

Prevalence of pulmonary hypertension among children with Down syndrome: A systematic review and meta-analysis

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Abstract

BACKGROUND

Pulmonary hypertension (PH) has serious short- and long-term consequences. PH is gaining increasing importance in high risk groups such as Down syndrome (DS) as it influences their overall survival and prognosis. Hence, there is a dire need to collate the prevalence rates of PH in order to undertake definitive measures for early diagnosis and management.

AIM

To determine the prevalence of PH in children with DS.

METHODS

The authors individually conducted a search of electronic databases manually (Cochrane library, PubMed, EMBASE, Scopus, Web of Science). Data extraction and quality control were independently performed by two reviewers and a third reviewer resolved any conflicts of opinion. The words used in the literature search were “pulmonary hypertension” and “pulmonary arterial hypertension”; “Down syndrome” and “trisomy 21” and “prevalence”. The data were analyzed by Comprehensive Meta-Analysis Software Version 2. Risk of bias assessment and STROBE checklist were used for quality assessment.

RESULTS

Of 1578 articles identified, 17 were selected for final analysis. The pooled prevalence of PH in these studies was 25.5%. Subgroup analysis was carried out for age, gender, region, year of publication, risk of bias and etiology of PH.

CONCLUSION

This review highlights the increasing prevalence of PH in children with DS. It is crucial for pediatricians to be aware of this morbid disease and channel their

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efforts towards earlier diagnosis and successful management. Community-based studies with a larger sample size of children with DS should be carried out to better characterize the epidemiology and underlying etiology of PH in DS.

Key Words: Down syndrome; Pulmonary hypertension; Prevalence; Trisomy 21; Persistent pulmonary hypertension; Congenital heart disease

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Core Tip: The objective of this review is to provide quantitative data on the prevalence of pulmonary hypertension (PH) in pediatric patients with Down syndrome (DS). In addition, we also wish to address the lack of consensus on screening guidelines for PH in DS, as it is frequently missed unless associated with an underlying congenital heart disease. We conclude that children with DS require early echocardiography irrespective of an underlying congenital heart disease. We, therefore, by means of this systematic review would like to increase the vigilance for PH in DS, with the ultimate goal of reducing the morbidity due to PH in these children.

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INTRODUCTION

Down syndrome (DS) was first clinically observed and described by Dr. Down[1] in his report on the "Observations on an ethnic classification of idiots" in 1866. The incidence of DS is approximately 1 in every 733 live births, which makes it the most common human malformation[2,3]. Children with DS are at an increased risk of developing pulmonary hypertension (PH). DS is the most common genetic syndrome associated with PH (with or without congenital heart disease), the others being DiGeorge syndrome, Scimitar syndrome, Noonan syndrome, Dursun syndrome and Cantu syndrome[4]. Regardless of the underlying etiology, PH has debilitating consequences on the health of the child and also reduces life expectancy. Approximately 75% of all deaths in DS may be attributed to pneumonia and infectious lung disease, congenital heart disease (CHD) and circulatory disease (vascular diseases such PH)[5]. There have been no studies estimating the precise disease burden of PH in children with DS even though PH is independently associated with death among children with DS[6]. This reflects the need to provide a multidisciplinary approach for children with DS and PH for better management. Recent recommendations from the pediatric task force of the 6th World Symposium on Pulmonary Hypertension (WSPH) have defined PH in the pediatric age group as a resting mean pulmonary artery pressure (mPAP) > 20 mmHg (decreased from 25 mmHg) in children greater than 3 months of age at sea level and includes children with pulmonary vascular resistance (PVR) ≥ 3 WU[4,7]. PH is classified into 5 groups on the basis of each category sharing similar hemodynamics, pathological findings as well as similar management strategies: pulmonary arterial hypertension (PAH; group 1), PH due to left heart disease (group 2), PH due to lung disease and/or hypoxia (group 3), chronic thromboembolic PH (group 4) and PH with unclear/multifactorial mechanisms (group 5)[8].

The risk factors associated with the development of PH in DS are multifactorial. Chromosomal abnormalities such as trisomy 21 have been attributed to an increased risk of developing PH with an odds ratio of 36 (95%CI: 4.15-312.24), implying a genetic contribution to PH development using univariate logistic regression[9]. The presence of congenital heart disease (CHD) is a major contributing factor to PH in the DS population. Other risk factors include defects in lung development (due to overexpression of anti-angiogenesis genes on chromosome 21)[10], pulmonary hypoplasia [11], endothelial dysfunction[12,13], pulmonary diseases[14-18], gastrointestinal diseases[19] and endocrine abnormalities[20]. At the molecular level, it has been proposed

that increased gene dosage of four interferon receptors encoded on chromosome 21 results in increased interferon activation which may contribute to various disease processes in DS[21]. In addition, high interferon gamma levels have also been observed in pulmonary hypertension and are believed to be responsible for pulmonary vascular remodeling[22]. This probable relationship, however, requires further study.

Herein, we describe the first systematic review and meta-analysis which consolidates our existing knowledge on the prevalence of PH in DS. Our objective was to establish the prevalence of PH in children with DS. This systematic review also aims to provide sufficient evidence which could guide policy-making aimed at the prevention and effective management of PH as well as underpin further research.

MATERIALS AND METHODS

Meta-analysis of observational studies in epidemiology (MOOSE) guidelines were followed for this systematic review[23]. The protocol for this systematic review and meta-analysis was registered at the International Prospective Register of Systematic Reviews (PROSPERO # CRD42020204914).

Search strategy

A two-stage search strategy was used for this study.

Bibliographic database search

Electronic databases (PubMed, Cochrane library, EMBASE, Scopus, Web of Science) were searched. The search was restricted by English language with published studies including human subjects only, but not restricted by date or publication types. Studies with insufficient data such as abstracts only, studies with adult participants, conference papers and duplicate publications were excluded. Studies whose data could not be accessed even after a request from the authors were also excluded. The process of data extraction and quality control was performed independently by two reviewers (DP and PZJ). In the event of a conflict, a third reviewer's (AT) opinion was sought. The last electronic search was carried out on 30th June, 2020. The search strategy included the following: ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("down syndrome"[MeSH Terms] OR ("down"[All Fields] AND "syndrome"[All Fields]) OR "down syndrome"[All Fields] OR ("downs"[All Fields] AND "syndrome"[All Fields]) OR "downs syndrome"[All Fields]) AND prevalence.

Searching other sources

An individual manual search was also performed which included examining the references of all the eligible papers and other related review articles as well as recent conference proceedings or recommendations on PH. Additional studies from these sources were then included in the review, provided they fulfilled the inclusion criteria.

All studies were handled by the literature management software Endnote X7. This was carried out to ensure no duplication. A preliminary screening of studies was performed by 2 independent authors (AT and PZJ). Screening of all titles and abstracts was done, and the full text was studied for any article considered relevant. After the initial round of screening, sorting was carried out again by re-reading all the articles. Methods were adapted as per PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines for meta-analyses[24].

Eligibility criteria for studies

Any observational study which determined the prevalence of PH in DS was considered for the analysis. These studies needed to mention the number of patients with PH and the number of children with DS who had PH.

Inclusion criteria

(1) All cross-sectional, case-control or cohort studies including children with DS reporting the prevalence of PH; (2) Studies must use either right heart catheterization for diagnosis with the cut-off being mPAP $\geq$ 25 mmHg or a 2D echocardiogram for determination of pulmonary arterial systolic pressure (PASP) ($>$ 25 mmHg); and (3) All published studies from 1st January 1980 to 30th June 2020 were included.

Exclusion criteria

(1) Studies performed in non-human subjects; (2) Case series, reviews, letters, commentaries and editorials; (3) Studies with insufficient data, abstracts, adult studies, conference abstracts and duplicate publications; and (4) Studies whose key data were not accessible even after a request from the authors.

Selection of studies

Two investigators (PZJ and DP) separately reviewed articles and screened them for eligibility. Full texts were downloaded for any articles which were deemed eligible. The investigators also checked the full texts of each study and studies which met the inclusion criteria were included. A third author (AT) was consulted to resolve any disagreements. A screening test was used to ensure that all review authors reliably applied the selection criteria. Agreement was measured using the kappa (κ) statistic [25].

Data extraction and management

A standard data extraction form was used to retrieve relevant information. Two review authors (PZJ and DP) participated in data extraction independently. PZJ and DP extracted data which included general information (authors, year, and country), study design, diagnostic criteria for PH, and prevalence of PH. In studies where only preliminary data were provided, such as sample size or number of outcomes, other required data were calculated based on these values. Data were extricated using a preconceived and standardized data abstraction form. Studies with un-interpretable data were excluded from the analysis. Level of agreement was ascertained by the κ statistic [25].

Quality appraisal of the studies included

Each included study was evaluated for quality of methodology and risk of bias by two investigators (PZJ and DP) using an adapted version of the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al* [26]. The STROBE checklist [27] was utilized to assess the reporting quality of each study. Reporting of Observational Studies in Epidemiology (STROBE) was performed by two authors. The STROBE statement has a total of 22 items on the checklist. These items relate to various parts of the study such as the article's title and abstract (item 1), the introduction (items 2 and 3), methods (items 4–12), results (items 13–17) and discussion sections (items 18–21), and other information (item 22 on funding). Agreement was measured using the κ statistic [25].

Statistical analysis

Each included study reported the prevalence of pulmonary hypertension as a probability of binominal distribution. Forest plot was used to determine the combined prevalence from the studies and extent of heterogeneity between them. As there was a large difference in the clinical data of patients across the studies, a random-effects meta-analysis was used to pool the data on prevalence [28], after stabilizing the variance of individual studies utilizing the Freeman-Tukey double arc-sine transformation [29]. Heterogeneity of the included studies was tested by Cochran's Q test and I^2 index [30]. The degree of heterogeneity was categorized into 3 categories under the I^2 index: heterogeneity lower than 25%, heterogeneity between 25% and 75% and heterogeneity more than 75%. While combining the prevalence of PH, a random effects model was used due to the wide heterogeneity among the studies. The impact of each study was also evaluated by sensitivity analysis. Subgroup analysis of PH was carried out to ascertain the cause of heterogeneity. Sub-group analysis was performed on the basis of geographical distribution (Asia *vs* non-Asia), age, sex, etiology, quality of the studies, year of publication and diagnostic methods. Meta-regression model (method of moments) was performed on the basis of the year of publication of studies [31]. Publication bias was identified by Egger and Begg's tests. Data were analyzed using Comprehensive Meta-Analysis Software Version 2 and values lower than 0.05 were considered to be significant. High-resolution forest plots, with random effects, were separately created [32].

RESULTS

Characteristics of the included studies

Initially, a total of 1578 articles were identified (Figure 1). After elimination of dup-

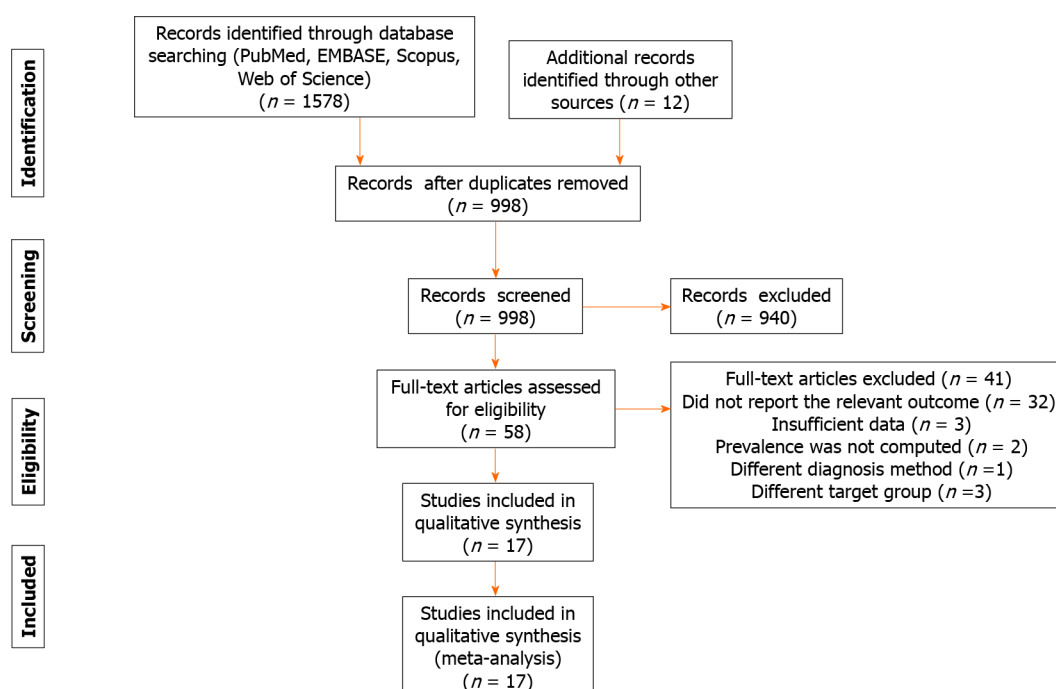


Figure 1 PRISMA flow chart diagram describing the process of identification and selection of studies for inclusion in the review.

licates, screening titles and abstracts, 940 papers were found to be completely irrelevant and excluded. Agreement between investigators on abstract selection was high ($\kappa = 0.90$, $P < 0.001$). Full texts of the remaining 58 studies were scrutinized for eligibility, among which 41 studies were excluded for various reasons. The investigators were in complete agreement for full text selection. Overall, seventeen studies were included for review in the meta-analysis (Figure 1).

All 17 studies noted the prevalence of PH without any analysis and no study reported the incidence of PH. The studies included were published from 2003 to 2020. Ten studies collected data retrospectively and seven studies collected the data prospectively. Study characteristics are summarized in Tables 1 and 2. The age of the patients ranged from neonate to 21 years. The studies differed in sample size varying from 35 to 1252 subjects with a summated sample size of 5393.

Quality of studies

The quality assessment results are presented in Table 3. No study met all criteria of the quality assessment score. Study quality varied from 10 to 17 as per the STROBE criteria. A score of < 14 was considered low quality, and > 14 was considered good/fair quality. The quality of reporting was low for two studies[33,34] and was good/fair for the remaining 15 studies. The most common limitations faced during STROBE assessment were inability to gauge the required sample size and poor projection of the results to the general population.

Risk of bias and heterogeneity

Quality assessment was also conducted for each study using the risk of bias assessment tool[26]. Among the 17 included studies (Table 4), there was low risk of bias for six studies (35.30%)[34-39], moderate risk for eight studies (47.05%)[40-47] and high risk for three studies (17.652%)[6,33,48]. Investigators' agreement on quality assessment of studies was high ($\kappa = 0.88$, $P < 0.001$). High heterogeneity was seen amongst the included studies according to Cochrane Q test (Q test; $P = 0.00001$) and I^2 test (98.4%).

Prevalence of pulmonary hypertension in DS children

Prior studies have estimated the prevalence of PH in children with DS to be as high as 6% and 15% at 1 and 10 years of life, respectively, but data from large populations are lacking[44]. A wide disparity was seen among the various studies for PH prevalence. The heterogeneity was high ($I^2 = 97.20\%$, $P < 0.001$). The overall prevalence of the meta-analysis of 17 studies, according to the Der Simonian-Laird random-effects model, revealed that the pooled prevalence of PH among children with DS was 25.5%

Table 1 Characteristics of studies included in the meta-analysis

Ref.	Year	Timing of data collection	Study design	Country	Population size	Cases with PH	Prevalence of PH
De Rubens <i>et al</i> [48]	2003	Retrospective	Observational	Mexico	275	41	14.90909
Shah <i>et al</i> [33]	2004	Retrospective	Observational	Canada	175	24	13.71429
Cua <i>et al</i> [35]	2007	Retrospective	Observational	USA	58	7	12.06897
Weijerman <i>et al</i> [40]	2010	Prospective	Cohort	Netherlands	820	25	3.04878
Banjar <i>et al</i> [41]	2012	Retrospective	Observational	Saudi Arabia	59	44	74.57
Mourato <i>et al</i> [42]	2013	Retrospective	Cross-sectional	Brazil	138	42	30.43478
Sharma <i>et al</i> [43]	2013	Prospective	Observational	India	35	18	51.42857
Shrestha <i>et al</i> [36]	2013	Prospective	Observational	Nepal	50	21	42
Espinola-Zavaleta <i>et al</i> [44]	2015	Prospective	Observational	Mexico city	127	102	80.31496
Bermudez <i>et al</i> [34]	2015	Retrospective	Observational	Brazil	1207	57	4.722452
Zonouzi <i>et al</i> [45]	2015	Prospective	Cross-sectional	Iran	110	23	20.90909
Joffre <i>et al</i> [6]	2016	Retrospective	Observational	France	66	19	28.78788
Okeniyi <i>et al</i> [37]	2017	Prospective	Observational	Nigeria	70	14	20
Bush <i>et al</i> [38]	2018	Retrospective	Cohort	USA	1252	346	27.63578
Martin <i>et al</i> [39]	2018	Retrospective	Cohort	Ireland	121	41	33.8843
Zahari <i>et al</i> [46]	2019	Retrospective	Cohort	Malaysia	754	160	21.22016
Alsuwayfee <i>et al</i> [47]	2020	Prospective	Cross-sectional	Iraq	76	23	30.26

PH: Pulmonary hypertension.

(95% CI: 17.4%–35.8%). The forest plot is shown in [Figure 2](#).

Stability of the meta-analysis was assessed by sensitivity analysis. The observations remained largely the same. This similarity between the results showed the stability of our meta-analysis. Also, no significant factor influencing the heterogeneity was identified by the sensitivity analysis.

Subgroup analysis was used to reduce heterogeneity. The pooled prevalence of different subgroups is illustrated in [Table 5](#). There were noteworthy differences for subgroups of gender, age group, region, year of publication, risk of bias and etiology of PH ($P < 0.05$). Four articles[35,38,45,47] presented prevalence linked to gender, with a prevalence of 24.3% among males and 26.2% among females. Some studies reported age distribution while others reported prevalence relating to each age group, which made the results difficult to compare. According to age group, 16 studies were subgrouped into two categories: studies conducted in infants (less than one year) (4 studies), and studies conducted in infants and children (12 studies). The prevalence of PH among studies including infants and children (33.7%; 95% CI: 22.6%–47%) was higher than studies including only infants (13.4%; 95% CI: 6.6%–25.4%). The prevalence of PH among children with DS from the Asian continent (38.4%; 95% CI: 23.7%–55.7%) was higher than non-Asian continents (19.8%; 95% CI: 10.9%–33.2%). The prevalence of PH was higher in studies published after 2011 (29.8%; 95% CI: 20.2%–41.7%) than those published before 2011 (0.09%; 95% CI: 0.04%–20.0%). Subgroup analyses showed the prevalence of PH among children with DS in studies with moderate risk (34%; 95% CI: 16%–57%) and low risk (20%; 95% CI: 9%–37%) to be higher than studies with high risk of bias (17.8%; 95% CI: 11.6%–26.5%). According to the etiology of PH, 7 studies included were divided into two categories *i.e.* with CHD and without CHD. The prevalence of PH attributable to CHD (14.4%; 95% CI: 7%–26.1%) was higher than in those without CHD etiology (8.9%; 95% CI: 4.4%–17.5%). Only one study, Bush *et al*[38] classified the etiologies as per WHO classification[8]. The diagnosis of PH was made in 82% of children, with 45% being associated with CHD, and 38% having persistent pulmonary hypertension of the newborn (PPHN). The Egger weighted regression statistics ($P = 0.94$) and Begg rank correlation statistics ($P = 0.45$) indicated no evidence of publication bias. There was no sign of publication bias and asymmetry in the funnel plot ([Figure 3](#)). The meta-regression model in [Figure 4](#) shows that the prevalence of PH among children with DS has increased in recent years. However, this relationship was

Table 2 Screening methodology of the included studies

Ref.	Diagnosis established by	Age group, (mean $\pm$ SD, yr)	Sex (M:F)	Diagnostic criteria for PH
De Rubens <i>et al</i> [48]	Echocardiography	Less than 16 yr	1:1	NM
Shah <i>et al</i> [33]	Echocardiography	Newborn	10:7	Right to left shunting at ductal or atrial level in the absence of severe pulmonary parenchymal disease
Cua <i>et al</i> [35]	Echocardiography	Neonate	25:33	Right-to-left shunt at the ductal level or flattening of the IVS in the absence of a PDA
Weijerman <i>et al</i> [40]	Echocardiography	Neonate	NM	Right-to-left shunt at the ductal level
Banjar <i>et al</i> [41]	Echocardiography	3.3 $\pm$ 3.9	34:25	> 50% of systolic systemic pressure
Mourato <i>et al</i> [42]	Echocardiography	Infant	61:77	mPAP > 25 mmHg
Sharma <i>et al</i> [43]	Echocardiography	Less than 12 yr	4:3	mPAP >25 mmHg
Shrestha <i>et al</i> [36]	Echocardiography	4 mo to 12 yr	1:1.4	NM
Espinola-Zavaleta <i>et al</i> [44]	Echocardiography	Up to 18 yr	64:63	mPAP > 30 mm Hg
Bermudez <i>et al</i> [34]	Echocardiography	Up to 11 mo	NM	mPAP > 25 mmHg
Zonouzi <i>et al</i> [45]	Echocardiography	1 mo-20 yr	53:57	NM
Joffre <i>et al</i> [6]	Echocardiography	1mo-16 yr	2:1	NM
Okeniyi <i>et al</i> [37]	Echocardiography	3 mo-9 yr	3:4	NM
Bush <i>et al</i> [38]	Echo or catheterization	Birth to 21 yr	688:564	mPAP > 25 mmHg; IVS flattening, RV dilation, or presence of RV hypertrophy
Martin <i>et al</i> [39]	Echocardiography	Neonate	62:59	Right to-left shunt across the PDA, IVS bowing into the left ventricle, or the presence of a TR jet
Zahari <i>et al</i> [46]	Echocardiography	Newborn	189:225	IVS flattening, a dilated main pulmonary artery, and dilated right cardiac chambers
Alsuwayfee <i>et al</i> [47]	Echocardiography	< 15 yr	0.85:1	mPAP > 25 mmHg

PH: Pulmonary hypertension; IVS: Interventricular septum; PDA: Patent ductus arteriosus; TR: Tricuspid regurgitation; PAP: Pulmonary artery pressure; NM: Not mentioned.

not statistically significant (meta-regression coefficient: 0.0947, 95%CI: -0.035 to 0.22, $P = 0.153$).

DISCUSSION

Children with DS are known to be at a higher risk of developing pulmonary hypertension (PH). This can be attributed to underlying CHDs, idiopathic PH and partly due to upper airway obstruction[49]. Other factors which may contribute to a higher risk include genetics, anatomical characteristics of the pulmonary vasculature, pulmonary hypoplasia, obstructive airway diseases, chronic infection and neuromuscular underdevelopment. Increased pulmonary blood flow due to underlying heart disease with left to right shunt increases the sheer stress on the endothelial lining and may induce endothelial dysfunction, eventually resulting in pulmonary vasculature remodeling. The sheer stress also leads to pathologic changes in the vessel wall such as endothelial cell proliferation and thickening of the vessel wall. The pathologic changes also include alveolar under-development. The production of prostacyclin and nitric oxide is diminished in DS, but endothelin-1 and thromboxane are elevated[50]. The lifetime incidence of PH in children with DS remains unknown [38]. Patients with DS have increased mortality due to pulmonary vascular disease with a standardized mortality odds ratio of 3.83 (95%CI: 3.60-4.07)[51].

In light of this, this is the first systematic review evaluating PH in children with DS. Despite extensive literature, there is large heterogeneity in the prevalence of PH in DS. The heterogeneity arises from multiple overlapping etiologies which are commonly associated with DS. The present study found the overall prevalence to be 25.5%

Table 3 Quality assessment of the included studies

STROBE quality of reporting						
Ref.	The title and abstract (Item 1)	Introduction (Item 2-3)	Methods (Item 4-12)	Results (Item 13-17)	Discussion and other information (Item 18-22)	Quality score (0-22)
De Rubens <i>et al</i> [48]	1	2	6	4	2	15
Shah <i>et al</i> [33]	0	2	5	2	3	12
Cua <i>et al</i> [35]	1	2	5	3	4	15
Weijerman <i>et al</i> [40]	1	2	4	4	4	15
Banjar <i>et al</i> [41]	1	2	4	4	4	15
Mourato <i>et al</i> [42]	1	2	5	2	4	14
Sharma <i>et al</i> [43]	1	2	5	3	4	15
Shrestha <i>et al</i> [36]	1	2	4	4	4	15
Espinola-Zavaleta <i>et al</i> [44]	1	2	5	3	3	14
Bermudez <i>et al</i> [34]	1	2	4	2	4	13
Zonouzi <i>et al</i> [45]	1	2	4	3	5	15
Joffre <i>et al</i> [6]	1	2	5	2	4	14
Okeniyi <i>et al</i> [37]	1	2	5	3	3	14
Bush <i>et al</i> [38]	1	2	5	3	5	16
Martin <i>et al</i> [39]	1	2	5	4	4	16
Zahari <i>et al</i> [46]	1	2	5	3	4	15
Alsuwayfee <i>et al</i> [47]	1	2	5	4	4	16

(95% CI: 17.4%-35.8%) from a pool of 17 studies which met the inclusion criteria. This finding has shown concordance with multiple studies[6,37,38,45,46]. In order to reduce heterogeneity, subgroup analysis was carried out according to age, gender, region, etiology of PH and bias. In neonates, the incidence of PH is estimated at 2 per 1000 live births, which is notably less when compared to that observed in neonates with DS[52]. Earlier studies assessing PH in children with DS report an incidence ranging from 1% to 5%, with the majority of these infants being classified as having pulmonary arterial hypertension (PAH). More recent studies, however, have noted a much higher figure ranging between 27% and 34%[38]. Additionally, children with DS have an increased risk of developing PPHN even in the absence of structural heart disease and should be followed up until resolution of PH[33].

According to age group, 16 of the included studies were divided into 2 subgroups: studies conducted in children < 1 year of age (7 studies) and studies conducted in children > 1 year of age (9 studies). The prevalence of PH in DS was highest in children followed by infants and neonates. This contrast was highlighted because of the identification that infants with DS have a higher prevalence of PPHN and abnormalities of developmental lung disorders (*e.g.*, reduced alveolarization, decreased vessel density, persistence of the double-capillary network and hypertensive arterial remodeling). This finding enforces that increasing age is a distinct risk factor for developing PH and its complications. Late PH is also important in contributing to adverse outcomes in children and adults with DS[38]. In the current review, 4 studies analyzed the prevalence of PH according to gender. The overall prevalence in females was 26.2% and in males it was 24.3%. Although, the prevalence was higher in females the difference was not statistically significant. When country of origin was considered in the analysis, it was noted that Asian countries showed a higher prevalence as compared to non-Asian countries (38.4% *vs* 19.8%). Studies published before 2011 recorded a pooled prevalence of only 9.4%, whereas after 2011 the prevalence was found to be 33%. This increased prevalence can be attributed to reasons such as increased survival of children with DS and CHD and increased birth rates. In a study conducted by Yang *et al*[51], among 17,897 patients with DS, the median age at death had increased from 25 years in 1983 to 49 years in 1997. A large percentage of PH in DS

Table 4 Risk of bias assessment of included studies using the Hoy *et al*[26] 2012 tool

Ref.	Representation	Sampling	Random selection	Non response bias	Data collection	Case definition	Reliability and validity of study tool	Method of data collection	Prevalence period	Numerator and denominator	Summary assessment
De Rubens <i>et al</i> [48]	HR	HR	HR	HR	HR	HR	LR	LR	HR	LR	HR
Shah <i>et al</i> [33]	HR	HR	HR	HR	HR	HR	LR	LR	HR	LR	HR
Cua <i>et al</i> [35]	LR	LR	LR	LR	LR	LR	LR	LR	HR	LR	LR
Weijerman <i>et al</i> [40]	HR	HR	HR	HR	HR	LR	LR	LR	HR	LR	MR
Banjar <i>et al</i> [41]	HR	HR	LR	HR	LR	HR	LR	LR	LR	LR	MR
Mourato <i>et al</i> [42]	HR	HR	HR	HR	LR	LR	LR	LR	HR	LR	MR
Sharma <i>et al</i> [43]	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	LR
Shrestha <i>et al</i> [36]	LR	LR	LR	HR	LR	LR	LR	LR	HR	LR	LR
Espinola-Zavaleta <i>et al</i> [44]	LR	LR	LR	HR	HR	HR	LR	LR	HR	LR	MR
Bermudez <i>et al</i> [34]	LR	LR	HR	HR	LR	HR	LR	LR	HR	LR	MR
Zonouzi <i>et al</i> [45]	HR	HR	HR	HR	LR	HR	LR	LR	HR	LR	MR
Joffre <i>et al</i> [6]	HR	HR	HR	HR	HR	HR	HR	HR	LR	LR	HR
Okeniyi <i>et al</i> [37]	LR	LR	LR	HR	HR	LR	LR	LR	HR	LR	LR
Bush <i>et al</i> [38]	LR	LR	LR	HR	HR	LR	LR	LR	HR	LR	LR
Martin <i>et al</i> [39]	LR	LR	LR	HR	HR	LR	LR	LR	HR	LR	LR
Zahari <i>et al</i> [46]	HR	LR	HR	HR	LR	HR	LR	LR	HR	LR	MR
Alsuwayee <i>et al</i> [47]	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	MR

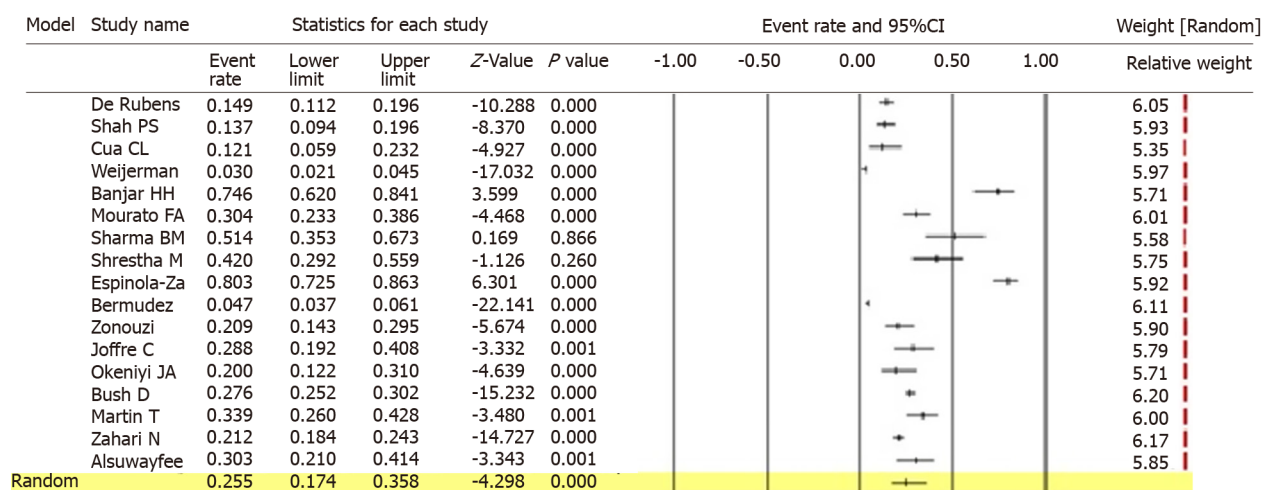
HR: High risk; LR: Low risk; MR: Moderate risk (LR: 0-3; MR: 4-6; HR: 7-9).

can be attributed to the concomitant presence of CHDs. Laursen *et al*[53] in 1976, found that the incidence of PH in patients with DS and CHDs to be just 2%, whereas a study conducted by Bush *et al*[38] in 2018 found the incidence of PH in DS to be as high as 28%. The incidence was noted to increase to 45% in the presence of a co-morbid CHD. They also noted that the higher age group in their study may be responsible for the higher incidence.

The risk of bias was high in 3 studies with the prevalence of PH being 17.8%, 6 studies had low risk of bias with a prevalence of 20% and 8 studies with moderate risk showed a prevalence of 34%. There were 7 studies which assessed the prevalence of PH in children with DS with an underlying CHD. These studies had a prevalence of 14.4% while studies having no underlying CHD (7 studies) had a prevalence of 8.9%. Patients with an underlying CHD showed a higher prevalence of PH. Other studies have observed similar findings. Smith *et al*[54] reported that DS patients had a higher prevalence of PH with or without an underlying CHD and the difference between the

Table 5 Prevalence in different subgroups

Stratification group	Number of studies	Total number of subjects	Total number of events	<i>I</i> ²	<i>P</i> value	Prevalence	95%CI
Sex							
Male	4	801	210	28.22	0.243	24.3	18.8-30.6
Female	4	695	189	56.44	0.076	26.2	18.8-35.3
Age							
Infant (< 1 yr)	7	3273	356	95.35	0.000	13.4	6.6-25.4
Children (> 1 yr)	9	2061	607	94.68	0.000	33.7	22.6-47.0
Region							
Asia	6	1084	289	93.68	0.000	38.4	23.7-55.7
Not Asia	11	4309	718	97.92	0.000	19.8	10.9-33.2
Studies published							
Before 2011	4	1328	97	93.79	0.000	9.4	4.1-20.2
2011 - 2020	13	4065	910	97.13	0.000	33.0	22.5-45.4
Risk of bias							
High risk	3	516	84	76.20	0.015	17.8	11.6-26.5
Moderate risk	8	2119	437	97.91	0.000	34.0	16.6-57.1
Low risk	6	2758	486	97.63	0.000	20.0	9.3-37.7
Etiology							
Cardiac	7	724	372	97.06	0.000	14.4	7.4-26.1
Non-cardiac	7	724	352	96.63	0.000	8.9	4.4-17.5

**Figure 2** Forest plots of pulmonary hypertension prevalence among children with Down syndrome.

two groups lies in the underlying etiology and the age of presentation. Iwaya *et al*[55] reported a lower pulmonary arterial compliance in individuals with CHD in DS when compared to CHD without DS. A noteworthy association was found between low pre-operative pulmonary compliance in DS and the need for postoperative oxygen therapy after discharge.

Study strengths and limitations

This is the only systematic review and meta-analysis assessing the prevalence of PH in the pediatric population with DS. A comprehensive search was undertaken wherein we included any study that reported the prevalence of PH in children with DS. Despite considerable heterogeneity between studies, our review provides the most

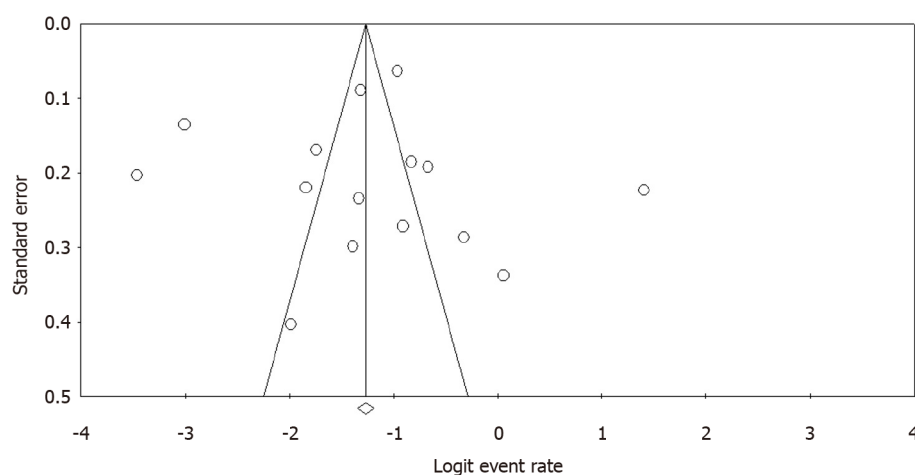


Figure 3 Funnel plots of pulmonary hypertension prevalence among children with Down syndrome.

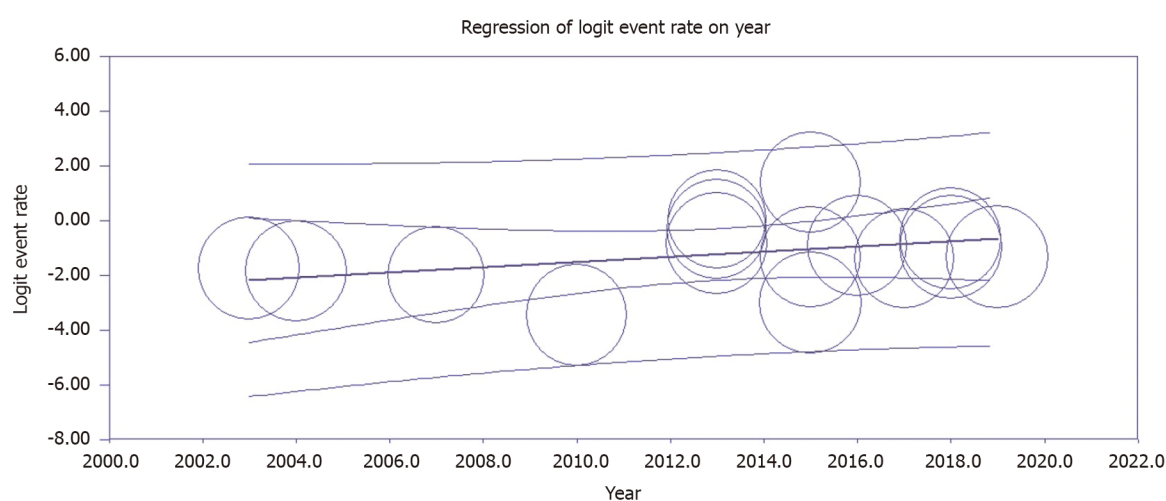


Figure 4 Meta-regression of pulmonary hypertension prevalence based on the year of the study.

comprehensive estimate of PH prevalence in children with DS to date, and most importantly, allows the comparison of prevalence between various groups of interest. Heterogeneity may arise from the data sources, populations examined and subjects with different ages, sex, risk of bias *etc.* This is not unexpected in view of the different populations studied and the nature of variations associated with the different methods used in estimating the prevalence. However, the sensitivity analysis showed that the heterogeneity had no significant impact on the pooled prevalence and a meta-analysis might still provide insights on the overall prevalence. The quality of the results and risk of bias of the studies included was at most, moderate, further highlighting that further such research may have a significant impact on our confidence in the estimate and might also change it. All included studies were observational; therefore, a cause effect relationship cannot be concluded between PH in children with DS. Longitudinal and interventional studies are still needed to determine the nature of any cause and effect relationship. Finally, some methodological limitations of the current meta-analysis were inevitable and should be taken into consideration while interpreting the results. Our study, although strengthened by rigid quality assessment, was limited by the fact that not all studies had classified all the etiologies of PH as per the WHO classification. The paucity of etiological data made it difficult to delineate individual causes of PH in patients with DS. This added to existing heterogeneity while analyzing the exact prevalence of PH in DS. More studies, specifically, ones with community screening for PH in DS are required to come to an exact estimate.

CONCLUSION

This article highlights the increasing prevalence of PH in children with DS. In order to improve the care given and reduce the disease burden, the attending pediatrician has a crucial role in being aware of this morbid disease and to channel his/her efforts towards routine screening of PH, earlier diagnosis and successful management. In addition, there should be early routine echocardiographic screening in children with DS even in the absence of CHDs. Community-based studies with a larger sample size of children with DS may be carried out to better characterize the epidemiology and underlying etiology. Our study reinforces what is already known and provides, in addition, reliable information about the prevalence of PH in DS.

ARTICLE HIGHLIGHTS

Research background

Children with Down syndrome (DS) have an increased likelihood of developing pulmonary hypertension (PH) with serious short- and long-term consequences. Approximately 75% of all deaths in DS may be attributed to pneumonia and infectious lung disease, congenital heart disease (CHD) and circulatory disease (vascular diseases such PH). Despite the overwhelming evidence of morbidity, there have been no studies estimating the precise disease burden of PH in children with DS.

Research motivation

Additional information is required to collate the prevalence rates of PH in order to undertake definitive measures for early diagnosis and management.

Research objectives

The objective of this study is to determine the prevalence of PH in children with DS.

Research methods

The electronic databases (PubMed, Cochrane library, EMBASE, Scopus, Web of Science) were searched. Any observational study which determined the prevalence of PH in DS was considered for the analysis. Data were extricated using a preconceived and standardized data abstraction form. The data were analyzed by Comprehensive Meta-Analysis Software Version 2.

Research results

Of 1578 articles identified, 17 were selected for final analysis. The pooled prevalence of PH in these studies was 25.5% (95%CI: 17.4%–35.8%). Subgroup analysis was carried out for age, gender, region, year of publication, risk of bias and etiology of PH.

Research conclusions

This article highlights the increasing prevalence of PH in children with DS. This is accounted for by the high prevalence of underlying CHDs in these children. In order to improve the care given and reduce the disease burden, the attending pediatrician has a crucial role in being aware of this morbid disease and to channel his/her efforts towards routine screening of PH, earlier diagnosis and successful management. In addition, there should be early routine echocardiographic screening in children with DS even in the absence of CHDs. Community-based studies with a larger sample size of children with DS may be carried out to better characterize the epidemiology and underlying etiology of PH in DS. Our study reinforces what is already known and provides, in addition, reliable information about the prevalence of PH in DS.

Research perspectives

Further studies are required to better characterize the epidemiology, underlying etiology, pathogenesis and risk factors of PH in children with DS.

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