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Review Article

Unveiling the Burden of Prevalence of Congenital Heart Defects in Down Syndrome Patients in Indonesia: A Systematic Review and Meta-analysis

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Abstract

Down syndrome or trisomy 21 is frequently accompanied by Congenital Heart Disease (CHD), which is a major cause of mortality and morbidity within the first two years of life in children with Down Syndrome (DS). This systematic review and meta-analysis aimed to analyze the literature to assess the pooled prevalence of overall CHDs among children with DS in Indonesia. The search was conducted across major databases, including PubMed, Google Scholar, ScienceDirect, Cochrane, and Garuda (an Indonesian database), using Boolean operators and a range of keywords. Citation management was performed using the Rayyan Intelligent Systematic Reviews website (https://www.rayyan.ai/). Quantitative data synthesis was conducted using Comprehensive Meta-Analysis version 4.0 (Biostat, Englewood, NJ, USA). Initially, 1,915 citations were retrieved from the primary search; after screening titles and assessing full texts, a total of 11 articles were included in this study. A total of 1,078 subjects from 11 different studies were analyzed. The overall pooled prevalence of CHDs among children with DS was 44.6% (95% CI: 34.9% to 54.8%). We also found a high degree of heterogeneity between the studies (I^2 = 88.8%), and inspection of the forest plot revealed that the distribution of the plotted data was asymmetrical. Approximately one in two children with DS in Indonesia has at least one type of CHD. These findings highlight the need for early routine cardiac screening to reduce morbidity and mortality. We recommend further research to provide more data to assess the prevalence of CHD

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Introduction

Down Syndrome (DS), also known as trisomy 21, is a genetic condition characterized by an extra copy of chromosome 21. Affected individuals usually have developmental variations and characteristic morphological traits, and one of the most common associated conditions is Congenital Heart Disease (CHD). Indonesia is believed to have around 300,000 individuals with DS, representing around 3.75% of the global population, which is roughly one case per 1,000 live births. This underscores the importance to identify the pattern and prevalence of congenital heart disease in the DS population.[1-2]

CHD is one of the major causes of morbidity and mortality among individuals with DS, particularly during the first two years of life. Therefore, understanding the prevalence of CHD among individuals with DS is crucial. Between 40% and 63.5% of individuals with DS are affected by CHD. Several common types of CHD in DS populations include Atrioventricular Septal Defects (AVSDs), Ventricular Septal Defects (VSDs), and Patent Ductus Arteriosus (PDA).[3]

Thus, the prevalence of CHD needs to be well known in this population for proper early diagnosis and intervention, especially in rural areas. Early diagnosis can significantly improve outcomes and quality of life through appropriate medical and surgical management.[4] Understanding the prevalence will help raise awareness, guide stakeholders, and inform healthcare policy, resource allocation, and the development of rules and protocols uniquely adapted to the needs of individuals with CHD and DS in Indonesia. Recognition of the high prevalence of congenital heart defects among individuals with DS serves as a cornerstone for further improvements in both clinical care and research in Indonesia.

Methods

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 recommendations.[5] This review is registered under CRD42024596794 PROSPERO, the international prospective register of systematic reviews (URL: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024596794).

Literature Search

This study was conducted from October 1, 2024, to October 25, 2024. The databases used in this review were PubMed, ScienceDirect, Google Scholar, Cochrane, and Garuda (an Indonesian journal database). Our search strategy involved the use of keywords, MeSH terms, and the Boolean operators AND and OR. The search keywords used were as follows: Down syndrome; trisomy 21; Down's Syndrome; congenital heart defect; congenital heart disease; CHD; Indonesia; prevalence; incidence; epidemiology. No language or year of publication restrictions were applied. The inclusion criteria were as follows: (1) patients with a confirmed diagnosis of DS, (2) studies conducted in Indonesia, and (3) pediatric populations. The exclusion criteria were (1) studies not reporting CHD prevalence, (2) studies outside of Indonesia. A detailed search strategy is provided in Supplementary Table 1 to ensure reproducibility of the systematic review.

Study Selection

The search and selection process was performed by the first two authors. Both authors evaluated the titles, abstracts, and full texts of the search results to determine if they met the inclusion criteria in this systematic review. Conflicts between the two authors were settled by discussion or agreement with a third author. When additional research information was needed, the two authors contacted the study's corresponding author of the study via the listed email address. Subsequently, all data required for this study were extracted from the included articles and recorded in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA).

Data Management

The initial search results from all databases were organized, and all duplicates were removed using the Rayyan platform for Intelligent Systematic Reviews (https://www.rayyan.ai/).[6] After screening the titles, abstracts, and full texts, all relevant data were documented and extracted into a Microsoft Excel spreadsheet.

Quality Assessment

The quality of the studies was assessed by two authors; any disagreements among the reviewers were resolved through discussion with the third author. Study quality was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists according to study design: prevalence/cross-sectional, cohort, or case-control. Each study was scored based on the proportion of applicable criteria met. Studies with >75% of criteria met were classified as high quality, those meeting 50–75% as medium quality, and those meeting <50% as low quality.[7]

Statistical Analysis

The meta-analysis in this study was conducted using Comprehensive Meta-Analysis (CMA) software, version 4.0 (Biostat, Englewood, NJ, USA).[8] Given the expected high heterogeneity among studies, a random-effects model was used. To explore the sources of heterogeneity, we conducted subgroup analysis stratifying studies by JBI score, publication year, study setting, and study location. Heterogeneity was assessed using Higgins' I^2 statistic; higher values indicate greater heterogeneity. Publication bias was assessed using Egger's regression test, Begg's test, and visual inspection of funnel plots. The symmetry of the plot indicates whether there is publication bias. A trim-and-fill method was applied to estimate the potential impact of missing studies.

Results

Search Results

The initial search across all the databases yielded a total of 1,915 studies, 46 duplicates were identified and removed; 1,869 studies remained eligible for title and abstract screening. During abstract screening, 1,839 studies were excluded for having unrelated objectives. Following full-text review of 25 studies, 11 articles were ultimately included in this study. The search and selection process is illustrated in Figure 1.

Characteristics of the Included Studies

A total of 11 studies met the inclusion criteria and were included in this study[9-19], originating from six different cities: Semarang (n=3), Yogyakarta (n=3), Bandung (n=2), Denpasar (n=1), Surabaya (n=1), and Surakarta (n=1). All studies were published between 2015 and 2024, with sample sizes ranging

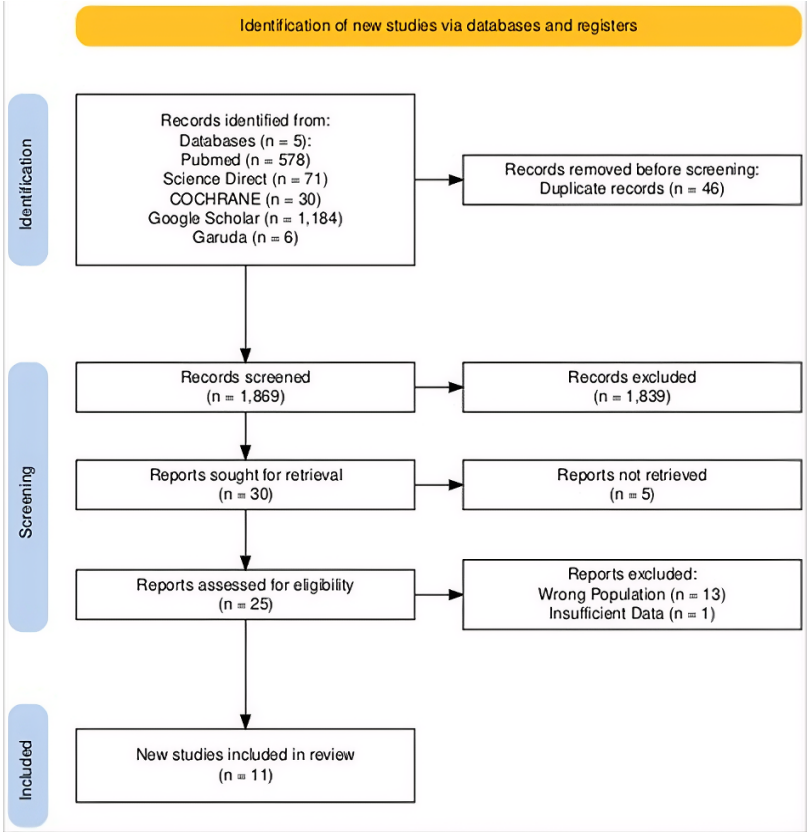

Figure 1. PRISMA flow chart for the summary of the search and screening processes.

from 30 to 355 individuals with DS. All studies employed observational designs, including cross-sectional, cohort, and case-control studies. Table 1 presents the main characteristics of the included studies, including study location, sample size, study design, and primary findings.

Overall Prevalence of CHDs

A random-effects meta-analysis was performed (Figure 2) to estimate the pooled prevalence of CHDs among individuals with DS in Indonesia, revealing a prevalence of 44.6% (95% CI: 34.9%–54.8%). The prevalence rates across studies ranged

Table 1. Basic characteristics of selected studies.

Study	City	Study Design	Sample Size	Age, range	Males	Prevalence (%)
Arifiyah *et al.*, 2017[9]	Semarang	Cross Sectional	41	6 months-6 years	58.5%	53.7
Azzahra *et al.*, 2022[16]	Semarang	Retrospective	66	4 months-6 years	NR	66.7
Gartika *et al.*, 2018[12]	Bandung	Cross Sectional	70	NR	NR	27.1
Hariyanti *et al.*, 2022[19]	Surakarta	Cross Sectional	36	2 months–5 years	58,33%	50.0
Hisbiyah *et al*, 2022[18]	Surabaya	Cross Sectional	80	1 month-18 years	61,25%	25.0
Patria *et al*, 2024[11]	Yogyakarta	Cross Sectional	355	NR	55.2%	64.8
Rajamany *et al*, 2018[17]	Bandung	Retrospective	95	0-14 years	NR	29.5
Santoso *et al.*, 2015[10]	Semarang	Cross Sectional	30	0-6 years	66,67%	33.3
Simamora *et al.*, 2022[14]	Yogyakarta	Cohort	236	0-3 years	50%	53.8
Windiani *et al.*, 2021[13]	Denpasar	Cross-sectional	32	1-12 years	28,1%	50.0
Zevanya *et al*, 2024[15]	Yogyakarta	Case Control	37	NR	51.4%	37.8

DS: Down Syndrome; JBI: Joanna Briggs Institute, NR: not reported

from 25.0% to 66.7%. Significant heterogeneity was observed (I^2 = 88.8%); Egger's test indicated a p-value of 0.045 as shown in Table 2, and the funnel plot (Figure 3) demonstrated an asymmetrical distribution of the data.

The Prevalence of CHD Subtypes

A random-effects meta-analysis was conducted, as shown in Table 3, to estimate the pooled prevalence of CHD subtypes in individuals with DS in Indonesia. The analysis revealed that the most common subtype was PDA, followed by Atrial Septal Defect (ASD) and AVSD.

The Subgroup and Sensitivity Analysis

To explore potential sources of heterogeneity, we performed subgroup analyses using different criteria. When stratified by the JBI score (quality of the study), eight studies rated as high quality had a pooled prevalence of 45.8% (95% CI: 34.3–57.7%), while medium-quality studies revealed a prevalence of 41.2% (95% CI: 25.9–58.3%), with no significant difference between subgroups (p = 0.66). Stratification by publication year revealed that studies published before 2022 reported a lower prevalence (37.5% [95% CI: 27.5–48.8%]) than

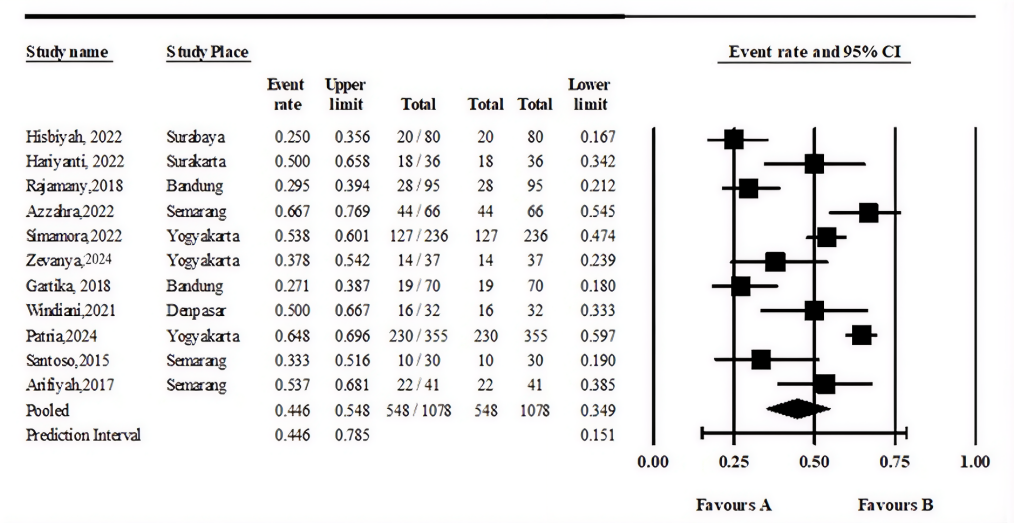

Figure 2. A forest plot illustrating the combined prevalence of Congenital Heart Disease (CHD) in individuals with Down syndrome (DS).

Table 2. Test for heterogeneity and publication bias.

Test for heterogeneity	
Q	89.964
DF	10
Significance level	P < 0.0001
I2 (inconsistency)	88.884%
Publication bias	
Egger's test	
Significance level	P = 0.045
Begg's test	
Kendall's Tau	-0,18182
Significance level	P = 0.43627

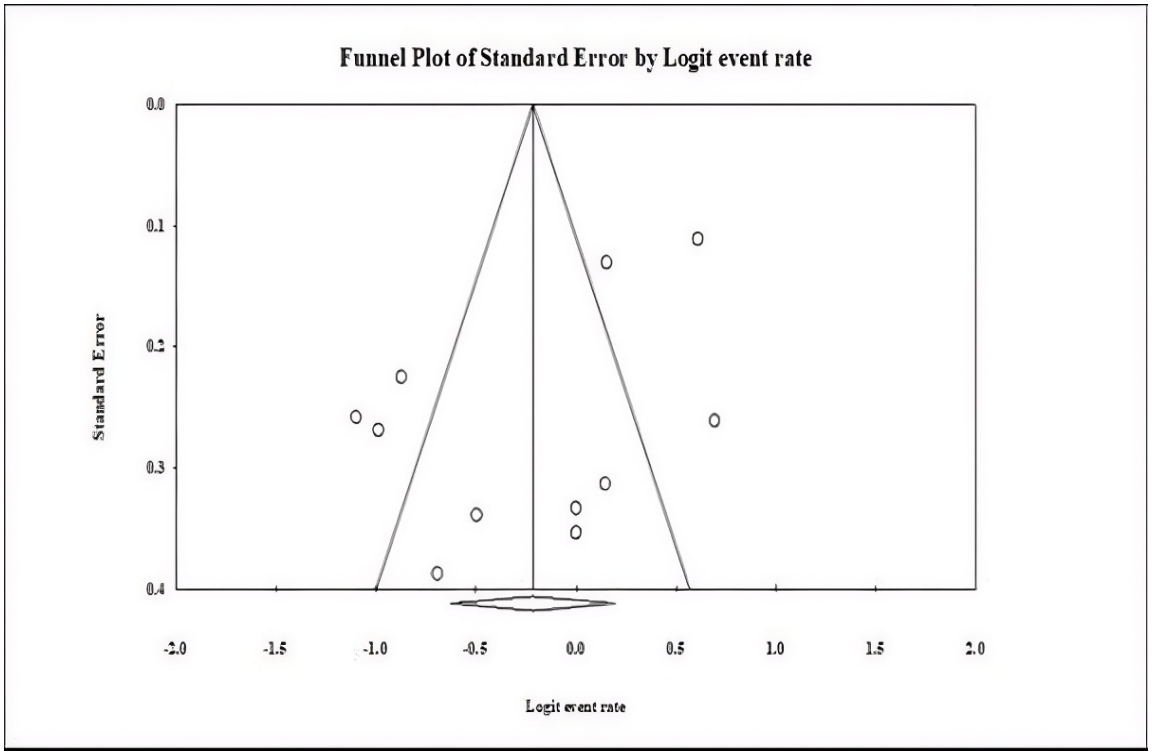

Figure 3. A funnel plot displaying the asymmetrical distribution of prevalence data points.

studies published after 2022 (50.1% [95% CI: 38.0–62.2%]), although the difference was not statistically significant (p = 0.13). Subgroup analysis by study setting showed that hospital-based studies had a higher pooled prevalence (47.5%; 95% CI: 37.0–58.2%) than community-based studies (31.3%; 95% CI: 22.1–42.3%; p = 0.036), suggesting a possible effect of diagnostic accessibility. Finally, subgroup analysis based on study location showed that Yogyakarta reported the highest prevalence with 54.4%, followed closely by Semarang with 52.3%. The complete results of the subgroup analyses are presented in Table 4

.

Quality and Risk of Bias

The quality of each study was assessed using the JBI critical appraisal checklist based on its type of study. Most studies showed low risk of bias, especially in the domains of sampling method, measurement of the outcome, and data analysis. We used a cutoff of 75% to define a good quality study, where 8 out of 11 studies met these criteria, where 3 studies were considered to be medium quality because the JBI score was between 50-75%, where the most common type of bias among these medium quality studies was confounding bias. Figure 4 illustrates the overall quality assessment results. Although the

Table 3. Test prevalence of CHD subtypes.

Subtype of CHD	Events Rate of CHD subtypes (95% CIs)
Patent ductus arteriosus	0.297 (0.205–0.409)
Atrial septal defect	0.278 (0.187–0.393)
Atrial-Ventricular septal defect	0.159 (0.116–0.215)
Ventricular septal defect	0.153 (0.115–0.201)
Tetralogy of fallot	0.038 (0.020–0.072)
Others	0.099 (0.043–0.215)

CHD : Congenital Heart Disease.

Table 4. Subgroup analysis of CHD prevalence in Indonesian down syndrome patients.

Subgroup	No. Studies	Pooled Prevalence (95% CI)	p (between)	I^2 (%)
JBI Score				
High	8	0.458 (0.343–0.577)	0.663	90.5
Medium	3	0.412 (0.259–0.583)		73.1
Year of Publication				
<2022	5	0.375 (0.275–0.488)	0.135	67.1
≥2022	6	0.501 (0.381–0.622)		89.3
Study Setting				
Community-Based	2	0.313 (0.221–0.423)	0.036	22.4
Hospital-Based	9	0.475 (0.370–0.582)		88.7
City				
Bandung	2	0.285 (0.221–0.359)	0.000	0
Semarang	3	0.523 (0.339–0.700)		77.5
Yogyakarta	3	0.544 (0.422–0.660)		85.7
Surakarta	1	0.500 (0.342–0.658)		0
Surabaya	1	0.250 (0.167–0.356)		0
Denpasar	1	0.500 (0.333–0.667)		0

JBI : Joanna Briggs Institute

funnel plot demonstrated asymmetry, suggesting possible publication bias, the trim-and-fill sensitivity analysis indicated that such bias did not materially affect the pooled estimate (Table 5).

Discussion

This systematic review and meta-analysis includes 1,078 individuals with DS from 11 studies conducted in Indonesia. Our pooled analysis revealed that the prevalence of CHD among DS patients in Indonesia was 44.6%, with reported rates across included studies ranging from 25.0% to 66.7%. This wide variation reflects substantial heterogeneity (I^2 = 88.88%). Such heterogeneity is likely attributable to differences in the geographic regions of the studies, variations in the methods and criteria used for CHD diagnosis, patient demographics, and study settings. Several reports have indicated that echocardiography, as an advanced tool for CHD diagnosis, and the availability of specialized centers for CHD may affect the reported prevalence of CHD among DS patients.[20-22]

The reported prevalence of CHD in DS patients in Indonesia is 44.6%, this number is relatively similar to previously mentioned international studies, but slightly lower compared to other studies from Saudi Arabia, which was 66.1%, Sweden, 54%, Turkey, 52.1%, and Brazil, with a prevalence rate of 50% 23–25, while slightly higher than reports from Sudan (43%) and Egypt (36%) 24,26. These variations could be due to disparities in health infrastructure, early diagnosis, and prevention. Previous studies have stated that in countries with higher incomes, where diagnostic tools are readily available, CHD in DS individuals is higher due to early detection and greater accuracy compared to lower income countries.[27-28]

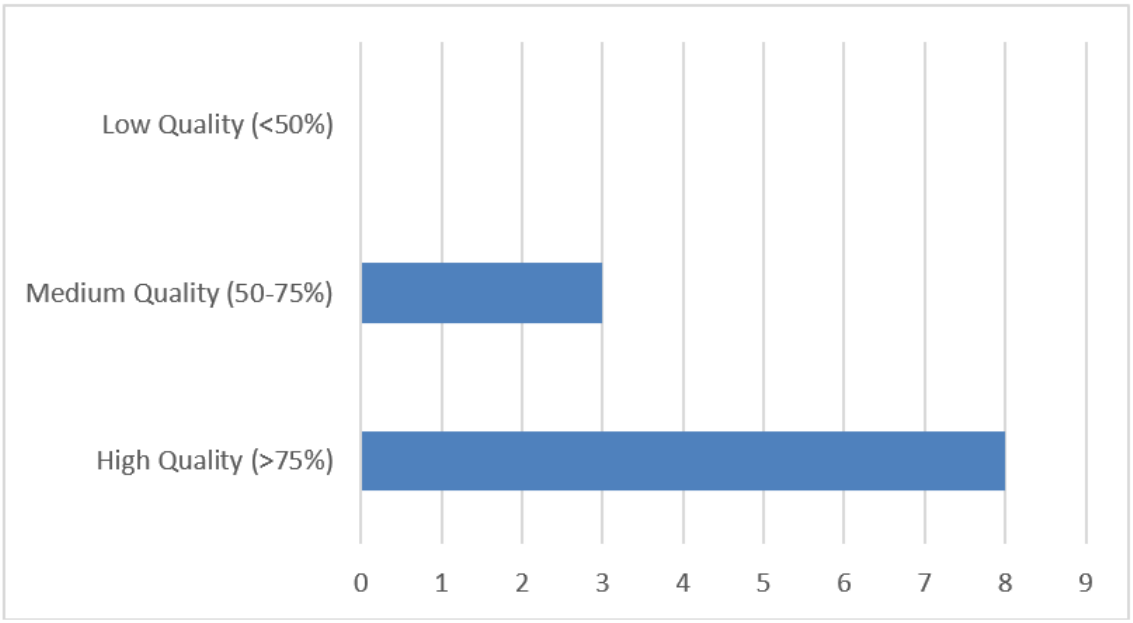

Figure 4. JBI quality assessment of included studies.

Table 5. JBI quality assessment of included studies.

Parameter	Original Meta-Analysis	Trim-and-Fill Adjusted
Number of studies	15	15
Number of imputed studies	-	0
Pooled prevalence (%)	44.6 95% CI (34.9 – 54.8)	44.6 95% CI (34.9 – 54.8)

To explore heterogeneity, we conducted a subgroup analysis, which revealed that hospital-based studies had a higher prevalence (47.5%) than community-based studies (31.3%; p = 0.036). These results indicate that diagnostic accessibility plays a key role in case detection. Similar results were observed in a subgroup analysis by location, with Yogyakarta and Semarang showing higher prevalence than other cities. These findings imply that geographic differences in healthcare access and referral pathways may influence CHD detection rates. In contrast, JBI Score (study quality) and publication year did not significantly explain heterogeneity. Unfortunately, we could not fully explore other potential sources of heterogeneity, such as diagnostic methods, genetic, ethnic, and age, due to limited data. These unmeasured factors may partially explain the variability in reported CHD prevalence across the 11 included studies.

The potential for publication bias was indicated by an asymmetrical funnel plot and a significant result of Egger's test (P = 0.045). This type of bias can occur when smaller studies with lower or non-significant prevalence estimates are unpublished, potentially raising the pooled prevalence. To examine this, we conducted a trim-and-fill analysis and found that no adjustments were necessary, no studies were added or removed. The pooled prevalence remained 44.6% (95% CI: 34.9–54.8%), suggesting minimal effect from bias. Nevertheless, underreporting of smaller, low-prevalence studies may still subtly elevate the estimate and contribute to the high heterogeneity observed across studies (I^2 = 88.8%).[29-31] Given these results, it is essential to approach the data with caution, particularly from smaller studies, and underscore the need for comprehensive reporting of all study outcomes. Developing centralized national databases and unified CHD assessment procedures could help minimize bias and improve the reliability of prevalence estimates in DS populations. Overall, despite evidence of possible publication bias, the stability of the pooled prevalence supports the validity of our main findings.

We also analyzed different types of CHD, previous studies have found that the type of CHD varies significantly between the different geographical regions. According to western studies, the most reported CHD in DS patients from Western countries is AVSD, followed by VSD and ASD[24,32].

However, a different pattern is observed in Asian countries such as Korea and Pakistan where the most common type of CHD is ASD and followed by VSD and PDA.[24,33] In our analysis in Indonesia, the most common types of CHDs are PDA and ASD, while AVSD was less common. These findings may thus reflect ethnic and genetic variation, together with differences in diagnostic tools and health practices across the regions.[21,34] The high number of PDA suggests that clinicians should prioritize early neonatal echocardiography, especially in regions with limited access to pediatric cardiology, to ensure timely detection and management of PDA, thereby reducing preventable complications.[35]

Our pooled estimate remained consistent across sensitivity and subgroup analyses, indicating strong reliability. Despite this, the high level of heterogeneity highlights the importance of implementing nationwide, uniform screening and reporting frameworks. As CHD remains the leading cause of morbidity and mortality in the DS population, strengthening early detection pathways and ensuring access to cardiology services, especially in rural areas, is important.

Limitations

The strengths of our study include a comprehensive search strategy; multiple databases were used with no language or date restrictions imposed. However, there are some limitations. First, most of the included studies were conducted in urban areas of Indonesia, which may not fully represent the national prevalence of CHD in DS patients. The absence of data from rural areas could give a biased view of the situation since healthcare access is poorer in those areas. Patients in urban tertiary centers are more likely to be diagnosed due to better access to echocardiography and specialized cardiology services.[36] Second, high heterogeneity was observed across all studies, although subgroup analysis and trim-and-fill test were performed, some heterogeneity may still persist. Finally, the small sample size in some included studies does not allow for drawing a conclusion representative of the broader population of DS patients in Indonesia. Therefore, large-scale epidemiological studies are needed to better characterize the true national burden of CHD among individuals with DS in Indonesia.

Conclusion

To our knowledge, this is the first meta-analysis reporting on the overall prevalence of CHD among DS patients in Indonesia. The pooled prevalence was 44.6%. This high prevalence underscores the urgent need for action by the government, healthcare workers, and community members. Therefore, integrated strategies and policies should be developed to promote early detection, prevention, and management of CHDs in the Indonesian DS population. However, the reliability of our findings is limited by significant inter-study heterogeneity and the risk of publication bias. We recommend further studies to provide higher-quality evidence regarding the prevalence of CHD.

List of Abbreviations

ASD	Atrial Septal Defect
AVSD	Atrioventricular Septal Defect
CHD	Congenital Heart Disease / Defect
CMA	Comprehensive Meta-Analysis
CI	Confidence Interval
DS	Down Syndrome
JBI	Joanna Briggs Institute
PDA	Patent Ductus Arteriosus
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
VSD	Ventricular Septal Defect

Ethical Clearance

Not applicable.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

The authors confirm their contributions to the paper as follows: study concept and formulated the methodology: PPPAS, SAF and LY; literature search, study selection, data collection, bias risk assessment and data analysis: PPPAS and SAF; prepared, reviewed and finalized the manuscript: PPPAS, SAF and LY; project supervision: LY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of Interest

None.

Availability of Data and Materials

Not applicable.

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Generative AI and AI-Assisted Technologies in the Writing Process

Authors acknowledge that artificial intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analyses, or conclusions presented in this manuscript.

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