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SYSTEMATIC REVIEW AND META-ANALYSIS

Health-Related Quality of Life in Children, Adolescents, and Adults With a Fontan Circulation: A Meta-Analysis

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BACKGROUND: People with a Fontan circulation experience a range of physical, psychosocial and neurodevelopmental challenges alongside, or caused by, their cardiac condition, with significant consequences for health-related quality of life (HRQOL). We meta-analyzed HRQOL outcomes reported by people with a Fontan circulation or their proxies and evaluated predictors of poorer HRQOL.

METHODS AND RESULTS: Six electronic databases were searched for peer-reviewed, English-language articles published before March 2019. Standardized mean differences (SMD) were calculated using fixed and random-effects models. Fifty articles reporting on 29 unique studies capturing HRQOL outcomes for 2793 people with a Fontan circulation and 1437 parent-proxies were analyzed. HRQOL was lower in individuals with a Fontan circulation compared with healthy referents or normative samples (SMD, −0.92; 95% CI, −1.36 to −0.48; $P<0.001$). Lower scores were reported across all HRQOL domains, with the largest differences found for physical (SMD, −0.90; 95% CI, −1.13 to −0.67; $P<0.001$) and school/work functioning (SMD, −0.71; 95% CI, −0.90 to −0.52; $P<0.001$). Meta-regression analyses found no significant predictors of self-reported physical functioning, but older age at Fontan operation was associated with poorer emotional functioning ($\beta=-0.124$; $P=0.004$), and diagnosis of hypoplastic left heart was associated with poorer social functioning ($\beta=-0.007$; $P=0.048$). Sensitivity analyses showed use of the PedsQL Core Module was associated with lower HRQOL scores compared with the Short-Form Health Survey-36.

CONCLUSIONS: HRQOL outcomes for people with a Fontan circulation are lower than the general population. Optimal care acknowledges the lifelong impact of the Fontan circulation on HRQOL and offers targeted strategies to improve outcomes for this growing population.

Key Words: chronic illness ■ congenital heart disease ■ Fontan circulation ■ health-related quality of life ■ mental health ■ psychological stress

The Fontan procedure is the final in a series of surgeries performed to palliate single-ventricle congenital heart disease (CHD), a class of highly complex CHD in which it is impossible to create a 2-ventricle circulation. Over 80% of children with single-ventricle CHD who progress to a Fontan circulation survive into adulthood, translating into a rapidly growing population of people living with a high burden of disease.[1]

Patients who have undergone the Fontan operation experience a range of comorbidities related to their cardiac condition and associated medical interventions. The impact of resulting stressors on the developing child can be profound, and individuals with a

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CLINICAL PERSPECTIVE

What Is New?

- This review and meta-analysis of health-related quality of life (HRQOL) in people with a Fontan circulation, synthesizes the findings of 50 articles reporting on 2,793 patients and 1,437 parent-proxies.
- People of all ages with a Fontan circulation report lower total HRQOL compared with referents, and poorer outcomes across all HRQOL domains, with a particularly large effect for physical functioning.
- Parents report lower HRQOL for their child with a Fontan circulation compared to parental reports for children from the general community.
- Meta-regression analyses revealed emotional and social functioning are more likely than physical functioning to be moderated by demographic and medical factors.

What Are the Clinical Implications?

- The Fontan circulation has a lifelong impact on HRQOL and wellbeing, and targeted strategies to improve long-term outcomes for this growing population are needed.

Nonstandard Abbreviations and Acronyms

BNP	brain natriuretic peptide
CHD	congenital heart disease
CHQ	Child Health Questionnaire
HLHS	hypoplastic left heart syndrome
HRQOL	health-related quality of life
PedsQL	Pediatric Quality of Life Core Module
PR	parent-report
SF-36	Short-Form Health Survey-36
SR	self-report
VO_2	oxygen uptake

Fontan circulation report physical, psychological, neurodevelopmental, and social challenges across their lifespan.[2,3] After surgery, patients and their families anticipate progressive functional limitations, serious cardiac and noncardiac morbidities, and the possibility of Fontan circulatory failure of sufficient severity to require cardiac transplantation or cause premature death. These lifelong challenges and risks can influence patients' overall well-being and health-related quality of life (HRQOL).

HRQOL is a multidimensional concept including domains related to physical, psychological, social, and occupational functioning.[4,5] Despite recognition that people with a Fontan circulation are at risk of poor HRQOL,[6] there is no consensus on the individual and environmental factors that influence this outcome. It is unclear, for example, whether CHD complexity itself is a risk factor for poorer HRQOL. While 3 reviews found greater CHD complexity was associated with lower HRQOL in children and adults,[7–9] 2 reviews reported no association.[10,11] Clinical factors, such as daily medication use, longer hospitalizations, and greater number of medical interventions, are associated with worse HRQOL among people with complex CHD.[8,11] Greater psychological stress, fewer social supports, and lower family socioeconomic status are also correlated with lower HRQOL[12–15]; however, no meta-analyses have examined the relative impact of these factors in people with a Fontan circulation.

With the Fontan population currently estimated at 70 000 individuals worldwide and predicted to double over the next 20 years,[16] there is an imperative to better understand HRQOL.[17] This review aimed to: (1) meta-analyze HRQOL outcomes reported by children, adolescents, and adults with a Fontan circulation and/or their proxies in comparison to the general population; (2) identify individual and environmental factors that predict HRQOL in people with a Fontan circulation and determine moderating effects; (3) examine associations between healthcare use (eg, frequency of visits to cardiac services), health service costs and HRQOL; and (4) critically appraise the quality of existing literature to set priorities for future clinical practice and research advancement.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement[18] for the purposes of identifying articles, extracting data, and synthesizing evidence. The protocol was registered with PROSPERO (CRD42015016610).

Data Sources and Search Strategy

Six electronic databases (Medline, CINHAL, Cochrane, Embase, PsycINFO, and Scopus) were searched for peer-reviewed studies, and autoalerts were created using the same unique search algorithm for each database, with studies published through March 7, 2019 incorporated into the review. Search terms defining the target population were combined with key HRQOL terms (Table S1).[19] Reference lists of included studies were manually scanned to identify additional articles.

Prolific author searching was used to identify additional articles.

Eligibility Criteria

Eligible studies met all following criteria: (1) reported on a sample of individuals with a Fontan circulation; (2) used a validated, quantitative self- or proxy-reported HRQOL measure; and (3) were published in an English-language, peer-reviewed format. Studies that defined participants only by univentricular diagnosis were included if >80% of the sample had a Fontan circulation. All study designs and comparison group types were considered eligible.

Study Selection and Data Extraction

Initially, one researcher (K.M.) screened all titles for duplicates and ineligible articles. Remaining abstracts and resulting full texts were then independently screened by 2 researchers (K.M., N.K.). In cases where eligibility was unclear, a third researcher (G.S.) was consulted or the corresponding author contacted (Figure 1). One researcher (K.M.) extracted data from each article, and a second checked for accuracy (N.K.). Disagreements were resolved through discussion and consensus. Among articles comparing people with a Fontan circulation with healthy controls or normative data, averages (means, medians) and distribution of self- and

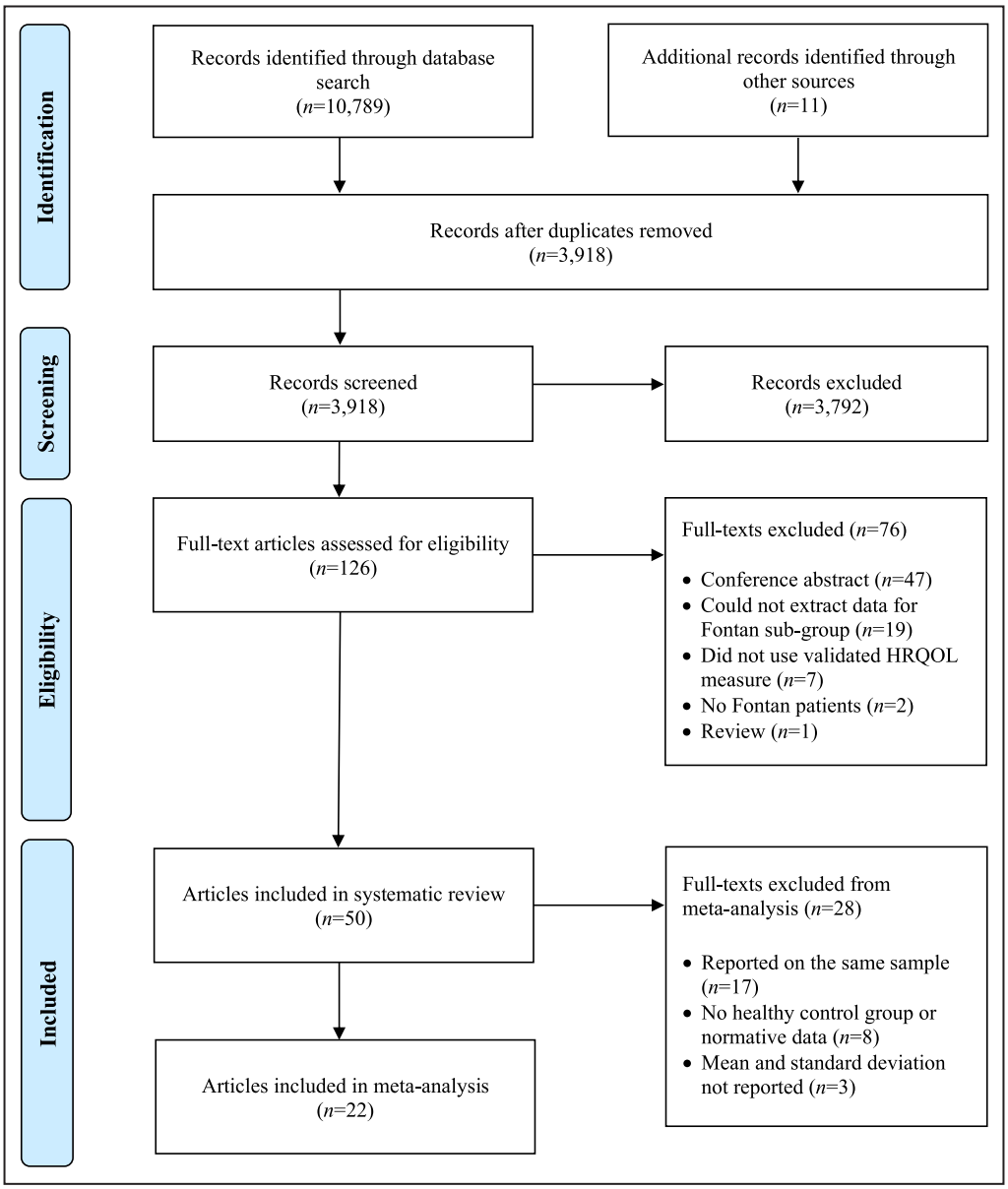

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram illustrating the systematic search process.
HRQOL indicates health-related quality of life.

parent-reported HRQOL scores were extracted for meta-analysis. For articles that did not report the SD of scores,[20–23] the Cochrane RevMan calculator[24] was used to estimate SD. Plot digitizer software (http://plotdigitizer.sourceforge.net/) was used to extract scores reported in graphs.[23,25] Where ≥2 articles reported on the same sample, data from the most recently published article were meta-analyzed.

Risk of Bias Analysis

Risk of bias was independently assessed for each study by 2 reviewers (K.M., D.C.). Assessments were performed using the 14-item criteria proposed by Kmet et al,[26] and item scores from 0 to 2 were assigned. A total mean summary score was then calculated, with higher scores indicating greater methodological rigor and lower risk of bias (>0.8=strong, 0.71–0.79=good, 0.50–0.70=adequate, and <0.50=limited).

Data Synthesis and Meta-Analysis

Based on an a priori assumption of outcome measurement heterogeneity, a narrative synthesis was used to report evidence from all 50 captured articles. Statistical analyses were performed using the Comprehensive Meta-Analysis Program, Version 3 (CMA 3.0; Englewood, NJ).[27] Standardized mean difference (SMD) scores were the primary summary measure, allowing for comparison of effect sizes across HRQOL measures.[28] All meta-analyses were initially conducted using a random-effects model, as described by DerSimonian and Laird,[29] as variation in the true effect size between studies caused by clinical (eg, CHD complexity, comorbidities) or methodological (eg, study design, risk of bias) heterogeneity was evident following data extraction.[30] Fixed-effects models have also demonstrated validity in the presence of heterogeneity;[31] thus, the primary meta-analyses were repeated using a fixed-effects model to enhance the practical inference of our results. Random- and fixed-effects analyses were performed for overall self- and parent-reported HRQOL. For each reporting method (self or proxy), separate analyses were then performed for each HRQOL domain, including physical and psychosocial summary domains and emotional, social, and school/work functioning. For articles in which the number of control participants was not reported, a conservative approach assuming the number equal to that of the patient group was used. Statistical heterogeneity between studies was assessed using Cochran's Q.[32] The I^2 statistic[27] was used as an estimate of the percentage of total between-study variance, with I^2 ≥50% indicating substantial heterogeneity.[33] A series of random-effects univariate meta-regression analyses were conducted to determine the effect of continuous moderator variables on the SMD, only if the number of studies was ≥4. Demographic, clinical, and social psychological variables were specified a priori, but only 4 variables (hypoplastic left heart syndrome [HLHS] diagnosis, mean age at Fontan procedure, mean age at HRQOL assessment, and sex) met criteria for regression analysis. Regression coefficients (β) were used to indicate the estimated increase in the effect size per unit increase in the moderator variable. The proportion of between-study variation explained by each moderator variable was calculated as R^2. Interactions among moderator variables were not tested because of insufficient power. Post hoc sensitivity analyses were performed to explore the potential effect of HRQOL measure. Only the PedsQL Core Module and Short-Form Health Survey-36 provided sufficient data for these analyses. For all statistical analyses, significance was set at $P<0.05$. Additional predictors of HRQOL not assessed via meta-analysis were captured using narrative synthesis.

Publication bias was investigated by visual inspection of the funnel plot for asymmetry on all outcome measures. Egger's weighted regression method[34] and the Begg-Mazumdar rank correlation method[35] were used to assess potential publication bias. If bias was detected ($P<0.05$), Duval and Tweedie's Trim and Fill procedure[36] with random-effects modeling was used to estimate the impact of bias on meta-analytic results.

RESULTS

Fifty articles examining HRQOL outcomes of individuals with a Fontan circulation were identified, after screening of 3907 titles or abstracts and review of 126 full texts (Figure 1). Captured articles reported on the outcomes of 29 unique samples, including 2793 patients and 1437 parent-proxies. Risk of bias was low, with a mean quality rating of 0.92 across the 50 articles (Table 1), and no studies were excluded because of bias. Studies sampled individuals from the United States (n=31),[2,3,6,22,23,37–62] Europe (n=14),[20,21,25,63–73] and Australia (n=2),[74,75] whereas 3 samples were recruited from multiple countries.[76–78] Most articles (76%) were published between 2010 and 2019.

Mean patient age at HRQOL assessment ranged from 3.0 to 27.0 years; 16 samples included people of all ages, 10 sampled children and adolescents, and 3 sampled adults only. Most samples (86%) included a larger proportion of male than female participants. Average time since Fontan completion ranged from 0.83 to 20.5 years, and mean age at Fontan operation ranged from 2.3 to 12.0 years. Nineteen studies relied on both parent- and self-reported HRQOL, 18 used self-report, and 13 captured only

Table 1. Characteristics of Included Studies

Article	Country	Risk of Bias Score*	No. of Participants	Mean or Median Age at HRQOL Assessment, y	Sex	Diagnosis	Mean or Median Age at Fontan, y	Mean or Median Time Since Fontan, y	SR or PR	HRQOL Measure(s)
Anderson et al[3] 2008†	United States	0.86	546	11.9	327 male, 219 female	TA: 119 HLHS: 112 DILV: 80 Heterotaxia: 42 DORV: 41 PA with intact ventricular septum: 33 MA: 31 Abnormal tricuspid valve: 22 Atrioventricular canal defect: 22 Other: 38	3.4	NR	PR	CHQ
Atz et al[37] 2007†	United States	0.81	546	12.2	327 male, 219 female	NR	5.1	7.2	SR, PR	CHQ
Atz et al[39] 2011†	United States	0.77	536	11.9	318 male, 218 female	DILV: F=47, NF=31 MA: F=21, NF=9 TA: F=75, NF=46 Unbalanced atrioventricular canal: F=14, NF=9 Heterotaxia: F=28, NF=12 HLHS: F=83, NF=26 Other: F=93, NF=42	F: 3.5 NF: 3.3	NR	PR	CHQ
Atz et al[38] 2013†	United States	0.95	546	11.9	327 male, 219 female	TA: 119 HLHS: 112 DILV: 80 Heterotaxia: 42 DORV: 41 PA with intact ventricular septum: 33 MA: 31 Abnormal tricuspid valve: 22 Atrioventricular canal defect: 22 Other: 38	SCC: 3.5 No SCC: 3.2	8.1	SR, PR	CHQ
Atz et al[41] 2015†	United States	0.86	427	18.4	249 male, 178 female	NR	NR	15.2	SR, PR	CHQ, PedsQL, SF-36
Atz et al[40] 2017†	United States	0.95	373	21.2	222 male, 151 female	NR	3.3	17.8	SR, PR	CHQ, PedsQL, SF-36
Banka et al[42] 2011†	United States	0.85	539	11.9	NR	NR	Coil: 3.9, No coil: 3.2	8.6	PR	CHQ
Blaufox et al[43] 2008†	United States	0.81	521	11.9	315 male, 206 female	NR	3.4	NR	PR	CHQ
Callegari et al[78] 2019	Germany and Italy	1.00	232	25.6	92 male, 140 female	NR	NR	NR	SR	SF-36

(*Continued*)

Table 1. Continued

Article	Country	Risk of Bias Score*	No. of Participants	Mean or Median Age at HRQOL Assessment, y	Sex	Diagnosis	Mean or Median Age at Fontan, y	Mean or Median Time Since Fontan, y	SR or PR	HRQOL Measure(s)
Cohen et al[44] 2010†	United States	1.00	544	11.9	NR	NR	NR	8.4	PR	CHQ
Czosek et al[76] 2015	United States and United Kingdom	1.00	318	11.9	182 male, 136 female	NR	NR	NR	SR, PR	PedsQL
d'Udekem et al[74] 2009	Australia	0.77	36	21.6	19 male, 17 female	DILV: 14 TA: 8 DORV: 3 Atrioventricular canal: 3 PA with intact ventricular septum: 2 Straddling atrioventricular valve: 1 Other: 5	5	16.6	SR	SF-36
Dulfer et al[20] 2014	The Netherlands	0.85	44	NR	NR	NR	3	NR	SR, PR	SF-36, TACQOL
Dulfer et al[63] 2016	The Netherlands	0.90	79	NR	47 male, 32 female	NR	NR	NR	SR, PR	TACQOL
Friedland-Little et al[45] 2017	United States	0.81	31	ECMO: 7.8 No ECMO: 6.8	24 male, 7 female	HLHS: 27 DILV: 1 TA with d-MGA: 1 Unbalanced atrioventricular septal defects: 1 DORV with hypoplastic LV: 1	NR	NR	SR, PR	PedsQL
Goldberg et al[46] 2014	United States	0.90	232	3.0	145 male, 87 female	HLHS: 207	NR	NR	PR	PedsQL
Goldstein et al[22] 2011	United States	0.90	51	15.0	31 male, 20 female	HLHS: 25 DILV: 8 TA: 6 AVSD with hypoplastic LV: 3 TGA with hypoplastic RV: 3 PA with intact ventricular septum: 3 Other: 3	6.2	NR	SR, PR	PedsQL
Gratz et al[66] 2009	Germany	0.86	31	22.1	16 male, 15 female	NR	2.9	NR	SR	SF-36
Hedlund et al[71] 2016†	Sweden	0.72	30	14.2	16 male, 14 female	NR	2.7	11.4	SR, PR	PedsQL
Hedlund et al[70] 2017†	Sweden	0.77	30	14.2	16 male, 14 female	NR	NR	NR	SR, PR	PedsQL

(*Continued*)

Table 1. Continued

Article	Country	Risk of Bias Score*	No. of Participants	Mean or Median Age at HRQOL Assessment, y	Sex	Diagnosis	Mean or Median Age at Fontan, y	Mean or Median Time Since Fontan, y	SR or PR	HRQOL Measure(s)
Heye et al[77] 2019	Germany and Switzerland	0.95	46	3.1	31 male, 15 female	HLHS: 26 PA with VSD: 2 PA with intact ventricular septum: 1 TA: 3 DILV with TGA: 1 l-TGA with hypoplastic LV: 1 Imbalanced AVSD: 6 Borderline LV: 4 DORV with TGA: 2	2.7	0.83	PR	PedsQL
Hock et al[67] 2018	Germany	0.95	78	12.0	57 male, 21 female	HLHS: 27 TA: 13 DILV: 12 d-MGA: 10 Atrioventricular anomaly: 5 HRHS: 4 Other: 7	2.3	NR	SR	KINDL-R
Idorn et al[21] 2013	Denmark	0.81	158	NR	93 male, 65 female	TA: 43 DILV: 39 AVSD: 15 HLHS: 12 PA with intact ventricular septum: 12 Other: 37	NR	NR	SR, PR	PedsQL, SF-36
Jacobsen et al[47] 2016†	United States	0.86	14	10.4	8 male, 6 female	TA: 4 HLHS: 4 DORV:1 Unbalanced AVSD: 2 d-TGA with MA: 1 HRHS: 1 Coarctation with MA, LV hypoplasia: 1	NR	7.3	SR, PR	PedsQL
Jacobsen et al[48] 2018†	United States	0.86	11	10.5	5 male, 6 female	NR	NR	7.4	SR, PR	PedsQL
Karamlou et al[49] 2013	United States	0.90	25	NR	NR	NR	NR	NR	SR	CHQ, PedsQL
Kukreja et al[50] 2015	United States	0.86	49	26	25 male, 24 female	NR	NR	NR	SR	SF-36
Lambert et al[51] 2009†	United States	0.81	328	13.9	195 male, 133 female	NR	3.6	NR	SR, PR	CHQ

(*Continued*)

Table 1. Continued

Article	Country	Risk of Bias Score*	No. of Participants	Mean or Median Age at HRQOL Assessment, y	Sex	Diagnosis	Mean or Median Age at Fontan, y	Mean or Median Time Since Fontan, y	SR or PR	HRQOL Measure(s)
Manlhiot et al[23] 2009	United States	0.90	68	13.0	24 male, 44 female	DILV: 20 TA: 15 HLHS: 4 Other: 29	4	NR	SR, PR	CHQ, PedsQL
McCrindle et al[2] 2006†	United States	0.95	537	11.9	323 male, 214 female	NR	NR	NR	PR	CHQ
McCrindle et al[52] 2007†	United States	0.95	147	11.6	91 male, 56 female	NR	3.5	8.1	SR, PR	CHQ
McCrindle et al[55] 2010†	United States	0.90	511	11.9	311 male, 200 female	NR	3.4	NR	PR	CHQ
McCrindle et al[54] 2014†	United States	0.90	325	13.9	193 male, 132 female	TA: 80 HLHS: 58 DILV: 53 Heterotaxia: 22 MA: 18 AVSD: 12 Other: 76	NR	NR	SR	CHQ
McCrindle et al[53] 2014†	United States	0.90	245	16.2	144 male, 101 female	NR	2.9	NR	PR	CHQ
Mellion et al[56] 2014‡	United States	0.95	208	Children: 9.6, Adolescents: 14.8	123 male, 85 female	HLHS: 57 DILV: 28 DORV: 3 MA: 17 TA: 39 Unbalanced atrioventricular canal: 19 RV-aorta with PA: 18 Superinferior ventricle: 4 Conotruncal anomalies: 135 TGA: 99 DORV: 16 Truncus arteriosus: 20	NR	NR	SR, PR	PedsQL
Menon et al[57] 2018	United States	0.95	299	NR	174 male, 125 female	HLHS: 98	NR	NR	SR, PR	PedsQL
Müller et al[69] 2009	Germany	0.81	57	NR	39 male, 18 female	NR	NR	NR	SR	CHQ, SF-36
Müller et al[68] 2012	Germany	0.81	57	NR	33 male, 24 female	NR	NR	NR	SR	SF-36

(*Continued*)

Table 1. Continued

Article	Country	Risk of Bias Score*	No. of Participants	Mean or Median Age at HRQOL Assessment, y	Sex	Diagnosis	Mean or Median Age at Fontan, y	Mean or Median Time Since Fontan, y	SR or PR	HRQOL Measure(s)
Overgaard et al[25] 2011	Denmark	0.90	62	NR	34 male, 28 female	DILV: 20 TA: 17 MA: 6 DORV: 6 AVSD: 4 PA with intact ventricular septum: 3 HLHS: 2 Other: 4	NR	NR	SR	SF-36
Pike et al[59] 2012	United States	0.95	54	26.0	26 male, 28 female	TA: 19 DILV: 13 Hypoplastic RV: 8 HLHS: 4 DORV: 3 Ebstein abnormality: 1 AVSD: 2 Other: 4	NR	NR	SR	SF-36
Prakash et al[58] 2010†	United States	0.95	123	12.1	69 male, 54 female	TA: 36 DILV: 22 HLHS: 14 d-TGA, PA: 9 Heterotaxia, DORV, SV: 9 PA with intact ventricular septum: 7 l-TGA, DORV, PA: 6 Unbalanced atrioventricular canal: 3 Other: 17	NR	NR	PR	CHQ
Smas-Suska et al[72] 2018	Poland	0.81	40	26.0	24 male, 16 female	Right ventricular hypoplasia: 25 Pulmonary stenosis: 9 Left ventricular hypoplasia: 3 DORV: 2 Complete atrioventricular canal: 1	4.8	20.5	SR	SF-36
Stephenson et al[60] 2010†	United States	0.95	520	11.9	315 male, 205 female	Single LV, DILV, and TA: IART=18, No IART=174 Single RV, DIRV, MA, HLHS: IART=5, No IART=135 SV, Unbalanced atrioventricular canal defect: IART=1, No IART=19 Other: IART=10, No IART=116 SV, Heterotaxia: IART=4, No IART=34	3.4	8.4	PR	CHQ

(*Continued*)

Table 1. Continued

Article	Country	Risk of Bias Score*	No. of Participants	Mean or Median Age at HRQOL Assessment, y	Sex	Diagnosis	Mean or Median Age at Fontan, y	Mean or Median Time Since Fontan, y	SR or PR	HRQOL Measure(s)
Sutherland et al[75] 2018	Australia	0.90	17	15	10 male, 7 female	DILV: 3 TA:5 HLHS: 3 TGA: 2 DORV: 1 PA with intact ventricular septum: 1 AVSD: 2	NR	NR	SR, PR	PedsQL
Uzark et al[6] 2016†	United States	0.95	408	18.5	237 male, 171 female	NR	3.8	15.2	SR	CHQ, PedsQL, SF-36
van den Bosch et al[64] 2004	The Netherlands	0.68	36	NR	18 male, 18 female	TA: 21 DILV: 9 Other: 6	12	NR	SR	SF-36
Williams et al[61] 2009†	United States	0.95	476	NR	280 male, 187 female	PA: 29 HLHS: 100 Atrioventricular valve, heterotaxia, unbalanced AVSD: 52 TA: 114 Anomalous venous return: 8	3.4	8.8	PR	CHQ
Williams et al[62] 2013†	United States	0.72	546	11.9	NR	SV, DILV: No pacemaker=62, pacemaker=20 SV, DIRV: No pacemaker=9, pacemaker=1 SV, MA: No pacemaker=29, pacemaker=1 SV, TA: No pacemaker=105, pacemaker=15 Unbalanced AVCD: No pacemaker=19, pacemaker=2 Heterotaxia: No pacemaker=33, pacemaker=7 HLHS: No pacemaker=100, pacemaker=10 Other: No pacemaker=118, pacemaker=15	NR	NR	PR	CHQ
Wolff et al[65] 2018	The Netherlands	0.90	21	27.0	7 male, 14 female	TA: 9 DILV: 6 AVSD: 4 PA with intact ventricular septum: 2	6	NR	SR	SF-36

(*Continued*)

Table 1. Continued

Article	Country	Risk of Bias Score*	No. of Participants	Mean or Median Age at HRQOL Assessment, y	Sex	Diagnosis	Mean or Median Age at Fontan, y	Mean or Median Time Since Fontan, y	SR or PR	HRQOL Measure(s)
Yildiz et al[73] 2011	Turkey	0.81	20	19.0	10 male, 10 female	TA with pulmonary stenosis: 10 PA with intact ventricular septum: 5 DILV: 3 DORV: 1 PA with VSD: 1	NR	NR	SR	PedsQL

AVCD indicates atrioventricular canal defect; AVSD, atrioventricular septal defect; CHQ, Child Health Questionnaire; DILV, double-inlet left ventricle; DIRV, double-inlet right ventricle; d-MGA, d-malposed great arteries; DORV, double-outlet right ventricle; d-TGA, dextrotransposition of the great arteries; ECMO, extracorporeal membrane oxygenation; F, fenestration; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; HRQOL, health-related quality of life; IART, intra-atrial reentrant tachycardia; KINDL-R, The Revised Children's Quality of Life Questionnaire; l-TGA, levotransposition of the great arteries; LV, left ventricle; MA, mitral atresia; NF, no fenestration; NR, not reported; PA, pulmonary atresia; PedsQL, PedsQL Core Module; PR, parent-report; RV, right ventricle; SCC, superior cavopulmonary connection; SF-36, Short-Form Health Survey-36; SR, self-report; SV, single ventricle; TA, tricuspid atresia; TACQOL, TNO AZL Children's Quality of Life; TGA, transposition of the great arteries; and VSD, ventricular septal defect.

*Higher scores indicate greater methodological rigor and lower risk of bias.

†Articles reporting on the same or overlapping study cohorts.

‡Articles reporting on multiple congenital heart disease diagnoses per participant.

parent proxy–reported HRQOL. Across all studies, 8 HRQOL measures were used; most common were the PedsQL Core Module[79] (PedsQL n=17; 14 samples; 1604 patients; 1181 parent-proxies), Short-Form Health Survey-36[80] (SF-36; n=16; 14 samples; 806 patients), and Child Health Questionnaire[81] (n=22; 4 samples; 665 patients; 546 parent-proxies). Twenty-two articles provided sufficient data for meta-analysis. Of these, 13 studies compared HRQOL outcomes of people with a Fontan circulation with those of an optimal healthy control sample, and 9 studies compared HRQOL scores with values derived from a normative sample (3 from a "healthy" sample, 6 from a "general community" sample). Given the diversity in comparator samples, the terms "referents" or "comparators" will be used herein to define control or comparison groups.

Health-Related Quality of Life

Self-reported HRQOL

Overall, self-reported HRQOL was significantly lower in individuals with a Fontan circulation compared with referents (SMD −0.92; 95% CI, −1.36 to −0.48; P<0.001; k=8; Table 2, Figure 2). Fontan patients reported lower scores across all HRQOL domains, with a large effect for physical functioning (SMD −0.90; 95% CI, −1.13 to −0.67; P<0.001; k=26) and moderate effects for school/work (SMD −0.71; 95% CI, −0.90 to −0.52; P<0.001; k=10) and for psychosocial (SMD −0.63; 95% CI, −0.87 to −0.39; P<0.001; k=14) and social functioning (SMD −0.56; 95% CI, −0.73 to −0.39; P<0.001; k=21) compared with referents. Emotional functioning was also poorer compared with referents; however, the effect size was small (SMD −0.35; 95% CI, −0.54 to −0.15; P=0.001; k=23). Fixed-effects analyses also found overall self-reported HRQOL was lower in individuals with a Fontan circulation compared with referents (SMD −0.89; 95% CI, −0.99 to −0.80; P<0.0001; k=8). Fixed-effect analyses followed the same pattern across all self-reported HRQOL domains, ranging from −0.84 to −0.26 SDs below the mean for referents (all P<0.001; Table S2).

Proxy-reported HRQOL

Parents reported lower overall HRQOL for their child with a Fontan circulation compared with parents of referents (SMD −1.05; 95% CI, −1.41 to −0.69; *P*<0.001; k=7; Table 2, Figure S1). All HRQOL domains were lower for individuals with a Fontan circulation compared with referents, ranging from −0.68 to −0.99 SDs below the mean for controls (all *P*<0.001; Table 2). Findings from fixed-effects analyses did not differ markedly from those of the primary (random-effects model) results; parents reported lower scores for their child across all

Table 2. Meta-Analysis Results Comparing Mean Self- and Parent-Reported HRQOL Scores for People With a Fontan Circulation With Healthy Referents

Variable	No. of Comparisons	No. of Participants		Test Statistics				Heterogeneity		
		Fontan Patients	Healthy Referents	SMD	95% CI		*P* Value	I^2	Q	*P* Value
Self-reported outcomes										
Total HRQOL	8	768	7697	−0.92	−1.36	−0.48	<0.0001*	93.89	114.62	<0.0001*
Physical functioning	26	1694	13 043	−0.90	−1.13	−0.67	<0.0001*	90.30	257.60	<0.0001*
Psychosocial functioning	14	1009	5963	−0.63	−0.87	−0.39	<0.0001*	84.03	81.41	<0.0001*
Emotional functioning	23	1603	10 590	−0.35	−0.54	−0.15	0.0001*	85.87	148.60	<0.0001*
Social functioning	21	1246	10 321	−0.56	−0.73	−0.39	<0.0001*	75.54	77.68	<0.0001*
School/work functioning	10	882	7986	−0.71	−0.90	−0.52	<0.0001*	68.45	28.53	0.001*
Parent-reported outcomes										
Total HRQOL	7	538	11 110	−1.05	−1.41	−0.69	<0.0001*	87.82	49.25	<0.0001*
Physical functioning	8	802	11 482	−0.99	−1.22	−0.76	<0.0001*	79.08	33.45	<0.0001*
Psychosocial functioning	8	802	11 502	−0.83	−1.18	−0.48	<0.0001*	91.66	83.88	<0.0001*
Emotional functioning	6	508	11 060	−0.69	−1.01	−0.39	<0.0001*	83.36	30.05	<0.0001*
Social functioning	6	508	11 051	−0.74	−1.12	−0.36	<0.0001*	89.30	46.74	<0.0001*
School/work functioning	4	239	9226	−0.68	−0.96	−0.40	<0.0001*	64.75	8.51	<0.0001*

HRQOL indicates health-related quality of life; and SMD, standardized mean difference.
*Statistically significant at $P<0.05$.

HRQOL domains, including total HRQOL (SMD −0.99; 95% CI, −1.10 to −0.87; $P<0.0001$; k=7) and physical (SMD −0.93; 95% CI, −1.02 to −0.84; $P<0.0001$; k=8), psychosocial (SMD −0.66; 95% CI, −0.75 to −0.57; $P<0.0001$; k=8), emotional (SMD −0.65; 95% CI, −0.76 to −0.54; $P<0.0001$; k=6), social (SMD −0.72; 95% CI, −0.84 to −0.61; $P<0.0001$; k=6), and school/work (SMD −0.78; 95% CI, −0.93 to −0.64; $P<0.0001$; k=4) functioning (Table S2).

Moderators of HRQOL

HLHS diagnosis

Using meta-regression, we found studies with a higher proportion of HLHS patients tended to report lower self-reported social functioning (β=−0.007; 95% CI, 0.015 to −0.0001; $P=0.048$). Conversely, HLHS diagnosis was associated with a smaller difference in parent-reported scores compared with referents for all domains, including total HRQOL (β=0.012; 95% CI, 0.009–0.016; $P<0.001$) and physical (β=0.010; 95% CI, 0.006–0.013; $P<0.001$), emotional (β=0.009; 95% CI, 0.005–0.013; $P<0.001$), social (β=0.012; 95% CI, 0.008–0.016; $P<0.001$), and school/work (β=0.009; 95% CI, 0.002–0.015; $P=0.004$) functioning (Table 3).

Age at Fontan operation

Older patient age at Fontan operation was associated with worse self-reported emotional functioning (β=−0.124; 95% CI, −0.210 to −0.038; $P=0.004$) compared with referents.

Patient age at HRQOL assessment

Older age at HRQOL assessment was associated with better self-reported psychosocial (β=0.043; 95% CI, 0.013–0.073; $P=0.004$) and social (β=0.034; 95% CI, 0.011–0.058; $P=0.004$) functioning (Table 3). In terms of parent-reported outcomes, older patient age at assessment was associated with poorer total HRQOL (β=−0.077; 95% CI, −0.119 to −0.035; $P=0.0003$) and emotional (β=−0.065; 95% CI, −0.089 to −0.040; $P<0.0001$) and social (β=−0.071; 95% CI, −0.130 to −0.011; $P=0.018$) functioning.

Sex

Relative to studies with a higher proportion of female patients, studies with a higher proportion of male patients yielded a smaller difference in parent-reported school functioning compared with referents (β=0.026; 95% CI, 0.008–0.042; $P=0.003$).

Publication Bias

For self-reported social functioning, visual inspection of the funnel plot and Egger's test indicated publication bias. Trim and Fill estimation still yielded a significant effect size (SMD −0.79; 95% CI, −0.98 to −0.06), and fail-safe N^{82} indicated it would take inclusion of 969 studies reporting null results for the findings to lose statistical significance. Visual inspection of the funnel plot suggested all other self- and parent-reported HRQOL domains were symmetric. Results of Egger's test and Begg-Mazumdar rank correlation test supported this assumption ($P>0.05$).

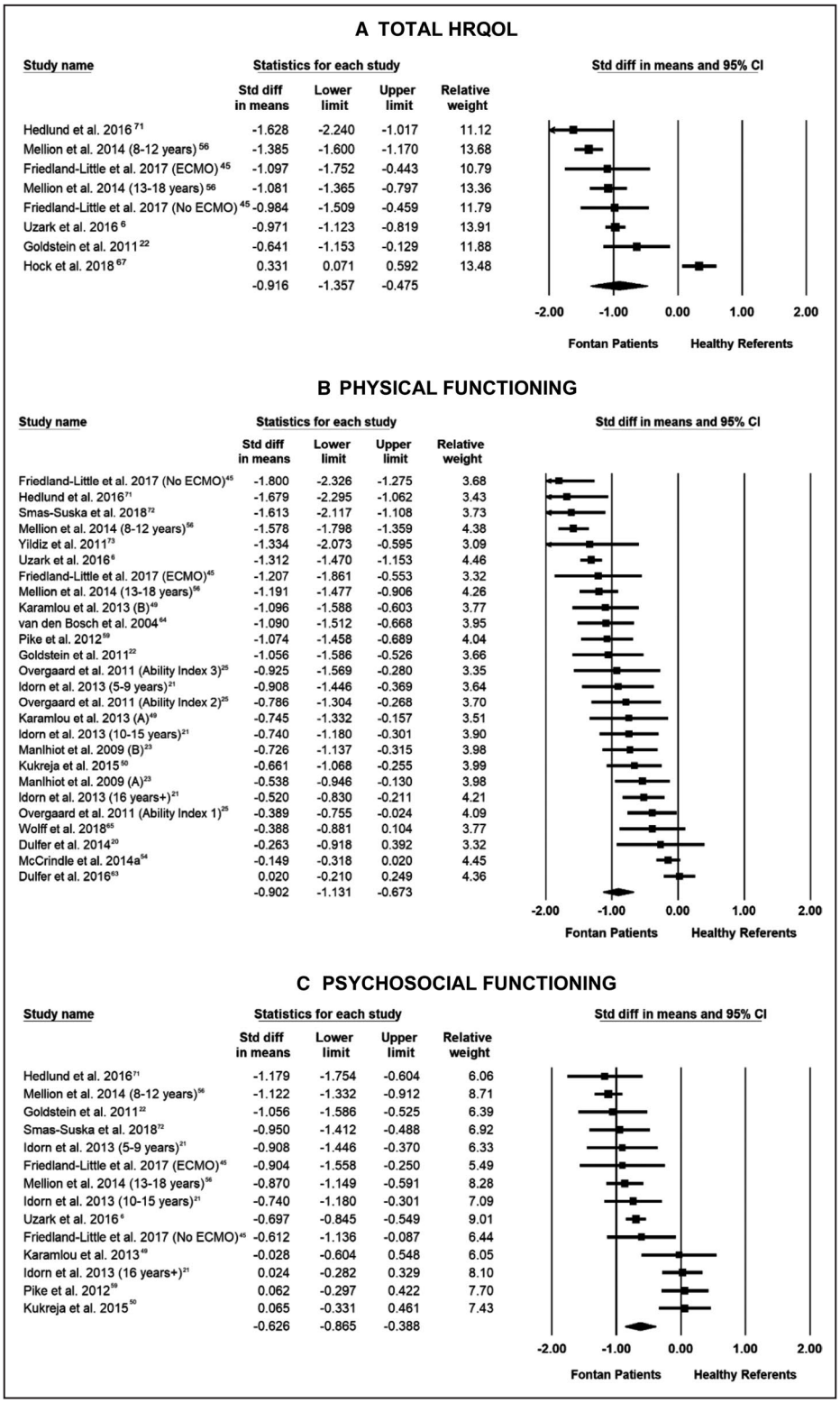

Figure 2. Forest plots of random-effects analysis of self-reported health-related quality of life (HRQOL), presented separately for total HRQOL (A), physical functioning (B), and psychosocial functioning (C).

Random-effect meta-analysis of between-group effect sizes. Box sizes are proportional to the weight of each study in the analysis, and the lines represent their 95% CIs. The thickest part of the diamond represents the pooled standardized mean difference with a width proportional to the 95% CI. ECMO indicates extracorporeal membrane oxygenation.

Table 3. Moderators of Self- and Parent-Reported HRQOL, Presented Separated for Total HRQOL and Functional Domain Scores, Based on Meta-Regression Results

Moderators	HRQOL Domain	No. of Comparisons	No. of Participants		Meta-Regression Statistics				
			Fontan Patients	Healthy Referents	Slope	95% CI		*P* Value	R^2
HLHS, % with diagnosis	Self-reported								
	Total HRQOL	6	298	6666	0.004	−0.006	0.014	0.440	0.00
	Physical functioning	15	1046	7346	−0.008	−0.019	0.001	0.108	0.17
	Psychosocial functioning	12	558	7041	−0.006	−0.016	0.003	0.203	0.18
	Emotional functioning	12	949	7285	−0.002	−0.012	0.007	0.660	0.02
	Social functioning	12	627	7052	−0.007	−0.015	−0.0001	0.048*	0.33
	School/work functioning	7	378	6699	−0.001	−0.006	0.005	0.868	0.00
	Parent reported								
	Total HRQOL	7	538	11 110	0.012	0.009	0.016	<0.0001*	1.00
	Physical functioning	7	538	11 091	0.010	0.006	0.013	<0.0001*	1.00
	Psychosocial functioning	7	538	11 111	0.013	0.009	0.016	<0.0001*	1.00
	Emotional functioning	6	508	11 060	0.009	0.005	0.013	<0.0001*	0.95
	Social functioning	6	508	11 051	0.012	0.008	0.016	<0.0001*	1.00
	School/work functioning	4	239	9226	0.009	0.002	0.015	0.004*	1.00
Age at Fontan operation	Self-reported								
	Total HRQOL	2	…	…	…	…	…	…	…
	Physical functioning	10	1183	5953	−0.015	−0.145	0.115	0.818	0.00
	Psychosocial functioning	6	590	545	0.101	−0.122	0.357	0.374	0.07
	Emotional functioning	10	1092	3498	−0.124	−0.21	−0.038	0.004*	0.48*
	Social functioning	8	735	3230	0.039	−0.05	0.128	0.393	0.00
	School/work functioning	3	…	…	…	…	…	…	…
	Parent reported								
	Total HRQOL	2	…	…	…	…	…	…	…
	Physical functioning	2	…	…	…	…	…	…	…
	Psychosocial functioning	2	…	…	…	…	…	…	…
	Emotional functioning	1	…	…	…	…	…	…	…
	Social functioning	1	…	…	…	…	…	…	…
	School/work functioning	0	…	…	…	…	…	…	…
Age at HRQOL assessment	Self-reported								
	Total HRQOL	8	768	7697	0.004	−0.158	0.166	0.961	0.00
	Physical functioning	21	1602	11 129	0.007	−0.039	0.053	0.758	0.00
	Psychosocial functioning	14	1009	7450	0.043	0.013	0.073	0.004*	0.51
	Emotional functioning	17	1511	8676	0.021	−0.010	0.053	0.185	0.00
	Social functioning	15	1154	8407	0.034	0.011	0.058	0.004*	0.33
	School/work functioning	10	882	7986	−0.003	−0.061	0.055	0.913	0.00
	Parent reported								
	Total HRQOL	7	538	11 110	−0.077	−0.119	−0.035	0.0003*	0.85
	Physical functioning	8	802	11 482	−0.039	−0.090	0.012	0.135	0.00
	Psychosocial functioning	8	802	11 482	−0.045	−0.141	0.050	0.353	0.00
	Emotional functioning	6	508	11 060	−0.065	−0.089	−0.040	<0.0001*	1.00
	Social functioning	6	508	11 051	−0.071	−0.130	−0.011	0.018*	0.64
	School/work functioning	4	239	9226	−0.071	−0.193	0.050	0.250	0.00
Sex, % male	Self-reported								
	Total HRQOL	8	768	7697	0.018	−0.016	0.053	0.296	0.29
	Physical functioning	20	1594	10 443	−0.013	−0.035	0.008	0.236	0.00

(*Continued*)

Table 3. Continued

Moderators	HRQOL Domain	No. of Comparisons	No. of Participants		Meta-Regression Statistics				
			Fontan Patients	Healthy Referents	Slope	95% CI		*P* Value	R^2
	Psychosocial functioning	13	995	7383	−0.009	−0.034	0.014	0.433	0.00
	Emotional functioning	18	1533	10 418	−0.003	−0.022	0.015	0.718	0.00
	Social functioning	16	1176	10 149	−0.011	−0.025	0.002	0.093	0.17
	School/work functioning	10	882	7986	−0.001	−0.018	0.014	0.827	0.00
	Parent reported								
	Total HRQOL	7	538	11 110	0.027	−0.002	0.056	0.075	0.24
	Physical functioning	7	538	11 091	0.021	−0.004	0.047	0.111	0.20
	Psychosocial functioning	7	538	11 111	0.029	−0.001	0.058	0.056	0.27
	Emotional functioning	6	508	11 060	0.021	−0.006	0.049	0.128	0.19
	Social functioning	6	508	11 051	0.017	−0.016	0.051	0.317	0.09
	School/work functioning	4	239	9226	0.026	0.008	0.042	0.003*	1.00

HLHS indicates hypoplastic left heart syndrome; and HRQOL, health-related quality of life.
*Statistically significant at $P<0.05$.

Sensitivity Analyses to Examine Potential Measurement Effects

Across studies, mean patient age at PedsQL assessment ranged from 3.0 to 18.5 years. When meta-analyses were restricted to only PedsQL scores, self-reported HRQOL remained lower among individuals with a Fontan circulation compared with healthy referents across all PedsQL domains, including total HRQOL (SMD −1.11; 95% CI, −1.32 to −0.90; $P<0.0001$; k=7) and physical (SMD −1.18; 95% CI, −1.39 to −0.97; $P<0.0001$; k=12), psychosocial (SMD −0.83; 95% CI, −1.01 to −0.65; $P<0.0001$; k=10), emotional (SMD −0.58; 95% CI, −0.79 to −0.37; $P<0.0001$; k=10), social (SMD −0.89; 95% CI, −1.01 to −0.77; $P<0.0001$; k=10), and school/work (SMD −0.77; 95% CI, −0.91 to −0.63; $P<0.0001$; k=9) functioning (Table S3). Compared with results of the primary analyses, when analyses included only PedsQL scores, effect sizes across self-reported HRQOL domains increased. Parent-proxy PedsQL scores followed the same pattern; parent-reported physical (SMD −1.02; 95% CI, −1.32 to −0.73; $P<0.0001$; k=7) and psychosocial (SMD −0.92; 95% CI, −1.29 to −0.56; $P<0.0001$; k=7) functioning was poorer compared with healthy referents, and these findings did not differ markedly from those of the primary analyses. Meta-regression analyses performed using only PedsQL scores found HLHS diagnosis was associated with a smaller difference in parent-reported physical (β=0.010; 95% CI, 0.007–0.014; $P<0.0001$) and psychosocial (β=0.013; 95% CI, 0.010–0.017; $P<0.0001$) functioning (Table S4). Older patient age at HRQOL assessment was associated with poorer parent-reported physical (β=−0.060; 95% CI, −0.098 to −0.022; $P=0.021$) and psychosocial functioning (β=−0.081; 95% CI, −0.123 to −0.040; $P<0.0001$) compared with healthy referents.

Across studies, mean patient age at SF-36 assessment ranged from 20.7 to 27 years. When meta-analyses included only SF-36 scores, people with a Fontan circulation reported lower physical (SMD −0.77; 95% CI, −1.01 to −0.53; $P<0.0001$; k=10) and social (SMD −0.21; 95% CI, −0.42 to −0.01; $P=0.044$; k=10) functioning compared with healthy referents (Table S3). Mental health component (SMD −0.18; 95% CI, −0.60 to 0.24; $P=0.405$; k=4) and domain scores (SMD −0.23; 95% CI, −0.57 to 0.12; $P=0.197$; k=11) did not differ between Fontan patients and healthy referents. Regression analyses performed using only SF-36 scores found older age at Fontan operation was associated with lower self-reported mental health scores (β=−0.225; 95% CI, −0.314 to −0.136; $P<0.0001$). Studies with a higher proportion of female patients yielded a smaller difference in self-reported physical functioning compared with referents (β=−0.041; 95% CI, −0.075 to −0.007; $P=0.018$; Table S5).

Factors Associated With HRQOL Identified via Narrative Synthesis

Demographic, clinical, social, and psychological factors associated with poorer self- and parent-reported HRQOL outcomes are summarized in Table 4.

Demographic factors

Five studies examined HRQOL and household income. Three cross-sectional studies found lower household income to be associated with lower parent-reported

Table 4. Demographic, Clinical, and Psychological Factors Associated With Poorer Self- or Parent-Reported HRQOL Outcomes

Variable	No. of Studies Examining Factor	HRQOL Domains					
		Total HRQOL	Physical Functioning	Psychosocial Functioning	Emotional Functioning	Social Functioning	School/ Work Functioning
Demographic factors							
Lower household income	5	↓ SR,[57] ⊘ PR[77]	⊘ SR,[6] ↓ PR,[2] ⊘ PR[53,77]	↓ SR,[6] ↓ PR[2]	⊘ SR,[6] ⊘ PR[77]	⊘ SR,[6] ⊘ PR[77]	↓ SR[6]
Lower patient education	1		⊘ SR[72]	⊘ SR[72]			
Higher maternal education	2	⊘ SR[6]	⊘ SR,[6] ↑ PR[53]	⊘ SR[6]	⊘ SR[6]	⊘ SR[6]	↑ SR[6]
Parent unemployment	1		↓ PR[2]	⊘ PR[2]			
Patient unemployment	1		⊘ SR[72]	⊘ SR[72]			
Parent married	1	⊘ PR[77]	⊘ PR[77]		⊘ PR[77]	⊘ PR[77]	
Patient married	1		⊘ SR[72]	⊘ SR[72]			
Having a sibling	1		↓ SR[23]	⊘ SR[23]	⊘ SR[23]	⊘ SR[23]	↓ SR[23]
Clinical factors, perioperative							
Dominant right ventricle	7	⊘ SR[67]	⊘ SR,[41,63,72] ↓ PR,[41] ⊘ PR[3,53,63]	⊘ SR[3,72]	⊘ SR,[63,74] ⊘PR[63]	⊘ SR,[63] ⊘ PR[63]	
SCC before Fontan	3		⊘ PR[3,38,53]	↓ PR[3,38]			
Intracardiac LT Fontan (type)	7		⊘ SR,[6,23,40,63,72] ⊘ PR[53,63]	⊘ SR[72]	⊘ SR,[23,63,74] ↓ PR[63]	↓ SR,[23] ⊘ SR[63]	↓ SR[23]
No fenestration at Fontan	4		⊘ SR,[72] ↓ PR,[2] ⊘ PR[39,53]	⊘ SR,[72] ⊘ PR[39]			
Greater weight at Fontan	1		↓ PR[2]	⊘ PR[2]			
Prenatal diagnosis	1	⊘ PR[77]	⊘ PR[77]		⊘ PR[77]	⊘ PR[77]	
Preterm birth	1	⊘ PR[77]	⊘ PR[77]		⊘ PR[77]	⊘ PR[77]	
Shunt type at Norwood	1	⊘ PR[46]	⊘ PR[46]	⊘ PR[46]	⊘ PR[46]	⊘ PR[46]	⊘ PR[46]
Heterotaxy syndrome	1		⊘ SR,[37] ⊘ PR[37]	⊘ SR,[37] ⊘ PR[37]			
ECMO before Fontan	1	⊘ SR,[45] ⊘ PR[45]	⊘ SR,[45] ⊘ PR[45]	⊘ SR,[45] ⊘ PR[45]	⊘ SR,[45] ⊘ PR[45]	⊘ SR,[45] ⊘ PR[45]	⊘ SR,[45] ⊘ PR[45]
Coil embolization of APCs	1		⊘ PR[42]				
Clinical factors, postoperative							
Greater time since surgery	3	⊘ PR[77]	↓ SR,[23] ⊘ SR,[72] ⊘ PR[77]	⊘ SR[72]	↓ SR,[23] ⊘ PR[77]	⊘ SR,[23] ⊘ PR[77]	↓ SR[23]
Greater No. of procedures after Fontan	1		↓ SR,[63] ↓ PR[63]		⊘ SR,[63] ⊘ PR[63]	⊘ SR,[63] ⊘ PR[63]	
Greater No. of medications	2	↓ PR[77]	↓ PR[2,77]			↓ PR[77]	
Use of β blocker	1		↓ PR[43]	⊘ PR[43]			
Use of class III antiarrhythmic agent	1		↓ PR[43]	⊘ PR[43]			
Arrythmia	4		↓ PR[2,43,53,60]	↓ PR,[2,60] ⊘ PR[43]			
Protein-losing enteropathy	1		↓ PR[53]				
Pacemaker	2		↓ PR[43,62]	⊘ PR[43,62]			
Atrioventricular valve regurgitation	3		⊘ SR,[72] ↓ PR[55]	⊘ SR[72]	⊘ SR[74]		
Elevated brain natriuretic peptide	6		↓ SR[40,54] ⊘ SR,[72] ↓ PR,[55] ⊘ PR[53]	⊘ SR,[72] ⊘ PR[55]	⊘ SR[74]		
Elevated serum albumin	1		↑ SR[72]	⊘ SR[72]			
Lower alanine aminotransferase	1		↑ SR[72]	⊘ SR[72]			
Lower resting heart rate	1		↑ PR[43]	⊘ PR[43]			

(*Continued*)

Table 4. Continued

Variable	No. of Studies Examining Factor	HRQOL Domains					
		Total HRQOL	Physical Functioning	Psychosocial Functioning	Emotional Functioning	Social Functioning	School/ Work Functioning
Higher peak heart rate	2		↑ SR,[72] ↑ PR[43]	∅ SR,[72] ∅ PR[43]			
Higher chronotropic index	2		↑ SR,[40] ∅ PR[55]				
Higher resting O_2 saturation	4		↑ SR,[40] ∅ SR,[72] ↑ PR[55]	∅ SR[72]	∅ SR[74]		
Higher % predicted VO_2 at peak exercise	6		↑ SR,[40] ∅ SR,[21,72] ↑ PR[52,55]	∅ SR,[21,72] ∅ PR[52,55]	∅ SR[21,74]	∅ SR[21]	∅ SR[21]
Higher % predicted VO_2 at anaerobic threshold	3		↑ PR[52,55]	∅ PR[52,55]	∅ SR[74]		
Higher % predicted maximum work rate	3		↑ SR,[40] ↑ PR[52,55]	↑ PR,[55] ∅ PR[52,55]			
Higher % predicted maximum oxygen pulse	4		∅ SR,[40] ↑ PR[55] ↓ PR[53]	↑ PR[55]			
Higher ejection fraction	4		↓ SR,[23] ∅ SR,[63,72] ∅ PR[53,63]	∅ SR[72]	↓ SR,[23] ∅ SR[63,74] ∅ PR[63]	↓ SR,[23] ∅ SR,[63] ∅ PR[63]	↓ SR[23]
Lower ventricular end-systolic volume	2		↑ PR,[55] ∅ PR[53]	∅ PR[55]			
Lower ventricular end-diastolic volume	3		↓SR,[63] ↑ PR,[55] ∅ PR[53,63]	∅ PR[55]	∅ SR,[63] ↓ PR[63]	↓ SR,[63] ∅ PR[63]	
Higher VE/VCO_2	2		∅ SR,[63,72] ∅ PR[63]	∅ SR[72]	∅ SR,[63] ∅ PR[63]	∅ SR,[63] ∅ PR[63]	
Reduced FEV_1	2		↓ SR[72,78]	∅ SR[72]			
Better peripheral vascular function	1	∅ SR[22]	∅ SR[22]		↑ SR[22]		
Presence of sinus node dysfunction	1		∅ SR,[63] ∅ PR[63]		∅ SR,[63] ↓ PR[63]	∅ SR,[63] ∅ PR[63]	
Better secondary ventricle function	1		∅ PR[58]				
Increased physical activity	2		∅ SR,[69] ∅ PR[52]	∅ PR[52]	↑ SR[69]	∅ SR[69]	
Abnormal body mass index	2	↓ SR[57]	∅ PR[44]	∅ PR[44]			
Delayed puberty	1	∅ SR[57]					
Shorter stature	1		↓ PR[44]	↓ PR[44]			
Psychological factors							
Behavioral or learning problems	2		↓ PR,[2] ∅ PR[53]	↓ PR[2]			
Greater psychological distress	1		∅ PR,[2] ∅ PR[53]	↓ PR[2]			

All associations at the $P<0.05$ level. ↓ indicates poorer HRQOL score; ↑, better HRQOL score; ∅, no association; APC, aortopulmonary collateral; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expiratory volume in 1 second; HRQOL, health-related quality of life; LT, lateral tunnel; PR, parent reported; SCC, superior cavopulmonary connection; SR, self-reported; VE/VCO_2, minute ventilation and carbon dioxide production; and VO_2, oxygen uptake.

physical functioning,[2] and lower self- and parent-reported psychosocial functioning[2,6] and overall HRQOL.[57] Two studies found no significant association with any HRQOL domain.[53,77] Patients with siblings reported poorer physical and school functioning; however, this factor was examined in only one study.[23] Two studies found higher maternal education was associated with better self-reported school/work functioning[6] and parent-reported physical functioning.[53] One study examined patient educational attainment, employment, and marital status; no association with any HRQOL domain was found.[72] Associations between parent marital status and HRQOL have also not been found.[77]

Clinical factors

Of the 7 studies investigating HRQOL and ventricular morphological characteristics, only 1 found children with dominant right ventricle had lower parent-reported physical functioning,[41] whereas 6 found no association.[3,53,63,67,72,74] Three studies examined HRQOL and timing of superior cavopulmonary connection. Two cross-sectional studies found

parent-reported psychosocial functioning is lower for children who undergo a superior cavopulmonary connection before their Fontan procedure.[3,38] No association between prior superior cavopulmonary connection and parent-reported physical functioning was found.[38,53] Seven studies investigated HRQOL and Fontan type; 6 found no association with physical[6,23,40,63,72] and emotional[23,63,74] functioning when assessed cross-sectionally, 1 found no association over time,[53] and 1 found children with an intracardiac lateral tunnel Fontan reported poorer social and school/work functioning compared with siblings.[23] Fenestration at time of Fontan was examined in 4 studies; 1 reported children without a fenestration had lower parent-reported physical functioning,[2] and 3 found no association.[39,53,72] Associations between HRQOL and prenatal diagnosis,[77] preterm birth,[77] type of shunt at Norwood procedure,[46] coil embolization of the aortopulmonary collateral vessels,[42] heterotaxy syndrome,[37] and use of extracorporeal membrane oxygenation after Norwood operation[45] have not been found.

Of 3 studies, 1 reported longer time since Fontan surgery was associated with lower physical, emotional, and social functioning in adolescents,[23] but this association was not found in children[77] or adults.[72] Parent-reported physical functioning was lower for patients who had more procedures after Fontan (only 1 study),[63] and those taking a greater number of medications (2 of 2 studies),[2,77] particularly β blockers[43] and class III antiarrhythmic drugs.[43] The same was found for patients with arrhythmias (4 of 4 studies)[2,43,53,60] or protein-losing enteropathy at follow-up (only 1 study),[53] and children with a pacemaker (2 of 2 studies).[43,62] Parents of children who presented with moderate to severe atrioventricular valve regurgitation reported lower physical functioning scores, although this association was evident only for children who had their Fontan at age ≤2 years (1 of 3 studies).[55] Two studies found no association between the degree of atrioventricular valve regurgitation and self-reported HRQOL.[72,74] Across the 6 studies assessing BNP (brain natriuretic peptide) levels, 3 found higher BNP was weakly associated with lower self- and parent-reported physical functioning[40,54,55] and 3 found no association with any HRQOL domain.[53,72,74] Higher serum albumin and lower alanine aminotransferase levels were associated with better self-reported physical functioning in adults;[72] however, these factors were examined by only one study.

Objective measures of better cardiopulmonary function, such as lower resting heart rate (1 study),[43] higher peak heart rate (2 of 2 studies),[43,72] higher peak work rate (3 of 3 studies),[40,52,55] and higher resting O_2 saturation (2 of 4 studies),[40,55] were associated with better physical functioning. Three of 6 studies found higher predicted oxygen uptake (VO_2) at peak exercise was associated with better physical functioning,[40,52,55] whereas 3 reported no association with physical[21,72] or emotional functioning.[74] Higher predicted VO_2 at anerobic threshold was associated with better parent-reported physical functioning across 2 of 3 studies.[52,55] Of the 3 studies that investigated echocardiographic variables (eg, end-diastolic and end-systolic volume, stroke volume, ejection fraction, and ventricular mass) using multivariate modeling, 2 found a weak relationship[40,54] and 1 reported no association with HRQOL.[55] Similarly, 1 of 2 studies found lower ventricular end-systolic volumes corresponded with better parent-reported physical functioning,[55] and 1 found no association.[53] Across the 3 studies assessing ventricular end-diastolic volume, 1 found lower scores were associated with better parent-reported physical functioning,[55] whereas 2 found no association.[53,63] Two (of two) studies found reduced forced expiratory volume in 1 second (FEV_1) was associated with lower physical functioning.[72,78] Physical activity levels and HRQOL was investigated by 2 studies. One study reported greater total daily activity was weakly associated with better self-reported psychosocial functioning,[69] although no associations with parent-reported HRQOL outcomes were found.[52] Across 2 (of 2) studies, self-reported physical functioning was predictive of clinical outcomes; poorer self-reported physical functioning was associated with higher risk of death or heart transplantation over follow-up.[40,41] Atz et al[41] found patients with an elevated brain natriuretic peptide and low physical functioning score were 6 times more likely to die or undergo transplant.

People with better peripheral vascular functioning reported better psychosocial functioning, but only one study examined this, and the correlation was modest.[22] Short stature was examined in one study; short height was associated with lower parent-reported physical and psychosocial functioning.[44] Of 2 studies investigating HRQOL and body mass index at follow-up, 1 found abnormal (higher or lower) body mass index was associated with lower self-reported HRQOL[57] One study found no difference in parent-reported HRQOL outcomes between patients with abnormal body mass index.[44]

Psychological factors

Two studies examined HRQOL and psychological factors. Presence of behavioral, attentional, or learning problems or greater anxiety or depression was associated with lower parent-reported psychosocial functioning in children and adolescents.[2] Learning problems were also associated with lower parent-reported physical functioning[2] when assessed cross-sectionally,[2] but not longitudinally.[53]

Healthcare use and costs

No study examined HRQOL and healthcare use or health service costs.

DISCUSSION

This review, the first to use meta-analytic methods to investigate HRQOL in this population, synthesizes the findings of 50 articles reporting on outcomes of 2793 people with a Fontan circulation and 1437 parent-proxies. We found people of all ages with a Fontan circulation report lower total HRQOL compared with referents, and poorer outcomes across all HRQOL domains, with a particularly large effect for physical functioning. Parents also report lower HRQOL for their child with a Fontan circulation compared with parental reports for healthy children or children from the general community. While greater CHD severity is known to be associated with lower self- and parent-reported HRQOL,[7–9] our work demonstrates the high physical and psychological burden experienced by people with a Fontan circulation.

Meta-analytic findings were generally robust; however, restricting analyses to only SF-36 scores rendered differences between Fontan patients and healthy referents on psychosocial and emotional functioning non-significant. Sensitivity analyses found studies measuring HRQOL using the PedsQL reported larger effect sizes compared with studies using the SF-36. Mean age at PedsQL assessment ranged from 3.0 to 18.5 years, whereas mean age at SF-36 assessment ranged from 20.7 to 27 years. Previous reviews have found adults with CHD report similar outcomes to healthy controls for psychosocial[10,11] and emotional[83] functioning. Moreover, Kahr et al[84] found SF-36 scores were not significantly different between adult CHD patients and healthy controls across all HRQOL domains. Effect size variation across HRQOL measures may be attributable to sample age differences; however, the potential effect of HRQOL measure on outcomes cannot be ruled out.

Meta-regression analyses revealed emotional and social functioning are more likely than physical functioning to be moderated by demographic and medical factors, such as diagnosis of hypoplastic left heart, age at Fontan operation, and age at HRQOL assessment. Neurodevelopmental impairments in children with CHD have also been shown to strongly predict psychosocial health in adolescence.[85] The high prevalence of neuropsychological deficits in children with a Fontan circulation[86–88] may predispose patients to poorer psychosocial outcomes in adulthood. According to the "disability paradox," peoples' perceptions of their physical health are embedded in their illness, such that individuals with a chronic illness may have no reference point for "normal" physical functioning as experienced by the general community.[89] This may explain why individual factors are less likely to predict physical functioning in people with single-ventricle CHD, who are born with their illness. Post hoc analyses indicate the associations between social functioning and HLHS and age at HRQOL assessment may not be robust to differences in HRQOL measure. Prospective studies examining predictive factors across people of all ages with a Fontan circulation using a common HRQOL measure are required to determine the strength of this result.

While patients with HLHS, on average, reported lower social functioning compared with others with a Fontan circulation, HLHS diagnosis was associated with better parent-reported HRQOL across all functional domains. It is possible parents may adjust (or lower) expectations of their child in the context of early counseling on the uncertainty of long-term outcomes. Mahle et al[90] found despite a higher incidence of neurocognitive deficits, most parents of children with HLHS perceived their child's health as "excellent" and described their child's school performance and exercise ability as "average or above." With male patients representing a greater proportion of HLHS patients than female patients, our findings may be influenced by sex effects, though we did not find meta-analytic evidence of this.

Compared with younger patients, those older at time of Fontan operation reported poorer emotional functioning. While evidence suggests older age at Fontan does not increase the incidence of physical complications, such as arrhythmias and PLE,[91] little is known about the psychological consequences of delaying Fontan surgery. Among other CHD groups, older age at surgery has been associated with higher anxiety and depression at follow-up.[92] From a developmental perspective, older children may have greater capacity to comprehend environmental stress,[93] potentially leading to greater acute distress and poorer long-term psychological outcomes. This finding is potentially confounded by older age at HRQOL assessment. Over half our sample (60%) were adults at the time of HRQOL assessment and likely underwent the Fontan procedure at an older age compared with contemporary practice; thus, our findings may reflect a bias toward adult outcomes.

Parents of older children at HRQOL assessment reported lower overall child HRQOL, as well as lower emotional and social functioning. This difference was not reflected in self-reported scores, with older patients reporting better psychosocial functioning than younger patients; however, post hoc analyses indicate this finding may be sensitive to HRQOL measure. Across the reviewed studies, the highest mean age reported was 27 years. It is possible with an aging

Fontan population, we will see an increase in challenges that influence psychosocial outcomes, such as greater physical morbidity, difficulties associated with childbearing, and fears of premature death. It is also difficult to determine the true discrepancy between self- and parent-reported outcomes, as the average patient age was higher among studies relying on self-report compared with parent-report. Of the 20 studies that included both parent-report and self-report, only 3 tested for differences and 2 of these found parent-reported outcomes were significantly lower than the child's own assessment.

Limitations of Captured Studies and the Current Review

While increasing attention is focused on HRQOL as a clinical indicator of health outcomes in the Fontan population, there remains considerable methodologic and measurement variation across studies. Conceptual challenges exist in CHD HRQOL research, including lack of common theoretical frameworks and operational definitions,[94] making it difficult to compare findings between studies and across time. Only 8 studies examined HRQOL using a longitudinal design, limiting causal inference. Changes in medical practices over time (eg, younger age at Fontan procedure in contemporary practice compared with previous surgical eras), and improving survival rates for HLHS patients, may introduce bias. Chance of collinearity between variables is also high,[95] making it difficult to determine the precise effect of risk factors on adverse HRQOL outcomes. In addition, the relatively young age of our cohort may limit the generalizability of our findings to older Fontan patients, who likely experience poorer HRQOL as morbidities arise with age. Factors known to be associated with HRQOL, such as socioeconomic deprivation, neurodevelopmental impairment, greater number of surgeries, and longer length of hospitalization, were not able to be meta-analyzed because of insufficient data, leaving the potential moderating effect of these variables undetermined. Similarly, while high psychological distress and limited social support are known to exert stronger influence on HRQOL within CHD cohorts than clinical factors,[11,15,96,97] we found only 2 studies examining this association, indicating an important knowledge gap. Furthermore, none of the reviewed studies examined HRQOL and healthcare use or fiscal costs; thus, the extent to which HRQOL is influenced by healthcare practices and vice versa remains unclear. Meaningful data could not be extracted from some studies because of incomplete reporting of raw data and lack of control conditions. Evidence of publication bias was found for self-reported social functioning; however, the result remained significant after the Trim and Fill procedure. While people with a Fontan circulation reported lower social functioning compared with healthy referents, the magnitude of this difference should be interpreted cautiously.

Our meta-analyses relied on aggregated study-level data, rather than individual-level data. Using individual-level data may provide greater detail and increase the chance of detecting predictor effects on HRQOL. Exclusion of non–English-language studies may also limit the generalizability of results.

Priorities for Clinical Practice and Research Advancement

Optimal care acknowledges the lifelong impact of the Fontan circulation on HRQOL and well-being. Targeted strategies are required to ensure long-term outcomes of this growing cohort continue to improve.[17] Population-based registries, such as the Australian and New Zealand Fontan Registry[98] and the U.S. National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC),[99] provide encouraging examples of large, rigorous, multisite collaborations designed to overcome the limitations of single-center initiatives. Additional recommendations include the following: (1) use of conceptually driven HRQOL frameworks to inform research questions, methods, and the development and trial of screening and intervention protocols; (2) consistency in measurement and reporting of outcomes and predictive, mediating, and moderating factors to ensure results can be pooled; and (3) longitudinal assessment of HRQOL to capture developmentally sensitive patient- and parent-reported outcomes, as well as potential changes in outcomes over time and with clinical advances. Culturally and developmentally tailored perioperative psychoeducation and psychological care is recommended to bolster psychological resilience, shared decision making, and coping skills among patients and their families.[100]

CONCLUSIONS

The Fontan procedure has led to a pathway of survival for people born with single-ventricle CHD, yet as this cohort ages, the burden of accompanying physical, neurodevelopmental, and psychological morbidities are becoming increasingly evident. This meta-analysis confirms people with a Fontan circulation and their proxies report poorer HRQOL when compared with the general community. While the quality of available evidence is high, our knowledge of the role of moderating factors and psychosocial variables is limited. Considerable work is needed to strengthen our knowledge of the determinants of HRQOL and institute targeted preventive approaches to improve outcomes for this population.

ARTICLE INFORMATION

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Supplementary Materials

Tables S1–S5
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Search strategy.

Area	Search terms
Population	Fontan OR "Single ventricle" OR "hypoplastic left heart syndrome" OR "tricuspid atresia" OR "Pulmonary Atresia" OR "univentricular heart" OR "double outlet right ventricle" OR "double inlet left ventricle" OR "atrioventricular septal defect" OR "complex congenital heart disease" AND LIMITS [English language] AND [humans]
Health related quality of life	"quality of life" OR "health related quality of life" OR QOL OR HRQOL OR HRQL OR "health status" OR function* OR "life satisfaction" OR "subjective wellbeing"

Table S2. Fixed-effects meta-analytic results comparing mean self- and parent-reported HRQOL scores for people with a Fontan circulation to healthy referents.

		Number of participants		Test statistics				Heterogeneity		
	Number of comparisons	**Fontan Patients**	**Healthy Referents**	**SMD**	**95% CI**		***p*-value**	**I^2**	**Q**	***p*-value**
Self-reported outcomes										
Total HRQOL	8	768	7697	-0.89	-0.99	-0.80	**<0.0001**	93.89	114.62	**<0.0001**
Physical functioning	26	1694	13043	-0.84	-0.90	-0.77	**<0.0001**	90.30	257.60	**<0.0001**
Psychosocial functioning	14	1009	5963	-0.67	-0.76	-0.58	**<0.0001**	84.03	81.41	**<0.0001**
Emotional functioning	23	1603	10590	-0.26	-0.34	-0.20	**<0.0001**	85.87	148.60	**<0.0001**
Social functioning	21	1246	10321	-0.68	-0.76	-0.60	**<0.0001**	75.54	77.68	**<0.0001**
School/work functioning	10	882	7986	-0.66	-0.75	-0.57	**<0.0001**	68.45	28.53	**0.001**
Parent-reported outcomes										
Total HRQOL	7	538	11110	-0.99	-1.10	-0.87	**<0.0001**	87.82	49.25	**<0.0001**
Physical functioning	8	802	11482	-0.93	-1.02	-0.84	**<0.0001**	79.08	33.45	**<0.0001**
Psychosocial functioning	8	802	11502	-0.66	-0.75	-0.57	**<0.0001**	91.66	83.88	**<0.0001**
Emotional functioning	6	508	11060	-0.65	-0.76	-0.54	**<0.0001**	83.36	30.05	**<0.0001**
Social functioning	6	508	11051	-0.72	-0.84	-0.61	**<0.0001**	89.30	46.74	**<0.0001**
School/work functioning	4	239	9226	-0.78	-0.93	-0.64	**<0.0001**	64.75	8.51	**<0.0001**

HRQOL, health-related quality of life; SMD, standardized mean difference.

Bold typeface indicates statistically significant at $p<0.05$.

Table S3. Meta-analytic results comparing mean self- and parent-reported HRQOL scores for people with a Fontan circulation and health referents, presented separately by HRQOL measure (PedsQL Core Module or the Short-Form Health Survey-36).

				Test statistics			Heterogeneity	
	Number of comparisons	**Fontan Patients**	**Healthy Referents**	**SMD**	**95% CI**	**p-value**	**I^2**	**Q**
Self-reported HRQOL								
PedsQL Core Module								
Total HRQOL	7	706	7008	-1.11	-1.32 -0.90	**<0.0001**	61.62	15.63
Physical functioning	12	900	7173	-1.18	-1.39 -0.97	**<0.0001**	70.42	37.19
Psychosocial functioning	10	812	7123	-0.83	-1.01 -0.65	**<0.0001**	57.42	21.13
Emotional functioning	10	856	7083	-0.58	-0.79 -0.37	**<0.0001**	69.80	29.80
Social functioning	10	857	7082	-0.89	-1.01 -0.77	**<0.0001**	0.00	4.86
School/work functioning	9	803	7056	-0.77	-0.91 -0.63	**<0.0001**	35.60	12.42
Short-Form Health Survey 36								
Physical functioning	10	310	2137	-0.77	-1.01 -0.53	**<0.0001**	66.64	26.98
Mental health component score	4	197	327	-0.18	-0.60 0.24	0.405	80.06	15.04
Mental health	11	346	2173	-0.23	-0.57 0.12	0.197	82.41	51.17
Social functioning	10	310	2137	-0.21	-0.42 -0.01	**0.044**	45.39	14.65
Parent-reported HRQOL								
PedsQL Core Module								
Physical functioning	7	538	11091	-1.02	-1.32 -0.73	**<0.0001**	81.68	32.76
Psychosocial functioning	7	538	11091	-0.92	-1.29 -0.56	**<0.0001**	88.32	51.40

HRQOL, health-related quality of life

Bold typeface indicates statistically significant at $p<0.05$.

Table S4. Meta-regression results showing moderators of self- and parent-reported HRQOL scores, using the PedsQL Core Module.

			Number of Participants		Meta-Regression Statistics				
Moderators	**HRQOL Domain**	**Number of comparisons**	**Fontan Patients**	**Healthy Referents**	**Slope**	**95% CI**		**p-value**	**R^2**
HLHS (% with diagnosis)	**Self-reported**								
	Total HRQOL	6	298	6666	0.004	-0.006	0.014	0.440	0.00
	Physical functioning	9	460	6749	-0.008	-0.017	0.001	0.085	0.24
	Psychosocial functioning	8	391	6714	0.002	-0.005	0.008	0.633	0.00
	Emotional functioning	8	430	6726	0.003	-0.005	0.010	0.490	0.00
	Social functioning	8	430	6725	-0.003	-0.009	0.003	0.306	0.00
	School/work functioning	7	378	6699	-0.005	-0.007	0.006	0.868	0.00
	Parent-reported								
	Physical functioning	7	538	11091	0.010	0.007	0.014	**<0.0001**	1.00
	Psychosocial functioning	7	538	11091	0.013	0.010	0.017	**<0.0001**	1.00
Age at Fontan operation	**Self-reported**								
	Total HRQOL	2	-	-	-	-	-	-	
	Physical functioning	5	390	426	0.015	-0.459	0.488	0.951	0.00
	Psychosocial functioning	4	501	456	-0.169	-0.842	0.504	0.622	0.00
	Emotional functioning	3	-	-	-	-	-	-	-
	Social functioning	3	-	-	-	-	-	-	-
	School/work functioning	2	-	-	-	-	-	-	-
	Parent-reported								
	Physical functioning	2	-	-	-	-	-	-	-
	Psychosocial functioning	2	-	-	-	-	-	-	-
Age at HRQOL assessment	**Self-reported**								
	Total HRQOL	7	706	7008	0.029	-0.021	0.078	0.256	0.33
	Physical functioning	12	900	7173	0.011	-0.056	0.078	0.744	0.00
	Psychosocial functioning	10	812	7123	0.022	-0.025	0.069	0.362	0.17
	Emotional functioning	10	856	7083	0.001	-0.051	0.052	0.995	0.18
	Social functioning	10	857	7082	0.001	-0.023	0.026	0.923	0.00

	School/work functioning	9	803	7056	0.024	-0.004	0.052	0.087	0.79
	Parent-reported								
	Physical functioning	7	538	11091	-0.060	-0.098	-0.022	**0.021**	0.83
	Psychosocial functioning	7	538	11091	-0.081	-0.123	-0.040	**0.0001**	0.86
Sex (% male)	**Self-reported**								
	Total HRQOL	7	706	7008	0.005	-0.018	0.028	0.673	0.67
	Physical functioning	11	886	7106	-0.003	-0.027	0.008	0.294	0.08
	Psychosocial functioning	9	798	7056	0.004	-0.015	0.022	0.692	0.00
	Emotional functioning	10	856	7083	0.001	-0.017	0.018	0.943	0.00
	Social functioning	10	857	7082	-0.008	-0.020	0.004	0.181	0.00
	School/work functioning	9	803	7056	-0.003	-0.017	0.011	0.658	0.00
	Parent-reported								
	Physical functioning	7	538	11091	0.021	-0.005	0.047	0.112	0.20
	Psychosocial functioning	7	538	11091	0.289	-0.0008	0.059	0.057	0.27

HRQOL, health-related quality of life: HLHS, hypoplastic left heart syndrome.

Bold typeface indicates statistically significant at $p<0.05$.

Table S5. Meta-regression results showing moderators of self- and parent-reported HRQOL scores, using the Short Form Health Survey-36.

			Number of Participants		Meta-Regression Statistics				
Moderators	**HRQOL Domain**	**Number of comparisons**	**Fontan Patients**	**Healthy Controls**	**Slope**	**95% CI**		**p-value**	**R^2**
HLHS (% with diagnosis)	Physical functioning	4	197	327	0.010	-0.206	0.226	0.925	0.00
	Mental health component score	4	197	327	0.048	-0.153	0.249	0.638	0.00
	Mental health	3	-	-	-	-	-	-	-
	Social functioning	3	-	-	-	-	-	-	-
Age at Fontan operation	Physical functioning	4	132	1899	-0.003	-0.219	0.212	0.976	0.00
	Mental health component score	2	-	-	-	-	-	-	-
	Mental health	5	168	1935	-0.225	-0.314	-0.136	**<0.0001**	0.95
	Social functioning	4	132	1899	-0.036	-0.171	0.099	0.603	0.00
Age at HRQOL assessment	Physical functioning	5	218	395	-0.051	-0.243	0.141	0.603	0.00
	Mental health component score	4	197	327	-0.063	-0.292	0.166	0.591	0.00
	Mental health	5	254	431	-0.001	-0.111	0.110	0.993	0.00
	Social functioning	4	164	223	-0.406	-0.901	0.089	0.108	0.67
Sex (% male)	Physical functioning	6	240	2137	-0.041	-0.075	-0.007	**0.018**	0.58
	Mental health component score	4	197	327	-0.030	-0.115	0.056	0.496	0.00
	Mental health	7	276	2173	-0.009	-0.078	0.059	0.787	0.00
	Social functioning	5	186	1965	0.016	-0.015	0.048	0.298	0.02

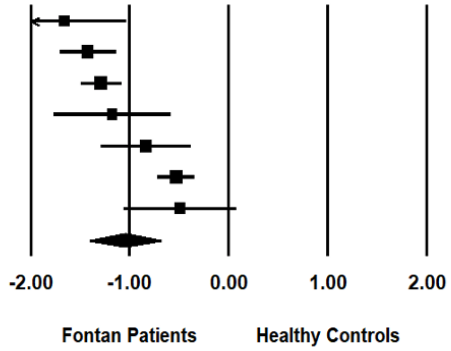
HRQOL, health-related quality of life: HLHS, hypoplastic left heart syndrome.

Bold typeface indicates statistically significant at $p<0.05$.

Figure S1. Forest plot of random effects analysis of parent-reported HRQOL, reported separately for (A) total HRQOL, (B) physical functioning, and (C) psychosocial functioning.

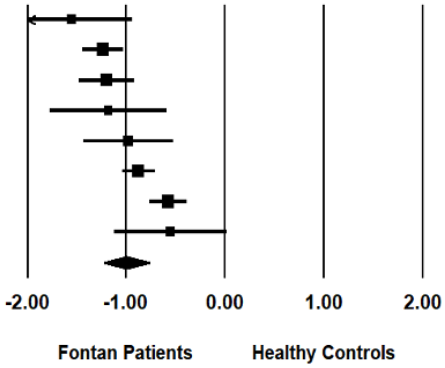
(A) TOTAL HRQOL

Study name	Std diff in means	Lower limit	Upper limit	Relative weight
Hedlund et al. 2016[71]	-1.661	-2.283	-1.040	11.67
Mellion et al. 2014 (13-18 years)[56]	-1.426	-1.707	-1.146	16.07
Mellion et al. 2014 (8-12 years)[56]	-1.292	-1.495	-1.089	16.85
Goldstein et al. 2011[22]	-1.179	-1.771	-0.587	12.06
Friedland-Little et al. 2017 (No ECMO)[45]	-0.836	-1.286	-0.386	13.95
Goldberg et al. 2014[46]	-0.534	-0.720	-0.348	17.00
Friedland-Little et al. 2017 (ECMO)[45]	-0.490	-1.057	0.076	12.40
	-1.051	-1.413	-0.689	



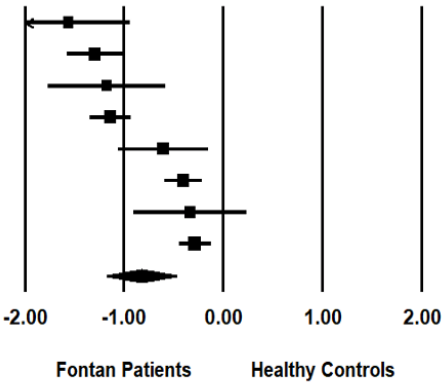
(B) PHYSICAL FUNCTIONING

Study name	Std diff in means	Lower limit	Upper limit	Relative weight
Hedlund et al. 2016[71]	-1.549	-2.154	-0.945	8.12
Mellion et al. 2014 (8-12 years)[56]	-1.233	-1.435	-1.031	16.13
Mellion et al. 2014 (13-18 years)[56]	-1.200	-1.474	-0.925	14.61
Goldstein et al. 2011[22]	-1.179	-1.770	-0.587	8.31
Friedland-Little et al. 2017 (No ECMO)[45]	-0.980	-1.430	-0.529	10.81
Atz et al. 2015[41]	-0.873	-1.036	-0.709	16.86
Goldberg et al. 2014[46]	-0.573	-0.759	-0.387	16.44
Friedland-Little et al. 2017 (ECMO)[45]	-0.550	-1.116	0.016	8.72
	-0.993	-1.223	-0.763	



(C) PSYCHOSOCIAL FUNCTIONING

Study name	Std diff in means	Lower limit	Upper limit	Relative weight
Hedlund et al. 2016[71]	-1.565	-2.178	-0.953	10.23
Mellion et al. 2014 (13-18 years)[56]	-1.295	-1.572	-1.018	13.64
Goldstein et al. 2011	-1.179	-1.771	-0.587	10.45
Mellion et al. 2014 (8-12 years)[56]	-1.144	-1.344	-0.943	14.22
Friedland-Little et al. 2017 (No ECMO)[45]	-0.607	-1.057	-0.157	11.96
Goldberg et al. 2014[46]	-0.404	-0.588	-0.220	14.32
Friedland-Little et al. 2017 (ECMO)[45]	-0.335	-0.902	0.231	10.72
Atz et al. 2015[41]	-0.291	-0.448	-0.134	14.48
	-0.831	-1.180	-0.482	



Box sizes are proportional to the weight of each study in the analysis, and the lines represent their 95% confidence intervals (CIs).

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