

SYSTEMATIC REVIEW

Birthweight and isolated congenital heart defects – A systematic review and meta-analysis

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Abstract

Background: Birthweight (BW) is an important prognostic factor in newborns with congenital heart defects (CHD).

Objectives: To give an overview of the literature on BW *z*-score in children with isolated CHD.

Search strategy: A systematic search was performed on isolated CHD and BW in PubMed, Embase, Web of Science, COCHRANE Library and Emcare.

Selection criteria: Neonates with isolated CHD were included if a BW percentile, BW *z*-score or % small-or-gestational age (SGA) was reported.

Data collection and analysis: BW *z*-score and percentage SGA were pooled with random-effect meta-analysis. Quality and risk of bias were assessed using the modified Newcastle Ottawa Scale.

Main results: Twenty-three articles (27 893 cases) were included. BW *z*-scores were retrieved from 11 articles, resulting in a pooled *z*-score of -0.20 (95% CI -0.50 to 0.11). The overall pooled prevalence of SGA <10th percentile was 16.0% (95% CI 11.4–20.5; 14 studies). Subgroup analysis of major CHD showed similar results (BW *z*-score -0.23 and percentage SGA 16.2%).

Conclusions: Overall BW in isolated CHD is within range of normality but impaired, with a 1.6-fold higher risk of SGA, irrespective of the type of CHD (major CHD vs all CHD combined). Our findings underline the association between CHD and BW. The use of BW *z*-scores provides insight into growth of all fetuses with CHD.

KEY WORDS

birthweight, congenital heart defects, fetal growth, intrauterine growth, meta-analysis, small for gestational age, systematic review

Tweetable abstract: Infants with a congenital heart defect (CHD) have a lower birthweight *z*-score and a higher incidence of small-for-gestational age (<10th percentile). This was encountered both in the major CHD-group as well as in all-CHD combined group analysis. Future research on the association between birthweight and CHD should include all types of CHDs (including mild cardiac defects) and

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placental-related disease, such as pre-eclampsia. We advocate the use of international standardised fetal growth and birthweight charts in CHD research.

1 | INTRODUCTION

Congenital heart defects (CHD) are the most common type of congenital malformation and affect approximately 5–9 neonates per 1000 live births.^{1,2} Despite the improved survival rates, CHD remains a major cause of mortality and morbidity in children and young adults.^{3–5} An important contributor to long-term morbidity in children with CHD is neurodevelopmental impairment, as it affects a significant number of cases.^{5–9}

An adequate bodyweight (BW) is important in vulnerable CHD neonates, as a great number of them require surgical interventions either immediately after birth or in the first months of life.¹ Small-for-gestational age (SGA) <10th percentile and low BW (weight <2500 g) are associated with worse outcome after cardiothoracic surgery.^{10–14} BW is independently associated with an increased mortality in individuals with CHD (hazard ratio 1.73, 95% CI 1.48–2.03).¹⁵ A recent study showed that BW even slightly under average is related to an increased risk of morbidity and mortality after cardiac surgery.¹⁶

Placenta-related abnormalities, including reduced placental weight, pre-eclampsia (PE) and abnormal fetal Dopplers, occur more frequently in pregnancies complicated by CHD.^{17–25} These signs of impaired placentation are also found in fetuses with an intrauterine growth restriction (IUGR), suggesting a shared pathway between CHD, fetal growth and placenta development.^{26,27} The precise pathophysiological association is, however, poorly understood.

The objective of this review was to better understand and objectify the association between BW and isolated CHD. A previous systematic review reported solely on the proportion of SGA below the 10th percentile in newborns with CHD.²⁸ Although the incidence of SGA in CHD is of most clinical relevance, as this is associated with an increased risk of morbidity and mortality, it does not address BW of all neonates with CHD. We hypothesise that children with isolated CHD show a reduced BW, but with weights lying within the limits of normality. Although SGA is a universal definition to discuss growth restriction, *z*-scores express BW of the entire group of CHD neonates. To test our hypothesis, we performed this systematic review and meta-analysis to provide an overview of overall BW in isolated CHD, expressed as *z*-scores.

2 | METHODS

2.1 | Search strategy

A systematic search was performed in PubMed, Embase, Web of Science, Cochrane and Emcare. The search terms contained 'BW' and 'congenital heart disease'. Publications

from 1 January 1980 to 11 January 2021 were included. The search was restricted to the English language. Details of the complete search are available in [Appendix S1](#).

2.2 | Study selection and management

Title/abstract screening and full text screening were both performed by two authors independently (MA, MS). A manual reference check was performed on all relevant articles for additional reports.

Discrepancies were resolved by a third researcher (MH).

Studies were considered eligible for inclusion if they met the following criteria: (1) newborns with isolated congenital heart disease (either pre- or postnatally diagnosed), (2) BW percentile, BW *z*-score, or % SGA was reported. SGA was defined as weight <10th or the 2.3th percentile (corresponding to –2 SD below the mean) for gestational age (GA). Exclusion criteria were: syndromic, genetic or major extracardiac disorders; multiple gestations; lack of definition of SGA; exclusion of SGA; reviews/opinions/case-reports/ animal studies, sample size <50 cases and studies on specific subgroups as these were not representative for all children with CHD (such as preterm birth or surgical outcome in low BW). In the case of multiple publications on (partially) the same cohort with equivalent outcomes (BW *z*-score and percentile), only the one with the largest sample size was included.

2.3 | Outcomes of interest and data extraction

The primary outcomes were mean BW *z*-score and percentage SGA in children with isolated CHD, as they represent BW corrected-for-gestational age. Data were extracted from the studies as percentiles or *z*-scores with corresponding SD or 95% confidence intervals (CI) for means, and interquartile range (IQR) for medians. Reported median percentiles or *z*-scores with IQR intervals were transformed to mean percentiles or *z*-scores with SD.²⁹ As BW percentiles and *z*-scores are equivalent measures, mean percentiles were converted to mean *z*-scores to facilitate comparability. When necessary, mean percentiles or *z*-scores with SD of different subgroups of CHD within one study were combined to acquire one result of the total included population. When combining *z*-scores corrected for confounders, independence was assumed. The statistical methods used for the transformation of the data are presented in [Appendix S2](#). Furthermore, the rate of newborns with SGA was extracted with the corresponding cut-off percentile value. If this cut-off value was reported as SD, it was converted to a percentile. The used

BW reference curve of each study was noted. The pooled mean BW z -score was compared with the z -score value of 0 as reference value. We also extracted data on the odds ratio (OR) or relative risk (RR) adjusted for confounders whenever available. A combined OR using reported OR over different subgroups of CHD was calculated within one study. We contacted the authors if relevant data were not reported in the original article.

2.4 | Quality and risk of bias assessment

Quality and risk of bias were assessed for each included study by two authors independently (MA, MS). The Newcastle–Ottawa Scale (NOS) was used and modified to fit our research question as recommended by the Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) guidelines.^{30,31} Each study is judged according to three domains: (1) selection of study population, (2) confounding and (3) assessment of outcome of interest. A maximum of three stars can be awarded for each item of the different domains corresponding to: not adequate (1 star), moderately adequate (2 stars) and adequate (3 stars). Furthermore, the risk of selection-, confounding- and information bias is assessed and divided into three categories (low-, intermediate- or high risk).

2.5 | Meta-analysis

Random-effect (RE) meta-analysis models were used to estimate the overall pooled means and percentage (with 95% CI). Models were constructed for the mean BW z -score and for the percentage SGA <10th percentile of all included CHD combined. Subsequently, subgroup analysis of major CHD was performed. Major CHD was defined as a defect that likely requires surgery or catheter intervention in the first year of life.

We compared BW outcome values in relation to reference population charts instead of to a study-specific included control group; in this way, a possible selection bias that could have occurred due to incorrect selection of the control group is prevented. In addition, more studies can be included in this systematic review, as not every article uses a control group. When multiple BW reference charts were assessed in one article, we included the data based on the national BW chart, as this best resembles the true distribution of BW in the reported population and eliminates ethnic or region-specific differences.

The following parameters were required for constructing the RE models: number of cases, effect size and corresponding SE. A forest plot and funnel plot were constructed for each meta-analysis model. The heterogeneity across studies was evaluated using I^2 statistics, which estimate the percentages of variation that are attributable to heterogeneity rather than chance between the studies.³² The statistical programme R (RStudio Version 1.3.1093) with the functions ‘Meta, Matrix and Metafor’ of the metaphor packages were

used for the meta-analysis. The COSMOS-E and PRISMA guidelines were followed.^{31,33}

2.6 | Patients and public involvement

There was no patient or public involvement in this study.

3 | RESULTS

The search identified 1970 original articles (Figure 1). After title/abstract evaluation, 178 articles were eligible for full-text screening and 22 articles were included. Cross-reference check resulted in one additional article that met the inclusion criteria, thus a total of 23 articles were included in the systematic review. Study characteristics are summarised in Table 1. The 23 articles included a total of 27 893 cases of CHD. The sample sizes of the cases per study ranged from 60 to 6903. Different categories of CHD were included: seven studies included all CHD, eight studies included ‘major’ CHD and eight studies specific subgroups of CHD. An overview of the included CHD per article is shown in Appendix S3. The used BW reference charts differed depending on the year of the study and demographic region. Twelve different standardised growth charts were used in the included articles; in the majority of the cases, these were the national charts. Three studies did not report on the used reference BW charts. Two studies utilised multiple reference charts assessing the BW. Matthiesen et al.³⁴ used their included control population as the reference value. The mean BW z -score was stated, or could be calculated, in 11 articles. Of the included studies, 16 studies described the percentage SGA of the newborns with CHD, of which 14 studies used the 10th birthweight percentile as cut-off value. The other two studies used the 2.3th percentile as the cut-off value for SGA.

A total of 21 articles were eligible for inclusion in the meta-analysis. Forest plots were created for BW z -score and percentage SGA below the 10th percentile. Three studies reported on both outcome measures and were therefore included in both forest plots. Subsequently, a subgroup meta-analysis was performed for major CHD. Further subdivision into specific CHD subtypes was not possible due to the heterogeneity of included diagnosis and the resulting small sample sizes per diagnosis.

The quality of the included studies was overall adequate (Table S1).

3.1 | Meta-analysis

3.1.1 | BW z -score—all CHDs combined

Data on the mean BW z -score was retrieved from 11 publications (7761 newborns). Two studies reported on all CHD combined,^{30,35} five on major CHD^{17,18,23,36,37} and four on

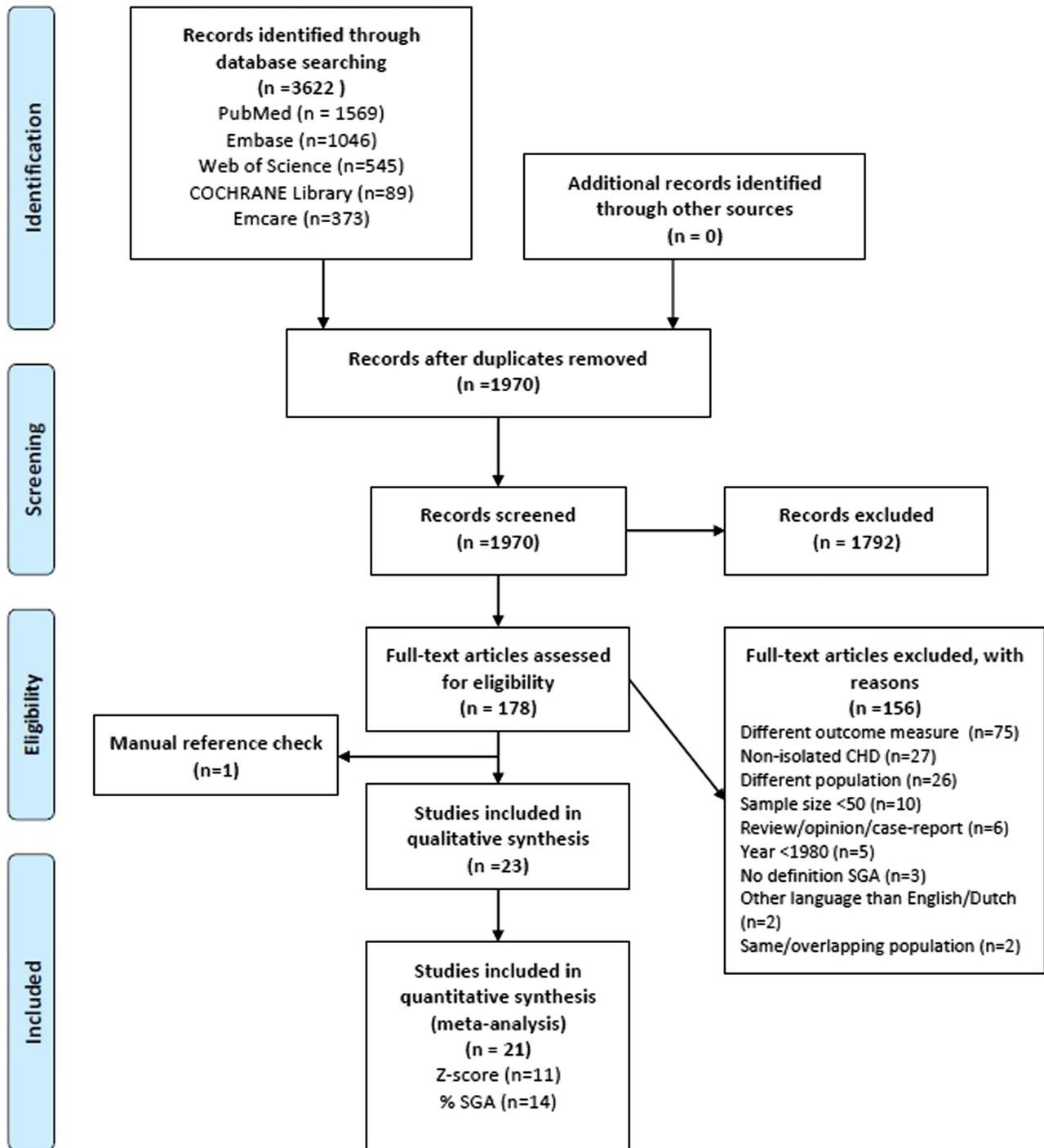


FIGURE 1 Flowchart of included studies

specific subgroups of CHD.^{35,38–40} Figure 2 shows that the pooled mean BW z -score was -0.20 (95% CI -0.50 to 0.11), indicating that neonates with CHD have a lower BW compared with the reference population. The 95% CI of the pooled mean BW z -score was wide due to high degree of heterogeneity between the study means, owing to the use of the RE model. All individual studies showed a mean z -score below 0. For only three of the ten studies, the 95% CI crossed the 0 value.^{18,23,37}

3.1.2 | SGA– all CHDs combined

In the meta-analysis, 14 studies on BW below the 10th percentile were included (15 800 cases). Figure 2B shows the pooled percentage SGA in all CHD. The overall pooled effect (16.0%; 95% CI 11.4–20.5) was higher than expected according to a normal birthweight distribution (10%). The reported prevalence varied from 7.3% to 24.2% with only two of 12 studies describing a prevalence <10th percentile.^{36,37} Two

TABLE 1 Overview of included studies

Author (year), country	Study design	Single (S)/multi(M)-centre	Inclusion time	Isolated cases (n)	Type of CHD	BW outcome	BW chart
Alsaied (2018), USA ³⁵	Retrospective case-control	M	January 2011–March 2015	67	TGA, HLHS or non HLHS-SV	Z-score	Olsen (2010)
Binder (2020), UK ¹⁷	Retrospective case-control	S	January 2009–January 2016	153	Major CHD requiring surgical or catheter-based intervention <6 months of life	Percentile % SGA	Poon (2016)
Cedergren ^a (2006), Sweden ⁴¹	Prospective cohort	M	January 1992–December 2001	5338	All CHD	% SGA	Källén (1995)
Giorgione (2020), Italy ³⁶	Retrospective case-control	S	2003–May 2018	401	Major CHD	Percentile % SGA	Poon (2012)
Graupner (2019), Germany ⁶⁴	Retrospective cohort	S	March 2008–March 2018	60	Left heart obstruction	% SGA	Voigt (2014) INTERGROWTH-21 (2014) Nicolaides (2018)
Inversetti (2020), Italy ³⁸	Prospective cohort	S	2011–2017	79	Cyanotic or non-cyanotic CHD	Percentile	Nicolaides (2018)
Jacobs (2003), China ³⁹	Retrospective cohort	S	January 1 1994–December 1995	419	Symptomatic CHD	Z-score	Unpublished Hong Kong birthweight reference (Dr Lao)
Lauridsen (2019), Denmark ⁶⁵	Prospective cohort	M	January 2012–December 2013	247	All CHD	Z-score	Matthiesen (2016)
Liu (2018), Australia ⁶⁶	Retrospective cohort	S	January 2010–April 2017	342	Major CHD (TGA, septal, RHL, LHL, other)	% SGA	Not reported
Malik (2007), USA ⁶⁷	Prospective case-control	M	October 1997–December 2002	3395	All CHD	% SGA	Zhang (1995)
Matthiesen ^a (2016), Denmark ³⁴	Retrospective cohort	M	January 1997–December 2011	4785 (5519) ^b	All CHD	Adjusted Z-score	Own population ^c
Perez ^a (2007), USA ⁴²	Retrospective case-control	S	January 1998–December 2001	125	All CHD	% SGA	Alexander (1996)
Puri (2018), USA ⁴⁰	Retrospective cohort	M	January 2000–June 2013	185	SV, CTA, d-TGA, septal defects, others	Z-score	Olsen (2010)
Rosenthal (1991), USA ⁶⁸	Prospective case-control	M	January 1981–March 1997	1299	d-TGA, ToF, endocardial cushion defect, HLHS, PS, AS, CoA, VSD, ASD	% SGA	Brenner (1976)
Rossi (2019), USA ⁶⁹	Retrospective cohort	M	2006–2015	836	Cyanotic CHD	% SGA	Alexander (1996)
Ruiz (2016), Spain ²²	Retrospective cohort	S	December 2003–December 2014	279	Major CHD (AV valve defects, CTA, LVOT)	% SGA	Not reported
Ruiz (2017), Spain ¹⁸	Retrospective cohort	M	June 2010–December 2014	119	Major CHD	Percentile	Figueras (2008)

(Continues)

TABLE 1 (Continued)

Author (year), country	Study design	Single (S)/multi(M)-centre	Inclusion time	Isolated cases (n)	Type of CHD	BW outcome	BW chart
Rychik (2018), USA ²³	Prospective cohort	S	Not stated	120	Haemodynamically important CHD requiring surgical or catheter-based intervention <6 months of life	Z-score	Fenton (2013)
Scholes (2019), Australia ³⁷	Retrospective cohort	S	January 2011–August 2017	452	CHD requiring surgery <4 weeks of life	Percentile % SGA	Olsen (2010)
Steurer (2018), USA ¹⁴	Retrospective cohort	M	2007–2012	6903	Critical CHD (defined as requiring neonatal intervention)	% SGA	Talge (2014)
Story (2015), UK ⁷⁰	Retrospective cohort	S	2006–2011	303	All CHD	% SGA	Population BW chart (name not reported), customised birthweight centiles (www.gestation.net)
Wallenstein ^a (2012), USA ⁴³	Retrospective cohort	S	1990–2008	107	All CHD	% SGA	Alexander (1996)
Williams ^a (2010), USA ⁷¹	Retrospective cohort	M	August 2003–May 2007	1145	Single ventricle	% SGA	U.S. National Center for Health Statistics (NCHS) 2005 Natality Data

Abbreviations: AS, aorta stenose; ASD, atrial septum defect; AV, atrioventricular; CHD, congenital heart defect; CoA, aortic coarctation; CTA, conotruncal anomalies; d-TGA, dextro-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; LHL, left heart lesions; LVOT, left-ventricle outflow tract obstruction; PS, pulmonary stenosis; RHL, right heart lesions; SV, single ventricle; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; VSD, ventricular septum defect.

^aIncluded genetic/extra-cardiac malformations, but subgroup analysis of isolated cases was possible.

^bAdjusted z-scores reported of 5519 cases with CHD, of which 4785 were isolated cases.

^cUsed included control group as reference population.

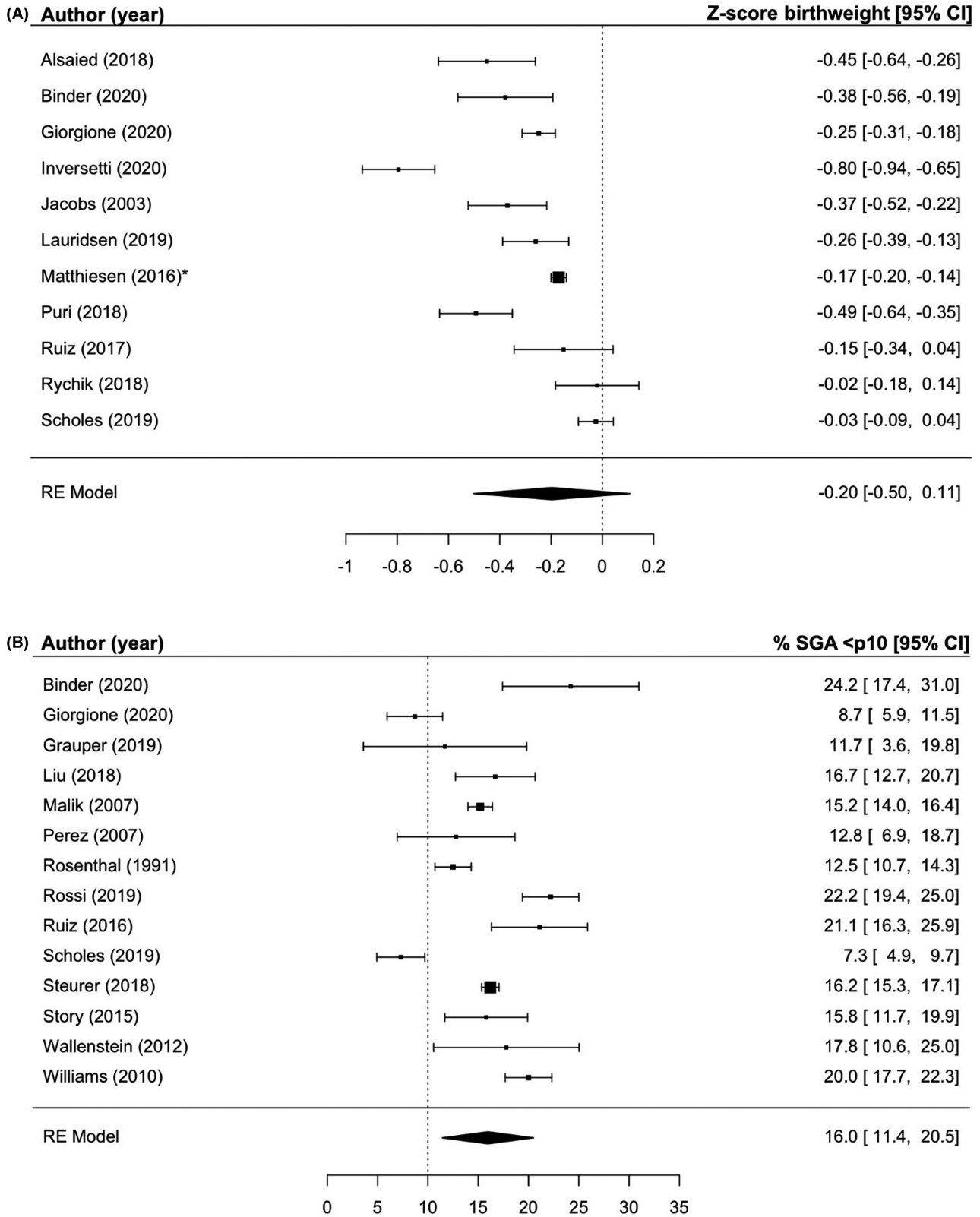


FIGURE 2 (A) Forest plot of the birthweight z-score of all congenital heart defects combined. *The z-score was adjusted for infant sex, origin, major extracardiac malformation, categories of infant syndromes, maternal prepregnancy BMI, hypertension, diabetes mellitus, parity, smoking, age, care of high-risk pregnancy and birth year. (B) Forest plot of percentage small-for-gestational age in all congenital heart defects combined with the 10th birthweight percentile as threshold for cut-off. CI, confidence interval; RE, random effects; SGA, small-for-gestational age

articles using the threshold of the 2.3th percentile reported a high prevalence of SGA, respectively 5.6% (95% CI 0.05–0.062)⁴¹ and 15% (95% CI 0.12–0.19).³⁹

3.1.3 | Subgroup analysis—major CHD

The subgroup meta-analysis of major CHD included 11 studies regarding the BW *z*-score of major CHD (Figure 3A; 5716 cases) and 12 studies reporting on percentage SGA <10th (Figure 3B; 13564 cases). We were able to extract the BW *z*-scores on major CHD of six studies that reported on all CHD combined. Two studies reporting on SGA were excluded, as data on major isolated CHD were not extractable.^{42,43} Figure 3 shows similar results as the forest plots of all CHD combined. The pooled mean BW *z*-score in the major CHD group is -0.23 (95% CI -0.58 to 0.11) and 16.2% (95% CI 11.0–21.3) of the newborns have a BW below the 10th percentile.

All meta-analysis models showed considerable heterogeneity, as I^2 was >90 (Appendix S4).

Therefore, the pooled effect of the BW *z*-score was not statistically significant, despite the consistent *z*-score below 0 reported in all studies. This can mainly be attributed to the study with the largest sample size, which showed a relatively moderate decrease of the BW *z*-score (Figures 2A and 3A)³⁴ compared with the other studies. The RE model used is appropriate in this situation.

3.2 | Adjusted analysis overview

Seven studies, with a study-specific control group, reported an adjusted outcome measure with correction for potential confounders (Table S2). Each study corrected for different variables, therefore the reported adjusted outcomes were not suitable for pooling. The most common identified confounder was maternal age, smoking, BMI/weight and maternal hypertensive disorders. After adjusted analysis, the SGA rate is significantly higher in the CHD group than in the controls, as none of the 95% CIs exceeded 1. Five included studies excluded potential confounders that could have an effect on fetal growth, as summarised in Table S3.

4 | DISCUSSION

4.1 | Main findings

The mean BW *z*-score of all CHD combined is -0.20 , which corresponds to the 42th percentile. This means that although the majority of the cases are not growth-restricted, the overall BW in neonates with isolated CHD is impaired, albeit within range of normality. Newborns with isolated CHD have a 1.6-fold higher risk of SGA <10th percentile. These findings were consistent throughout subgroup analysis of major CHD versus all CHD combined (BW *z*-score -0.23 and percentage SGA 16.2%).

4.2 | Strengths and limitations

This is the first meta-analysis on BW *z*-scores and the largest meta-analysis reporting on the percentage SGA in isolated CHD. As *z*-score is a standardised value, it enhances comparability after eradicating the effect of GA and deviations in growth can be detected.

An important limitation of this review is the heterogeneity in the selected study populations, as this differed greatly among the included studies, limiting the comparability and generalisability of the studies slightly. Of the 23 included studies, 12 different BW charts were used. Recently, the INTERGROWTH-21st study has demonstrated that variation in fetal growth across different populations is due to differences in environmental, nutritional and socio-economic factors rather than race and ethnicity.⁴⁴ Use of an international standardised chart would improve research on fetal growth and BW and facilitate comparability. Despite the high heterogeneity in inclusion criteria and used charts, all of the included studies pointed in the same direction, which means that neonates with CHD display a decreased BW.

The second major limitation is that subgroup stratification in specific CHD types was not feasible due to large differences in included CHD diagnoses, differences in categorisation of the type of CHD and small sample sizes. This information might have improved our understanding of the underlying mechanism of reduced BW in CHD considerably. Major CHD is overrepresented in this review, particularly in the analysis of % SGA, as $>80\%$ of the included cases concerned major defects, thus possibly over- or underestimating the pooled estimate. Five of the 24 included studies excluded cases or controls with certain risk factors that might influence fetal growth or placental function, for example hypertensive disorders, therefore possibly causing selection and confounding bias. Furthermore, as new genomic techniques (whole exome sequencing) were not offered routinely in the past because of lack of availability, a possible underestimation of genetic anomalies in the included studies may be present.

4.3 | Interpretation

Although a BW *z*-score of -0.20 seems of limited clinical importance, it provides insight in the growth of fetuses with CHD. It has been well established that impaired growth is associated with adverse outcomes in CHD. A number of studies address the association between BW *z*-score and postnatal outcomes. Two large studies reported a higher postoperative mortality in infants with a BW *z*-score between -1.0 and <0.5 ($n = 25,244$, adjusted OR 1.38; 95% CI 1.17–1.64 and $n = 6903$, adjusted OR 1.78; 95% CI 1.10–2.89).^{14,16} Furthermore, it has been reported that children with a BW *z*-score <1 have a higher hazard ratio for 5-year mortality.¹⁵

Several studies have raised the question of whether fetal circulatory changes due to the CHD are the cause of

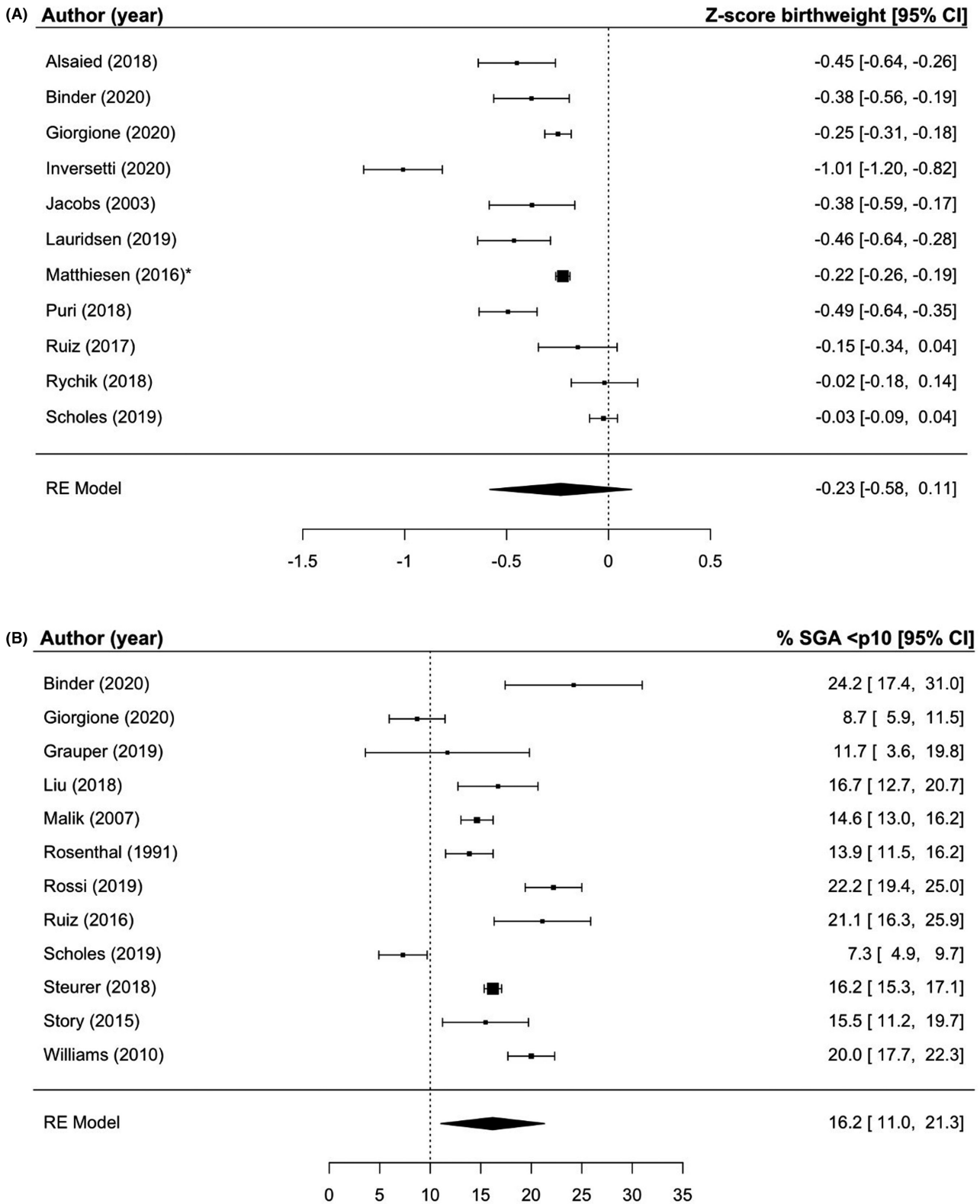


FIGURE 3 (A) Forest plot of the birthweight z-score of major congenital heart defects. *The z-score adjusted for infant sex, origin, major extracardiac malformation, categories of infant syndromes, maternal prepregnancy BMI, hypertension, diabetes mellitus, parity, smoking, age, care of high-risk pregnancy and birth year. (B) Forest plot of percentage small-for-gestational age in major congenital heart defects with the 10th birthweight percentile as threshold for cut-off. CI, confidence interval; RE, random effects; SGA, small-for-gestational age

impaired fetal growth. Alsaied et al.³⁵ evaluated the effect of combined cardiac output and fetal Dopplers on BW in fetuses with single ventricle anatomy or transposition of the great arteries, but demonstrated no effect. Another study classified 119 fetuses with CHD according to expected pattern of blood supply to the brain, and found no significant difference in BW percentile between the groups.¹⁸ A decreased BW *z*-score was encountered in all CHD groups by Puri et al.,⁴⁰ except for the TGA group. In contrast, Inversetti et al.³⁸ reported that neonates with cyanotic CHD had a significantly lower BW percentile compared with the non-cyanotic group (10th versus 26th percentile, $P = 0.007$). Studies on diminished head growth in CHD also do not support the hypothesis of altered haemodynamics as the primary cause of small head circumference.^{34,45,46} Although most studies in this review report on major CHD, we found no apparent differences in the pooled outcomes in the all-CHD combined compared with the subgroup of major CHD. As mild CHD comprises 26% of all cases in the BW *z*-score analysis, a notable difference is expected if diminished fetal growth is caused by the altered haemodynamics due to the CHD.

Another explanation is that the reduced BW in CHD is caused by impaired placentation. Reduced umbilical vein oxygenation has been reported in fetuses with CHD using MRI, suggesting altered placental function.⁴⁷ Shared regulatory pathways of the heart and placenta have been described as both organs develop concurrently, which is referred to as the placenta–heart axis.⁴⁸ An impressive example of how both organs interact is that ablation of peroxisome proliferator-activated receptors (PPAR), important for trophoblast differentiation, resulted in cardiac abnormalities in mice and that dysregulation of PPARs is associated with recurrent miscarriage, PE and IUGR.^{49,50} Another example is the finding of altered levels of placental growth factor (PlGF), soluble fms-like tyrosine kinase-1, soluble endoglin and markers of hypoxia observed in maternal blood, fetal cord blood and heart tissue in pregnancies complicated by fetal CHD, suggesting a concurrent abnormal placental angiogenesis and chronic hypoxia in cases with fetal CHD.^{51–53} Furthermore, a significant correlation between maternal PlGF levels and BW percentile was found in cases with fetal CHD.⁵² These signs of angiogenetic imbalance as well as histological placenta changes are similar to the findings in pregnancies affected by SGA and/or PE.^{23,24,51,54–62} A high incidence of placental pathology (41%) and placental-weight-to-BW ratio <10th percentile (77%) was reported by Rychik²³ and confirmed by others, indicating a more impaired placental weight than expected based on BW solely.^{59,60} Further evidence of the association between CHD and placental maldevelopment is the increased risk of PE in pregnancies complicated by CHD,^{19–21,63} up to a seven-fold increased risk of early PE.²¹

The exact pathophysiological interaction between fetal heart and placenta development has not, however, yet been established. It is still impossible to determine whether altered placental characteristics contribute to the multifactorial

origin of cardiac defects, or whether CHD affects placental development due to altered vascular pathways. Another possibility is a mutual disrupted pathway, which affects both cardiac and placental development. The latter possibility underlines that placental complications such as PE in studies on BW in CHD should not be excluded, which is often the case. If PE is excluded, one study considered this a confounder, but it could be a mediator or collider in the causal pathway instead. By excluding PE, the true effect of CHD on BW is underestimated.

5 | CONCLUSION

Our results suggest that the overall BW in neonates with isolated CHD is within range of normality but impaired. The use of BW *z*-scores provides insight into the growth of all fetuses with CHD. Understanding of fetal growth in CHD provides an opportunity to improve antenatal care in the future. We advocate that future research include all CHDs (including mild cardiac defects) and that placental-related disease, such as pre-eclampsia, should not be excluded in studies that explore the association between BW and CHD. Uniform international growth charts should be used in future research to enhance comparability.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTERESTS

None declared. Completed disclosure of interest forms are available to view online as supporting information..

AUTHOR CONTRIBUTIONS

MA and MCH contributed to the design of the study. MA conducted the search. MA and MCS independently selected eligible studies, extracted data and performed the meta-analysis. NvG provided statistical advice and double-checked the performed analysis. The manuscript was written by MA and MCH. MA, MCS, NvG and MCH were involved in revising the review and approving the final version for publication.

ETHICAL APPROVAL

Ethical approval was not required, as the data used have been published previously.

DATA AVAILABILITY STATEMENT

Data used for the current review are available from the corresponding author on reasonable request.

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