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RESEARCH

# The Association Between Congenital Heart Disease and Autism Spectrum Disorder: A Systematic Review and Meta-Analysis

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## Abstract

Congenital heart disease (CHD) is linked to an increased incidence of neurodevelopmental impairments in young patients. Given the number of published studies on this topic, a synthesis of the literature is timely and needed. We performed a systematic review and meta-analysis of the medical literature to assess the evidence linking CHD to incidence of autism spectrum disorder (ASD). A systematic review of studies on CHD and ASD in PubMed, Cochrane and Institute for Scientific Information (ISI) from 1965 to May 2021 was conducted. Quantitative estimates of association between CHD and ASD were extracted from eligible studies for the meta-analysis. Pooled estimates were obtained using a random effect models fit by a generalised linear mixed model. We screened 2709 articles and 24 articles were included in this review. Among the 24 studies, there was a total of 348,771 subjects (12,114 CHD, 9829 ASD and 326,828 controls). Seven of 24 studies were eligible for the meta-analysis, which included information on a total of 250,611 subjects (3984 CHD, 9829 ASD, and 236,798 controls). The summary estimate indicated that having CHD is associated with almost double the odds of ASD compared with patients without CHD (OR 1.99, 95% CI 1.77–2.24, $p < 0.01$). Early developmental delay, perinatal factors, and genetics were potential risk factors and etiologies for the onset of ASD symptoms in CHD patients. Having CHD is associated with an increased risk of presenting with a diagnosis or symptoms suggestive of ASD.

**Keywords** Congenital heart disease · Autism spectrum disorder · Systematic review · Meta-analysis

## Introduction

Congenital Heart Disease (CHD) is the most prevalent group of congenital malformations in newborns [1], with an incidence of 8–12 out of 1000 live births worldwide [2]. CHD represents a heterogeneous group of diseases ranging from minor abnormalities with no significant hemodynamic disturbance to severe, life-threatening abnormalities requiring intervention in the first few days of life [1, 3]. In approximately 30% of cases, CHD is associated with chromosomal or genetic abnormalities such as 22q11.2 deletion, Williams syndrome, or Turner syndrome [4, 5]. One in every 100 children has known genetic or chromosomal abnormalities associated with CHD [6].

Despite increasing survival rates due to advances in medical therapy, surgical and catheter interventions, this management remains palliative and survivors have long-term hemodynamic and cardiovascular abnormalities [7, 8]. Postoperatively, patients who have undergone any cardiac surgery are at high risk for complications involving the heart and other organs such as the brain, kidney and lungs [9]. The disruption of the normal flow of oxygenated blood in the cerebral circulation may result in hypoxemia of the blood supplied to the brain [10].

Due to the success of medical management, children with CHD now survive into childhood and adolescence. They frequently present with neurological deficits, which include intellectual disability, developmental difficulties and problems with behaviour and academic performance [11–13]. Neurodevelopmental impairments are among the most prevalent long-term morbidities in pediatric patients with CHD, affecting approximately half of survivors of

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complex CHD [14, 15]. Previous reports indicate that patients with CHD may be at increased risk for autism spectrum disorder (ASD) [16]. A higher prevalence of neurobehavioural deficits including cognitive and executive function impairment, impulsive behavior, and decreased social skills have been observed in patients with CHD [17]. Current ASD diagnostic criteria are defined by the DSM-5 [18]. Prior to publication of the DSM-5 in 2013, studies of ASD relied on previous versions of the DSM (IV and IV-TR). Evaluation for ASD involves the administration of standardized diagnostic assessment tools and interpretation of these results by a professional with expertise in ASD diagnostics. Examples of ASD assessment tools include the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). Measurement of cognitive ability and adaptive behaviour, evaluation of communication abilities such as speech and language development, and overall clinical impressions are critical in the evaluation process. While some studies included in this review identified "ASD cases" that may not have undergone the comprehensive assessments as listed above, findings from these studies may still be applied to enrich current knowledge and patient care.

ASD is a heterogeneous neurodevelopmental disability characterized by early onset difficulties in social communication and repetitive and restricted behaviors [16, 19]. The prevalence of ASD among CHD patients may be significantly higher than the worldwide prevalence of about 1%, yet this health issue is not yet well-characterized [19, 20]. Early identification and treatment of developmental disabilities in children can be beneficial [16]. By doing so, families can be better informed and appropriate support can be provided as children transition from infancy into the school system and beyond [16].

Due to the limited literature that largely consists of small retrospective cohort studies, any existing prevalence estimates on the co-occurrence of CHD and ASD may be subject to bias. The current systematic review aims to summarize findings about potential associations between CHD and ASD symptoms. We reviewed the medical literature in order to investigate whether young children with CHD have a higher risk of ASD compared to children without CHD.

## Methods

### Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [21] in order to systematically examine the evidence linking CHD to ASD (Fig. 1). We searched Pubmed, ISI and Cochrane databases for articles published between 1965 and June 2021. Retrospective or prospective cohort, case–control, and cross-sectional human studies in the English language were included. Reviews, editorials, case reports, conference proceedings, and abstract-only studies were excluded. Articles not relevant to this review were removed, including articles discussing genetic syndromes such as 22q11.2 microduplication syndrome, Timothy Syndrome and Turner Syndrome, as we are examining associations with ASD and not genetic or chromosomal disorders. A primary literature review was first performed by two authors (S.G. and A.K.)

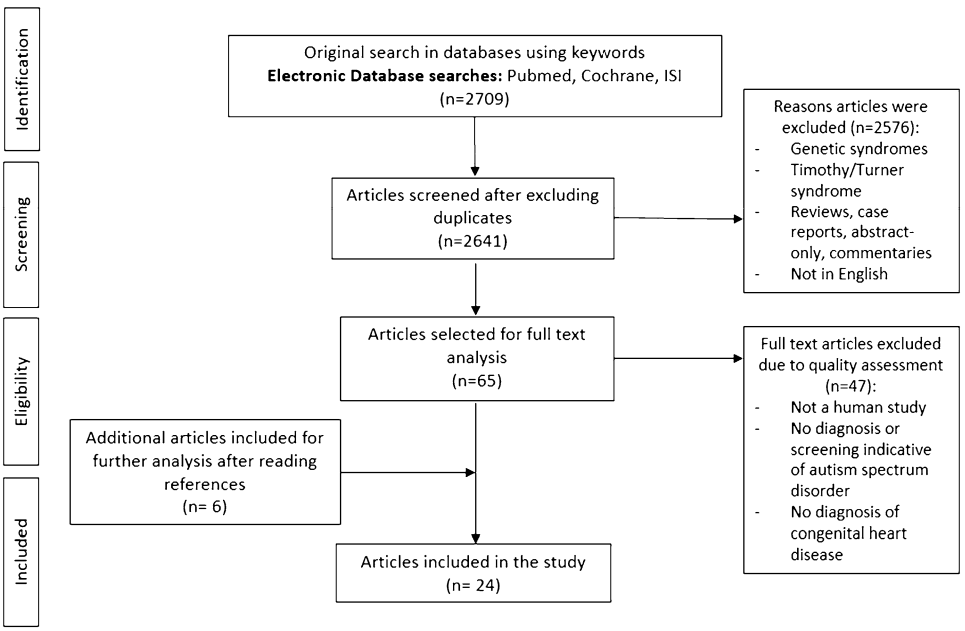


**Fig. 1** Flowchart of the systematic review process. Numbers of articles for each step of the process are indicated

through the PubMed scientific database using the following terms: (*autism* OR *autistic disorder* OR *behavior disorder*) AND (*heart disease* OR *congenital cardiac disease* OR *congenital heart defect* OR *congenital cardiac defect*). To expand the number of eligible studies, we performed a secondary search (S.G. and A.K.) using ISI and Cochrane using the same search terms. Search terms were determined by literature review, database query, and consensus among the authors. Two authors (S.G. and A.K.) verified that each publication met the inclusion criteria, with reconciliation through discussion. Full text articles that appeared relevant were obtained and data extracted. Studies included in the analysis needed to report the following: (1) diagnostic criteria or other indicators suggesting possible ASD, and (2) diagnosis of congenital heart disease. There was no requirement of an age range. After the initial extraction of potentially relevant papers, the references were also checked for potential studies to include. During this process, we identified several academic centers that published cohorts with overlapping patients. To minimize this source of bias, we avoided analyzing one cohort multiple times using the following protocol: (1) The authors/affiliations of articles and the cohort descriptions were reviewed to identify articles with potentially overlapping cohorts. (2) If overlap between cohorts was suspected after this screening, we then contacted the senior author on each article in question to ask if patient overlap existed across more than one article. (3) If the senior author confirmed that overlap among cohorts existed, we included the article with the more relevant endpoints, specifically endpoints with clear CHD or ASD diagnoses. If different endpoints or subgroups were reported, the overlapping cohorts were used.

## Data Extraction

Study subjects included those with CHD diagnoses, an ASD diagnosis, a suspicion of possible ASD based on screening and symptom measures, as well as control subjects (children with CHD without ASD and heart-healthy subjects). Data including demographics, diagnoses, results from clinical testing, and risk factors was extracted. The main endpoints collected were sex, age, CHD diagnosis and ASD diagnosis/screening. Data extraction was checked for accuracy by another co-author (S.F.).

## Comparisons Conducted

We categorized the studies for the meta-analysis based on the following study designs: (1) cohort studies to compare CHD vs. control non-CHD group and then examine the outcomes for ASD; (2) case–control studies to compare ASD vs. control non-ASD group and then examine the outcomes for CHD; (3) cohort studies to compare different intervention/exposure groups among CHD patients and then examine the ASD outcomes.

Type 1 and 2 studies were used to assess the association between CHD and ASD, and thus were included for meta-analysis. Type 3 studies were only used to summarize the ASD outcomes for CHD patients and compare associations between CHD surgery type and ASD outcome.

## Meta-Analysis

The quantitative estimates (frequencies of ASD and CHD, odds ratio [OR] and the corresponding 95% confidence intervals [95% CI]) of association between CHD and ASD were extracted from each eligible study. Where the frequencies of CHD were not directly reported, they were reverse calculated from the reported OR, 95% CI and frequencies of ASD. Quantitative results not included in the meta-analysis were summarized using descriptive statistics. Risk factors identified from these papers were also summarized.

Pooled estimates were obtained using a random effect models fit by a generalised linear mixed model [22]. Estimates were presented as odds ratios (OR) with 95% CI and presented graphically in forest plots. To quantify statistical heterogeneity between studies, the maximum-likelihood estimator was used to estimate the $\tau^2$ statistic (the estimate of between-study variance); the standard chi-square test was applied to examine the statistical significance of heterogeneity; and the $I^2$ statistics was reported to estimate the percentage of variability across studies attributable to heterogeneity beyond chance. Hartung-Knapp adjustment was also applied for the random effects model to adjust test statistics and confidence intervals.

In order to examine the influence of study design on the effect estimate between CHD and ASD, a subgroup analysis by study design was also conducted [23]; thus, the pooled estimates for each design and overall are reported, and a test for subgroup differences was used. Funnel plot was generated to assess any publication reporting bias (Fig. 2). When there is no publication bias, points will be scattered uniformly on each side of the center line; deviation from this pattern may be indicative of publication bias. No test for funnel plot asymmetry was performed due to small number of studies ($< 10$) included in the meta-analysis, which may cause a low power of test so as not to distinguish chance from real asymmetry. A *p*-value of less than 0.05 was considered statistically significant for all analyses. All statistical analyses were performed with R (Package "meta" [24]), version 4.1.0.

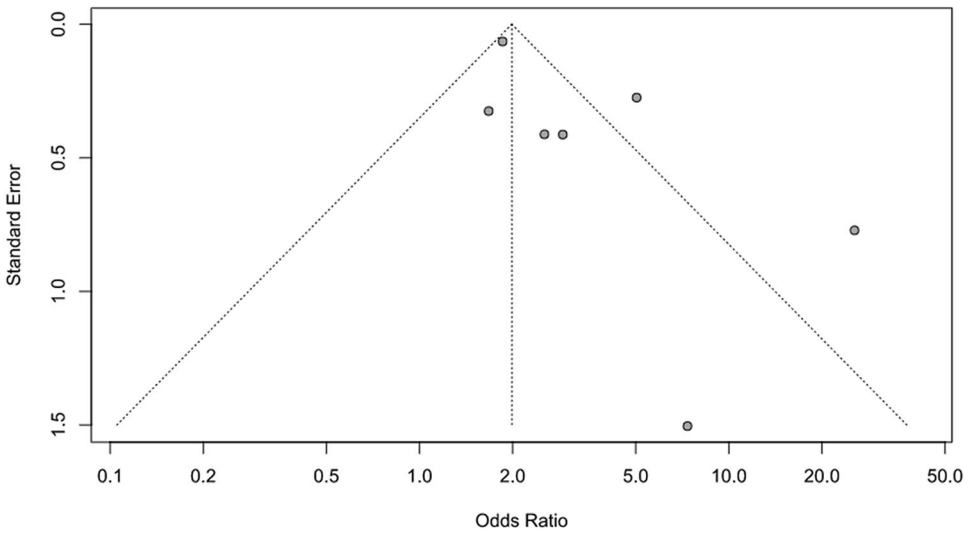


**Fig. 2** Funnel plot to assess the reporting bias

## Results

### Screening Articles

A comprehensive review in Pubmed, Web of Science and Cochrane databases led to 2448 articles from Pubmed, 20 from Cochrane, and 241 from ISI for a total of 2709 articles. We removed 2576 articles including duplicates and those that were irrelevant. In total, 65 published articles were selected for full text reading. Six additional articles were extracted from the references of selected articles and included for further analysis. A further 47 full text articles were excluded due to quality assessment, such as lack of sufficient information about links between CHD and ASD. In total, 24 articles met the inclusion criteria and were included in the analysis (Fig. 1).

### Demographics

These 24 studies were conducted based on 16 unique study populations. Among the 16 unique study populations, there was a total of 348,771 subjects (12,114 CHD, 9829 ASD and 326,828 controls). Patient age (range of 0–26 years) was reported in all studies, while most studies (15/16) reported an age range of 0–17 years. The proportion of males in the CHD, ASD and control groups were 50, 80, and 55%. CHD diagnosis ranged from non-specific (10/16), single ventricle lesion (2/16), dextro-transposition of the great arteries (2/16), hypoplastic left heart syndrome (1/16) and tetralogy of Fallot (1/16). Eight of the 16 studies reported CHD subjects who underwent cardiac surgery (Table 1). Thirteen studies commented on other risk factors for ASD (Table 1). Risk factors included preterm birth and the mother's mental health during early childhood. Risk factors investigated but not found to be associated with ASD risk included hospital length of stay, use of extracorporeal membrane oxygenation (ECMO) and age at first surgery.

Eleven studies were retrospective and six were prospective in study design. Out of the 24 included studies, 20 were cohort studies and four were case–control studies (Table 1).

### ASD and CHD Endpoints

The endpoints included number of subjects classified as having ASD according to the DSM-IV-TR, DSM-IV or DSM-5 or an assigned International Classification of Diseases (ICD) code for ASD (7/20), the autism spectrum quotient (ASQ) (7/20), the Pervasive Developmental Problem (PDP) Scale (4/20), the Social Responsiveness Scale (SRS) (2/20), the Social Communication Questionnaire (SCQ) (1/20), and being identified as "at risk for autism" (1/20). The "at risk for autism" category refers to when a child was evaluated by a psychologist or referred to an autism specialist due to symptoms but it was unclear whether the child met the criteria for an ASD diagnosis [25]. Many studies also used screening tests such as the ASQ or PDP rather than assessment tools such as the ADOS and ADI-R. The scores on screening measures such as the ASQ, PDP or SRS are not indicative of an ASD diagnosis but assess for symptoms that may indicate the presence of a diagnosis. The ASQ is a screening instrument based on the diagnostic criteria for ASD and can be used with all age groups. It has good discriminative validity to separate ASD from non-ASD [26, 27]. The Child Behaviour Checklist (CBCL)/1.5–5 PDP is also a measure that covers a variety of behavioral and emotional problems, and includes a screening scale for ASD and pervasive developmental disorders [28]. The SCQ is a screening instrument with validity against ADI-R, but could result in false positive findings, particularly

**Table 1** Summary of the included studies

| Study | Design | Geographic region | Recruitment period | Sample | Comparison group | Autism measure | Results | Risk factors for ASD |
|---|---|---|---|---|---|---|---|---|
| Asschenfeldt et al. (2020) [33] | Prospective Cohort | Denmark | March 2018 to November 2018 | $N=66$<br>Mean age: 25.6 ± 5.2 years (mean ± SD)<br>Gender: 20 male (30%), 46 female<br>Diagnosis: isolated atrial septal defect ($N=34$) or ventricular septal defect ($N=32$) closed surgically between 1990 and 2000 | Healthy group- age, sex and education matched<br>$N=40$<br>Mean age: 25.6 ± 4.7 years (mean ± SD)<br>Gender: 14 male (35%), 26 female | Social Responsiveness Scale, Second Edition (SRS-2) | The CHD group scored significantly worse in the SRS-2 self-report and informant report compared to the control group. On the self-report, every third (32%) of the CHD group scored > = 60 ("indicating mild to moderate deficits, or higher"), compared with 8% of the control group ($p=0.005$). On the informant reports, these were 22 and 3% ($p=0.02$) | No potential clinical or surgery-related risk factors for poor neuropsychological performance |
| Bellinger et al. (2011) [56] | Prospective Cohort | Boston (BCAS) | April 1988-February 1992 | $N=139$<br>Mean age: 16.1 ± 0.5 (mean ± SD)<br>Gender: 106 male, 33 female<br>Diagnosis: all d-TGA, ASO by 3 months | None. Intact ventricular septum ($N=107$) vs ventricular septal defect ($N=32$) | Autism spectrum quotient | Combined VSD group score was significantly higher (i.e., worse) than the intact ventral septum group ($p=0.04$). Scores of DHCA and LFBP (treatment) groups did not differ significantly ($p=0.46$) | Genetic abnormality, 3 or more total operations |

**Table 1** (continued)

| Study | Design | Geographic region | Recruitment period | Sample | Comparison group | Autism measure | Results | Risk factors for ASD |
|---|---|---|---|---|---|---|---|---|
| Bellinger et al. (2015) [57] | Retrospective Cohort | Boston | 2010–2012 | $N=156$<br>Mean age: 14.5 ± 2.9 (mean ± SD)<br>Gender: 61 male, 95 female<br>Diagnosis: all single ventricle lesion who underwent Fontan procedure | Healthy referent subjects of a similar age ($N=111$) used for the purpose of comparing brain MRI | Autism spectrum quotient | The Norwood group scored significantly worse on the Autism Spectrum Quotient than the non-Norwood group ($p=0.03$) | Scores on several endpoints worse among patients of Hispanic ethnicity, had a possible genetic abnormality, required more operations/catheterizations, experienced more operation/catheterization complications, were of younger gestational age, had an open first operation, or had seizure occurrence |
| Bellinger et al. (2015) [58] | Retrospective Cohort | Boston | 2004–2008 | $N=91$<br>Mean age: 14.6 ± 1.2 years<br>Gender: 55% male (50 males, 41 females)<br>Diagnosis: tetralogy of Fallot with or without pulmonary atresia, cardiac surgery for repair at least 6 months before testing | Referents $N=87$<br>Age range: 13–16 years | Autism spectrum Quotient | Adolescents with tetralogy of Fallot scores significantly higher (worse) than referents | No risk factors identified |
| Calderon et al. (2016) [45] | Retrospective Cohort | Boston | 2010–2012 | $N=133$<br>Mean age: 14.6 ± 3.0 (mean ± SD)<br>Gender: 82 male (62%), 51 female<br>Diagnosis: all single ventricle lesion who underwent Fontan procedure | None. Early term birth ($N=33$) vs full term birth ($N=100$) | Autism spectrum quotient | The early term group scored worse than the full term group on the Autism Spectrum Quotient ($p=0.09$) | Preterm birth |

**Table 1** (continued)

| Study | Design | Geographic region | Recruitment period | Sample | Comparison group | Autism measure | Results | Risk factors for ASD |
|---|---|---|---|---|---|---|---|---|
| Davidson et al. (2015) [32] | Retrospective Cohort | London, UK | 1995–2003 | *N* = 58<br>Median age: 12.3 (10.2–17.8); non-HLHS group 13.5 (10.5–17.8)<br>Gender: 37 male, 21 female<br>Diagnosis: HLHS | Single ventricle lesion and non-HLHS<br>*N* = 44<br>Median age: 13.5 (10.5–17.8)<br>Gender: 32 male, 12 female | % with formal autism diagnosis, test not specified | 7% of HLHS group diagnosed with autism compared to none in non-HLHS patient group ($p = 0.13$) | |
| Gaynor et al. (2009) [17] | Prospective Cohort | Philadelphia | September 1998-April 2003 | *N* = 381<br>Age range: 4–5 yrs<br>Gender: 215 male (56%), 166 female<br>Diagnosis: CHD having had cardiac surgery with cardiopulmonary bypass with or without deep hypothermic circulatory arrest (DHCA) at </= 6 mths of age | Normative data – stratified sample (*N* = 907) | Pervasive Developmental Problem (PDP) Scale; parental report of autism diagnosis | 9 out of 381 children with CHD reported being diagnosed with autism vs 1/150 in general population. 15% of the CHD cohort were in the at risk of clinically significant range of the PDP scale compared with 9% for the normative data ($p < 0.00001$) | APOE genotype |
| Gaynor et al. (2013) [52] | Prospective Cohort | Philadelphia | September 1998-April 2003 | *N* = 132<br>Age range: 4–5 yrs<br>Gender: 75 male, 57 female<br>Diagnosis: CHD with cardiac surgery with cardiopulmonary bypass with or without DHCA at </= 6 mths of age | None. EEG seizure (*N* = 14; 8 male, 6 female) vs no EEG seizure (*N* = 118, 67 male, 51 female) | Pervasive Developmental Problem (PDP) Scale | No difference between patients with or without a history of seizures. Patients with HLHS had a higher prevalence of deficits in social interactions and repetitive/restricted behaviours ($p = 0.05$) | Occurrence of EEG seizure |

**Table 1** (continued)

| Study | Design | Geographic region | Recruitment period | Sample | Comparison group | Autism measure | Results | Risk factors for ASD |
|---|---|---|---|---|---|---|---|---|
| Gaynor et al. (2014) [59] | Prospective Cohort | Philadelphia | September 1998-April 2003 | $N=365$<br>Age range: 4–5 yrs<br>Gender: 209 male, 156 female<br>Diagnosis: CHD with cardiac surgery with cardiopulmonary bypass with or without DHCA at </=6 mths of age | None. Biventricular repair ($N=253$, 141 male, 112 female) vs Fontan procedure ($N=112$, 68 male, 44 female) | Pervasive Developmental Problem (PDP) Scale | No significant difference between the PDP scores of the BV repair cohort and Fontan cohort ($p=0.15$) | No risk factors reported |
| Hultman et al. (2002) [35] | Retrospective Case–Control | Sweden | 1987–1996 | $N=408$<br>Mean age: 4.4 yrs for males and 4.6 yrs for females<br>Gender: 321 male, 87 female<br>Diagnosis: infantile autism (ICD-9 code 299A) | Controls- age, gender and hospital of birth matched ($N=2040$) | Congenital malformations | Increased congenital malformations in autistic children largely attributed to heart and circulation malformations | Infants born small for gestational age. Low five-minute Apgar score suggests association between perinatal asphyxia and risk of autism. Infants born to mothers born outside of Europe or North America |
| Jaworski et al. (2017) [31] | Prospective Cohort | Philadelphia | 1998–2003 | $N=195$<br>Mean age: $4.79 \pm 0.2$ (mean + SD)<br>Gender: 312 male (58.4%), 229 female<br>Diagnosis: CHD with cardiac surgery with cardiopulmonary bypass with or without DHCA at </=6 mths of age | N/A | Parental report of autism diagnosis; Social Communication Questionnaire (SCQ) | Children with CHD have a higher risk of screening positive on ASD screener | Delayed sternal closure after surgery |

**Table 1** (continued)

| Study | Design | Geographic region | Recruitment period | Sample | Comparison group | Autism measure | Results | Risk factors for ASD |
|---|---|---|---|---|---|---|---|---|
| Kim et al. (2012) [54] | Prospective Cohort | Philadelphia | October 1998-April 2003 | *N* = 316<br>Age range: 4–5 yrs<br>Gender: 180 male, 136 female<br>Diagnosis: CHD with cardiac surgery with cardiopulmonary bypass with or without DHCA at </= 6 mths of age | N/A | Pervasive Developmental Problem (PDP) Scale | Five SNPs reached genome-wide significance for association with CBCL/1.5–5 | 5 genome-wide association study single nucleotide polymorphisms rs2261722, rs10516292, rs11206315, rs12965975, and rs228144 |
| Lauritsen et al. (2002) [36] | Retrospective and Prospective Case–Control | Denmark | 1970–1993 | *N* = 244<br>Age: N/A<br>Gender: male-to-female ratio 2.4:1<br>Diagnosis: ICD-8 diagnosis of autism before age 3 | Controls- sex and year of birth matched<br>*N* = 33,916 (139:1)<br>Gender: male-to-female ratio 2.4:1 | Congenital anomalies | The autism cohort has a higher rate of congenital heart malformations than the general population | |
| Neal et al. (2015) [60] | Retrospective Cohort | Boston | June 2004-September 2007 | *N* = 91<br>Age: 14.6 ± 1.2<br>Gender: 55% male<br>Diagnosis: tetralogy of Fallot who had undergone repair | Referent *N* = 85<br>Age: 15.2 ± 1.1<br>Gender: 55% male | Autism Spectrum Quotient | Lower psychosocial (PsS) scores were associated with worse performance on the Autism Spectrum quotient (r = -0.35, *p* = 0.006) | |
| Neufeld et al. (2008) [30] | Prospective Cohort | Edmonton | September 1996-May 2003 | *N* = 65<br>Mean age: 58 ± 9 mths<br>Gender: 42 male, 65%<br>Diagnosis: all TGA who underwent the arterial switch procedure | None. Simple TGA (*N* = 36, 55% male) vs TGA with septal defect (*N* = 19, 31% male) vs complex TGA (*N* = 10, 14% male) | DSM-IV autism diagnosis | Four out of 65 patients diagnosed with autism: all four had TGA with intact ventricular septum, three had septostomy and two of these required DHCA, the fourth had DHCA without septostomy | Children undergoing ASO (arterial switch operation) |

**Table 1** (continued)

| Study | Design | Geographic region | Recruitment period | Sample | Comparison group | Autism measure | Results | Risk factors for ASD |
|---|---|---|---|---|---|---|---|---|
| Olsen et al. (2011) [34] | Retrospective Cohort | Denmark | January 1, 1977-January 1, 2002 | *N* = 6927<br>Mean age: born in between 1977 and 2002<br>Gender: 49.0% male<br>Diagnosis: primary diagnosis of CHD at any age (ICD-8 746 to 747 except 746.7 and 747.5–747.9 and ICD-10 Q20-Q26 except Q26.5-Q26.6) | Controls- sex and birth year matched<br>*N* = 68,185<br>Mean age: born 1977–2002<br>Gender: 49.0% male | Pervasive developmental disorders (F.84) | Risk of admission for developmental disorders were elevated among CHD patients | The severity of CHD is not strongly related to the risk of psychiatric disorders |
| Razzaghi et al. (2015) [37] | Retrospective Cohort | US | 1997–2011 | *N* = 420<br>Age range: 0–17 yrs<br>Gender: 216 male, 204 female<br>Diagnosis: CHD | Controls- age and gender matched<br>*N* = 180,048<br>Age range: 0–17 yrs<br>Gender: 92,518 male, 87,530 female | Autism diagnosis, test not specified | fivefold increased odds of autism spectrum disorder OR = 4.6, CI = 1.9–11 in children with CHD compared to those without CHD | |
| Robson et al. (2019) [61] | Prospective Cohort | Boston (BCAS) | 1988–1992 | *N* = 139<br>Mean age = 16.1 ± 0.5 years<br>Gender: 77% male<br>Diagnosis: d-TGA with intact ventricular septum or ventricular septal defect, ASO by 3 mos, | Referent group of healthy adolescents<br>*N* = 85<br>Mean age = 15.2 ± 1.1 years<br>Gender: 55% male | Autism Spectrum Quotient | Lower psychosocial (r = -0.33, $p = < 0.001$) and physical (r = -0.09, $p = 0.33$) scores were associated with worse performance on the Autism Spectrum quotient | |
| Rollins et al. (2014) [62] | Prospective Cohort | Boston (BCAS) | April 1988- February 1992 | *N* = 49<br>Mean age = 16.2(16–16.4)<br>Gender = 41 male, 8 female<br>Diagnosis: d-TGA, ASO by 3 mos | Controls-age matched<br>*N* = 29<br>Mean age = 14.9 (14.2–16.1)<br>Gender = 15 male, 14 female | Autism Spectrum Quotient | The d-TGA cohort scored significantly worse on the autism spectrum quotient than the control data ($p = 0.003$) | Regional fractional anisotropy in the right precentral region |

**Table 1** (continued)

| Study | Design | Geographic region | Recruitment period | Sample | Comparison group | Autism measure | Results | Risk factors for ASD |
|---|---|---|---|---|---|---|---|---|
| Sigmon et al. (2019) [39] | Retrospective Case–Control | US | Birth between October 2001-September 2013 | *N* = 8760<br>Mean age = 7.01 years<br>Gender:79.9% male<br>Diagnosis: Autism diagnosis (ICD-9-CM) | Controls- age, sex, date of birth, enrollment time frame matched<br>*N* = 26,280<br>Mean age = 7.01 years<br>Gender: 79.9% male | CHD diagnosis or cardiac surgery | CHD is associated with increased odds of developing ASD | CHD subtypes atrial septal defect and ventricular septal defect. Potentially the early onset of seizures |
| Tan et al. (2020) [25] | Retrospective Cohort | Atlanta | February 2018-February 2019 | *N* = 134<br>Mean age = 9 years (3–19 years)<br>Gender: 64.2% male<br>Diagnosis: high risk CHD diagnosis, cardiac surgery within first year | N/A | Thorough assessment, developmental history via parent interview, and behavioural observations OR diagnosis by autism specialist | Children with CHD have a higher incidence of being "at risk for autism" | |
| Tsao et al. (2017) [20] | Retrospective Cohort | Taiwan | January 1, 1997-December 31, 2009 | *N* = 3552<br>Mean age = 2.21 ± 4.08 years<br>Gender: 1737 male, 1815 female<br>Diagnosis: children < /= 18 years with diagnosis of CHD | Controls- age, sex and enrolled time matched<br>*N* = 14,208<br>Mean age = 2.21 ± years<br>Gender: 6948 male, 7260 female | Autism diagnosis (ICD-9-CM) | Risk for ASD was significantly higher in children with CHD | Preterm or low birth weight. Presence of early developmental delay or intelligence disability |
| Werninger et al. (2020) [44] | Prospective Cohort | Zurich, Switzerland | 2004–2009 | *N* = 125<br>Median range = 10.17 years (9.5–11.25)<br>Gender: 75 male, 50 female<br>Diagnosis: CHD, underwent CPB surgery < /= 6 years | N/A | Social Responsiveness Scale (SRS) | Prevalence of ASD similar to general population (ASD = < 1%) | Total IQ at 4 years and BSI at 4 years. Mother's mental health during early childhood |
| Wier et al. (2006) [38] | Retrospective Case–Control | North California | January 1995-June 1999 | *N* = 417<br>Age = data from first year of life<br>Gender: 341 male, 76 female<br>Diagnosis: autism spectrum disorder (ICD-9-CM) | Controls- age, gender and hospital of birth matched<br>*N* = 2067<br>Gender: 1681 male, 386 female | Congenital anomalies | 3.1% of ASD patients diagnosed with autism vs 1.9% in non-ASD group | |

Bellinger et al. [57] and Calderon et al. [45] are the same cohort; All Gaynor studies, Kim et al. [54], Jaworski et al. [31] are the same cohort; Bellinger et al. [58] and Neal et al. [60] are from the same cohort; Bellinger et al. [56], Robson et al. [61], and Rollins et al. [62] are from the same cohort (but they all report different endpoints)

when it is not used in the context of a comprehensive assessment as described above [29]. Studies that relied solely on these parent-reported screening tools were only included in the systematic review, while studies that explicitly identified an ASD diagnosis were eligible for the meta-analysis. Some studies reported two different ASD endpoints.

The remaining four studies reported congenital anomaly findings (3/4) or CHD diagnosis (1/4) in subjects with ASD. All studies reported increased congenital cardiac malformations in children with ASD.

## Systematic Review

Six studies that were not added to the meta-analysis also revealed an increased rate of diagnosis of ASD or increase in symptoms suggestive of ASD in CHD patients compared to the national or global prevalence of ASD [17, 25, 30–33]. Overall, five articles reported a 4.66-fold increase in the risk of ASD cases in patients with CHD compared to that in the general population: (5.87 vs 1.14% of ASD cases in CHD vs the general population). The sixth study used a different method of reporting results.

Two studies with survival analysis have also reported an increased likelihood of being diagnosed with an ASD among patients with CHD compared to a control cohort, with up to a 5.02 hazards ratio [20, 34]. When adjusting for variables such as extracardiac defects, being born at term, perinatal and early developmental delay (EDD) comorbidities, the risk was still higher for ASD in the CHD group than in the control group, confirming that CHD increased the risk of subsequent ASD later in life [20].

## Meta-Analysis

Studies that were (1) cohort studies comparing CHD vs. control non-CHD and examined the outcomes for ASD and (2) case–control studies comparing ASD vs. control non-ASD and examined outcomes for CHD were included in the meta-analysis. Also studies that included patients with an ASD diagnosis using the gold standard were included in the meta-analysis. Seven articles were eligible for the meta-analysis [20, 32, 35–39], which included information on a total of 250,611 subjects (3984 CHD, 9829 ASD). Three of them were cohort studies involving 947 ASD cases in 176,479 individuals; while 4 were case–control studies which included 9,829 ASD cases in 74,132 individuals.

The overall summary estimate from these seven studies combined indicated that the odds of having ASD in individuals with CHD was 99% greater than those without CHD: OR 1.99 (95% CI: 1.77–2.24). There was significant heterogeneity ($p < 0.01$) most of which was due to differences between studies ($I^2$ statistic = 76.0%, 95% CI: 49.4–88.6%) (Fig. 3).

The pooled summary estimates from the cohort studies indicated that the odds of having ASD in individuals with CHD was 329% greater than those without CHD: OR 4.29 (95% CI: 2.84–6.49). Heterogeneity could not be reliably estimated ($I^2$ statistic = 0). The pooled summary estimates from the case–control studies indicated that the odds of having ASD in individuals with CHD was 88% greater than those without CHD: OR 1.88 (95% CI: 1.66–2.12). There was significant heterogeneity ($p < 0.01$) most of which was due to differences between studies ($I^2$ statistic = 75.2%,

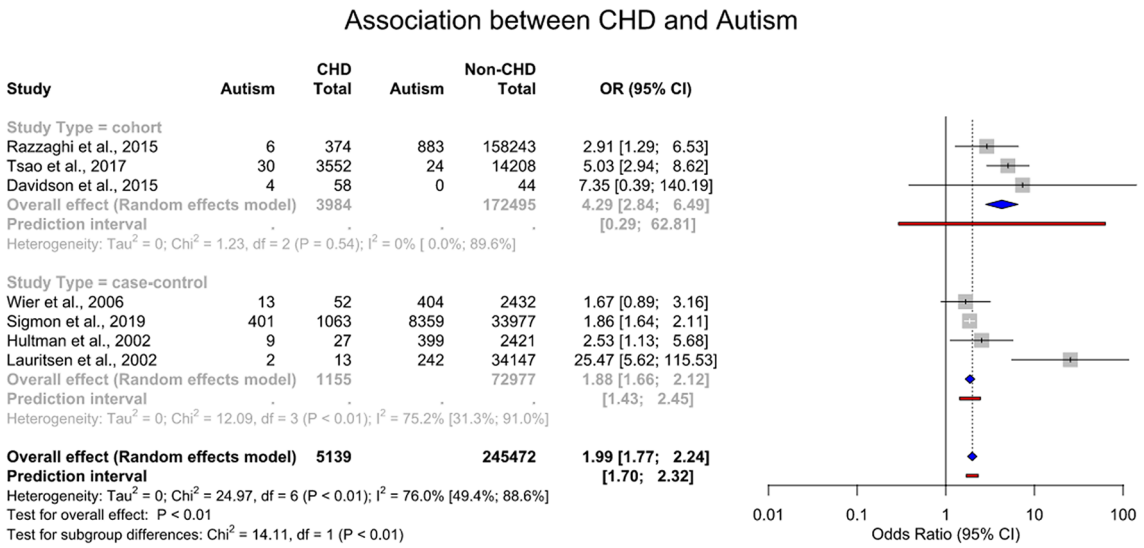


**Fig. 3** Forest plot on the association between CHD and ASD

95% CI: 31.3%–91.0%). The Lauritsen study [36] reported a significantly increased odds of ASD compared to the other studies; because the CHD population had a low sample size, the study contributes low weight to the overall meta-analyses estimate so it is unlikely to skew the result.

Both cohort and case–control studies were consistent with an increase in odds of ASD with CHD; however, cohort studies generally had larger effect sizes: OR 4.29 (95% CI: 2.84–6.49) versus 1.88 (95% CI: 1.03–2.26); $p < 0.01$ (Fig. 3). Although the effect estimates between-study designs varied, the directions of the association between CHD and ASD were consistent. Funnel plots showed some asymmetry and thus possible reporting bias (Fig. 2). The asymmetrical funnel plot indicates some evidence that studies with positive findings were reported selectively.

## Discussion

The aim of this study was to determine the association between CHD and the incidence of ASD. Our results suggest that CHD patients are overall at increased risk of features of ASD. Explanations for the link between CHD and ASD remain to be further investigated, but certain risk factors during neonatal and childhood development, such as pre-eclampsia, delayed cerebral development, postnatal white matter injury, preterm birth as well as genetics and cerebral hypoperfusion in the brain have been proposed [39–45].

### Risk of ASD in CHD

As Jenabi et al. have shown, CHD is associated with an increase in ASD [46]. Based on our meta-analysis, we show that CHD patients are twice as likely to be diagnosed with ASD compared to non-CHD patients (Fig. 3). In fact, a study by Razzaghi et al. showed that children with CHD diagnoses had an approximately five-fold increased odds of an ASD diagnosis [37]. While most studies find an increased diagnosis of ASD, one study found the prevalence of ASD diagnoses of children with complex CHD to be similar to that of the general population at < 1%. This result from this specific study may have resulted from the fact that authors defined the ASD diagnoses on the basis of parental reports only, rather than the "gold standard" comprehensive multidisciplinary diagnostic approach [44]; it is possible that if the children had received comprehensive ASD evaluations, the rate of ASD diagnosis may have been increased. The current "gold standard" diagnostic method is to conduct a thorough evaluation by a qualified professional or a team of professionals, involving clinical history, observations, and results from standardized assessments, to determine whether a patient meets the DSM-5 criteria for ASD. However, many previous studies used the DSM-IV criteria or ICD-9 codes for ASD. Regarding changes to the ASD diagnostic criteria from earlier versions of the DSM to the most recent one, there is evidence that fewer individuals who met criteria for ASD or pervasive developmental disorder (PDD) with DSM-IV or DSM-IV-TR also meet ASD criteria using the DSM-5 [47, 48]. Nevertheless, there is evidence suggesting that although this may be the case, a greater proportion of individuals met ASD criteria with both DSM-IV-TR and DSM-5, and that those who have more significant symptoms are more likely to meet criteria with both DSM versions [49].

Three studies evaluated the effect of CHD severity on ASD or neurodevelopmental (ND) impairment. In one study, the majority of children with CHD scored within the average range across different subscales of social interaction problems, revealing that ND impairment was subclinical [44]. Another study found that ND discrepancies were similar in the simple types of CHD and in complex CHD [33]; similarly, Sigmon found significant associations of ASD with more mild types of CHD and generally no significantly higher risk of ASD with more severe CHD types [39].

### Risk Factors

One key independent risk factor for ASD identified in the literature is the presence of EDD such as early cognitive and global developmental delays, which are usually detected during the preschool stage [20]. Similarly, cognitive measures of CHD patients during early childhood (4 years of age) were consistently predictive of later behavioural outcomes at 10 years of age [44].

There is differing literature on whether perinatal factors are risk factors. Preterm birth and the mother's mental health during early childhood are risk factors for outcomes in children with CHD [44, 45]. Yet another study did not find that comorbid perinatal disorders were independent risk factors for ASD [20]. Factors such as congenital malformations, open heart surgery in infancy, low birthweight, and birth injury are factors typically associated with ASD risk [50]. Clinical factors that impact risk for developmental outcomes in CHD patients include prematurity, genetic abnormalities, history of mechanical support such as ECMO, prolonged length of stay in hospital (> 2 weeks in hospital) and abnormalities on neuroimaging among others [16].

### Etiology

It has been postulated that part of the etiology between CHD and ASD involves a shared gene or environmental insult [17]. Although there may be a common genetic mechanism such as 22q11.2 deletion syndrome or CHARGE syndrome, the association between CHD and ASD exists when controlling for these known genetic syndromes [39]. Previous

reports from the literature indicate that there are at least 9 chromosomal anomalies where ASD was associated with CHD [51] and much overlap of the mutated genes in CHD and ASD [43].

Impaired neurological development may play a role in the developmental-behavioural phenotype of children with CHD [34]. Brain MRI studies reveal that neonates with CHD have immature brain development and smaller brain volumes, possibly due to abnormal fetal perfusion and oxygenation [42]. This brain immaturity at the time of cardiac surgery is associated with worse ND outcomes [45], as this may be coupled with treatment-related variables such as reduced cerebral blood flow or cerebral embolization, which may affect neurological development [34].

The occurrence of a seizure in the period right after CHD repair is associated with a higher frequency of repetitive and restricted behaviors, characteristics of ASD [52]. Epilepsy also has an increased prevalence among children with ASD, leading to the hypothesis that CHD is linked to the development of ASD by cerebral hypoperfusion [39]. Previous research suggests that the more significant the cerebral hypoperfusion in the brain, the more significant the ASD symptoms [53].

### Improving Outcomes for Children with CHD and ND

The improvement of the clinical outcomes of children with CHD begins with early identification of risk factors [20] as ND disorders like ASD emerge during childhood rather than later in life [34]. Early identification will allow for early treatment and care from both clinicians and parents. In order to improve the quality of diagnosis, it is important to follow gold standard diagnostic methods for assessing ASD where indicated. If children show emerging features of ASD, close and consistent follow-up to assess for developing symptoms is helpful [25].

It is also important to identify ND disorders early, so that optimal educational planning and interventions can be implemented to improve longer-term outcomes. There is a higher incidence of educational difficulties and a higher requirement for special needs schooling and remedial academic services in CHD patients compared to non-CHD patients [32, 54]. Tan et al. [25] demonstrated that patients with CHD who are at risk for ASD are younger and required more community and academic services than the subset of patients not at risk for ASD. By identifying those patients earlier, they can be better supported academically as they transition through school.

### Limitations

The main limitation of this manuscript is the low number of studies reporting on associations between CHD and ASD. Few articles explicitly explored the association between CHD and ASD as the main focus of the article. Quite a few studies comparing ASD outcomes between CHD and non-CHD groups used different tests that revealed symptoms of ASD, and thus a limited meta-analysis was conducted. While the meta-analysis indicates a positive association between ASD and CHD, the size of the effect is uncertain and more comprehensive studies are needed to measure the possible causal effect. We did not have sufficient studies to explore the impact of various moderators to explain the high heterogeneity. In addition, due to the small number of cohort studies included in the analyses, the heterogeneity estimate may tend to be 0 ($I^2$ statistic = 0.0%, 95% CI: 0.0%–89.2%) (Fig. 3), which should be interpreted with caution [55]. Heterogeneity is a measure of how much variation there is in the effects across studies. When the heterogeneity is high, it can indicate that studies may not be comparable and/or some moderators should be included to model the possible reason for heterogeneity. The measurement of 0% heterogeneity is likely due to the low number of studies and therefore no possibility of accurately estimating the $I^2$ statistic, and not because the actual heterogeneity is 0%.

Some of the common limitations of the studies conducted were small sample size and limited comprehensiveness of medical information. Although there is no rule about the size of included studies, smaller studies have less precision and often higher risk of bias. Other limitations with the review were the inclusion of publications in our systematic review with non-formal screening assessments which could result in a false positive ASD diagnosis. Due to inconsistencies regarding the diagnostic criteria for ASD used in the studies included in our analysis (e.g., a comprehensive, multidisciplinary diagnostic evaluation versus an elevated score on a self-reported measure such as SRS), the number of ASD patients included could be inflated. It is imperative that future studies investigating the association between CHD and ASD include patients diagnosed with ASD using the "gold standard" approach to ASD diagnosis, which includes an evaluation by a multi-disciplinary team of professionals using standardized ASD assessment tools such as ADOS, ADI-R, as well as measures of cognitive ability, adaptive skills, and speech/language assessment for more accurate ASD identification. A further limitation of our study was the inability to differentiate and analyze whether there was an association between different CHD types and ASD.

## Conclusions

This review outlines that patients with CHD are at an increased risk of presenting with an ASD diagnosis or symptoms suggestive of ASD. Early developmental delay, perinatal factors, genetics and neurological development were

potential risk factors and etiologies for the onset of ASD in patients with CHD. Systematic early screening and identification is needed in order to assess for possible ASD among the CHD population as early as possible. Future larger prospective studies exploring the relationship between CHD severity and ASD is warranted.

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## Declarations

**Conflict of interest** The authors declare no competing interests.

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