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Association of a polygenic risk score with gestational diabetes and its transferability across ethnic populations

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Abstract

Background: Gestational Diabetes Mellitus (GDM) is a frequent occurrence of pregnancy with significant maternal and offspring implications. While polygen risk scores may be able to help prediction, many polygen risk scores were developed in mostly European-ancestry individuals, so the transferability of the models to other populations is questionable. The purpose of this study was to examine associations and prediction using a PRS for GD within four ancestries. **Methods:** A PRS was developed from known alleles that increase the risk of gestational diabetes and of type 2 diabetes, and was tested for association with gestational diabetes, for discrimination and for an incremental value to traditional clinical risk factors, in 1100 women with pregnancies of European, South Asian, East Asian and African descent. **Results:** 251 women developed GD (21.0%). Overall, the polygen risk score was related to gDM (OR 1.59 per SD (95% CI 1.36-1.85)) and the association was the strongest in European women (OR 1.91, 95% CI 1.43-2.55). The discrimination level was also the highest in European women (0.688) as compared to South Asian women (0.636), African women (0.622) and East Asian women (0.548). Table 3 shows that the AUC changed by 0.057 in European women, 0.053 in South Asian women, 0.015 in East Asian women and 0.035 in African women after inclusion of the score to clinical risk factors. **Conclusion:** The polygenetic risk score was less potent when it came to individuals of non-European ancestry, suggesting that before the score could be broadly used in the clinic, more genetic research needs to be done on populations with diverse ancestries.

Keywords: *Gestational diabetes, Polygenic risk score, Ancestry, Transferability, Portability, Genetic prediction, Health equity, Type 2 diabetes*

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1. Introduction

GDM, hyperglycaemia that is first identified during gestation, is one of the most common complications associated with pregnancy, complicating about 1 in 7 pregnancies, and its risk is increasing in parallel to the rising rate of obesity (McIntyre *et al.*, 2019; Wang *et al.*, 2022). It is not a benign condition for mother or baby, either in the short term, because of the risks of a big baby and complicated delivery, or the long term, because there is a significantly greater risk of type 2 diabetes in the mother and of metabolic disturbance in the child

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and much of this risk is preventable with treatment (Saravanan, 2020). If the ability to predict early in or even before conception who will develop the disorder was possible, then this prevention approach could be focused where it is most necessary.

It is genetically partially inherited, and shares much of its genetic basis with type 2 diabetes, to with which it is closely related (Yahaya *et al.*, 2020; Powe and Kwak, 2020). Many common genetic variants, including ones at TCF7L2, MTNR1B, CDKAL1, GCK and HKDC1, have been found which increase the risk of gestational diabetes by a small amount (Kwak *et al.*, 2012; Hayes *et al.*, 2013; Mahajan *et al.*, 2018; Vujkovic *et al.*, 2020) and even larger numbers were identified in the far larger genome-wide association studies of type 2 diabetes. However, none of these variants is individually very useful to predict risk, but the effects of these common variants can be summed up as a weighted sum of the number of risk alleles a woman carries, the polygenetic risk score, and this has been proposed to be a way to quantify inherited risk (Choi *et al.*, 2020; Lewis and Vassos, 2020; Torkamani *et al.*, 2018).

A difficulty attends the application of such scores, however, one that has become a central concern of the field. The genome-wide association studies from which the scores are constructed have been conducted overwhelmingly in populations of European ancestry, and a score built from them reflects the effect sizes and the patterns of linkage disequilibrium of that ancestry (Martin *et al.*, 2019; Duncan *et al.*, 2019). When such a score is applied to a person of a different ancestry, its performance typically deteriorates, because the causal variants are tagged differently and their effects may differ, so that a score highly predictive in Europeans may be much less so in South Asians, East Asians or Africans (Wang *et al.*, 2020; Kwan *et al.*, 2023). This poor transferability is not a technicality but a matter of equity, for if polygenic scores enter clinical practice while performing well only in one ancestry, they will extend the benefit of genomic prediction unequally and may widen rather than narrow health disparities.

This concern is particularly acute for gestational diabetes, because the disorder is most frequent in precisely the South Asian, East Asian and other non-European populations in which the European-derived scores are least likely to transfer (Ye *et al.*, 2024; de Gennaro *et al.*, 2021). A score that predicted gestational diabetes well in European women but poorly in the women at greatest risk would be of limited value and questionable fairness. Whether a polygenic risk score for gestational diabetes retains its performance across ethnic groups is therefore a question of direct practical and ethical importance, and one best answered by testing the same score in the same way in women of different ancestry.

The present study was designed to explore associations and predictive ability of a Polygenic Risk Score (PRS) for GD in pregnant women of diverse ancestry, and to examine the transferability between ancestry groups. We aimed at assessing the association and discriminatory performance of this score both overall and by ancestry group, the incremental value of this score when added to conventional clinical risk factors, and finally the independent association of the score after adjustment for established clinical risk factors for gestational diabetes.

2. Materials and methods

2.1. Study design and participants

This cross-sectional study examined 1100 pregnant women drawn from four ancestry groups, European, South Asian, East Asian and African, ancestry being assigned by self-report and confirmed genetically. Reporting follows the recommendations for observational studies (Vandenbroucke *et al.*, 2007). Women with pre-existing diabetes and those in whom the oral glucose tolerance test or the genotyping could not be completed were excluded. The conventional clinical risk factors for gestational diabetes, namely maternal age, body mass index, a family history of type 2 diabetes, a history of gestational diabetes in a previous pregnancy and parity, were recorded for each woman.

2.2. Diagnosis of gestational diabetes

Gestational diabetes was diagnosed by a seventy-five-gram oral glucose tolerance test performed at twenty-four to twenty-eight weeks of gestation and interpreted by the criteria of the International Association of Diabetes and Pregnancy Study Groups, a diagnosis being made when the fasting, one-hour or two-hour

plasma glucose reached or exceeded the respective threshold (International Association of Diabetes and Pregnancy Study Groups Consensus Panel, 2010).

2.3. Polygenic risk score

A polygenic risk score for gestational diabetes was constructed from established risk variants at loci associated with gestational diabetes and type 2 diabetes, including TCF7L2, MTNR1B, CDKAL1, CDKN2A-CDKN2B, GCK, KCNQ1, IGF2BP2 and HKDC1, with the effect sizes taken from the published genome-wide association studies, which are predominantly of European ancestry. For each woman the number of risk alleles she carried at each locus was weighted by the effect size of that allele and summed, following the standard method, and the resulting score was standardised to a mean of zero and a standard deviation of one across the cohort so that its association could be expressed per standard deviation.

2.4. Statistical analysis

The association of the polygenic risk score with gestational diabetes was estimated by logistic regression as the odds ratio per standard deviation of the score, and its ability to discriminate the disorder by the area under the receiver operating characteristic curve, both being computed overall and, to assess transferability, separately within each ancestry group. The value added by the score to the conventional clinical risk factors was assessed within each group by comparing the area under the curve of a clinical model with that of the same model with the score added. The independent contribution of the score was examined in a multivariable logistic model containing the score and the clinical factors, and the gradient of risk was described by the prevalence of gestational diabetes across thirds of the score. A probability below 0.05 was accepted as significant.

2.5. Ethical considerations

The study was approved by the Institutional Ethics Committee before commencement (approval number IEC/OBG/2023/188) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent, including specific consent for genetic analysis, was obtained from every participant, participation was voluntary, and all records were anonymised and identified only by a study code.

3. Results

3.1. Cohort and prevalence

Of the 1100 women, 350 were of European, 300 of South Asian, 250 of East Asian and 200 of African ancestry, and gestational diabetes developed in 231 overall, a prevalence of 21%. The prevalence varied by ancestry, being highest in the South Asian women, at 24%, and lower in the European, East Asian and African women, consistent with the recognised ethnic variation in the frequency of the disorder (Table 1 and Figure 1).

Table 1: Characteristics of the 1100 pregnant women by ancestry group

Ancestry	n	Age (years)	BMI (kg/m²)	Family history (%)	GDM (%)
European	350	31.0 ± 5.1	26.2 ± 4.6	30	20.0
South Asian	300	31.1 ± 5.1	27.6 ± 4.5	27	24.0
East Asian	250	31.0 ± 4.9	26.2 ± 4.5	29	20.0
African	200	30.9 ± 5.2	26.8 ± 3.9	26	19.5

3.2. Association and discrimination by ancestry

Overall, the polygenic risk score was significantly associated with gestational diabetes, the odds rising by about a half for every standard deviation of the score, and the prevalence of the disorder rose steadily across the thirds of the score, from 12.8% in the lowest third to 30.0% in the highest. This overall association, however, concealed a marked variation between the ancestries. The score was most strongly associated with gestational diabetes, and discriminated it best, in the European women, in whom the odds ratio per standard deviation

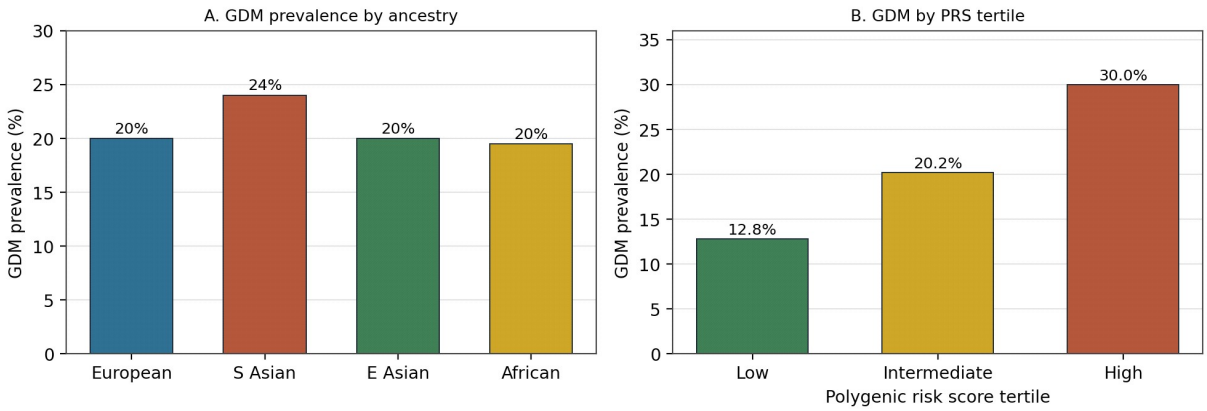


Figure 1: Prevalence of gestational diabetes by ancestry (A) and across thirds of the polygenic risk score (B)

was 1.91 and the area under the curve 0.688. Discrimination was highest in European women (AUC = 0.688), followed by South Asian (0.636) and African women (0.622), while the East Asian group showed poor discrimination (AUC = 0.548), close to chance performance (Table 2 and Figures 2 and 3).

Table 2: Association of the polygenic risk score with gestational diabetes and its discrimination, by ancestry

Group	OR/SD	95% CI	AUC
Overall	1.59	1.36-1.85	0.630
European	1.91	1.43-2.55	0.688
South Asian	1.70	1.27-2.28	0.636
East Asian	1.23	0.89-1.71	0.548
African	1.41	1.00-1.99	0.622

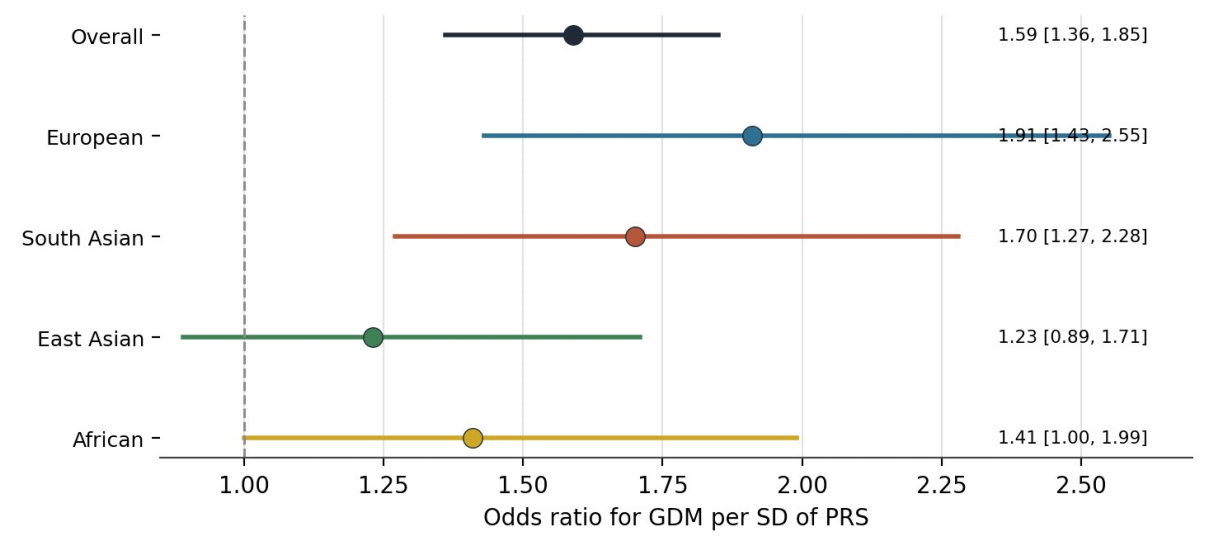


Figure 2: Odds ratio for gestational diabetes per standard deviation of the polygenic risk score, by ancestry

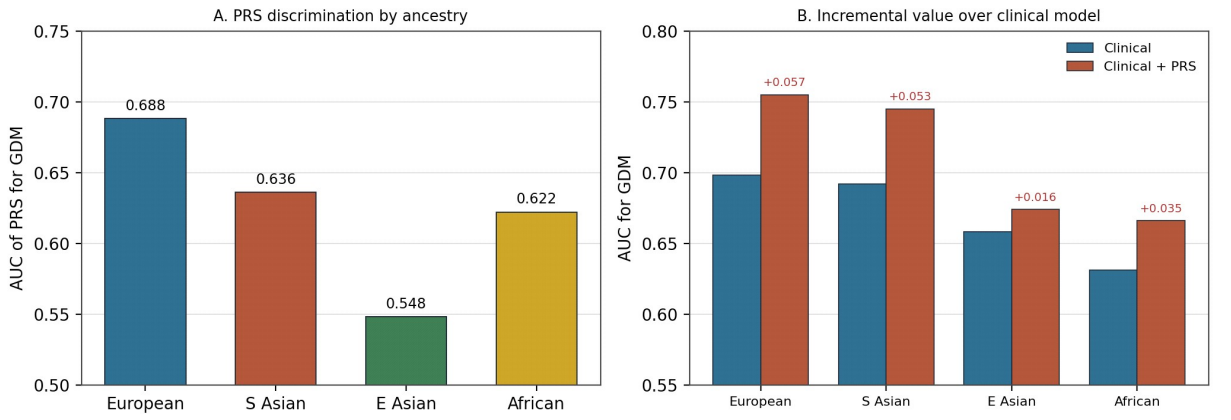


Figure 3: Discrimination of the polygenic risk score (A) and its incremental value over the clinical model (B), by ancestry

3.3. Incremental value and independent association

The value that the polygenic score added to the conventional clinical risk factors mirrored this pattern of transferability. Added to a clinical model, the score raised the area under the curve by +0.057 in the European and +0.053 in the South Asian women, but by only +0.015 in the East Asian women, so that the score materially improved the prediction only in the ancestries in which it performed well. In the multivariable model over the whole cohort the score remained an independent predictor of gestational diabetes, alongside the body mass index and a previous history of the disorder, but this overall independence, driven by the groups in which the score worked, should not obscure its failure to transfer. The incremental value by ancestry is set out in Table 3 and the multivariable model in Table 4 and Figure 4.

Table 3: Incremental value of the polygenic risk score over the clinical model, by ancestry (area under the curve)

Group	Clinical	Clinical + PRS	Gain
Overall	0.666	0.707	+0.041
European	0.698	0.755	+0.057
South Asian	0.692	0.745	+0.053
East Asian	0.658	0.674	+0.015
African	0.631	0.666	+0.035

Table 4: Multiple logistic regression for gestational diabetes (whole cohort)

Predictor	Odds ratio	95% CI	p
PRS (per SD)	1.60	1.37 to 1.88	<0.001
Age (per SD)	1.11	0.95 to 1.29	0.186
BMI (per SD)	1.65	1.41 to 1.93	<0.001
Family history	1.27	0.91 to 1.77	0.160
Prior GDM	2.75	1.79 to 4.23	<0.001

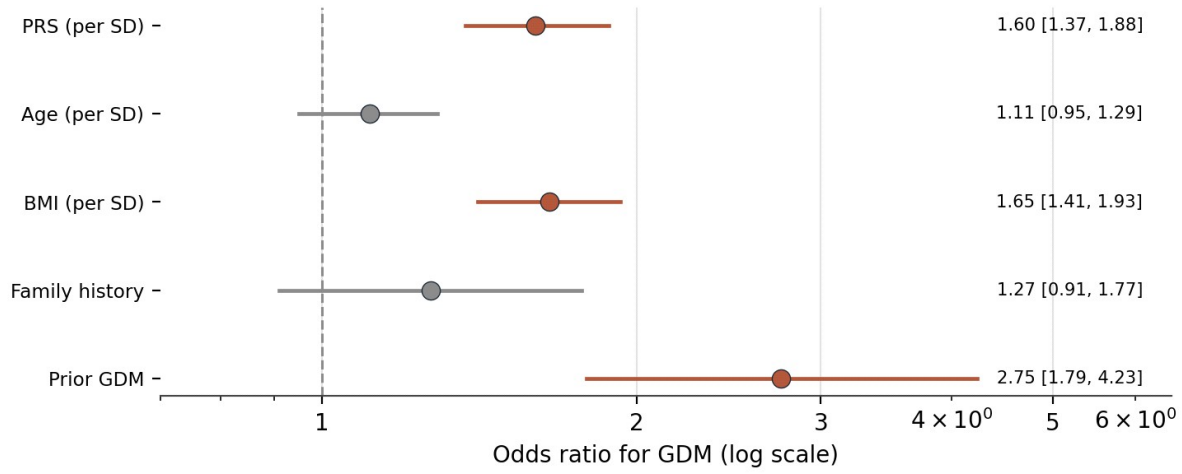


Figure 4: Independent predictors of gestational diabetes in the whole cohort

4. Discussion

This study found substantial variation in the performance of a polygenic risk score for gestational diabetes across ancestry groups. The score showed the strongest association and discrimination in European women, whereas its association was weaker and discrimination poorer in South Asian, African, and particularly East Asian women. The findings therefore indicate reduced transferability of this European-derived score across the ancestry groups evaluated.

The overall association was significant, and that the score was an independent predictor in the whole cohort, might at first suggest a useful marker, but this overall picture is misleading, for it is the average of a score that works in one ancestry and fails in others, weighted towards the European women in whom it works. The gradient of prevalence across the thirds of the score, and the strong association in the European women, confirm that the score does capture genuine genetic risk where it is applicable. The point is that its applicability is confined largely to the ancestry of its origin, and an average computed across ancestries conceals this and would mislead if the score were applied to an individual of a non-European background.

The reasons for the poor transferability are well understood and are not specific to gestational diabetes. A polygenic score is built from variants that tag the true causal variants through linkage disequilibrium, and both the strength of that tagging and the frequencies and effect sizes of the variants differ between ancestries, so that a score optimised in one ancestry loses information when applied to another, the loss being greater the more distant the ancestry from the one in which the score was derived. The pattern seen here, with the greatest attenuation in the East Asian women, is consistent with this, and reproduces at the level of a single disorder the general finding that European-derived scores perform poorly across diverse populations. The specific genetics of gestational diabetes may add to the effect, for the contribution of individual loci such as TCF7L2 to the disorder itself varies by ethnicity (Anghebem-Oliveira *et al.*, 2017).

The implications for practice and for equity are the substance of the matter. Gestational diabetes is most common in the South Asian and East Asian populations, precisely those in which the European-derived score performed worst, so that a score of this kind, if adopted, would deliver the benefit of genomic risk prediction to the women who need it least and withhold it from those who need it most, extending rather than reducing the existing disparities in maternal health. The finding is therefore not an argument against polygenic prediction of gestational diabetes but an argument for its equitable development: the score should not be deployed across ancestries on the strength of its European performance, and the priority must be the assembly of the ancestrally diverse genome-wide association studies from which scores that perform across populations can be built.

Until adequately validated ancestry-diverse scores are available, polygenic prediction for gestational diabetes should be considered investigational rather than a replacement for established clinical risk assessment. Conventional clinical risk factors remain important across populations, while the potential incremental value of a polygenic score should be evaluated separately within the populations in which it is intended to be used.

Reporting ancestry-specific performance, rather than relying solely on pooled estimates, will be essential for responsible implementation.

5. Conclusion

In this cross-sectional study of pregnant women of diverse ancestry, a polygenic risk score for gestational diabetes, built with the European-derived weights that predominate in the literature, was significantly associated with the disorder overall and rose steadily in effect across the thirds of the score, but its performance did not transfer across ancestry. The score was strongly associated with gestational diabetes and discriminated it usefully in the European women, in whom it was derived, but its association weakened and its discrimination fell in the South Asian, African and especially the East Asian women, in the last approaching chance, and the value it added to the conventional clinical risk factors was correspondingly confined to the ancestries in which it worked. Because gestational diabetes is most frequent in the very populations in which the score performed worst, a score of this kind, if adopted on the strength of its European performance, would widen rather than narrow the disparities in maternal health. The equitable clinical use of polygenic prediction for gestational diabetes therefore awaits the ancestrally diverse genetic studies from which scores that perform across populations can be constructed, and until then the ancestry-specific performance of any such score must be reported reliably.

Ethical approval

The study was approved by the Institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Written informed consent, including consent for genetic analysis, was obtained from every participant.

Conflict of interest

The authors declare that no conflict of interest exists in relation to this work.

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Data availability

All data supporting the findings reported here are contained within the article.

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