ORIGINAL RESEARCH

Effect of Fetal Growth on 1-Year Mortality in Neonates With Critical Congenital Heart Disease

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***Background*—**Infants with critical congenital heart disease (CCHD) are more likely to be small for gestational age (GA). It is unclear how this affects mortality. The authors investigated the effect of birth weight *Z* score on 1-year mortality separately in preterm (GA <37 weeks), early-term (GA 37–38 weeks), and full-term (GA 39–42 weeks) infants with CCHD.

***Methods and Results*—**Live-born infants with CCHD and GA 22 to 42 weeks born in California 2007–2012 were included in the analysis. The primary predictor was *Z* score for birth weight and the primary outcome was 1-year mortality. Multivariable logistic regression was used. Results are presented as adjusted odds ratios and 95% confidence intervals (CIs). The authors identified 6903 infants with CCHD. For preterm and full-term infants, only a *Z* score for birth weight <−2 was associated with increased mortality compared with the reference group (*Z* score 0–0.5, adjusted odds ratio, 2.15 [95% CI, 1.1–4.21] and adjusted odds ratio, 3.93 [95% CI, 2.32–6.68], respectively). In contrast, in early-term infants, the adjusted odds ratios for *Z* scores <−2, −2 to −1, and −1 to −0.5 were 3.42 (95% CI, 1.93–6.04), 1.78 (95% CI, 1.12–2.83), and 2.03 (95% CI, 1.27–3.23), respectively, versus the reference group.

***Conclusions*—**GA seems to modify the effect of birth weight *Z* score on mortality in infants with CCHD. In preterm and full-term infants, only the most severe small-for-GA infants (*Z* score <−2) were at increased risk for mortality, while, in early-term infants, the risk extended to mild to moderate small-for-GA infants (*Z* score <−0.5). This information helps to identify high-risk infants and is useful for surgical planning. **(*J Am Heart Assoc*. 2018;7:e009693. DOI: 10.1161/JAHA.118.009693.)**

Key Words: birth weight *Z* score • congenital cardiac defect • congenital heart disease • fetal growth • mortality

Congenital heart disease (CHD) is the most common category of birth defect, with an incidence rate between 0.3% and 0.8%.[1,2] Critical CHD (CCHD)—defined as requiring neonatal intervention—is reported to have an incidence rate of 0.17%.[3] Despite advances in medical and surgical management of affected infants, mortality and morbidity remain relatively high.[4,5]

Research has mainly focused on specific anatomical details, surgical techniques, and postnatal complications as factors affecting mortality and morbidity, while the impact of other infant characteristics remains less well understood.[6] Two recent studies investigated the impact of gestational age (GA) at birth on postnatal outcomes in infants with CCHD.[7,8] Both studies found that the length of gestation independently affects mortality, postoperative complications, and neonatal morbidity after adjusting for severity of CHD, and that early-term infants (GA 37–38 weeks) are at higher risk for poor outcomes compared with full-term infants (GA ≥39 weeks).

Birth weight (BW) percentile (or the corresponding *Z* score), standardized for GA and infant sex, is also an important infant characteristic, representing fetal growth. It has been shown that infants with CHD are more likely to be born small for GA (SGA; defined as BW for GA and sex <10th percentile).[9,10] In infants without CHD, the negative effect of severe SGA (BW <5th percentile) on neonatal outcomes has been documented in preterm and term infants.[11] To date, the few studies that

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Clinical Perspective

What Is New?

- The effect of small for gestational age (GA) on 1-year mortality seems to be modified by GA in infants with critical congenital heart disease.
- In preterm and full-term infants, only most severe small-for-GA infants (*Z* score <−2) were at increased risk for mortality, while, in early-term infants, the risk extended to mild to moderate small-for-GA infants (*Z* score <−0.5).

What Are Clinical Implications?

- This study identifies early-term infants (GA 37–38 weeks) as a group particularly sensitive to the effects of low birth weight on survival in infants with critical congenital heart disease.
- In contrast, mild to moderate small-for-GA (−2> birth weight *Z* score >−0.5) preterm and term infants with critical congenital heart disease do not appear to be at increased risk for mortality and this may assist in the counseling of parents regarding possible surgical interventions.

have evaluated the effect of SGA on mortality in infants with CHD are either relatively small (n=136–308)[12–14] or have examined BW *Z* score as a dichotomous variable (eg, SGA versus adequate for GA [AGA]). While these studies provide useful information, they potentially missed a more complex relationship between fetal growth and mortality in this patient population.[15] None of these studies investigated the potentially differential effect of BW *Z* score on mortality within GA categories.

The aim of this analysis was to investigate the role of BW *Z* score on 1-year mortality in preterm, early-term, and full-term infants with CCHD. We hypothesized that not only would severely SGA infants (<5%ile, *Z* score −1.96) with CCHD have a higher mortality but that this effect would extend to infants with higher BW *Z* scores. We further investigated whether the association is different in different GA groups. Additionally, we report survival estimate curves, which have greater utility for counseling and planning of medical treatment than odds or hazard ratios from statistical models.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data use agreement with the California Office of Statewide Health Planning and Development (OSHPD) prohibits distribution of any patient-level data. Data can be requested from OSHPD (https://www.oshpd.ca.gov/HID/HIRC/index.html) by qualified researchers for a fee. All other analytic methods and study materials are available upon reasonable request from the corresponding author.

OSHPD maintains a birth cohort database containing 3 160 268 live births from the years 2007 to 2012. This database includes detailed information on infant characteristics derived from hospital discharge records (birth hospitalization and readmissions) and is linked to birth and death certificates, from birth to 1 year of age. The file provides diagnosis and procedure codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*).[16]

This same database has been used by our group to investigate the effect of GA on mortality and severe neonatal morbidity in infants with CCHD.[7]

We included all live-born infants with GA 22 to 42 completed weeks and excluded newborns with known chromosomal abnormalities or major structural birth defects other than CCHD. Structural birth defects were considered "major" if determined by clinical review to result in mortality or major morbidity and likely to be identified at birth or lead to hospitalization during the first year of life.[17]

Infants with CCHD were identified by *ICD-9-CM* diagnostic and procedure codes present in the birth, transfer, or readmission records. CCHD was defined as one or a combination of the following lesions: hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, transposition of the great arteries, tricuspid atresia, truncus arteriosus, total anomalous venous return, coarctation of the aorta, double outlet right ventricle, Ebstein anomaly, and single ventricle.[3,18] Additionally, we included pulmonary and aortic stenosis requiring intervention during the first year of life.[18] Two study collaborators (M.A.S. and A.M.G.) reviewed all cases according to a proposed framework based on morphogenetically similar developmental mechanisms[3,19] to ensure correct classifications of infants with multiple *ICD-9-CM* codes. Final diagnosis was reached by consensus. Infants with multiple CCHD codes consistent with heterotaxy were also classified as CCHD.

To adjust for complexity of CCHD, we used 6 severity groups modified from risk adjustment in congenital heart surgery (RACHS)[20] as further detailed in Steurer et al.[7] It was not possible to use RACHS in its original form, since some surgical details needed for classifications were not available in this database.

The outcome assessed was 1-year mortality determined by death certificate. Our main predictor was *Z* score for BW calculated using data published by Talge et al,[21] who derived *Z* scores for BW by GA and sex from US live-birth files maintained by the National Center for Health Statistics (years 2009–2010) and corrected for implausible GA estimates. We used this reference because of the similarity of the population

and time period to our study cohort. Infants with a *Z* score <−4 and >+4 were excluded from the analysis because of the likelihood of either implausible GA or BW (n=40). Given that the above-mentioned data[21] to calculate BW *Z* score were derived from singleton gestations only, we performed a sensitivity analysis excluding multiple gestation infants from our cohort.

We first divided the cohort into the 3 groups most widely used when assessing fetal growth: SGA (BW <10th percentile for GA and sex, corresponding to a *Z* score <−1.27), adequate for GA (AGA; BW 10–90th percentile for GA and sex, *Z* sore −1.27 to 1.27), and large for GA (LGA; BW >90th percentile for GA and sex, *Z* score >+1.27).

We then planned to evaluate BW z-score as a continuous predictor variable separately in 3 different gestational age groups: preterm (<37 weeks), early-term (37–38 weeks), and full-term (39–42 weeks) infants. However, the lowest plots suggested departure from linearity between log odds of mortality and *Z* score for BW in all 3 groups (not shown). The relationship was best modeled using logistic regression with restricted cubic splines for *Z* score for BW with knots at −2, 0, and +2. To graphically represent the logistic models involving cubic splines, we derived curves for predicted probability of death separately in each group. *Z* score–specific margins were calculated for different GA categories while adjusting for sex, multiple gestation, and complexity of CHD (all confounders were kept at their mean values). To numerically quantify the effect and the nonlinear relationship, *Z* score for BW was used as a categorical variable with 8 categories (<−2, ≥−2 to −1, ≥−1 to −0.5, ≥−0.5 to 0, ≥0–0.5, ≥0.5–1, ≥1–2, and >2). Multivariable models were adjusted for complexity of CCHD (by modified RACHS), GA, sex, and multiple gestation. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs).

To describe baseline characteristics, *t* test was used to compare means and chi-square was used to compare proportions. A $P<0.05$ was considered significant.

All analyses were performed using Stata version 14.2 (version 14, StataCorp LP). The study was approved by the Committee for the Protection of Human Subjects within the California Health and Human Services Agency. The informed consent requirement was waived.

Results

We identified 6903 live-born infants with CCHD born between 22 and 42 weeks of gestation without chromosomal anomalies, corresponding to an incidence of 0.23% (6903/2 968 566 live births). Overall, mean BW in infants with CCHD was 3090 g (SD 733.8 g) and 3306.7 g (SD 555.3 g) in infants without CCHD, respectively (*t* test, $P<0.001$). A total of 16.2% of infants with CCHD were SGA (n=1120), while 8.9% of infants without CCHD were classified as SGA (n=266 133, chi-square test; $P<0.001$). There was no difference in the percentage of infants born LGA (CCHD: 9.6%, n=664; no CCHD: 9.8%, n=293 001 [chi-square test, $P=0.57$]). Overall, 18.1% (1246/6903) of infants with CCHD were born prematurely (<37 weeks' gestation) compared with 8.4% of infants without CCHD (251 029/2 983 022; chi-square test, $P<0.001$).

Table 1 shows the baseline characteristics of infants with CCHD born SGA, AGA, and LGA. When compared with AGA infants, SGA infants were more likely to be women ($P=0.016$) and less likely to be singleton ($P<0.001$), while LGA infants were more likely to be singleton ($P<0.001$). SGA and LGA infants were more likely to be born to a mother with preeclampsia (SGA: $P<0.001$ and LGA: $P=0.025$), and LGA infants were also more likely to be born to a mother with diabetes mellitus ($P<0.001$) (Table 1).

For infants with CCHD, Figure 1 shows the crude rates of mortality by GA group for AGA, SGA, and LGA infants. In preterm infants (GA <37 weeks), the OR for mortality was not significantly higher for SGA infants compared with AGA infants in each GA group (Table 2). In contrast, for infants born at 37, 38, 39, or 40 weeks GA, SGA had a significantly higher crude and adjusted OR for mortality when compared with AGA. LGA infants of any GA group did not have significantly higher crude or adjusted ORs than AGA infants (Table 2).

Table 3 shows the effect of fetal growth as a categorical variable on mortality in preterm (<37 weeks), early-term (37–38 weeks), and full-term (39–42 weeks) infants with CCHD. In preterm infants, the highest mortality was in infants with a *Z* score of 1 to 2 (34/108, 31.5%) and the lowest mortality was in infants with a *Z* score of 0.5 to 1 (21/115, 18.3%). In early-term infants, the highest mortality was in infants with a *Z* score of <−2 (30/111, 25.2%) and the lowest mortality was in infants with a *Z* score of 0.5 to 1 (20/245, 8.2%). In full-term infants, the mortality rate decreased from 23.7% (31/131) in the *Z* score category <−2% to 2.7% (3/111) in the *Z* score category >+2. In preterm and full-term infants—after adjusting for severity of CCHD, sex, multiple gestation, and GA in weeks, only the groups with the most severe growth restriction (*Z* score <−2) had a higher adjusted OR for mortality (OR, 2.15 [95% CI, 1.10–4.21] in preterm and OR, 3.61 [95% CI, 2.18–5.96] in full-term infants, respectively) than the reference group (*Z* score 0–0.5). There was a trend towards higher mortality in preterm infants with a *Z* score of 1 to 2 compared with the reference group, but this did not reach statistical significance (adjusted OR, 1.49; 95% CI, 0.83–2.70). In contrast, in full-term infants, there was a trend towards lower mortality as the *Z* score increased, but, again, this did not reach statistical significance. In early-term infants, the crude and adjusted ORs for mortality were increased for *Z*

Table 1. Characteristics of Infants With Critical Congenital Heart Disease by BW Category for Gestational Age

	AGA (Reference)	SGA	*P* Value	LGA	*P* Value
Sample	5119	1111		633	
BW					
Mean BW (SD), g	3139.4 (598.5)	2339.2 (519.0)		3987.4 (657.2)	
Mode of delivery			<0.0001		<0.0001
Cesarean	2023 (39.5)	547 (49.2)		344 (54.3)	
Vaginal	3096 (60.5)	564 (50.8)		289 (44.7)	
Race			<0.0001		0.0010
White not Hispanic	1460 (28.5)	261 (23.5)		174 (27.5)	
Hispanic	2383 (46.6)	491 (44.2)		334 (52.8)	
Black	235 (4.6)	86 (7.7)		32 (5.1)	
Asian	568 (11.1)	169 (15.2)		39 (6.2)	
Other	473 (9.2)	104 (9.2)		54 (8.5)	
Sex			0.0168		0.4497
Female	2063 (40.3)	491 (44.2)		265 (41.9)	
Male	3056 (59.7)	620 (55.8)		368 (58.1)	
Gestation			<0.0001		<0.0001
Singleton	4893 (95.6)	986 (88.8)		630 (99.5)	
Multiple	226 (4.4)	125 (11.3)		3 (0.5)	
Maternal education			0.2319		0.1384
<12 y	1215 (23.7)	251 (22.6)		171 (27.0)	
12 y	1303 (25.5)	301 (27.1)		170 (26.9)	
>12 y	2308 (45.1)	482 (43.4)		261 (41.2)	
Missing	293 (5.7)	77 (6.9)		31 (4.9)	
Payment for delivery			0.7391		0.0419
Private insurance	2361 (46.1)	532 (47.9)		275 (43.4)	
Public insurance	2513 (49.1)	531 (47.8)		337 (53.2)	
Self-pay	68 (1.3)	16 (1.4)		11 (1.7)	
Other	168 (3.3)	30 (2.7)		10 (1.5)	
Missing	9 (0.2)	2 (0.2)		0 (0.0)	
Parity			0.0001		<0.0001
Nulliparous	1950 (38.1)	500 (45.0)		168 (26.5)	
Multiparous	3165 (61.8)	610 (54.9)		464 (73.3)	
Missing	4 (0.1)	1 (0.1)		1 (0.2)	
Oligohydramnios			<0.0001		0.0158
No	4947 (96.6)	1011 (91.0)		623 (98.4)	
Yes	172 (3.4)	100 (9.0)		10 (1.6)	
PROM			0.3010		0.7490
No	4737 (92.5)	1018 (91.6)		588 (92.9)	
Yes	382 (7.5)	93 (8.4)		45 (7.1)	
Chorioamnionitis			0.2341		0.9064
No	5002 (97.7)	1092 (98.3)		619 (97.8)	
Yes	117 (2.3)	19 (1.7)		14 (2.2)	

Continued

Table 1. Continued

	AGA (Reference)	SGA	*P* Value	LGA	*P* Value
Maternal age, y			0.1807		0.0029
<18	140 (2.7)	32 (2.9)		8 (1.3)	
18–34	3979 (77.7)	855 (77.0)		475 (75.0)	
>34	1000 (19.5)	223 (20.1)		150 (23.7)	
Missing	0 (0.0)	1 (0.1)		0 (0.0)	
Maternal diabetes mellitus			0.6181		<0.0001
None	4422 (86.4)	972 (87.5)		437 (69.0)	
Preexisting	152 (3.0)	30 (2.7)		61 (9.6)	
Gestational	545 (10.7)	109 (9.8)		135 (21.3)	
Maternal BMI*			<0.0001		<0.0001
Underweight	231 (4.5)	73 (6.6)		8 (1.3)	
Normal weight	2194 (42.9)	541 (48.7)		182 (28.8)	
Overweight	1241 (24.2)	225 (20.3)		175 (27.7)	
Obese	1016 (19.9)	179 (16.1)		211 (33.3)	
Missing	437 (8.5)	93 (8.4)		57 (9.0)	
Mental illness			0.4323		0.6244
No	4867 (95.1)	1050 (94.5)		599 (94.6)	
Yes	252 (4.9)	61 (5.5)		34 (5.4)	
Smoking during pregnancy			0.1255		0.5942
No	4834 (94.4)	1036 (93.3)		601 (94.9)	
Yes	285 (5.6)	75 (6.8)		32 (5.1)	
Illicit drug use			0.2088		0.1611
No	5012 (97.9)	1081 (97.3)		625 (98.7)	
Yes	107 (2.1)	30 (2.7)		8 (1.3)	
Hypertension			0.1047		0.4981
None	4920 (96.1)	1052 (94.8)		607 (95.9)	
Preexisting	84 (1.6)	27 (2.4)		14 (2.2)	
Gestational	115 (2.3)	31 (2.8)		12 (1.9)	
Preeclampsia			<0.0001		0.0890
No	4875 (95.2)	996 (89.7)		593 (93.7)	
Yes	244 (4.8)	115 (10.4)		40 (6.3)	

Values are expressed as number (percentage) unless otherwise indicated. Chi-square test was used to compare variables. $P<0.05$ was considered statistically significant. AGA indicates adequate for gestational age; BW, birth weight; LGA, large for gestational age; PROM, premature rupture of membranes; SGA, small for gestational age.
*Underweight: body mass index (BMI) <18.5 kg/m^2; normal weight: BMI 18.5 to 24.9 kg/m^2; overweight: BMI 25.0 to 29.9 kg/m^2; and obese: BMI ≥30.0 kg/m^2.

score groups of <−2, −2 to −1, and −1 to −0.5 compared with the reference group. Table 4 shows the results of the sensitivity analysis excluding multiple-gestation infants without major changes of the results. For easy reference, Figure 2 shows mortality predictions using cubic splines adjusted for multiple gestation, sex, and complexity of CCHD by GA in preterm (Figure 2A), early-term (Figure 2B), and full-term (Figure 2C) infants to model the effect of *Z* score for BW while keeping the adjusted confounders at their mean level.

Discussion

This population-based study of infants with CCHD investigated the effect of fetal growth measured by BW *Z* score on 1-year mortality and found a different pattern of its effect in different GA groups. In preterm infants, only severe SGA (*Z* score <−2) was associated with increased mortality compared with infants with a BW *Z* score of 0 to 0.5 and there was a trend toward increased mortality in LGA infants that did not reach

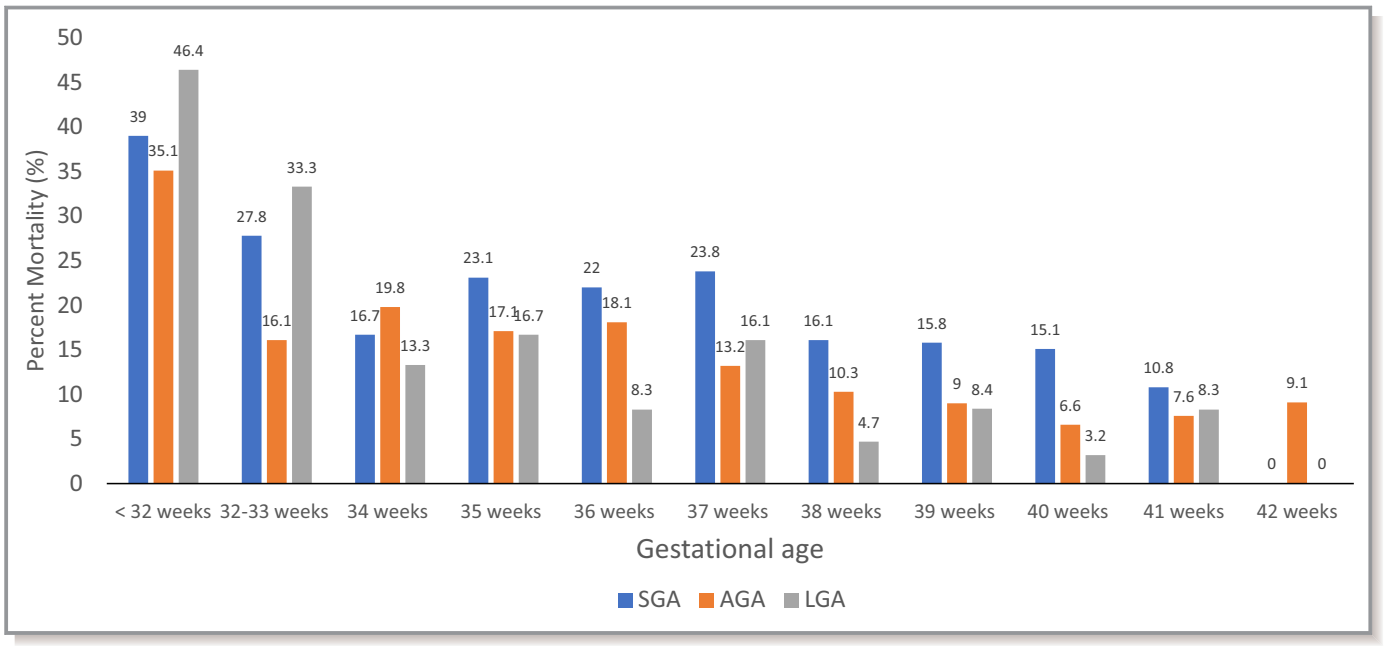

Figure 1. Fetal growth and 1-year mortality rates by gestational age in infants with critical congenital heart disease. AGA indicates adequate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

statistical significance. In early-term infants, a more pronounced association between low BW (LBW) *Z* score and mortality was found. Infants with a *Z* score up to −0.5 experienced a higher mortality rate than infants with a *Z* score 0 to 0.5. Similar to preterm infants, in full-term infants, only severe SGA (*Z* score <−2) was associated with increased mortality. However, in contrast to preterm infants, mortality in full-term infants continued to decrease as the *Z* score increased, although this did not reach statistical significance.

Several reports show higher mortality and morbidity rates in LBW infants with CHD compared with infants with normal BW.[22–24] It is important to distinguish between LBW and SGA since they represent 2 different concepts. The term LBW includes appropriately grown but preterm infants, thus a group of infants with LBW will have a lower mean GA than a group of infants with normal BW. In contrast, SGA, AGA, LGA, and *Z* score for BW all report measures standardized for GA and sex, and as such are often used as surrogate markers for fetal growth. Increased mortality in LBW infants with CHD does not address the question of whether fetal growth—as measured by SGA/AGA/LGA or *Z* score for BW—impacts this outcome since the increased mortality rate in LBW infants is mainly driven by lower GA, and it is well known that GA is a major determinant of mortality in infants with[7,8,25] and without CHD.[26]

Overall, infants with CHD are more likely to be SGA.[10] However, few studies have investigated the impact of SGA birth on postnatal outcomes in this patient population. In a single institution, retrospective review of 230 infants requiring neonatal cardiothoracic intervention, SGA infants had a higher 30-day and discharge mortality rate compared with AGA infants.[12] This study was relatively small, only adjusted for sex in the multivariate models, and did not have the power to address a potential interaction between SGA and GA. Another small single-institution study (n=76)[14] compared SGA and non-SGA infants of similar absolute weights and found no differences in postoperative mortality. This result was most likely explained by the higher GA at birth in the SGA versus non-SGA infants. Best and colleagues[15] recently published data on long-term survival estimates in 5093 infants with CHD born between the years 1985 and 2003 in the north of England. They divided the cases into 3 *Z* score categories and found that infants with *Z* score <−1 had a higher crude and adjusted hazard ratio for 5-year mortality than infants with a *Z* score 1≤ *Z* ≤1, and infants with a *Z* score >1 had a slightly lower adjusted hazard ratio. While these findings are similar to our findings in full-term infants, the study by Best and colleagues assessed only 3 *Z* score categories and, although they adjusted for GA, they did not include a statistical interaction term in their model between *Z* score for BW and GA, nor did they stratify by GA and, as such, they were potentially missing a more complex relationship.

Our study is novel and unique in that it assesses the effect of BW *Z* score on mortality as a multicategorical variable and not just as SGA versus non-SGA. Second, it stratifies the analysis by different GA groups in order to explore a potentially different impact of *Z* score for BW on mortality in preterm, early-term, and full-term infants with CCHD. We found that across all 3 GA groups, severely SGA infants with CCHD were at increased risk for mortality. These results are similar to findings in infants without CCHD.[11] In infants

Table 2. Effects of Small and Large for Gestational Age on Mortality by Gestational Age in Infants With Critical Congenital Heart Disease

	SGA vs AGA		LGA vs AGA	
Gestational Age	Crude OR	Adjusted OR*	Crude OR	Adjusted OR*
<32 wk (n=280)	1.18 (0.60–2.36)	1.61 (0.77–3.36)	1.60 (0.72–3.55)	1.46 (0.61–3.52)
32–33 wk (n=178)	2.00 (0.83–4.83)	2.29 (0.85–6.20)	2.6 (0.98–6.94)	2.26 (0.78–6.57)
34 wk (n=161)	0.81 (0.28–2.34)	0.93 (0.29–3.0)	0.62 (0.13–2.95)	0.46 (0.09–2.41)
35 wk (n=222)	1.45 (0.67–3.14)	1.82 (0.76–4.36)	0.97 (0.26–3.59)	0.58 (0.14–2.34)
36 wk (n=385)	1.27 (0.72–2.27)	1.73 (0.91–3.29)	0.41 (0.12–1.40)	0.46 (0.13–1.65)
37 wk (n=731)	2.1 (1.32–3.21)†	2.75 (1.69–4.48)†	1.27 (0.62–2.62)	1.92 (0.88–4.21)
38 wk (n=1363)	1.67 (1.11–2.53)†	1.64 (1.05–2.57)†	0.43 (0.19–1.0)	0.51 (0.21–1.20)
39 wk (n=2004)	1.90 (1.32–2.73)†	1.88 (1.29–2.76)†	0.93 (0.52–1.65)	1.03 (0.57–1.86)
40 wk (n=1206)	2.51 (1.51–4.16)†	2.60 (1.52–4.43)†	0.47 (0.17–1.31)	0.51 (0.18–1.46)
41 wk (n=299)	1.48 (0.47–4.65)	1.32 (0.39–4.44)	1.11 (0.24–5.11)	0.72 (0.15–3.51)
42 wk (n=34)	N/A‡	N/A‡	N/A‡	N/A‡

AGA indicates adequate for gestational age; OR, odds ratio.
*Adjusted for severity of critical congenital heart disease, sex, and multiple gestation.
†Statistically significant with *P* value <0.05.
‡No deaths in the small-for-gestational age (SGA) or large-for-gestational age (LGA) groups.

without CCHD, SGA has been linked to the development of early systemic hypertension,[27] type 2 diabetes mellitus,[28] hyperlipidemia,[28] and reduced renal function.[29,30] We hypothesize that this link is even more apparent in infants with CCHD. Further studies should focus on follow-up of SGA infants with CCHD to understand its implications not only for mortality but also for long-term outcomes and to develop early interventions.

Most interestingly, we found that in early-term infants with CCHD, the association between BW *Z* score and mortality is much more pronounced than in other GA categories and that even *Z* scores as high as −1 to −0.5 present an increased risk for mortality. Historically, term infants born at 37 to 42 weeks have been considered a uniform group.[31] However, more recently, early-term infant vulnerability has been documented and several studies in infants without CCHD have shown that early-term infants born at 37 to 38 weeks have a higher incidence of respiratory distress, developmental morbidities, and even infant mortality.[32,33] In infants with CCHD, 2 studies have shown increased mortality, neonatal morbidities, and postoperative complications in early-term versus full-term infants.[7,8] Our current study suggests that *Z* score for BW has the most granular effect in early-term infants with CCHD, making this group particularly vulnerable. A possible explanation for these findings is that in preterm infants, GA is a much stronger driver of mortality and that BW plays a less important role. Similarly, in full-term infants, the mature GA seems to be protective against increased mortality from lower *Z* score for BW. In early-term infants, on the other hand, the effects of lower BW *Z* scores become most apparent. These findings should be validated in other cohorts of infants with CCHD.

It is also interesting to mention that the effect of high BW *Z* scores appears to be different in preterm versus term infants, although this did not reach statistical significance. In term infants, there is a trend toward decreased mortality with higher BW *Z* score, while in preterm infants, there is a trend toward higher mortality with a BW *Z* score >1 (Figures 1 and 2). We speculate that this trend in preterm infants is caused by hydrops fetalis that might be present in severe cases of CCHD, leading to preterm delivery of LGA infants.

The results of this study provide important information for the medical team taking care of these infants. BW *Z* score as low as −2 in preterm infants with CCHD should not automatically be considered as a risk factor for mortality when counseling parents or when deciding whether to provide surgical interventions. It is unclear whether our results should impact timing of delivery of early-term infants with low estimated fetal weight corresponding to a low *Z* score. In fact, early delivery might be a confounder in the relationship between LBW *Z* score and mortality if the elective early deliveries were initiated because of poor fetal growth. With regards to postnatal care, weight gain of early-term infants with CCHD, even if only mildly growth restricted, should be followed carefully. However, it is unclear what postnatal growth trajectory should be targeted since there is some evidence that early catch-up growth in SGA infants might be

Table 3. Effects of BW *Z* Score on Mortality in Preterm (<37 Weeks of Gestation), Early-Term (37–38 Weeks of Gestation), and Full-Term (39–42 Weeks of Gestation) Infants With Critical Congenital Heart Disease

	Mortality, %	Crude OR (95% CI)	Adjusted OR (95% CI)*
Preterm: GA <37 wk			
Z score <−2 (n=78)	26.9	1.10 (0.59–2.02)	2.15 (1.10–4.21)†
Z score −2 to −1 (n=262)	23.7	0.92 (0.59–1.45)	1.40 (0.85–2.31)
Z score −1 to −0.5 (n=214)	18.7	0.68 (0.42–1.12)	0.94 (0.55–1.61
Z score −0.5 to 0 (n=214)	22.4	0.86 (0.54–1.38)	1.13 (0.67–1.90)
Z score 0–0.5 (n=167)	25.2	Reference	Reference
Z score 0.5–1 (n=115)	18.3	0.66 (0.37–1.20)	0.63 (0.33–1.20)
Z score 1–2 (n=108)	31.5	1.37 (0.80–2.34)	1.49 (0.83–2.70)
Z score >2 (n=61)	21.3	0.81 (0.40–1.63)	0.87 (0.40–1.88)
Early term: GA 37–38 wk			
Z score <−2 (n=111)	25.2	3.42 (1.93–6.04)†	3.63 (1.98–6.67)†
Z score −2 to −1 (n=402)	14.9	1.78 (1.12–2.83)†	1.69 (1.04–2.75)†
Z score −1 to −0.5 (n=366)	16.7	2.03 (1.27–3.23)†	1.78 (1.10–2.89)†
Z score −0.5 to 0 (n=371)	10.5	1.19 (0.72–1.96)	1.13 (0.68–1.90)
Z score 0–0.5 (n=334)	8.9	Reference	Reference
Z score 0.5–1 (n=245)	8.2	0.90 (0.50–1.77)	0.79 (0.43–1.46)
Z score 1–2 (n=189)	8.5	0.94 (0.50–1.77)	1.0 (0.52–1.94)
Z score >2 (n=71)	8.5	0.94 (0.37–2.34)	1.08 (0.42–2.77)
Term: GA 39–42 wk			
Z score <−2 (n=131)	23.7	3.61 (2.18–5.96)†	3.93 (2.31–6.68)†
Z score −2 to −1 (n=574)	11.0	1.43 (0.96–2.14)	1.48 (0.98–2.24)
Z score −1 to −0.5 (n=591)	8.3	1.05 (0.69–1.60)	1.17 (0.76–1.80)
Z score −0.5 to 0 (n=709)	9.0	1.15 (0.78–1.71)	1.18 (0.78–1.78)
Z score 0–0.5 (n=581)	7.9	Reference	Reference
Z score 0.5–1 (n=445)	6.7	0.84 (0.52–1.36)	0.90 (0.56–1.56)
Z score 1–2 (n=398)	6.5	0.81 (0.49–1.35)	0.93 (0.56–1.56)
Z score >2 (n=111)	2.7	0.32 (0.10–1.06)	0.39 (0.12–1.30)

BW indicates birth weight; CI, confidence interval; OR, odds ratio.
*Adjusted for severity of critical congenital heart disease, sex, multiple gestation, and gestational age (GA) in weeks.
†Statistically significant with *P*-value < 0.05.

associated with childhood and adulthood obesity.[34,35] Further studies are needed to address these important questions in infants with CCHD.

The underlying mechanism by which fetal growth affects outcome in CCHD remains speculative. Recently, the fetal environment has been recognized as a potential important contributor to postnatal outcomes in infants with CCHD.[36,37] Gaynor and colleagues[36] showed that after cardiac surgery in neonates, the presence of an impaired maternal-fetal environment, defined as preeclampsia, SGA, or preterm birth, was associated with lower survival at 36 months of age. Miller et al[37] found that uteroplacental insufficiency was associated with asymmetric prenatal growth, poor weight gain, and decreased myocardial performance in infants with hypoplastic left heart syndrome. Future studies should investigate potential underlying biological mechanisms explaining these finding.

Study Limitations

This study has some important limitations. First, the data set used does not contain data on longitudinal intrauterine growth or information on head circumference, thus we were unable to assess fetal growth restriction per se because this term implies an in utero insult that led to a fetus not meeting its growth potential.[38] Assessing the growth potential in infants with CCHD is further complicated by

Table 4. Sensitivity Analysis

	Mortality, %	Crude OR (95% CI)	Adjusted OR (95% CI)*
Preterm: GA <37 wk			
Z score <−2 (n=56)	28.6	1.12 (0.56–2.25)	1.92 (0.90–4.12)
Z score −2 to −1 (n=189)	25.4	0.96 (0.58–1.58)	1.25 (0.72–2.18)
Z score −1 to −0.5 (n=158)	19.0	0.66 (0.38–1.14)	0.84 (0.46–1.52)
Z score −0.5 to 0 (n=158)	25.3	0.95 (0.56–1.60)	1.16 (0.65–2.06)
Z score 0–0.5 (n=137)	26.3	Reference	Reference
Z score 0.5–1 (n=101)	19.8	0.69 (0.37–1.29)	0.64 (0.32–1.27)
Z score 1–2 (n=102)	32.4	1.34 (0.76–2.36)	1.45 (0.78–2.70)
Z score >2 (n=60)	21.7	0.78 (0.38–1.60)	0.86 (0.39–1.89)
Early term: GA 37–38 wk			
Z score <−2 (n=94)	27.7	3.94 (2.13–6.90)†	3.93 (2.11–7.31)†
Z score −2 to −1 (n=363)	14.9	1.75 (1.09–2.82)†	1.61 (1.04–2.63)†
Z score −1 to −0.5 (n=346)	16.8	2.02 (1.26–3.23)†	1.75 (1.07–2.85)†
Z score −0.5 to 0 (n=366)	10.7	1.20 (0.73–1.98)	1.16 (0.69–1.94)
Z score 0–0.5 (n=331)	9.1	Reference	Reference
Z score 0.5–1 (n=241)	8.3	0.91 (0.50–1.64)	0.80 (0.43–1.46)
Z score 1–2 (n=188)	8.5	0.93 (0.50–1.76)	1.0 (0.52–1.94)
Z score >2 (n=71)	8.5	0.93 (0.37–2.32)	1.07 (0.42–2.74)
Term: GA 39–42 wk			
Z score <−2 (n=128)	23.4	3.55 (2.14–5.91)†	3.85 (2.26–6.57)†
Z score −2 to −1 (n=572)	11.0	1.44 (0.96–2.14)	1.49 (0.98–2.25)
Z score −1 to −0.5 (n=590)	8.3	1.05 (0.69–1.60)	1.17 (0.76–1.80)
Z score −0.5 to 0 (n=709)	9.0	1.15 (0.78–1.71)	1.18 (0.78–1.78)
Z score 0–0.5 (n=580)	7.9	Reference	Reference
Z score 0.5–1 (n=445)	6.7	0.84 (0.52–1.35)	0.90 (0.55–1.47)
Z score 1–2 (n=398)	6.5	0.81 (0.49–1.34)	0.93 (0.56–1.55)
Z score >2 (n=111)	2.7	0.32 (0.10–1.06)	0.39 (0.12–1.30)

CI indicates confidence interval; OR, odds ratio. Effects of birth weight *Z* score on mortality in preterm (<37 weeks of gestation), early-term (37–38 weeks of gestation), and full-term (39–42 weeks of gestation) singleton infants with critical congenital heart disease.

*Adjusted for severity of critical congenital heart disease, sex, and gestational age (GA) in weeks.

†Statistically significant with *P*-value < 0.05.

the fact that cardiac lesion–specific differences in BW have been described.[39] Additionally, with the lack of head circumference data, we were unable to distinguish between symmetric and asymmetric growth restriction.[38] Future studies should focus on these unanswered questions and assess lesion-specific outcomes to better understand the nuanced relationship between BW and GA in neonates with CCHD.

Another potential limitation is the fact that identification of the cases with CCHD depended on *ICD-9-CM* codes. Thus, it is possible that we missed cases if the *ICD-9* coding was incomplete. With regards to the classification of CCHD, although 2 physicians independently reviewed every case with multiple codes for CCHD, we could not exclude misclassification of infants with CHD based on *ICD-9* codes.[40] Lack of data regarding surgical repair details made grouping of CCHD according to RACHS or another established surgical classification system challenging, and we ended up modifying the RACHS classification. Still, given that the only purpose of classification and severity grouping of CCHD cases in this study was to ensure that CCHD severity was adjusted for across *Z* score categories, and we are confident that this goal was achieved. It is also important to mention that we were unable to include fetal demises or stillbirths, which could

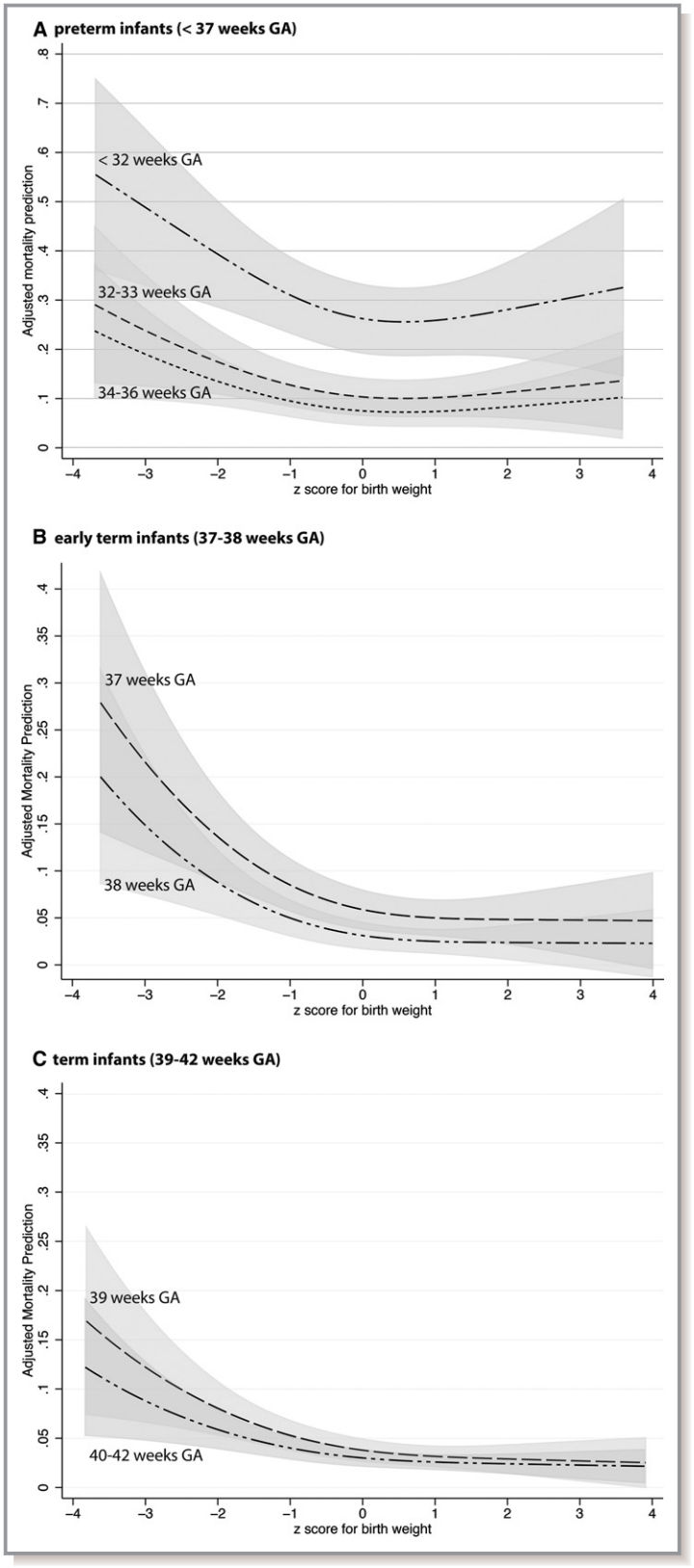

Figure 2. Adjusted mortality prediction by *Z* score for birth weight in preterm (A), early-term (B), and term (C) infants with critical congenital heart disease. Mortality predictions are adjusted for sex, severity of critical congenital heart disease, and multiple birth. All predictors are kept at their mean. GA indicates gestational age.

potentially have an impact on our findings. A significant benefit of this study is its population-based nature, and, in contrast to studies from surgical databases, it is less prone to selection bias as it includes infants who died before surgical interventions.

Conclusions

This study provides further important insight into the association of fetal growth and 1-year mortality in neonates with CCHD. We identified the strongest association between LBW *Z* score and mortality in early-term infants with CCHD. This information could be of great value for counseling of parents and for medical providers caring for this patient population.

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Disclosures

None.

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