ORIGINAL RESEARCH

Long-Term Survival of Individuals Born With Congenital Heart Disease: A Systematic Review and Meta-Analysis

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***Background*—**Estimates of long-term survival are required to adequately assess the variety of health and social services required by those with congenital heart disease (CHD) throughout their lives.

***Methods and Results*—**Medline, Embase, and Scopus were searched from inception to June 2015 using MeSH headings and keywords. Population-based studies that ascertained all persons born with CHD within a predefined area and reported survival estimates at ≥5 years were included. Unadjusted survival estimates for each CHD subtype at ages 1 year, 5 years, 10 years, and so forth were extracted. Pooled survival estimates for each age were calculated using meta-analyses. Metaregression was performed to examine the impact of study period on survival. Of 7840 identified articles, 16 met the inclusion criteria. Among those with CHD, pooled 1-year survival was 87.0% (95% CI 82.1–91.2), pooled 5-year survival was 85.4% (95% CI 79.4–90.5), and pooled 10-year survival was 81.4% (95% CI 73.8–87.9). There was significant heterogeneity of survival estimates among articles ($P<0.001$ for 1-, 5-, and 10-year survival). A more recent study period was significantly associated with greater survival at ages 1 year ($P=0.047$), 5 years ($P=0.013$), and 10 years ($P=0.046$). Survival varied by CHD subtype, with 5-year survival being greatest for those with ventricular septal defect (96.3%, 95% CI 93.7–98.2) and lowest for those with hypoplastic left heart (12.5%, 95% CI 0.0–41.4).

***Conclusions*—**Among persons with CHD, the mortality rate is greatest during the first year of life; however, this systematic review and meta-analysis showed that survival decreases gradually after infancy and into adulthood. **(*J Am Heart Assoc*. 2016;5: e002846 doi: 10.1161/JAHA.115.002846)**

Key Words: congenital • heart defects • survival

Congenital heart disease (CHD) composes the largest group of congenital anomalies and affects ≈1% of births in the United States and Europe.[1–3] CHD is a leading cause of stillbirth and infant death and accounts for 4.2% of neonatal deaths in the United States.[4] Babies with severe CHD subtypes require complex surgeries for survival. With advances in medical, surgical, and intensive care interventions, an estimated 83% of babies with CHD now survive infancy in the United States.[5] Although 1-year survival estimates have been described,[3,6–11] long-term survival estimates are not well researched, and survival may continue to decrease into adulthood.

A previous systematic review of the long-term prognosis of CHD included only hospital-based studies that ascertained cases postsurgically or in adulthood; estimates were not representative of all persons with CHD.[12] We conducted a systematic review and meta-analysis of population-based studies reporting long-term survival of persons born with CHD. The aim was to assess and quantify long-term survival to inform health services planning and decision making.

Methods

Search Strategy

We conducted comprehensive literature searches of Medline, Embase, and Scopus from inception (1946, 1974, and 1996, respectively) to June 18, 2015. MeSH terms and keywords were entered systematically into the databases. The keywords included *congenital* and *heart* or *cardiac* or *cardiovascular* and subject heading searches such as "exp Heart Defects, Congenital/ep, mo" but varied according to database. The list of search terms is available from the authors.

After systematic searches of each database, the citations were extracted, and titles and abstracts were screened according to the inclusion criteria. Full articles were retrieved for all relevant citations. Reference lists of included articles

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were scanned and examined, and key journals were searched using keywords.

Inclusion Criteria

Population-based original studies were included if they (1) ascertained all persons born with CHD within a predefined geopolitical area; (2) reported survival estimates (or the number of patients born and the number or proportion alive) at age ≥5 years; (3) reported survival estimates for all CHD combined or a single CHD subtype including ventricular septal defect, pulmonary valve stenosis, atrial septal defect, aortic valve atresia or stenosis, atrioventricular septal defect, coarctation of aorta, common arterial truncus, pulmonary valve atresia (with ventricular septal defect or with intact ventricular septum), tetralogy of Fallot, total anomalous pulmonary venous return, transposition of great vessels, tricuspid atresia, single ventricle, hypoplastic left heart, and Ebstein's anomaly; (4) were available from the British Library or the Internet and were written in the English language.

Exclusion Criteria

Articles were excluded if patients were not followed from birth (eg, follow-up began in adulthood or after surgical correction); patients were not born in well-defined regions (ie, hospital-based); survival was not estimated as a proportion of those born with CHD (eg, age-specific population mortality rates); survival was reported only for certain subtype groups (eg, "severe" CHD). For multiple articles reported on the same data set, the largest study or the study with the most recent study period was included. Both articles were included if they reported survival for different CHD subtypes or ages.

Data Extraction

K.E.B. performed the literature searches, screened citations, and reviewed 40 full papers. J.R. screened 10% of the titles and all abstracts to confirm decisions about inclusion, and extracted data from all included papers. There were no discrepancies between reviewers regarding article inclusion.

Study characteristics including study design, quality, data sources, prevalence estimates, and the percentage of cases with extracardiac anomalies (ie, cases of CHD occurring with another congenital anomaly not of the cardiovascular system, such as Down syndrome or cleft lip) were extracted from each article. If it was unclear whether cases with extracardiac anomalies were included, the authors were contacted.

Kaplan–Meier survival estimates and corresponding 95% CIs were obtained from each included study at ages 1 year, 5 years, 10 years, and so forth. If 95% CIs were not reported, the authors were contacted. If this was unsuccessful, the number of patients born and the proportion that survived were used to estimate binomial 95% CIs, assuming no cases were censored. Survival estimates for all CHD subtypes combined and for each CHD subtype were extracted. If survival estimates were presented only graphically, the authors were contacted for survival estimates. If this was unsuccessful, survival estimates were extracted using Plot Digitizer software.[13,14]

Statistical Analysis

If there were at least 3 studies reporting survival, pooled estimates of survival were calculated using a meta-analysis with random effects. Weighting for each article was allocated using the inverse of the variance. If the number of studies is small, the estimation of between-study variance is thought to be imprecise in random-effects models.[15] Consequently, if there were only 3 studies reporting survival, the pooled survival was also estimated using fixed-effects meta-analysis to allow comparison. To stabilize the variance and adjust the study weights, a simplified double-arcsine transformation was performed on the survival estimates and 95% CIs.[16] The Cochrane Q test and the I^2 statistic were used to test for heterogeneity in survival estimates between articles, with I^2>50% indicating substantial heterogeneity.[17] Random-effects metaregression was performed for all CHD subtypes combined to assess year of delivery as a source of heterogeneity. In this analysis, the year in which the study commenced was used as an explanatory variable. The adjusted R^2 value was used to estimate the proportion of between-article variation accounted for by the year of study commencement. A bubble plot was used to present the fitted metaregression model. In this analysis, bubbles represent each article, with sizes dependent on the

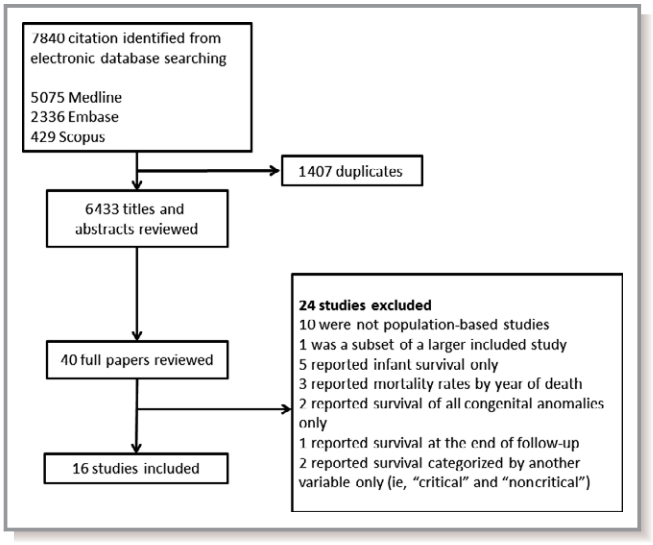

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram for the flow of articles through the review.

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Table 1. Descriptions of the Included Articles

Study	Included Birth Years	Study Location	Included CHD Subtypes (ICD Codes)	Inclusion of ECAs	Age Limit for Diagnosis	Source of Cases	Source of Death Information	Percentage of Traced Cases	Prevalence per 1000 Live Births
Dastgiri et al[20]	1980–1997	Glasgow, Scotland	All CHD subtypes (ICD 10: Q20–26)	Author's response: excluded	No age limit	Glasgow register of Congenital Anomalies	Registrar General for Scotland	97% (all congenital anomalies)	Not stated
Fixler et al[21]	1996–2003	Texas, USA	SV physiology: HLH (ICD 9: 746.7), PVA-IVS (746.0), SV (745.3), TA (746.1), d-TGV (745.1)	Cases with trisomy 13 or 18 were excluded; 14.1% of HLH, 21.0% of SV, 15.3% of PVA-IVS, 17.9% of TA, 9.3% of d-TGV had ECAs	1 year	Texas Birth Defects Registry	Medical records, death certificates, national death index	N/A, nontraced cases considered alive	Not stated
Frid et al[22]	1973–1997	Sweden	AVSD (ICD 9: 745G, ICD 10: 21.2)	Cases with trisomy 13 or 18 were excluded; 68.9% had trisomy 21	None stated	Register of Congenital Malformations, Register of Congenital Heart Malformations, and the Medical Birth Register; local registries at 4 pediatric cardiology centers were also searched for the beginning of the study period	National population database and medical records	98.7% of all cases with AVSD	0.3
Garne[23]	1986–1998	Funen County, Denmark	All CHD subtypes (EUROCAT criteria ie, ICD 10: Q20–26)	Cases with ECAs were included, 21% of cases	5 years and diagnosed before 2002	EUROCAT Registry of Congenital Malformations for Funen County	National registration system	99.6%	7.9
Idorn et al[24]	1977–2009	Denmark, Europe	HLH (ICD 10: Q234), PVA-IVS (Q220), TA (Q224)	Cases with ECAs were included, 10% of cases	All ages	Danish register of congenital heart disease, local surgical registries, medical records, local fetal ultrasound registries	Civil registration system	Not stated	0.4
Jackson et al[25]	1979–1988	Merseyside, England	All CHD subtypes (ICD 9: 745.00–747.49)	Cases with ECAs were included, percentage not stated	No age limit	Liverpool Registry of Congenital Malformations	Liverpool Registry of Congenital Malformations and hospital records	Not stated	7.6
Meberg et al[26]	1982–1996	Vestfold, Norway, Europe	All CHD subtypes (no ICD codes stated)	Cases with ECAs were included, 20% of cases	None stated	Vestfold County Central Hospital, regional cardiology services, Child Health Centers and pediatric departments of the hospitals in neighboring counties	Hospital records	100%	10.2

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Table 1. Continued

Study	Included Birth Years	Study Location	Included CHD Subtypes (ICD Codes)	Inclusion of ECAs	Age Limit for Diagnosis	Source of Cases	Source of Death Information	Percentage of Traced Cases	Prevalence per 1000 Live Births
Miller et al[27]	1979–2003	Metropolitan Atlanta, GA, USA	AVSD (ICD 9: 745.000–747.999)	Cases with trisomy 13 or 18 were excluded, 52.4% had trisomy 21	None stated	Metropolitan Atlanta Congenital Defects Program	Hospital records and vital records from the state of Georgia, National Death Index	Not stated but number of untraced "assumed to be small"	Not stated
Moons et al[28]	2002	Belgium	All CHD subtypes (no ICD codes specified)	Author response: cases with ECAs were included, percentage not stated	5 years	Pediatric cardiology database covering 7 tertiary care centers in Belgium	Medical records	Not stated	8.3
Nembhard et al[29]	1996–2003	Texas, USA	ICD 9 (746–747)	Cases with trisomy 13 or 18 were excluded, 20.7% of cases had ECAs	1 year	Texas birth defects register	Death certificates linked to the Texas birth defects register	Not stated	8.7
Olsen et al[30]	1977–2006	Denmark	All CHD subtypes: ICD 8: 746 to 747 (except 746.7 and 747.5–747.9) and ICD-10: Q20–Q26 (except Q26.5–Q26.6)	Cases with ECAs were included, 20.0% of cases	1 year	Danish National Registry of Patients	Civil registration system	100%	3.7
Samanek and Voriskova[31]	1980–1990	Bohemia, Czech Republic	All CHD subtypes (no ICD codes specified)	Not stated	None stated	Hospital records	Autopsy reports	Not stated	6.2
Tennant et al[32]	1985–2003	Northeast England	All CHD subtypes (ICD 10: Q20–26)	Cases with ECAs were excluded, percentage not stated	16 years of age (1985–2001) or, from 2001, to age 12 years	Northern Congenital Abnormality Survey	Office for National Statistics death registrations	99% (of all congenital anomalies)	6.8
Wang et al (2011)[33]	1983–2006	New York State, USA	TGV (ICD 9: 745.10–745.12, 745.19), ToF (745.2), HLH (746.7), AVA/S (746.3), CAT (745.0), AVSD (745.6), CoA (747.10)	Cases with ECAs were included, percentage not stated	None stated	Congenital Malformations Registry	Death certificates files maintained by the New York State Department of Health	97% (of all congenital anomalies)	9.5

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Table 1. Continued

Study	Included Birth Years	Study Location	Included CHD Subtypes (ICD Codes)	Inclusion of ECAs	Age Limit for Diagnosis	Source of Cases	Source of Death Information	Percentage of Traced Cases	Prevalence per 1000 Live Births
Wang et al (2013)[34]	1983–2006	New York State, USA	TGV (ICD 9: 745.10–745.12, 745.19), ToF (745.2), HLH (746.7), CoA (747.10)	Cases with ECAs were included, percentage not stated	2 years	Congenital Malformations Registry	Death certificate files maintained by the New York State Department of Health	Not stated	Not stated
Wang et al (2015)[35]	1991–2007	Arizona, Colorado, Florida, Georgia (5 counties of Metropolitan Atlanta), Illinois, Massachusetts, Michigan, Nebraska, New Jersey, New York (excluding New York City), North Carolina, Texas	TGV (ICD 9: 745.10–745.12, 745.19), ToF (745.2), HLH (746.7), AVA/S (746.3), CAT (745.0), AVSD (745.6), CoA (747.10)	Cases with ECAs included, percentage not stated	None stated	Arizona Birth Defects Monitoring Program, Metropolitan Atlanta Congenital Defects Program, Colorado Responds to Children with Special Needs, Florida Birth Defects Registry, Illinois Adverse Pregnancy Outcomes Reporting System, Massachusetts Birth Defects Monitoring Program, Michigan Birth Defects Registry, Nebraska Birth Defects Registry, New Jersey Special Child Health Services Registry, New York State Congenital Malformations Registry, North Carolina Birth Defects Monitoring Program, and Texas Birth Defects Epidemiology, and Surveillance Branch	Death certificates, hospital discharge files (Arizona, Texas), medical records (Arizona, Texas), and the National Death Index (Georgia, Michigan)	Not stated	2.1

AVA/S, aortic valve atresia or stenosis; AVSD, atrioventricular septal defect; CAT, common arterial truncus; CHD, congenital heart disease; CoA, coarctation of aorta; d-TGV, dextro-TGV; ECA, extracardiac anomaly; HLH, hypoplastic left heart; ICD, International Classification of Disease; IVS, intact ventricular septum; N/A, not available; PVA, pulmonary valve atresia (with ventricular septal defect or IVS); SV, single ventricle; TA, tricuspid atresia; TGV, transposition of great vessels; ToF, tetralogy of Fallot.

precision of the survival estimates. Publication bias was assessed with the Egger test.[18]

Analysis was performed in Stata 13 (StataCorp), and $P<0.05$ was considered statistically significant.

Quality Appraisal

Quality appraisal was based on 4 of the 6 domains developed by Hayden et al to assess potential bias in systematic reviews of prognostic studies.[19] The domains used were study ascertainment, study attrition, outcome ascertainment, and analysis. The domains relating to confounding and prognostic factors were not relevant to this review because the primary aim was to investigate unadjusted survival estimates.

Results

Figure 1 shows a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram for the flow of articles through the review. Of 7840 identified articles, 16 met the inclusion criteria.[20–35]

Study Characteristics

All included studies were conducted in high-income Western populations, with 10 in Europe and 6 in the United States (Table 1). Although several articles reported survival of subsets of the same population, all were included because survival was reported for different CHD subtypes or at different ages. The oldest article included patients born between 1973 and 1997,[22] and the most recent article included patients born between 1991 and 2007.[35] Of the 16 included articles, 9 included cases with extracardiac anomalies, with ≈20% of cases occurring with other congenital anomalies in each article.[23–26,28,30,33–35] Four articles excluded patients with trisomy 13 (Patau syndrome) and 18 (Edward syndrome) only.[21,22,27,29] Two articles excluded cases of CHD with any extracardiac anomalies,[20,32] and 1 did not state whether cases with extracardiac anomalies were included.[31] Prevalence estimates were reported by most studies and ranged from 3.7[30] to 10.2[26] per 1000 live births when considering all CHD as a composite group.

Survival Estimates

Survival was reported to age 5 years in 5 articles,[20,21,23,28,29] to age 8 years in 1 article,[35] to age 10 years in 3 articles,[25–27] to age 15 years in 2 articles,[22,31] to age 20 years in 1 article,[32] to age 25 years in 3 articles,[30,33,34] and to age 30 years in 1 article.[24]

For all CHD (as a composite group), pooled 1-year survival from 6 articles was 87.0% (95% CI 82.1–91.2), pooled 5-year survival from 8 articles was 85.4% (95% CI 79.4–90.5), and pooled 10-year survival from 4 articles was 81.4% (95% CI 73.8–87.9) (Figure 2). It was not possible to pool estimates beyond 10 years because there were too few articles; however, Figure 3 shows the survival estimates plotted over increasing age, up to age 25 years. The fitted metaregression showed that survival decreases very gradually with increasing age over 25 years. There was no evidence of publication bias according to Egger tests ($P=0.748$ for 1 year, $P=0.237$ for 5 years, and $P=0.601$ for 10 years). There was significant

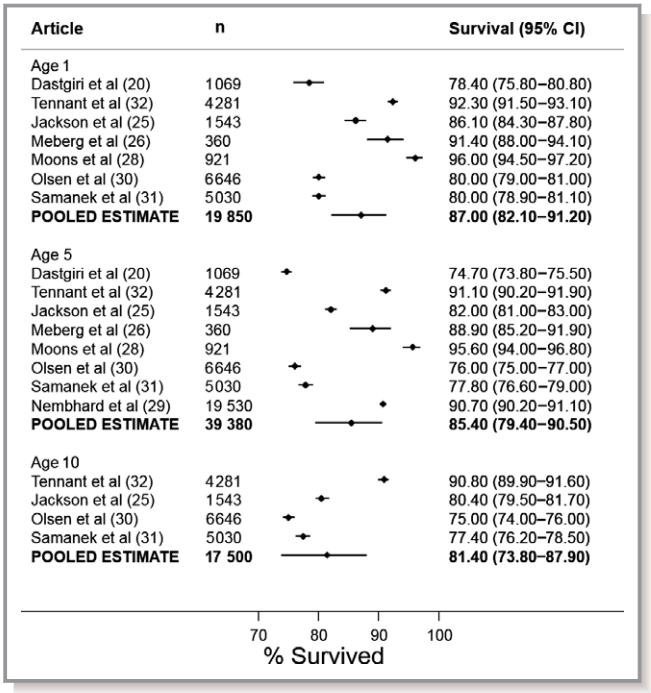

Figure 2. Forest plot for all congenital heart disease at ages 1, 5, and 10 years.

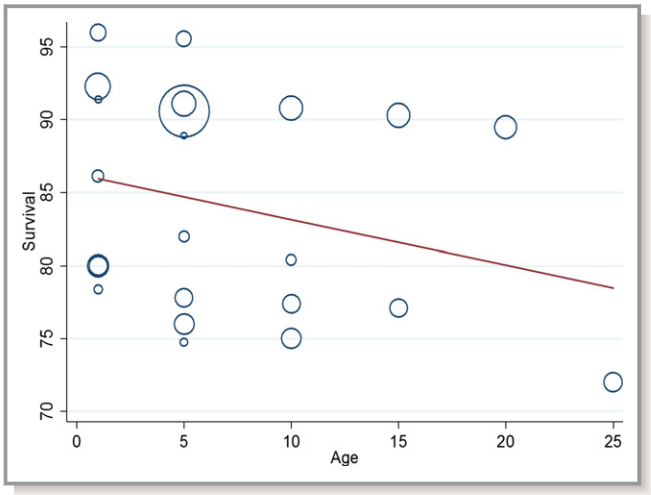

Figure 3. Bubble plot of survival estimates for all congenital heart disease at ages 1 to 25 years.

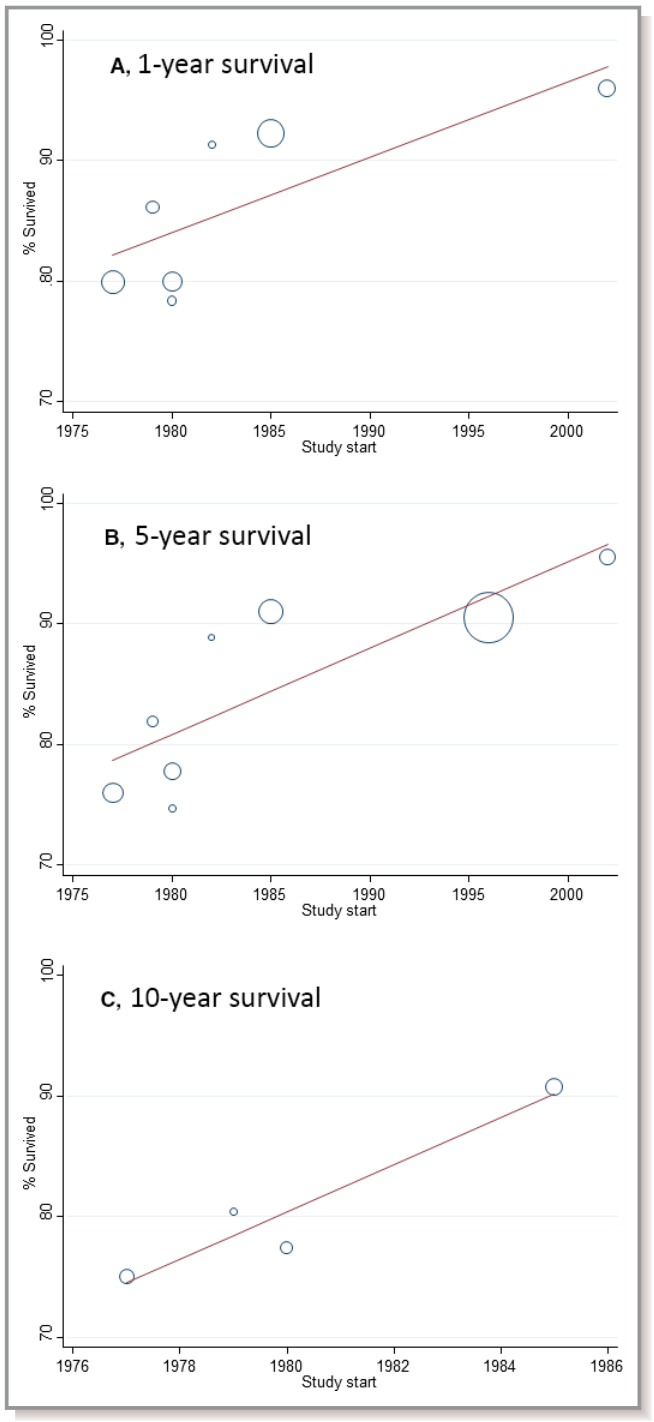

Figure 4. Bubble plots showing the association between study period and survival for all congenital heart disease. A, 1-year survival. B, 5-year survival. C, 10-year survival.

heterogeneity between articles for survival at 1 year (I^2=99.0%, P<0.001), 5 years (I^2=99.6%, P<0.001), and 10 years (I^2=99.5%, P<0.001). Metaregression showed that a more recent study period was significantly associated with increased 1-, 5-, and 10-year survival (P=0.047, P=0.013, and P=0.046, respectively) (Figure 4). According to the adjusted R^2 values, study period accounted for 50.9%, 62.8%, and 87.0% of the between-article variance for 1-, 5-, and 10-year survival. After adjustment for study period, however, substantial residual heterogeneity remained that was attributable to between-study heterogeneity (I^2=98.2% at age 1 year, I^2=98.4% for survival at age 5 years, and I^2=93.7% for survival at age 10 years).

Table 2 shows the survival estimates and pooled survival estimates for persons with CHD by subtype. Pooled 1-year survival was lowest for those with hypoplastic left heart (17.4%, 95% CI 0.0–54.5) and greatest for those with ventricular septal defect (95.5%, 95% CI 89.0–99.2). There was significant heterogeneity of survival estimates among articles for all CHD subtypes, with the exception of tetralogy of Fallot (I^2=0%, P=0.169). Heterogeneity of estimates for single ventricle was of borderline statistical significance (I^2=65.0%, P=0.057). Pooled 5-year survival varied by subtype, with survival for hypoplastic left heart at 12.5% (95% CI 0.0–41.4) and survival for ventricular septal defect at 97.7% (95% CI 93.5–99.8). With the exception of tetralogy of Fallot (I^2=0.0%, P=0.957) and single ventricle (I^2=26.9%, P=0.250), there was significant heterogeneity of survival estimates among articles (Table 2). It was possible to calculate pooled 15-year survival estimates for aortic valve atresia or stenosis, atrioventricular septal defect, common arterial truncus, and coarctation of aorta but not for any other CHD subtypes. There were too few studies to calculate pooled survival beyond age 15 years, although in the few studies that reported survival into adulthood, survival was still gradually declining.

For subtypes for which just 3 studies reported survival, pooled estimates were also calculated using fixed-effect meta-analysis (Table 2). Pooled survival estimates were generally similar for the random- and fixed-effects models, with the exception of the 10- and 15-year pooled estimates for common arterial trunk (28.9% versus 35.4% and 36.5% versus 54.4%, respectively).

Quality Appraisal

Quality appraisal is shown in Table 3. All articles satisfied the study ascertainment domain because, by definition, population-based studies are representative of the population. The attrition domain was satisfied by 31% of articles because of studies failing to report the proportion of untraced cases; however, many of the studies classed unmatched cases as alive, so it is possible that all cases were traced. The outcome ascertainment domain was satisfied by 94% of studies, and the analysis domain was satisfied by 81%. Studies that did not satisfy the analysis domain were those that did not perform survival analysis and instead reported the proportion alive, which does not account for case censorship. This may have slightly inflated survival in these studies.

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Table 2. Survival Estimates at Age One to 25

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 years	20 years	25 years
All congenital heart disease	Dastgiri et al[20]	1069	78.4 (75.8–80.8)*	74.7 (73.8–75.5)†				
	Jackson et al[25]	1543	86.1 (84.3–87.8)*	82.0 (81.0–83.0)	80.4 (79.5–81.7)†			
	Meberg et al[26]	360	91.4 (88.0–94.1)*	88.9 (85.2–91.9)*				
	Moons et al[28]	921	96.0 (94.5–97.2)*	95.6 (94.0–96.8)*				
	Nembhard et al[29]	19 530		90.7 (90.2–91.1)*				
	Olsen et al[30]	6646	80 (79–81)	76 (75–77)*	75 (74–76)			72 (70–73)
	Samanek et al[31]	5030	80.0 (78.9–81.1)	77.8 (76.6–79.0)	77.4 (76.2–78.5)	77.1 (75.9–78.3)		
	Tennant et al[32]	4281	92.3 (91.5–93.1)	91.1 (90.2–91.9)	90.8 (89.9–91.6)	90.3 (89.3–91.2)	89.5 (88.4–90.6)	
	Pooled estimate (95% CI)		87.0 (82.1–91.2)	85.4 (79.4–90.5)	81.4 (73.8–87.9)			
	Heterogeneity I^2 & *P*-value		99.0%, *P*<0.001	99.6%, *P*<0.001	99.5%, *P*<0.001			
Ventricular septal defect	Garne[23]	195		96.9 (93.4, 98.9)*				
	Moons et al[28]	303		99.3 (97.6–99.9)*				
	Nembhard et al[29]	10 382		93.9 (93.5–94.4)*				
	Olsen et al[30]	1559	94 (93–95)		90 (89–91.7)			
	Samanek et al[31]	2092	91.1 (89.8–92.3)*			89.4 (88.0–90.7)		
	Tennant et al[32]	1805	99.2 (98.7–99.5)	99.1 (98.6–99.5)	99.1 (98.5–99.4)	99.1 (98.5–99.4)	98.3 (96.6–99.1)	
	Pooled estimate (95% CI)		95.5 (89.0–99.2)	97.7 (93.5–99.8)				
			95.5 (95.0–96.0)					
	Heterogeneity I^2 & *P*-value		99.0%, *P*<0.001	98.1%, *P*<0.001				
Pulmonary valve stenosis	Garne [23]	33		97.0 (84.2–99.9)*				
	Nembhard et al[29]	1170		91.6 (89.9–93.1)*				
	Samanek et al[31]	292	96.2 (94.0–98.5)	95.6 (93.1–98.0)	95.6 (93.1–98.0)	95.6 (93.1–98.0)		
	Tennant et al[32]	382	98.7 (96.8–99.5)	98.1 (96.1–99.1)	98.1 (96.1–99.1)	98.1 (96.1–99.1)	98.1 (96.1–99.1)	
	Pooled estimate (95% CI)			95.6 (91.1–98.6)				
	Heterogeneity I^2 & *P*-value			89.6%, *P*<0.001				
Atrial septal defect	Garne[23]	78		98.7 (93.1, 100.0)*				
	Moons et al[28]	162		99.4 (96.6–100.0)*				
	Nembhard et al[29]	9164		89.9 (89.3–90.5)*				
	Olsen et al[30]	361	93 (90–95.3)		91 (88–95.6)			84 (72–91)

Continued

Table 2. Continued

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 years	20 years	25 years
	Samanek et al[31]	436	94.0 (92.4–96.3)		92.9 (90.1–95.1)*	92.9 (90.1–95.1)*		
	Tennant et al[32]	365	97.3 (95.0–98.5)	97.0 (94.6–98.3)	97.0 (94.6–98.3)	96.3 (93.3–98.0)	96.3 (93.3–98.0)	
	Pooled estimate (95% CI)		94.9 (92–97.2)	96.8 (90.8–99.7)	94.0 (89.9–97.1)			
			94.8 (93.5–96.0)	95.4%, $P<0.001$	*94.3 (92.7–95.6)*			
	Heterogeneity I^2 & P-value		77.4%, $P<0.001$		81.6%, $P=0.004$			
Aortic valve atresia/ stenosis	Garne[23]	24		87.5 (67.6, 97.3)*				
	Moons et al[28]	36		100.0 (90.3–100.0)*				
	Samanek[31]	391	90.3 (87.3–93.3)			88.4 (85.1–91.7)		
	Tennant et al[32]	171	92.4 (87.3–95.5)	91.2 (85.9–94.6)	91.2 (85.9–94.6)	89.3 (83.2–3.3)	89.3 (83.2–3.3)	
	Wang et al[33]	877				74.1 (71.0–77.0)		73.4 (70.1–76.4)
	Wang et al[35]	2646	83.6 (82.1–84.9)	81.5 (79.7–83.2)				
	Pooled estimate (95% CI)		88.7 (82.4–93.8)	92.1 (81.3–98.4)		84.4 (73.1–93.1)		
			85.0 (83.7–86.2)	92.7%, $P<0.001$		*82.2 (80.3–84.0)*		
	Heterogeneity I^2 & P-value		91.3%, $P<0.001$			96.8%, $P<0.001$		
Atrioventricular septal defect	Frid et al[22]	502	77.1 (73.2–80.7)*	66.5 (62.2–70.7)*	64.3 (59.9–68.5)*	63.1 (58.8–67.4)*		
	Garne[23]	20		50 (27.2–72.8)*				
	Miller et al[27]	338			57.9 (49.7–65.3)			
	Moons et al[28]	37		91.9 (78.1–98.3)*				
	Olsen et al[30]	354	75 (70–79)		65 (59–70)			59 (51–65)
	Samanek et al[31]	201	62.2 (55.4–69.0)	54.7 (47.7–61.8)	54.2 (47.1–61.2)	54.2 (47.1–61.2)		
	Tennant et al[32]	94	84.0 (74.9–90.1)	80.9 (71.3–87.5)	79.7 (70.1–86.6)	79.7 (70.1–86.6)	79.7 (70.1–86.6)	
	Wang et al[33]	1004				59.5 (56.3–62.6)	58.1 (56.5–61.4)	56.6 (52.8–60.2)
	Wang et al[34]	4884	80.1 (79.0–81.2)	76.7 (75.3–78.1)				
	Pooled estimate (95% CI)		75.9 (70.5–81.0)	71.2 (61.9–79.6)	64.0 (57.2–70.5)	63.4 (56.3–70.3)		
	Heterogeneity I^2 & P-value		89.0%, $P<0.001$	92.7%, $P<0.001$	81.4%, $P<0.001$	85.9%, $P<0.001$		
Coarctation of aorta	Garne[23]	12		58.3 (27.7–84.8)*				
	Moons et al[28]	46		91.3 (79.2–97.6)*				
	Nembhard et al[29]	1145		78.6 (76.1–80.9)				
	Olsen et al[30]	334	84 (79–87)		82 (77–85)			78 (61–82)
	Samanek et al[31]	266	68.0 (62.3–73.8)	65.4 (59.6–71.3)	65.0 (59.2–70.9)	65.0 (59.2–70.8)		
	Tennant et al[32]	189	91.5 (86.6–94.7)	91.5 (86.6–94.7)	90.9 (85.8–94.3)	90.9 (85.8–94.3)	89.6 (83.7–93.5)	

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Table 2. Continued

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 years	20 years	25 years
	Wang et al[33]	2529	79.4 (77.8–81.0)	77.0 (75.4–78.6)		76.0 (74.3–77.7)		75.2 (73.3–77.0)
	Wang et al[34]	6365	84.5 (83.6–85.4)	81.9 (80.7–83.0)				
	Pooled estimate (95% CI)		82.7 (75.4–89.0)	81.0 (70.7–89.4)	80.3 (65.0–92.0)	78.2 (65.9–88.4)		
					79.5 (76.6–82.2)	*76.2 (74.6–77.7)*		
	Heterogeneity I^2 & *P*-value		93.7%, *P*<0.001	93.0%, *P*<0.001	87.3%, *P*<0.001	95.6%, *P*<0.001		
Common arterial trunk	Moons et al[28]	7		85.7 (42.1–99.6)*				
	Olsen et al[30]	78	45 (34–55)	45 (34–55)	45 (34–55)	45 (34–55)	45 (34–55)	45(34–55)
	Samanek et al[31]	55	12.7 (3.7–21.7)	10.5 (4.1–22.2)*	7.3 (0–15.4)	7.3 (0–15.4)		
	Tennant et al[32]	36	36.1 (21.0–51.4)	36.1 (21.0–51.4)	36.1 (21.0–51.4)			
	Wang et al[33]	460				59.2 (54.4–63.6)		55.2 (49.5–60.5)
	Wang et al[35]	956	75.1 (72.7–77.7)					
	Pooled estimate (95% CI)		41.8 (14.1–72.6)	47.4 (21.8–73.8)	28.9 (16.3–43.3)	36.5 (14.6–62)		
					35.4 (30.0–41.0)	*54.4(50.2–58.6)*		
	Heterogeneity I^2 & *P*-value		97.6%, *P*<0.001	96.3%, *P*<0.001	87.3%, *P*<0.001	94.5%, *P*<0.001		
Pulmonary valve atresia (with IVS)	Fixler et al[21]	118	59.3 (49.9–67.6)	55.7 (45.8–64.4)				
	Idorn et al[24]	75	41.7 (30.1–53.3)*	37.5 (26.4–49.2)*	35.3 (24.0–46.5)*	37.5 (26.4–49.2)*	35.3 (24.0–46.5)*	37.5 (26.4–49.2)*
	Moons et al[28]	6		83.3 (36.5–99.1)*				
	Samanek et al[31]	53	18.9 (8.1–29.6)	7.6 (0.3–14.8)	7.6 (0.3–14.8)	7.6 (0.3–14.8)		
	Pooled estimate (95% CI)		39.7 (18.5–63.3)	41.1 (17.2–67.6)				
			45.5 (39.2–52.0)					
	Heterogeneity I^2 & *P*-value		92.1%, *P*<0.001	92.0%, *P*<0.001				
Pulmonary atresia	Garne et al[23]	5		60.0 (14.7–94.7)*				
Pulmonary valve atresia (with VSD)	Moons et al[28]	6	67 (19–96)*	50 (11.8–88.2)*				
	Samanek et al[31]	55	61.8 (48.7–74.9)	54.5 (41.1–68.0)	45.2 (30.8–59.6)	45.2 (30.8–59.6)		
Tetralogy of Fallot	Garne[23]	7		82.6 (61.2–95.0)*				
	Moons et al[28]	52	83 (70–92)*	82.7 (69.7–91.8)*				
	Olsen et al[30]	381	83 (79–87)		70 (65–74)			67 (58–74)
	Samanek et al[31]	169	84.6 (79.0–90.2)		76.6 (70.1–83.2)	76.6 (70.1–83.2)		
	Tennant et al[32]	190	90.5 (85.4–93.9)	83.7 (77.6–88.2)	83.1 (76.9–87.7)	83.1 (76.9–87.7)	80.8 (72.8–86.6)	

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Table 2. Continued

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 years	20 years	25 years
	Wang et al[34]	5208	87.1 (86.1–87.9)	84.7 (83.5–85.8)				
	Wang et al[34]	1739						86.9 (85.3–88.4)
	Pooled estimate (95% CI)		86.3 (83.7–88.6)	84.6 (83.5–85.7)	81.4 (77.5–85)			
					81.6 (78.6–84.4)			
	Heterogeneity I^2 & *P*-value		0.0%, *P*=0.097	0.0%, *P*=0.957	36.1%, *P*=0.209			
Total anomalous pulmonary venous return	Garne[23]	5		20 (0.5–71.6)*				
	Samanek et al[31]	40	52.5 (36.7–8.23)	50.0 (34.2–65.8)	50.0 (34.2–65.8)	50.0 (34.2–65.8)		
	Tennant et al[32]	54	72.2 (58.2–82.2)	72.2 (58.2–82.2)	72.2 (58.2–82.2)	72.2 (58.2–82.2)	72.2 (58.2–82.2)	
	Pooled estimate (95% CI)			53.7 (30–76.6)				
				61.2 (51.2–70.6)				
	Heterogeneity I^2 & *P*-value			76.6%, *P*=0.014				
Transposition of the great vessels	Garne[23]	21		76.2 (52.8, 91.8)*				
	Moons et al[28]	29		100.0 (88.1–100.0)*				
	Olsen et al[30]	461	74 (70–78)		62 (38–67)			50 (41–59)
	Samanek et al[31]	271	61.6 (56.7–67.5)	56.5 (50.3–62.4)*	53.9 (46.8–60.9)	53.9 (46.8–60.9)		
	Tennant et al[32]	189	82.5 (76.3–87.3)	81.0 (74.6–85.9)	80.3 (73.8–85.3)	78.4 (71.6–83.9)	74.1 (64.4–81.5)	
	Wang et al[34]	1840						74.5 (72.4–76.4)
	Wang et al[34]	4330	83.7 (82.6–84.4)	81.1 (79.7–82.4)				
	Pooled estimate (95% CI)		76.0 (65.5–85.1)	81.9 (68.9–91.9)	66.1 (46.0–83.5)			
					67.1 (62.5–71.5)			
	Heterogeneity I^2 & *P*-value		96.9%, *P*<0.001	95.9%, *P*<0.001	93.6%, *P*<0.001			
Tricuspid atresia	Fixler et al[21]	67	76.1 (64.0–84.6)	74.6 (62.4–83.4)				
	Idorn et al[24]	106	68.0 (58.2–76.7)*	61.7 (51.4–70.6)*	60.5 (50.4–69.7)*	57.4 (47.6–67.1)*	57.4 (47.6–67.1)*	57.4 (47.6–67.1)*
	Moons et al[28]	4	100 (39.8–100.0)*	100 (39.8–100.0)*				
	Samanek et al[31]	39	46.2 (30.2–62.1)		35.9 (20.5–51.3)	35.9 (20.5–51.3)		
	Tennant et al[32]	24	83.3 (61.5–93.4)	66.7 (44.3–81.7)	62.5 (40.3–78.4)	62.5 (40.3–78.4)		
	Pooled estimate (95% CI)		71.4 (57.2–83.7)	53.7 (30.0–76.6)	53.1 (36.5–69.2)	53.3 (37.2–69.1)		
					55.1 (47.3–62.9)	*56.2 (49.1–63.1)*		
	Heterogeneity I^2 & *P*-value		74.4%, *P*=0.004	93.9%, *P*<0.001	72.4%, *P*=0.027	72.9%, *P*=0.025		
Hypoplastic left heart	Garne	22		4.5 (0.1–22.8)*				
	Idorn et al[24]	252	12.5 (8.9–17.5)*	10.4 (6.9–14.8)*	10.4 (6.9–14.8)*	8.8 (5.6–12.9)*		

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Table 2. Continued

Subtype	Article	N	Survival Estimates (95% CI)					
			1 year	5 years	10 years	15 years	20 years	25 years
	Moons et al[28]	10	50 (18.7–81.3)*	40.0 (12.2–73.8)*				
	Samanek et al[31]	172	0 (0.0–2.1)*	0 (0.0–2.1)*	0 (0.0–2.1)*	0 (0.0–2.1)*		
	Tennant et al[32]	73	4.1 (1.1–10.5)	2.9 (0.5–8.9)				
	Wang et al[34]							33.1 (30.6–35.7)
	Wang et al[34]	2976	55.2 (53.4–56.9)	50.6 (48.4–52.7)				
	Pooled estimate (95% CI)		17.4 (0.0–54.5)	12.5 (0.0–41.4)				
	Heterogeneity I^2 & *P*-value		99.5%, $P<0.001$	99.1%, $P=0.036$				
Single ventricle	Fixler et al[21]	286	64.7 (58.8–69.9)	56.1 (49.9–61.7)				
	Garne[23]	16		56.3 (29.9– 80.2)*				
	Moons et al[28]	9	56 (21–86)*	55.6 (21.2–86.3)*				
	Tennant et al[32]	31	83.9 (65.5–93.0)	74.2 (55.0–86.2)	74.2 (55.0–86.2)	64.5 (43.1–80.0)		
	Pooled estimate (95% CI)		70.4 (54.1–84.4)	59.8 (50.4–68.8)				
			69.5 (63.3–75.3)					
	Heterogeneity I^2 & *P*-value		65.0%, $P=0.057$	26.9%, $P=0.250$				
Ebstein's anomaly	Garne[23]	5		60.0 (14.7–94.7)*				
	Moons et al[28]	3		100 (29.2–100.0)*				
	Nembhard et al[29]	160		68.8 (61.0–75.8)*				
	Samanek et al[31]	22	67.9 (50.2–86.5)	64.3 (46.2–82.4)	64.3(46.2–82.4)	64.3(46.2–82.4)		
	Tennant et al[32]	55	67.3 (53.2–78.0)	58.0 (43.8–69.7)	58.0 (43.8–69.7)	54.6 (39.7–67.2)	54.6 (39.7–67.2)	
	Pooled estimate (95% CI)			65.6 (57.5–73.2)				
	Heterogeneity I^2 & *P*-value			18.0%, $P=0.300$				

Pooled estimated are calculated using random effects meta-analysis. But where there are ≤3 studies, pooled estimates are also calculated using fixed effects meta-analysis with these results being shown in italics. AVA/S in Wang et al's studies refers to aortic valve stenosis only. IVS indicates intact ventricular septum; VSD, ventricular septal defect.

*Indicates that 95% CIs were not reported in the study, but 95% binomial exact 95% CIs were calculated by the authors.

†95% CIs obtained from author

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Table 3. Quality Appraisal of Included Articles

Domain	Quality Items, Potential Bias	Yes	No	Not Stated	Number of Studies, %
Study ascertainment	The study population is adequately described for key characteristics (ie, CHD subtype frequency, sex distribution, ethnicity)	21–23,25,27,29,30,33,34	20,24,26–28,31,32,35		9 (56%)
	Ascertainment is adequately described, including method of ascertainment included birth years, study location	20–35			16 (100%)
	Inclusion and exclusion criteria are adequately described (ie, ICD codes stated and inclusion of extracardiac anomalies	21–27,29,30,32–35	20,27,28,31		13 (81%)
	There is adequate ascertainment	20–35			16 (100%)
	POTENTIAL BIAS: The study sample represents the population of interest on key characteristics sufficient to limit potential bias to the results	20–35			16 (100%)
Study attrition	The proportion of traced cases is stated and adequate	20,22,23,29,32		21,24–28,30,31,33–35	5 (31%)
	Reasons for untraced cases are provided	20,23,29,32	22	21,24–28,30,31,33–35	4 (25%)
	Untraced cases are adequately described for key characteristics (ie, CHD subtype)	20,22,23,29,32		21,24–28,30,31,33–35	5 (31%)
	There are no important differences between key characteristics and outcomes in participants who were traced and untraced			20–35	0 (0%)
	POTENTIAL BIAS: Untraced cases are not associated with key characteristics (ie, the study data adequately represent the sample), sufficient to limit potential bias	20,22,23,29,32		21,24–28,30,31,33–35	5 (31%)
Outcome ascertainment	Frequency of outcome is recorded	20–29,32–35	30,31		14 (88%)
	The method of ascertainment of deaths is valid and reliable to limit misclassification bias	20–35		25	15 (94%)
	POTENTIAL BIAS: The outcome of interest is adequately measured in study participants to sufficiently limit potential bias	20–35		25	15 (94%)
Analysis	There is sufficient presentation of results (ie, number of cases and 95% CIs)	21,24,25,27,29–35	20,22,23,26–28		11 (69%)
	The analysis is adequate for the design of the study	20,21,24,25,27–35	22,23,26		13 (81%)
	Results are not selectively reported	20–35			16 (100%)
	POTENTIAL BIAS: The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results	20,21,24,25,27–35	22,23,26		13 (81%)

CHD indicates congenital heart disease; ICD, International Classification of Disease.

Discussion

In this systematic review and meta-analysis, we found that 87.0% of individuals born with CHD survived to age 1 year, 85.4% survived to age 5 years, and 81.4% survived to age 10 years. Few studies reported survival beyond age 10 years, but survival appeared to continue to gradually decrease into adulthood. There was substantial variation in survival estimates among articles, some of which was accounted for by study period, which positively affected survival.

The main strength of this systematic review is its restriction to population-based studies. Although including hospital-based studies would have increased the amount of data available, such studies underascertain milder CHD subtypes that do not require major medical intervention. In addition, children with severe CHD may travel to centers with specialist expertise; therefore, the survival estimates reported by hospital-based studies can be unrepresentative of the general population of individuals with CHD. The robustness of the individual rates of bias was examined using a quality assessment with previously published domains and items.[19] Although each study failed to satisfy at least 1 quality item because of the population-based study designs, the potential for bias in each domain remained low. Moreover, for all CHD, we did not identify any significant publication bias according to the Egger test.

A further strength is the comprehensive nature of our search strategy. Three databases were searched for relevant citations, along with key journals and reference lists; therefore, the likelihood of missing key studies was limited. Full articles were reviewed by both authors to ensure that they fully met the inclusion criteria and that data were extracted correctly. A further strength is that we reported pooled estimates calculated from fixed- and random-effects meta-analyses if there were just 3 studies reporting survival. Random-effects meta-analysis may calculate pooled estimates using an imprecise between-study variance if the number of studies is low.[15] The pooled estimates from the fixed-effect meta-analyses were broadly similar to those from the random-effects meta-analyses but with smaller confidence intervals.

There were also several limitations. The maximum follow-up was just 30 years, with 5 of the included studies reporting survival to just 5 years. The greatest risk of death occurred in infancy, but survival continued to decrease over follow-up, although at a much lesser rate. A study of CHD-related mortality rates between 1999 and 2006 in the United States showed a high mortality rate of 41.5 per 100 000 in infancy, which decreased to 1.38 between ages 1 and 4 years and stabilized at ≈0.55 between the ages of 5 and 65 years. After age 65 years, the mortality rate doubled to 1.10 per 100 000.[36]

A further limitation is that longer term survival estimates may not be representative of children born with CHD today. Even in the most recent studies, 25-year survival rates related to persons born in the 1990s; in our metaregression of 1-, 5-, and 10-year survival, we showed that survival estimates improved over time.

All included studies were performed in high-income Western populations. Evidence suggests that infant mortality rates associated with congenital anomalies are greater in low-income countries.[37] Consequently, the survival estimates in this review are not likely to be globally representative. Although we included only articles written in the English language, we did not identify any relevant articles written in other languages.

Most of the included articles included cases with extracardiac anomalies[20–31,33,34]; therefore, it is difficult to assess how much of the mortality was accounted for by CHD as opposed to the co-occurring congenital anomalies. Nevertheless, cases with extracardiac anomalies accounted for only 20% of cases, and some extracardiac anomalies were not likely to be life threatening; therefore, the impact on survival is likely to be low. All articles used all-cause mortality, meaning that deaths may not have been directly related to the CHD diagnosis.

Although this review provides insight into long-term mortality associated with CHD, we did not account for morbidity. Research suggests that quality of life is lower in those with CHD and that those who live with CHD can have morbidities such as endocarditis, cerebrovascular accidents, myocardial infarctions, and arrhythmias.[38–40] The American Heart Association has also reported that children with CHD are at increased risk of developmental disorders.[41] Research suggests that children with CHD are more likely to require special education services, regardless of CHD severity.[42]

In our metaregression, we found that a more recent study period positively affected survival estimates; however, even after adjustment for study period, there was still a high degree of heterogeneity. Although we adjusted for study period using the year of study commencement, the lengths of the study periods varied by article; therefore, our adjustment for the year of study commencement is not likely to have fully accounted for the changes in survival over time. Further heterogeneity is likely attributable to a variety of sources. Case ascertainment is likely a major cause. Olsen et al reported lower survival estimates even after accounting for study period, but their prevalence of CHD was almost half that of other studies. Given that they included only cases diagnosed before age 1 year, it is likely that they underascertained cases with milder CHD subtypes, such as ventricular septal defect.[30] The data sources used may also have contributed to variation in ascertainment, with articles using hospital records as opposed to congenital anomaly registers (which use multiple sources for ascertainment) contributing to lower survival estimates, likely due to the milder cases being underascertained.[31]

Variation in study periods is arguably the greatest source of heterogeneity for survival estimates. Survival has improved over time because of advances in surgical correction. The Fontan operation, for example, for repair of single ventricle, hypoplastic left heart, and tricuspid atresia and the conduit repair for cases of common arterial trunk were introduced in the late 1970s and developed throughout the 1980s and 1990s.[43,44] The arterial switch operation for treatment of transposition of the great vessels was introduced in 1975[45] and fully replaced the atrial switch operations in the early 1990s, resulting in improved long-term survival.[46] Survival is also likely to have improved over time because of advances in prenatal diagnosis. Greater prenatal diagnosis rates may have led to an increase in rates of termination (for fetal anomaly). If cases with the more severe subtypes were terminated, this would have resulted in better survival. Prenatal diagnosis also allows quicker intervention at birth or even in utero, which may also improve survival.[47] In addition, survival is likely to have improved because of the introduction of prostaglandin, which underwent trials in neonates with cyanotic CHD in the 1970s,[48,49] although it was not frequently administered until the 1980s.

The improvement in survival rates over time has led to an emerging population of adolescents and adults with CHD. These patients require long-term follow-up, sometimes leading to reinvestigation and reoperation. Consequently, population-based surveillance of CHD is crucial to adequately assess the variety of health and social services required by those with CHD throughout their lives.

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