Congenital Heart Disease and Risk of Cardiovascular Disease: A Meta-Analysis of Cohort Studies

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Background—Despite remarkable success in the surgical and medical management of congenital heart disease (CHD), some survivors still experience cardiovascular complications over the long term. The goal of this study was to evaluate the association between CHD and risk of cardiovascular disease (CVD) by conducting a meta-analysis of cohort studies.

Methods and Results—A systematic literature search of several databases was conducted through April 2018 to identify studies reporting the risk of CVD, stroke, heart failure, and coronary artery heart disease in CHD survivors. The quality of individual studies was assessed using the Newcastle-Ottawa scale. The overall risk estimates were pooled using fixed-effects meta-analysis. Subgroup analyses were performed to explore possible sources of heterogeneity. Nine cohort studies comprising 684 200 participants were included. The overall combined relative risks for people with CHD compared with the controls were 3.12 (95% CI, 3.01–3.24) for CVD, 2.46 (95% CI, 2.30–2.63) for stroke, 5.89 (95% CI, 5.58–6.21) for heart failure, and 1.50 (95% CI, 1.40–1.61) for coronary artery heart disease. Significant heterogeneity was detected across studies regarding these risk estimates. Heterogeneity in the risk estimate of CVD was explained by geographic region, type of study design, sample source, age composition, and controlled confounders.

Conclusions—This meta-analysis of cohort studies of CHD found an association of increased risk of CVD in later life, although we cannot determine whether this association is confounded by a risk factor profile of CVD among CHD survivors or whether CHD is an independent risk factor. (***J Am Heart Assoc***. 2019;8:e012030. DOI: 10.1161/JAHA.119.012030.)

Key Words: cardiovascular disease • congenital heart disease • coronary heart disease • heart failure • meta-analysis • stroke • systematic review

Congenital heart disease (CHD) is the most common congenital malformation diagnosed in newborns,[1] with birth prevalence reported to be 10‰ of live births world-wide[2,3] and 8.9‰ of live births in China.[4] Early diagnosis and advances in cardiac surgery and interventional cardiology have significantly increased survival of patients with CHD over the past several decades. As reported, the number of people with CHD who reach adulthood has also risen,[5] which is estimated to be >1 million in the United States[2,5] and 1.2 million in Europe.[6]

Despite remarkable success in the surgical and medical management of CHD, many interventions are palliative rather than curative, and some survivors still have significant residual hemodynamic and electrical conduction abnormalities and experience cardiovascular complications over the long term.[7–9] Surgical and medical interventions for CHD, including intervention with stents, frequent catheterization, long-term medication, and so on, have been confirmed to increase the risk of cardiovascular disease (CVD).[10–13] In addition, studies suggested that risk factors of CVD, such as hypertension and obesity, were more prevalent in people with CHD than those without CHD.[14–16] The combination of anatomic abnormalities, clinical intervention, and increased CVD risk factors among CHD survivors is likely to increase the risk of CVD. Over the past few years, interest in testing this hypothesis has grown rapidly. Several previous epidemiologic studies[14,15,17–24] have consistently identified higher risk of CVD in association with CHD. However, the

Clinical Perspective

What Is New?

- This study evaluated the association between congenital heart disease and risk of cardiovascular disease including stroke, heart failure, and coronary artery heart disease in later life by conducting a meta-analysis of cohort studies.

What Are the Clinical Implications?

- Individuals with congenital heart disease are at a higher risk of cardiovascular disease, and this suggests that the risk assessment for cardiovascular disease based on conventional cardiovascular risk factors as well as interventions for reducing cardiovascular disease risk should be considered in these patients.

magnitudes of the effect sizes varied greatly between studies. In the literature, there is no meta-analysis performed on the effect of CHD and risk of CVD among survivors. The pooled risk estimate of CVD after CHD remains to be estimated, which will help to guide future management and contribute to guidelines for clinicians.

To this end, we performed a systematic review and meta-analysis of cohort studies to quantify the future risk of CVD, stroke, heart failure, and coronary artery heart disease among people with CHD.

Methods

The authors declare that all supporting data are available within the article.

Search Strategy

The present meta-analysis was conducted following the Preferred Systematic Reviews and Meta-analyses[25] and Meta-analysis of Observational Studies in Epidemiology[26] reporting guidelines. Two authors independently identified longitudinal studies published in English and Chinese before April 15, 2018, and reported data on cardiovascular outcomes among participants with and without CHD. PubMed, Embase, Google Scholar, Cochrane Libraries, China Biology Medicine disc, Chinese Scientific Journals Fulltext Database, China National Knowledge Infrastructure, and Wanfang Database were systematically searched. The search terms used in combination: (1) congenital heart disease, congenital heart defect, congenital heart malformation, congenital heart anomalies, congenital cardiac disease, congenital cardiac defect, congenital cardiac malformation, congenital cardiac anomalies, congenital cardiovascular disease, cardiovascular malformation, cardiovascular defect, and

cardiovascular anomalies; and (2) cardiovascular diseases, coronary disease, coronary thrombosis, coronary stenosis, coronary restenosis, coronary artery disease, coronary artery heart disease, acute coronary syndrome, ischaemic heart disease, ischemic heart disease, myocardial ischemia, myocardial infarction, heart failure, cardiac failure, cerebrovascular disorders, cerebrovascular disease, cerebrovascular accident, and stroke. In addition, the reviewers manually searched the reference lists of identified articles to identify any relevant studies missed in the initial search.

Exposure and Outcomes

The key exposure variable was the presence or absence of CHD at baseline. Outcomes of interest included CVD, stroke, coronary artery heart disease, and heart failure. CVD was defined as any of the following events: stroke, coronary artery heart disease, heart failure, and cardiac arrest. Outcomes of stroke were defined as any acute cerebrovascular event, composite stroke, stroke unspecified, and stroke/transient ischemic attack. Coronary artery heart disease was defined as ischemic heart disease, acute myocardial infarction, and coronary artery disease.

Study Selection

At the stage of title and abstract screening, we purposely broadened the inclusion criteria to obtain any relevant study. First, studies were considered for inclusion if they were published in Chinese or English and reported on CVD among patients with CHD. Then, the full texts of all selected studies were reviewed. Studies were included if they (1) were cohort in design, (2) had at least 2 groups (1 with CHD and 1 without CHD), and (3) provided sufficient information to allow for accurate risk estimates to be calculated. Conversely, studies were excluded if they (1) were review papers, conference abstracts, case reports, experimental studies, qualitative studies, or cross-sectional or case-control studies; (2) regarded individuals with acquired heart disease undergoing cardiac surgery as the nonexposed cohort; (3) had incomplete or unclear data; or (4) were duplicate publications. When there was >1 study involving the same population of CHD, only the most recent published or comprehensive one was included.

Data Extraction

Two reviewers independently extracted and evaluated the data for each included article using a self-designed data abstraction form. Disagreements were resolved through discussion or consultation with a third reviewer when consensus could not be achieved. The following data were extracted: the first author and year of publication, geographic

region, study period, type of study design, participant selection, controlled confounders, sample size, age composition, percentage of female participants, and reported outcomes.

Study Quality Assessments

Study quality of included studies was assessed using the Newcastle-Ottawa Scale for cohort studies. The gold standards for the 8 criteria were as follows: (1) the exposed cohort was selected from the general population of CHD; (2) the nonexposed group was selected from the same population; (3) exposure was ascertained by the reliable way, such as the *International Classification of Diseases* (*ICD*) codes; (4) excluded the ones who had CVD of interest before or at the start of study; (5) confounders were accounted for, such as age, sex, smoking, body mass index, and other cardiovascular risk factors; (6) outcomes were assessed prospectively or through record linkage; (7) the follow-up time was long enough for outcomes to occur; (8) described the loss of follow-up, and the follow-up rate was >80% in each cohort. A final score ≥6 (median) was regarded as high quality.

Statistical Analyses

Relative risk (RR) was used as the measure of the association between CHD and risk of any CVD, stroke, coronary artery heart disease, and heart failure in this study. The pooled RRs and corresponding 95% CIs were calculated using fixed-effects meta-analyses.[27] The Cochran Q test and the I^2 statistic were used to assess the heterogeneity of RRs across studies. The Cochran Q test was used to evaluate whether the variation across studies was compatible with chance, and $P<0.1$ was considered to indicate significant heterogeneity. The I^2 statistic was a quantitative indicator used to evaluate the percentage of total variance in prevalence estimates attributable to statistical heterogeneity rather than chance or sampling error ($I^2>75\%$ indicates high heterogeneity, 51%–75% indicates substantial heterogeneity, 26%–50% indicates moderate heterogeneity, and ≤25% indicates low heterogeneity). To explore possible sources of heterogeneity, subgroup analyses were performed using fixed-effects meta-analyses and basing on different categories: geographic region (eg, Europe, North America, Asia), type of study design (eg, prospective cohorts, retrospective cohorts, bidirectional cohorts), sample source (eg, general population, noncardiac surgery receivers), age composition (eg, adults only, adults and children, children only) and controlled confounders (eg, adjusted for age and sex, adjusted for factors other than age and sex). Then, a Q test for heterogeneity was used to compare the subgroup differences under the fixed-effects model (FEM; here, Q would be distributed as chi-squared with

degrees of freedom = 1, and $P<0.05$ indicated statistically significant differences).[28] Given the limited amount of included studies for other outcomes, subgroup and sensitivity analyses were performed only for CVD. Sensitivity analyses were also performed by recalculating the pooled estimates using the random-effects meta-analysis and comparing the fixed-effects and random-effects estimates. Publication bias was evaluated using Egger's line regression test ($P<0.05$ indicated statistically significant differences). All analyses were performed using RevMan version 5.3 (Nordic Cochrane Center) and R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Identification and Characteristics of Studies

In total, 14 697 unique citations were identified after an initial search. Of these, 14 430 were excluded after screening titles and abstracts, mainly because they were duplicates, case-control studies, reviews, or not related to our study (Figure 1). Then, the full text of 265 articles were reviewed, 9[13–15,17–20,22,23] of which were considered to be eligible and included in the systematic review and meta-analysis.

The characteristics of the 9 cohort studies, which included 684 200 participants (CHD, 81 137; no CHD, 603 063) and were published between 2008 and 2018, are shown in Table 1. The design was prospective in 4 studies, retrospective in 4 studies, and bidirectional in 1 study. Three studies were conducted in Denmark, 2 in Sweden, 2 in the United States, and each of the other 2 in the United Kingdom and China, respectively. Two studies targeted individuals undergoing noncardiac survey, and the rest were conducted in the general population. Outcome assessments were mainly from medical records. Six studies adjusted for age and sex only when estimating the risk of CVD associated with CHD, whereas the remaining studies adjusted more conventional risk factors for CVD, such as race and smoking.

Study Quality

The quality of the 9 studies included here was evaluated using the Newcastle-Ottawa Scale as shown in Table 2. The quality of those studies was generally good as all studies got 6 to 8 stars. The overall sample representativeness was well, as nearly 70% of the studies (6/9, 66.7%) sampled CHD from the general population. All studies used reliable methods of ascertaining CHD from databases based on *ICD* codes, as well as obtaining cardiovascular outcomes from the same databases. Seven studies described the follow-up time, of which 3 described the loss of follow-up with a follow-up rate ≥80%.
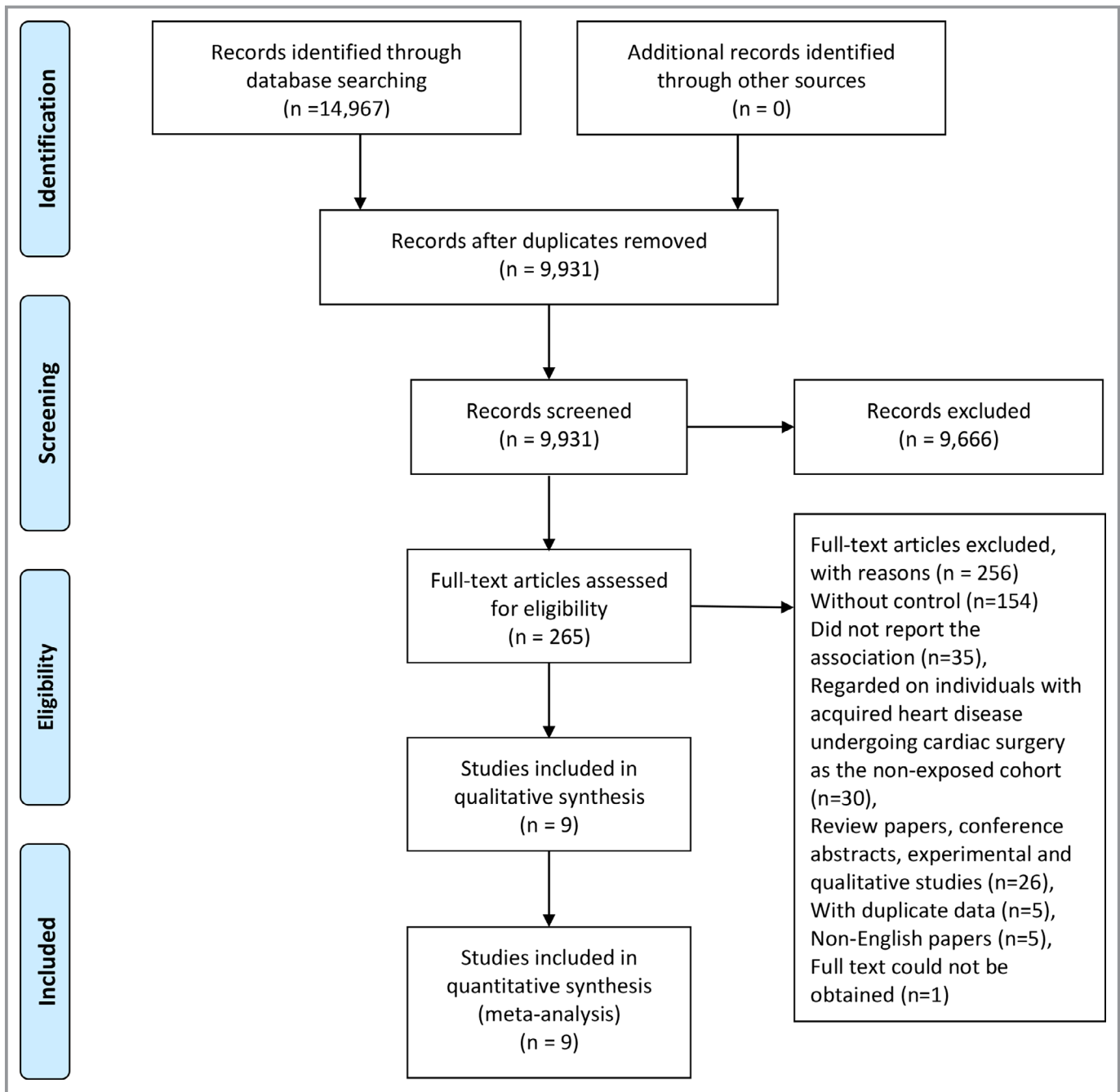
Figure 1. Flow chart of study selection.

CHD and Risk of Cardiovascular Outcomes

The risk estimate of CVD associated with CHD is summarized in Figure 2. The RRs for the association reported by included studies ranged from 1.48 to 10.76. Meta-analytic pooling of those risk estimates yielded a summary RRs of 3.12 (95% CI, 3.01–3.24), with substantial heterogeneity (I^2=99%; P<0.001). Visual inspection of the funnel plot did not identify substantial asymmetry (Figure 3). The Egger's regression test also did not indicate a potential publication bias (t=−0.100, P=0.923).

The relationships between CHD and stroke, heart failure and coronary artery heart disease are summarized in Figure 4. The overall RRs in relation to CHD were 2.46 (95% CI, 2.30–2.63; I^2=97%; P<0.001) for stroke, 5.89 (95% CI, 5.58–6.21; I^2=93%; P<0.001) for heart failure, and 1.50 (95% CI, 1.40–1.61; I^2=91%; P<0.001) for coronary artery heart disease. No evidence of publication bias was detected by using the Egger's test (stroke: t=1.362, P=0.236; heart failure: t=−0.006, P=0.995; coronary artery heart disease: t=0.242, P=0.825).

Table 1. Selected Characteristics of 9 Cohort Studies of CHD and CVD

First Author, Year	Geographic Region	Study Period	Type of Study Design	Participants	Controlled Confounders	Sample Size	Age Composition	Outcomes
Schwartz 2018[17]	Denmark, Europe	1997–2013	Prospective cohort	EG: CHD survivors alive at age 18 years identified from 2 national population-based cohort studies; NEG: subjects selected from the general population using the Civil Registration System	Age and sex.	EG: 14 860 NEG: 146 787	Adults only	CVD and heart failure
Olsen 2017[18]	Denmark, Europe	1977–2012	Prospective cohort	EG: CHD survivors alive at age 30 years identified from 2 national population-based cohort studies; NEG: subjects selected from the general population using the Civil Registration System	Age, sex, education level, and history of cancer or chronic obstructive pulmonary disease	EG: 10 501 NEG: 101 661	Adults only	CVD and coronary artery heart disease
Faraoni 2016[19]	United States, North America	2012	Retrospective cohort	EG/NEG: children <18 years of age with/without CHD undergoing noncardiac surgery recorded in the 2012 American College of Surgeons National Surgical Quality Improvement Program database	Age and sex.	EG: 4494 NEG: 4494	Children only	CVD
Mandalenakis 2016[14]	Swedish, Europe	1970–2011	Prospective cohort	EG: individuals born between January 1970 and December 1993 who had a diagnosis of CHD and were registered in the Inpatient, Outpatient, or Cause-of-Death Register; NEG: individuals selected from the Swedish Total Population Register	Age and sex.	EG: 25 985 NEG: 259 750	Adults and children	CVD and stroke
Videbæk 2016[13]	Denmark, Europe	1976–2013	Prospective cohort	EG: Children with simple CHD alive at age 15 years; NEG: subjects selected from the general population using the Civil Registration System	Age and sex.	EG: 1241 NEG: 12 254	Adults only	CVD, stroke, heart failure, and coronary artery heart disease
Dellborg 2015[20]	Swedish, Europe	1987–2012	Bidirectional cohort	EG: adult individuals with CHD identified from the Swedish National Diabetes Register and the Swedish National Patient Register; NEG: adult individuals without CHD identified from the 2 registers mentioned above	Age and sex	EG: 833 NEG: 4165	Adults only	CVD, stroke, heart failure, and coronary artery heart disease
Lin 2014[22]	China, Asia	2000–2010	Retrospective cohort	EG: adult patients with CHD identified from Registry of Catastrophic Illness Patients database; NEG: adults without CHD selected from the Longitudinal Health Insurance Database	Age and sex.	EG: 3267 NEG: 6534	Adults only	CVD, stroke, heart failure, and coronary artery heart disease
Maxwell 2013[23]	United States, North America	2002–2009	Retrospective cohort	EG/NEG: adult CHD/non-CHD patients within the subset of records containing a major noncardiac, nonobstetric therapeutic procedure	Age, sex and race.	EG: 10 004 NEG: 37 581	Adults only	CVD, stroke, and coronary artery heart disease
Billett 2008[15]	United Kingdom, Europe	2003–2015	Retrospective cohort	EG/NEG: individuals with/without a recorded diagnosis of CHD who were alive and registered with a QRESEARCH practice on January 1, 2005, and for the previous 6 months	Age, sex and smoking status.	EG: 9952 NEG: 29 837	Adults and children	CVD, stroke, and heart failure

CHD indicates congenital heart disease; CVD, cardiovascular disease; EG, exposed group; NEG, nonexposed group.

Table 2. Study Quality Assessment Overview

Study	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration that Outcome of Interest Was Not Present at Start of Study	Comparability	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow-Up of Cohorts	Total
Schwartz 2018[17]	*	*	*	*	*	*	*		7
Olsen 2017[18]	*	*	*	*	*	*	*		7
Faraoni 2016[19]		*	*	*	**	*		*	7
Mandalenakis 2016[14]	*	*	*	*	*	*	*	*	8
Videbæk 2016[13]	*	*	*	*	*	*	*	*	8
Dellborg 2015[20]		*	*	*	*	*	*		6
Lin 2014[22]	*	*	*	*	*	*	*		7
Maxwell 2013[23]		*	*	*	**	*			6
Billett 2008[15]	*	*	*	*	*	*	*		7

Note: a study can be awarded a maximum of one star (*) for each numbered item within the Selection (items 1–4) and Exposure (items 6–8) categories. A maximum of two stars (**) can be given for Comparability (item 5).

Subgroup Analyses

Subgroup analyses for the pooled risk estimates of CVD associated with CHD are summarized in Table 3. After subgroup analyses, the variables, including geographic region, type of study design, sample source, age composition, and controlled confounders, were shown to be associated with the between-study heterogeneity (all $P<0.001$). The differences for risk of developing CVD associated with CHD were statistically significant for different geographic region (test for subgroup differences [TSD]: $P<0.001$, $I^2=99.6\%$), type of study design (TSD: $P<0.001$, $I^2=99.7\%$), sample source (TSD: $P<0.001$, $I^2=99.8\%$), age composition (TSD: $P<0.001$, $I^2=98.1\%$) and controlled confounders (TSD: $P<0.001$, $I^2=99.9\%$).

Overall, individuals with CHD were still at a higher risk of CVD among all subgroup data. Specifically, when data were restricted to studies conducted in European countries (4.25; 95% CI, 4.06–4.45), studies with a prospective cohort design (4.79; 95% CI, 4.56–5.04), studies with samples from the general population (4.12; 95% CI, 3.94–4.30), studies included adult and child survivors (10.15; 95% CI, 8.07–12.77), and studies only adjusted for age and sex (4.81; 95% CI, 4.59–5.04), the risk of developing CVD associated with CHD increased further.

Sensitivity Analyses

Sensitivity analysis was performed by comparing the summarized risk estimates of CVD, stroke, heart failure, and coronary artery heart disease associated with CHD from FEM, and random-effects model (REM). Results showed that the estimates based on the 2 methods for CVD (FEM: 3.12, 95% CI,
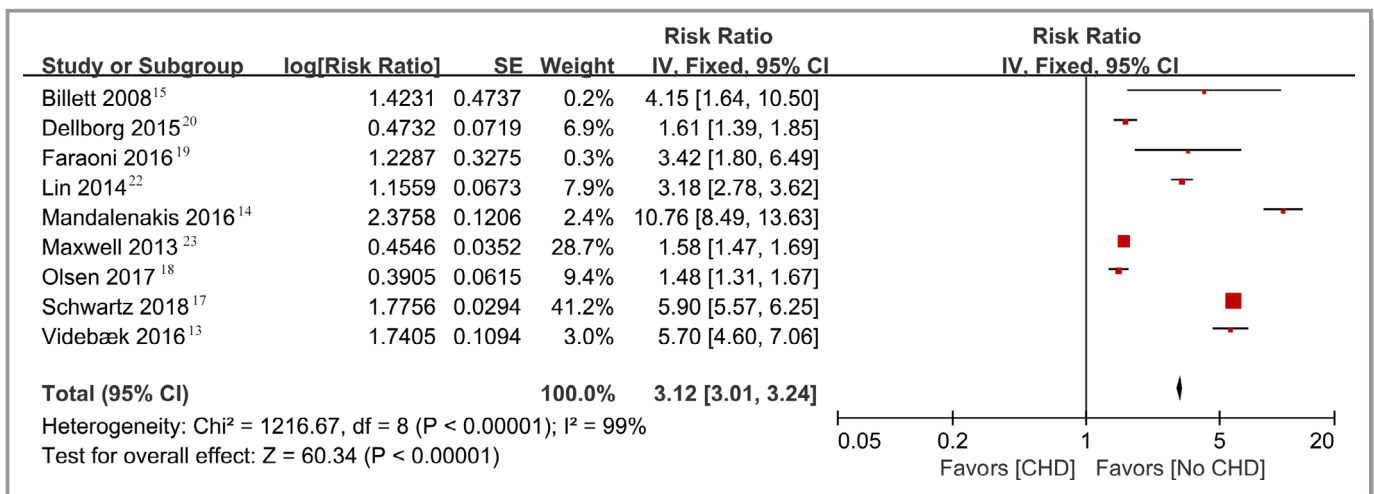
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Billett 2008[15]	1.4231	0.4737	0.2%	4.15 [1.64, 10.50]
Dellborg 2015[20]	0.4732	0.0719	6.9%	1.61 [1.39, 1.85]
Faraoni 2016[19]	1.2287	0.3275	0.3%	3.42 [1.80, 6.49]
Lin 2014[22]	1.1559	0.0673	7.9%	3.18 [2.78, 3.62]
Mandalenakis 2016[14]	2.3758	0.1206	2.4%	10.76 [8.49, 13.63]
Maxwell 2013[23]	0.4546	0.0352	28.7%	1.58 [1.47, 1.69]
Olsen 2017[18]	0.3905	0.0615	9.4%	1.48 [1.31, 1.67]
Schwartz 2018[17]	1.7756	0.0294	41.2%	5.90 [5.57, 6.25]
Videbæk 2016[13]	1.7405	0.1094	3.0%	5.70 [4.60, 7.06]
Total (95% CI)			**100.0%**	**3.12 [3.01, 3.24]**

Heterogeneity: Chi² = 1216.67, df = 8 (P < 0.00001); I² = 99%
Test for overall effect: Z = 60.34 (P < 0.00001)

Favors [CHD]   Favors [No CHD]

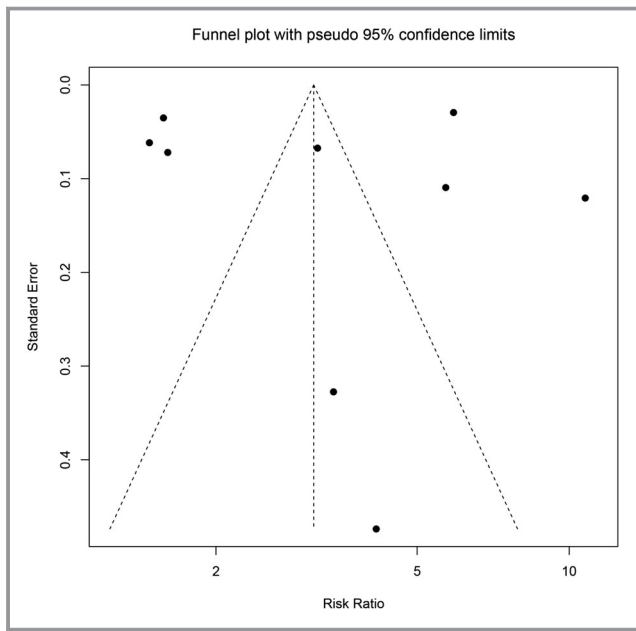**Figure 2.** Risk of cardiovascular disease associated with congenital heart disease (CHD).

Figure 3. Funnel plot with 95% confidence limits of the risk of cardiovascular disease associated with congenital heart disease. The solid line represents the summary effect estimates, and the dotted lines are pseudo 95% confidence limits.

3.01–3.24; REM: 3.37, 95% CI, 2.01–5.65), stroke (FEM: 2.46, 95% CI, 2.30–2.63; REM: 3.70, 95% CI, 1.94–4.86), heart failure (FEM: 5.89, 95% CI, 5.58–6.21; REM: 5.90, 95% CI, 4.14–8.42), and coronary artery heart disease (FEM: 1.50, 95% CI, 1.40–1.61; REM: 1.57, 95% CI, 1.19–2.06) were not significantly different.

Discussion

This meta-analysis included 81 137 individuals with CHD out of 684 200 study participants in 9 cohort studies. Our study provides evidence that CHD is associated with an increased risk of CVD, stroke, heart failure, and coronary artery heart disease. On average, the risk estimates were 3.12 for CVD, 2.46 for stroke, 5.89 for heart failure, and 1.50 for coronary artery heart disease, when compared with participants without a history of CHD. To the best of our knowledge, this study is the first meta-analysis assessing the association between CHD and risks of cardiovascular end points over the long term, which can supply helpful information to both clinicians and CHD survivors and help to guide further clinical management of CHD.

The underlying mechanisms involved in the association between CHD and CVD are manifold. Residual anatomic and hemodynamic abnormalities in CHD survivors have been confirmed to be an important factor contributed to the risk for

CVD. The cumulative result of flow obstruction, shunts, arrhythmia, valvular abnormalities, or persistent anatomic defects (eg, single ventricle), even after repair surgery, can lead to an impaired cardiovascular system in patients with CHD.[29] Hemodynamic disturbances, including myocardial ischemia, myocardial scarring, ventricular hypertrophy, abnormal volume, or pressure loading, can also induce myocardial dysfunction in patients with CHD.[29] Any of these disorders may cause systolic or diastolic impairment and ultimately lead to heart failure. CHD patients with anatomic abnormalities of the coronary arteries[30,31] or with an inherent arterial vasculopathy[32–34] (eg, coarctation of the aorta, Marfan syndrome, or Turner syndrome) may particularly be vulnerable to coronary artery heart disease and stroke.

Surgery and medical intervention is another important factor that can induce or promote the cardiovascular events. Patients with CHD who needs manipulation of their coronary arteries in the process of cardiac repair have suture lines very close to the coronary ostia, which may lead to ostial stenosis or abnormal coronary blood flow. In addition, proximal blood vessels may be kinked or stretched because of the intervention. Therefore, patients with CHD who have undergone an arterial switch procedure, a Ross procedure, or a coronary stent reimplantation may particularly be vulnerable to coronary artery heart disease.[35–37] Interventional sites (grafts or stents), frequent catheterization and the use of anticoagulants also increase the risk of stroke in CHD patients.[11,12] Additionally, constriction as an effect of prior surgical intervention may cause heart failure symptoms.

In addition, mutations associated with CHD can also cause CVD, especially for heart failure. For example, mutations in the *MYH7* gene, *MYH6* gene, *ACTC1* gene, *MYBPC3* gene, and *TNNI3* gene have been described with both CHD and cardiomyopathy, which is a common cause of heart failure.[38–43] Likewise, mutations in developmental signaling pathways known to be associated with CHD, such as the Notch pathway and noncanonical Wnt signaling, also cause cardiomyopathy in animal models and humans.[44–46] Furthermore, genetic syndromes associated with CHD, such as Marfan syndrome and Noonan syndrome, also cause heart failure in a subset of affected individuals.[47,48]

The strength of this study is the large sample size from recent studies with a total of 684 200 study participants which helps to enhance statistical power to provide more reliable and precise risk estimates. At the beginning of the study, a comprehensive search strategy was used to identify relevant studies. Moreover, the process including literature retrieval and screening, and data extraction were performed by 2 reviewers independently. All the included studies were published in the past 10 years, which means that the findings are more likely to be related and more generalizable to current practice.
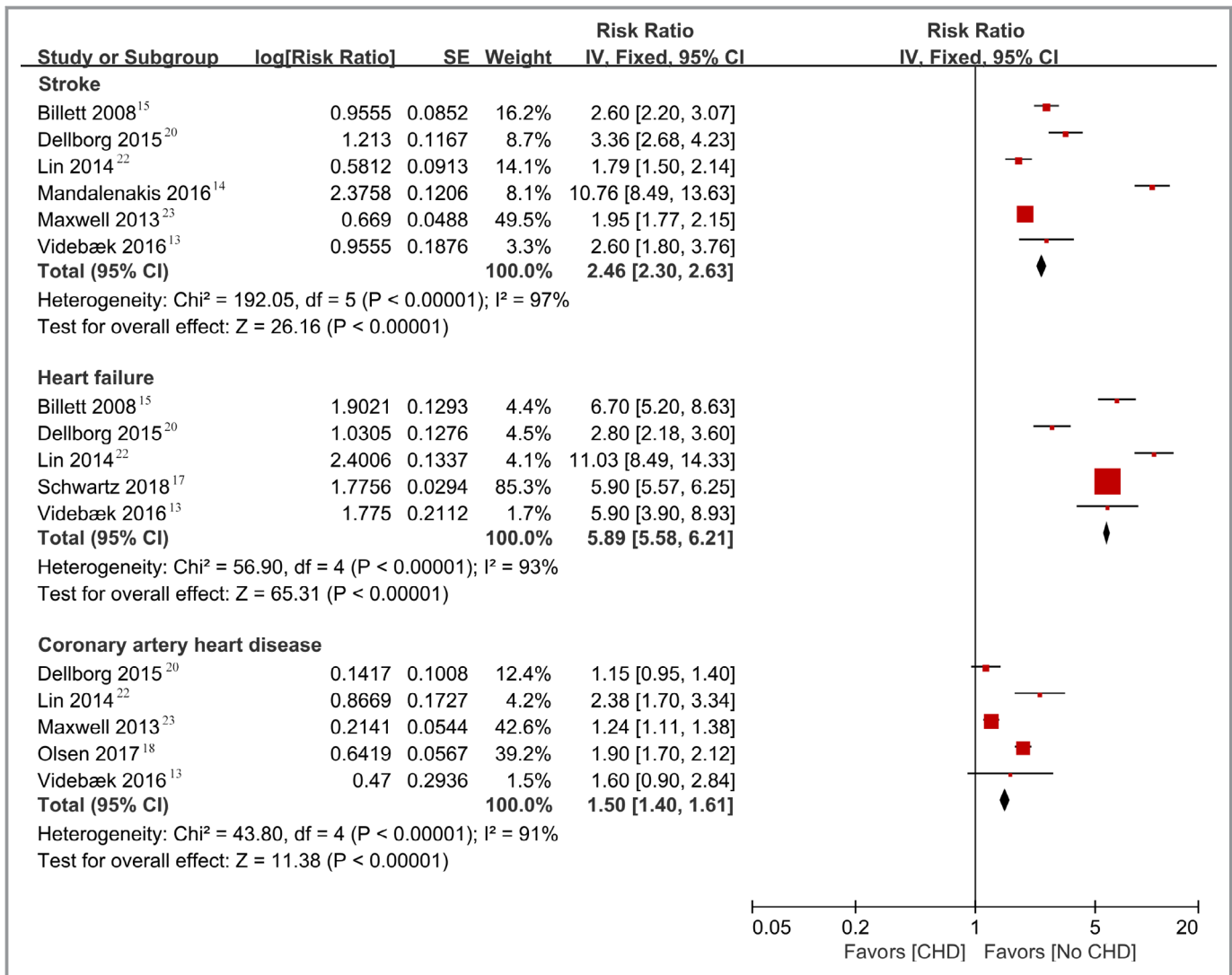
Figure 4. Risk of stroke, heart failure, and coronary artery heart disease associated with congenital heart disease (CHD).

One potential limitation of this meta-analysis was the significant heterogeneity among studies for the association between CHD and risk of CVD. That is not surprising given the difference in study design and characteristics of populations. Fortunately, our subgroup analyses have identified several variables associated with the between-study heterogeneity, including geographic region, type of study design, sample source, age composition, and controlled confounders. In addition, the variability and complexity of CHD might contribute to the heterogeneity given underlying mechanisms involved in the association between CHD and CVD. However, we were unable to obtain adequate information to test the hypothesis. Of the 9 included studies, only 1 study reported the risk of stroke in patients with different lesions[14]; 1 study reported the risk of CVD according to CHD status (cyanotic versus noncyanotic)[22]; and 1 study reported the risk of CVD, stroke, heart failure, and coronary artery heart disease in simple

CHD.[22] Furthermore, because of the sparsity of relevant studies, the outcomes including CVD, stroke, and coronary artery heart disease were composed of >1 disease as defined in our study; this may also contribute to the heterogeneity.

A second limitation is that significant unmeasured confounding factors may have contributed to the observed association between CHD and CVD. Although all studies included here have attempted to control for some potential confounding factors, none of the studies have adequately controlled all conventional cardiovascular risk factors reported in the previous studies, such as age, body mass index, diabetes mellitus, blood pressure, cholesterol, and family history of CVD. The overlap between the controlled confounding factors among the studies was also limited. In addition, 1 study presented the cardiovascular risk factors including body mass index and smoking among patients with CHD and the control group,[20] while 1 study presented risk

Table 3. Subgroup Analyses for the Association Between CHD and CVD

Subgroup	No. of Studies	RR (95% CI)	I^2 (%)	P Value for Heterogeneity	Test for Subgroup Differences		
					χ^2	P Value	I^2 (%)
Geographic region							
Europe	6	4.25 (4.06, 4.45)	99	<0.001	457.83	<0.001	99.8
Non-Europe	3	1.84 (1.73, 1.96)	98	<0.001			
Type of study design							
Prospective cohorts	4	4.79 (4.56, 5.04)	99	<0.001	657.84	<0.001	99.8
Nonprospective cohorts	5	1.81 (1.71, 1.91)	96	<0.001			
Sample source							
General population	7	4.12 (3.94, 4.30)	99	<0.001	524.48	<0.001	99.8
Noncardiac surgery receivers	2	1.59 (1.48, 1.70)	82	0.02			
Age composition							
Adults only	6	3.02 (2.91, 3.14)	100	<0.001	104.69	<0.001	98.1
Adults and children	2	10.15 (8.07, 12.77)	74	0.05			
Children only	1	3.42 (1.80, 6.49)	…	…			
Controlled confounders							
Adjusted for factors other than age and sex	3	1.56 (1.47, 1.65)	61	0.08	843.93	<0.001	99.9
Adjusted for age and sex	5	4.81 (4.59, 5.04)	99	<0.001			

CHD indicates congenital heart disease; CVD, cardiovascular disease; RR, risk ratio.

factors including diabetes mellitus and hypertension.[14] Both of them calculated the between-group difference and showed significant differences in cardiovascular risk factors.[15] Since many studies included here have not controlled the key confounding factors for CVD, it is possible that the increased risks shown in our study are partially driven by differences in those risk factors of CVD between people with CHD and the control group. Further studies are needed to determine whether CHD increase the risk of CVD independently.

In addition, all the outcomes reported in this study relied on a limited number of studies and might be limited by the lack of quality studies on the subjects. More relevant studies should be included in future systematic reviews to provide further support for our results. Finally, although an attempt was made to minimize the possible bias in the process of document retrieving with specific searches in major English-Chinese databases (including master and doctoral theses), there may still be some unidentified papers.

Our finding of an association between CHD and future risk of CVD has important implications for CHD survivors and health policy. Individuals with CHD are at a higher risk of CVD, and this suggests that the risk assessment for CVD based on conventional cardiovascular risk factors should be considered in these patients. Clinicians may find it helpful to educate CHD survivors regarding their increased cardiovascular risk and motivate them to reduce the modifiable risk factors.

Conclusions

This meta-analysis of cohort studies of CHD found an association of increased risk of CVD, stroke, heart failure, and coronary artery heart disease in later life, although we cannot determine whether this association is confounded by a risk factor profile of CVD among CHD survivors or whether CHD is an independent risk factor.

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