

## ORIGINAL RESEARCH

# Differences in prediction of adverse perinatal outcome in term pregnancies by choice of fetal growth reference: A validation study

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## Abstract

**Introduction:** Our objectives were to evaluate the association between fetal growth abnormalities and adverse perinatal outcomes in term pregnancies using four different fetal growth references: the recently published Swedish references by Lindström et al., the currently used Swedish references by Maršál et al., and the international standards by the WHO and INTERGROWTH-21st (IG21st). The study aimed to evaluate the performance of each reference and determine which reference most accurately identifies small for gestational age (SGA) infants at risk of perinatal mortality and morbidity.

**Material and Methods:** This population-based cohort study included 1 126 059 singleton term births in Sweden from 2010 to 2020. Data were obtained from national registers, including the Swedish Medical Birth Register and the Swedish Neonatal Quality Register. Birthweight centiles were calculated using each growth reference. Adverse perinatal outcomes were categorized by severity and included stillbirth, neonatal death, and serious neonatal morbidity. Logistic regression models were used to assess predictive performance, and sensitivity and false positive rates (FPR) were calculated for SGA thresholds (<3rd and <10th centiles).

**Results:** The distribution of birthweight centiles varied significantly across references. For SGA <3rd centile, the rate ranged from 9.6% for Lindström, 2.5% for Maršál, 1.9% for WHO, to 0.7% for IG21st. All references showed similar overall predictive performance (C-index ≈ 0.67) but with different discriminatory ability. The predicted risk of perinatal death increased at lower centiles for the Lindström reference than for the Maršál and WHO references, and at higher centiles for the IG21st reference. The Lindström reference identified the highest proportion of infants as SGA and

**Abbreviations:** BMI, body mass index; EFW, estimated fetal weight; FGR, fetal growth restriction; FPR, false positive rate; GA, gestational age; HIE, hypoxic ischemic encephalopathy; ICD-10, International Classification of Diseases 10; IG21st, INTERGROWTH-21st Project; LGA, large for gestational age; MBR, Medical Birth Register Sweden; SGA, small for gestational age; SNQ, Swedish Neonatal Quality Register; WHO, World Health Organization.

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had the highest sensitivity but also the highest FPR for detecting adverse outcomes. The IG21st reference classified the smallest proportion as SGA, resulting in the lowest sensitivity and FPR.

**Conclusions:** While all fetal growth references showed comparable predictive ability for adverse perinatal outcomes, they differed substantially in sensitivity and FPR. When the top priority is to identify as many at-risk fetuses as possible, Lindström et al.'s reference seems to be the best choice. However, when the top priority is a balanced sensitivity versus FPR, the WHO reference seems most suitable for clinical practice in this population of term births.

#### KEYWORDS

fetal growth retardation, growth charts, perinatal care, perinatal death, perinatal mortality, pregnancy high-risk, pregnancy outcome, pregnancy trimester third

## 1 | INTRODUCTION

Abnormal growth during fetal life is associated with increased risk of perinatal mortality and morbidity in the short and long term.<sup>1-4</sup> Fetal weight can be estimated by sonographic biometric measurements of the fetus. Fetal size alone is a poor marker for detecting fetal growth restriction (FGR) and is often combined with functional parameters, such as fetal and maternal Doppler or repeated measurements to assess growth velocity.<sup>5,6</sup> Detection of accelerated or restricted growth allows clinicians to closely monitor the pregnancy and intervene if necessary, which reduces the risk of adverse perinatal outcome.<sup>7</sup>

In order to assess growth velocity and if the fetus is small, appropriate, or large for gestational age (SGA, AGA, and LGA, respectively), the estimated fetal weight (EFW) is compared with a fetal growth reference or standard. The growth reference should be based on intrauterine longitudinal measurements of fetuses with expected normal growth.<sup>8,9</sup> Internationally, the 10th centile is widely, yet arbitrarily, used as a cut-off to define SGA, and the 90th centile for LGA.<sup>5</sup> By contrast, in Sweden, the cut-offs  $-2$  and  $2$  standard deviations (SD) define SGA and LGA in clinical practice.<sup>10</sup> With differences in expected fetal weight for gestational age (GA) between references, the choice of reference and cut-offs for SGA and LGA affects how well fetuses at increased risk of adverse perinatal outcome are identified.<sup>11</sup>

Since the publication of the currently used Swedish references for fetal size by Maršál et al.<sup>12</sup> in 1996, a large variety of population-based and international growth references and standards have been developed. Even though the international standards published by the World Health Organization (WHO)<sup>13</sup> and INTERGROWTH-21st (IG21st) Project<sup>14</sup> were intended to present normal fetal growth, regardless of maternal ethnicity, it has repeatedly been shown that such standards are non-consistent and may fail to identify many small fetuses or neonates at increased risk of adverse outcomes.<sup>3,15-17</sup> Therefore, growth references

#### Key message

The predictive ability for adverse perinatal outcomes was comparable across the references but showed notable differences in sensitivity and false positive rate. The WHO reference demonstrated balanced performance in detecting at-risk fetuses, suggesting its suitability for clinical use in Swedish term pregnancies.

should be tested and monitored in different populations before implementation, and cut-offs adjusted to avoid over- or underestimating the number of fetuses with abnormal growth.<sup>11,18</sup> In 2021, our research group published new Swedish reference ranges for EFW and growth.<sup>19</sup> The ability of this new reference to identify fetuses with growth disorders and increased risk of adverse perinatal outcome has not yet been evaluated.

The primary aim of this study was to assess the association between standardized fetal size and perinatal death or perinatal morbidity in term-born infants, comparing four different fetal weight references and standards (Lindström et al.,<sup>19</sup> Maršál et al.,<sup>12</sup> WHO,<sup>13</sup> and IG21st Project<sup>14</sup>). The secondary aim was to compare the performance of the same set of references to detect term SGA infants with increased risk of perinatal death or serious neonatal morbidity. For our primary objective, we hypothesized that the new Swedish reference ranges would have a stronger association between fetal growth disorders and adverse outcomes than the currently used references (Maršál) and international standards, as the study population in the underlying study behind the Lindström reference better represents the background population compared with the Maršál reference and the international standards. For our secondary objective, we hypothesized that there would be substantial differences between the references in the classification of SGA and the detection of fetuses at risk of adverse pregnancy outcomes.

## 2 | MATERIAL AND METHODS

### 2.1 | Data sources

In this population-based cohort study, we used Swedish registry data that were cross-linked using the personal identity numbers assigned to all residents in Sweden.

The Swedish Medical Birth Register (MBR) contains prospectively collected data from antenatal, obstetric, and neonatal care.<sup>20</sup> From MBR, we obtained information about maternal, delivery, and infant characteristics, including maternal and infant diagnoses at discharge after delivery. Diagnoses were obtained as International Classification of Diseases (ICD-10) codes of diseases and interventions. The MBR is considered a high-quality registry and includes information of 97–99% of all births in Sweden during the study period.<sup>20</sup>

The Swedish Neonatal Quality Register (SNQ) is a quality register that contains information on neonatal care and complications in infants admitted to a neonatal care unit in close relation to birth. The registry has a high coverage with validated data on neonatal outcomes.<sup>21</sup> We obtained information on birthweight, GA at delivery, sex, neonatal resuscitation, therapeutic interventions, and complications during neonatal care including neonatal mortality and ICD-10 diagnoses at discharge from neonatal care unit.

Birthweight, GA at delivery, and infant sex were primarily derived from MBR. If not available in MBR, the variables were derived from SNQ. Structural malformations or chromosome aberrations were identified by infant diagnosis of ICD-10 code Q00–Q99.

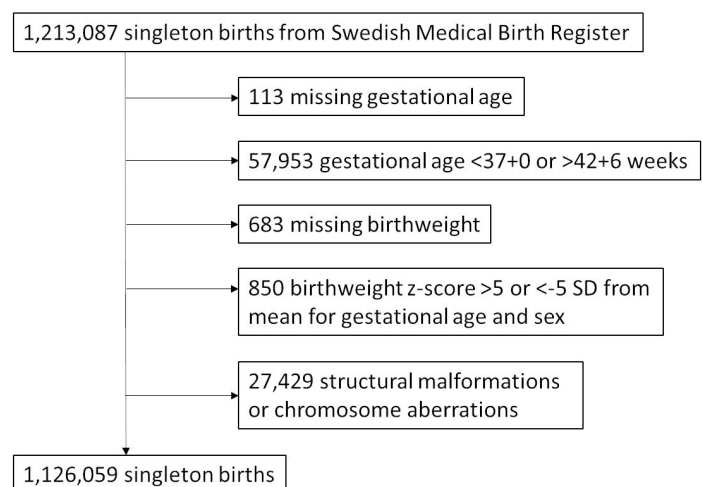
We acquired data on maternal country of birth from the Register of Total Population and education status from the Swedish Register of Education. Data on postnatal deaths, including age at death, were retrieved from the Cause of Death Register to ensure that all stillbirths were identified.

### 2.2 | Study population

All pregnancies resulting in singleton births during the years 2010–2020 were identified in the MBR,  $n=1\,213\,087$ . We excluded pregnancies with unknown GA at birth, GA <37+0 or >42+6 weeks at birth, and pregnancies with missing birthweight. Birthweight z-scores exceeding  $\pm 5$  SD from the mean for GA and sex according to Lindström et al.<sup>19</sup> were considered misclassified and hence excluded, as were infants with structural malformation or chromosome aberration. Diagnoses Q65 (congenital dislocation of hip) and Q53 (undescended testicle) were not considered as clinically relevant structural malformations and hence not excluded. The final study population consisted of 1 126 059 singleton births, see [Figure 1](#).

### 2.3 | Fetal growth references

All four included fetal growth reference ranges or standards (Lindström et al.,<sup>19</sup> Maršál et al.,<sup>12</sup> WHO,<sup>13</sup> and IG21st Project<sup>14</sup>) are based on longitudinal intrauterine estimations of fetal weight. For readability, local reference ranges and international standards are hereafter referred to as reference ranges or references. The reference ranges can be used both for assessment of intrauterine fetal weight and growth, as well as a reference for birthweight by GA. The Lindström reference covers the longest gestational span (gestational week 12–42), with an intermediate study population size (585 women). The Maršál reference begins at 25 weeks with the smallest study population (86 women). The WHO and IG21st references end at 40 gestational weeks with the largest study populations (1362 and 4231 women, respectively). The references are described in detail in Supporting Information.



**FIGURE 1** Selection of study population.

## 2.4 | Small and large for gestational age

In this study, we used both SGA defined as <3rd centile and as <10th centile. SGA <3rd centile corresponds fairly well to the Swedish definition of SGA (EFW or birthweight less than -2 SD of expected for GA and sex [standardized weight], equals to <2.3rd centile). SGA <10th centile is considered as below normal size in a global perspective. Equivalently, we defined LGA as EFW or birthweight >90th and >97th centile.

## 2.5 | Outcomes

Adverse perinatal outcomes were defined according to the consensus agreement of a Swedish Perinatal Core Outcome Set for management of labor and delivery at or near term.<sup>22</sup> The outcomes available in the registries and relevant for this study were classified according to seriousness, where 1 is most severe and 5 least severe:

1. **Perinatal death**
  - a. Stillbirth (antenatal or intrapartum death)
  - b. Neonatal death (death within 28 days after birth)
2. **Serious neonatal morbidity** (composite outcome incorporating postnatal diagnosis of any of the following: intraventricular lesions, posthemorrhagic hydrocephalus, periventricular lesions, other central nervous system hemorrhages, or infarctions, severe respiratory disease including need for nitric oxide treatment, extracorporeal membrane oxygenation, or necrotizing enterocolitis within 28 days after birth) and/or **Severe asphyxia** (need for neonatal resuscitation in combination with metabolic acidosis followed by hypoxic ischemic encephalopathy [HIE]) and/or **HIE grade 3**.
3. **HIE grade 2** and/or **Hypothermia treatment** and/or **Neonatal sepsis** (at least one episode of laboratory confirmed culture-based diagnosis of early or late bacterial sepsis)
4. **Neonatal resuscitation ≥10 min** (need of positive pressure ventilation, intubation or chest compressions) and/or **HIE grade 1** and/or **Admission to neonatal ward**
5. **Metabolic acidosis** (pH <7.0 and/or base deficit ≥16.0 mmol/L in umbilical artery blood) and/or **Apgar score <6 at 10 min** and/or **Instrumental vaginal delivery or cesarean section indicated by fetal distress**.

Stillbirth was identified in MBR and the Cause of Death Register, and neonatal death in SNQ. The individual perinatal complications that were part of the composite outcome "serious neonatal morbidity" were identified by checkboxes in SNQ. Abnormal blood gases (arterial pH <7.0 and/or arterial base deficit ≥16.0 mmol/L) were identified in SNQ. Diagnosis of HIE, hypothermia treatment, and neonatal sepsis were identified by checkboxes in SNQ. In cases

with several HIE diagnoses, the highest grade of HIE was selected. Neonatal resuscitation was identified by checkboxes in the MBR or SNQ. Admission to neonatal ward was identified by inclusion in the SNQ. Metabolic acidosis and Apgar score <6 at 10 min were identified in the MBR or SNQ. Instrumental vaginal delivery or cesarean section indicated by fetal distress was identified by registered instrumental mode of delivery in combination with ICD-10 code diagnosis O68 in the MBR.

## 2.6 | Covariates

Covariates were maternal country of birth, level of education, parity, maternal age, height, and body mass index (BMI) in kg/m<sup>2</sup> at first antenatal visit to maternity care, maternal smoking in early pregnancy, and cohabitation with the other parent. Educational level was categorized according to the Swedish educational system, where compulsory school covers 9 years of attendance and more than 12 years represent studies at college or university. BMI was categorized according to the WHO as underweight (<18.5 kg/m<sup>2</sup>), normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25.0–29.9 kg/m<sup>2</sup>), obesity class 1 (30.0–34.9 kg/m<sup>2</sup>), and obesity class 2–3 ≥35.0 kg/m<sup>2</sup>.

Maternal diseases were identified by checkboxes registered by the responsible midwife at first antenatal visit and ICD codes registered by the responsible obstetrician at discharge after birth.

## 2.7 | Statistical analyses

Background maternal and delivery characteristics were explored using descriptive statistics.

For each fetal growth reference, the rate of SGA <3rd centile, SGA <10th centile, LGA >90th centile, and LGA >97th centile births was calculated. Next, the study population was divided into 20 groups based on the infants' birthweight centile, where each group represented a five-centile interval.

The rate of the outcomes per 1000 births was calculated.

For neonatal death, only live births were included in the analysis.

Infants who died before 28 days of life were excluded from all analyses of morbidity outcomes, whereas a study person alive after 28 days may be represented in several morbidity severity strata.

Potentially confounding maternal diseases were pregestational and gestational diabetes (checkbox for pregestational diabetes and/or ICD-10 codes E10, E11, E14, O24.0, O24.1, O24.3, and O24.4), essential hypertension (checkbox and/or ICD-10 O10), gestational hypertension (ICD-10 O13), preeclampsia and eclampsia (ICD-10 O11, O14, and O15), systemic lupus erythematosus (checkbox and/or ICD-10 M32), antiphospholipid syndrome (ICD-10 D686A), and chronic kidney disease (checkbox and/or ICD-10 N0 and N1).

To evaluate how well the different growth references assess risk of adverse outcomes in case of fetal growth disorder, we constructed prediction models for adverse perinatal outcome

separately for the outcomes grouped according to severity level (1–5). Two sets of binary logistic regression models were fitted for each growth reference. The first model only included GA in weeks, standardized birthweight, and the interaction between GA and standardized birthweight. The second model contained maternal country of birth (Nordic country, remaining Europe, outside Europe), level of education (<10 years, 10–12 years, >12 years), parity (0, 1–2, ≥3), age, height, BMI, smoking status in early pregnancy, parental cohabitation, diagnoses of diabetes, hypertension, SLE, and kidney disease, in addition to GA and standardized birthweight. All continuous variables (GA, standardized birthweight, age, height, and BMI) were fitted using restricted cubic splines with four knots placed at each variable's 5th, 35th, 65th, and 95th percentiles. The interaction between GA and standardized birthweight was omitted for IG21st due to numerical issues during model fitting. The incidence of adverse perinatal outcomes per 1000 births, with 95% confidence intervals (CIs), was predicted from the models over a grid of gestational ages ranging from week 37+0 to 42+6 averaging over the empirical distribution of centiles below the 3rd and 10th centiles, respectively. Next, the incidence of adverse perinatal outcomes was predicted over a grid of centile values (0.5th to 99.5th centile, except for the Maršál reference which is only shown for 1.5th to 98.5th centile due to extreme values in the lowest centiles), averaging over the empirical distribution of gestational ages in weeks 37+0 to 38+6, 39+0 to 40+6, and 41+0 to 42+6.

Since the aim of the study was not to assess causal inference, but rather to construct a predictive model in order to identify differences in predictive value of the growth references, factors for adjustment of the models were used if there are known associations between the covariate, fetal growth, and the selected outcomes.

The discrimination, as judged by the C-index, which is a measure of discrimination and corresponds to the area under a receiver-operating characteristic (ROC) curve, and calibration of each model was assessed using the Efron-Gong optimism bootstrap using 200 replicates. This estimates the optimism in apparent indices of model performance and allows the use of all data in model building.

Last, the performance of each reference to identify newborns with fetal growth disorders and increased risk of adverse perinatal outcome was explored. For each growth reference, both thresholds for SGA (<3rd centile and <10th centile) were investigated regarding the number and rate of adverse outcome events (stillbirth, neonatal death, and the composite outcome serious neonatal morbidity), sensitivity, and false positive rate (FPR) in cases diagnosed SGA <3rd centile and SGA <10th centile, respectively. Rates of the adverse outcome were calculated both as rate of adverse outcome events per 1000 births (the denominator including all birthweights) and rate of adverse outcome events per 1000 SGA births (the denominator only including infants born SGA <3rd centile or <10th centile, respectively). Sensitivity and FPR were calculated with 95% confidence intervals.

Data management and statistical analyses were performed using IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp and R version 4.2.3 R Core Team (2023).

### 3 | RESULTS

**Table 1** shows maternal, delivery, and infant characteristics.

The distribution of birthweight centiles in the study population differed substantially depending on the growth reference used (**Figure 2**).

The proportion of infants born with birthweight <3rd centile varied between the growth references: 9.6% according to Lindström, 2.5% for Maršál, 1.9% for WHO, and 0.7% according to the IG21st reference (**Table 2**). The weight difference between the Lindström and the IG21st references for infants with birthweight at the 3rd centile was 535 grams for boys and 402 grams for girls, and at the 10th centile 489 grams for boys and 377 grams for girls at 40+0 gestational weeks. Birthweight >97th centile spanned from 1.7% in Lindström, 4.1% in Maršál, 4.2% in WHO, to 14.4% in IG21st. The weight difference at the 90th centile between the Lindström and the IG21st reference was 419 grams for boys and 291 grams for girls, and at the 97th centile 586 grams for boys and 466 grams for girls at 40+0 weeks.

The main outcomes, stillbirth and neonatal death, occurred in 1.5 and 0.2 per 1000 births, respectively (**Table 3**). Most secondary outcomes were rare in infants who survived beyond 28 days after birth, with an incidence of serious neonatal morbidity of 0.9 per 1000 neonatal survivors, severe asphyxia 0.2 per 1000 neonatal survivors, and HIE grade 3 0.1 per 1000 neonatal survivors.

The prediction models showed that at diagnosis of SGA, either defined as <3rd or <10th centile, the incidence of perinatal death (outcome severity strata 1) was highest in early-term gestations and remained very low from 39 gestational weeks (**Figure 3**). The predicted incidence of perinatal death followed similar patterns for all references, but the decrease in perinatal death incidence from week 37 to 39 in infants born SGA <3rd or SGA <10th centile was the least steep for the Lindström reference. All perinatal morbidity outcomes by severity strata showed U-shaped patterns of the predicted incidences, with the nadir at 39–40 gestational weeks. The predicted incidence of all perinatal morbidity outcomes was lower for the Lindström reference compared with all the other references for SGA <3rd centile, and higher for IG21st for SGA <10th centile. The confidence intervals between the Lindström reference and the other references were non-overlapping for outcome severity strata 1 and 5 at all gestational ages for SGA <3rd centile. Likewise, the confidence intervals between the IG21st and the other references were separated for outcome severity strata 1, 4, and 5 before 41 completed gestational weeks for SGA <10th centile, indicating statistically significant differences.

When the prediction models were used to evaluate the references over the entire centile span, stratified by early-term (37–38 weeks), late-term (39–40 weeks), and post-term (41–42 weeks) gestation, obvious differences were seen, in particular for perinatal death (outcome severity strata 1) (**Figure 4**). The predicted risk began to increase at lower centiles for the Lindström reference than for the Maršál and WHO references, and at considerably higher centiles for the IG21st reference. In early-term gestation, the predicted incidence of perinatal death

**TABLE 1** Maternal, delivery, and infant characteristics (n=1 126 059).

|   |               |
|---|---------------|
| Maternal characteristics                  |               |
| Country of birth, n (%)                   |               |
| Nordic country                            | 830345 (73.7) |
| Remaining Europe                          | 89824 (8.0)   |
| Outside Europe                            | 205430 (18.2) |
| Missing                                   | 460 (<0.1)    |
| Level of education, n (%)                 |               |
| <10 years                                 | 103104 (9.2)  |
| 10–12 years                               | 376449 (33.4) |
| >12 years                                 | 618222 (54.9) |
| Missing                                   | 28284 (2.5)   |
| Parity, n (%)                             |               |
| 0   | 482960 (42.9) |
| 1–2                                       | 574966 (51.1) |
| ≥3  | 68132 (6.1)   |
| Missing                                   | 1 (<0.1)      |
| Maternal age, n (%)                       |               |
| <25 years                                 | 143419 (12.7) |
| 25–34 years                               | 736075 (65.4) |
| 35–39 years                               | 200772 (17.8) |
| ≥40 years                                 | 45791 (4.1)   |
| Missing                                   | 2 (<0.1)      |
| Body Mass Index, n (%)                    |               |
| <18.5 kg/m <sup>2</sup>                   | 26574 (2.4)   |
| 18.5–24.9 kg/m <sup>2</sup>               | 617269 (54.8) |
| 25.0–29.9 kg/m <sup>2</sup>               | 274091 (24.3) |
| 30.0–34.9 kg/m <sup>2</sup>               | 102679 (9.1)  |
| ≥35.0 kg/m <sup>2</sup>                   | 44378 (3.9)   |
| Missing                                   | 61068 (5.4)   |
| Maternal smoking, n (%)                   |               |
| Yes                                       | 53404 (4.7)   |
| Missing                                   | 54370 (4.8)   |
| Parental cohabitation, n (%)              |               |
| No  | 72198 (6.4)   |
| Missing                                   | 48639 (4.3)   |
| In vitro fertilization, n (%)             |               |
|   | 36966 (3.3)   |
| Hypertensive disease <sup>a</sup> , n (%) |               |
|   | 51886 (4.6)   |
| Diabetes mellitus <sup>b</sup> , n (%)    |               |
|   | 28255 (2.5)   |
| Systemic Lupus Erythematosus, n (%)       |               |
|   | 1605 (0.1)    |
| Kidney disease, n (%)                     |               |
|   | 4868 (0.4)    |
| Delivery characteristics                  |               |
| Onset of delivery, n (%)                  |               |
| Spontaneous                               | 842489 (74.8) |
| Induction of labor                        | 190151 (16.9) |
| Elective cesarean section                 | 91076 (8.1)   |
| Missing                                   | 2343 (0.2)    |
| Delivery mode, n (%)                      |               |
| Spontaneous vaginal                       | 868043 (77.1) |

**TABLE 1** (Continued)

|   |               |
|---|---------------|
| Ventouse or forceps                     | 68273 (6.1)   |
| Cesarean section                        | 174950 (15.5) |
| Missing                                 | 14793 (1.3)   |
| Infant characteristics-                 |               |
| Infant sex, n (%)                       |               |
| Boy                                     | 574838 (51.0) |
| Girl                                    | 551220 (49.0) |
| Unknown                                 | 1 (<0.1)      |
| Gestational age at birth (weeks), n (%) |               |
| 37+0–38+6                               | 209863 (18.6) |
| 39+0–40+6                               | 618468 (54.9) |
| 41+0–41+6                               | 221401 (19.7) |
| 42+0–42+6                               | 76327 (6.8)   |
| Birthweight (grams), median (IQR)       | 3570 (640)    |

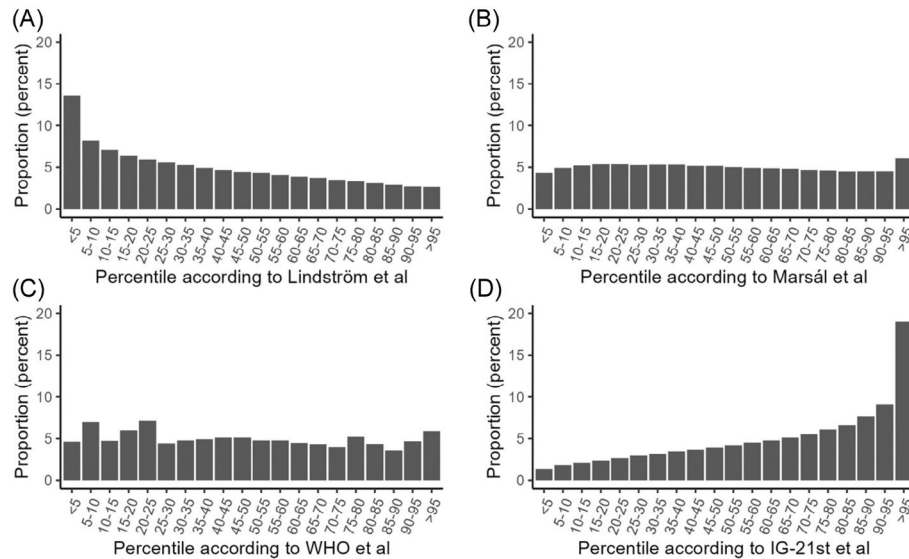
<sup>a</sup>Hypertensive disease includes diagnosis of chronic hypertension, pregnancy-induced hypertension, preeclampsia or eclampsia.

<sup>b</sup>Gestational or pregestational diabetes mellitus.

was approximately 1% at <1st centile for the Lindström reference, at the 3rd centile for the Maršál and WHO references, and at the 10th centile for the IG21st reference. In late-term gestation, the risk of perinatal death was lower, but showing the same pattern across the references as in early-term gestation. In post-term gestation, the predicted incidence of perinatal death was approximately 0.3% at the 3rd centile for Lindström, the 5th centile for Maršál and WHO, and the 20th centile for IG21st. For the morbidity outcome strata, the results were comparable for the references, with overlapping CIs. However, the Maršál reference showed rapidly increasing risks at the lowest and highest centiles, indicating worse performance at extreme centiles. For the least severe outcome strata, the IG21st showed significantly higher risk of adverse outcomes than the other references at all centiles below the 40–50th centile.

The unadjusted calibration of the prediction model for perinatal mortality and morbidity was comparable for all references except the Maršál reference, which overestimated the risk of perinatal death in SGA pregnancies (C-index for predicting neonatal mortality 0.6734 for the Maršál reference, and 0.6668–0.6680 for the remaining three references, [Figure S1](#) and [Table S1,S3](#)). After adjustment for covariates, the prediction model was less accurate ([Figure S2](#)).

Among infants born SGA <3rd or SGA <10th centile, the number of adverse outcome events per 1000 births was highest for the Lindström reference and lowest for the IG21st reference ([Table 4](#)). When SGA was defined as birthweight <3rd centile, the sensitivity, or proportion of cases among SGA infants, for detecting stillbirths by SGA diagnosis was 28.9% for the Lindström, 11.8% for Maršál, 11.3% for WHO, and 6.0% for the IG21st reference. The FPR in detection of stillbirth cases using the same SGA definition varied between 9.6% for Lindström and 0.7% for IG21st. The sensitivity and FPR for detecting neonatal death and serious neonatal morbidity using SGA <3rd centile



**FIGURE 2** Distribution of standardized birthweight centiles of the study population for (A) the Lindström<sup>19</sup> reference, (B) the Maršál<sup>12</sup> reference, (C) the WHO<sup>13</sup> reference, and (D) the INTERGROWTH-21st<sup>14</sup> reference.

**TABLE 2** Distribution of standardized birthweights and mean birthweight by centile, all by respective reference.

| Birthweight centile           | Reference curve |                 |                 |                  |
|-------------------------------|-----------------|-----------------|-----------------|------------------|
|                               | Lindström       | Maršál          | WHO             | INTERGROWTH-21st |
| <3rd, n (%)                   | 108 234 (9.6%)  | 27 683 (2.5%)   | 21 957 (1.9%)   | 8 236 (0.7%)     |
| 3rd, boys week 40+0 (grams)   | 3110            | 2780            | 2812            | 2575             |
| 3rd, girls week 40+0 (grams)  | 2977            | 2694            | 2652            | 2575             |
| <10th, n (%)                  | 245 121 (21.8%) | 66 522 (5.9%)   | 131 187 (11.7%) | 35 452 (3.1%)    |
| 10th, boys week 40+0 (grams)  | 3307            | 3075            | 3143            | 2818             |
| 10th, girls week 40+0 (grams) | 3195            | 2980            | 3012            | 2818             |
| >90th, n (%)                  | 60 487 (5.4%)   | 129 268 (11.5%) | 119 141 (10.5%) | 317 328 (28.2%)  |
| 90th, boys week 40+0 (grams)  | 4277            | 4193            | 4149            | 3858             |
| 90th, girls week 40+0 (grams) | 4149            | 4063            | 4129            | 3858             |
| >97th, n (%)                  | 18 862 (1.7%)   | 46 583 (4.1%)   | 47 637 (4.2%)   | 161 899 (14.4%)  |
| 97th, boys week 40+0 (grams)  | 4687            | 4488            | 4551            | 4101             |
| 97th, girls week 40+0 (grams) | 4567            | 4350            | 4318            | 4101             |

and for detecting stillbirth, neonatal death, and serious neonatal morbidity using SGA <10th centile followed the same pattern, that is, the highest sensitivity and highest FPR for the Lindström reference and the lowest sensitivity and lowest FPR for IG21st.

## 4 | DISCUSSION

In this cohort study of 1 126 059 births in Sweden, we found substantial differences in the distribution of birthweight centiles when four different intrauterine references for fetal growth were used. Using the most recently published Swedish reference by Lindström et al.,<sup>19</sup> a high proportion of the cohort was defined as SGA, and a low proportion as LGA. The reference currently used

in Sweden by Maršál et al.<sup>12</sup> and the WHO reference<sup>13</sup> showed rather evenly distributed centiles. Using the IG21st reference,<sup>14</sup> very few infants were defined as SGA, while a considerable number were identified as LGA. The prediction model showed that the growth references were comparable in predicting risk of adverse perinatal outcomes, but with substantial differences in the centile at which the risk of adverse perinatal outcomes associated with small fetal size began to increase. Differences in centile distributions led to significant differences in sensitivity and FPR between the growth references.

This is the first study evaluating the performance of the reference ranges by Lindström et al. Moreover, we are not aware of any previous study comparing the performance of the references by Maršál et al. with the WHO standard.

**TABLE 3** Perinatal outcome, events per 1000 births ( $n=1\,126\,059$ ).

| Perinatal outcome                                      | N      | Rate/1000 births |
|--|--------|------------------|
| <b>1. Perinatal death</b>                              |        |                  |
| Stillbirth   | 1667   | 1.5              |
| Antenatal  | 1546   | 1.4              |
| Intrapartal  | 121    | 0.1              |
| Neonatal death (<28 days) <sup>a</sup>                 | 211    | 0.2              |
| Early, <7 days   | 169    | 0.2              |
| Late, ≥7 days  | 42     | <0.1             |
| <b>2. Neonatal morbidity<sup>a</sup></b>               |        |                  |
| Serious neonatal morbidity <sup>b</sup>                | 1045   | 0.9              |
| Severe asphyxia <sup>c</sup>                           | 268    | 0.2              |
| Hypoxic ischemic encephalopathy grade 3                | 145    | 0.1              |
| <b>3. Neonatal morbidity<sup>a</sup></b>               |        |                  |
| Hypoxic ischemic encephalopathy grade 2                | 604    | 0.5              |
| Hypothermia treatment                                  | 672    | 0.6              |
| Neonatal sepsis  | 587    | 0.5              |
| <b>4. Neonatal morbidity<sup>a</sup></b>               |        |                  |
| Need for support of transition or resuscitation ≥10min | 11 173 | 9.9              |
| Hypoxic ischemic encephalopathy grade 1                | 730    | 0.6              |
| Admission to neonatal ward                             | 55 788 | 49.6             |
| <b>5. Neonatal morbidity<sup>a</sup></b>               |        |                  |
| Metabolic acidosis <sup>d</sup>                        | 2141   | 1.9              |
| Apgar score <6 at 10min                                | 2894   | 2.6              |
| Instrumental vaginal delivery indicated by asphyxia    | 32 165 | 28.6             |
| Caesarean section indicated by asphyxia                | 29 056 | 25.8             |

<sup>a</sup>Rate of neonatal death only includes live born infants ( $n=1\,124\,392$ ), and neonatal morbidity rates only infants alive at 28 days of age ( $n=1\,124\,181$ ).

<sup>b</sup>Composite outcome, includes incorporate of intraventricular lesions, posthemorrhagic hydrocephalus, periventricular lesions, other central nervous system hemorrhages or infarctions, severe respiratory disease including need for nitric oxide (NO) treatment, extracorporeal membrane oxygenation, or necrotizing enterocolitis within 28 days after birth.

<sup>c</sup>Need for resuscitation in combination with metabolic acidosis followed by hypoxic ischemic encephalopathy (grade 1–3 [ $n=1479$ ] and grade unknown [ $n=8$ ]).

<sup>d</sup>pH <7.0 or base deficit ≥16.0 mmol/L in umbilical artery blood.

Several studies have evaluated the international standards by the WHO and IG21st in comparison with other references in different populations. Our results are consistent with previous studies, identifying significant differences in SGA and LGA classification followed by variations in the strength of association between SGA

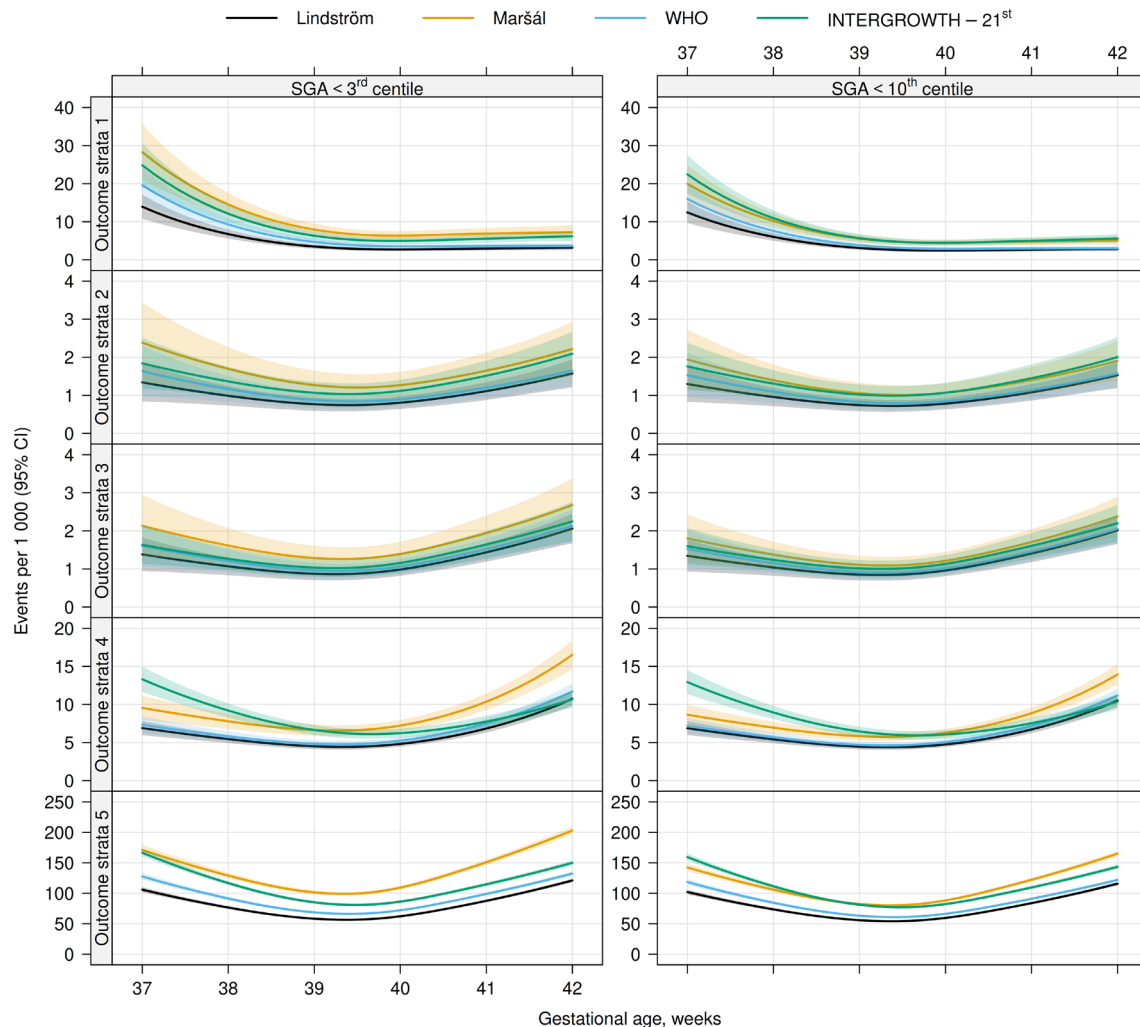
diagnosis and adverse perinatal outcomes.<sup>3,16,17,23–25</sup> In accordance with our results, Liauw et al.<sup>26</sup> found comparable performance albeit with alterations in optimal cut points for classification of abnormal growth in different growth references. Similar results were shown by Vieira et al.<sup>25</sup> in a study including 200 000 Swedish births comparing conditional centiles and IG21st. Common to all these studies of high-income populations, and in conformity with our results, is a small proportion of fetuses or infants classified as SGA, and a large proportion as LGA using the IG21st references.

Mascherpa et al.<sup>27</sup> evaluated the extent of association between FGR and adverse perinatal outcome using different definitions of FGR and several EFW references/standards, including EFW <2.3rd centile according to Maršál et al. ("Swedish definition of FGR"). Consistent with our results, they found a uniformly low sensitivity for predicting adverse perinatal outcome. However, different cut-offs for SGA and LGA were not compared as in our study, and the results are thereby not comparable.

There are only a few studies large enough to study restricted fetal growth according to different growth references and stillbirth or neonatal death as separate outcomes. Similar to our findings, Choi et al.<sup>3</sup> and Hirsch et al.<sup>23</sup> showed that IG21st identified substantially fewer infants as SGA, resulting in a smaller cohort of SGA fetuses at high risk of perinatal death. However, IG21st failed to identify fetuses with slow growth who subsequently developed an increased risk of perinatal death compared with the WHO standards.

Our prediction models showed similar overall predictive performance across all references, even though the Maršál reference seemed less precise at the extreme centiles. We think this lack of precision is primarily due to the size of their study cohort (86 pregnancies) and the outdated statistical methods used at the time the reference was published. The study protocols underlying each reference differed in important ways. Unlike the WHO and IG21st references, Lindström et al. excluded study participants with identified pregnancy complications, for example, gestational diabetes, hypertensive disorders, suspected FGR, stillbirth, and preterm birth. This may, to some extent, explain the higher fetal weights and birthweights observed by Lindström et al. compared with the other references. Even though the sampling methods and study protocols were similar across the WHO and the IG21st studies, there are essential differences between the centile distributions. Choi et al.<sup>3</sup> suggested that the IG21st study population, with higher rates of adverse perinatal outcomes, was likely to include sicker newborns than the WHO study population. The even healthier study population of Lindström et al., followed by higher mean EFWs, further supports this hypothesis.

In clinical settings, the true weight of the fetus is unknown at the time point when decisions are made. Thus, clinical decisions are based on estimated fetal size and growth. There is a discrepancy between estimated and true fetal weight, which differs between weight estimation formulae.<sup>28</sup> The Lindström and WHO references used the same EFW formula, Hadlock's third, which is often regarded as one of the most accurate formulae,<sup>28,29</sup> whereas the formula used in the Maršál



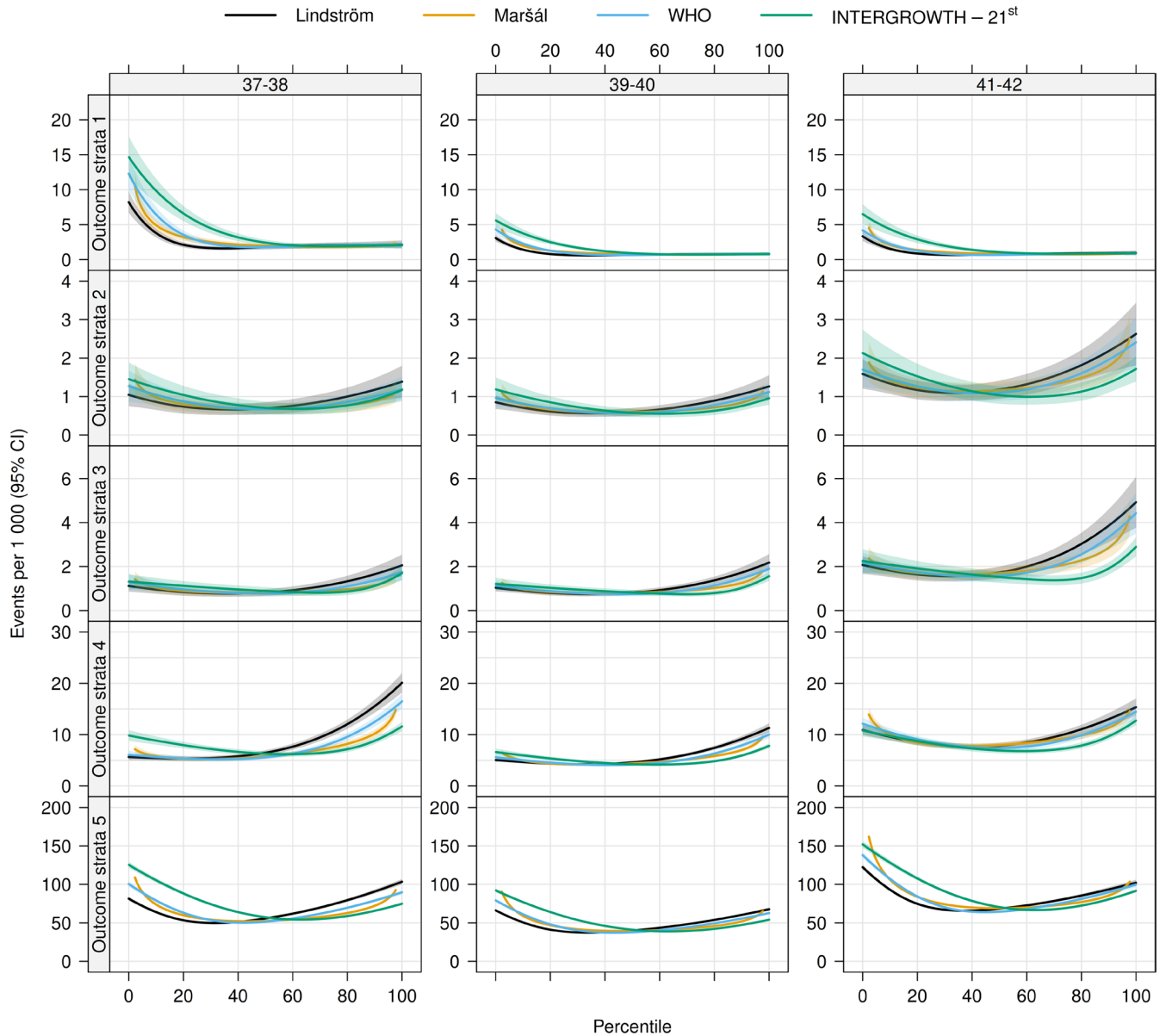
**FIGURE 3** Predicted incidence of adverse perinatal outcomes at the 3rd (left panels) and 10th (right panels) centiles. The outcomes are stratified by severity level, where 1 is most severe and 5 least severe (1: Perinatal death; 2: Serious neonatal morbidity (composite outcome), severe asphyxia, or hypoxic ischemic encephalopathy (HIE) grade 3; 3: HIE grade 2, hypothermia treatment, or neonatal sepsis; 4: Neonatal resuscitation >10 min, HIE grade 1, admission to neonatal ward; 5: Metabolic acidosis, Apgar score <6 at 10 min, instrumental vaginal delivery or cesarean section indicated by fetal distress).

reference (Persson and Weldner's formula)<sup>30</sup> is, to our knowledge, not compared with neither Hadlock's third nor the IG21st formula. It is important to keep this imprecision in mind when results based on birthweights are extrapolated to assess fetal weights. Using a different weight estimation formula than the one that was used when the reference ranges were constructed introduces potential error as systematic over- and underestimation of fetal weight differs between formulae.<sup>31</sup>

The main strength of this study is the population-based study design including the vast majority of Swedish term singleton births over 10 years, representing the target population for the studies by Lindström et al.<sup>19</sup> and Maršál et al.<sup>12</sup> All delivery units in Sweden are obliged to report data on all births prospectively, which minimizes the risk of selection bias and recall bias. Furthermore, data on socioeconomic variables were linked from other national registries. The size of the cohort allows for investigating rare outcomes, such as stillbirth and neonatal death, which is a major advantage due to the high clinical importance of identifying fetuses at risk of such deleterious outcomes.

Another strength of the study was the use of a prediction model, which showed mostly comparable discriminatory capacity for adverse perinatal outcomes in various severity strata for all included growth references, but with varying sensitivity and false positive rates. The use of predictive modeling allowed us to compare the discriminatory performance across the entire centile range, rather than only comparing the references at the commonly used, however arbitrary, cut-offs for SGA. This has, to our knowledge, not been done before.

Data from the SNQ are only available for infants who were admitted to neonatal care after birth. Information on, for example, neonatal resuscitation may be more detailed and comprehensive in the SNQ, which is a limitation. Moreover, umbilical blood gases data were missing for the majority of the infants. Accordingly, we suspect that metabolic acidosis is underreported. Another limitation is that unexpected neonatal deaths outside the hospital within 28 days after delivery cannot be identified in our data since age at death (with the exception of stillbirths) was presented in years by the Cause of Death



**FIGURE 4** Predicted incidence of adverse perinatal outcomes at gestational week 37–38, 39–40, and 41–42. The outcomes are stratified by severity level, where 1 is most severe and 5 least severe (1: Perinatal death; 2: Serious neonatal morbidity (composite outcome), severe asphyxia, or hypoxic ischemic encephalopathy (HIE) grade 3; 3: HIE grade 2, hypothermia treatment, or neonatal sepsis; 4: Neonatal resuscitation >10min, HIE grade 1, admission to neonatal ward; 5: Metabolic acidosis, Apgar score <6 at 10min, instrumental vaginal delivery or cesarean section indicated by fetal distress).

Register to ensure anonymity. The MBR does not include information on the number of days between fetal demise and birth. Accordingly, the fetal weight centile is expected to be higher at the time of death than at birth due to a lower GA when the fetus ceased to grow, and deterioration and expected dehydration postmortem. However, the centile divergence should be non-differential and affect centile allocation similarly across all references.

In Sweden today, no regions have implemented a universal third-trimester growth scan. Thus, only birthweight, rather than EFW, is possible to evaluate on a population-based level, which is a limitation since pre- and postnatal diagnoses of FGR differ considerably in detection rates of infants at risk of adverse

outcomes.<sup>32</sup> Moreover, there is no national consensus on indications for selective screening for or follow up of suspected FGR. As a consequence, it is likely that fetuses with abnormal growth are not uniformly detected or clinically managed in our study population. In our dataset, we cannot determine which growth-restricted fetuses were detected prenatally, which is a limitation. Indicated delivery due to FGR may prevent stillbirth or, conversely, cause neonatal transitional problems in fetuses falsely suspected as growth-restricted by exposure to unnecessary interventions in early-term gestation, that is, intervention bias.<sup>33</sup> In our cohort, suspicion of FGR after an SGA diagnosis, followed by obstetric interventions, was based on EFW values below those expected

**TABLE 4** Performance in detection of fetuses at risk of stillbirth, neonatal death, and serious neonatal morbidity for the different fetal growth references.

|   | Lindström        | Maršál           | WHO              | INTERGROWTH-21st |
|---|------------------|------------------|------------------|------------------|
| <b>SGA &lt;3rd centile</b>                    |                  |                  |                  |                  |
| <b>Stillbirth</b>                             |                  |                  |                  |                  |
| Nr of events                                  | 482              | 224              | 188              | 100              |
| Rate/1000 births                              | 0.43             | 0.20             | 0.17             | 0.09             |
| Rate/1000 SGA births                          | 4.45             | 8.09             | 8.56             | 12.14            |
| Sensitivity (95% CI)                          | 28.9 (26.8–31.1) | 11.8 (10.4–13.4) | 11.3 (9.8–12.9)  | 6.0 (4.9–7.2)    |
| FPR (95% CI)                                  | 9.6 (9.5–9.6)    | 2.4 (2.4–2.4)    | 1.9 (1.9–2.0)    | 0.7 (0.7–0.7)    |
| <b>Neonatal death</b>                         |                  |                  |                  |                  |
| Nr of events                                  | 42               | 14               | 12               | 9                |
| Rate/1000 births <sup>a</sup>                 | 0.04             | 0.01             | 0.01             | 0.01             |
| Rate/1000 SGA births <sup>a</sup>             | 0.39             | 0.51             | 0.55             | 1.09             |
| Sensitivity (95% CI)                          | 19.8 (14.8–25.5) | 6.6 (3.8–10.5)   | 5.7 (3.1–9.3)    | 4.2 (2.1–7.5)    |
| FPR (95% CI)                                  | 9.6 (9.5–9.6)    | 2.4 (2.4–2.5)    | 1.9 (1.9–2.0)    | 0.7 (0.7–0.7)    |
| <b>Serious neonatal morbidity<sup>b</sup></b> |                  |                  |                  |                  |
| Nr of events                                  | 161              | 58               | 46               | 28               |
| Rate/1000 births <sup>c</sup>                 | 0.14             | 0.05             | 0.04             | 0.02             |
| Rate/1000 SGA births <sup>c</sup>             | 1.49             | 2.11             | 2.10             | 3.40             |
| Sensitivity (95% CI)                          | 15.4 (13.3–17.7) | 5.6 (4.3–7.0)    | 4.4 (3.3–5.8)    | 2.7 (1.8–3.8)    |
| FPR (95% CI)                                  | 9.6 (9.5–9.6)    | 2.4 (2.4–2.5)    | 2.0 (1.9–2.0)    | 0.7 (0.7–0.7)    |
| <b>SGA &lt;10th centile</b>                   |                  |                  |                  |                  |
| <b>Stillbirth</b>                             |                  |                  |                  |                  |
| Nr of events                                  | 721              | 369              | 527              | 255              |
| Rate/1000 births                              | 0.64             | 0.33             | 0.47             | 0.23             |
| Rate/1000 SGA births                          | 2.94             | 5.55             | 4.02             | 7.19             |
| Sensitivity (95% CI)                          | 43.3 (40.9–45.6) | 22.1 (20.2–24.2) | 31.6 (29.4–33.9) | 15.3 (13.6–17.1) |
| FPR (95% CI)                                  | 21.7 (21.7–21.8) | 5.9 (5.8–5.9)    | 11.6 (11.6–11.7) | 3.1 (3.1–3.2)    |
| <b>Neonatal death</b>                         |                  |                  |                  |                  |
| Nr of events                                  | 69               | 26               | 49               | 18               |
| Rate/1000 births <sup>a</sup>                 | 0.06             | 0.02             | 0.04             | 0.02             |
| Rate/1000 SGA births <sup>a</sup>             | 0.28             | 0.39             | 0.37             | 0.51             |
| Sensitivity (95% CI)                          | 32.7 (26.6–39.2) | 14.6 (9.9–20.3)  | 23.1 (17.8–29.1) | 8.5 (5.2–12.7)   |
| FPR (95% CI)                                  | 21.7 (21.7–21.8) | 5.9 (5.8–5.9)    | 11.6 (11.6–11.7) | 3.1 (3.1–3.2)    |
| <b>Serious neonatal morbidity<sup>b</sup></b> |                  |                  |                  |                  |
| Nr of events                                  | 277              | 110              | 184              | 62               |
| Rate/1000 births <sup>c</sup>                 | 0.25             | 0.1              | 0.16             | 0.06             |
| Rate/1000 SGA births <sup>c</sup>             | 1.13             | 1.65             | 1.40             | 1.75             |
| Sensitivity (95% CI)                          | 26.5 (23.9–29.3) | 10.5 (8.8–12.5)  | 17.6 (15.4–20)   | 5.9 (4.6–7.5)    |
| FPR (95% CI)                                  | 21.7 (21.7–21.8) | 5.9 (5.8–5.9)    | 11.6 (11.6–11.7) | 3.1 (3.1–3.2)    |

Note: Rate of events/1000 SGA births (<3rd and <10th centile, respectively), proportion of events detected by classifying SGA as birthweight <3rd and <10th centile (sensitivity with 95% confidence interval, CI), and false positive rate (FPR) with 95% CI.

<sup>a</sup>Rate per 1000 live births.

<sup>b</sup>Composite outcome, includes incorporation of intraventricular lesions, posthemorrhagic hydrocephalus, periventricular lesions, other central nervous system hemorrhages or infarctions, severe respiratory disease including need for nitric oxide (NO) treatment, extracorporeal membrane oxygenation, or necrotizing enterocolitis within 28 days after birth.

<sup>c</sup>Rate per 1000 births for infants alive at 28 days of age.

for GA according to the reference by Maršál et al. Accordingly, we presume that the proportion of infants born SGA subjected to intervention bias may differ depending on the growth reference used to define SGA, potentially influencing the results. Lastly, with the formulae and references currently used in clinical practice in Sweden, EFW below the 3rd centile in term pregnancy is associated with a 44% higher risk of poor fetal weight estimation compared with EFW 10th-90th centile, with systematic underestimation of the fetal weight.<sup>34</sup> This implies that using birthweight instead of EFW may skew the results, which is a limitation. The greater inaccuracy in EFW precision among the smallest fetuses may also lead to heterogeneity in the intervention bias.

There are several risk factors associated with perinatal mortality and serious morbidity, and FGR only accounts for a limited share of the adverse outcomes. The poor performance of fetal growth references to predict stillbirth, neonatal death, and serious neonatal morbidity highlights the importance of a holistic view in risk assessment during pregnancy. Functional parameters, such as growth velocity and fetoplacental blood flow investigations using Doppler techniques, add information, but still many fetuses at risk are not captured using available screening methods.<sup>27,32</sup> If too many pregnancies are identified as high risk, it may have health economic consequences and crowding out patients in need of limited resources. Moreover, exaggerating risks may lead to unnecessary interventions, whereas failure to capture true high-risk pregnancies may lead to renounced actions. Our results suggest that when the top priority is to identify as many at-risk fetuses as possible, the Lindström reference seems to be the best choice. However, when the top priority is a balanced sensitivity in relation to the false positive rate, the WHO reference seems to be most suitable for clinical practice in this population of Swedish term-born infants and similar populations.

It is difficult to investigate how a change in clinical routines would affect rare pregnancy complications, such as stillbirth, unless a substantial study population is included. If Sweden were to adopt a more contemporary fetal growth reference, a national implementation study using, for example, cluster randomization, may be a way forward to evaluate whether adverse perinatal outcomes can be prevented by better identification of fetuses who could benefit from timely interventions.

## 5 | CONCLUSION

All investigated fetal growth references had similar performance in predicting adverse pregnancy outcome, but with significant differences in sensitivity and false positive rates of fetuses at risk of perinatal mortality and morbidity. In all, the WHO reference had the best fit for classifying infants as SGA and LGA in term births to avoid low sensitivity and high false positive rates. Forthcoming studies including preterm deliveries are needed before a clinical recommendation can be made.

## AUTHOR CONTRIBUTIONS

LL came up with the original idea. LL performed validation and cleaning of data, LL and EL performed the statistical analyses, and LL wrote the first draft of the manuscript. All authors contributed to study conception and design, analytic plan, interpretation of data, and critical revision and approval of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

None of the authors have a conflict of interest to declare.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ETHICS STATEMENT

Ethics approval was obtained from the National Ethical Review Board (Diary number 2021-03123) on July 14, 2021. All procedures involving humans were carried out in accordance with the 1964 Helsinki declaration. Informed consent from each study subject was not required since data were merged and pseudonymized before being available to the research group.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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