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REVIEW ARTICLE

The association between congenital heart disease and the risk of Autism spectrum disorders or attention-deficit/hyperactivity disorder among children: a meta-analysis

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KEYWORDS
Autism spectrum disorders;
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Abstract
Background and objective: To our knowledge, this is the first meta-analysis conducted about the association between congenital heart disease (CHD) and the risk of attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorders (ASD) based on observational studies.
Methods: PubMed, Web of Science, and Scopus were systematically searched from the earliest possible year to December 2020. Heterogeneity was conducted using the chi-square test and its quantity was measured using the I^2 statistic. The publication bias was assessed using Egger's and Begg's line regression tests. The results were reported using the odds ratio (OR) estimated with its 95% confidence interval (CI) using a random-effects model.
Results: In total, 812 citations were included in the search initial until December 2020 with 467,164 children. Based on the random effect model, the estimated OR of the risk of ASD associated with CHD was OR=1.35 (95% CI: 1.17, 1.52; 6 studies; I^2=0.0%) and the risk of ADHD associated with CHD was OR=3.04 (95% CI: 1.58, 4.49; 15 studies; I^2=88.1%).
Conclusions: Our findings suggested that CHD is a risk factor for ASD and ADHD. Therefore, Screening for ASD and ADHD should be considered among young children with CHD.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) and Autism spectrum disorder (ASD) are two neurodevelopmental disorders with a steadily increasing prevalence during the past decades.[1] ASD among children is manifested by impaired social interactions; communication deviance; and restricted, stereotypical behavioral patterns. Current data from WHO reported an average prevalence of ADHD among children of 2.2%.[2] The prevalence of ASD in the USA was reported 1 in 58, respectively.[3] The reported prevalence of ASD varies considerably by country and continent, gender, geographic area, and socioeconomic status.[4]

The etiology of the disorder is considered largely genetically determined, although early environmental factors may be associated with ASD and ADHD occurrence. Children with ASD or ADHD have been reported to have an increased frequency of perinatal complications compared with normal children. These risk factors included preterm labor, low birth weight, small for gestational age (SGA), number of pregnancies and delivery, infancy complications, smoking in the mother, maternal substance abuse, and maternal body mass index.[5–9] Neuropathology reports have provided clues about the course of the disease and brain development abnormalities with prenatal and early postnatal origins.[10]

One of the most common defects among neonates is congenital heart disease (CHD).

The incidence of moderate and severe forms of CHD is 1% of live births.[11] As CHD treatment progresses, many patients are surviving to adulthood age. In 2012, the American Heart Association published a scientific statement evaluating and managing the consequences of neurodevelopment in children with CHD.[12] In particular, little research is available on ASD as a result of the development of CHD and the mental health implications (ADHD and ASD) of critical CHD survivors.[13–15] There were some reports about the association between CHD and the risk of ASD or ADHD,[15–17] while some studies did not report this association.[10,18]

So far, no meta-analysis has been carried out in this regard. Therefore, we conducted the first meta-analysis about the association between CHD and the risk of ASD or ADHD based on observational studies.

Materials and methods

The present systematic review was conducted by the Preferred Reporting Items for Systematic Reviews (PRISMA) statement.

Eligibility criteria

The exposure variable was CHD and the outcome of interest was included ASD and ADHD. Epidemiological studies including cohort, cross-sectional and case-control design were considered as inclusion studies, irrespective of language, date of publication, nationality, race, and age. The exclusion studies were review articles, case reports, experimental articles, letter to the editor, and studies with incomplete data.

Information sources and search

PubMed, Web of Science, and Scopus were systematically searched from the earliest possible year to December 2020 using the search terms in combination: (congenital heart disease, congenital heart defect, congenital cardiac anomalies, congenital cardiac disease, congenital cardiac malformation, cardiovascular defect, or cardiovascular anomalies) and (ASD, autism spectrum disorders or autism and ADHD or attention-deficit/hyperactivity disorder). In addition, the reference lists were manually searched to identify studies missed.

Study selection

Endnote software reference manager was used for merging the search results and duplicate records of the same results were removed. Also, the two authors independently extracted all information and any disagreement was argued and resolved by consultation with the supervisor. We retrieved the full texts of the potentially relevant reports and examined the full papers determined for eligibility criteria.

Data extraction

Information from the included studies was extracted by an electronic data collection in Stata software. The following data were included: first author (year of publication), country, study's design, sample size, control for confounding variables (adjusted, unadjusted), ASD, and ADHD.

Methodological quality

Quality assessment of the 10 articles was conducted using the Newcastle Ottawa Scale (NOS).[19] A study could achieve a maximum of 9 NOS stars: 4 stars for quality of selection, 2 stars for comparability, and 3 stars for quality of exposure (case-control studies or cohort studies). A score equal to or greater than 7 was considered as the study with high quality.

Heterogeneity and reporting biases

Heterogeneity was conducted using the chi-square test[20] and its quantity was measured using the I^2 statistic.[21] The publication bias was assessed using Egger's and Begg's[22] line regression tests.

Summary measures

We expressed the association between CDH and the risk of ASD or ADHD using odds ratio (OR) or hazard ratio (HR) with its 95% confidence interval (CI). We used fully adjusted forms of OR or HR controlled for some potential confounding factors such as maternal age, gestational diabetes, genetic syndrome, gestational age, newborn epilepsy, birth asphyxia, low birth weight, comorbid perinatal conditions, and comorbid early developmental disorders.

A random-effects model was used for the analysis of the results.[23] The significance level of 0.05 was used for performing statistical analyses by Stata software, version 13 (StataCorp, College Station, TX, USA).

Table 1 Characteristics of the studies in the meta-analysis.

1st aut, year	Country	Design	Sample	Diagnose method	Child age (year)	Outcome	Estimate	Adjustment	Quality
Gonzalez, 2020[25]	USA	Cross-sectional	250214	ICD-9,10	<18	ADHD	OR	Crude	Abstract available (conference)
Sigmon, 2019[17]	USA	Case-control	35040	ICD-9	7.01	ASD	OR	Adjusted	High
Tsao, 2017[15]	Taiwan	Cohort	17760	ICD-9	<18	ADHD/ASD	HR	Adjusted	High
DeMaso, 2017[14]	USA	Cohort	267	Not reported	10-19	ADHD	OR	Crude	High
Razzaghi, 2015[16]	USA	Cohort	158617	Not reported	<17	ADHD/ASD	OR	Crude	High
Davidson, 2015[13]	UK	Case-control	102	ICD-9	10.2-17.8	ASD	OR	Crude	High
Yamada, 2013[18]	Canada	Case-control	116	DSM-IV	7-15	ADHD	OR	Crude	High
Hansen, 2012[26]	USA	Cross-sectional	116	DSM-IV	7-15	ADHD	OR	Crude	High
Wier, 2006[10]	USA	Cohort	2484	ICD-9	<17	ASD	OR	Adjusted	High
Hultman, 2002[24]	Sweden	Case-control	2448	ICD-9	<10	ASD	OR	Crude	High

ASD: Autism spectrum disorders; ADHD: Attention-deficit/hyperactivity disorder; OR: Odds ratio; HR: Hazard ratio

Results

Description of studies

In total, 812 citations were included until December 2020. Of these, 311 were excluded due to duplication. Then, 483 citations were excluded through reading titles and abstracts which were not compatible with our criteria. In total, 18 references were included for reading the full papers, of which, 8 full papers did not consider to be eligible. Finally, our meta-analysis collected data from a total of 10 articles. We identified four studies[10,14–16] with the cohort, four studies[13,17,18,24] with case-control, and two studies[25,26] with cross-sectional designs. The total number of the studied population was 467,164. All studies were published in English and nine of them were reported odds ratio (OR) and one was reported hazard ratio (HR)[15] (Table 1) (Fig. 1).

Effects of exposure

Figs. 2 and 3 assessed the association between CHD and the risk of ASD or ADHD, separately. Based on the random effect model, the estimated OR of the risk of ASD associated with CHD was 1.35 (95% CI: 1.17, 1.52; 6 studies; I^2=0.0%) (Fig. 2) and the risk of ADHD associated with CHD was 3.04 (95% CI: 1.58, 4.49; 15 studies; I^2=88.1%) (Fig. 3). Therefore, there was a significant association between CHD and the risk of ASD or ADHD. Gonzalez et al. reported that the risk of ADHD and ASD among children with simple CHD and complex CHD, separately.[25]. Therefore, we separately reported them in Fig. 3.

Publication bias

Publication bias was performed for conducting Begg's and Egger's tests. The p values for Begg's and Egger's regression among children with ASD were 0.142 and 0.071, and among children with ADHD were 0.453 and 0.395, respectively. Evidence of publication bias was not detected among studies showing the association between CHD and the risk of ASD or ADHD.

Quality of the studies

According to the NOS scale, all studies had high quality. In a study, only abstract was available (This study was published in the book of abstract proceeding)[25] (Table 1).

Discussion

To our knowledge, this is the first meta-analysis conducted based on observational studies about the association between CHD and the risk of ASD or ADHD. Our findings suggested that CHD is a risk factor for ASD and ADHD occurrence. There was heterogeneity among studies that reported an association between CHD and the risk of ADHD, but the results between CHD and the risk of ASD were homogenous.

A study reported that almost half of all severe CHD survivors had mild to severe degrees of developmental delay.[27]

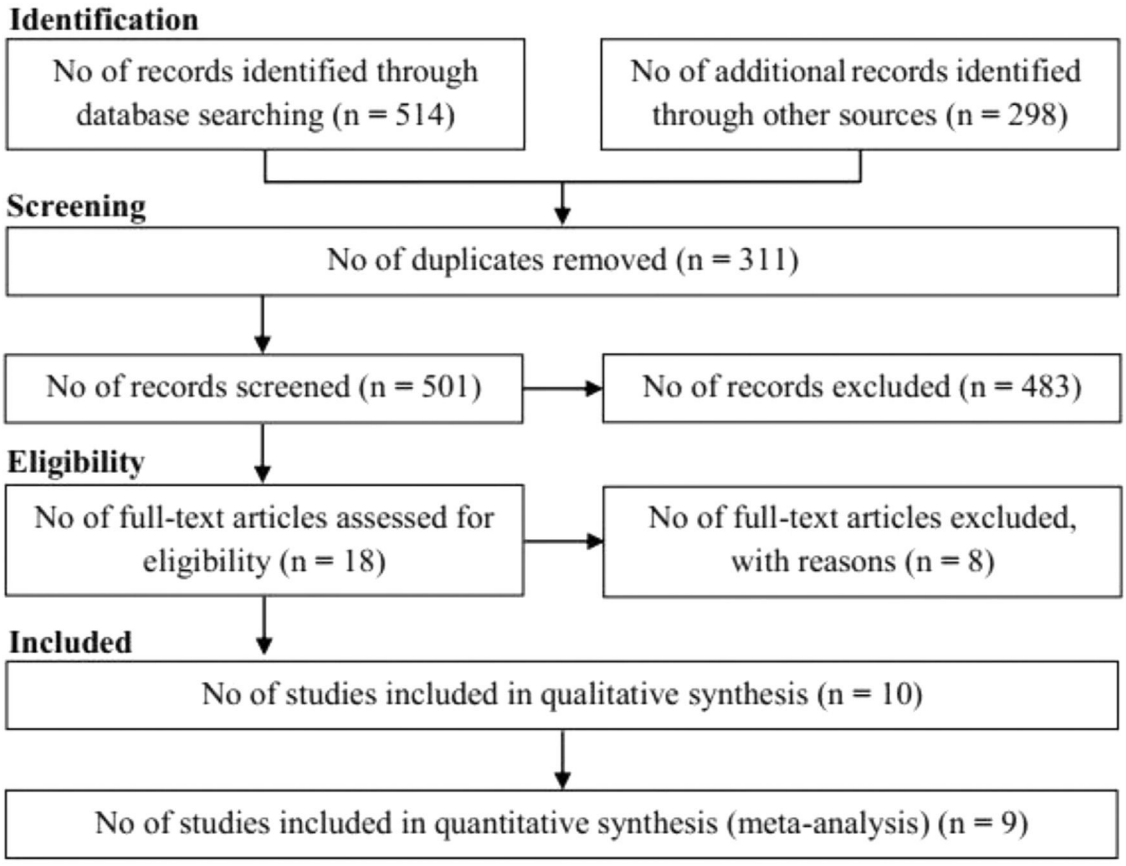

Fig. 1 Flow of information through the different phases of the systematic review.

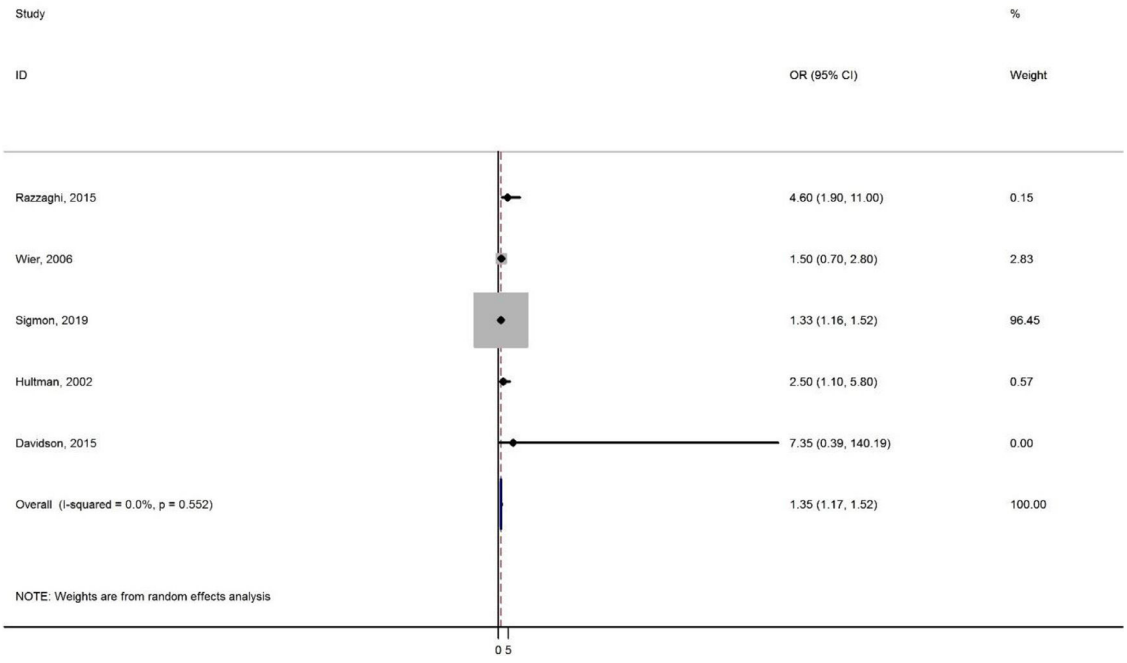

Fig. 2 Forest plot of the association between congenital heart disease (CHD) and the risk of autism spectrum disorders (ASD).

The association between CHD and ASD or ADHD is unclear. It may be due to the common genetic mechanisms. Some studies have been conducted regarding ASD and 22q11.2 deletion syndrome, often known as DiGeorge or velocardiofacial syndrome in which 75–85% of patients have CHD, most often conotruncal defects involving the great arteries.[28]

The most determining stressor is the level and duration of hypoxemia which was experienced by the patients with CHD.

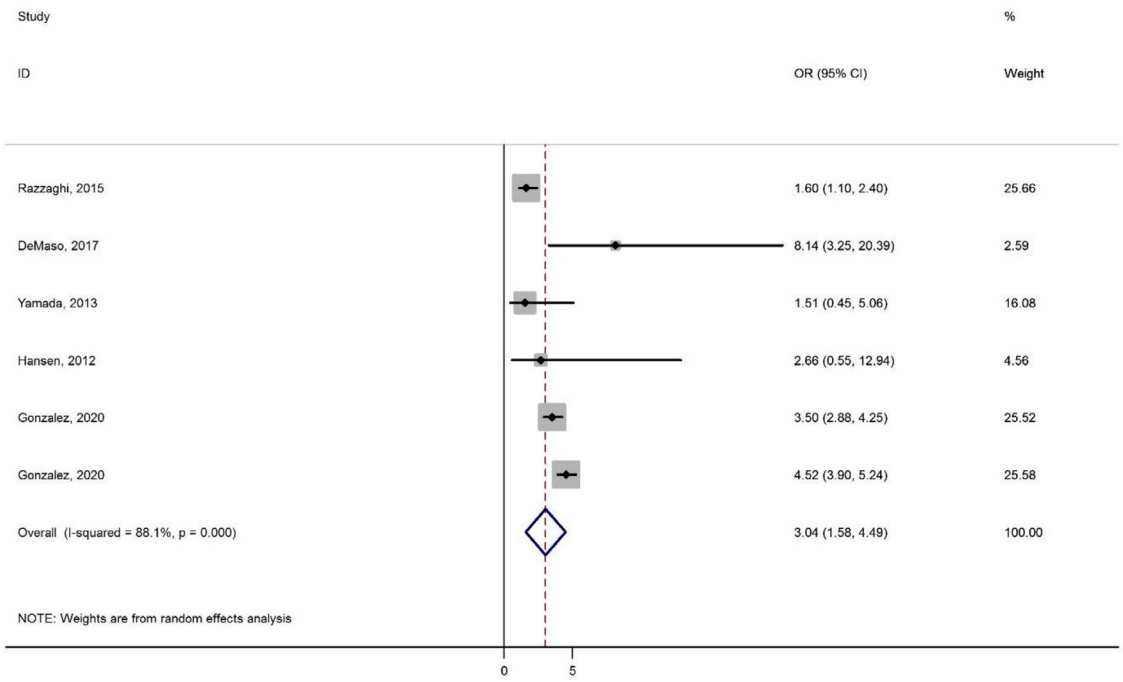

Fig. 3 Forest plot of the association between congenital heart disease (CHD) and the risk of attention-deficit/hyperactivity disorder (ADHD).

Hypoxemia has been shown to damage the prefrontal cortex and striate body of the brain. These high oxygen-sensitive areas are assumed to be related to the executive attention control network.[29] In addition, some studies have shown that children with CHD are usually seen with abnormal hemodynamic changes, which may lead to impaired cerebral blood flow, subsequent abnormal nerve growth, and impaired immune regulation, which are considered in the development of ADHD and ASD.[30,31] Therefore, identifying the risk of ADHD and ASD is important at two times, one at the neonatal period and the other at early childhood. In addition, intervention and rehabilitation may better the outcomes of ADHD and ASD among children with CHD. It would be emphasized that initial developmental screening for ASD starting at 18 months of age should be routine, so earlier interventions lead to better results. The results of the present meta-analysis convince the pediatricians and cardiologists for screening of the children with CHD for ADHD and ASD evaluation.

We used the adjusted form to check known risk factors of ASD and ADHD. This was one of our limitations. However, some studies reported only the unadjusted form of OR. This might introduce information bias in our results. Also, all studies did not mention the types of CHD, therefore, we could not perform a subgroup analysis based on the types of CHD and this was another limitation of this study. In addition, there was heterogeneity among studies that reported an association between CHD and the risk of ADHD among children. Also, the result of one study[25] was reported in the book of abstract proceedings and we couldn't find the full paper. Despite the above limitations, the present meta-analysis could efficiently estimate the association between CHD and the risk of ASD or ADHD.

We hope this information will enable pediatricians to better care for children and advise families on the expected developmental period for children with CHD. Future research guidelines on this subject include further clarification of possible mechanisms that could provide opportunities for intervention and clinical trials.

Conclusion

Our results suggested that CHD is a risk factor for ASD and ADHD. Therefore, Screening for ASD and ADHD should be considered among young children with CHD.

Ethical considerations

The study protocol was accepted by the ethical committee of Hamadan University of Medical Sciences with code IR.UMSHA.REC.1399.788.

Conflict of interest

Conflict of interest statement.

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