



## PREVALENCE OF CONGENITAL HEART DEFECTS IN IRANIAN CHILDREN WITH DOWN'S SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Conflicts of Interest: Nil

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### ABSTRACT

**Aim:** The aim of this systematic review and the meta-analysis was to evaluate the Prevalence of congenital heart defects in Iranian children with Down's syndrome.

**Methods:** The proposed protocol and the methods used in this systematic study were developed based on the Cochrane Handbook for Systematic Reviews of Interventions and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Observational studies conducted on the general population are attached and studies on specific populations (acute conditions, home care centers) were excluded.

**Results:** According to the results of the randomized method (95% CI), the overall congenital heart defects (ASD) prevalence rate among 221 persons was 16.7% (95% CI 11.8% - 21.5%),  $I^2 = 40.4\%$  and, the overall congenital heart defects (VSD) prevalence rate among 276 persons was 22.6% (95% CI 17.8% - 27.4%),  $I^2 = 72.6\%$ .

**Conclusion:** This is very important to know that congenital heart anomaly is the most important cause of death in this patient, especially during their first two years of life. In other side, it should be considered that major studies have been done for examining timely treatment of congenital heart anomaly, in both medical and surgery forms. Many of them agree that timely treatment of this anomaly, particularly surgery, improve quality of life, extend lifespan, and reduce mortality and disability in these patients. Thus, it seems that timely diagnosis of heart anomaly and knowing the kind of congenital defects in patients with down syndrome are very important in choosing appropriate health care.

**Key words:** Down's syndrome, Congenital Heart Defects, Cardiac anomalies, Echocardiography

### INTRODUCTION

Down syndrome is one of the most common chromosome abnormalities in humans, it occurs in one per 700 births (1).

Some causes have been suggested, but it seems that the most important risk factor is the mother's high childbearing age (2). Unlike other chromosome abnormalities parents' relation is not considered as a risk factor (3).

Down syndrome is caused by 21<sup>st</sup> trisomy and it accompanies various anomalies including heart anomaly (4).

Due to endocardial cushion defect evolution heart defect occurs in patients with Down syndrome, so it leads to a range of involving defects of atrial interventricular septum and heart valve (5). Intensity of this lesions are various from the atrioventricular valves and the membranous ventricular septal defects to ostium primum defect with valves abnormalities (6).

### Methods

#### Enrollment and Inclusion Criteria

The proposed protocol and the methods used in this systematic study were developed based on the

Cochrane Handbook for Systematic Reviews of Interventions and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Observational studies conducted on the general population are attached and studies on specific populations (acute conditions, home care centers) were excluded. The results were formulated as reported in the study. The minimum sample size was 25 patients per study. The target population was the entire Iranian children with Down's syndrome.

International databases (PubMed, Google Scholar, WOS, and Scopus) and national databases (SID, MAGIRAN) and national publications were reviewed to find similar studies without language and regional constraints from September 1 to 30, 2019. The MEDLINE research strategy was used to search for other databases. Specific research strategies were developed by the Health Sciences Library specializing in systematic reviews based on the Peer Review of Electronic Search Strategies (PRESS). Also, PROSPERO was used for ongoing and recently completed systematic reviews. Boolean operator (AND, OR, and NOT), Medical Subject Headings (MeSH), cut "\*", and related textual words were used to search for titles and abstracts with the

following keywords: Down's syndrome, Congenital Heart Defects, Cardiac anomalies, Echocardiography, and IRAN.

### Research Selection and Data Extraction

According to the research protocol, two researchers separately reviewed the research titles and abstracts based on the inclusion criteria. In the next step, after excluding repeated studies, the full manuscripts of the studies were reviewed according to the inclusion criteria and the required data and information were extracted. The consensus method was used to resolve differences and inconsistencies between the two researchers. The data extracted included general information (first author, year, and place), research characteristics (the research design, the sample size, location, study period, and bias risk), participants' characteristics and output (prevalence) calculations.

### Quality Assessment

To assess the quality of the methodology and the bias risk, each observational study was evaluated using the instrument developed by Hoy et al. This 10-item instrument assessed the quality of the study in two dimensions, including external validity (items 1 to 4 assessed the target population, the sampling frame, the sampling method, and the minimum indirect neglect) and internal validity (items 5 to 9 assessed the methods of data

collection, case definitions, instruments, and data collection modes, and item 10 evaluated the analysis-related bias). The bias risk was assessed separately by two researchers and any inconsistency was resolved by consensus.

### Data Synthesis

All studies that met the inclusion criteria were synthesized after a systematic evaluation. The data were combined with the accumulation graph. The random-effects model was evaluated based on the overall quality of life. The heterogeneity of the initial studies was assessed by  $I^2$  tests. The subgroup analysis was performed to determine heterogeneity based on gender and age. The meta-analysis was performed using STATA14 software (STATA CORP, COLLEGE STATION, TX, USA).

## Results

### General Findings

#### Research Selection

In the initial review, 112 articles were selected from different databases. Of the 107 non-useful studies identified in the review of titles and abstracts, 49 articles were deleted because they had inappropriate titles. Of the 58 studies, 4 met the inclusion criteria. Of the 54 excluded studies, 3 were revision studies, 1 letter to editor and 47 articles did not meet the minimum requirements to be included in the review (Fig. 1).

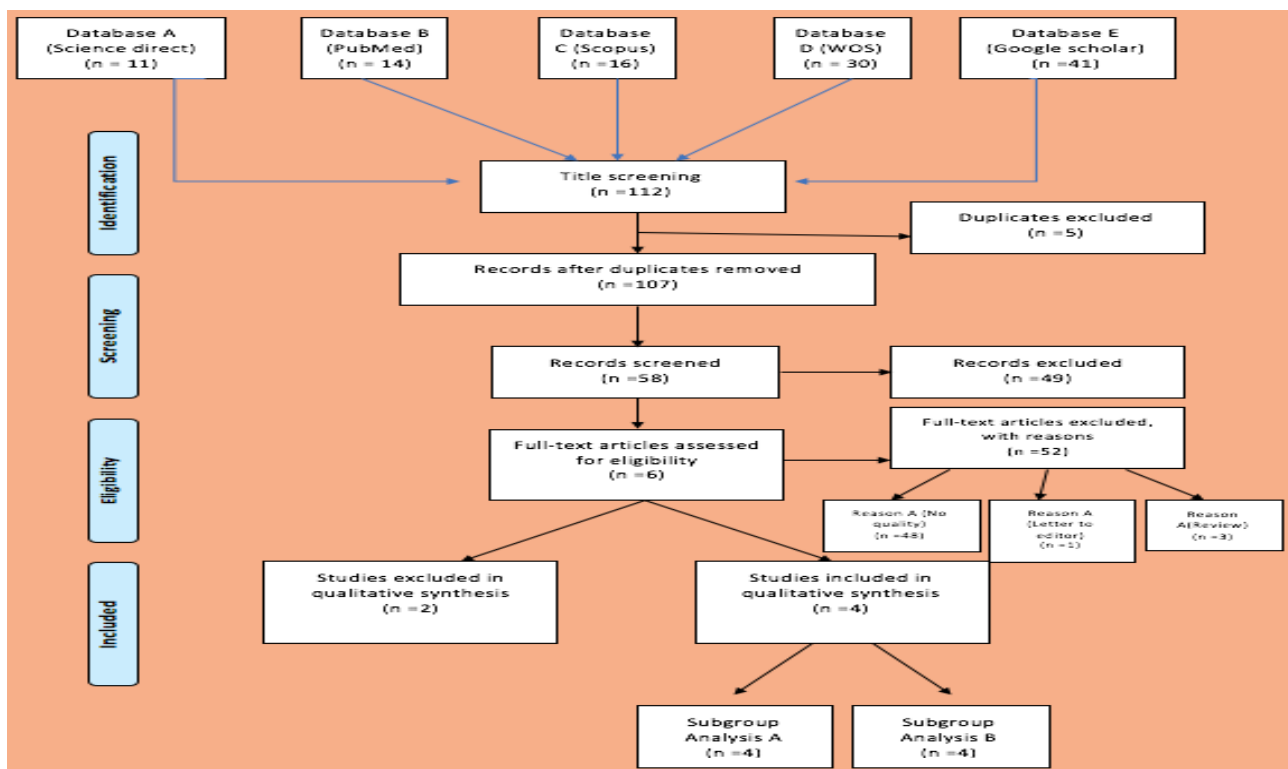


Fig 1: PRISMA flow diagram

### Research Characteristics

The study was conducted on 276 participants. Their ages ranged from 1 to 14 years. All 4 included studies had cross-sectional data. 4 studies were selected from 3 provinces (2 studies from Tehran. Two studies were selected from other provinces including mashhad and Kermanshah, each with one study. The most frequently used sampling method was multistage random sampling (N = 3). All studies had a low bias risk. (Table 1).

### Main Results

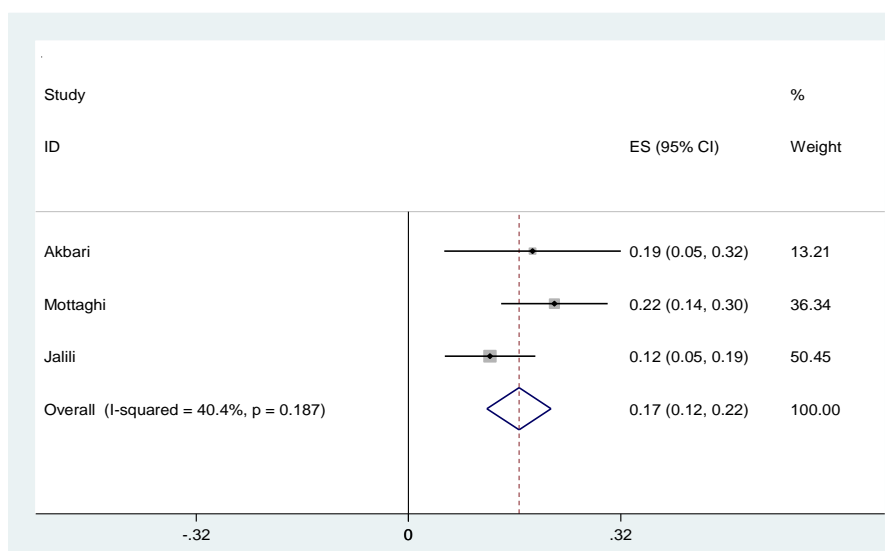
According to the results of the randomized method (95% CI), the overall congenital heart defects (ASD ) prevalence rate among 221 persons was 16.7% (95% CI 11.8% - 21.5%),  $I^2 = 40.4\%$  (Fig. 2) and the overall congenital heart defects (VSD ) prevalence rate among 276 persons was 22.6% (95% CI 17.8% - 27.4%),  $I^2 = 72.6$  (Fig 3).

**Table 1: Characteristics of final included studies about Prevalence of congenital heart defects in Iranian children with Down's syndrome**

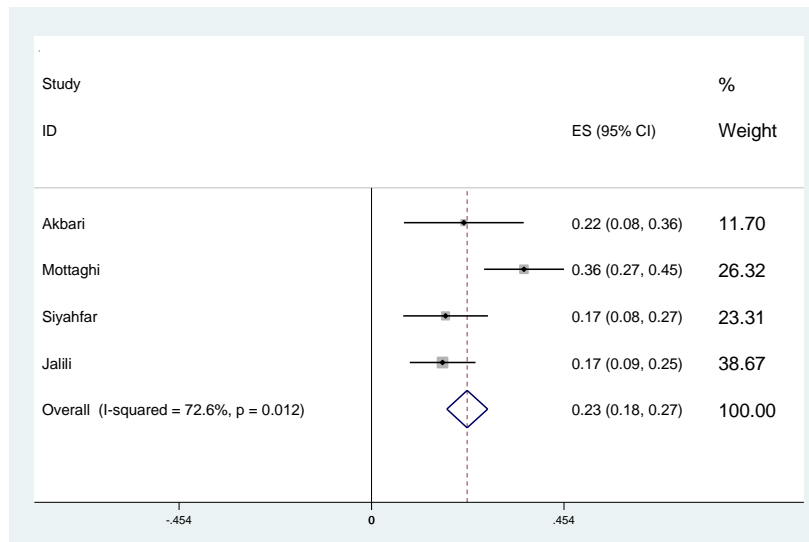
	First author	Publication year	Participants	SEX		prevalence		City or province
				Male	Female	ASD	VSD	
1	Akbari	2007	32	59%	41%	18.7%	21.8%	Tehran
2	Mottaghi	2015	100	48%	52%	22%	36%	Mashhad
3	Siyahfar	2003	55	42%	58%	-----	17.5%	Tehran
4	Jalili	2013	89	38%	62%	12.3%	16.8%	Kermanshah

**Table 2: Prevalence of congenital heart defects in Iranian children with Down's syndrome**

Author	Publication year	ASD				VSD				Province
		ES	LOW	UP	weight	ES	Low	up	weight	
Akbari	2007	0.187	0.054	0.320	13.21	0.218	0.077	0.359	11.70	Tehran
Mottaghi	2015	0.220	0.140	0.300	36.34	0.360	0.266	0.454	26.32	Mashhad
Siyahfar	2003	-	----	----	----	0.175	0.075	0.275	23.31	Tehran
Jalili	2013	0.123	0.055	0.191	50.45	0.168	0.090	0.246	38.67	Kermanshah
Pooled ES	-----	0.167	0.118	0.215	100	0.226	0.178	0.274	100	-----



**Fig 2:** Prevalence of congenital heart defects in Iranian children with Down's syndrome (ASD) and its 95% interval for the studied cases according to the year and the city where the study was conducted based on the model of the random effects model. The midpoint of each section of the line estimates the % value and the length of the lines showing the 95% confidence interval in each study.



**Fig 3:** Prevalence of congenital heart defects in Iranian children with Down's syndrome (VSD) and its 95% interval for the studied cases according to the year and the city where the study was conducted based on the model of the random effects model. The midpoint of each section of the line estimates the % value and the length of the lines showing the 95% confidence interval in each study.

### Discussion:

According to the results of the randomized method (95% CI), the overall congenital heart defects (ASD) prevalence rate among 221 persons was 16.7% (95% CI 11.8% - 21.5%),  $I^2 = 40.4\%$  and the overall congenital heart defects (VSD) prevalence rate among 276 persons was 22.6% (95% CI 17.8% - 27.4%),  $I^2 = 72.6$ . Limitation of atrial septal defects to trisomy 21 is approved by observing % 70 of atrial septal defects in patients with Down syndrome and different assumptions has raised based on the relationship between increased expression of chromosome 21 genes and valves disorders (7).

With Chromosomal analysis on patients with Down syndrome, a great mass of studies have shown existence of three main changes in chromosome analyzing (8). These changes include: None disjunction-21 in % 90 to %95; translocation-21 in %2 to %5; and mosaicism-21 in %1-2 cases, respectively (9). However, we must note that heart anomalies and respiratory infections are the most important cause of death in patients with Down syndrome (10). Therefore, timely diagnosis of this defect seems necessary and it will be more important if we know that many studies showed the early treatment greatly reduces mortality rate and disabilities in this patients (11). Echocardiography is a noninvasive methods approved by many doctors to make a timely diagnosis of these defects (12). Various studies also have shown that this method along other

noninvasive methods like chest electrocardiography and radiography are normally comprehensive for evaluating and determining treatment ways in the future (13).

Because of high risk of the congenital heart anomaly in patients with down syndrome, they are examined in treatment centers and heart parts numerously (14). This is very important to know that congenital heart anomaly is the most important cause of death in this patients, especially during their first two years of life (15). In other side, it should be considered that major studies have been done for examining timely treatment of congenital heart anomaly, in both medical and surgery forms (16). Many of them agree that timely treatment of this anomaly, particularly surgery, improve quality of life, extend lifespan, and reduce mortality and disability in these patients (13). Thus, it seems that timely diagnosis of heart anomaly and knowing the kind of congenital defects in patients with down syndrome are very important in choosing appropriate health care (17).

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