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Received: 23 August 2022 | Revised: 17 September 2022 | Accepted: 5 October 2022

DOI: 10.1111/apa.16562

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

REVIEW ARTICLE

Somatic growth in single ventricle patients: A systematic review and meta-analysis

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Funding information
Belgian American Educational Foundation

Abstract

Aim: To map somatic growth patterns throughout Fontan palliation and summarise evidence on its key modifiers.

Methods: Databases were searched for relevant articles published from January 2000 to December 2021. Height and weight *z* scores at each time point (birth, Glenn procedure, Fontan procedure and >5 years after Fontan completion) were pooled using a random effects meta-analysis. A random effects meta-regression model was fitted to model the trend in *z* scores over time.

Results: Nineteen studies fulfilled eligibility criteria, yielding a total of 2006 participants. The *z* scores for height and weight were markedly reduced from birth to the interstage period, but recovered by about 50% following the Glenn procedure. At >10 years after the Fontan procedure, the *z* scores for weight seemed to normalise despite persistent lower height, resulting in increased body mass index. The review revealed a number of modifiers of somatic growth, including aggressive nutritional management, timing of Glenn/Fontan, prompt resolution of complications and obesity prevention programmes in adolescence and adulthood.

Abbreviations: APC, atriopulmonary connection; BMI, body mass index; CHD, congenital heart disease; CI, confidence interval; ECC, extra-cardiac conduit; GH, growth hormone; HLHS, hypoplastic left heart syndrome; IGF1, insulin-like growth factor 1; LT, lateral tunnel; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; REML, restricted maximum likelihood.

Jef Van den Eynde and Simone Bartelse first authors contributed equally to the manuscript.

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Conclusion: This review mapped the somatic growth of single ventricle patients and summarised key modifiers that may be amendable to improvement. These data provide guidance on strategies to further optimise somatic growth in this population and may serve as a benchmark for clinical follow-up.

KEYWORDS
congenital heart disease, development, Fontan procedure, functionally univentricular hearts, growth

1 | INTRODUCTION

Congenital heart disease (CHD) is the most common type of congenital defect, with a global prevalence of 1 in 100 live births.[1] About a quarter of these children require intervention in the first year of life.[2] In defects with only a single functional ventricle, the current approach is a staged surgical palliation resulting in the creation of a Fontan circulation.[3] Stage 1 is a high-risk procedure performed in neonates and consists of the creation of aortopulmonary shunts, pulmonary artery banding or the Norwood procedure depending on the underlying condition. Connection of the superior caval vein to the pulmonary circulation to create a bidirectional cavopulmonary connection or Glenn connection usually occurs between 3 and 6 months of age. Fontan completion, by connecting the inferior caval vein to the pulmonary circulation, usually occurs between 2 and 4 years of age. In the Fontan circulation, blood flow is redirected such that the single ventricle sustains the systemic circulation, while systemic venous return flows passively through the pulmonary vascular bed without a sub-pulmonary pump. Ever since the introduction of the Fontan circulation in 1968,[4] several modifications have been made in the surgical techniques and medical management, resulting in improved rates of survival.[5] Nonetheless, single ventricle patients with a Fontan circulation still experience substantial short- and long-term complications.[6]

Changes in somatic growth are commonly used as an indicator of poor health and may be useful to follow the health status of single ventricle patients over time. In general, poor weight gain and growth restriction have been well documented in patients with CHD.[7–10] Impaired somatic growth is a known risk factor for poor surgical outcomes.[11] The aetiology is believed to be multifactorial, with varying contributions of abnormal haemodynamics, hypoxia, inadequate caloric intake, hypermetabolism, endocrine disorders, fluid restriction, fatigue during feeding, frequent respiratory infections, multiple surgical interventions at young age and subsequent complications.[12,13] While in most cases, the negative effects of the underlying CHD can be largely reversed after curative repair,[13] palliative approaches such as the Fontan circulation are thought to have a life-long impact on somatic growth.[14]

Previous studies have indicated that somatic growth is impaired in patients with single ventricle physiology, however, their results apply to different stages throughout Fontan palliation.[15–18] In this systematic review and meta-analysis, we aimed to map the somatic growth patterns at birth through the various stages of Fontan palliation and long term after Fontan completion. In addition, we aimed to provide a summary of the available evidence on key modifiers of somatic growth in single ventricle patients.

Key notes

- In single ventricle patients, the *z* scores for height and weight were markedly reduced from birth to interstage period, but recovered by about 50% following the Glenn procedure.
- At >10 years after the Fontan procedure, the *z* scores for weight seemed to normalise despite persistent lower height.
- Proactive assessment and aggressive nutritional support, appropriate surgical timing, prompt resolution of complications and multidisciplinary obesity prevention programmes are necessary to optimise somatic growth in these patients.

2 | METHODS

2.1 | Eligibility criteria, databases and search strategy

We followed the internationally recognised Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[19] Studies were included if (i) the population consisted of patients with a single ventricle physiology, (ii) patients underwent staged surgical palliation for the creation of a Fontan circulation, (iii) somatic growth, as assessed based on weight and/or height *z* scores, was investigated at different times during and after the Fontan trajectory and (iv) studies were prospective or retrospective observational studies or randomised controlled trials. Exclusion criteria: (i) non-original articles such as review articles, meta-analyses, guidelines, consensus statements, conference abstracts, editorials, letters and book reviews, (ii) in vitro or in vivo preclinical research or (iii) publications did not include data on weight and/or height *z* scores.

PubMed/MEDLINE and Embase were searched for articles meeting our inclusion criteria and published between 1 January 2000 and 31 December 2021. In addition, reference lists of relevant articles were screened. The search strategy contained two key concepts: single ventricle ('Single Ventricle' OR 'Univentricular Heart' OR 'Single Ventricle Palliation' OR 'Fontan' OR 'Fontan Procedure' OR 'Cavopulmonary Connection') and somatic growth ('Height' OR 'Weight' OR 'Body Height' OR 'Body Weight' OR 'Body Mass Index' OR 'Child Development' OR 'Birth Weight' OR 'Growth' OR 'Insulin-Like Growth Factor I' OR 'Somatic Growth' OR 'Growth Charts'). The following steps were taken: (1) identification of titles of records through databases searching, (2) removal of duplicates, (3) screening and selection of abstracts, (4) assessment for eligibility through full text articles and (5) final inclusion in the study. Studies were selected by two independent reviewers. Discrepancies were resolved by consensus.

2.2 | Data items

The following data were extracted from all eligible studies: centre, total number of single ventricle patients, type of Fontan [classic/original, atriopulmonary connection (APC), extra-cardiac conduit (ECC), lateral tunnel (LT)], ventricular dominance (right, left, mixed), mean age at Glenn and Fontan procedures, follow-up time after Fontan and *z* scores for weight and height. When *z* scores for weight and/or height were reposed by means of a graph or chart, the web-based tool 'WebPlotDigitizer' was used to extract these data; the extracted data were compared to the matching data in the results of the article to validate that the measurement method was accurate.[20] Two reviewers independently extracted the data. Discrepancies were resolved by consensus.

2.3 | Statistical analysis

First, all available data points for weight and height *z* score were plotted in two graphs to give a rough overview of growth patterns in the included articles. Subsequently, two meta-analysis methods were used to quantitatively summarize the evidence: (i) meta-analysis of means at single time points and (ii) meta-regression to model trends in *z* scores over time. With regard to the first method, the *z* scores at various time points (birth, Glenn procedure, Fontan procedure, 6 months to 2 years after the Fontan procedure, 2.5 to 5 years after the Fontan procedure and >5 years after the Fontan procedure) were pooled and presented as mean with 95% confidence interval (CI). A random effects meta-analysis (restricted maximum likelihood, REML) was used to pool the data.[21] I^2, describing the percentage of total variation across studies that is attributable to heterogeneity rather than chance, and τ, the between-study standard deviation, were calculated to assess the degree of statistical heterogeneity. Their accompanying *p* value was obtained using the chi-square test of the Cochran Q heterogeneity statistic. Forest plots were used to visualise the means in the individual studies with pooled estimates.

In the second method, a random effects meta-regression model was fitted to all measurements to model the trend in height and weight *z* scores over time. This model considered that the measurements in different studies were taken at different time points, and that there were multiple measurements per study. The model estimated the mean *z* score at birth, Glenn procedure and Fontan procedure and fitted a smoothed function for the period after Fontan procedure, using restricted cubic splines with knots at 1, 2, 5 and 10 years after Fontan procedure. The analyses were performed using the 'meta', 'metafor' and 'rms' R packages. All analyses were completed with R Statistical Software (version 4.1.1, Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Study selection and characteristics

A total of 95 citations were identified, of which 36 publications were potentially relevant and retrieved as full text. Nineteen reports[9,15–18,22–35] of an equal number of individual studies fulfilled our eligibility criteria (Figure 1). Characteristics of each study and their participants are shown in Table 1. A total of 2006 participants were included from observational studies published between 2000 and 2020. Thirteen (68.4%) of the studies originated from North America, while the remainder were conducted in Europe. Ventricular dominance was right in 45.6%, left in 42.7% and mixed in 11.7% (18 studies). The pooled mean age of the participants was 6.9 months (10 studies) at the Glenn procedure and 3.8 years (16 studies) at the Fontan procedure. The majority of the patients (90.6%) received a contemporary Fontan type (ECC or LT), while 8.1% received an APC and 1.4% received a classic/original Fontan procedure (19 studies). Among studies specifying the contemporary Fontan type, 52.1% had an ECC and 47.9% had a LT (7 studies). A total of 13 studies had follow-up after the Fontan procedure available, ranging from 2 to 17 years with a pooled mean of 12.1 years.

3.2 | Synthesis of results

3.2.1 | Height *z* scores

A total of 16 studies[9,15,16,18,22,23,26–35] including 1715 participants reported on height *z* scores. Observed results are shown in Figure 2A. Meta-analysis of means per time point revealed a mean height *z* score of −0.28 (95% CI −0.70 to 0.15; $I^2 = 98.4\%$, $\tau = 0.528$, $p < 0.001$; 6 studies) at birth, −1.22 (95% CI −1.64 to −0.79; $I^2 = 81.7\%$, $\tau = 0.390$, $p < 0.001$; 4 studies) at the Glenn procedure, −0.78 (95% CI −0.91 to −0.65; $I^2 = 47.4\%$, $\tau = 0.149$, $p < 0.001$; 11 studies) at the Fontan procedure, −0.61 (95% CI −0.93 to −0.30; $I^2 = 90.6\%$, $\tau = 0.425$, $p < 0.001$, $\tau = 0.339$, $p < 0.001$; 8 studies)

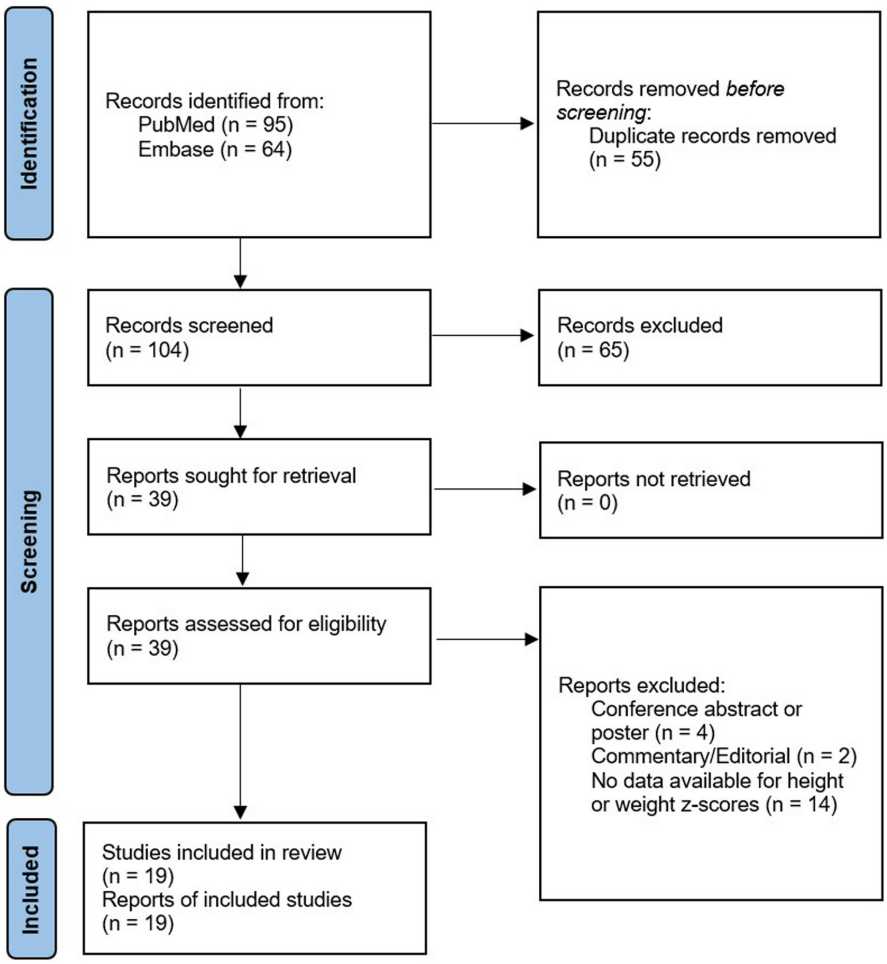

FIGURE 1 PRISMA flow diagram of studies included in data search.

at 6 months to 2 years after the Fontan procedure, −0.79 (95% CI −1.09 to −0.50; $I^2 = 88.0\%$, $\tau = 0.339$, $p < 0.001$; 6 studies) at 2.5 to 5 years after the Fontan procedure and −0.74 (95% CI −0.95 to −0.53; $I^2 = 88.8\%$, $\tau = 0.299$, $p < 0.001$; 9 studies) at >5 years after the Fontan procedure (Figures 3A–F). Meta-regression using all data confirmed a trend with (a) a sharp decrease in the height *z* score at the Glenn procedure, (b) about 50% recovery of the height *z* score at the time of the Fontan procedure and (c) stabilisation of the height *z* score during follow-up around a mean *z* score of −0.7 (Figure 2B, Table 2).

3.2.2 | Weight *z* scores

A total of 17 studies[9,15–18,22–25,27–29,31–35] including 1419 participants reported on weight *z* scores. The available data points are plotted in Figure 2C. Meta-analysis of single means revealed a weight *z* score of −0.41 (95% CI −0.63 to −0.19; $I^2 = 90.5\%$, $\tau = 0.353$, $p < 0.001$; 11 studies) at birth, −1.58 (95% CI −1.83 to −1.33; $I^2 = 83.3\%$, $\tau = 0.345$, $p < 0.001$; 9 studies) at the Glenn procedure, −0.93 (95% CI −1.09 to −0.76; $I^2 = 77.2\%$, $\tau = 0.260$, $p < 0.001$; 13 studies) at the Fontan procedure, −0.53 (95% CI −0.75 to −0.31; $I^2 = 82.5\%$, $\tau = 0.282$, $p < 0.001$; 8 studies) at 6 months to 2 years after the Fontan procedure, −0.49 (95% CI −0.74 to −0.24; $I^2 = 85.3\%$, $\tau = 0.287$, $p < 0.001$; 6 studies) at 2.5 to 5 years after the Fontan procedure and −0.37 (95% CI −0.68 to −0.07; $I^2 = 88.8\%$, $\tau = 0.393$, $p < 0.001$; 9 studies) at >5 years after the Fontan procedure (Figures 4A–F). Meta-regression using all data confirmed a trend with (a) a sharp decrease in the weight *z* score at the Glenn procedure, (b) about 50% recovery of the weight *z* score at the time of the Fontan procedure and (c) gradual further recovery of the weight *z* score during follow-up (Figure 2D, Table 2).

4 | DISCUSSION

4.1 | Summary of evidence

In this meta-analysis, we have mapped *z* scores for height and weight at birth, Glenn, Fontan and during long-term follow-up (Figure 5). Our main findings were as follows: (a) there is a drastic reduction in *z* scores for height and weight prior to the Glenn procedure; (b) following the Glenn procedure, *z* scores for height and weight recover by about 50%; (c) by >10 years after the Fontan, *z* scores for weight seemed to normalise despite persistent lower height (height *z* score −0.7, corresponding to a mean loss of final adult height of approximately 5 cm). These findings underpin critical aspects of somatic growth during staged palliation and long-term follow-up. Furthermore, they have potential implications for nutritional

TABLE 1 Study and participant characteristics

Study	Location	Sample size, *n*	Fontan type				Ventricular dominance			Mean age at Glenn, months	Mean age at Fontan, years	Mean follow-up after Fontan, years
			Classic, *n* (%)	APC, *n* (%)	ECC, *n* (%)	LT, *n* (%)	Right, *n* (%)	Left, *n* (%)	Mixed, *n* (%)			
Cohen et al. (2000)	Philadelphia	65	0	0	2	63	45	18	2	6.8	1.7	7
Day et al. (2000)	Utah	65	0	0	65		7	48	10	NR	6	7
Stenbog et al. (2000)	Denmark	20	0	8	0	12	2	18	0	NR	8.2	2
Ovroutski et al. (2004)	Berlin	30	0	0	30	0	NR	NR	NR	NR	3	4.8
Kelleher et al. (2006)	Boston	50	0	0	50		50	0	0	6.9	NR	0
Ono et al. (2007)	Hannover	90	0	19	0	71	30	19	41	NR	1.1	15
Vogt et al. (2007)	Toronto	126	1	0	89	36	46	80	0	8.4	2.7	7
Hasan et al. (2008)	Indianapolis	80	9	0	8	63	20	34	26	NR	3.5	10
Srinivasan et al. (2010)	Arkansas	46	0	28	0	18	0	46	0	5.5	1.9	0
Anderson et al. (2011)	Cincinnati	55	0	0	53	2	28	25	2	5.1	4.9	0
Francois et al. (2011)	Belgium	64	0	0	64		22	34	8	11.2	3.2	8
Williams et al. (2011)	Utah	230	0	0	230		164	40	26	6.5	NR	0
Anderson et al. (2012)	Cincinnati	132	0	0	132		132	0	0	5	5	0
Hessel et al. (2013)	Copenhagen	94	0	0	94		38	56	0	7.9	3.1	11
Avitabile et al. (2015)	Philadelphia	41	0	0	26	15	17	14	10	NR	2.9	8
Wellnitz et al. (2015)	San Francisco	84	0	0	84		48	28	8	NR	4.7	5
Freud et al. (2016)	Chicago	139	18	109	0	12	20	119	0	NR	5.6	17
Chan et al. (2017)	London	49	0	0	49		49	0	0	6.1	3.4	0
Lambert et al. (2020)	Multicentre	546	0	0	546		184	265	97	NR	NR	16

Abbreviations: APC, atriopulmonary connection; ECC, extra-cardiac conduit; LT, lateral tunnel; NR, not reported.

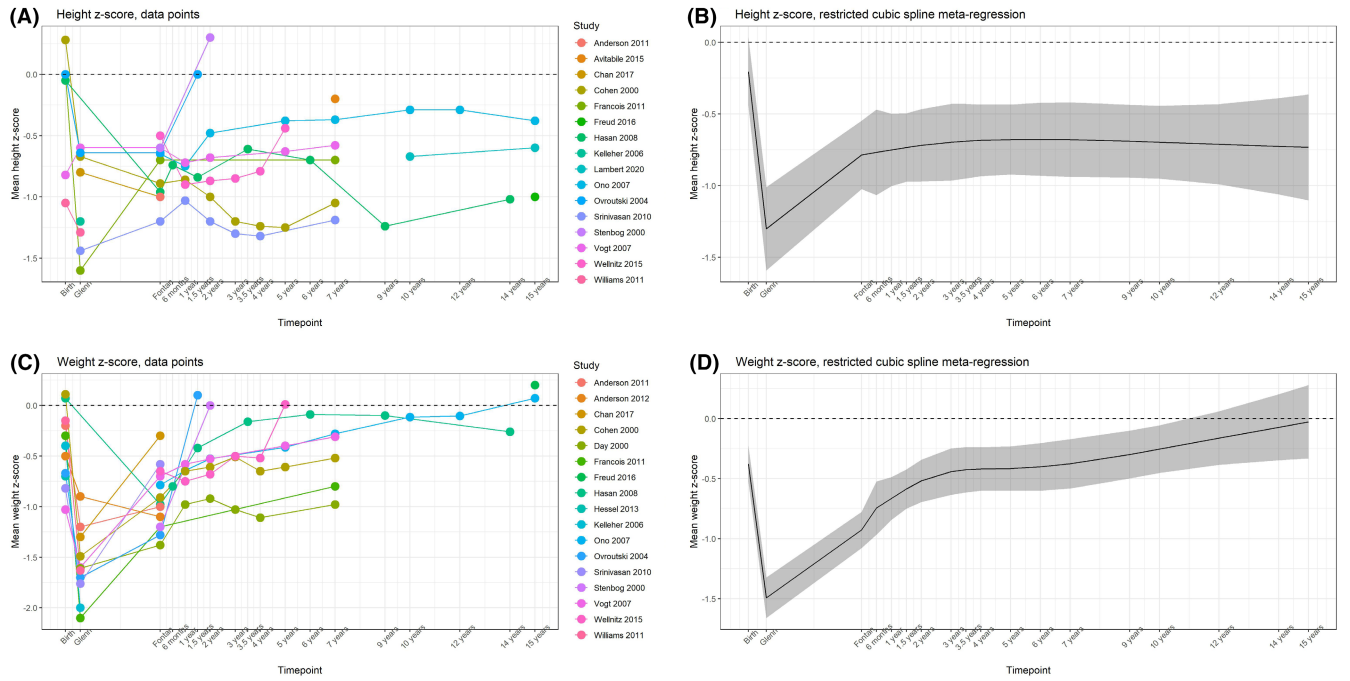

FIGURE 2 Summary of longitudinal data for height and weight *z* scores.Data at each time point per study for (A) height and (C) weight *z* scores. Estimated mean (B) height and (D) weight *z* scores with 95% confidence interval obtained from a random effects meta-regression model.

support, timing of staged palliation, management of co-morbidities and follow-up (Table 3).

4.2 | Somatic growth retardation: from birth to Glenn

Growth retardation in patients with single ventricle lesions may start in utero. Cnota et al.[36] observed that foetuses with hypoplastic left heart syndrome (HLHS) had decreased growth velocity during later pregnancy. This is supported by the finding of lower birth weight (mean *z* score −0.28) observed in our meta-analysis. The most intense somatic growth retardation, with a >1 standard deviation reduction in *z* scores for both height and weight, was observed post-natally from birth to the Glenn procedure. Several explanations have been put forward, the principal one being the very physiology of the single ventricle.[9,17,31,34,35] Having to handle both the pulmonary and systemic circulations in parallel results in higher metabolic expenditure and disruption of the growth hormone – insulin-like growth factor 1 (GH-IGF1) axis.[26,37] Moreover, imbalances in pulmonary and systemic vascular resistance can easily lead to pulmonary overcirculation, volume overload, poor systemic (and particularly splanchnic) perfusion and early congestive heart failure, all of which negatively impact somatic growth.[34] Hypermetabolism from chronic cyanosis may be further compounded by intercurrent episodes of critical illness, surgical stress, gastrointestinal problems and underlying genetic syndromes.[38] Finally, nutritional intake is disrupted, with up to 75% of infants with single ventricle not reaching 50% of the recommended daily amount of calories[39] and feeding disorders occurring in about 22%.[40]

Since poor somatic growth has a major impact on post-operative outcomes, interstage survival[41] and neurodevelopmental outcomes,[42] optimising nutritional status was highlighted as a key target in the Joint Council on Congenital Heart Disease Quality Improvement Task Force's quality improvement collaborative.[43] Studies by Williams et al.[23] and Anderson et al.[24] demonstrated large between-centre variability in *z* scores in conjunction with large variability in feeding strategies. Anderson et al.[24] found that centres with the most favourable interstage weight-for-age *z*-score change used standard feeding evaluation prior to stage 1 discharge and home monitoring. This bundle approach was associated with a median improvement of 1 standard deviation in *z* scores for weight, suggesting reducing practice variations may be a first step in improving outcomes. Strategies involving aggressive parenteral and high-calorie enteral feeding around the stage 1 procedure had a beneficial impact on interstage growth.[34] Others have linked home-based surveillance to improved growth[38] and better survival.[44] Recently, nutritional algorithms specifically designed for HLHS have been proposed.[45]

4.3 | Somatic growth recovery: the Glenn and Fontan procedures

We found the greatest degree of catch-up growth to occur between the Glenn procedure and the Fontan procedure. Formation of the superior cavopulmonary (Glenn) connection with accompanying

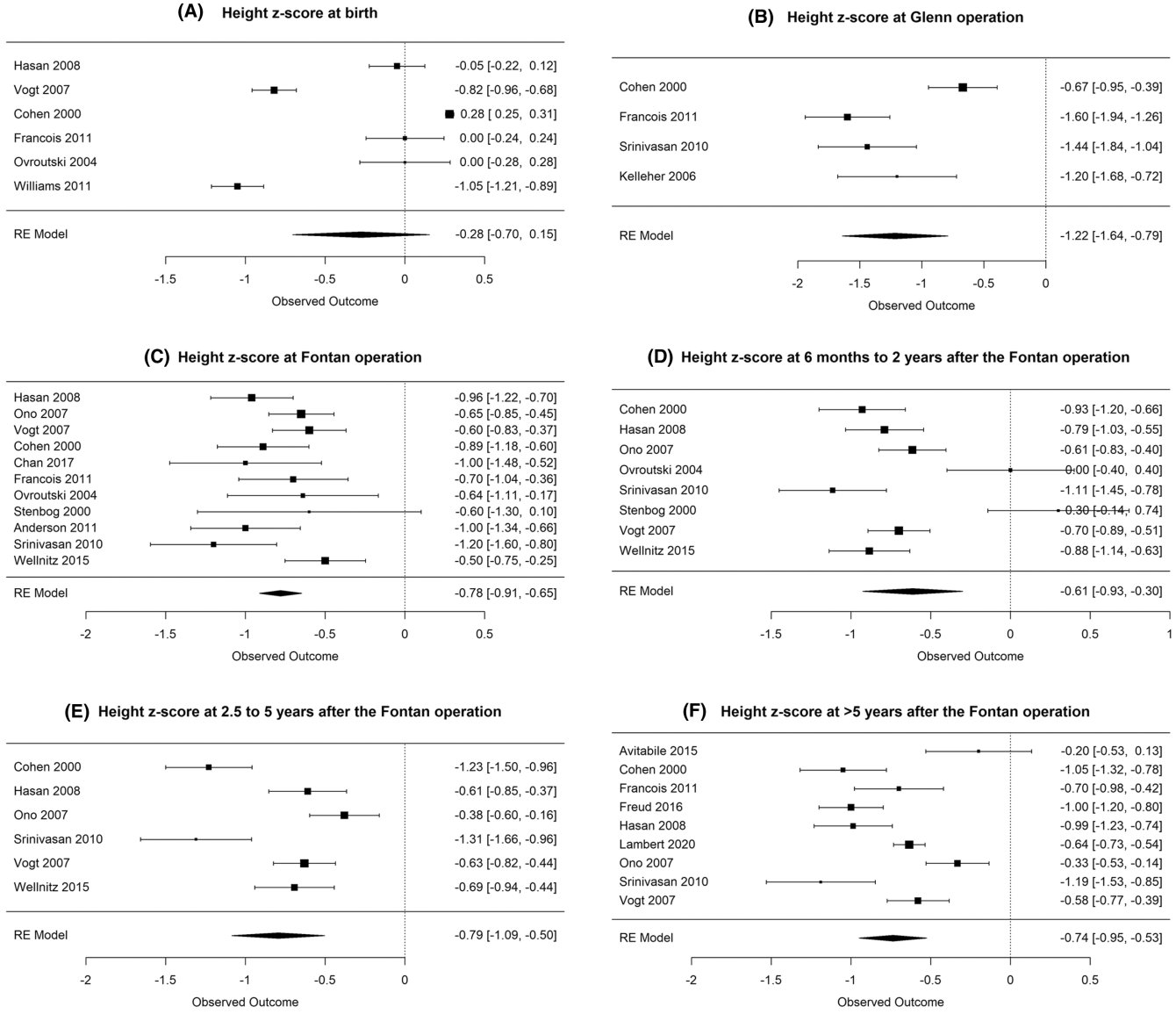

FIGURE 3 Forest plots summarising the meta-analysis of simple means for height *z* scores at birth (A) at Glenn operation (B) at Fontan operation (C) at 6 months to 2 years after the Fontan operation (D) at 2.5 to 5 years after the Fontan operation (E) and at >5 years after the Fontan operation (F). The mean *z* scores with their 95% confidence intervals in the individual studies and the weighted result from the random effects (RE) model are presented on the right.

volume unloading and transition from parallel to single-ventricle in-series circulation has been proposed as a major contributor to the restoration of energy efficiency and normalisation of nutritional status.[15,16,18,32,35] Several studies[16,23,35] have highlighted the favourable effect of the Glenn procedure on somatic growth above other haemodynamics factors such as underlying anatomy, ventricular dysfunction, severity of atrioventricular valve regurgitation and various residual lesions – all of which were either not or poorly associated with the change in *z* score for weight around this period.

Additional mechanisms for catch-up growth besides volume unloading should also be considered as the change in the resting energy expenditure achieved with volume unloading alone is insufficient to explain this finding.[46] The Glenn procedure heralds a major change in the life of single ventricle patients: while the interstage is accompanied by a multitude of hospitalisations, investigations and interventions that put the growth process 'on hold',[47] the period between the Glenn and Fontan procedures is usually marked by less intensive management. Once these children are discharged home, they can adapt to regular feeding and metabolism and their somatic growth is allowed to catch-up. At the same time, feeding is usually much less troublesome at this age (6 months) than in early infancy. As such, contextual factors coinciding with the Glenn procedure might have an (even more) important impact on somatic growth.

Most studies agree that an earlier Glenn procedure results in the largest improvement in haemodynamic status and somatic growth.[9,15–18,23] Nonetheless, potential disadvantages of performing the Glenn procedure too early should be considered, such as sub-optimal growth of the pulmonary arteries.[48] A multivariable

TABLE 2 Results from restricted cubic spline meta-regression

	Height *z* score		Weight *z* score	
Time point	Estimated mean	95% CI	Estimated mean	95% CI
Birth	−0.20	−0.44; 0.03	−0.38	−0.53;−0.23
Glenn procedure	−1.30	−1.59; −1.01	−1.49	−1.66; −1.32
Fontan procedure	−0.79	−1.02; −0.55	−0.93	−1.08; −0.78
Follow-up after Fontan				
6 months	−0.77	−1.06; −0.47	−0.75	−0.97; −0.52
1 year	−0.75	−1.00; −0.50	−0.66	−0.84; −0.49
1.5 years	−0.73	−0.97; −0.50	−0.59	−0.75; −0.42
2 years	−0.72	−0.97; −0.47	−0.52	−0.70; −0.34
3 years	−0.70	−0.96; −0.43	−0.44	−0.63; −0.25
3.5 years	−0.69	−0.95; −0.43	−0.43	−0.61; −0.24
4 years	−0.68	−0.93; −0.43	−0.42	−0.60; −0.24
5 years	−0.68	−0.92; −0.43	−0.42	−0.60; −0.23
6 years	−0.68	−0.93; −0.42	−0.40	−0.60; −0.20
7 years	−0.68	−0.94; −0.42	−0.38	−0.58; −0.17
9 years	−0.69	−0.94; −0.44	−0.30	−0.50; −0.10
10 years	−0.70	−0.95; −0.44	−0.25	−0.45; −0.06
12 years	−0.71	−0.99; −0.43	−0.16	−0.39; 0.06
14 years	−0.73	−1.06; −0.39	−0.07	−0.35; 0.20
15 years	−0.73	−1.10; −0.36	−0.03	−0.33; 0.28

Note: Estimated means and 95% confidence invervals (CI) for height and weight *z* scores at different time points are presented.

competing risk analysis by Friedman et al.[49] identified age ≤3 months at the Glenn procedure as an independent risk factor for death or heart transplant as well as decreased rate of Fontan completion, suggesting 3 months might reasonably be considered the lower limit for most patients. Furthermore, it remains crucial that nutritional status is optimised by the time that the Glenn procedure is performed, given its impact on post-operative outcomes.[41] In aggregate, the evidence suggests that substantial and early restoration of somatic growth can be achieved after the Glenn procedure, provided that the procedure is performed between 3 and 6 months of age and is preceded by standardised nutritional programmes and home-based surveillance.

Additional catch-up in somatic growth is seen after the Fontan procedure. Stenbog et al.[32] observed that catch-up growth was rarely seen in patients undergoing the Fontan procedure after the age of 5 years. Others have similarly demonstrated that the post-Fontan acceleration of somatic growth in those operated under 4–5 years of age is greater compared to those palliated later.[9,16,18,31–33] Possibly, a critical window of mesenchymal growth potential exists within which the Fontan procedure should ideally be performed. These findings may be influenced by the fact that patients who undergo the Fontan procedure at a later age are often worse candidates. Regardless, it should be noted that multiple factors should be taken into account at all times when deciding about optimal timing. Such include not only age limit (ideally 2–4 years of age), but also body weight (ideally 10–14 kg), adequate development of the inferior vena cava, concerns on the haemodynamic adequacy of an undersized Fontan conduit[50] and several other well-established selection criteria for optimal Fontan procedure.[3]

4.4 | Impact of complications and increasing adiposity in the setting of persistent lower height: follow-up after Fontan

During follow-up after the Fontan procedure, gradual catch-up of *z* scores for weight occurred despite persistent lower height. This pattern, whereby height is affected more by the underlying pathophysiology than weight, is unique and stands in contrasts with other CHD types.[9,31,51] It is unlikely that the incomplete catch-up in height is merely due to familial lower height, because these patients are also smaller compared to their normal stature parents and siblings.[31] Delayed bone age resulting from chronic hypoxemia and/or reduced physical activity at young age has been observed in Fontan patients and may explain their lower height.[52,53] In addition, it is possible that a *z* score for height around −0.70 is the upper limit of what the average Fontan circulation can support in terms of adequate tissue perfusion before growth-limiting acidosis at the growth plate level occurs. Furthermore, complications such as protein-losing enteropathy, venous collaterals and conduit obstruction have all been

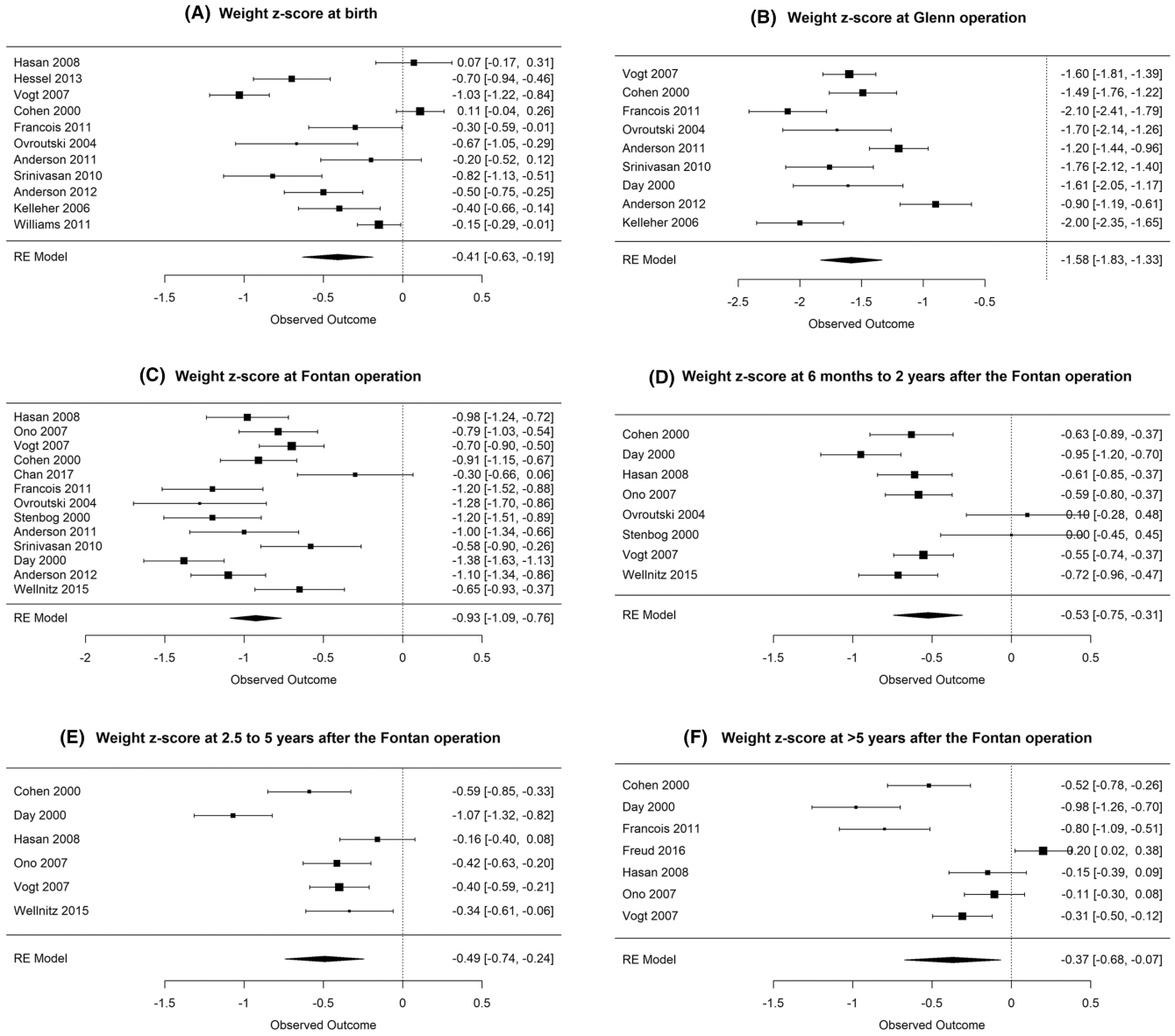

FIGURE 4 Forest plots summarising the meta-analysis of simple means for weight *z* scores at birth (A) at Glenn operation (B) at Fontan operation (C) at 6 months to 2 years after the Fontan operation (D) at 2.5 to 5 years after the Fontan operation (E) and at >5 years after the Fontan operation (F). The mean *z* scores with their 95% confidence intervals in the individual studies and the weighted result from the random effects (RE) model are presented on the right.

associated with markedly abnormal *z* scores for height during follow-up after the Fontan procedure,[16,17,31] and their prompt resolution has been shown to restore optimal somatic growth potential.[16,33] Part of the growth may be explained by decreased hepatic IGF-1 production due to elevated hepatic venous pressures or hepatic GH resistance in the setting of malnutrition. Regardless of the exact aetiology, lower height has prognostic relevance; poor height gain after Fontan is associated with decreased exercise capacity, worse quality of life and greater risk of mortality.[30]

The consequence of weight increasing more than height is that body mass index (BMI) increases as patients with a Fontan circulation age. According to our meta-analysis, an 'average' 5-year-old male Fontan patient would have a height *z* score of −0.75 and a weight *z* score of −0.66, which corresponds to a weight of 16.8 kg, a stature of 1.05 m and a calculated BMI of 15.2 kg/m^2, reflecting underweight.[54] By the age of 18, the same patient would have a height *z* score of −0.73 and a weight *z* score of −0.07, corresponding to a weight of 67 kg, a stature of 1.58 m and a calculated BMI of 26.8 kg/m^2, indicating overweight. Two longitudinal studies included in our meta-analysis showed a trend of increasing BMI in adolescence and early adulthood.[16,24] Among 546 participants in the Paediatric Heart Network Fontan study, Lambert et al.[30] reported overweight/obesity in about 36% by the age of 19.

The emergence of obesity in Fontan patients is likely multifactorial. Throughout the palliation trajectory, parents and children are counselled on ways to promote adequate weight gain,

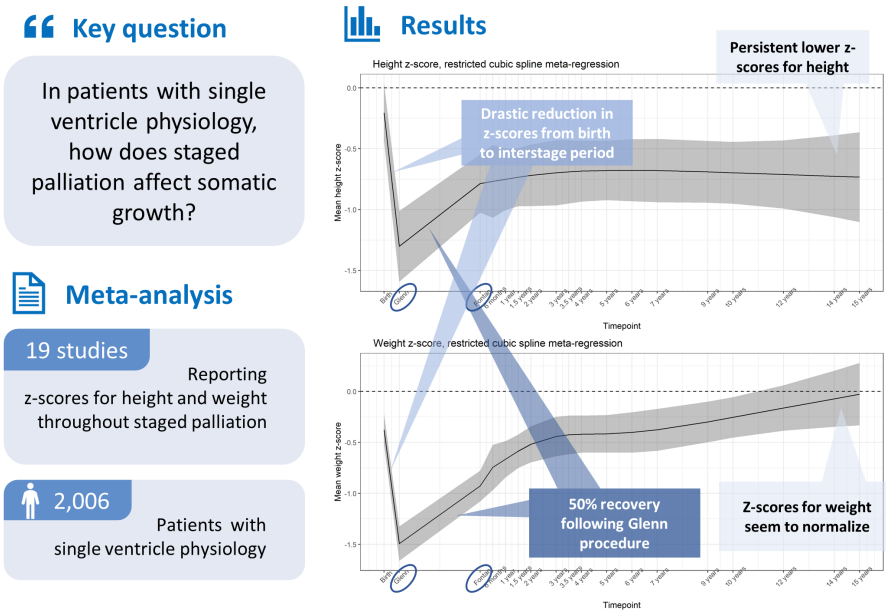

FIGURE 5 Graphical summary of the main study findings. In this meta-analysis, we sought to investigate how staged palliation of patients with single ventricle physiology affects somatic growth. The *z* scores for height and weight are markedly reduced from birth to the interstage period, but recovered by about 50% following the Glenn procedure. At >10 years after the Fontan procedure, the *z* scores for weight seemed to normalise despite persistent lower height. This meta-analysis may be used as a benchmark for clinical management. Proactive assessment and aggressive nutritional support, appropriate surgical timing, prompt resolution of complications and multidisciplinary obesity prevention programmes in adolescence/adulthood are necessary to optimise somatic growth in these patients.

emphasising the need for increased nutritional intakes.[44] However, once metabolic expenditures have normalised following the Glenn and Fontan procedures, these habits often persist and failure to take into account the relative reduction in caloric requirements in the child's diet may result in excessive weight gain. In addition, measured physical activity levels in children and adolescents with a Fontan circulation are low independent of their exercise capacity due to sedentary lifestyle and patient/parent/physician-imposed activity limits.[55]

Even though the prevalence of obesity might be lower than in the general population,[30] its impact on patients with single ventricle physiology is disproportionately worse. Not only is obesity a risk factor for various acquired cardiovascular co-morbidities such as myocardial infarction, stroke, hypertension, diabetes mellitus and chronic kidney disease.[56] It is also associated with reduced lung compliance and increased pulmonary vascular resistance, both undesirable to the Fontan circulation.[57] Increased ventricular mass and systemic vascular resistance (resulting in diastolic dysfunction) and autonomic imbalance (resulting in arrhythmias) are obesity-related features that can destabilise the single ventricle circulation. Notably, increases in BMI after the Fontan procedure are associated with complications, reduced exercise capacity and poor quality of life.[30] These findings suggest that a comprehensive approach involving education about cardiovascular risk factors, serial risk assessment and therapeutic lifestyle management are key to prevent overweight/obesity and ensure optimal outcomes in these patients. Structured exercise programmes have shown promising results in adults with a Fontan circulation.[58]

4.5 | Strengths and limitations

This meta-analysis synthetized the data from a range of studies, surmounting the barriers of low sample sizes, heterogeneity and limited follow-up, and thereby creating a comprehensive benchmark for expected somatic growth throughout the Fontan trajectory. However, a few limitations should be considered. First, the meta-analytic approach using aggregated data per study did not allow stratified analyses according to specific scenarios (aggressive nutritional management, right vs. left ventricular dominance, early vs. late Glenn, early vs. late Fontan, complications, etc.). As an alternative, pertinent data from individual studies on modifiers of somatic growth in single ventricle patients were synthetized in the Discussion section and Table 3. Even so, our systematic review identified limited direct data about the impact on nutritional intake, daily activity patterns, socioeconomic status and access to nutrition on somatic growth. Alternative measures of somatic growth and body composition such as subcutaneous fat, triceps skinfold measurements, muscle mass, head circumference, bioelectrical impedance and whole-body dual X-ray absorptiometry were beyond the scope of this review, but have been investigated in the single ventricle population by others.[59–66] These studies have shown sarcopenia and deficits in bone density and structure to be major components of body composition in Fontan patients. Second, selection bias is plausible because most participants were by definition considered good candidates for the Fontan procedure; these data therefore assume that a thorough clinical assessment has preceded the decision to pursue the Fontan trajectory

TABLE 3 Factors contributing to poor somatic growth in single ventricle patients

Domain	Problem	Solution
Nutritional intake	• Up to 75% patients with single ventricle do not reach 50% of the recommended daily amount of calories.[39] • Shorter duration of parenteral nutrition therapy and fewer calories of enteral nutrition are associated with lower *z* scores for weight.[34] • Feeding disorders occur in 22% after stage 1 procedure[40] and are associated with lower *z* scores for weight.[9]	• Aggressive parenteral and high-calorie enteral nutritional therapy in the period prior to the Glenn procedure is associated with improved nutritional status.[34] • Standard feeding evaluation prior to stage 1 discharge and close monitoring for weight gain/loss red flags in the interstage period are associated with better growth.[24] • Home-based surveillance leads to improved growth[38] and improved survival.[44]
Metabolic expenditure	• Metabolic expenditure may be 28–35% higher in uncorrected/unpalliated CHD.[37] • Chronic hypoxemia and reduced physical activity may lead to delayed bone age.[52,53]	• The post-Fontan acceleration of somatic growth is greater in those operated on under 4–5 years of age is greater compared to those with delayed palliation, while vascular growth is not negatively affected.[9,16,18,31–33]
Nutrient losses	• PLE, occurring in 5–15% of Fontan patients, is associated with impaired haemodynamics and results in frequent stools, oedema, ascites, hypoalbuminemia and immunodeficiency. It has been associated with markedly abnormal *z* scores for height and weight during follow-up after the Fontan procedure.[16,17,31]	• Treatment of PLE with haemodynamic optimization, medium chain triglycerides, heparin, budesonide and/or octreotide results in restoration of somatic growth and improved survival.[68] • However, oral steroids such as budesonide may be absorbed systemically and may temporarily suppress growth.[69]
Haemodynamic factors	• Factors reflecting worse underlying cardiac condition, such as longer hospital and ICU length of stay, higher diuretic dosage, worse RV function, atrioventricular valve regurgitation, more frequent readmissions, higher oxygen saturation (reflecting pulmonary overcirculation, RV volume overload and decreased splanchnic perfusion), higher right atrial pressure and systemic venous collaterals are associated with lower *z* scores for weight around the stage 1 palliation and Glenn procedure.[9,17,31,34,35] • Central shunt and pulmonary artery reconstruction (reflecting hypoplasia or distortion of the pulmonary arteries) and RV dominance are associated with lower *z* scores for weight after the Fontan procedure.[16,25] • Need for heart failure treatment after Fontan completion is associated with decreased late somatic development.[18] • Although not seen in the majority of patients, oversizing, bending or compression of the Fontan conduit may lead to thrombosis and protein loss, and thus to growth retardation.[33]	• The volume-unloading procedure (Glenn procedure) results in the greatest improvement in haemodynamic status and permits improved somatic growth, especially when performed at an early age.[9,15–18,23] • The RVPA shunt is associated with higher diastolic pressures, better splanchnic perfusion and a more attenuated decrease in *z* scores for weight prior to the Glenn procedure.[67] • Early detection and resolution of residual haemodynamic lesions, such as obstructions to flow and venous collateral vessels, are essential to maintain optimal somatic growth potential.[16,33]
Endocrinological factors	• IGF1 levels are decreased in uncorrected/unpalliated CHD, particularly those with a large volume burden,[52] but seem to catch-up after the Fontan procedure.[32] • IGF1 levels are associated with longer interval since Fontan (reflecting greater heart failure burden), higher log-BNP and lower systemic flow.[26]	• Growth hormone given at an early age has been shown to increase the cardiac index and overall exercise performance, though has not been investigated in the Fontan population.[70]
Environmental factors	• In children living at moderately high altitude (0.9–2.3 km; mild alveolar hypoxia and mildly increased PVR), *z* scores for height and weight were worse after the Fontan procedure compared to the Glenn procedure.[17]	• Children living at moderately high altitude might benefit from later timing of the Fontan procedure.[17]
Exercise	• Measured physical activity levels in children and adolescents with a Fontan circulation are low, independent of their exercise capacity, due to sedentary lifestyle and patient/parent/physician-imposed activity limits.[55]	• Structured exercise programmes have shown promising results in adults with a Fontan circulation.[58]

Abbreviations: CHD, congenital heart disease; ICU, intensive care unit; IGF1, insulin-like growth factor 1; PLE, protein-losing enteropathy; PVR, pulmonary vascular resistance; RV, right ventricle/ventricular; RVPA, right ventricle-to-pulmonary artery.

and may not be representative of the overall single ventricle population. Similarly, our analysis was likely influenced by survivor bias, as those with the worst somatic growth were more likely to die or require a heart transplant[30,35]; data at later time points are therefore mostly composed of patients who were well enough to survive staged palliation. While 15-year survival rates following the Fontan procedure have increased to >95%,[5] substantial attrition still occurs related to the stage 1 operation (mortality rate 15%–20%) and the interstage period (6%–18%),[67] suggesting the potential role of the survivor bias cannot be overstated. Fourth, the timing of the Glenn and Fontan procedures in each of the studies might have been guided by somatic growth – for example the observation of poor growth might have triggered a decision to perform the Glenn procedure earlier.[34] Finally, management strategies have evolved over time and might have shown between-centre variability, for which we were unable to account.

5 | CONCLUSIONS

In summary, this meta-analysis mapped trends in *z* scores for height and weight of single ventricle patients throughout the Fontan trajectory and long-term follow-up, and may be used as a benchmark for clinical management. In addition, we have summarised key modifiers of somatic growth that are amendable to improvement. Proactive assessment and aggressive nutritional support, appropriate surgical timing, prompt resolution of complications and multidisciplinary obesity prevention programmes in adolescence and adulthood seem necessary to ensure optimal somatic growth, functional capacity and outcomes in single ventricle patients.

ACKNOWLEDGEMENT

Jef Van den Eynde was supported by the Belgian American Educational Foundation.

FUNDING INFORMATION

None declared.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article. The code used for the analyses will be shared on reasonable request to the corresponding author.

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How to cite this article: Van den Eynde J, Bartelse S, Rijnberg FM, Kutty S, Jongbloed MRM, de Bruin C, et al. Somatic growth in single ventricle patients: A systematic review and meta-analysis. Acta Paediatr. 2023;112:186–199. https://doi.org/10.1111/apa.16562