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Twin chorionicity-specific population birth-weight charts adjusted for estimated fetal weight

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KEYWORDS: birth weight; chorionicity-specific; reference charts; twin pregnancy; ultrasound

CONTRIBUTION

What are the novel findings of this work?

We developed novel estimated fetal weight (EFW)-adjusted population birth-weight charts for twins. The median birth weight for twins was consistently lower than that reported for singletons. Twin birth weight was consistently lower than the last recorded EFW. Therefore, it could not be assumed that median EFW and median birth weight are equal at any given gestational age.

What are the clinical implications of this work?

The use of singleton charts in the assessment of fetal growth in twins is controversial. This study presents EFW-adjusted twin birth-weight charts that show that the median birth weight for twins is consistently lower than that for singletons. The use of these novel charts may reduce misclassification and improve identification of growth restriction in twins.

ABSTRACT

Objectives *To construct chorionicity-specific birth-weight reference charts for dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twin pregnancies, incorporating estimated-fetal-weight (EFW) data in order to adjust for the relationship between suboptimal growth and preterm delivery. An additional aim was to determine if the inclusion of complicated twin pregnancies impacts on the reference charts produced.*

Methods *The inclusion criteria for this retrospective cohort study were twin pregnancy of known DCDA or MCDA chorionicity, known pregnancy outcome, last ultrasound scan within 14 days before birth and delivery between 25 and 38 weeks' gestation (Analysis A). An analysis was also conducted excluding pregnancies with complications recorded (Analysis B). Previously published twin EFW reference ranges were used in the analysis. A joint statistical model for EFW and observed birth weight for each pregnancy was created in order to estimate population birth-weight reference ranges corresponding to the distribution expected if all pregnancies delivered at any given gestational age. It was not assumed that the median EFW was equal to birth weight for any given gestational age. The models were fitted using a Bayesian approach.*

Results *We retrieved data on 1664 twin pregnancies, of which 707 DCDA and 241 MCDA pregnancies met the inclusion criteria. In Analysis A, the estimated population median birth weight was similar to the median EFW at around 27 weeks' gestation but fell below the EFW values with increasing gestation, being 156 g lower in both DCDA and MCDA pregnancies at 35 weeks; this finding was confirmed by direct comparison of the last EFW and birth-weight values in each pregnancy. When the analysis was repeated after excluding complicated twin pregnancies (Analysis B), compared with Analysis A, there was very little difference in the median birth-weight results obtained across gestation. The largest absolute difference between Analyses A and B for DCDA twins was at 31, 32 and 33 weeks, with a 9-g lower median birth weight in Analysis A compared with Analysis B. The largest absolute difference for MCDA twins was greater than that for DCDA twins, with a 21-g lower median*

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birth weight at 25 weeks in Analysis A compared with Analysis B.

Conclusions *We have established population chorionicity-specific birth-weight reference charts for DCDA and MCDA twin pregnancies, corresponding to the range expected were all pregnancies to deliver at any given gestational age. In this population of twins, the median birth weight was consistently lower than that reported for singletons, and there was variation in the median birth weight at different gestational ages according to chorionicity.*

INTRODUCTION

Twin pregnancies accounted for 1.4% of all UK births in 2018 but are at disproportionately increased risk of perinatal mortality and morbidity[1], particularly prematurity and fetal growth restriction (FGR)[2,3], making it vital that these pregnancies are monitored appropriately. Current evidence suggests that singleton charts are inaccurate when used to assess for pathological growth in twin pregnancy[2–5]. It has also been shown that twin estimated-fetal-weight (EFW) charts are more specific for identifying small-for-gestational-age (SGA) twin infants when compared with singleton charts, and that they perform just as well at identifying those at risk of stillbirth[6]. Despite this, there are still no valid nomograms or birth-weight charts that are used routinely for twin pregnancies[2]. This inadequacy resulted in the inclusion of the following questions in the top 10 research priorities for multiple pregnancies of The Global Twins and Multiples Priority Setting Partnership: 'What are the expected growth patterns of SGA multiples?' and 'How can we assess the growth of infant multiples and ensure that they follow a satisfactory growth trajectory?'[7].

Evidence suggests that the median birth weight of twins is significantly lower than that of singletons, noticeable from around 30–32 weeks' gestation[3,4,8]. However, the reason for this difference in growth pattern remains debated. Firstly, twin–singleton birth-weight divergence may be suggestive of a truly growth-restricted infant, with studies indicating that second-trimester growth is essentially the same in twins and singletons[9,10]. However, it is in the third trimester that energy demands cannot be met and therefore true placental insufficiency sets in[11], with studies suggesting that the use of individualized growth-assessment charts may be more appropriate[12]. Secondly, twins may just be smaller than singleton babies, and assessing their growth in comparison may therefore be less accurate[6].

Several birth-weight reference charts have been generated for twins, charting the birth weight according to gestational age (GA)[13–18]. These studies opted to analyze actual observed birth weight; however, this is a limitation owing to the correlation between preterm delivery and growth restriction and other pathological conditions[19]. For this reason, birth-weight reference charts for singletons have been developed that incorporate ultrasonographic data in order to include fetuses still *in utero* for estimation of the true weight distribution at any given GA[19]. In addition, a number of studies opted to assess birth-weight differences between male and female twins rather than according to chorionicity[13,14,16,17].

In this study, we developed new population reference charts for birth weight in dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twin pregnancies, incorporating EFW data in order to adjust for the relationship between suboptimal growth and preterm delivery, similar to those developed by Nicolaides *et al.*[19] for singletons. The second aim of this study was to determine if the inclusion of complicated twin pregnancies impacts on the reference charts produced.

METHODS

Study population

This was a retrospective cohort study of twin pregnancies attending the clinic at St George's University Hospital NHS Foundation Trust, London, UK, between January 2000 and August 2019. The data were gathered from ultrasound and delivery databases, collectively recorded on and identified by searching electronic maternity records (ViewPoint version 5.6.26.148 (ViewPoint Bildverarbeitung GmbH, Wessling, Germany) and E3 (Euroking Maternity Software Solutions Ltd, UK)). The inclusion criteria were uncomplicated twin pregnancy of known DCDA or MCDA chorionicity, known pregnancy outcome, last ultrasound scan within 14 days before delivery and delivery between 25 and 38 weeks' gestation (Analysis A). Ethical approval was not required for this retrospective study of routinely collected anonymous data, as determined by local institutional review board guidance.

A second analysis (Analysis B) was performed excluding complicated twin pregnancies with the following additional exclusion criteria: fetal structural or chromosomal abnormality; early neonatal death; stillbirth (antenatal death ≥ 24 weeks or intrapartum death); intrauterine death (< 24 weeks); twin–twin transfusion syndrome; twin anemia–polycythemia sequence; and selective FGR (sFGR). This additional analysis was performed to determine whether the exclusion of these high-risk pregnancies made a significant impact on the overall birth-weight reference charts produced.

Study variables

The chorionicity of the pregnancy was determined by the number of placentae and the presence or absence of the lambda sign at the intertwin membrane–placenta junction, as well as the intertwin membrane thickness at the site of placental insertion in the chorion at 11–14 weeks' gestation. Chorionicity could also be determined by the number of placentae and fetal gender after 14 weeks[20–22]. GA was determined in the first trimester by assessing the crown–rump length of the larger fetus in cases of spontaneous conception. If *in-vitro* fertilization had taken place, dating was performed according to the oocyte retrieval date or the embryonic age from fertilization. After 14 weeks, GA was determined using the head circumference of the larger fetus[22–24].

sFGR was defined as birth weight of one twin below the 10th centile and a birth-weight discordance of more than 25%, or birth weight of one twin below the 3rd centile[25], using the singleton standard reported by Poon *et al.*[26] or the twin chorionicity-specific standard reported by Ananth *et al.*[18].

This analysis focused on EFW obtained within 14 days before birth. EFW was calculated using the formula published by Hadlock *et al.*[27]: $\log_{10}\text{EFW} = 1.326 - (0.00326 \times \text{AC} \times \text{FL}) + (0.0107 \times \text{HC}) + (0.0438 \times \text{AC}) + (0.158 \times \text{FL})$, where AC is fetal abdominal circumference, FL is fetal femur length and HC is fetal head circumference.

Ultrasound studies were performed by experienced sonographers or by clinicians trained in fetal medicine, and measurements for the purpose of determining EFW were obtained following the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[20,28,29].

Statistical analysis

The twin EFW reference ranges reported by Stirrup *et al.*[4,30] were used for the analysis, with model parameters derived from the prior study treated as fixed and known. To adjust for gaps of up to 2 weeks between the last EFW assessment and delivery, a predicted EFW was generated on the date of delivery for each twin. This was achieved by calculating the equivalent percentile value for the GA at delivery (termed 'shifted EFW'). Pregnancies in which either twin showed a last recorded EFW with a Z-score of > 4 or < -4 were excluded from the model, to account for any data errors.

A joint statistical model for the shifted EFW values and the observed birth weight for each pregnancy, on the $\log_{10}$ transformed scale, was created (Appendix S1). The four observations in each pregnancy were modeled as a multivariate normal distribution, with the mean and the marginal variance and covariance for the shifted EFW values at delivery GA determined according to the model reported by Stirrup *et al.*[30]. The birth-weight variance was modeled as a multiple (τ) of the marginal EFW variance, with the scaling factor allowed to vary with GA at delivery according to the formula: $\tau i = \exp(\tau 1 + (\tau 2 \times \text{GA}i))$, where τi is the birth-weight variance expressed as a multiple of the marginal EFW for the ith individual, dependent on the GA at delivery of the ith individual (GAi), and $\tau 1$ and $\tau 2$ are parameters estimated in the model fitting process.

Correlation parameters were defined for the association between EFW and birth weight within twin pairs, and between the two birth weights for each pregnancy. Median birth weight at delivery was not assumed to be equal to the median EFW for any given GA but was instead allowed to deviate as a quadratic function of GA (with three β parameters and the quadratic term multiplied by 0.01 for numerical stability). The model was fitted using a Bayesian approach implemented in the Stan statistical software[31] (Stan Development Team, New York City, NY, USA), with results reported as the posterior mean and 95% credibility interval (CrI). The τ and β parameters were assigned a weakly informative standard normal prior, and the correlation parameters were assigned uniform priors over the interval $(-1, 1)$. The median and variance of $\log_{10}$(birth weight) as a function of GA were calculated based on the posterior distributions of the β and τ parameters, conditioned on the observed data, in combination with the parameters of the published EFW model[4,30].

The objective of the study was to establish population reference ranges for twin pregnancies, rather than normal ranges. We therefore included all pregnancies in our final analysis, as did Nicolaides *et al.*[19] when creating birth-weight references for singletons. The statistical approach described by Nicolaides *et al.*[19] was considered for the present study. However, we found that the birth weight of twin pregnancies was on average consistently lower than the last recorded EFW. These discrepancies were present even if the EFW was recorded close to delivery, which is consistent with the published literature[32]. Therefore, it could not be assumed that median EFW and median birth weight are equal at any given GA. This was the rationale for fitting a joint model for birth weight and EFW, in which the median for the two variables could differ according to GA. We aimed to estimate birth-weight reference ranges for the hypothetical situation that all pregnancies were to deliver at any given GA, which would help to adjust for the fact that growth restriction and timing of delivery are likely to be associated.

RESULTS

We retrieved data on 1664 twin pregnancies. According to the inclusion criteria, 17 monochorionic monoamniotic (MCMA) pregnancies were excluded, as well as 36 for unknown chorionicity, five because GA at delivery was missing, eight because birth weight was not recorded for both twins, 17 because GA at delivery was < 25 weeks, 142 because GA at delivery was > 38 weeks and 491 because the last ultrasound scan was missing or was performed ≥ 14 days before delivery. This left 707 DCDA and 241 MCDA twin pregnancies for analysis (Figure 1). Information regarding maternal demographics is reported in Table 1.

Analysis A

Of 707 DCDA and 241 MCDA twin pregnancies, 15 and 12, respectively, were excluded from Analysis A because of an EFW Z-score of > 4 or < -4, leaving a total of

692 DCDA and 229 MCDA twin pregnancies (Figure 1). The birth-weight reference values resulting from the fitted model are given in Table 2 for DCDA and MCDA twins. In addition, plots of *Z*-scores calculated for observed birth-weight values using the newly derived reference standard according to GA at delivery are presented in Figure 2a,b. For both DCDA and MCDA twins, the observed birth-weight values were on average lower than the expected population average (i.e. if all pregnancies were to deliver at any given GA) until around 36 weeks' gestation.

The fitted birth-weight reference standards for both DCDA and MCDA twin pregnancies had a median value below that of EFW for GAs beyond around 27 weeks. Overestimation of birth weight by EFW for EFW values above around 2000 g was confirmed both by plotting birth weight against the shifted EFW values (Figure 3a) and by plotting birth weight against the observed EFW only for cases with an interval from assessment to delivery of ≤ 2 days (Figure 3b).

Furthermore, birth weight and last recorded EFW before delivery were plotted onto the EFW reference charts[30] used in the analysis for DCDA and MCDA pregnancies (Figure 4). In addition, histograms of birth-weight *Z*-scores relative to the newly derived reference ranges for the 692 DCDA pregnancies and the 229 MCDA pregnancies included in Analysis A are shown in Figure S1.

Table 1 Demographic characteristics of study population of 948 twin pregnancies, according to chorionicity

	Chorionicity	
Characteristic	*DCDA (*n = *707)*	*MCDA (*n = *241)*
Maternal age (years)	34 (30–37)	32 (28–35)
GA at birth (weeks)	36.9 (34.7–37.4)	35.7 (33.0–36.6)
Maternal BMI (kg/m^2)*	24.5 (21.9–28.5)	23.9 (21.6–27.9)
Nulliparous	349/654 (53.4)	124/227 (54.6)
Gestational diabetes	33 (4.7)	14 (5.8)
Gestational hypertension	14 (2.0)	0 (0)
IVF treatment†	40/105 (38.1)	5/33 (15.2)
Self-reported ethnicity		
White	386/644 (59.9)	140/222 (63.1)
Black	115/644 (17.9)	23/222 (10.4)
Asian	74/644 (11.5)	28/222 (12.6)
Mixed	4/644 (0.6)	3/222 (1.4)
Other	65/644 (10.1)	28/222 (12.6)
Smoker	33/684 (4.8)	14/231 (6.1)
Alcohol use during pregnancy	41/687 (6.0)	17/234 (7.3)
Fetal gender‡		
Male	707/1414 (50.0)	227/482 (47.1)
Female	707/1414 (50.0)	253/482 (52.5)
Indeterminate	0/1414 (0)	2/482 (0.4)

Data are given as median (interquartile range), *n* (%) or *n*/*N* (%). *Available for 477 dichorionic diamniotic (DCDA) and 156 monochorionic diamniotic (MCDA) pregnancies. †Only those pregnancies recorded definitively as having or not *in-vitro* fertilization (IVF) were considered. ‡Data expressed as percentage of fetuses. BMI, body mass index; GA, gestational age.

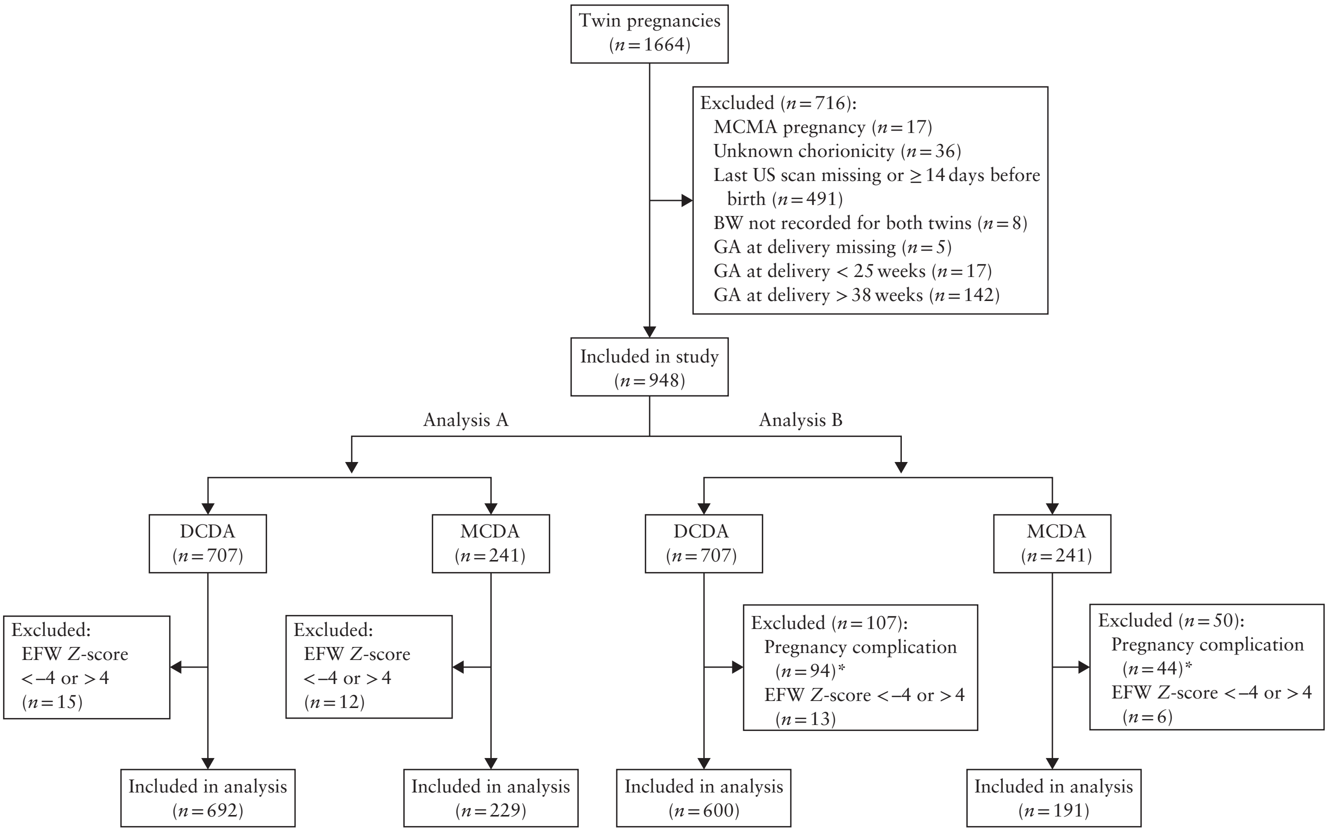

Figure 1 Flowchart showing inclusion of twin pregnancies in study for development of chorionicity-specific birth-weight reference charts, in Analysis A (including complicated pregnancies) and in Analysis B (excluding complicated pregnancies). *Pregnancy complications are detailed in Table S1. BW, birth weight; DCDA, dichorionic diamniotic; EFW, estimated fetal weight; GA, gestational age; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; US, ultrasound.

Analysis B

Of 707 DCDA and 241 MCDA twin pregnancies, respectively, 94 and 44 were excluded from Analysis B owing to various complications diagnosed using the ISUOG twin guidelines[20] (Table S1) and an additional 13 and six because of an EFW *Z*-score of > 4 or < -4, leaving a total of 600 DCDA and 191 MCDA twin pregnancies (Figure 1). The birth-weight reference values derived from the fitted model are given in Table 3 for DCDA and MCDA twins. Plots of birth-weight *Z*-scores calculated using the new reference standard according to GA at delivery are presented in Figure 2c,d. For both DCDA and MCDA twins, the observed birth-weight values were on average lower than the expected population average until around 36 weeks' gestation.

The fitted birth-weight reference standards for both DCDA and MCDA twin pregnancies had a median value below that of EFW for GAs beyond around 27 weeks. Overestimation of birth weight by EFW for EFW values above around 2000 g was confirmed both by plotting birth weight against the shifted EFW values (Figure 3c) and by plotting birth weight against the observed EFW only for cases with an interval from assessment to delivery of ≤ 2 days (Figure 3d).

Analysis A *vs* Analysis B

It should be noted that, when comparing Analysis A with Analysis B, there was very little difference in the median birth weight across gestation. The largest absolute difference between Analysis A and Analysis B for DCDA twins was a 9-g lower median birth weight at 31 (percentage difference (PD), 0.6%), 32 (PD, 0.5%) and 33 (PD, 0.5%) weeks' gestation in Analysis A compared with Analysis B. The largest absolute difference for MCDA twins was greater than that for DCDA twins, with a 21-g lower median birth weight at 25 weeks (PD, 2.5%) in Analysis A compared with Analysis B.

In addition, there is considerable overlap of the CrIs between Analyses A and B. For example, at 31 weeks, for DCDA pregnancies, the 50th percentile was 1563 g (95% CrI, 1542–1585 g) in Analysis A compared with 1572 g (95% CrI, 1552–1593 g) in Analysis B. This overlap was similar for MCDA pregnancies. For example, at 25 weeks, the 50th percentile was 835 g (95% CrI, 769–917 g) in Analysis A, compared with 856 g (95% CrI, 772–947 g) in Analysis B.

Included *vs* excluded pregnancies

The main analyses presented above were run either including complicated pregnancies in the model or excluding them, meaning that differences between the excluded and

Table 2 Birth-weight (BW) reference values for dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twins in Analysis A (i.e. including complicated pregnancies)

Gestational age (weeks)	*Log_{10}(BW) (mean ± SD)*	*BW (g)*					*95% CrI of BW P50 (g)*	
		P5	*P10*	*P50*	*P90*	*P95*	*Lower*	*Upper*
DCDA								
25	2.892 ± 0.06858	602	638	780	955	1011	743	818
26	2.949 ± 0.06749	689	729	890	1085	1148	855	924
27	3.003 ± 0.06643	784	829	1008	1226	1296	978	1040
28	3.055 ± 0.06541	886	936	1135	1377	1454	1108	1163
29	3.104 ± 0.06443	996	1051	1271	1537	1622	1247	1296
30	3.150 ± 0.06352	1112	1172	1414	1705	1798	1392	1437
31	3.194 ± 0.06271	1233	1299	1563	1881	1982	1542	1585
32	3.235 ± 0.06201	1358	1430	1718	2063	2172	1697	1739
33	3.273 ± 0.06146	1487	1565	1876	2249	2368	1857	1897
34	3.309 ± 0.06108	1616	1701	2037	2439	2567	2017	2057
35	3.342 ± 0.06090	1745	1836	2198	2630	2768	2181	2216
36	3.372 ± 0.06094	1871	1969	2357	2821	2968	2343	2371
37	3.400 ± 0.06121	1992	2097	2512	3009	3167	2497	2525
38	3.425 ± 0.06172	2106	2218	2661	3193	3362	2635	2683
MCDA								
25	2.921 ± 0.09652	580	629	835	1110	1204	769	917
26	2.967 ± 0.09205	655	707	927	1215	1313	867	996
27	3.011 ± 0.08782	736	791	1025	1328	1429	975	1083
28	3.053 ± 0.08385	824	884	1131	1448	1554	1087	1178
29	3.095 ± 0.08014	920	983	1245	1577	1686	1207	1284
30	3.136 ± 0.07674	1022	1090	1367	1714	1828	1331	1403
31	3.175 ± 0.07365	1133	1204	1497	1860	1978	1461	1531
32	3.213 ± 0.07091	1250	1326	1634	2015	2138	1598	1668
33	3.250 ± 0.06854	1373	1454	1780	2179	2308	1745	1814
34	3.286 ± 0.06653	1503	1589	1934	2353	2488	1904	1965
35	3.321 ± 0.06490	1639	1730	2095	2538	2679	2069	2122
36	3.355 ± 0.06363	1780	1877	2264	2732	2881	2239	2290
37	3.387 ± 0.06270	1925	2028	2441	2936	3094	2405	2477
38	3.419 ± 0.06209	2074	2185	2624	3151	3319	2562	2691

CrI, credibility interval; P5, 5th percentile; P10, 10th percentile; P50, 50th percentile; P90, 90th percentile; P95, 95th percentile.

included groups of pregnancies in Analysis B were not estimated directly. We therefore ran an additional model for all DCDA and for all MCDA pregnancies, in which the 'included' and 'excluded' groups shared a variance structure, but the difference in median birth weight was estimated explicitly in relation to GA with quantification of statistical uncertainty. The results are presented in Tables S2–S4 and do not show clear statistical evidence of an overall difference in birth weight between the included and excluded groups. There was some evidence of lower birth weight among the excluded cases, but there was no strong statistical evidence for this owing, at least in part, to the relatively small number of pregnancies in the excluded groups.

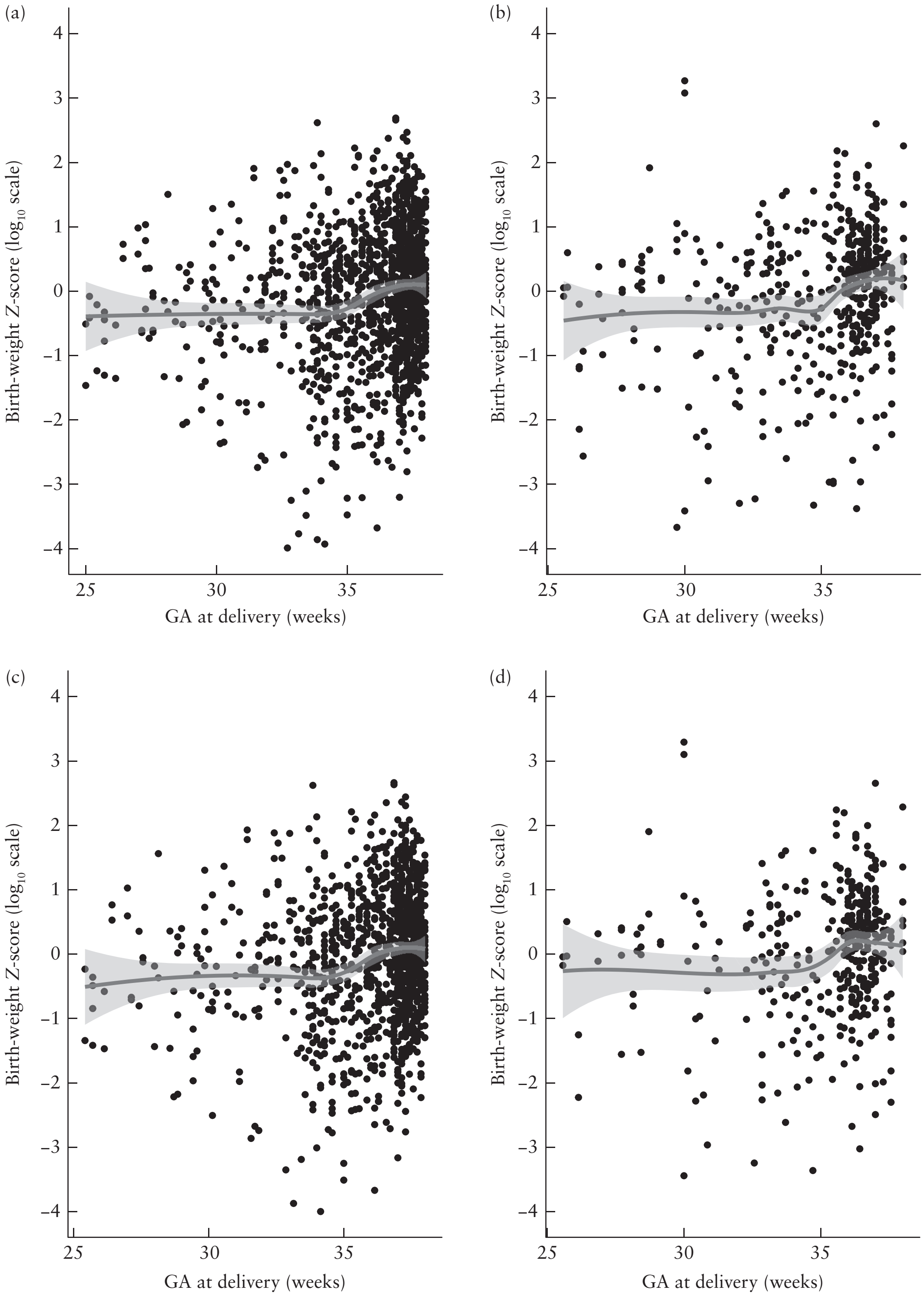

Figure 2 Birth-weight *Z*-scores in dichorionic diamniotic (a,c) and monochorionic diamniotic (b,d) pregnancies in Analysis A (including complicated pregnancies) (a,b) and in Analysis B (excluding complicated pregnancies) (c,d), calculated using birth-weight reference standard derived in Analysis A, according to gestational age (GA) at delivery between 25 and 38 weeks. ——, LOESS smoothed estimate of the mean, with 95% CI (shaded area).

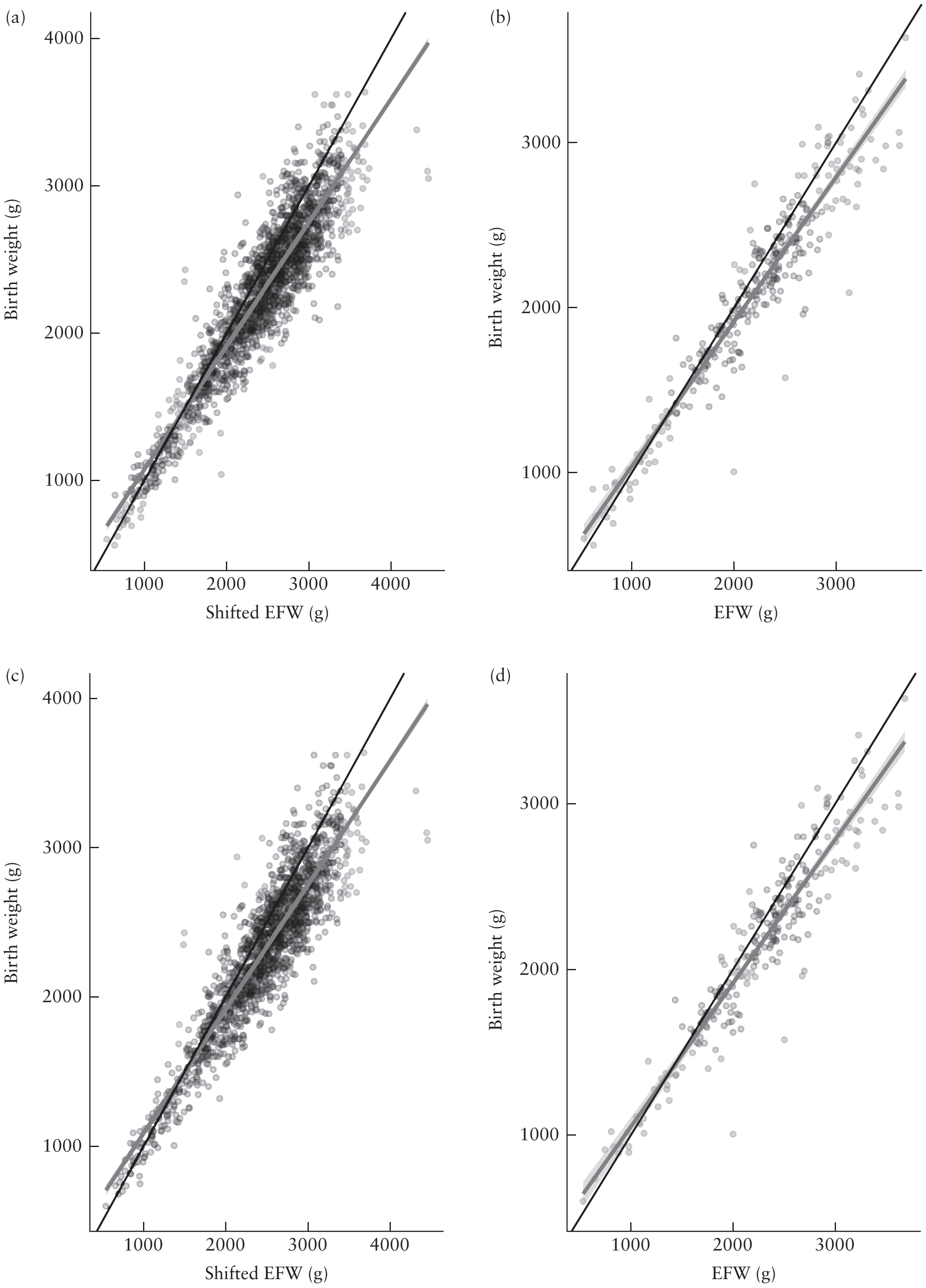

Figure 3 Birth weight plotted against shifted estimated fetal weight (EFW) in all twin pregnancies included in Analysis A (*n* = 921) (a) and those included in Analysis B (*n* = 791) (c), and against EFW in twin pregnancies with EFW assessed within 2 days prior to delivery in Analysis A (*n* = 144) (b) and in Analysis B (*n* = 121) (d). ——, Line of equality; —— linear regression line with 95% CI (shaded area), though these are very narrow and thus barely visible on the plots.

DISCUSSION

Summary of study findings

Using EFW and birth weight from a diverse population of twin pregnancies, we have created birth-weight reference charts for DCDA and MCDA twins. When comparing the median birth weight of our newly generated charts with that of singleton charts across gestation, differences were noted. In addition, the median values differ between MCDA and DCDA twins, highlighting the importance of chorionicity-specific charts. We also noticed that, within our population, EFW often overestimated the true birth weight of the twin. For example, the estimated population median birth weight was similar to the median EFW at around 27 weeks but fell below the EFW values with increasing gestation, being 156 g lower in both DCDA and MCDA pregnancies at 35 weeks.

Additionally, we found that, when comparing the complicated pregnancies excluded with the uncomplicated pregnancies included in Analysis B, for both DCDA (Table S2) and MCDA (Table S3) pregnancies, the exclusion of complicated pregnancies made no significant difference to the reference ranges achieved. Therefore, we decided that reference ranges from Analysis A should be used, as it would be logical to generate reference charts based on the entire population, including abnormal twins. We also note that the exclusion criteria for Analysis B relate to prenatal or early neonatal outcomes, and so do not necessarily reflect how birth weight would predict longer-term outcomes beyond the immediate neonatal period.

Interpretation of study findings and comparison with existing literature

We compared our birth-weight percentiles to those of Nicolaides *et al.*[19], who created birth-weight references for singletons from 95 579 pregnancies. Median birth weight of DCDA twins was similar to that of singletons until 28 weeks. For example, at 25 weeks, the median birth weight was 780 g for DCDA twins and 797 g for singletons (PD, 2.2%); at 28 weeks, the birth weights were 1135 g and 1228 g (PD, 8.2%), respectively. This absolute birth-weight difference increased steadily with

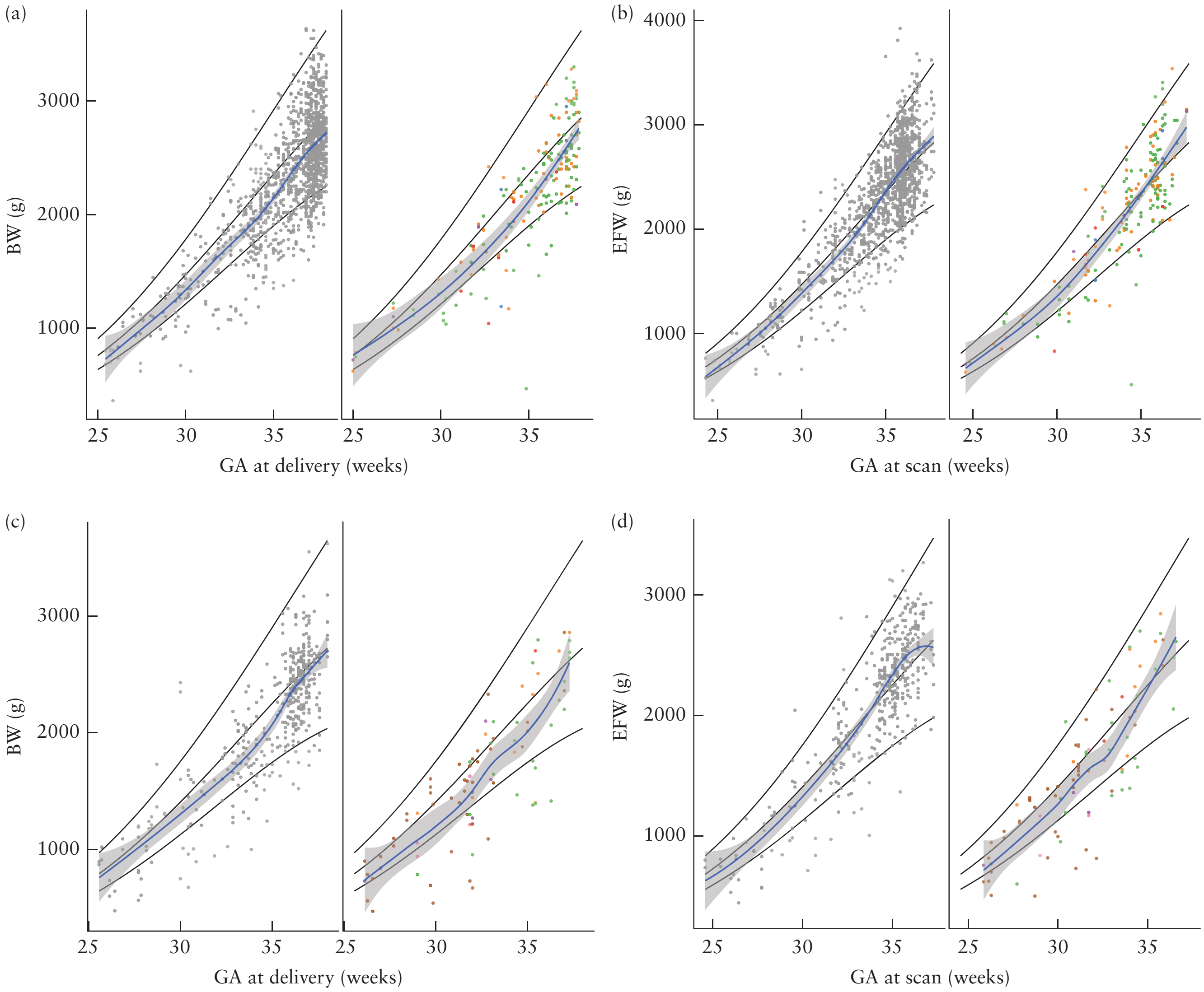

Figure 4 Scatterplots of birth weight (BW) (a,c) and last recorded estimated fetal weight (EFW) (b,d), in relation to gestational age (GA) at delivery and at last assessment, respectively, of dichorionic diamniotic (a,b) and monochorionic diamniotic (c,d) twins in uncomplicated (left) and complicated (right) pregnancies, plotted on the previously published EFW reference chart[30] used in the analysis (median, 5th and 95th centiles shown as black lines). ——, LOESS smoothed estimate of the mean, with 95% CI (shaded area). Plotted cases of stillbirth include one recorded early neonatal death. ●, Fetal abnormality; ●, intrauterine death; ●, selective fetal growth restriction; ●, stillbirth; ●, twin anemia–polycythemia sequence; ●, twin–twin transfusion syndrome; ●, unaffected twin; ●, uncomplicated pregnancy.

GA, with a median birth weight of 2661 g and 3219 g (PD, 21.0%) at 38 weeks for DCDA twins and singletons, respectively.

MCDA twins were initially heavier than singletons at 25 weeks (median birth weight, 835 g *vs* 797 g (PD, 4.6%)), although there is considerable uncertainty in our estimate (95% CrI, 769–917 g). The absolute birth-weight difference between MCDA twins and singletons increased from 28 weeks (median birth weight at that GA, 1131 g and 1228 g, respectively (PD, 8.6%)). The discrepancy at 25 weeks in the MCDA cohort is probably due to the smaller sample size.

Beyond 28 weeks, both MCDA and DCDA twins had a marked reduction in size when compared with singletons, a trend that is a consistent finding in the literature[2–4,14]. In addition, a larger absolute difference was noted in the birth weight of MCDA than of DCDA twins when compared with singletons.

Our analysis made explicit use of the EFW reference ranges published by Stirrup *et al.*[30]. We found that median birth weight drops below the median EFW as pregnancy progresses. For example, at 27 weeks, the estimate for the 50th percentile value of EFW in DCDA twins was 1011 g, compared with our median birth-weight estimate of 1008 g (PD, 0.3%). However, at 38 weeks, the median EFW was estimated to be 2853 g compared with an estimated median birth weight of 2661 g (PD, 7.2%).

We also compared our estimated 50th percentile birth-weight values with those of other twin birth-weight studies that compiled reference ranges according to chorionicity[15,18]. When compared with the study of Ananth *et al.*[18], the largest difference in the birth weight of DCDA twins occurred at 35 weeks' gestation, with a median birth weight of 2198 g in our study compared with 2359 g in their study (PD, 7.3%). At 38 weeks, the absolute difference was smaller, with respective birth weights of 2661 g and 2753 g (PD, 3.5%). For MCDA twins, the largest discrepancy occurred at 33 weeks' gestation, with our study showing a median birth weight of 1780 g compared with 1980 g in the study of Ananth *et al.*[18] (PD, 11.2%). However, by 38 weeks, this discrepancy had decreased, with respective birth weights of 2624 g and 2660 g (PD, 1.4%). In comparison, when we compared our dataset with that of Premkumar *et al.*[15], our cohort showed consistently larger median birth weight across all GAs in both MCDA and DCDA pregnancies. These differences could be a result of population variance. However, it should be noted that the data presented in both of these previous studies[15,18] are based on observed birth-weight measurements.

Table 3 Birth-weight (BW) reference values for dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twins in Analysis B (i.e. excluding complicated pregnancies)

Gestational age (weeks)	*Log$_{10}$(BW) (mean ± SD)*	*BW (g)*					*95% CrI of BW P50 (g)*	
		P5	*P10*	*P50*	*P90*	*P95*	*Lower*	*Upper*
DCDA								
25	2.892 ± 0.06332	615	648	781	941	992	738	826
26	2.950 ± 0.06279	703	741	891	1072	1130	852	932
27	3.005 ± 0.06227	799	842	1011	1215	1280	977	1046
28	3.057 ± 0.06177	903	950	1140	1368	1440	1111	1171
29	3.106 ± 0.06131	1013	1066	1277	1530	1610	1252	1303
30	3.153 ± 0.06091	1129	1188	1421	1701	1790	1399	1443
31	3.196 ± 0.06058	1250	1314	1572	1879	1977	1552	1593
32	3.237 ± 0.06036	1374	1445	1727	2063	2170	1706	1748
33	3.275 ± 0.06028	1500	1578	1885	2252	2369	1865	1907
34	3.311 ± 0.06037	1627	1711	2045	2444	2570	2024	2067
35	3.343 ± 0.06065	1752	1843	2204	2636	2773	2186	2224
36	3.373 ± 0.06115	1872	1970	2360	2827	2975	2345	2376
37	3.400 ± 0.06189	1986	2092	2511	3014	3174	2496	2527
38	3.424 ± 0.06288	2092	2205	2655	3196	3368	2629	2681
MCDA								
25	2.932 ± 0.09703	594	644	856	1138	1234	772	947
26	2.974 ± 0.0923	666	719	943	1237	1336	870	1019
27	3.016 ± 0.08784	745	801	1037	1344	1446	976	1101
28	3.057 ± 0.08366	831	891	1139	1458	1563	1087	1193
29	3.097 ± 0.07977	924	988	1249	1580	1689	1204	1294
30	3.136 ± 0.0762	1025	1092	1367	1712	1824	1327	1407
31	3.174 ± 0.07296	1133	1205	1494	1852	1969	1455	1532
32	3.212 ± 0.07009	1249	1325	1629	2003	2124	1591	1667
33	3.249 ± 0.06758	1373	1452	1773	2164	2290	1734	1812
34	3.285 ± 0.06546	1503	1588	1926	2337	2468	1890	1964
35	3.320 ± 0.06371	1641	1731	2089	2521	2659	2057	2122
36	3.354 ± 0.06233	1786	1881	2261	2718	2863	2234	2289
37	3.388 ± 0.06129	1937	2039	2443	2927	3081	2405	2481
38	3.421 ± 0.06057	2095	2204	2635	3150	3314	2564	2706

CrI, credibility interval; P5, 5th percentile; P10, 10th percentile; P50, 50th percentile; P90, 90th percentile; P95, 95th percentile.

Strengths and limitations

Our sample size is substantial for a twin study, and the population used was from a diverse tertiary care center. Moreover, we used only one ultrasound scan per fetus; it can therefore be assumed that we have used only routinely collected data to establish these new charts.

Given the long study period, delivery protocols for each twin may have differed from the current UK National Institute for Health and Care Excellence protocol, which may have affected a small fraction of the total pregnancies, particularly those delivered before 2011. Maternal characteristics, fetal sex and their effects on fetal growth were not considered, similarly to previous studies[2,13,14,16,17,19]. Furthermore, around 10% of our pregnancies were dated in the second trimester, which may have led to some inaccuracies in GA. A caveat of this study is that the CrIs at some points indicate substantial uncertainty. This is particularly the case at lower GAs and for MCDA twins, owing to the smaller sample size. MCMA pregnancies were excluded entirely.

Clinical and research implications

The birth-weight charts described in this study add to the limited research in this area. However, the extent to which this approach could improve the detection of FGR needs to be tested in prospective studies. For example, a small infant is defined as one whose weight is below the 10th percentile[33]. When comparing our charts with the World Health Organization (WHO) EFW charts[34], the 10th percentiles of our birth-weight charts are lower than those presented in the WHO study. At 36 weeks' gestation, the 10th percentiles of our charts for DCDA and MCDA twins were 1969 g (PD, 19.5%) and 1877 g (PD, 25.3%), respectively, compared with 2352 g for singletons in the WHO charts. Moreover, when compared with the 10th percentile of the singleton birth-weight charts of Nicolaides *et al.*[19] (2439 g at 36 weeks), who sampled a larger population, the absolute difference was even higher.

It is important to acknowledge that outcomes for twins are worse when compared with those for singletons, which may be a result of lower GA at birth or lower birth weight. However, it is not possible to rule out effects of other covariates on overall development. Reclassifying this group of infants may change the interventions received, leading to poorer outcomes, so prospective analysis is needed before implementation of these birth-weight charts in order to minimize the risk of false-negative results.

Conclusions

We present a novel method for generating twin chorionicity-specific EFW-adjusted population birth-weight charts. We have demonstrated substantial differences compared with equivalent charts for singletons and non-EFW-adjusted twin birth-weight reference charts, and that there is a distinct difference between MCDA- and DCDA-specific birth-weight charts. Observational studies and randomized trials are required to evaluate the use of these charts in clinical practice and assess their ability to predict adverse neonatal events.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Technical description of statistical model

Figure S1 Histograms of birth-weight Z-scores relative to newly derived reference ranges for the 692 DCDA pregnancies (a) and the 229 MCDA pregnancies (b) included in Analysis A. Z-scores were calculated on the $\log_{10}$(birth weight) scale.

Table S1 Breakdown of pregnancies excluded from Analysis B owing to complications

Table S2 Estimation of difference in median birth weight according to gestational age (GA) at birth between dichorionic diamniotic (DCDA) pregnancies excluded from Analysis B and those included in Analysis B

Table S3 Estimation of difference in median birth weight according to gestational age (GA) at birth between monochorionic diamniotic (MCDA) pregnancies excluded from Analysis B and those included in Analysis B

Table S4 Summary of fitted analysis models and model used for comparison of subgroup of pregnancies included in Analysis B and subgroup excluded from Analysis B