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Congenital heart disease in Down syndrome – A review of temporal changes

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Abstract

Background: Congenital heart disease (CHD) is a well-known co-occurring condition in Down syndrome (DS). We aimed to review the literature to evaluate the current evidence to address key questions.

Methods: A series of key questions were formulated a priori to inform the search strategy and review process. These addressed the topics of prevalence, type of CHD, severity, and screening. Using the National Library of Medicine database, PubMed, detailed literature searches were performed. The quality of available evidence was then evaluated, the existing literature was summarized, and knowledge gaps were identified.

Results: Fifty-six relevant original articles were identified which addressed at least one key question. Study details, including: research design, internal validity, external validity, and relevant results are presented. The total prevalence of CHD reported in DS ranged from 20 to 57.9%. In later decades, the prevalence remained constant at 40—55%. The types and classification of CHD varied considerably between studies. Some studies indicate a trend towards a milder phenotype, but this was not consistent. Over time, some studies observed an improved prognosis for CHD in DS. Studies investigating screening for CHD by physical examination, chest X-ray, and electrocardiogram report sensitivities of 71–95%.

Conclusion: To further improve knowledge on CHD in DS, we suggest that future studies cover a wide range of nations and regions, with a longitudinal design, and account for potential confounding factors.

Keywords: Down syndrome, Trisomy 21, Cardiology, Cardiac, Congenital heart disease

Introduction

Down syndrome (DS) is present in one in 800 infants born in the United States, making it the most common chromosomal condition associated with a unique medical and developmental profile [1, 2]. Congenital heart disease (CHD) is one of the co-occurring medical diagnoses associated with DS [3, 4]. Among patients with DS, the presence of CHD is a known contributor to morbidity and mortality [5].

Although the association of CHD with DS has been known for decades, much has changed over time in terms of available diagnostics, medical care, and treatments. We conducted this project to present an updated literature review on CHD in DS. The overarching goals of this review were to: 1) Formulate key questions a priori and identify which original articles address these key questions. 2) Search PubMed to identify original research articles that address the cardiac phenotype of individuals with DS. 3) Assess these articles using United States Preventative Services Task Force (USPTF) methods [6]. 4) Summarize the published literature and identify gaps in evidence.

Methods

Key questions

In accordance with USPSTF practice we formulated a series of key questions as outlined in a prior review [7].

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By consensus, the following key questions were formulated by the authors:

1. What is the total prevalence of congenital heart disease in DS? And, has the prevalence of congenital heart disease in DS changed over time?
2. What is the type of congenital heart disease in DS? And, has the type of congenital heart disease in DS changed over time?
3. What is the severity of congenital heart disease in DS in terms of treatment and prognosis? And, has the severity of congenital heart disease in DS changed over time?
4. What screening for congenital heart disease in DS is performed in studies? And, has the screening for congenital heart disease in DS changed in the published literature over time?

PubMed literature search

Literature searches were conducted in August – September 2020 using the National Library of Medicine (NLM) biomedical literature database PubMed (MEDLINE) (NCBI 1946–2020) to identify original research manuscripts addressing our prioritized topics. We used the Medical Subject Headings (MeSH) (the NLM controlled vocabulary thesaurus for indexing) to capture related entry terminology in our searches. For example, the MeSH term "Down syndrome" included the search entry terms: Downs syndrome, Down's syndrome, Mongolism, Trisomy 21, Partial Trisomy 21. The MeSH term "Down syndrome" was combined using the Boolean operator 'AND' with the MeSH term "congenital heart defect" which included the search entry terms of specific cardiac malformations, to capture the unfiltered literature. Then, the limiters "Human", "English" were applied to narrow the scope of the search to filtered literature. We did not use subject age as a limiter. We also did not exclude articles based on timing of study either prenatal or postnatal, and did not filter our search to only live births. Abstracts were reviewed and included according to their relevance to key questions. Whenever an abstract made mention of any key question (or there was doubt) the full article was procured. The methods and results sections were then reviewed to determine which articles met inclusion or exclusion criteria. A single reviewer conducted the literature searches, reviewed articles for inclusion, and extracted data. Article inclusion criteria included: data addresses at minimum one key question and supporting data is original (not previously published). Exclusion criteria included: data does not address at least one key question, study uses an uninterpretable methodology, case series < 5, does not provide supporting data, did not present data specific to DS, focused on a single type of CHD, is a unique subset of DS (e.g. surgical patients) which would not generalize to answer our key questions.

Using only the PubMed articles meeting inclusion, data pertaining to key questions were extracted from the abstract, methods, and results sections and entered into a preformatted Excel data template for analysis. For graphical representation of temporal changes, we grouped reported CHD's according to [15]. to facilitate comparisons across studies [8]. See Fig. 1 for an overview of the identification, inclusion and exclusion process and Supplemental Table for details of extracted data.

Factors which may impact these key questions such as: publication year, population details (number of subjects studied, age of sample, location, source of subjects and demographics: gender, race, prenatal or postnatal diagnosis of CHD, prenatal or postnatal diagnosis of DS) if provided, and research methodology were recorded.

Evidence ratings by condition

Included articles were critically appraised by a single reviewer to determine each study's research design, subject ascertainment, total number of subjects, source of control subjects, and the extent of internal validity and external validity. The evaluation of *internal validity* considers study design factors such as ascertainment and selection bias, test procedures and consideration of confounding variables. For example, the internal validity of a cohort study is rated as good if it "Meets all criteria: comparable groups are assembled initially and maintained throughout the study (follow-up greater than or equal to 80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs" (USPSTF Procedure Manual (2015), p. 70 [6]). *External validity* considers the generalizability of findings to a broader (more representative) population [6]. See appendix VII in the USPSTF report for criteria on research design hierarchy and the rating system used for scoring internal and external validity [6]. See Fig. 1 for summary of evidence rating, and the Supplemental Table for rating of each article.

Results

Original literature review

Through review of the literature, we identified 56 articles which fit our criteria of having original data, answering a key question about DS and types of CHD, in humans, and reported on more than 5 cases (Fig. 1, Table 1). These studies were published from 1950 to 2019, and used various study designs including: cohort studies [$N = 22$], cross-sectional studies [24], case-control studies [10], and case-series [2]. The study methods

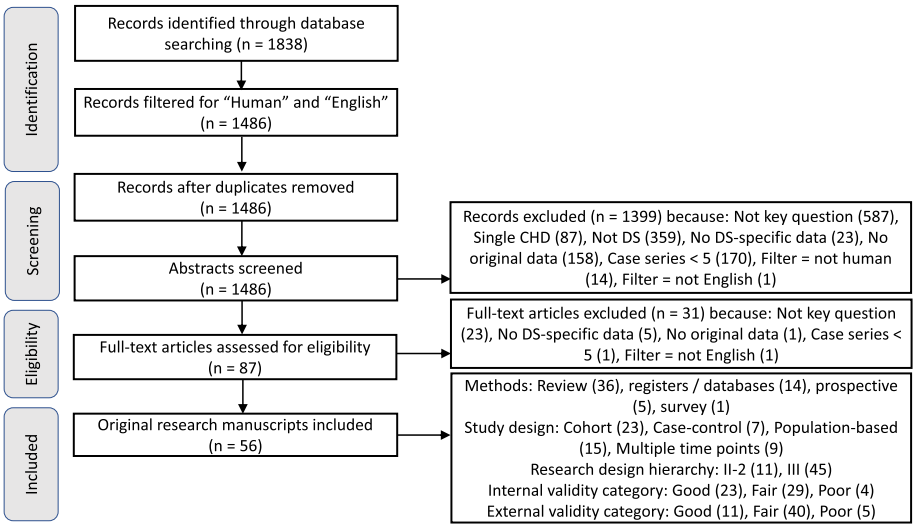

Fig. 1 PRISMA Diagram of Articles Identified, Screened, Eligible, and Included in Review of CHD Phenotype in Down Syndrome. Research design hierarchy in accordance with United States Preventative Services Task Force methods

included: retrospective review [24] registries and databases [26], prospective screening programs [5], and parent survey [3]. Nearly all studies reported on a cohort, of which some were population-based samples [23] and some reported data longitudinally [5]. Some studies compared those with DS and CHD to those with DS without CHD. In addition to the bracketed number of studies, please see the Supplemental Table for specific details on each of the 56 studies.

Data extracted from original literature review which addressed one of our four key questions are presented below. We report studies based in the United States followed by international results.

1. What is the total prevalence of congenital heart disease in DS? And, has the prevalence of congenital heart disease in DS changed over time?

Eighteen articles answered this key question from a variety of locations

In the United States, in national discharge data of 11,372 DS births, approximately 36% recorded selected cardiac malformations in 2007 [9]. Publications from the population-based National DS Project reported prevalence of CHD in infants with DS; in 2008, 649 of 1469 (44.2%), and in 2011, 483 of 1079 (44.8%) [10, 11]. Prior, data from the population-based registry, the California Birth Defects Monitoring Program, reported CHD in 385 of 687 (56%) infants with DS in one publication [12], and in another 1620 of 2894 (56%) infants with DS had a cardiovascular system birth defect [13].

Publications from the population-based Metropolitan Atlanta Congenital Defects Program (MACDP) found 227 DS cases, of which 44% had CHD in 1989 to 1995 [14], and in 1968 to 1989 saw that 173 of 552 DS cases (33%) had cardiovascular malformations [15]. Over time, the frequency of these defects increased dramatically from about 20% in the early 1970s to more than 50% in the late 1980s ($p = 0.0001$), which the authors attributed to improvement in the ascertainment of cardiovascular malformations among infants with DS in a surveillance population [15].

To describe prevalence in CHD over time, eight additional international studies provided longitudinal data. In Sweden, among 2588 singleton live-born infants with DS between 1992 and 2012, 1387 infants had a diagnosed congenital heart defect, giving an overall birth prevalence of 54% which was similar over time [8]. In a multi-site European study of 14,109 cases with DS, of whom 6738 were live births, 306 fetal deaths, and 7065 terminations of pregnancy for fetal anomaly in 2000–2010, the overall prevalence of cardiac anomaly was 43.6% (95% confidence interval (CI): 42.4–44.7%) and had remained nearly constant [16]. A study of birth defects registries in France, Italy and Sweden in 1978–1993, found that cardiac defects were registered in 26% of the 5581 infants with DS [17]. In a Norwegian study no apparent increasing or decreasing trend in the prevalence of CHD in live born infants with DS was observed during 1994–2009 [18]. No significant change in prevalence was seen in Thailand with 64 of 149 with DS born in 2009–2013 who had CHD (43%) compared with 112 in 295 (38.6%) DS patients born in 1992–2002 [19]. In the United Kingdom, 342 of 821 live born infants (42%) in 1985–2006 had CHD [20]. Present a figure showing an increasing prevalence from approx. 30% in the late

Table 1 Overview of included articles. Studies from the United States are presented followed by international studies

	Country or region	Study design	Data source	Year of birth or study period	Study participants with DS (n)	Internal validity / external validity (good, fair, poor)
Bean et al. (2011) [9]	United States; Georgia, New York, Arkansas, Iowa, New Jersey, California	Case-control, population-based	National registry	Born 2001–2004	1097	Good / Good
Bogarapu et al. (2016) [25]	United States; Utah, Idaho	Cohort, population-based	Regional database and medical records	Born 2000–2012	408	Good / Fair
Cleves et al. (2007) [8]	United States; multiple states	Case-control, population-based	National database	Infant discharged 1993–2002	11,372	Good / Good
Cua et al. (2017) [15]	United States; multiple states	Cohort, population-based	National database	Born 2000–2014	5737	Good / Fair
Ferencz et al. (1989) [31]	United States; Maryland, Washington DC, Virginia	Cross-sectional, population-based	Review of records	Enrolled (< 1 year of age) 1981–1986	218	Fair / Fair
Freeman et al. (1998) [13]	United States; Georgia	Cross-sectional, population-based	Regional database	Born 1989–1995	227	Good / Good
Freeman et al. (2008) [10]	United States; Georgia, New York, Arkansas, Iowa, New Jersey, California	Case-control, population-based	National registry, review of records, and parent survey	Born 2000–2004	1469	Good / Good
Greenwood et al. (1976) [27]	United states; Massachusetts	Cohort, single-center	Review of records	Admitted 1962–1973	369	Fair / Fair
Khoury et al. (1992) [14]	United States; Georgia	Repeated cross-sectional, population-based	Regional database	Born 1968–1989	532	Good / Good
McElhinney et al. (2002) [29]	United States; Pennsylvania	Cohort, single-center	Review of records	Neonatal examination 1988–1999	114	Fair / Fair
Park et al. (1977) [32]	United States; Maryland, Pennsylvania	Cohort, two-center	Review of records	Referred to clinics 1964–1972	251	Fair / Fair
Spahis et al. (1999) [30]	United States; Texas	Cohort, single-center	Review of records	Attending clinic 1993–1999	216	Good / Fair
Tandon et al. (1973) [28]	United States; Minnesota	Cross-sectional, single-center	Post mortem examinations	Not reported	55	Poor / Fair
Torfs et al. (1998) [12]	United States; California	Cross-sectional, population-based	Regional database	Born 1983–1993	2894	Good / Good
Torfs et al. (1999) [12]	United States; California	Case-control, population-based	Regional database and interview of mothers	Born 1991–1993	687	Good / Fair
Wells et al. (1994) [26]	United States; Alabama	Case series, single-center	Review of records	Born 1988–1992	102	Good / Good
Ali et al. (2009) [61]	Sudan	Cohort, single-center	Review of records	Attending clinic 2004–2007	80	Poor / Fair
Aynaci et al. (1998) [55]	Turkey	Cohort, single-center	Review of records	Not reported	31	Fair / Fair
Benhaourech et al. (2016) [59]	Morocco	Cohort, single-center	Hospital registry	Diagnosed with DS 2008–2014	128	Fair / Fair
Bergstro et al. (2016) [15]	Sweden	Repeated cross-sectional, population-based	National registry	Born 1992–2012	2588	Good /Good
Bermudez et al. (2015) [39]	Brazil	Cross-sectional and cohort, single-center	Review of records	Attending clinic 2005–2013	1207	Fair / Fair

Table 1 Overview of included articles. Studies from the United States are presented followed by international studies *(Continued)*

	Country or region	Study design	Data source	Year of birth or study period	Study participants with DS (n)	Internal validity / external validity (good, fair, poor)
Boussouf et al. (2017) [58]	Algeria	Case-control, multicenter	Clinical examination and medical history	Enrolled 2009–2010	110	Fair / Fair
Brodwall et al. (2018) [18]	Norway	Cohort, population-based	National registry	Born 1994–2009	1251	Good / Fair
Corona-Rivera et al. (2019) [34]	Mexico	Case-control, single-center	Hospital registry	Born 2009–2018	231	Good / Fair
El-Gilany et al. (2017) [21]	Egypt	Case-control, single-center	Review of records	Born 1992–2016	1720	Good / Fair
Elmagrpy et al. (2011) [60]	Libya	Cross-sectional, single-center	Review of records	Referred to clinic 1995–2008	1193	Good / Fair
Evans et al. (1950) [47]	England	Cross-sectional, single-center	Post mortem examinations	Necropsies 1911–1949	28	Fair / Poor
Irving et al. (2011)	United Kingdom	Cohort, population-based	Regional database	Born 1985–2006	821	Fair / Fair
Jaruratanasirikul et al. (2017) [19]	Thailand	Cohort, population-based	Regional registry and medical examination	Born 2009–2013	153	Good / Fair
Källén et al. (1996) [17]	France, Italy, Sweden	Cross-sectional, population-based	Regional and national registries	Born 1976–1993	5571	Fair / Good
Kim et al. (2014) [24]	Korea	Cross-sectional, population-based	National database	Born 2005–2006	394	Good / Fair
Körten et al. (2016) [41]	Germany	Cohort, population-based	National registry	Born 1950s-post 2000	1549	Good /Fair
Liu et al. (1959) [46]	England	Case series and case-control, single-center	Review of records and post mortem examinations	Admitted to hospital 1944–1958	216	Fair / Poor
Livingstone-Sinclair et al. (2018) [35]	Jamaica	Cohort, single-center	Review of records	Attending clinic 2012–2015	41	Fair / Poor
Matsuo et al. (1972) [56]	Japan	Cross-sectional, single-center	Clinical examination and post mortem examinations	Referred to clinic 1966–1968	106	Fair / Fair
Mokhtar et al. (2001) [22]	Egypt	Case-control, single-center	Review of records and parent survey	Attending clinic 1995–2000	514	Fair / Fair
Morris et al. (2014) [16]	Europe, 28 countries	Repeated cross-sectional, population-based	National and regional registries	Born 2000–2010	7044	Good / Good
Morsy et al. (2016) [49]	Saudi Arabia	Cross-sectional, single-center	Local database	Referred to clinic 2008–2013	302	Fair / Fair
Muntha et al. (2019) [57]	Ethiopia	Cohort, single-center	Review of records	Born 2010–2015	116	Fair / Poor
Narayanan et al. (2014) [52]	India	Cross-sectional, single-center	Clinical examination	Attending clinic 2005–2012	418	Fair / Fair
Nisli et al. (2008) [54]	Turkey	Cross-sectional, single-center	Review of records	Attending clinic 1994–2007	1042	Fair / Fair
Pinto et al. (1990) [44]	Portugal	Cross-sectional, single-center	Review of records	Attending clinic 1970–1987	210	Fair / Fair
Rowe et al. (1961) [33]	Canada	Cohort, single-center	Clinical and post mortem examination	Referred to clinic 1955–1957	174	Fair / Poor

Table 1 Overview of included articles. Studies from the United States are presented followed by international studies *(Continued)*

	Country or region	Study design	Data source	Year of birth or study period	Study participants with DS (n)	Internal validity / external validity (good, fair, poor)
Santoro et al. (2018) [40]	Italy	Cross-sectional, population-based	Regional registry	Born 2003–2015	230	Fair / Fair
Selikowitz et al. (1992) [62]	Australia	Cross-sectional	Parent survey, recruited at conference	Born 1974–1987	204	Poor / Fair
Sica et al. (2015) [38]	Brazil	Cross-sectional, single-center	Review of records	Attending clinic 2011–2012	68	Fair / Fair
Stoll et al. (1998) [45]	France	Case-control, population-based	Regional registry	Born 1979–1996	398	Fair / Fair
Stoll et al. (2001) [42]	Europe; 12 countries	Cross-sectional, population-based	National and regional registries	Registered 1996–1998	239	Good / Good
Tan et al. (2013) [51]	Singapore	Cross-sectional, two-center	Review of records	Born 1996–2010	588	Fair / Fair
Tomlinson et al. (2010) [36]	Jamaica	Cohort, single-center	Hospital registry	Born 1995–2004	76	Fair / Fair
Tubman et al. (1991) [43]	Ireland	Cohort, population based	Clinical examination	Born 1987–1989	81	Fair /Fair
Venugopalan et al. (2003) [53]	Oman	Cross-sectional, single-center	Review of records	Attending clinic 1995–1998	54	Fair / Fair
Vida et al. (2005) [37]	Guatemala	Cross-sectional, single-center	Review of records	Attending clinic 1997–2003	349	Fair / Fair
Weijerman et al. (2010) [23]	The Netherlands	Cohort, population-based	National registry	Born 2003–2006	482	Good / Good
Yaqoob et al. (2019) [50]	Pakistan	Cohort, single-center	Review of records	Attending clinic 2010–2016	350	Poor / Fair
Zahari et al. (2019) [48]	Malaysia	Cohort, two-center	Hospital database and review of records	Born 2006–2015	754	Good / Fair

Year of birth denotes birth of the DS cases included in each study
DS Down syndrome

1980s to approx. 50% in the early 1990s following which the prevalence seemed to stabilize around 40–50% until 2006 [20]. In Egypt, a downward trend in the prevalence of CHD (from 56.2% in the birth cohort 1992–1996 to 25% in the birth cohort 2012–2016) was observed in one clinic ($p < .001$) [21], while in another, the proportion of infants with DS and CHD increased from 29.8% in 1995 to 48.2% in 2000 [22].

Prevalence of CHD was reported at single time points in two international studies, including: 207 of 482 (43%) children with DS in the Netherlands born 2003–2006 [23] and 224 of 394 (56.9%) infants with DS in Korea in 2005–2006 [24]. One article was initially included, but on critical review was identified to have exclusion criteria which would make results regarding prevalence not generalizable, and is excluded from Fig. 2 [25].

In summary, in the eighteen studies cited above, we found that the total prevalence of CHD in DS ranged from 20 to 57.9%, mean 44.8% in DS patients born from the early 1970s to 2015 (Fig. 2). Over time, studies show an increasing prevalence in the late 1980s-early1990s from around 30% to around 50% following which the prevalence seems to stabilize around 40–55% until 2015 (Fig. 2). The findings indicate an apparent increase in reported CHD prevalence in the first 10–15 years of this period from around 20–30% to around 40–55%. The total prevalence rates varied over time: increased in Atlanta from 1970s to 1980s due to increased CHD ascertainment [15], decreased in Egypt from 1992 to 1996 to 2012–2016 [21], and was unchanged in Sweden from 1992 to 2012, in Europe from 2000 to 2010, and in Thailand from 1992 to 2013 [8, 16, 19].

2. What is the type of congenital heart disease in DS? And, has the type of congenital heart disease in DS changed over time?

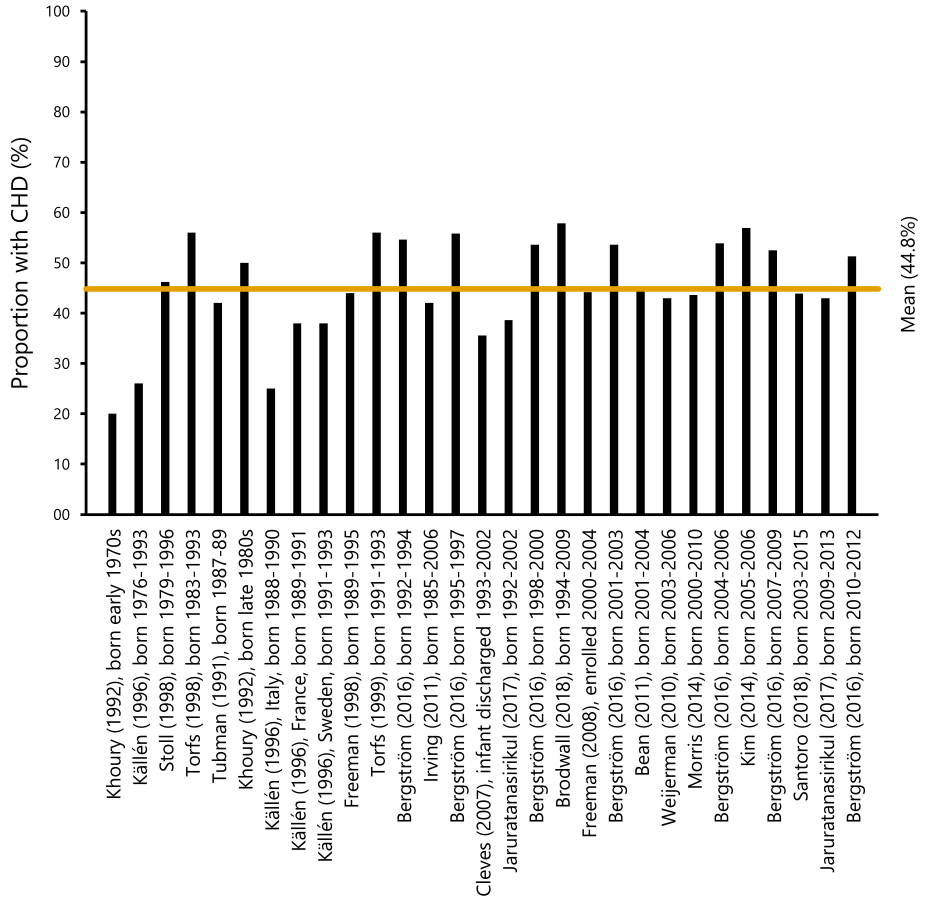

Fig. 2 CHD total prevalence. Overview of studies (assessed as population-based) reporting total prevalence of CHD among all DS patients. Studies are ordered according to period of birth midpoint/study period midpoint. CHD: congenital heart defect. DS: Down syndrome

Fifteen studies in the United States specified the types of CHD

With the study population in a single city [2] of Atlanta [14, 15], specific states [7] including Alabama [26], California [12, 13], Massachusetts [27], Minnesota [28], Pennsylvania [29] and Texas [30], regions [2] of Maryland / Washington DC / Virginia [31], and Maryland / Pennsylvania [32], or multiple states [4] [5, 10, 11, 25]. These studies used databases, registries, and clinical records, and were all retrospective reviews. None of these fifteen studies described the type of CHD longitudinally.

Thirty-nine articles outside the United States provided data on the type of CHD in DS

Five studies in North America including: Canada [33], Mexico [34], Jamaica [35, 36], and Guatemala [37]. Two studies in South America, including: Brazil [38, 39]. Eleven in Europe including: Italy [40], Norway [18], Germany [41], United Kingdom [20], Netherlands [23], Europe (multiple countries) [42], Ireland [43], Portugal [44], France [45], England [46, 47]. Eleven studies in Asia including: Malaysia [48], Thailand [19], Saudi Arabia [49], Pakistan [50], Korea [24], Singapore [51], India [52], Oman [53], Turkey [54], Turkey [55], Japan [56]. Seven studies in Africa including: Ethiopia [57], Algeria [58], Egypt [21], Morocco [59], Libya [60], Sudan [61], Egypt [22]. One study from Australia [62]. The type of CHD for all studies is reported in the Supplemental Table and summarized in Fig. 3 (including studies where CHD types are reported as proportion of DS patients) and Fig. 4 (including studies where CHD types are reported as proportion of all CHD types found). The figures show variable proportions of types of defects across periods of birth/study periods. In Fig. 3, the majority of studies covering the period approx. Late 1960s to mid 1990s observe a greater proportion of complex defects (atrioventricular septal defect (AVSD), aortic arch abnormalities, tetralogy of Fallot, transposition of the great arteries, and single ventricle hearts) compared with shunt defects (isolated ventricular septal defect (VSD), isolated atrial septal defect (ASD), and isolated patent ductus arteriosus). In contrast, studies covering later years more often find the proportion of shunt defects exceeding the proportion of complex defects. In studies

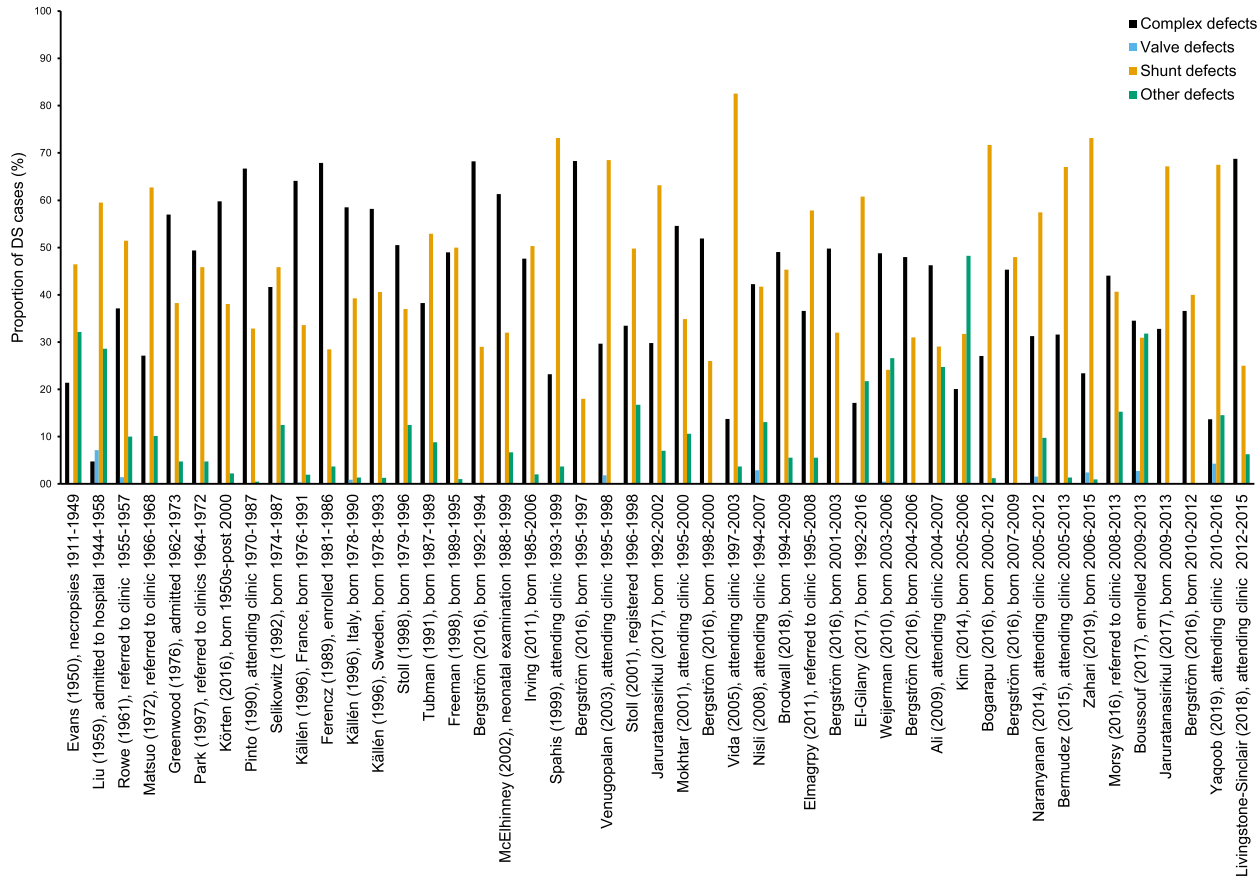

Fig. 3 Distribution of CHD types among DS patients. Proportion of DS patients with a given CHD grouped according to [15, 8]: complex defects (AVSD, aortic arch abnormalities, tetralogy of Fallot, transposition of the great arteries, and single ventricle hearts), valve defects (aortic, pulmonary, and mitral-tricuspid valve defects), shunt defects (isolated VSD, isolated ASD, and isolated patent ductus arteriosus), and other defects [15]. do not report prevalence rates for the latter three groups according to year of birth, so for this study only proportions of complex defects are displayed in the figure. CHD: congenital heart defect. DS: Down syndrome. AVSD: atrioventricular septal defect. VSD: ventricular septal defect. ASD: atrial septal defect

reporting on the number of CHD types out of all CHDs covering the period 1968–2018 (Fig. 4) shunt defects were consistently reported at higher proportions than complex defects.

Six articles described the type of CHD longitudinally

In the United States, one study found an increasing prevalence during the 1980s of ascertained patent ductus arteriosus, endocardial cushion defects and ASD [15]. In Sweden, the risk of complex CHD (as defined in Figs. 3 and 4) decreased over time: compared with 1992 to 1994, the risk in 2010 to 2012 was reduced by almost 40% (adjusted risk ratio 0.62, 95% confidence interval 0.48–0.79) [8]. In contrast, chances for isolated VSD or ASD showed significant increases during later years, and although AVSD was far more common than VSD in 1992 to 1994, they were equally common in 2010 to 2012 [8]. Results from the United Kingdom, may support this finding [20]. Here, the proportions of ASD increased from approx. 9% in 1985–1989 to approx. 19% in 2000–2006 (our estimates based on the Fig. 3 in the article by Irving et al. [20]).

However, a 28-country, population-based study using congenital anomaly registries in Europe in 2000–2010 found no evidence of a trend in the proportions of births with DS with a severe cardiac anomaly (either of: single ventricle, hypoplastic left heart, hypoplastic right heart, Ebstein anomaly, tricuspid atresia, pulmonary valve atresia, common arterial truncus, AVSD, aortic valve atresia/stenosis, transposition of great vessels, tetralogy of Fallot, total anomalous pulmonary venous return, and coarctation of aorta) since 2000 [16]. There was no observed change in prevalence of ASD and VSD among births with DS over the 10 years of study [16]. The authors suggested that population screening for DS and subsequent terminations has not influenced the prevalence of specific congenital anomalies in these European infants [16]. Similarly, there was no apparent trend towards

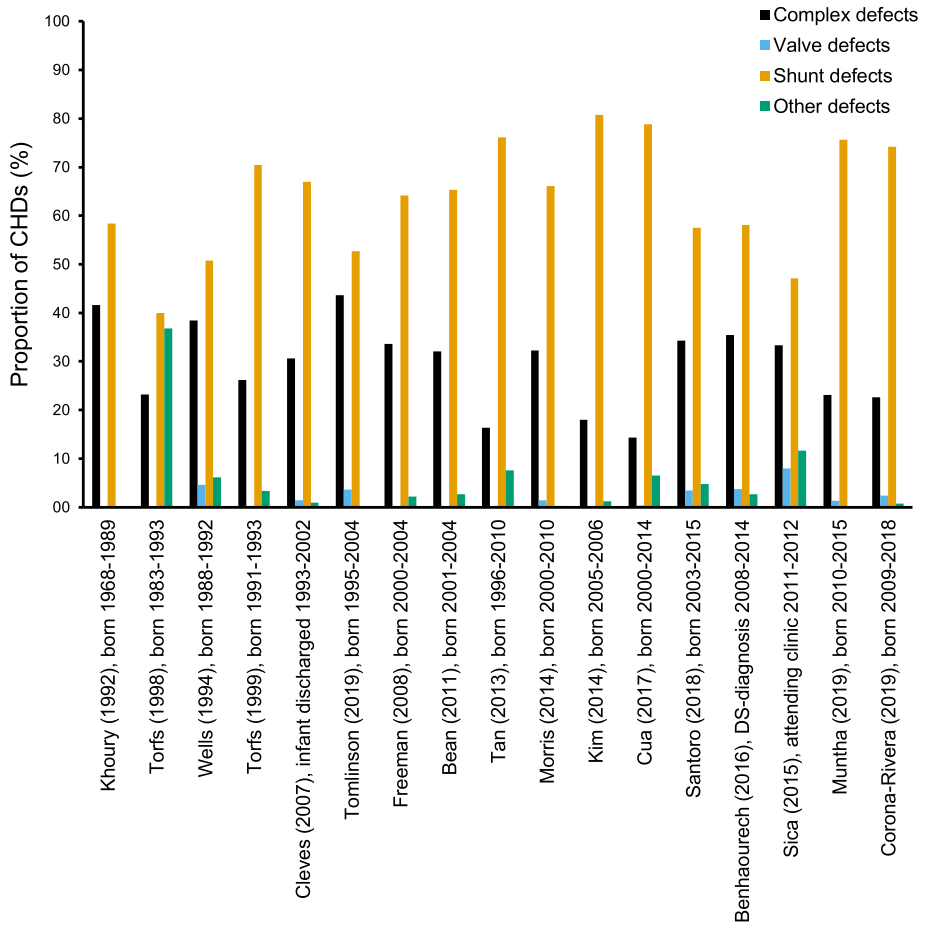

Fig. 4 CHD types as proportion of all CHDs. Frequencies of CHD types out of the total number of CHDs grouped according to [15, 8]: complex defects (AVSD, aortic arch abnormalities, tetralogy of Fallot, transposition of the great arteries, and single ventricle hearts), valve defects (aortic, pulmonary, and mitral-tricuspid valve defects), shunt defects (isolated VSD, isolated ASD, and isolated patent ductus arteriosus), and other defects. CHD: congenital heart defect. DS: Down syndrome. AVSD: atrioventricular septal defect. VSD: ventricular septal defect. ASD: atrial septal defect

lower prevalence of AVSD among live born DS patients in Norway in 1994–2009 [18]. An Egyptian study found a decreasing prevalence of isolated CHD (as opposed to multiple CHD) from 56.2% in the birth cohort 1992–1996 to 19.8% in the birth cohort 2012–2016 [21].

In summary, in the included articles, the type of CHD reported varies greatly (Fig. 3). The studies which provided longitudinal data differed in the location and year; there was no clear consensus if, or how, the prevalence of specific types (complex, or severe) of CHD were changing over time.

3. What is the severity of congenital heart disease in DS in terms of treatment and prognosis? And, has the severity of congenital heart disease in DS changed over time?

Seven articles addressed this key question regarding CHD severity

In the United States during 2000–2014, neonates with DS who died were significantly more likely to have the diagnosis of complete transposition of the great vessels (37.5 vs 7.5%, respectively), double outlet right ventricle (17.7 vs 7.4%, respectively), Ebstein's anomaly (29.4 vs 7.4%, respectively), left-sided obstructive lesion (14.9 vs 6.9%), or pulmonary venous abnormality (26.1 vs 7.5%, respectively) compared to those who survived [5]. Rates of surgical management were reported in two studies: in one study, all with AVSD underwent surgery [49], and in a second study, surgery was the most common treatment modality (54.3%) [59].

In Norway, the five-year hazard ratio for death was highest for children with conotruncal defects, then AVSD and then other CHDs [18]. Mortality was

especially high for children with DS who had extracardiac malformations with 93% dying in first year [18]. In Malaysia, one study reported on children with DS and CHD of which 30% of lesions closed spontaneously, 35% underwent surgery / intervention, 9% died before surgery / intervention, and 10% were treated with comfort care [48]. The authors assess proportions of cases in each DS patient category for each birth year in 2006–2015, however, the small numbers limit interpretation of potential changes in time. The overall 1-, 5-, and 10-year survival rates for cases with DS and CHD were 85.5, 74.6, and 72.9%, respectively, with 31% of deaths being cardiac related [48]. One-year survival was reported comparable in 2006 (87%) and 2015 (84%) [48]. A German study found a temporal change in treatment: the likelihood of surgical treatment increased from 0% for DS patients born in the 1950s/1960s to 2.1% in the 1970s and 85.6% among patients born after 2000 [41]. Further, the authors report the proportion of patients developing Eisenmenger syndrome decreasing from 53.3% in the earliest birth cohort to 0.5% in the latest birth cohort. Results from the United Kingdom supports the improved prognosis: compared with 1985–1995, DS infants in 1996–2006 more often underwent surgery (62% vs. 72%), had lower mortality following surgery (30% vs. 5%) including lower early postoperative mortality [20]. Overall, the 1-year survival among DS infants with CHD improved from 82 to 94% from the early to the late cohort [20].

4. What screening for congenital heart disease in DS is performed in studies? And, has the screening for congenital heart disease in DS changed in the published literature over time?

Some studies specified that all had an echocardiogram [49, 59], while others relied on retrospective review and were limited by documentation and the possibility that echocardiogram may not have been performed for all. Echocardiogram appeared to be generally accepted as the diagnostic standard. One study evaluated if screening with physical examination, ECG, and chest X-ray is an effective method of identifying which infants with DS should have an echocardiogram, and found that this method would have resulted in 69 (17%) fewer echocardiograms without missing infants with major CHD, but missing cases of patent ductus arteriosus and ASD [25]. In a similar study investigating the ability of clinical examination, chest X-ray, and ECG soon after birth separately and in combination to detect CHD, the three modalities combined showed a sensitivity of 71% and a specificity of 91% [43]. Another study assessed the accuracy of physical examination alone for identifying CHD in neonates with DS and report a sensitivity of 80% and specificity of 56%, concluding that physical examination is not a sufficient screen for CHD [29].

Discussion

Through literature review using MeSH terms in PubMed, we identified 56 articles which provided original data about DS to answer one of our key questions on prevalence, types of CHD, severity, and screening. We found that:

1) The total prevalence of CHD in DS ranged from 20 to 57.9% in 18 studies; the earliest studies indicated an increase in prevalence, while in later decades, the reported prevalence appeared constant around 40–50% (Fig. 2) The total prevalence rates over time were reported in 9 studies and were: increased in Atlanta from 1970s to 1980s due to increased CHD ascertainment [15], increased in the United Kingdom from the late 1980s to early 1990s [20], decreased and increased at two sites in Egypt from 1992 to 1996 to 2012–2016 and 1995 to 2000, respectively [21, 22], and unchanged in Sweden from 1992 to 2012, in Europe from 2000 to 2010, and in Thailand from 1992 to 2002 to 2009–2013 [8, 16, 19].
2) The types of CHD identified varied considerably between studies (Figs. 3 and 4). The six studies which provided longitudinal data differed in location and year; there was no clear consensus if the prevalence of specific types of CHD in DS changed over time, although some studies indicated a trend towards increasing relative proportion of milder lesions.
3) Seven articles addressed the key question of CHD severity. These showed links to mortality for specific types of CHD in DS, and some reported on rates of surgical (and non-surgical) treatment. Generally, the last decades have shown improvements in treatment outcomes and mortality.
4) Echocardiogram remains the accepted diagnostic approach, though some have evaluated additional approaches and timing and frequency of echocardiogram.

In conducting this literature review, a number of confounding factors of the studies arose. First, the source of information differed between studies with some reviewing medical records and others employing registry data. Varying data quality may have been an issue – for example the extent to which a CHD diagnosis was captured in databases/registries. We initially coded CHD as published by authors, without additional interpretation or modification. For subsequent figures CHD types were

grouped according to [15]. and we considered endocardial cushion defect and complete atrioventricular canal as AVSD [8](Figs. 3 and 4). Differences in classification of CHD among the studies could lead to validity issues as we try to summarize the available literature. As such, Figs. 3 and 4 should be interpreted with caution. Additionally, the method in which CHD was counted in studies differed, with some studies presenting results in number of defects (with multiple defects possible for a single patient) while some report results in number of patients. Also, in many studies the specific CHD was listed, but some studies grouped CHD in a variety of ways, including: right- or left-sided CHD, severity of CHD, primary or secondary CHD, isolated or complex CHD, or size of the VSD. In defining CHD some studies include isolated PDA, while others only include if remains open at given age [29]. There may be a selection bias in studies: for example, if severe cases of CHD in DS are more likely to have a clinic visit, the prevalence of severe CHD in a single-center study from this clinic could be falsely high.

Over the years, several factors may have impacted on prevalence, diagnosis, and management of CHD in DS. These factors are important to take into account when answering our key questions based on the results from 56 studies. In one study, the prevalence of CHD increased from 1970s to 1980s due to improvement in the ascertainment of cardiovascular malformations among infants with DS [15]. Both improved echocardiography techniques and availability of cardiac testing could impact the reported prevalence rates over time. Additionally, improved cardiac care, and surgical outcomes for CHD as a whole over time could impact neonatal mortality and prevalence of CHD in children with DS. The impact of elective terminations could impact how many infants are born with DS [2]; and it is possible that those with DS and prenatal diagnosis of CHD could undergo elective terminations at a rate different from those with DS and no CHD. Over the last decade, prenatal diagnosis of DS has become more widely available through use of cell-free fetal DNA (cff-DNA). A prenatal diagnosis of DS through cff-DNA could lead to additional fetal testing and identification of CHD prenatally. Increased elective terminations due to the advent of cff-DNA and fetal cardiac testing, could impact both the overall prevalence of CHD in DS, as well as the type of CHD. Most of the 56 studies we identified focused on CHD postnatally, but a multi-site European study of 14,109 cases with DS reported the proportion with any cardiac anomaly in live births and fetal deaths (43.6% of 3068 (95% CI: 42.4–44.7%)), and in all terminations of pregnancy for fetal anomaly (8.1% of 570 (95% CI: 7.4–8.7%)), and in terminations of pregnancy for fetal anomaly who had a postmortem examination (18.1% of 220 (95% CI: 16.0–20.4%)), but had under-reporting of medium and low mortality cardiac anomalies in TOPFAs [16].

Location of study may impact findings, and how we summarize results. For example, local resources may differ by location and impact some of the confounding factors described above, such as: the timing of diagnosis of DS or CHD, the availability of echocardiography and cardiac testing, the availability and uptake of prenatal diagnosis of DS (including cff-DNA testing in later years), the quality and availability of pediatric cardiac care, and the availability and outcomes of surgical management. In addition, there may be differences in racial and ethnic composition of the population by location. In one study of infants with DS, CHD was the most frequently reported cause of death from death certificates and the case fatality rate among infants with DS was significantly higher among blacks than whites, with the greatest racial disparity observed among infants without CHD who died in the post-neonatal period [63]. The genetic makeup of the population may lead to differences in the prevalence of CHD in DS, for example, in instances of consanguinity, as found in one study in which parental consanguinity was an independent predictors of CHD in children with DS, with adjusted odds ratio (OR) of 1.9 [21]. Altogether, local trends in CHDs in DS are potentially overshadowed in studies including data from different populations and may impact on our ability to assess general trends.

There may be other covariates which differ among these 56 studies, and influence the answers to our key questions. Lack of maternal folic acid supplementation was more frequent among infants with DS and atrioventricular septal defects (OR 1.69; 95% CI: 1.08–2.63; p 5 0.011) or atrial septal defects (OR 1.69; 95% CI, 1.11–2.58; p 5 0.007) than among infants with Down syndrome and no heart defect [10]. Parental origin of chromosome 21 may be relevant; one study found that CHD were more frequent in cases with a maternally derived extra chromosome 21 [64].

This literature review is limited by the information presented and published in the existing medical literature. For some of the confounding factors such as naming, diagnosing, counting, grouping and selecting cases, it would be useful to have a standard nomenclature or protocol when describing CHD in DS to allow studies to be compared. Also, when including results in Figs. 2, 3 and 4, we sorted studies based on midpoint of birth period/study period though some span a great number of years with overlapping time periods, which limits the interpretation of our figures. In addition, the 56 articles were identified through searching with MeSH terms and the PubMed database; relevant articles may have been

missed and we have been made aware of three such articles [65–67]. Additionally, changes over time and by location, complicate our ability to combine results of studies and draw broad conclusions. To address this, we present original data from studies and our full review data in the Supplemental Table.

Future studies to update current findings of CHD in DS could address some of the gaps in the literature which we have highlighted, including: considering use of a standard nomenclature and protocols to increase consistency across sites. Ideally, an international population-based database could be created to focus on CHD in DS, and could begin to collect prospective information from time of initial diagnosis, including prenatal diagnoses, then tracking diagnostic outcomes and treatments longitudinally. Regional changes could also be due to local issues, and more longitudinal studies assessing changes in time and taking local factors into consideration may also provide important insights.

Conclusion

CHD has remained a consistently common co-occurring condition in DS for decades. Recent studies show there may be trends in specific types of CHD with increases in isolated, less severe types and decreased types which are complex, more severe, however not all studies support this. Future studies would ideally be international, population-based, longitudinal, use consistent nomenclature, and account for factors which impact prevalence and severity of CHD.

Supplementary Information

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Additional file 1.

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Authors' contributions

SLS conceptualized the project, conducted the literature reviews, critically-reviewed articles, and analyzed, interpreted the data, and drafted first version of the manuscript. EHS reviewed literature review data, interpreted articles, created figures and tables, revised manuscript. All authors read and approved the final manuscript.

Authors' information

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Availability of data and materials

The data that support the findings of this study were derived from the following resources available in the public domain: PubMED at https://www.ncbi.nlm.nih.gov/pubmed/ and the full data from our review is listed in the Supplemental Table.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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