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Abstract

Oral glucose tolerance test (OGTT) is universally recommended for screening and diagnosis of gestational diabetes (GDM). This pure glucocentric approach is inadequate as other risk factors contribute to adverse perinatal outcomes. Our study tested the performance of a population-specific composite risk score-based risk stratification on perinatal outcomes. This was carried out in three prospective early pregnancy cohorts in the UK, India and Kenya and was externally validated in two real-world datasets. Our analysis illustrated clear differences in risk factors and rates of perinatal outcomes across the populations, highlighting the need for a population-specific approach. Our data also showed that rates of perinatal outcomes increased with increasing risk categories. Incorporation of key maternal risk factors that contribute to adverse perinatal outcomes with HbA1c offers a move away from an OGTT-based approach to GDM screening and a pragmatic solution for settings with limited health infrastructure where OGTT is difficult to perform.

Introduction

Gestational diabetes mellitus (GDM) affects an estimated 23 million pregnancies each year, most of them in countries least equipped to detect it. South and southeast Asia account for over 90% of cases worldwide, with nearly one in four pregnancies in India affected by GDM^{1,2}. Far less is known about GDM in Africa and Central and South America, leaving the true global distribution uncertain. GDM accounts for at least 80% of all diabetes in pregnancy¹, and its prevalence is rising rapidly, with recent UK national data showing a relative increase of 50% over five years (Sanchez-Soriano et al., in press, *BMJ Medicine*).

There is no international consensus on how GDM should be screened for or diagnosed. Guidelines disagree on whom to screen, when, with what test, and at what threshold. Some recommend a one-step approach, in which a diagnostic 75-g OGTT performed in all eligible women (universal or selective screening), while others use a two-step approach, in which a non-fasting 50-g glucose challenge test is followed by a diagnostic OGTT, only in those who screen positive³⁻⁶. Most screen only at 24–28 weeks, despite guidelines recommending some form of early-pregnancy testing for undiagnosed prediabetes/diabetes in women at high risk. Yet even where national guidelines recommend screening, uptake is often low. Direct estimates of OGTT completion are not readily available, including in high-risk populations with limited public health infrastructure such as India. But availability alone is a substantial constraint. In a recent report, the Indian Ministry of Health and Family Welfare highlighted that the facilities required to perform an OGTT are present in only 34% of community health centres and 12% of primary health centres. As fewer than half have trained staff, actual screening likely occurs in only a small proportion of centres^{7,8}. Screening rates are estimated at around 20% across Africa, reaching only 67% in research settings in Kenya⁹⁻¹¹. Adherence is inconsistent even in high-income settings: in a UK study spanning 41 maternity units, the proportion of at-risk women screened varied from 20% to 100% between units (median 85%), leaving around a quarter of eligible women unscreened¹². In a large US pragmatic trial, only 66% of women assigned to one-step screening completed it¹³. Poor adherence is multifactorial, but the demands of the test are central: the OGTT is burdensome for women and resource-intensive for services, requires an overnight fast, a prolonged facility visit, standardised glucose solutions, trained staff, and timed venous samples for laboratory

processing ^{14,15}. Simplifying screening is therefore urgently needed to increase uptake in the face of a growing burden of GDM.

GDM is associated with poor maternal and neonatal outcomes and effective treatment reduces them ¹⁶. However, hyperglycaemia that goes undetected in pregnancy carries both immediate and lifelong consequences ¹⁷. Those who are at high risk for developing GDM but do not get screening are at significantly higher odds of having adverse perinatal outcomes including stillbirth ¹². On the other hand, pure OGTT-based glucose centric approach in early pregnancy may increase the rates of small for gestational age (SGA) babies ¹⁸. The recent TOBOGM study showed that diagnosis by OGTT before 20 weeks, using International Association of Diabetes in Pregnancy Study Group (IADPSG) thresholds, while beneficial for certain neonatal outcomes at higher glycaemic thresholds, can increase the rates of SGA in women with lower glycaemic thresholds (when fasting plasma glucose is below 5.3mmol/L). For selective screening, most national and international guidelines recommend presence of certain risk factors (yes/no) to identify whom to screen but none recommend a composite risk score incorporating multiple key risk factors for adverse perinatal outcomes such as age, BMI or family history ⁴. In addition, none recommend a population-specific approach for the screening, diagnosis or management of GDM. We recently showed that a pragmatic, population-specific approach in early pregnancy (10-15 weeks) using a composite risk score by combining these three commonest risk factors with HbA1c can risk stratify women (low-, medium- and high- risk) and reduce the need for OGTT at 24-28 weeks by 50-65% in three populations (UK, India and Kenya) ¹¹. While HbA1c is a measure of glycaemia, this was used as one component of multifactorial risk rather than as a standalone diagnostic threshold. Here we present the perinatal outcomes of this approach in all three populations and externally validated in two real-world datasets from the UK and India.

Results

The flow of study participants across the three populations are shown in Extended data Figures 1a-1c. In the PRiDE study, a total of 4746 eligible women were recruited at a mean gestation of 12.5±1.4 weeks. 4320 women completed an OGTT (3885 had complete data with early pregnancy HbA1c and OGTT). Of the women who completed OGTT, 4250 had birth outcome data available. In STRiDE-India, 3070 women were recruited (mean gestation:

10.3±3.0); 2115 women completed OGTT and 1789 had birth outcome data available. STRiDE-Kenya recruited 4104 women (mean gestation: 14.8±3.2); 2142 completed OGTT and birth outcome data were available for 1846 of these (Extended data Figures 1a-1c).

Maternal and neonatal characteristics of all three cohorts are provided in Table 1. The prevalence of GDM by OGTT using IADPSG criteria in UK, India and Kenya were 14.5%, 19.2% and 3.0% respectively. In the UK, 12.5% of women were diagnosed with GDM using the NICE 2015 guidelines thresholds and their characteristics are provided in Extended data Table 1. The mean venous HbA1cs at baseline were 5.24% (33 mmol/mol), 5.08% (32 mmol/mol) and 5.23% (33 mmol/mol) in the UK, India and Kenya, respectively. The venous and POC HbA1c in India and Kenya were similar (Table 1).

Maternal risk factors and outcomes

The maternal risk factors and outcomes based on our previously published risk categories, i.e. low (GDM ruled out), medium (GDM indeterminate) and high (GDM ruled-in) ¹¹, are shown in Table 2, Figure 1a-1c and Extended data Figure 2a-2d. The population differences were clear across the populations both on the key maternal risk factors and the prevalence of outcomes, with stark differences in hypertensive disorders of pregnancy (HDP) and caesarean section (C-section) rates.

Indian women had the lowest mean HbA1c levels, despite the highest prevalence of GDM. They were also shortest compared to UK and Kenyan population. Moving from the low- to high-risk categories, the women were older, had higher BMI and higher systolic and diastolic blood pressure (BP) (BP data not available for UK) (Table 2, Extended data Figure 2a-2d). HDP and C-section rates increased significantly from the low to high-risk groups in both the UK and Kenya cohorts, with similar increase in pre-eclampsia rates with increasing risk categories in Kenya. A similar trend was noted for C-section rates in India but there were no differences in rates of pre-eclampsia or HDP (Table 2, Figure 1a-1c)

Neonatal outcomes

The key neonatal outcomes are shown in Table 3 and Figure 2a-2b. Mean birthweight centiles, using WHO and INTERGROWTH calculators increased progressively in all three populations between the low, medium and high-risk groups. Rates of LGA and macrosomia

increased with increasing risk categories in UK and Kenya. The SGA rates were lower with increasing risk categories, but these were not statistically significant. Although the macrosomia rates were numerically increased across risk categories in India, LGA rates were highest in the low-risk group. There was a statistically significant reduction in SGA rates with increasing risk categories (Table 3). Preterm birth rates were highest in the high-risk group in the UK and Kenya but in the low-risk group in India, further highlighting population differences on these key neonatal outcomes. The composite neonatal outcome rates were numerically highest in the high-risk group in all three populations but were not statistically significant. Interestingly, the mean GA at delivery was 5 days earlier in the Indian population compared to the UK or Kenya (Table 1).

Impact of risk stratification approach

Women who had false positive results (high-risk but OGTT negative) in all three populations, showed higher proportion of adverse maternal and neonatal outcomes compared to true negative women (non-GDM in low- and medium- risk categories), although not all were statistically significant (Extended data Tables 2a-2c). Specifically, higher rates of HDP, C-section, preterm birth and composite neonatal outcomes in the UK; higher C-section rates in India; and higher rates on pre-eclampsia and higher birthweight centiles in Kenya were observed. In the women with false positive results, the rates of HDP, C-section, preterm births and composite neonatal outcomes were higher in the UK; higher C-section rates in India; and higher rates of preeclampsia and birthweight centiles in Kenya, when compared to all GDM women (Extended data Table 3a-3c). However, all GDM women would have received treatment for GDM.

Women in the low-risk group, but positive for OGTT (false-negative), had lower HbA1c levels compared to women classified as true negative (OGTT-negative low and medium risk) in all three countries. Their maternal and neonatal outcomes were similar. Interestingly, the C-section rates were lower in the false-negatives in India compared to women classified as true negative. The numbers in Kenya, however, were too small to make any meaningful comparisons (Extended data Table 4a-4c).

External validation

UK:

The baseline characteristics and adverse outcomes of the real-world data in UK are shown in Table 4. The risk categories performed similar to the PRiDE population on the key maternal risk factors (age, BMI and HbA1c) and perinatal outcomes. The Area Under the Receiver Operating Characteristic curve (AUC) for prediction of GDM (yes/no) using the composite risk score was similar to that of the PRiDE study results published in our earlier paper (Extended data figure 3a). Comparison of false positives (high risk and OGTT negative) with true negatives (OGTT-negative low and medium risk) is shown in Extended data Table 5 and with all GDM women is shown in Extended data Table 6. These show that women with false positive results have significantly higher parameters of the included risk factors, and their perinatal outcomes were numerically higher or similar, although not all perinatal outcomes were available to compare. But these are not statistically significant. Similarly, comparison of false negatives (low risk and OGTT positive) with true negatives (OGTT-negative low and medium risk) (Extended data Table 7), show that these women have lower risk factor parameters and the perinatal outcomes were similar, broadly consistent with the PRiDE population.

India:

The baseline characteristics and adverse outcomes of the real-world data in India are shown in Table 4. The risk categories performed similar to STRiDE-India population on the key maternal risk factors (age, BMI and HbA1c) and perinatal outcomes. The AUC for prediction of GDM (yes/no) using the composite risk score was similar to that of the STRiDE-India population (Extended data figure 3b). Women with false positive results (high risk and OGTT negative) showed significantly higher risk factor values, higher rates of HDP and C-section and higher birth centiles compared to true negatives (OGTT-negative low and medium risk) (Extended data Table 8). Compared to all GDM women, the values were similar in false positive women, although the C-section rates were lower (Extended data Table 9). Women with false negative results (low risk and OGTT positive) had lower risk factor values, but higher birthweight centiles compared to true negatives, although the numbers were too small for conclusive analysis (Extended data Table 10).

Discussion

We recently showed that population-specific, early pregnancy composite risk score categories combining three common risk factors for GDM (age, BMI and family history of diabetes) with HbA1c in three populations can reduce the need for cumbersome OGTT by 50-65%¹¹. In this analysis, we assessed the performance of these risk categories on key perinatal outcomes to reassure that our proposed approach may offer other advantages compared to the current approach. There are four key findings: firstly, there were clear population differences on maternal risk factors and rates of various perinatal outcomes, emphasising the need for a population-specific approach in screening and managing GDM. Secondly, our composite risk score-based stratification robustly identifies a gradient with increasing obstetric outcomes such as C-section rates in all populations and HDP in the UK and Kenya when moving from low- to high-risk categories. Thirdly, neonatal size showed a population-specific but consistent positive correlation with maternal risk category in terms of adjusted birthweight centiles and rates of macrosomia, with a trend of higher composite neonatal outcomes in the high-risk category. Finally, reclassification of women based on our risk stratification approach may indeed be worthwhile by *treating* the false positives (high risk but OGTT negative) and may do less harm by *not treating* the false negatives (low risk but OGTT positive), although this would need to be proven in interventional studies. External validation of our approach in two independent real-world datasets strengthened our findings.

The current approach to the diagnosis of GDM has increasingly been criticised for the following reasons: screening occurs too late in pregnancy¹⁹, the same glucose thresholds are used for all race and ethnic groups^{3,20} and being OGTT-based 'glucentric'. It relies predominantly on same maternal glycaemic thresholds to define disease despite the multifactorial determinants of adverse perinatal outcomes. The landmark Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study demonstrated a continuous association between maternal glucose concentrations on OGTT and perinatal adverse outcomes even at glucose levels previously considered normal, suggesting the role of other factors²¹. Ethnicity, age, maternal BMI, adiposity, dyslipidaemia and excess gestational weight gain all independently influence adverse outcomes and may not correlate closely with glucose thresholds alone²¹⁻²⁴. Hence a call for a more nuanced approach to the identification and

management of women with hyperglycaemia in pregnancy is required, which our approach offers.

Another major criticism is the difficulty and reliability of OGTT across the world, especially in settings with limited health infrastructure and the recommendation of universal screening using OGTT in high-risk populations such as India. Even within high-risk populations, there will be women with varying risks of GDM and adverse perinatal outcomes. Accurate risk stratification early in pregnancy can identify and manage women who are at the highest risk and reassure women who are at the lowest risk. The worst perinatal outcomes, including stillbirths, occur in untested, undiagnosed and untreated GDM ^{12,25}. Our proposed new approach addresses most of these criticisms with a simple pragmatic solution that can be implemented as early as the booking visit and identifies women at high risk of perinatal adverse outcomes, even when their OGTT at 24-28 weeks is normal. While the recent TOBOGM study suggested early pregnancy OGTT based diagnosis and management may offer benefit in reducing adverse neonatal outcomes in those in the ‘higher glucose thresholds’, it also raised concerns about the potential harm in women in ‘lower glucose thresholds’ with higher rates of SGA, further highlighting the problems of this OGTT-based glucocentric approach ^{18,26}. The GO MOMs study explored the utility of continuous glucose monitoring (CGM) and OGTT in early pregnancy on adverse outcomes (LGA) in the USA ²⁷. It showed that CGM in early pregnancy may not offer any superior predictability than OGTT but did not use our multifactorial risk-stratification approach. In addition, this early-OGTT approach does not negate the difficulties highlighted previously about conducting OGTT in resource-constrained settings.

When considering factors contributing to adverse perinatal outcomes, aside from maternal glycaemia, maternal adiposity, inflammation and biomarkers, such as leptin, have been shown to be equally or even stronger contributors than hyperglycaemia ^{18,21,26,28}.

Interestingly, this relationship may differ across ethnicity and have variable impact on fetal growth, further supporting the need for ethnicity/population-based approach ²⁹. While our risk score did not include any novel biomarkers, it offers a simple, easy to implement approach by combining the three common risk factors with HbA1c. This could also be easy to implement in settings with limited healthcare infrastructure, especially if POC HbA1c is used.

The Indian cohort demonstrated a pattern distinct from UK and Kenya: progressive reduction in SGA rates when moving from low- to high-risk categories, accompanied by paradoxically lower categorical LGA rates despite rising mean birthweight centiles. This pattern is consistent with the longstanding observation that South Asian pregnancies complicated by hyperglycaemia may manifest as growth restriction (or the attenuation of it) rather than overt macrosomia³⁰⁻³³. The observation of such high SGA rates in India, with one of the highest prevalence of GDM in the world is counter-intuitive and highlights the stark population differences observed in our study. This further strengthens the argument that a population-specific approach is needed and a ‘birthweight or birthweight centiles’-based approach may be too simplistic in certain populations such as India²⁰. Previous studies have shown that South Asian neonates exposed to maternal hyperglycaemia tend to have disproportionately preserved adiposity with reduced lean mass, thereby remaining metabolically vulnerable, a phenotype described as “thin–fat”^{19,34-36}. In this context, a reduction in SGA across increasing risk strata, rather than a rise in overt LGA, is biologically plausible.

The earlier mean gestational age at delivery observed in the Indian cohort may be due to several factors including lower gestational weight gain trajectories even in otherwise uncomplicated pregnancies³³, higher rates of placental insufficiency and fetal growth restriction^{37,38} and iatrogenic (earlier obstetric intervention)³⁹⁻⁴¹. Taken together, these studies suggest that birthweight, particularly in South Asian babies is more complex with several interacting biological, maternal nutritional and anthropometric factors at play. Hence, we suggest that measuring neonatal or infant adiposity would be superior in this population than crude birthweight or birthweight-derived indices.

There is a strong correlation between GDM and pre-eclampsia highlighting a potential common aetiology for the two conditions¹⁶. The rates of pre-eclampsia are also distinctly different across the three populations. India had the lowest rate despite a very high prevalence of GDM and the opposite was seen in Kenya. Our risk stratification could also potentially identify who is at risk of pre-eclampsia and HDP in the Kenyan population at the booking visit. With increasing evidence for strategies that can prevent pre-eclampsia, our proposed new screening strategy for GDM may offer additional benefits.

From a health economic perspective, the diagnosis of GDM poses particular challenges in settings with limited healthcare infrastructure, due to direct health-system costs and

substantial indirect costs to women through travel, lost wages, and time away from caregiving or informal work. Economic evaluations suggest that in high-income settings, universal OGTT-based screening and treatment of mild GDM may be cost-effective with regards to prevention of obstetric and neonatal complications⁴²⁻⁴⁴, although the C-section rates are higher in women with GDM in real-world settings⁴⁵. In addition, in settings where laboratory testing and specialist antenatal care consume a higher proportion of per-capita health expenditure, the widespread diagnosis of mild GDM—often defined by a single marginally elevated glucose value—can generate a disproportionate burden and indeed could cause harm if the GDM diagnosis is based on ‘lower levels of glycaemia’, especially in settings without established care pathways^{26,46,47}. The high rates of SGA observed in the Indian population despite the highest rates of GDM, may be partly due to ‘treatment effect’, as treating mild hyperglycaemia can restrict growth and increase SGA rates. These observations further highlight the urgent need for ethnic/population-specific approach. Our proposed strategy presents a plausible solution to such a situation by two ways: firstly, the risk calculator allows different countries or healthcare institutions to determine the sensitivity and specificity thresholds for the low-, medium- and high-risk categories (e.g., 80/90% or 90/90% or 95/95%) based on the total burden and resources rather than glucose thresholds alone. Secondly, the decision on whether further screening or intervention should be offered to women in low and medium risk groups can also be determined by resource availability, with additional reassurance that women who become OGTT-positive in the low-risk group do not demonstrate worse perinatal outcomes than non-GDM women. This would allow the limited resources to be spent on women with the highest risk of adverse outcomes. We have also shown that in situations where laboratory access is limited, POC HbA1c performs equally as well as venous HbA1c, similar to other studies^{48,49}. Similar to the observations in the HAPO study, the volume of adverse perinatal outcomes was observed in the low and medium-risk categories with clear linear trajectory between our risk score and perinatal outcomes, but this was population-specific. Therefore, the risk stratification thresholds can also be determined to answer the question, ‘at what level this composite-risk score approach is cost-effective in a given population?’. However, detailed cost-effectiveness analyses are beyond the scope of this paper.

Our study has some unique strengths in that we were able to develop and test a risk stratification tool for GDM using data from >11,000 pregnancies from early gestation with external validation. It incorporates the key risk factors for GDM, maternal age and BMI, in a

linear fashion along with HbA1c as a marker of glycaemia. Additionally, our approach offers 50-65% lesser requirement for OGTT and focus the care on those with highest risk in terms of adverse perinatal outcomes, which will be beneficial in resource-constrained settings including high-income countries. It must be reiterated that most adverse outcomes happen in women who require but miss GDM screening, including higher rates of stillbirth¹². Our suggested method is population-specific, moves away from a glucocentric approach, and can be adjusted based on available resources in a particular country. Our results also suggest that relying on HAPO based 75gm OGTT as the gold standard is flawed and incomplete as those results are not correlated with key perinatal outcomes and provide evidence for the argument to change current screening to a population-specific fashion. This could ensure that our efforts are aligned with perinatal outcomes that are relevant in a given population, rather than using same glucose thresholds at OGTT for diagnosing and managing GDM across the world. Another strength is that measurement of HbA1c in early pregnancy could identify women with undiagnosed diabetes, which is particularly important given the rapid rate of increase in women of reproductive age⁵⁰⁻⁵².

However, there are some important limitations. Although we have been able to show the association between the risk categories and adverse perinatal outcomes, to assess whether this approach improves outcomes, interventional studies are required compared to the current approach. Since women were managed by standard clinical care after the OGTT, the treatment effect could have under- or over-estimated the risk of outcomes, particularly in the false positive and false negative group. However, it is notable that women classified as false positive (OGTT negative and hence untreated) had worse risk factors and perinatal outcomes compared to other non-GDM women. Similarly, while the lower perinatal outcomes observed in women classified as false negative, which may have been due to 'treatment effect', their younger age and lower BMI suggest that they may be at low risk for perinatal outcomes. They can also be placed on a 'watchful-wait' pathway and be offered a OGTT at 24-28 weeks if their perceived risk changes (eg., excessive gestational weight gain or high fetal abdominal circumference at 20 weeks anomaly scan). We also did not have insulin or C-peptide measurements in our study to elucidate different subtypes of GDM (such as insulin resistant or secretory defect). GDM sub-types have been shown to contribute differentially to outcomes⁵³⁻⁵⁵ with insulin-resistant GDM associated with worse perinatal outcomes as well as higher childhood obesity and impaired glucose tolerance⁵⁶⁻⁵⁸. Our high-risk score may be a surrogate for the insulin resistant GDM sub-type, as the high-risk group across all three

populations had the highest maternal BMI, which is typically associated with higher insulin resistance. Finally, our composite risk score is currently applicable only to the three populations studied and need to be validated in other populations for generalisability of our findings.

In conclusion, our study offers a population-specific, composite risk score approach to risk stratify women in early pregnancy by incorporating key maternal risk factors that contribute to adverse perinatal outcomes. Validation of our approach in other populations needs to be carried out for wider use. However, using our risk equations that is closer to a specific population, our proposed approach can be readily utilised in healthcare systems across the world. This may potentially improve the screening rates, especially in LMICs where more than 90% of the burden of dysglycaemia in pregnancy currently resides.

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Methods

Study design

The three prospective, early pregnancy cohorts used to develop and test the composite risk factor screening models were from the PRiDE (10 centres, UK) and STRiDE (7 centres, South India, and 7 centres, Western Kenya) studies^{11,59}. The detailed protocols for both these studies have been published elsewhere^{11,59}. In brief, in PRiDE study, women were eligible if they met the National Institute for Health and Care Excellence (NICE) criteria to be screened for GDM and universal screening was carried out in the STRiDE cohorts^{3,4}. Pregnant women aged 18-50 years, who were under 16 weeks gestation (<20 weeks in Kenya), were eligible and the exclusion criteria for all cohorts were pre-gestational type 1 or 2 diabetes, severe anaemia (<8g/L), haemoglobinopathies or multiple gestation. Additionally in STRiDE, women were excluded from subsequent OGTT if their early pregnancy glucose parameters were abnormal (FPG ≥ 5.1 mmol/l; random plasma glucose ≥ 11.1 mmol/l or HbA1c $\geq 6.5\%$)^{3,60}. All other women proceeded to a 2 hour, 75g OGTT at 24 to 28 weeks gestation.

The population-specific risk scores are calculated using the logistic transformation:

Risk Score = $\exp(\text{Model}) / (1 + \exp(\text{Model}))$, where the model equations for the three cohorts are given by:

UK: $-15.402 + 2.022 \times \text{HbA1c} + 0.042 \times \text{Age} + 0.049 \times \text{BMI} + 0.063 \times \text{FH}$

STRiDE-India: $-5.213 + 0.518 \times \text{HbA1c} + 0.037 \times \text{Age} + 0.0003 \times \text{BMI} + 0.303 \times \text{FH}$

STRiDE-Kenya: $-15.057 + 1.596 \times \text{HbA1c} + 0.025 \times \text{Age} + 0.085 \times \text{BMI} + 0.424 \times \text{FH}$

In all models, FH denotes a family history of diabetes and is coded as 1 if a family history is present and 0 otherwise.

Women are classified into low-, medium-, and high-risk categories according to their estimated risk score using the following cohort-specific thresholds:

UK: low risk (≤ 0.107), medium risk ($0.107 - 0.237$), high risk (≥ 0.237)

STRiDE-India: low risk (≤ 0.164), medium risk ($0.164 - 0.229$), high risk (≥ 0.229)

STRiDE-Kenya: low risk (< 0.022), medium risk ($0.022 - 0.100$), high risk (≥ 0.100)

Following recruitment, eligible pregnant women had anthropometric measurements (height, weight, BMI and waist circumference) and blood tests which included venous HbA1c (UK)

or fasting plasma glucose, venous and point-of-care (POC) HbA1c (India and Kenya). They went on to have a fasting 2-hour 75g OGTT between 24-28 weeks gestation and women diagnosed with GDM were managed according to local guidelines. Birth weight and other perinatal outcomes were collected at delivery.

For the external validation of the risk score categories and key perinatal outcomes, two real-world datasets from the UK and India were used. In the UK, data from all singleton women registered at George Eliot Hospital NHS Trust, Nuneaton (one of the PRiDE centres) who had OGTT with at least one perinatal outcome recorded (n=1332) were included. All women had HbA1c of <6.0% (<42mmol/mol) at booking visit. In India, data on all singleton women who booked and delivered at Seethapathy Hospitals (two obstetric units, part of STRiDE study) in South India were included. All women had fasting blood glucose of <5.1 mmol/L and HbA1c <6.0% (<42mmol/mol) at booking visit, OGTT and at least one perinatal outcome recorded (n=2092).

Outcomes

GDM was defined by the International Association of Diabetes and Pregnancy Study Group (IADPSG) 2010 criteria (at least one of FPG ≥ 5.1 mmol/l, 1-hour PG ≥ 10.0 mmol/l or 2-hour PG ≥ 8.5 mmol/l) across all three populations^{60,61}. In the PRiDE study, only the fasting and 2-hour thresholds were used as 1-hour blood sample was not available as per the current NICE guidelines. As treatment for GDM was based on NICE 2015 criteria (FPG ≥ 5.6 mmol/l or 2-hour PG ≥ 7.8 mmol/l)⁴ in the UK, additional sensitivity analyses were performed using these thresholds.

The following maternal and neonatal outcomes were used for the analysis of the performance of risk score categories. Pre-eclampsia, hypertensive disorders of pregnancy (HDP), caesarean section (total), preterm delivery, birth centiles (both WHO and INTERGROWTH), macrosomia, large for gestational age (LGA) and small for gestational age (SGA) by country-specific WHO centiles, and composite neonatal outcomes. Composite neonatal outcomes included the following: NICU admissions (including neonatal hypoglycaemia) and birth injury (shoulder dystocia and other birth injuries) for PRiDE UK; neonatal hypoglycaemia, NICU admissions for other reasons, birth injury (shoulder dystocia and other birth injuries), polycythaemia and hyperbilirubinemia for STRiDE-India and STRiDE-Kenya. These were defined by standard international definitions.

Statistical Analysis

Maternal and neonatal characteristics were summarised and compared across the three cohorts using descriptive statistics in tables and figures. Continuous variables were reported as mean (standard deviation) and categorical variables as percentages (counts). Within each cohort, women were classified as low, medium, or high risk of developing GDM using the criteria we proposed in Saravanan et al. based on early pregnancy age, BMI, and family history of diabetes and HbA1c¹¹. Baseline characteristics and maternal and neonatal outcomes were compared across risk groups within and across each cohort. Analysis of variance was used for continuous variables and chi-squared tests for categorical variables. Results were presented in both tabular and graphical formats. A p-value <0.05 was considered statistically significant.

The risk stratification approach designates women as low risk (unlikely to have GDM), high-risk women (likely to have GDM), and recommends OGTT for those at medium risk. Based on OGTT results and the risk stratification, high-risk/OGTT-negative cases were classified as false positives and low-risk/OGTT-positive cases as false negatives. To ensure our approach is at least as good as the current OGTT based (yes/no for GDM) approach and does not cause harm in false positives and false negatives, the perinatal outcomes of these women were compared to ‘worst-case’ scenarios. False positives were compared against true negatives (combined OGTT-negative women in low- and medium-risk categories) and all positives (OGTT-positive women in all risk categories; ‘all GDM’). False negatives were compared with true negatives (combined OGTT-negative women in low- and medium-risk categories). Continuous variables will be analysed using t-tests, and categorical variables using chi-squared or Fisher’s exact tests where appropriate.

The risk stratification model was externally validated using real-world datasets. The PRiDE risk stratification model was validated against UK data, and the STRiDE India model using Indian data as described in the methods section. Similar to PRiDE and STRiDE results, baseline characteristics and perinatal outcomes were compared and presented across risk categories in the real-world data. The overall performances were assessed by comparing the Area Under the Receiver Operating Characteristic curve (AUC) for prediction of GDM (yes/no) with PRiDE and STRiDE-India cohorts. The adverse perinatal outcomes were compared and presented for the three risk categories. Comparisons between false positives with true negatives and all GDM, and false negatives with true negatives were also presented.

Ethical Approval

Ethical approval for PRiDE was obtained from the National Research Ethics Committee (12/WM/0010, clinicaltrials.gov number: NCT03008824). The STRiDE study (NCT03005600) was approved by respective ethics committees in India and Kenya (India: JIP/IEC/2017/0088; MDRF/NCT/07-06/2015; Kenya: IREC/2015/179). Ethical approval was not required for the UK validation set, as data collection was undertaken under the framework of a quality improvement project (GEH QIP number: 1574_1074). Ethics approval for the real-world analysis of data from India was approved by Fetal Care Research Foundation FCRF/ IEC-P5 /2025.

Author contributions

PS conceived the idea, designed the study, and developed this further with NW, NS, VM, UR, SS, and SDP, and was responsible for securing the grants (STRiDE and PRiDE). VM and SDP were responsible for the conduct of STRiDE in India and Kenya. MD and RMA were responsible for the day-to-day running in India, and ACD and WKK led this in Kenya. UR, TS, SDK, PD and SSur led the obstetric side in India. WH, CS, SH, NS, VK, JNH, BK and GA led study recruitment and coordinated site activities in each centre. YGW and HA conducted the analysis with input from NSt. SP, SSe, JW, SN, SSuk contributed to the UK and UR, MT, NSa and KG to the Indian real-world data collection. All authors contributed to the drafting and revision of the manuscript, and approved the final version, and PS had final responsibility for the decision to submit for publication. PS, VM, and SDP vouch for the accuracy and completeness of the data and for the adherence of the study protocol.

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Table 1 Baseline characteristics of women from the three cohorts

	UK (n=3885)* mean (sd) or % (n)		India (n=2115) mean (sd) or % (n)		Kenya (n= 2142) mean (sd) or % (n)	
Age (years)	3885	30.6 (5.2)	2115	26.9 (4.10)	2142	26.2 (5.0)
Height (cm)	3885	164.3 (6.8)	2115	156.2 (6.2)	1781	161.2 (6.9)
Weight (kg)	3885	83.4 (20.4)	2115	59.2 (12.6)	2142	63.7 (12.0)
BMI (kg/m ²)	3885	30.8 (7.0)	2115	24.2 (4.6)	1781	24.5 (4.5)
Waist circumference (cm)	3577	98.6(16.3)	1872	85.5 (10.0)	2135	86.9 (10.3)
Nulliparous	3885	81.7% (3175)	2115	61.0% (1291)	2141	49.6% (1063)
Family History of diabetes	3885	1659 (42.7%)	2115	860 (40.7%)	2131	310 (14.5%)
Systolic blood pressure (mm Hg)		-	1837	102.3 (10.5)	2137	113.2 (11.7)
Diastolic blood pressure (mm Hg)		-	1837	68.8 (9.4)	2137	68.96 (9.7)
Socio-economic status	3165		2115		1561	
Lower Class		24.3% (770)		23.6% (499)		40.5% (632)
Middle Class		27.5% (871)		55.7% (1177)		40.5% (633)
Upper Class		48.2% (1542)		20.8% (439)		19.0% (296)
GA at recruitment (weeks)	3885	12.5 (1.4)	2115	10.3 (3.0)	1982	14.8 (3.2)
HbA1c at recruitment	3885	5.24% (0.32)	1946	5.08% (0.33)	2111	5.23% (0.44)
Venous POC		NA	1729	5.15% (0.49)	2117	5.13% (0.56)
GA at OGTT (weeks)	3801	26.8 (2.7)	1883	25.4 (3.6)	2004	25.5 (2.5)
OGTT Fasting glucose (mmol)	3870	4.48 (0.55)	2066	4.53 (0.45)	2142	4.2 (0.48)
OGTT 1-hour glucose	NA	NA	1991	7.63 (1.71)	2142	5.71 (1.4)
OGTT 2-hour glucose	3845	5.88 (1.51)	1995	6.57 (1.45)	2142	5.3 (1.14)
Prevalence of GDM by IADPSG	3885	14.5% (565)	2115	19.2% (407)	2142	3.03% (65)
GA at delivery (weeks)	3810	39.4 (1.8)	1919	38.6 (1.9)	1868	39.3 (2.5)
Male gender	3806	51.7% (1968)	1799	51.9% (934)	1452	49.7% (722)
Mean birthweight (g)	3809	3398.7 (585.6)	1916	2927.1 (465.2)	1798	3207.9 (532.9)
LGA (WHO centiles)	3789	12.1% (459)	1789	3.5% (62)	1415	7.5% (106)
SGA (WHO centiles)	3789	8.6% (325)	1789	25.4% (455)	1415	18.8% (266)
Mode of delivery	3476		1907		1805	
Normal vaginal		56.2%		52.0%		81.8%
Assisted delivery		10.1%		5.5%		0.3%
C-section		33.7%		42.5%		17.9%

Data are mean (SD) or % (n). GA = gestational age, OGTT = oral glucose tolerance test, LGA = large for gestational age, SGA = small for gestational age

* n=3885 are women who had complete HbA1c and OGTT data (n=4320 had OGTT in total)

Table 2 Maternal characteristics in three populations according to risk categories

UK	N	Risk Score categories			p-value
		low N = 1,771	medium N = 1,903	high N = 564	
Age (years)	4,238	28.6 (4.9)	31.3 (5.0)	33.8 (5.0)	<0.001
BMI (kg/m ²)	4,238	27.7 (6.1)	31.7 (6.2)	37.1 (7.5)	<0.001
Family History of Diabetes	4,238	45.2% (800)	40.6% (773)	41.5% (234)	0.017
HbA1c (%)	4,238	5.0 (0.2)	5.3 (0.2)	5.7 (0.3)	<0.001
India		low N = 536	medium N = 967	high N = 443	p-value
Age (years)	1,946	23.9 (3.0)	27.1 (3.4)	30.5 (3.6)	<0.001
BMI (kg/m ²)	1,946	22.4 (4.2)	24.5 (4.3)	26.3 (4.7)	<0.001
Systolic BP (mm Hg)	1,922	100.6 (10.2)	101.9 (9.9)	104.1 (9.9)	<0.001
Diastolic BP (mm Hg)	1,922	69.5 (10.2)	68.1 (8.6)	69.1 (8.1)	0.05
Family History of Diabetes	1,946	6.0% (32)	46.0% (445)	86.0% (381)	<0.001
HbA1c (%)	1,946	4.8 (0.3)	5.1 (0.3)	5.4 (0.3)	<0.001
Kenya		low N = 1,028	medium N = 654	high N = 69	p-value
Age (years)	1,751	24.9 (4.4)	27.8 (5.1)	31.0 (5.9)	<0.001
BMI (kg/m ²)	1,751	22.7 (3.0)	26.6 (4.2)	33.0 (6.4)	<0.001
Systolic BP (mm Hg)	1,751	111.3 (10.0)	113.1 (10.9)	116.6 (10.7)	<0.001
Diastolic BP (mm Hg)	1,751	67.7 (8.0)	69.2 (8.7)	72.3 (10.0)	<0.001
Family History of Diabetes	1,751	8.8% (90)	22.2% (145)	34.8% (24)	<0.001
HbA1c (%)	1,751	5.0 (0.3)	5.5 (0.3)	6.1 (0.6)	<0.001

*Continuous variables are shown in mean (sd) and categorical variables and prevalence rates are shown in % (n).

Table 3 Neonatal outcomes in three populations according to risk categories

UK	N	Risk score categories			p-value
		low N = 1,771	medium N = 1,903	high N = 564	
WHO centiles	3,945	49.1 (28.4)	53.4 (28.8)	56.3 (30.4)	<0.001
INTERGROWTH centiles	3,845	58.1 (29.4)	62.1 (28.8)	63.5 (30.0)	<0.001
LGA (WHO) (n)	3,945	9.4% (154)	12.3% (221)	18.1% (93)	<0.001
SGA (WHO) (n)	3,945	9.4% (155)	8.3% (148)	7.8% (40)	0.35
Macrosomia (>4kg) (n)	3,967	11.5% (189)	13.8% (249)	16.9% (88)	0.004
Preterm birth	3,970	6.3% (103)	7.3% (132)	10.7% (56)	0.003
Composite Neonatal Outcome (n)	3,841	8.0% (126)	7.0% (123)	9.8% (50)	0.12
India		low N = 536	medium N = 967	high N = 443	p-value
WHO centiles	1,692	29.7 (27.7)	30.6 (24.8)	33.6 (26.7)	0.016
INTERGROWTH centiles	1,692	34.9 (29.2)	36.8 (26.9)	39.8 (28.5)	0.015
LGA (WHO)	1,692	5.6% (24)	2.3% (20)	3.2% (13)	0.008
SGA (WHO)	1,692	31.0% (132)	24.0% (207)	20.8% (84)	0.002
Macrosomia (>3.5kg)	1,816	7.4% (34)	8.1% (75)	11.1% (48)	0.11
Subscapular skinfold (mm)	1039	4.83 (2.71)	5.48 (2.28)	5.55 (2.03)	0.009
Triceps skinfold (mm)	1039	4.46 (2.40)	5.32 (2.20)	5.37 (1.93)	<0.001
Preterm birth	1,822	12.6% (58)	7.9% (73)	10.4% (45)	0.017
Composite Neonatal Outcome	1,657	12.3% (49)	11.6% (99)	12.3% (50)	0.91
Kenya		low N = 1,028	medium N = 654	high N = 69	p-value
WHO centiles	1,152	6.5 (28.4)	42.1 (30.7)	50.9 (31.4)	<0.001
INTERGROWTH centiles	1,132	45.1 (30.0)	50.5 (31.9)	60.2 (30.1)	<0.001
LGA (WHO)	1,152	5.3% (36)	9.1% (39)	22.5% (9)	<0.001
SGA (WHO)	1,152	19.9% (136)	18.5% (79)	7.5% (3)	0.14
Macrosomia (>4kg)	1,471	3.1% (26)	7.0% (39)	6.3% (4)	0.002
Preterm birth	1,535	7.9% (70)	6.5% (38)	10.8% (7)	0.34
Composite Neonatal Outcome	1,507	8.4% (73)	9.9% (57)	14.3% (9)	0.25

Data are mean (SD) or % (n)

Composite neonatal outcome (all groups combined):

The composite neonatal outcome was defined as positive if any one of its components was positive. Component specific complete case percentages were:

UK – NICU admissions including neonatal hypoglycaemia (296 out of 4281 (6.9%)),

Combined birth injury (shoulder dystocia + birth injuries; 41 out of 883 (4.6%));

India – Neonatal hypoglycemia (23 out of 1693 (1.4%)), Other NICU Admissions (156 out of 1705 (9.2%)), Combined birth injury (shoulder dystocia + other birth injuries; 12 out of 1704 (0.7%)) and Combined polycythemia + hyperbilirubinemia (55 out of 1695 (3.2%));

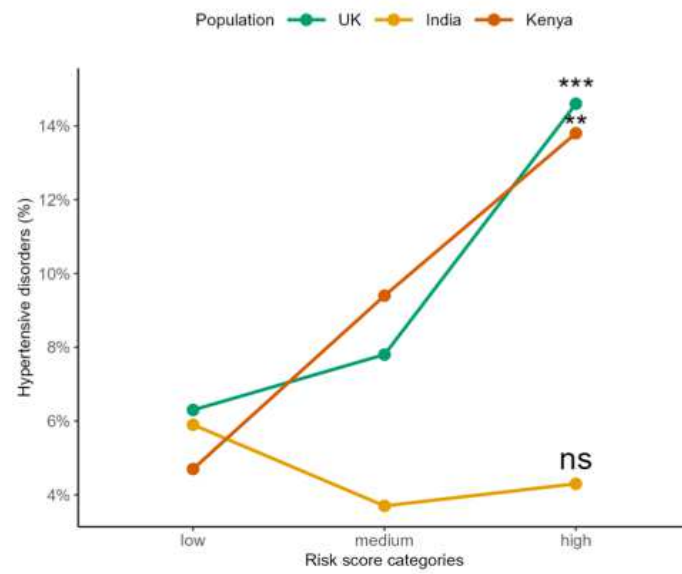
Kenya – Neonatal hypoglycemia (6 out of 60 (10.0%)); Other NICU admissions (133 out of 1773 (7.5%)), Combined birth injury (shoulder dystocia + other birth injuries; 27 out of 1840 (1.5%)) Combined polycythemia (4 out of 259 (1.54%)) + hyperbilirubinemia (15 out of 54 (27.8%))

Table 4: Key maternal characteristics, maternal and neonatal outcomes in Real-World validation datasets in the UK and India

UK	N	Risk Score categories			p-value
		Low N=407	Medium N=624	High N=301	
Age (years)	1,332	27.4 (4.7)	30.5 (4.5)	33.5 (4.9)	<0.001
BMI (kg/m ²)	1,332	32.1 (3.6)	33.8 (4.4)	37.7 (6.4)	<0.001
Family History of Diabetes	1,332	20.9% (85)	23.7% (148)	38.9% (117)	<0.001
HbA1c (%)	1,332	5.0 (0.2)	5.3 (0.1)	5.8 (0.5)	<0.001
Total C-section rates	1,332	40.5% (165)	46.3% (289)	53.2% (160)	0.004
Preterm	1,289	7.9% (31)	7.1% (43)	12.0% (35)	0.04
WHO centiles	1,259	60.2 (25.6)	62.2 (26.8)	65.2 (27.4)	0.016
INTERGROWTH centiles	1,258	64.1 (26.2)	65.8 (27.5)	67.1 (28.4)	0.09
SGA (WHO)	1,258	2.6% (10)	3.1% (18)	2.8% (8)	0.91
LGA (WHO)	1,258	17.4% (67)	24.4% (144)	29.3% (83)	0.001
Macrosomia (>4.0kg)	1,326	9.6% (39)	13.7% (85)	12.3% (37)	0.14
INDIA		low N = 258	medium N = 1151	high N = 1256	
Age (years)	2,665	25.2 (2.8)	27.5 (3.2)	30.4 (3.6)	<0.001
BMI (kg/m ²)	2,665	24.4 (4.1)	25.4 (4.4)	26.9 (5.0)	<0.001
Family History of Diabetes	2,665	14.3% (37)	41.8% (481)	84.8% (1065)	<0.001
HbA1c (%)	2,665	4.8 (0.3)	5.1 (0.3)	5.5 (0.3)	<0.001
Pre-eclampsia	2,182	0.9% (2)	1.0% (9)	0.5% (5)	0.35
Hypertensive disorders	2,665	1.2% (3)	0.5% (6)	1.5% (19)	0.05
Total C-section rates	2,665	36.0% (93)	40.1% (462)	45.0% (565)	0.007
Preterm	2,665	8.5% (22)	7.0% (81)	8.2% (103)	0.50
WHO centiles	2,612	41.1 (25.1)	36.3 (24.6)	40.6 (25.2)	<0.001
INTERGROWTH centiles	2,612	45.1 (26.7)	39.6 (26.4)	44.0 (26.8)	<0.001
SGA (WHO)	2,612	10.4% (26)	14.8% (167)	11.9% (146)	0.05

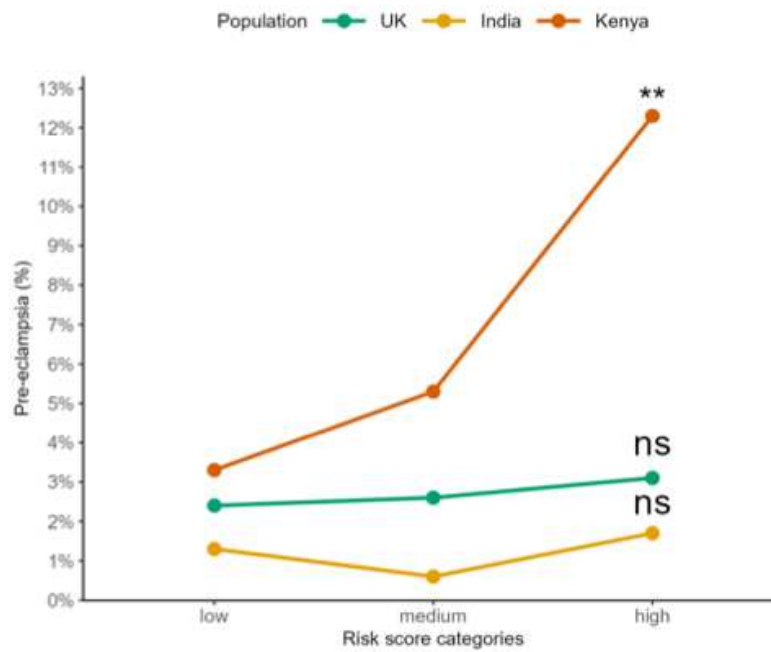
LGA (WHO)	2,612	4.0% (10)	4.0% (45)	4.1% (51)	0.98
Macrosomia (>3.5kg)	2,613	14.3% (36)	9.5% (107)	11.2% (138)	0.06

Figure 1a: Hypertensive disorders across the risk categories



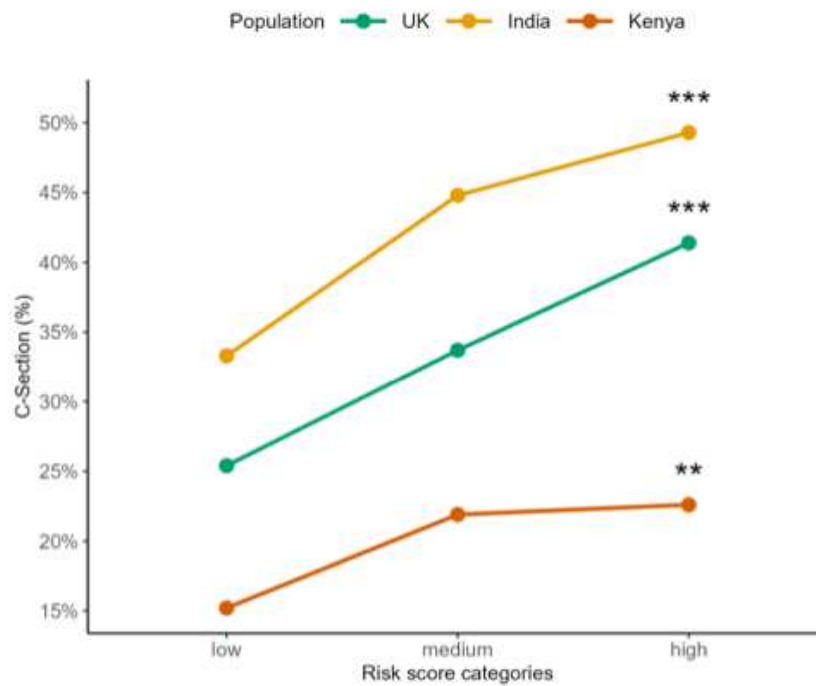
Percentage of hypertensive disorders across risk score categories for participants in PRiDE UK, STRiDE India and STRiDE Kenya; dots represent group values, asterisks indicate statistical significance (***: $p < 0.001$, **: $P < 0.01$) and *ns* denotes a *non-significant difference*.

Figure 1b: Rates of pre-eclampsia across the risk categories



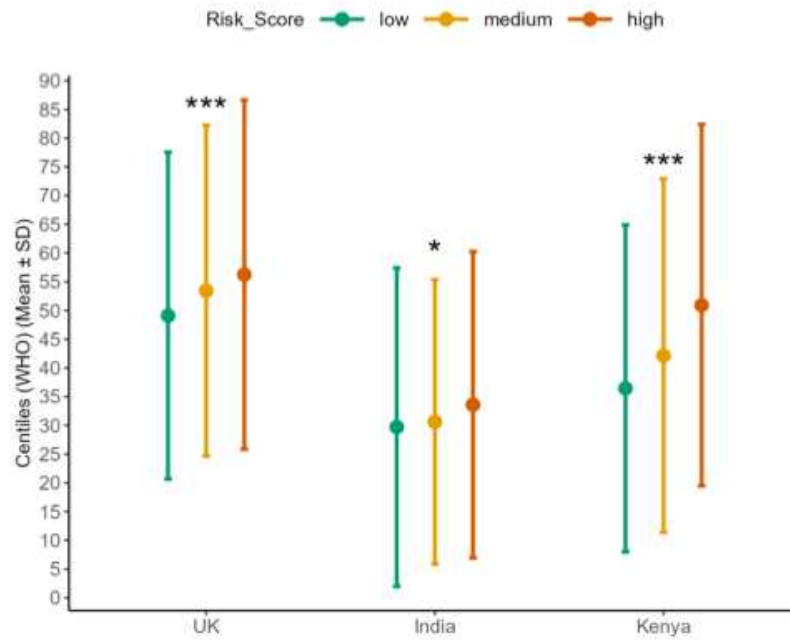
Rates of pre-eclampsia across risk score categories for participants in PRiDE UK, STRiDE India and STRiDE Kenya; dots represent group values, asterisks indicate statistical significance (**: $P < 0.01$) and *ns* denotes a *non-significant difference*

Figure 1c: Rates of caesarean section across the risk categories



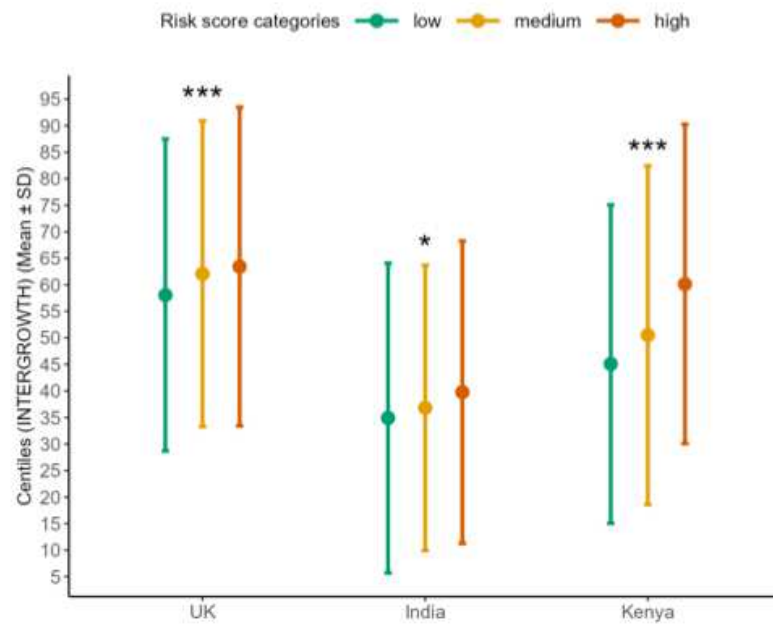
Percentage of c-section across risk score categories for participants in PRiDE UK, STRiDE India and STRiDE Kenya; dots represent group values, asterisks indicate statistical significance (***: $p < 0.001$, **: $P < 0.01$).

Figure 2a: WHO Birth centiles across the risk categories



Mean WHO birthweight centiles ($\pm$ SD) for participants in PRiDE UK, STRiDE Kenya and STRiDE India across risk score categories. Asterisks indicate statistically significant group differences (***: $p < 0.001$, *: $p < 0.05$).

Figure 2b: INTERGROWTH Birth centiles across the risk categories



Mean INTERGROWTH birthweight centiles ($\pm$ SD) for participants in PRiDE UK, STRiDE Kenya and STRiDE India across risk score categories. Asterisks indicate statistically significant group differences (***: $p < 0.001$, *: $P < 0.05$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [ExtendeddataFiguresSubmitted25thJul26.pptx](#)
- [ExtendeddataTablesSubmitted25thJul26.docx](#)