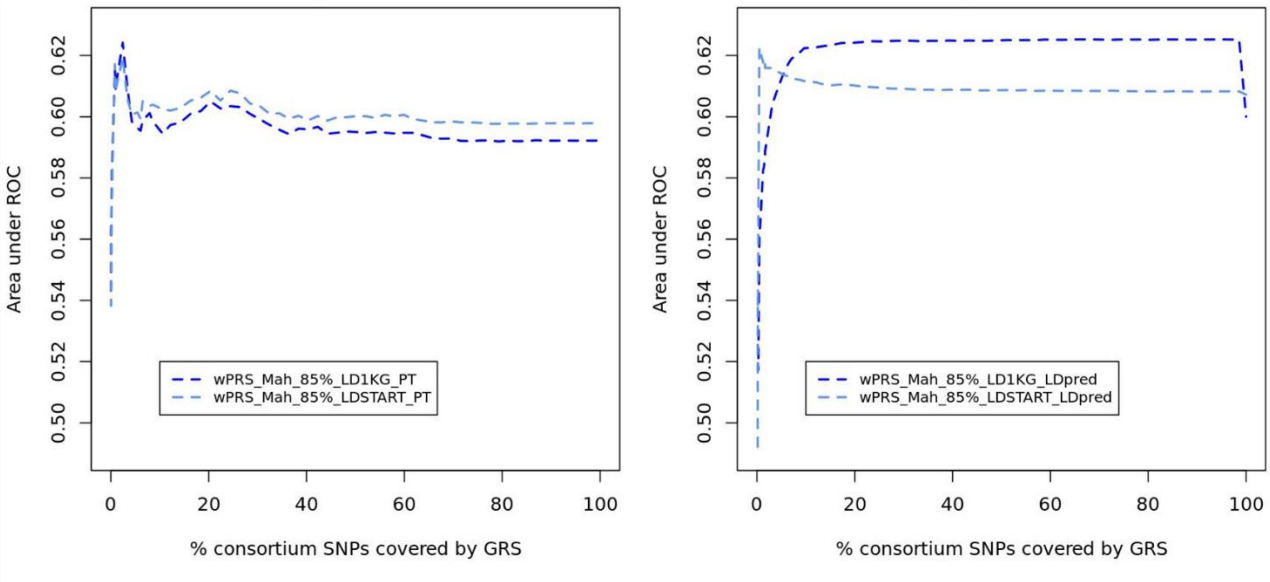

Figure 5; AUCs of Mahajan *et al.* $N_{85\%}$ based LD_{START} P+T and LDpred PRSs and their LD_{1KG} counterparts. Abbreviations: 85 and 95%, PRS including a subset of SNPs tested in at least 85 and 95% of the total samples of the consortium study respectively; 1KG, 1000 Genomes; AUC area under the curve; PRS, Polygenic Risk Score; LD, Linkage disequilibrium; P+T, Pruning and thresholding; START, South Asian Birth Cohort; ROC, receiver operating characteristic; wPRS, weighted PRS.