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Research Article

Incidence of Congenital Heart Disease: A 10-Year Incidence Meta-Analysis and Systematic Review of the Importance of Neonatal Screening

Afnan Abdulrahman Aljohani[1]* and Wedad Saleh Alotaiby[2]

[1]*Department of Pediatric, Alaziziyah Maternity and Children Hospital, Jeddah, Saudi Arabia*

[2]*Department of Pediatric, East Jeddah Hospital, Jeddah, Saudi Arabia*

***Corresponding Author:** Afnan Abdulrahman Aljohani, Department of Pediatric, Alaziziyah Maternity and Children Hospital, Jeddah, Saudi Arabia.

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Abstract

Introduction: Despite being the most common congenital anomaly in neonates and the most important cause of death at this young age, congenital heart diseases (CHD) have no accurate estimates of its incidence.

Methods: Nine electronic search engines/libraries were systematically searched for relevant publications. Studies were screened for eligibility and data was then extracted. A Total of 39 studies were included into the sample, 11 for the meta-analysis and 28 for review. Incidence rate analysis of the meta-analysis was conducted to detect the average incidence of CHD in the last 10 years with a systematic review to understand the importance of neonatal screening.

Results: CHD incidence was found on an average of 30 cases per 1,000 neonates, being ventricular septal defect (VSD) the most common CHD type, with a representation of 2.6 cases in 100 neonates, followed by TGA and ASD. The single ventricle was the least common type of CHD. Also, the most important screening method used in the studies was pulse oximetry, increasing its accuracy and sensitivity when combined with clinical examination and perfusion index. Echocardiography and ultrasound were better when used in the foetal screening.

Conclusions: VSD is the most common diagnosed cause of CHD. Combination of multiple screening methods will increase screening accuracy. Still, more studies with more precise study design are needed to determine the best detecting methods.

Keywords: *Congenital Heart Disease; Ventricular Septal Defect; Neonatal Screening; Foetal Screening; Pulse Oximetry*

Introduction

Congenital heart diseases (CHD) are "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance" [1]; this definition includes all structural abnormalities of the heart e.g. septal defect or valve abnormalities [2]. Therefore, any abnormalities in the conduction of electrical activity of the heart are excluded.

Also, many classifications of CHD are based on either on cyanosis, a major common symptom, the structural abnormality and the blood flow inside the heart, or the severity of the condition [3,4]. Between this CHD types, ventricular septal defect was the most common type of the CHD found, with an increased prevalence every year, while Tetralogy of Fallot was the most common cyanotic heart disease [2]. The usual presentation of CHD was either asymptomatic or symptomatic, with fast breathing and poor weight gain being the most common symptoms [5,6].

Congenital heart disease is considered the most common congenital anomaly in neonates [7]. Furthermore, CHD is a leading cause of infant death and responsible for 10 % of aborted foetuses [8,9]. Every year, it affects 400 of 400,000 live births in the U.S. and 11.1 per 1,000 live births in China [7,10]. This numbers have been increasing every year from 0.6 per 1,000 live births in 1930-1934 to 9.1 per 1,000 live births after 1995. However, the number is believed to be stabilized at 1.35 million live births [7,10]. Despite this data, there are still different populations that do not possess accurate numbers at the moment.

Another study suggested that Asian countries had more pulmonary outflow obstructions, lower TGA birth prevalence and less left ventricular outflow tract obstructions than Europe and North America [11]. It was also found the existence of a significant difference of prevalence cases between high and low-income countries [11]. The high-income countries had an estimated prevalence of 8.0 per 1,000 live births, which is higher compared to upper-middle-income countries (7.3 per 1,000 live births). In addition, a significant difference of CHD prevalence between male and female live births was identified [11], probably caused due to genetic variation which account for 25% of cases [7]. The fact that 30% of CHD are accompanied by other developmental anomalies also confirm this genetic theory [7].

CHD result in increased morbidity and mortality rates in patients, with emotional stress also decreasing the quality of life for patients and their families. In the United States alone, hospital costs for CHDs in 2004 were about $1.4 billion, with $511 million being spent in severe cases of CHDs [7]. Early diagnosis of CHD is then considered crucial for improving quality of life and allow early intervention procedures.

Neonatal screening has become a crucial necessity for early discovery of neonatal diseases, which may cause significant mortality and morbidity. The main objective of neonatal screening is to detect a life-threatening congenital heart disease before its clinical symptoms and signs are medically significant [12]. Now, there are three major methods for screening: complete history shared with physical examination, pulse oximetry, and echocardiography [12]. Ultrasound has also been reported as a method for screening intrauterine CHD [13-15].

Further study has divided the screening for CHD based on age of the population screening. For fetal screening, the ultrasound is used but still depends on the availability of an ultrasound machine and a radiologist. For neonates, physical examination and pulse oximetry were considered. For school children only physical examination is used [12], with studies assessing the accuracy of physical examination, with murmurs, central cyanosis, abnormal precordial pulsation having better specificity than pulse oximetry, besides this, pulse oximetry still showed increased sensitivity [5,9,16]. A Cochrane review also suggested adding pulse oximetry as a screening tool for CHD due to its very low false positive rates [17].

Besides there is no gold standard for screening CHD, with many cons and pros for each method, the addition of improved screening methods for early detection and diagnosis of CHD, in addition to other procedures, would be helpful in order to determine the incidence of CHD and the real size of this problem, also contributing to determine its causes.

In this study, we reviewed different types of designs to determine the incidence of CHD in neonates and infants in the recent years, as well as related literature to determine the importance of the neonatal screening for diagnosis of new cases.

Methods

Search strategy and selection criteria

Authors have conducted this review based on the PRISMA guidelines [18]. A systematic search of the medical literature on July 11, 2018, was performed, including an electronic search within 9 major databases: PubMed, Scopus, ISI Web of Science, POPLINE, Virtual Health Library (VHL), SIGLE (System for Information on Grey Literature in Europe), Global Health Library (GHL), The New York Academy of Medicine (NYAM) and Google Scholar.

The following search strategy was used to find relevant articles for the incidence of the CHD: (22q11 Deletion Syndrome OR DiGeorge Syndrome OR Alagille Syndrome OR Aortic Coarctation OR Arrhythmogenic Right Ventricular Dysplasia OR Barth Syndrome OR Cor Tria-

triatum OR Coronary Vessel Anomalies OR Bland White Garland Syndrome OR Myocardial Bridging OR Crisscross Heart OR Dextrocardia OR Kartagener Syndrome OR Patent Ductus Arteriosus OR Ebstein Anomaly OR Ectopia Cordis OR Eisenmenger Complex OR Heart Septal Defects OR Aortopulmonary Septal Defect OR Endocardial Cushion Defects OR Heart Septal Defects OR Heterotaxy Syndrome OR Hypoplastic Left Heart Syndrome OR Isolated Noncompaction of the Ventricular Myocardium OR LEOPARD Syndrome OR Levocardia OR Marfan Syndrome OR Noonan Syndrome OR Tetralogy of Fallot OR Transposition of Great Vessels OR Double Outlet Right Ventricle OR Tricuspid Atresia OR Trilogy of Fallot OR Trisomy 13 Syndrome OR Trisomy 18 Syndrome OR Turner Syndrome) AND (incidence OR "new cases"). For neonatal screening, we added the following terms to search terms ("New-born Infant Screening" OR "Infant Screening" OR "New-born Screening" OR "Neonatal screening", "pulse oximetry", "echocardiography", "ultrasound"). Further search of the reference lists of all included articles was also done for additional studies. We did not apply any restrictions with respect to language or publication period.

All original studies about the incidence of CHD since 2008 (recruitment of patients from 2008) and the importance of screening in the last 10 years for early diagnosis of CHD were included. There were excluded from this sample all observational studies, case reports, case series, letters, editorials, theses, reviews, book chapters or news with no available full texts. Finally, it was also excluded any material which data cannot be extracted or with overlapped data sets. Papers studying only specific groups (e.g., only Down syndrome), or case studies of rare defects were eliminated. Papers focusing on aetiology, comparisons of treatment, prognosis, or animal research were also rejected.

All the studies were available through searching databases with no need of contacting authors. For foreign language studies, the translation was made using a professional translation programme, for the search database there was no specific search software used.

Authors independently screened all selected titles and abstracts to identify articles for potential inclusion. When an abstract was included, the full-text article was retrieved and evaluated for inclusion.

Data extraction

Following data was extracted including a baseline of the neonates and maternal characteristics, also cases per person time for CHD and for each reported types of CHD were included. If not available, then we would extract the new cases of CHD and total population. A template in Microsoft Excel was developed to extract data. Controversies were resolved through discussion and consensus among the authors.

Statistical analysis

All data was analyzed using R version 3.3.4 software [19] and meta package [20]. Events and person time year were analyzed to compute pooled Incidence Rate (IR) based on the inverse variance method. If the person time year was not reported, the method reported in Szklo., *et al.* [21] was then applied. A fixed-effects model was included when there was a lack of significant heterogeneity, while implementing random-effects when it was present. Heterogeneity was assessed with Q statistics and I^2-test considering it significant with I^2 value > 50% or P value < 0.01.

Publication bias was addressed with the Egger's linear regression test [22] and represented graphically by Begg's funnel plot when 10 or more studies were present [23].

Quality assessment of included studies

Authors independently monitored the quality and risk of bias in included studies using the NIH quality assessment tool, a 14 questions instrument which assess the quality of observational studies, each question offering "yes" or "no" answers [24].

Results

Search results

Our database search yielded 5,562 papers relative to our research terms for incidence and 1,294 for the importance of screening study. The flow of the search is illustrated in figure 1.

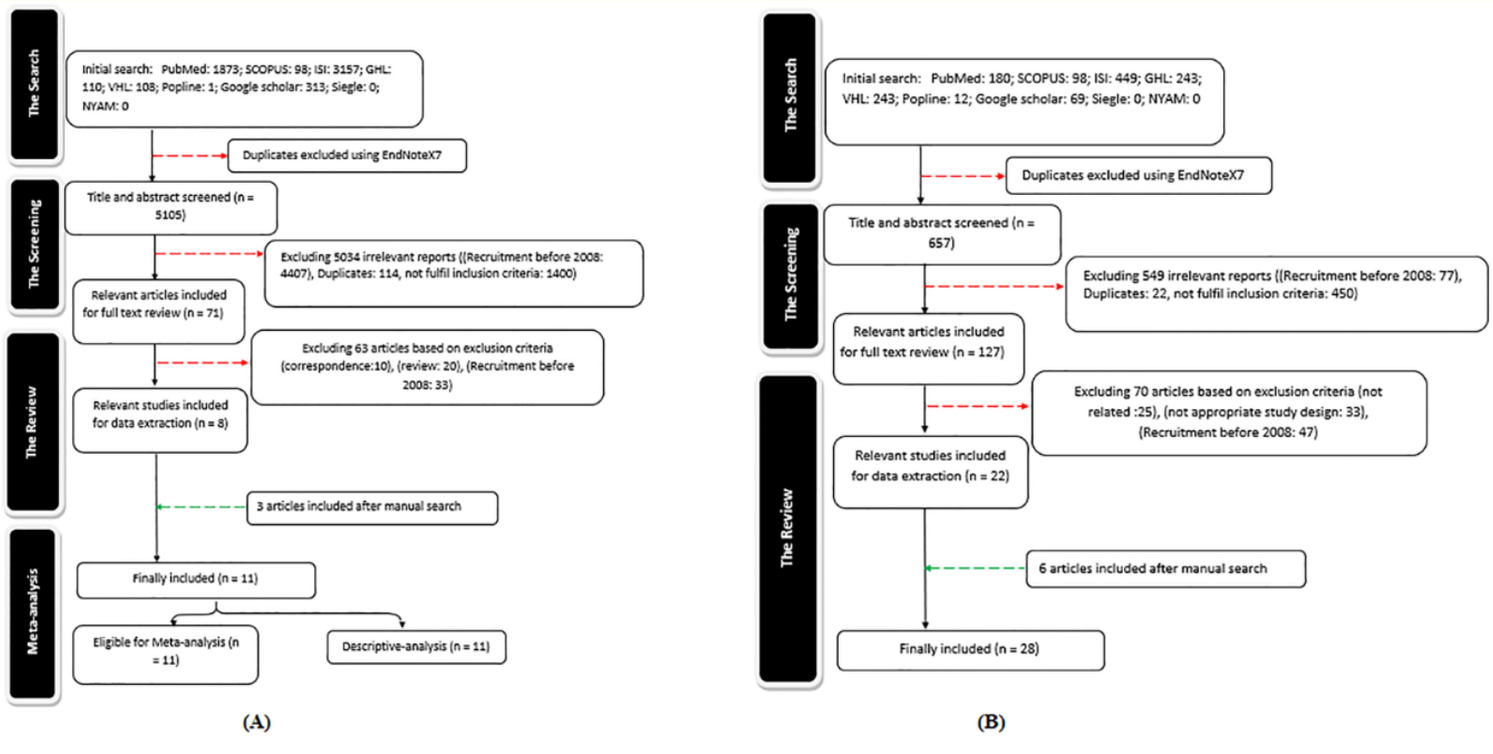

Figure 1: *The flow chart of the search process.*

Study characteristics

We included 39 studies with 1,491,589 live births. The baseline characteristics of patients are illustrated in table 1. As part of the results, nearly all studies had used pulse oximetry for screening and diagnosis.

ID	Country	Year of assessent	Type of studies	Screening and diagnosis of Congenital heart	Congenital heart disease assessed	Age (N)	Gender	Number of CHD (Total popuaion) or incience reported	Calculated Incidence of conenital anomalies (per 100)	Quality ass-essent
Al-esned/2012 [25]	Saudi-Arabia	January 2008 to December 2010	Retropective cohort	Routine history, physical examination, and electrocardiography	Severe cases	neonate	NA	316 (58908)	1	Good quality

Begum/2016 [26]*	India	June 2014 to May 2015	Propective cohort	routine investigaions, chest x-ray, ECG and Electrocardiography and echocardiograph	Cyanotic and non-cyanotic	1 month to 12 years	male (55), Female (27)	82 (3359)	5	Fair quality
Dhanardhono/2012 [27]*	Sigaore	2008-2009	Retropective cohort	ultrasonography	Not specified	first tri-mester screening	NA	38 (9834)	1	Good quality
Dulal/2016 [28]	India	February 2015 to January 2016	Propecive cohort	pulse oximetry	Not specified	neonate	NA	34(1720)		Good quality
Egbe/2014 [29]*	USA	January to Decemer 2008	Retrospecive cohort		Mild lesions, Moderate lesions	Birth-hospital discharge	6,773 males (52%) and 6,320 females (48%)	13,093 (1,204,887)	2	Fair quality
Froehlich/2017 [30]	USA	Between 2010 and 2014	Retrospecive cohort	Both anatomic survey and fetal echocardiography were performed between 16 and 26 weeks of gestation	Not specified	16 and 26 weeks fetus	NA	5 (1,052)		Fair quality
Goetz/2016 [31]	USA	In 2013 and 2014	Retrospecive cohort	pulse oximetry	Critical congenital heart disease	neonate	Female (454), male (551)	287 (1005)		Fair quality
Gomez-Rodriez/2015 [32]	Mexico	July, 2010 to April, 2011	Prospecive cohort	pulse oximetry	Critical congenital heart disease	38.9 (1.1)	Female (490), male (547)	14 (1037)		Fair quality
Hamilçıkan/ 2017 [33]	Turkey	October 1, 2015 and October 31, 2016	Prospective cohort	pulse oximetry	Critical congenital heart disease	Average is 38 weeks	Female (2049), male (2186)	8 (4518)		Good quality
Han/2013 [34]	USA	10 months in 2012	Prospective cohort	pulse oximetry	Not specified	neonate	NA	1 (1069)		Fair quality
Huessain/2014 [35]*	Pakistan	Septemer 2008 to August 2011	Prospective cohort	Clinical assessment, pulse oxymetry, electrocardiogram (ECG), X-ray chest and echocardiography		neonate		87 (5800)	3	Good quality

Itsukaichi/2017 [36]	Japan	October 2010 and March 2012	Prospective cohort	Fetal ultrasound screening was performed by obstetricians at 18-21 gestational weeks (GW) and pulse oximetry in neonates	Not specified	18-21 gestaional weeks and neonates	NA	37 (3005)		Fair quality
Jørgensen/2015 [37]	Denmark	01.01.2008-31.12.2010	Retrospective cohort	prenatal ultrasound	Not specified	fetuses in the second and third trimester	NA	831 (86121)		Fair quality
Johnson/2014 [38]	USA	January 1 to December 31, 2013,	Retrospecive cohort	Pulse oximetry	Critical congenital heart disease	live births of ≥35 weeks' gestation	NA	111 (6838)		Good quality
Korkmaz/2015 [39]*	Turkey	February 2013 - September 2014	Retrospective cohort	Clinical assessment and Echocardiography	Cyanotic and non-cyanotic	neonate	NA	35 (326)	19	Fair quality
Kumar/2015 [40]*	India	May 2013 to June 2013	Cross sectional study	History, clinical assessment and Echocardiography	Cyanotic and non-cyanotic	< 1Yr (18), 1-4yr (6), 4-8yr (10), 8-12yr (16)	Male (32), female (18)	50		Fair quality
Kumar/2017 [41]*	India	July 2015 to June 2016	Prospective cohort	History, clinical assessment and Echocardiography	Cyanotic and non-cyanotic	1month to 12 years	Male (2,653) and female (1,916)	112 (4569)	5	Good quality
Lyengar/2013 [43]	USA	November 7 to December 31, 2011 (group 1), and from August 1 to October 9, 2012 (group 2)	Retrospective cohort	pulse oximetry	Critical congenital heart disease	37 (3.42)	Female (128), male (111)	0 (500)		Good quality
Manja/2015 [44]	USA	1/1/2010 and 12/31/2013	Prospective cohort	Pulse oximetry	Critical congenital heart disease	Neonate	NA	1 (1508)		Fair quality

Mathur/2015 [45]	India	April 2013 and January 2014	Prospective cohort	Pulse oximetry		Neonate	Female (158), male (262)	20 (950)		Good quality
Methlouthi/2016 [46]	Tunisia	1st February 2014 to 31st January 2015	Prospective cohort	Pulse oximetry	Not specified	Neonate	NA	26 (10447)		Fair quality
Miller/2016 [47]	USA	January 2013 through December 2014	Prospective cohort	Pulse oximetry	Critical congenital heart disease	Neonate	NA	5 (1616)		Fair quality
Mouledoux / 2013 [48]	USA	1 January and 31 December 2011	Prospective cohort	Pulse oximetry	Not specified	Neonate	NA	15 per 100000		Fair quality
Mouledoux/ 2017 [49]	USA	2013	Retrospective cohort	Tennessee algorithm	Critical congenital heart disease	Neonate	NA	51 (232)		Fair quality
Narayen/2016 [50]	Netherlands	October 2013 and October 2014	Prospective cohort	Pulse oximetry		Neonate	NA	0 (3625)		Fair quality
Nayak/2016 [51]*	India	2008 and 2012	Prospective cohort	Echocardiography	Not specified	Foetal	NA	20.3 (1000)	4	Good quality
Otaigbe/2014 [52]	Nigeria	April 2009 and March 2013	Prospective cohort	Chest radiographs, electrocardiograms (ECG) and an echocardiogram (echo)	Cyanotic and non-cyanotic	0.25 to 180 months with a mean of 26.1 months	174 males (52.4%) and 158 females (47.6%)	332 (23124)	3	Fair quality
Ozalkiya/2015 [53]	Turkey	January 2014 and December 2014	Prospective cohort	Pulse Oximetry	Not specified	Neonate	NA	1 per 1000		Good quality
Paranka/2018 [54]	USA	November 2012 and February 2016	Prospective cohort	Pulse Oximetry	Critical congenital heart disease	Gestational age was 35-44 weeks	Female (3032), male (3012)	65(6109)		Fair quality
Pasierb/2017 [55]	USA	December 2008 to December 2015	Retrospective cohort	History, maternal examination, ultrasound, and fetal echocardiography.	fetal	NA		22(699)		Good quality
Sahin/2018 [56]	Turkey	21 August 2014, and 21 August 2015	Prospective cohort	Pulse Oximetry	Not specified	Neonates of >35 weeks' gestation	NA	812 (1246)		Fair quality

Samuel/2013 [57]	Israel	2012	Prospective cohort	Pulse Oximetry	Not specified	37-41 complete weeks of gestation	NA	199		Fair quality
Schena/2017 [58]	Italy	June 2011 to November 2013	Prospective cohort	Pulse oximetry and perfusion index	NA	NA		1 (1115)		Fair quality
Taksande/2013 [59]	India	April 2012 to January 2013	Prospective cohort	Pulse Oximetry	Critical congenital heart disease	Age range (38.2-8.6 gestaional weeks)	Male: 1071; Female: 1039	7 (2110)		Fair quality
Torky/2016 [60]*	Egypt	January 2012 to June 2013	Retrospective cohort	History, general examination, all ultrasound scans whether two-dimensional (2D) or three dimensional (3D), Doppler and fetal echocardiography.	Severe (Major), moderate and mild cases	14 weeks fetuses or more	NA	105 (5499)	4	Fair quality
Tsao/2016 [61]	Taiwan	October 1, 2013, and March 31, 2014	Retrospective cohort	History, maternal examination, ultrasound, pulse oximetry and fetal echocardiography.	Critical congenital heart disease	NA	NA	5 (6,296)		Good quality
Zhang/2017 [62]	China	October 2011 to June 2012	Prospective cohort	History, maternal examination, ultrasound, pulse oximetry and fetal echocardiography.	Age range (0-3)	Males (98) and females (77)		166 (10281)		Fair quality
Zhao/2013 [63]	Shanghai	June 25, 2012, to October 23, 2012	Retrospective cohort	Complete physical examination and pulse oximetry measurement and echocardiography	Severe (Major), moderate and mild cases	Median gestational age was 39 weeks (range 28-42 weeks)	Male (2761), female (2429)	1380 (5190)		Fair quality
Zuppa/2014 [64]	Italy	from 2009 to 2010	Prospective cohort	Clinical assessment, pulse oximetry	Not specified	NA	NA	4 (5750)		Fair quality

Table 1: *The characteristics table of included studies for meta-analysis and systematic review.*

**The studies included in the meta-analysis.*

Quality assessment

Based on NIH bias tool, twelve studies showed good quality while the rest showed a fair quality. Most studies lacked blinding and had absence of reference test. The explanation of assessment of the quality is explained in a more detailed way on supplementary table 1.

ID	1. Was the research question or objective in this paper clearly stated?	2. Was the study population clearly specified and defined?	3. Was the participation rate of eligible persons at least 50%?	4.Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	5. Was a sample size justification, power description, or variance and effect estimates provided?	6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	9.Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	10. Was the exposure(s) assessed more than once over time?	11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	12. Were the outcome assessors blinded to the exposure status of participants?	13. Was loss to follow-up after baseline 20% or less?	14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Result
Al-Mesned/2012 [25]*	1	1	1	1	0	1	1	1	1	0	1	0	1	0	Good quality
Begum/2016 [26]*	1	1	1	1	1	1	0	0	1	0	0	0	1	0	Fair quality
Dhanardhono/2012 [27]*	1	1	1	1	0	1	0	1	1	0	1	0	1	1	Good quality
Dulal/2016 [28]	1	1	1	1	0	1	0	1	1	0	1	0	1	1	Good quality
Egbe/2014 [29]*	1	1	1	0	0	1	0	1	1	0	0	0	1	1	Fair quality
Froehlich/2017 [30]	1	1	1	0	1	1	0	0	1	1	1	0	1	0	Fair quality
Goetz/2016 [31]	1	1	1	0	1	1	0	0	1	1	1	0	1	0	Fair quality
Gomez-Rodriguez/2015 [32]	1	1	1	0	0	1	0	1	1	0	0	0	1	1	Fair quality
Hamilçıkan/2017 [33]	1	1	1	1	0	1	1	1	1	0	1	0	1	0	Good quality
Han/2013 [34]	1	1	1	1	1	1	0	0	1	0	0	0	1	0	Fair quality
Huessain/2014 [35]*	1	1	1	0	1	1	1	1	1	0	1	0	1	1	Good quality
Itsukaichi/2017 [36]	1	1	1	0	0	1	0	1	1	0	0	0	1	1	Fair quality
Jørgensen/2015 [37]	1	1	1	1	1	1	0	0	1	0	0	0	1	0	Fair quality
Johnson/2014 [38]	1	1	1	0	1	1	1	1	1	1	1	0	1	1	Good quality
Korkmaz/2015 [39]*	1	1	1	0	1	1	0	0	1	1	1	0	1	0	Fair quality
Kumar/2015 [40]*	1	1	1	1	1	1	0	0	1	0	0	0	1	0	Fair quality
Kumar/2017 [41]*	1	1	1	1	0	1	1	1	1	0	1	0	1	0	Good quality
Lise/2014 [42]	1	1	1	1	1	1	0	0	1	0	0	0	1	0	Fair quality
Lyengar/2013 [43]	1	1	1	1	0	1	0	1	1	0	1	0	1	1	Good quality
Manja/2015 [44]	1	1	1	0	1	1	0	0	1	1	1	0	1	0	Fair quality
Mathur/2015 [45]	1	1	1	0	1	1	1	1	1	0	1	0	1	1	Good quality
Methlouthi/2016 [46]	1	1	1	0	0	0	0	0	1	0	1	0	1	0	Fair quality
Miller/2016 [47]	1	1	1	1	0	0	0	0	0	0	1	0	1	1	Fair quality
Mouledoux /2013 [48]	1	1	1	1	0	0	0	0	0	0	1	0	1	1	Fair quality
Mouledoux/2017 [49]	1	1	1	1	0	0	0	0	0	0	1	0	1	1	Fair quality
Narayen/2016 [50]	1	1	1	0	0	1	0	1	1	0	0	0	1	1	Fair quality
Nayak/2016 [51]*	1	1	1	1	0	1	0	1	1	0	1	0	1	1	Good quality
Otaigbe/2014 [52]*	1	1	1	1	0	0	0	0	0	0	1	0	1	1	Fair quality
Ozalkiya/2015 [53]	1	1	1	1	0	1	0	1	1	0	1	0	1	1	Good quality
Paranka/2018 [54]	1	1	1	0	0	1	0	1	1	0	0	0	1	1	Fair quality
Pasierb/2017 [55]	1	1	1	1	0	1	1	1	1	0	1	0	1	0	Good quality
Sahin/2018 [56]	1	1	1	0	0	0	0	0	1	0	1	0	1	0	Fair quality
Samuel/2013 [57]	1	1	1	1	0	0	0	0	0	0	1	0	1	1	Fair quality
Schena/2017 [58]	1	1	1	1	1	1	0	0	1	0	0	0	1	0	Fair quality
Taksande/2013 [59]	1	1	1	1	0	0	0	0	0	0	1	0	1	1	Fair quality
Torky/2016 [60]*	1	1	1	0	0	0	0	0	1	0	1	0	1	0	Fair quality
Tsao/2016 [61]	1	1	1	1	0	1	0	1	1	0	1	0	1	1	Good quality
Zhang/2017 [62]	1	1	1	1	0	0	0	0	0	0	1	0	1	1	Fair quality
Zhao/2013 [63]	1	1	1	0	0	1	0	1	1	0	0	0	1	1	Fair quality
Zuppa/2014 [64]	1	1	1	0	0	1	0	1	1	0	0	0	1	1	Fair quality

Supplementary Table 1: *Supplementary figure explaining the cause of the authors' judgement.*

Incidence rate meta-analysis

Total incidence rate of CHD

The total incidence rate for congenital heart disease was 0.03 with 95% CI of (0.02; 0.04); this is interpreted as 30 CHD patients per 1,000 population (Figure 2). Sensitivity analysis did not reveal any significant changes in results upon removal of each study in the meta-analysis (Figure 3). No publication bias was found (p = 0.8).

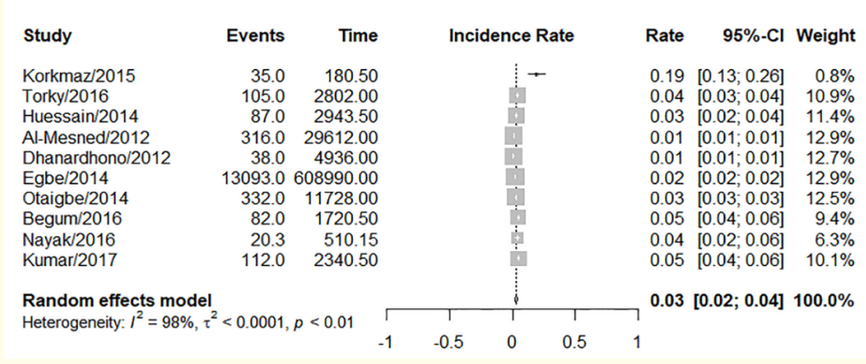

Figure 2: *Random effect meta-analysis of total CHD reported in the included studies. column time represent person time risk.*

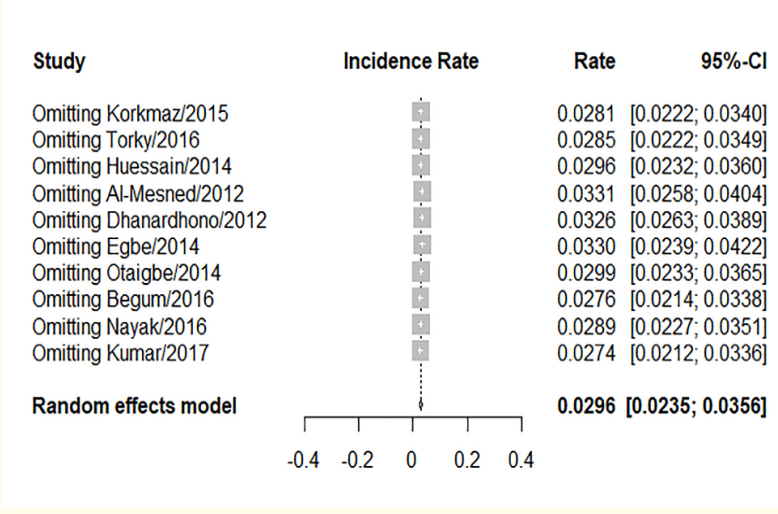

Figure 3: *The sensitivity analysis by removal of each study, the range is considered with in the reported range.*

Incidence of ventricular septal defect (VSD), atrial septal defect (ASD) and atrioventricular septal defect (AVSD)

Random effect model meta-analysis revealed that VSD had an incidence rate of 0.026 with 95% CI (0.021; 0.031) while ASD had a lower incidence, estimated to be 0.004 with 95% CI (0.0021; 0.0053) (Figure 4). No publication bias was present in the meta-analysis (p = 0.67). Surprisingly, the atrioventricular septal defect had the highest incidence of 0.10 with 95% CI (0.03; 0.33); there was significant heterogeneity [I^2 = 92%, P < 0.01).

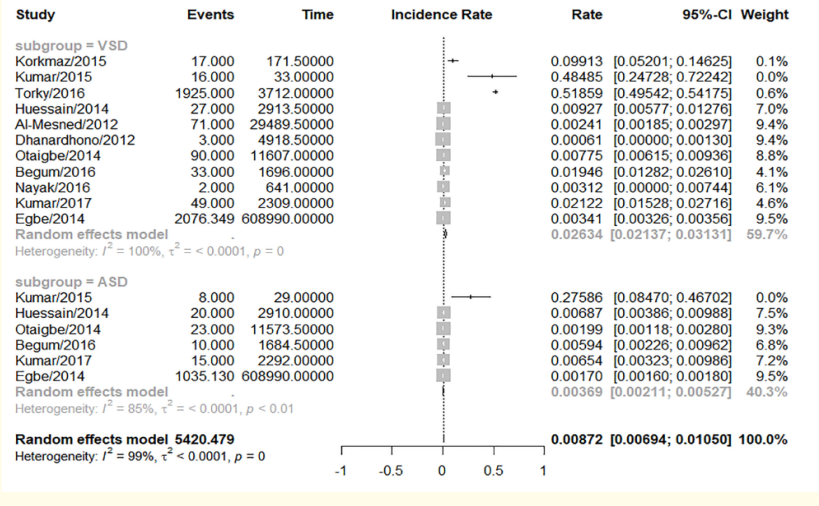

Figure 4: *Random effect meta-analysis of ASD and VSD reported in the included studies. Column time represent person time risk.*

Incidence of aortic and pulmonary vessels congenital anomalies

Pulmonary stenosis, aortic coarctation, and aortic stenosis were reported in about six studies. Aortic coarctation was the most common anomaly [IR = 0.0014, 95% CI (0.0002:0.0025)] followed by Pulmonary stenosis [IR = 0.0007, 95% CI (0.0002:0.0011)] followed by Aortic stenosis [IR = 0.0004, 95% CI (0.0000:0.0009)] (Figure 5). The overall incidence for aortopulmonary anomalies was 8 cases per 10,000 population.

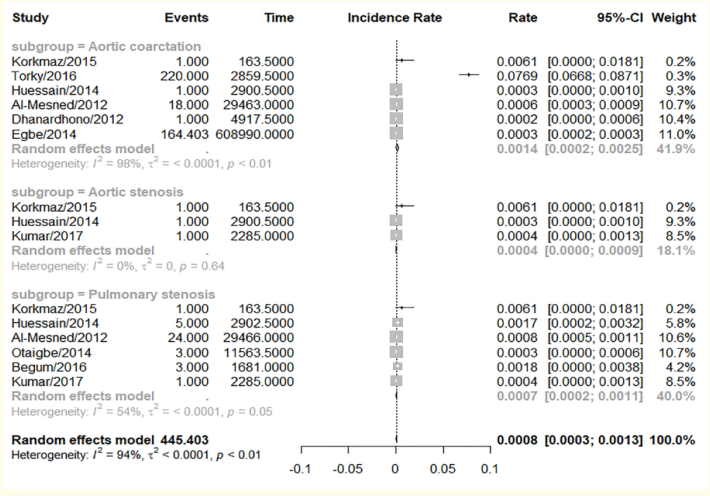

Figure 5: *Random effect meta-analysis of Aortopulmonary anomalies reported in the included studies. Column time represent person time risk.*

Sensitivity analysis showed different significant results, but it is considered within the same range.

Incidence of PDA, truncus arteriosus (TA) and ebstein anomaly

The pooled incidence rate for PDA was the most common with IR = 0.003 followed by Ebstein anomaly [IR = 0.00052. 95% CI (0.00; 0.0014)] followed by TA [IR = 0.0001. 95% CI (0.00; 0.00028)] (Figure 6). Sensitivity analysis did not reveal any significant effect on the overall model.

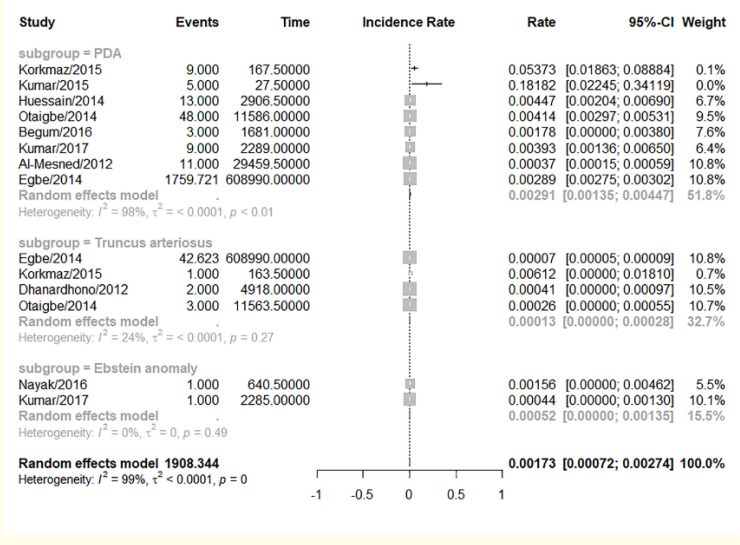

Figure 6: *Random effect meta-analysis of PDA, TA, Ebstein anomaly reported in the included studies. Column time represent person time risk.*

Tricuspid atresia (TA), DOUBLE OUTLET RIGHT VENTRICLE (DORV) and single ventricle incidence rate

The incidence rate of these anomalies is considered low in comparison to others. The highest incidence rate was for the DORV, which was estimated to be approximately 2 cases out of 1,000 followed by TA which had an incidence rate of 2 of a 10,000 population, finally followed by single ventricle (1 case in 10,000) (Figure 7).

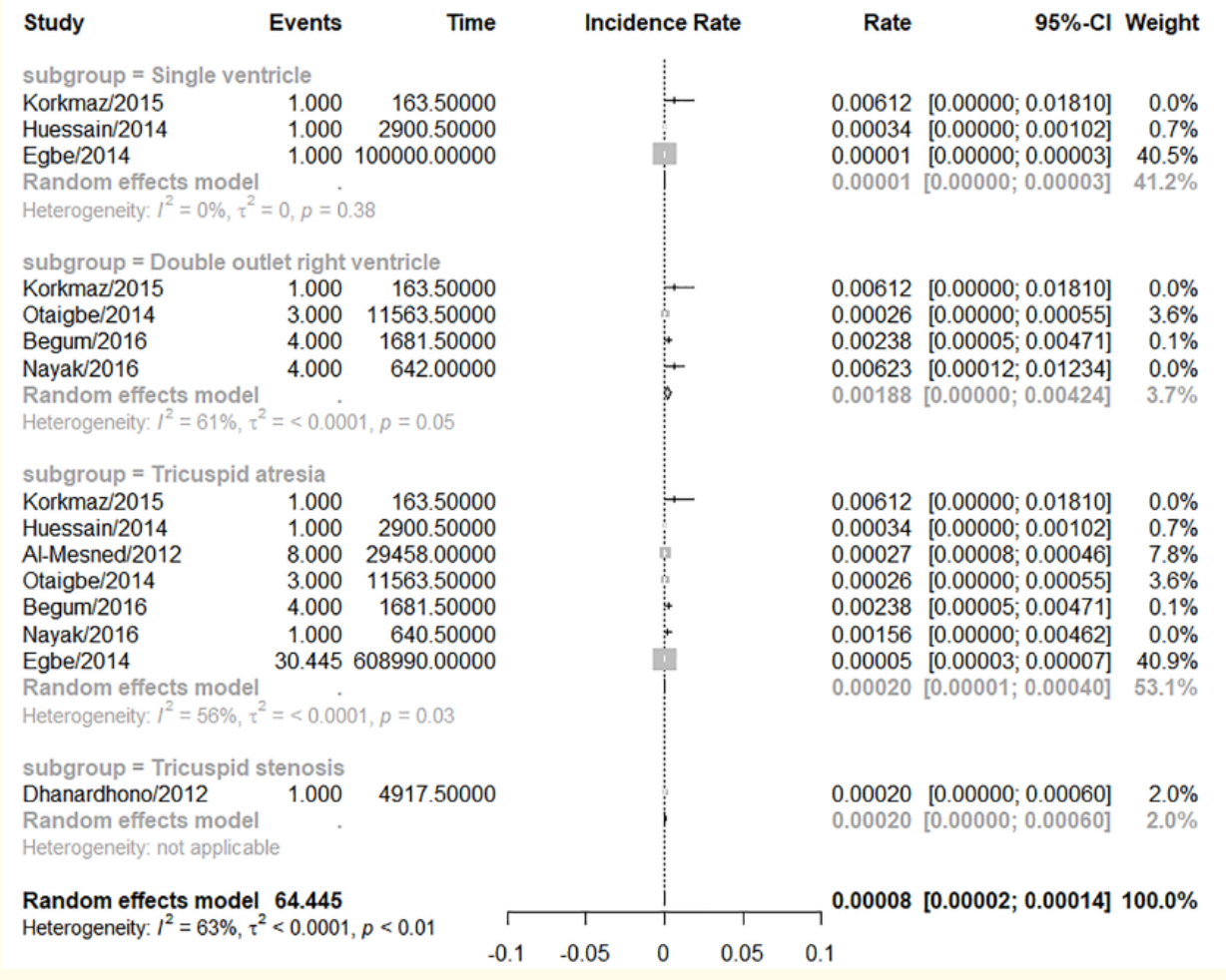

Figure 7: *Random effect meta-analysis of TS, TA, truncus arteriosus and single ventricle reported in the included studies. Column time represent person time risk.*

Incidence rate of tetralogy of fallot (TOF) and transposition of great arteries (TGA)

The pooled incidence rate of TGA was 0.005 with 95% CI (0.003; 0.007) followed by TOF [IR = 0.004, 95%CI (0.002; 0.005)] (Figure 8). Sensitivity analysis did not reveal any significant difference in the pooled incidence. Publication bias was not found in each subgroup (p = 0.87). The total incidence rate of these cyanotic heart disease was 3 in 1,000 population.

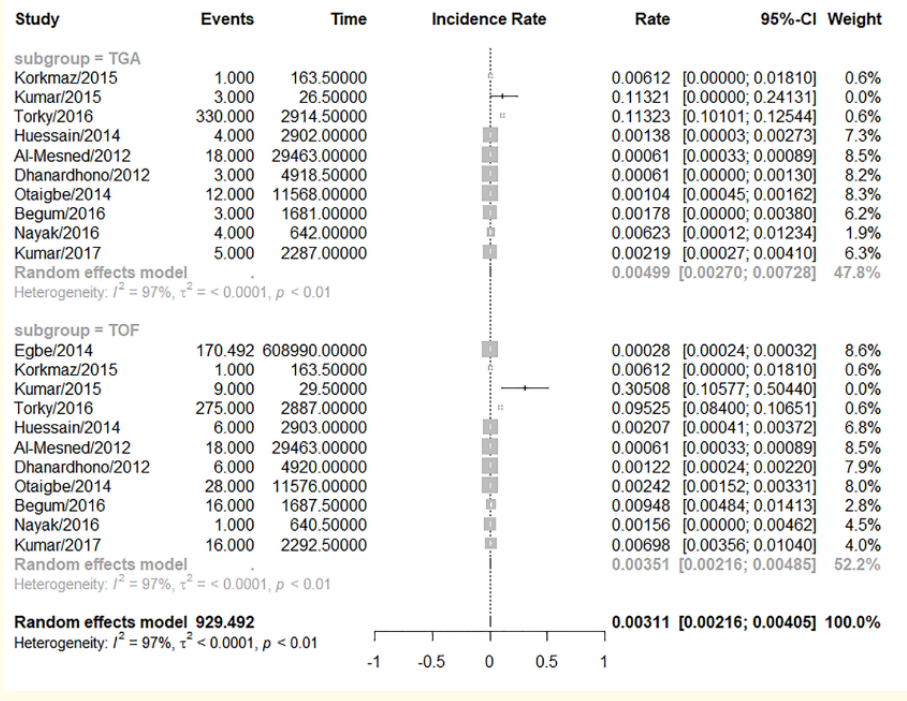

Figure 8: *Random effect meta-analysis of TOF and TGA reported in the included studies. Column time represent person time risk.*

Based on our results, the VSD had the highest IR among other CHD followed by TGA, ASD, TOF and PDA, in that order. The single ventricle had the lowest incidence (Figure 9).

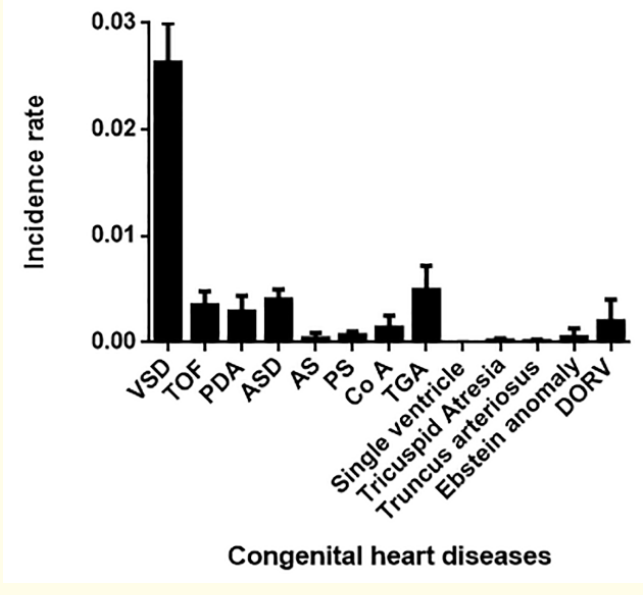

Figure 9: *The ranking of the CHD based on incidence rate.*

Source of heterogeneity in the meta-analysis

A random effect model was used due to high heterogeneity in the meta-analysis. Baujat plot was used to determine the cause of heterogeneity (Figure 10).

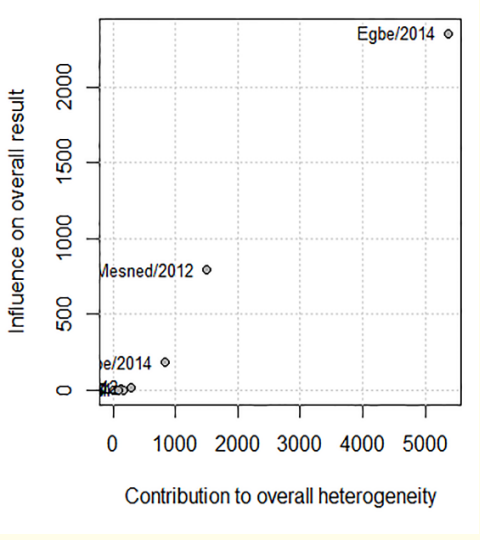

Figure 10: *Baujat plot to detect the cause of heterogeneity in the included studies and its influence on the results.*

Review of literature and the importance of neonatal screening in the last 10 years

In this systematic review, we included 29 studies that assessed neonatal and fetal screening in the last 10 years. There were three main methods for screening: pulse oximetry, echocardiography and foetal ultrasound. Most studies assessed the screening for critical congenital heart disease. Other methods used for screening or accompanying these methods are presented in figure 11.

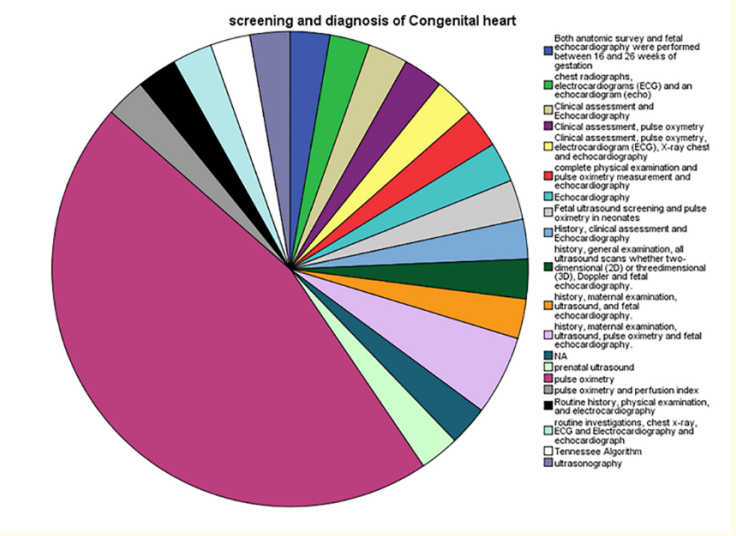

Figure 11: *The methods used for fetal and neonatal screening for CHD in the last decade.*

Echocardiography

Two studies in the review evaluated the efficacy of echocardiography in the screening, other studies included it as a confirmatory test. Nayak., *et al.* performed the echo in prenatal period and successfully diagnosed CHD cases, recommending it should be included for prenatal screening with other routine investigations [65]. China also used this method for neonatal screening, proving a higher accuracy than other methodologies used [66].

Pulse oximetry for screening of critical congenital heart disease (CCHD)

Rodriguez., *et al.* had applied pulse oximetry for screening (POS) on the full-term new-born, finding it has 100% sensitivity and a negative predictive value [67]. For this reason, they suggested that combined screening of POS with clinical assessment e.g. rapid respiratory rate, will enhance the screening of CCHD [67]. On the other hand, Taksande assessed the accuracy of POS four hours after delivery; also finding they could detect CCHD in clinically normal new-borns [68]. This result revealed that cut off values of PO_2 below 90% had 100% sensitivity, 99.95% specificity, 87.50% positive predictive value and 100% negative predictive value. This was also supported by other studies that found the high sensitivity of pulse oximetry [17,69-71]. Finally, Zubba., *et al.* found that combining the POS with clinical examination would increase the diagnostic accuracy of POS [72].

Hamilçıkan., *et al.* investigated the timing of application of pulse oximetry for neonatal screening. They performed POS less than and after 24 hours [73], not finding any critical CHD during this period and the POS having identified nine false positive out of 4109 live births. The POS also identified other cardiac pathologies but not critical cases [73].

Other studies assessed and compared screening of CCHD in home delivery with hospital delivery using pulse oximetry [71,73,74]. They found that the application of POS at home or after early discharge from hospital had the same sensitivity and screening accuracy as hospital delivered babies. This information could be used to support universal postnatal screening at home deliveries.

Neonatal screening in the neonatal ICU was also suggested by Manga., *et al.* investigating the accuracy and benefit of POS for CCHD diagnosis at late preterm and in neonates younger than 35%. They found out that clinical assessment in neonatal ICU was not enough for excluding CCHD and that it would lead to missed cases while applying pulse oximetry had successfully identified all cases. Yet, POS had high false positive results compared to clinical assessment of asymptomatic live births [75]. This was also supported by Iyengar., *et al.* who found that POS should be added to the protocol and it would help in the diagnosis of CCHD [76].

In contradiction, Goetz., *et al.* obtained that POS was not feasible in neonatal ICU due to supplemental oxygen. In addition to this, CCHD was usually diagnosed by physicians before the POS could be applied. Subsequently, they advised that it can be used in suspected cases to develop symptoms of CCHD [77].

To assess the effects of high altitude on the reading of pulse oximetry and consequently, its sensitivity for diagnosis of CCHD, Han., *et al.* applied the POS screening protocol at a high of 806m finding that POS had a less false positive rate, also they advised there is no need for modification of protocol at high altitudes [78]. This was contradicted by Paranka., *et al.* who found that high altitude measures were characterized by high false positive rates which complicated the screening. They came to the conclusion of comparing results between three heights: at 2,000 feet, 4,700 to 6,000 and above 6,000 feet [79], not being able to enrol at more than 8,163 feet due to high positive rate. This was also supported by Samuel., *et al*. who recommended a change in the guidelines for screening at high altitudes, in order to perform more accurate diagnosis [80]. One of the reasons for this statement was the fact they compared results between sea level and mild altitudes, finding significant lower PO_2 at mild altitude than at sea level [80].

Despite all the recommendations for usage of pulse oximetry in CCHD screening programs, Mouledoux., *et al.* found that there are common lesions currently missed by POS e.g. coarctation of the Aorta. In this case, they proposed that undetectable CCHD should be added in the protocol and that investigators should be careful about it [81]. This finding was also supported by Ozalkiya., *et al.* who showed that despite the accuracy for diagnosis of CCHD by POS, seventy-five percent of false negative diagnosis with pulse oximetry had coarctation of the aorta [82]. This was solved by Schena., *et al.* which reported that perfusion index could detect missed cases including coarctation

of aorta [83]. They also supported the combination of the usage of perfusion index and pulse oximetry for screening of these cases [83]. Finally, Johnson., *et al.* suggested that high prenatal diagnosis of CHD would decrease the requirements for POS [84].

There are also other cases of studies that developed its own protocol for screening using pulse oximetry [61,85]. As one example, Mouledoux., *et al.* assessed the Tennessee algorithm that do not use two readings of POS for diagnosis of CCHD.

They found that depending on only one reading at lower extremities with a cut off value of 97% or higher would have passed the screening, decreasing the need for over 150,000 pulse oximetry determinations in Tennessee with had no influence over the accuracy of the results (85). In Taiwan, a procedure proposed by Tsao., *et al.* applied a six months protocol with cut off level of 95% in the first 24 to 36 hours of delivery, finding that POS had a high sensitivity and accuracy [61].

Ultrasound for diagnosis of fetal CHD

Fetal ultrasound is usually applied in the second and third trimester for early detection of CHD. Jorgenson., *et al.* found that the use of ultrasound nuchal translucency had detected 15% of major CHD, with more than 50% being detected at weeks 18 - 21 [86]. Itsukaichi., *et al.* suggested that a combination of four-chamber and three-vessel views at 18 - 21 GW by obstetricians during routine second semester screening will be useful for detecting severe structural abnormalities, but not valvular abnormalities. This can be overcome by usage of colour doppler [87].

Discussion

This study was set out with the aim to understand the true incidence of congenital heart disease in the last ten years and how the neonatal screening aided epidemiologists and doctors to detect early asymptomatic CHD.

Our results investigated the incidence rate in the last 10 years with studies that started the recruitment of patients since 2008. They suggested that the total incidence of CHD in the last ten years was 0.03 with 95% CI of (0.02; 0.04) which can be interpreted as two to four cases of CHD per 100 neonates. Based on our analysis, VSD had the highest IR (0.026) followed by transposition of great vessels anomalies (IR = 0.005, 95% CI (0.003;0.007)) and by ASD and PDA, both with an incidence rate of 4 cases per 1,000 neonates. The one with the lowest rate was single ventricle anomaly which reflected an incidence rate of 1 in 10,000 neonates.

The results of this study compared to previous findings in the incidence of this disease, reveal that our outcomes are higher than the incidence rate reported in the past findings [11,81,88-90]. The reported total incidence in these studies ranged from eight to fourteen cases per 1,000 neonates [2,89,90]. Hoffman., *et al.* who did their study at 1978 found that the incidence of CHD was 9 per 1,000 [50] while earlier study done by Mitchell., *et al.* reported an incidence rate of 8.14 per 1,000 total births [1].

In 1995, a study done by Hoffman revealed the increase of incidence in western countries from 5 to 12 per 1,000 postnatal cases [89]. He argued that these incidence rates were before the training of paediatrician, cardiologists, and advances of neonatal screening together with early detection took place [89]. In addition, the reported incidence did not include the African or Asian countries. Furthermore, Hoffman had investigated the prenatal incidence of CHD in a separated study and found that 1 per 100 had a prenatal diagnosed CHD [90].

On another line, a prevalence study compared different incidence rates among different periods. It was found that the incidence of CHD experienced a steep increase since 1971 to 1995 reaching 9.1 per 1,000. After this, the incidence rate did not change since then till 2009, with no meta-analysis or incidence rate estimations over the last 10 years being performed [8].

Our study pooled incidence rates since 2008, with an explanation for our high rate being possibly because we included both foetal and neonates in our meta-analysis. This will increase the incidence, as it is reported in another study in which 57% to 83% of CHD were diagnosed prenatal [91]. In addition, unlike the previous studies, half of the included studies were from low income, developing countries (Figure 12), also one of the studies included was from Nigeria after the application of POS system [92]. The high-income countries including both European countries and USA were few in the meta-analysis (Table 1). This is explained as these countries had surge of pulse

oximetry and other screening measures to identify incidence before 2008, with the focus of the new papers being mainly on either new methods for diagnosis, screening, or developing new protocols for screening which we could not include in our meta-analysis [81,85].

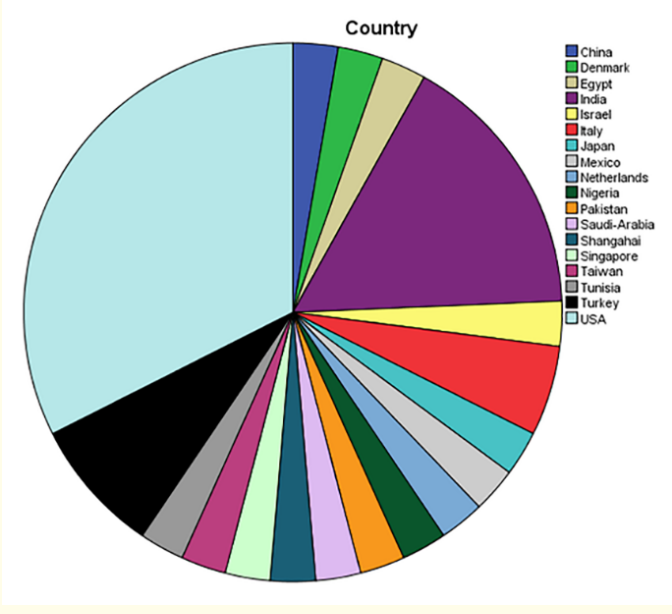

Figure 12: *The countries investigating the neonatal screening for CHD in the last decade.*

Many variable incidents have been reported in previous studies around the globe. For instance. For instance, Linde., *et al.* also found that its highest of CHD in Asian countries, 9 per 1,000; this may be attributed to the genetic basis of CHD [7,93]. Additionally, it was found that CHD had a high incidence in new-borns of consanguineous parents, being this is a tradition that is present in our included studies from Saudi Arabia, India, Pakistan, Egypt, and Tunisia [88,94]. We also believe that the high incidence reported in our study may be due to advances of the techniques used for screening and diagnosis of CHD [11,94-96].

Another explanation for the high reported incidence is the high survival rate of the CHD patients whose offspring would have a higher risk for CHD, thus increasing the incidence of foetal and neonatal diagnosis [97]. Furthermore, the increased risk of CHD in the recent years can be also attributed to environmental and parental factors. A review study found a significant effect of urbanization behaviours with increased vitamin A use, marijuana use, exposure to organic solvents and parental exposures to different environmental factors [98]. For all the mentioned reasons, we believe that our high incidence represents the approximated actual incidence over the last ten years.

In our study, we found that VSD had the highest incidence among other CHD types, being this fact also supported by other studies [2,11]. However, ASD was not the next common disease in our results; as other studies did show. In the case of this study, it was TGA which appeared in second place. Also, the high prevalence of TGA was found in European CHD, but not in Asian countries [8,11]. It was also reported that pulmonary outflow obstructions (PS and TOF) and left ventricular outflow tract obstructions were more common in Asian countries [8,11]. This was contradicted by a Chinese prevalence study which concluded there was also high prevalence of left sided CHD [10,99]. Nevertheless, we could not find an explanation for the cause of high TGA in our analysis.

Most included studies had good to fair quality, which is mainly attributed to the lack of blinding, sampling bias and no analysis of maternal study design or foetal factors that would affect the analysis. There was also evidence of statistical heterogeneity which was mainly

due to Egbe., *et al.* study [29]. This study done in the U.S. and with retrospective characteristics, was the only U.S. study in the analysis; and it may be attributed to it some high detection rates of CHD.

For neonatal screening, we reviewed literature in the last ten years, finding clinical examination, pulse oximetry, echocardiogram machine and ultrasound used either in combination or each one alone. The importance of screening in this case is many times more attributed to early detection and treatment of CHD than the screening method. It is also important to note that the choice of neonatal screening is limited due to the cost or the lack of knowledge about the screening protocol [100].

Furthermore, pulse oximetry is very important due to the low false positive results and its low cost of implementation [101,102]. A systematic review of 35,960 new-borns to understand the accuracy of pulse oximetry for screening of asymptomatic patients. The authors suggested that it has only 0.2% false positive rates with sensitivity of 63%. The results were limited due to absence of blinding, and absence of reference standard [101]. Another limitation of pulse oximetry was its efficacy at high altitudes [39,40]. A review supported the results of two studies and found out a high false positive rate of pulse oximetry at high altitudes, which does not make it very effective for screening purposes [102,103]. In the same line some studies shown that the pulse oximetry could not be used alone as a screening tool, as other studies shown concluding it was not sensitive enough and it should be combined with clinical examination [102].

Another crucial drawback to pulse oximetry was left-to-right shunts, aortic coarctation or other CHD not affecting oxygenation. This urged researchers to develop protocols, new techniques or add perfusion index to enhance its sensitivity [43,102].

A previous systematic review done for assessing the benefit of pulse oximetry with inclusion of 229, 421 new-born babies [103] showed high specificity (99.9%) and moderate sensitivity (76.5%) of pulse oximetry in detecting critical congenital heart defects [105]. In a Chinese prospective multicentre study of 122,738 new-born babies, the addition of pulse oximetry to screening process improved sensitivity for detection of critical congenital heart disease from 77·4% to 93·2% [104].

Ultrasonography and echocardiography are considered the gold standard for diagnosis but not for screening due to the high cost [14,100]. Second and third trimester screening using ultrasound was found to be highly sensitive, only requiring well trained obstetricians who can observe the structural abnormality [105,106]. Despite the current routine among doctors to only do echocardiography for high risk individuals, a study compared between echocardiography results for both high risk and low risk pregnancy revealed no significant differences of CHD incidence between both groups, recommending routine echocardiography for all pregnant woman [103].

Neonatal screening was found to have a significant effect on the reported incidence of CHD. Pulse oximetry was found to have an important role in the incidence of the CHD especially in the countries with no formal screening program [31,107]. Other studies could detect missed cases by pulse oximetry before implementation of the screening protocol [41]. This means that more application and involvement of pulse oximetry in neonatal screening program would detect more cases thus increase the incidence of CHD. In addition, studies supported the involvement of ultrasound and echo for routine neonatal screening.

Still, the studies that assesses the tools used for neonatal screening lacked the reference test, blinding, control of human factor and most of them were of fair quality.

Limitation

We could not test the influence of maternal and fetal confounders on the incidence rate of CHD. The small number of studies conducted after the 2008 may also limit our results. The fair quality of most studies used in the review, mainly because of the absence of blinding and reference testing are needed to be improved in future studies. Another emerging useful technique is the diagnostic cardiac catheterization which showed a positive contribution for determination of the management plans for more than 84% of cases [108]. Adding such a technique to our study may give some extra insights; however, there's no enough studies in the same topic.

Conclusion

In the last ten years, the incidence of fetal and neonatal CHD had increase to be 30 cases per 1,000. VSD and TGA were the most common while single ventricle was the least diagnosed CHD. Neonatal screening is a crucial step for the detection of CHD and should be applied

formally. Additionally, the screening methods showed a relatively variability in detecting different CHD; thus, affecting the incidence itself. Accordingly, the development of screening protocol that suits each country economic and environmental factor should be encouraged.

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Conflict of Interest

None.

Ethical Approval

This study was approved to be conducted by the Saudi Commission of Health Specialities.

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