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Screening and Etiology of Congenital Heart Disease in Developing Countries : A Comprehensive Systematic Review

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ABSTRACT

Introduction: The increasing number of newborns with congenital heart disease (CHD) shows that the global burden of CHD is still significant. This indicates that screening and prevention have not been carried out optimally. This study aims to determine the differences of screening and etiology of congenital heart disease (CHD) between developed and developing countries. **Methods:** A systematic review adhering to PRISMA 2020 guidelines was conducted. Studies from 2015 to 2025 focusing on the screening and etiology of CHD in developing and developed countries were included. **Results:** Twenty-three relevant studies were included. Combination of pulse oximetry (PO) and auscultation, or PO alone were the most common postnatal screening tools in developed and developing countries. For prenatal screening, ultrasound was commonly used. Artificial intelligence and genetic testing were only used in developed countries. The etiology such as genetics, maternal lifestyle or conditions were discussed. **Conclusion:** The urgent need for affordable early detection of congenital heart disease (CHD) in developing countries cannot be overstated, as it holds the potential to significantly reduce the global burden of this condition. By implementing comprehensive prenatal and postnatal screening programs, we can identify at-risk infants early, enabling timely interventions and improved health outcomes. Addressing this critical issue not only enhances individual lives but also strengthens healthcare systems and fosters healthier communities.

Keywords: prenatal screening, postnatal screening, etiology, congenital heart disease

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INTRODUCTION

Congenital heart disease (CHD) represents the predominant category of significant congenital anomalies.[1] Despite minor discrepancies among various population-based research, the estimated incidence ranges from 4 to 13 per 1,000 live births, exhibiting comparable prevalence globally, and occurs in 10% of aborted fetuses.[1–3] CHD is also the primary cause of death resulting from birth abnormalities.[1,2] Prior studies have projected 250,000 annual fatalities due to congenital heart disease worldwide, 1.35 million annual births of neonates with congenital heart disease internationally, and 2.4 million individuals residing with congenital heart disease in the United States alone.[4] Approximately 20–30% of these cardiac anomalies are classified as serious, characterized by their potential life-threatening nature and the necessity for surgical intervention during the first year of life.[5]

The delayed diagnosis of CHD is regrettably prevalent, with as many as 25% of affected infants being overlooked at birth when detection relies solely on clinical symptoms or indicators of cardiac disease, even in environments with standard prenatal ultrasounds.[3,6] The significant global burden indicates that screening for CHD remains inadequate, particularly in low-risk populations, where it does not exceed 35–40%. Moreover, prevention strategies have not been adequately executed. The Sustainable Development Goals (SDGs) seek to decrease neonatal mortality to fewer than 12 deaths per 1,000 live births and child mortality to fewer than 25 deaths per 1,000 live births. Therefore, the optimal screening and prevention are needed. The screening of CHD is crucial for prenatal counseling, establishing suitable prenatal care, and considering potential therapeutic approaches.[7] It facilitates the scheduling of delivery at a tertiary-care facility, ensuring best neonatal and perisurgical management. Additionally, parents may

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contemplate termination of pregnancy (TOP) in critical situations.[3] This review will assess the differences of screening and etiology of congenital heart disease in developing and developed countries.

METHODS

Protocol

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, consistency, and reproducibility.

Criteria for Eligibility

This review will include studies published between 2015 and 2025 that examine the screening and etiologies of CHD in developing and developed countries. Eligible studies must be peer-reviewed and involve clinical or experimental assessments of screening and etiology of CHD in developing and developed countries.

Inclusion Criteria

- **Participants:** Pregnant women or neonates
- **Intervention:** Prenatal or postnatal screening for congenital heart disease, etiology of CHD
- **Outcomes:** Detection of CHD
- **Study Design:** Prospective or retrospective cohort studies, cross-sectional studies, case-control studies.
- **Language:** Studies published in English.

Exclusion Criteria

- Review articles, meta-analyses, conference abstracts, or expert opinions.
- Studies not directly assessing the screening and etiology of CHD in developing and developed countries.
- Animal studies or in vitro experiments.

Search Strategy

A systematic search will be conducted using electronic databases, including PubMed, Science Direct, and Cochrane Library. Search terms will focus screening, etiology, and CHD: (("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass

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screening"[All Fields] OR "early detection of cancer"[MeSH Terms] OR ("early"[All Fields] AND "detection"[All Fields] AND "cancer"[All Fields]) OR "early detection of cancer"[All Fields] OR "screen"[All Fields] OR "screenings"[All Fields] OR "screened"[All Fields] OR "screens"[All Fields] OR ("aetiologie"[All Fields] OR "aetiologies"[All Fields] OR "aetiology"[All Fields] OR "etiologies"[All Fields] OR "etiology"[MeSH Subheading] OR "etiology"[All Fields] OR "causality"[MeSH Terms] OR "causality"[All Fields])) AND ("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("congenital"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]) OR "congenital heart disease"[All Fields])) AND ((y_10[Filter]) AND (english[Filter])).

Data Retrieval

After reading the abstract and the title of each study, the writers examined to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilize as sources for their article and selected those studies. After looking at several different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't be seen anywhere else.

Quality Assessment and Data Synthesis

Two independent reviewers will evaluate the methodological quality of included studies using the GRADE framework, focusing on study design, sample size, and reliability of outcome measures. Discrepancies will be resolved through discussion or consultation with a third reviewer. A qualitative synthesis will summarize the findings, comparing the screening and etiology. If data homogeneity permits, a meta-analysis will be conducted to estimate pooled effect sizes for key outcomes.

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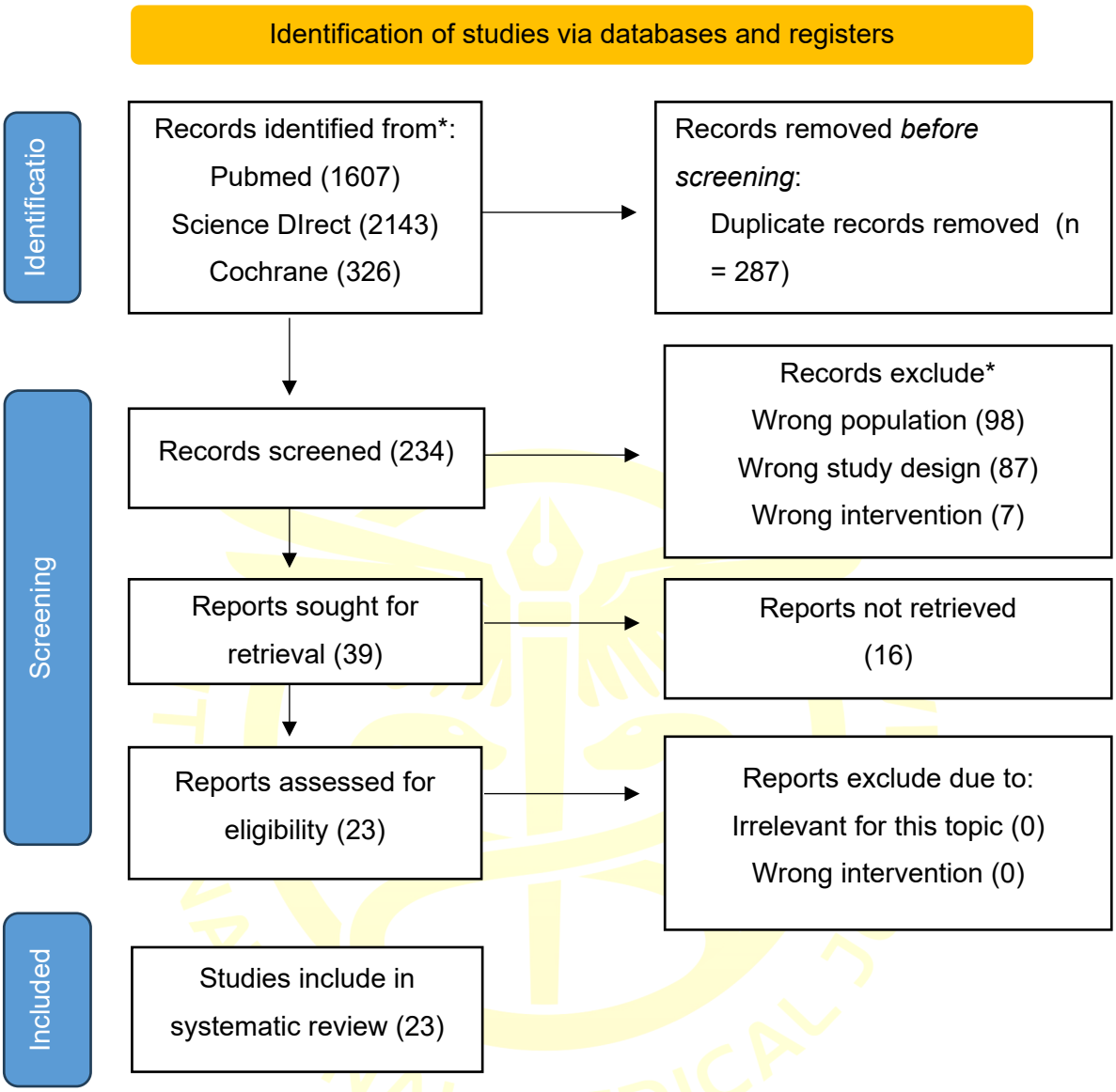


Figure 1. PRISMA Flowchart

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RESULT

Our research team first gathered publications from reputable sources such as Pubmed, Science Direct, and Cochrane. After a thorough three-level screening procedure, only eight papers were determined to be directly relevant to our ongoing systematic evaluation. Following that, these sections were picked for additional research and a close reading of the entire manuscript. The material that was evaluated for this analysis is compiled in Table 2 for ease of viewing.

Table 1. The literature included in this study

Author	Origin	Method	Sample Size	Screening Method	Result
Atitlan-Gil, 2020[8]	Mexico	Observational	1,748 newborns (NBs)	Pulse oximetry (PO) and a knowledge management model (KMM)	During a six-month period, 1,748 newborns were screened at two hospitals. Twenty-nine NBs tested positive, with 14 cases (62%) exhibiting simple CHD and 3 instances (13.8%) presenting with CCHD. Furthermore, one clinically identified CCHD did not necessitate screening.
Cody, 2024[9]	Dublin	Retrospective study	49,950 pregnant women	Ultrasound, genetic testing	In a concurrent cohort of 49,950 pregnancies across four years, a prenatal diagnosis of CCHD was established in 96 instances, resulting in an incidence of 1.9 per 1,000 infants. In the prenatally diagnosed cohort, 37% of cases were complicated by extracardiac anatomical anomalies, a genetic diagnosis, or both. Eight more infants were identified with CCHD during the neonatal period, resulting in a prenatal detection rate of 92% (96/104, 95% CI = 84%-96%).
Choudhury, 2022[10]	USA	NA	NA	NA	Approximately 40% of CHD cases can be attributed to identifiable genetic risk factors. Recent literature reviews estimate that chromosomal aneuploidies account for about 13% of CHD cases, chromosomal copy number variations (CNVs) for approximately 25% of syndromic and 10% of non-syndromic cases, and single nucleotide variants (SNVs) for 12% of CHD cases, encompassing both syndromic and non-syndromic forms.

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Dinarti, 2020[11]	Indonesian	Prospective study	6,116 school students	Cardiac auscultation and a 12-lead ECG	Out of 6,116 students, 329 (5.38%) were identified with anomalies. Among them, 278 children (84.49%) had an abnormal ECG, 45 students (13.68%) presented with cardiac murmurs, and 6 students (1.82%) displayed both abnormalities. A subsequent test was conducted for 260 school pupils, revealing that 18 students (6.9%) exhibited heart abnormalities, including 7 (2.7%) verified cases of septal anomalies and 11 (4.2%) with valve abnormalities. The total prevalence was 0.29% (18 of 6116).
Gireada, 2022[12]	Romania	Retrospective study	1,596 pregnant women	Ultrasound	The scans were conducted via transabdominal and transvaginal approaches. A total of 46 fetuses with CHD were detected, resulting in an overall incidence of 2.86% and a significant CHD incidence of 0.87%. Grayscale 4C identified 47.8% of all congenital heart defects (CHD), increasing to 71.7% with the inclusion of grayscale 3VT, leaving no significant CHD undiscovered when both grayscale 4C and 3VT are utilized.
Hamilcikan, 2017[13]	Turkey	Prospective study	4,518 NBs	PO and echocardiography	In a cohort of 4109 newborns checked 24 hours post-birth, the mean pre- and postductal oxygen saturations (SpO2) were 96.5 ± 1.99 and 97.7 ± 1.98, respectively. In contrast, 127 infants screened within 24 hours exhibited mean preductal and postductal SpO2 values of 91.33 ± 2.64 and 94.0 ± 4.44, respectively. No congenital critical heart disease was identified during the study period. Pulse oximetry screening yielded false positives for congenital critical heart disease (CCHD) in 9 out of 4,109 babies (0.02%). Echocardiography identified noncritical abnormalities in six neonates, including two cases of atrioventricular septal defect (AVSD), three cases of ventricular septal defect (VSD), and one case of patent ductus arteriosus (PDA).
Helle, 2020[14]	USA	NA	NA	NA	Despite the evident association between maternal obesity and glucose metabolism with the risk of CHD, the mechanisms by which this risk is conveyed from mother to fetus, as well as the causative variables that disrupt fetal cardiac development, remain little elucidated. Comprehending the causation variables and transmission mechanisms will establish the essential framework for tackling two significant real-world outcomes: the primary prevention of heart disease (CHD) and the enhancement of prenatal screening for CHD.

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Hu, 2017[15]	China	Prospective study	167,190 NBs	Auscultation and PO	CHD screening was conducted in all 15 hospitals, with a screening percentage between 94.0% and 99.8%. Out of 167,190 asymptomatic newborns, 203 were diagnosed with significant CHD (44 critical and 159 criticalcases). The sensitivity of POX combined with cardiac auscultation was 95.5% (95% confidence interval 84.9%-98.7% for critical CHD and 92.1% (95% confidence interval 87.7%-95.1%) for criticalCHD. The false-positive rate for detecting CCHD was 1.2%, whereas for severe CHD it was 1.1%.
Huang, 2022[16]	China	Retrospective study	44,147 neonates	Auscultation and PO	At the examined hospital, there were 44,147 live births, among which 498 suspected cases of CHD were identified: 27 through pulse oximetry screening and 471 via cardiac auscultation. The diagnosis was further confirmed in 458 neonates through echocardiogram. This outcome presented an overall diagnostic rate of 92.0%. Cardiac auscultation identified the majority of CHD patients, totaling 438 (95.6%), whereas pulse oximetry recognized only 20 (4.4%) cases. Notably, no cases of CHD were identified during either auscultation examination or pulse oximetry screening. Auscultation identified the majority of prevalent forms of CHD, but pulse oximetry demonstrated superior efficacy in detecting rare and important instances. POX screening alone had a low accuracy with a positive predictive value (PPV) of 74.07%. Auscultation demonstrated effective performance regarding positive predictive value (PPV) and negative predictive value (NPV) at 92.99% and 99.95%, respectively; however, the incorporation of pulse oximetry (POX) enhanced the overall screening efficacy, achieving a 100% NPV. We further corroborate the finding with data collected six months post-study period.
Jain, 2022[17]	India	Prospective study	5,874 neonates	PO	In a study of 5,874 neonates, researchers identified 164 infants with substantial hypoxemia via pulse oximetry, and 44 cases of CHD were diagnosed through echocardiography within the initial three days of life, yielding a positive predictive value (PPV) of 12.2%. Pulse oximetry screening identified thirty-four infants with other congenital heart problems. Additionally, 108 instances of hypoxemia attributed to alternative sources were identified and observed.

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Janicki, 2019[18]	New England	Retrospective study	2,395 pregnant women	Ultrasound, checklist-based approach	The implementation of a checklist enhanced the completion rate of cardiac examinations by 8.9%. Utilizing the checklist, 1,083 out of 1,202 exams (90.1%) were completed, in contrast to 987 out of 1,193 (82.7%) prior to the checklist, p<0.001. No significant difference was observed in the instances categorized as abnormal and referred for echocardiography: 25 (2.1%) with the checklist and 16 (1.3%) prior to the checklist, p=0.16. No additional cases of congenital cardiac disease were identified: 12 (1.0%) with checklist screening and 5 (0.4%) prior to checklist implementation, p=0.14. Critical congenital cardiac disease was not overlooked in any group.
Janjua, 2022[19]	India	Prospective study	1,082 neonates	PO, clinical examination	The prevalence of critical CHD in asymptomatic neonates was determined to be 0.5% (5/1000 live births). Echocardiography verified five instances of criticalCHD. Pulse oximetry alone could identify 80% of CHD cases, and clinical examination alone could identify 60%, however the combination of both approaches achieved a 100% detection rate. In conclusion, pulse oximetry is an uncomplicated, economical, and dependable instrument for diagnosing critical CHD.
Li, 2019[20]	China	Prospective study	1,337 neonates	Echocardiography, follow up	The prevalence of CHD in asymptomatic neonates was 27.8%, comprising secundum atrial septal defect (ASD) [175 (62.7%)], patent ductus arteriosus (PDA) [61 (21.9%)], ventricular septal defect (VSD) [8 (2.9%)], and multiple abnormalities [35 (12.6%)]. Additionally, 19.4% of NICU patients exhibited a comparable spectrum, excluding two individuals with criticalCHD who succumbed prior to discharge. At 12 to 18 months of follow-up, 30% of congenital heart defects (CHD) persisted in an open state. Thirteen individuals manifested mild to severe pulmonary arterial hypertension (PAH), with two succumbing to heart failure.
Ma, 2023[21]	China	Prospective study	801,831 NBs	Auscultation and PO	A total of 801,831 (99.48%) neonates underwent screening for CHD, 16,489 (2.06%) screened positive, and 3,541 (21.47%) of those screened positive were diagnosed with CHD. Seven hundred fifty-two patients with coronary heart disease underwent surgical or interventional treatment, with a success rate of 94.81%. Between 2015 and 2021, the infant mortality rate (IMR) experienced an approximate halving, declining from 4.58‰ to 2.30‰, while the percentage of under-five mortality (U5M) due to CHD decreased from 25.93% to 16.61%. The dual-index technique demonstrated high sensitivity and specificity in clinical practice for both critical (100.00% and 97.72%) and significant coronary heart disease (98.47% and 97.76%).

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Mires, 2022[22]	UK	NA	NA	NA	There is not enough evidence to confidently determine if maternal micronutrient deficiency (vitamin D, vitamin B12, folate, vitamin A, zinc, copper, selenium, and ferritin) increases the risk of CHD in fetuses.
Murni, 2022[23]	Indonesian	Cross sectional study	1,452 NBs	PO	Out of 1,452 newbornseligible for screening, 10 yielded positive results and were subsequently submitted for echocardiographic assessment. Among these, 8 (6 per 1000 live births, 8 out of 1452) were diagnosed with congenital critical heart disease (CCHD). Obstacles encountered during screening processes were linked to hospital protocols, apparatus, healthcare staff, and the state of the neonate.
Ngeow, 2021[24]	Singapore	Retrospective study	16,059 live births	Prenatal ultrasound and postnatal clinical examintation by attending neonatologist	The prevalence of CHD was 9.7 per 1,000 live births. The most prevalent congenital heart problem was ventricular septal defect (54.8%). The prenatal detection rate in the critical CHD group was thrice greater (64.0%) than that of the whole group (21.1%). The screening had a sensitivity of 64.5% and a specificity of 99.7% for all CHD, while for the critical CHD group, the sensitivity was 92.9% and the specificity was 99.1%. The positive likelihood ratios were 215 and 103, but the negative likelihood ratios were 0.36 and 0.07 for all CHD and criticalCHD, respectively.
Siefkes, 2019[25]	USA	Prospective study	144 NBs	Peripheral perfusion index (PIx)	A total of 123 normal babies and 21 newborns with CHD (including five with significant systemic outflow blockage) were included. Four of the five critical systemic obstruction cases successfully passed the SpO2-based screening. Four of the five individuals did not pass the PIx-based screening. The sensitivity for identifying systemic obstruction CCHD in comparison to healthy newborns rose from 20% (95% confidence interval [CI]: 1–72%) with SpO2 screening alone to 80% (95% CI: 28–100%) using the combined SpO2-PIx screening method. Nevertheless, 2.44% of typical infants did not pass the PIx screening.
Slitine, 2020[26]	Morocco	Prospective study	8,013 NBs	PO	Screening was conducted on 8,013 out of 10,451 (76.7%) asymptomatic neonates. The algorithm indicated that 7998 cases successfully passed the screening test (99.82%), which included one inconclusive test that was subsequently redone an hour later and yielded a normal result. Fifteen neonates did not pass the screening test (0.18%): five with critical CHD (CCHD), five false positives, and five with CHD that was non-serious. A false negative instance was identified at two months of age.

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Tsao, 2023[27]	Taiwan	Prospecti ve study	93,05 8 NBs	PO	Throughout the research period, 93,058 out of 94,204 (98.8%) newborns without prenatal suspicion underwent screening. The referral rate was 0.17% (156/93,058), with up to 90% of test-positive newborns referred within 48 hours of birth. Forty-two cases of congenital critical heart disease (CCHD) without prenatal suspicion were identified, with 97.6% diagnosed within 72 hours of birth. Among the examined neonates, four cases of critical CHD (CCHD) successfully completed the screening. The percentages of false positives and false negatives were 0.12% and 0.04%, respectively.
Vries, 2023[5]	Netherlands	An artificial neural network	122 cases	Fetal ECG and AI	Analysis of 122 measures, comprising 65 healthy individuals and 57 cases of CHD, revealed an accuracy of 71%, sensitivity of 63%, and specificity of 77%. The sensitivity was 75% for CHD cases necessitating intervention during the newborn period and 69% throughout the first year of life. A favorable correlation between measurement time and detection performance was noted, achieving optimal results with 14 electrocardiography segments (37.5 minutes) or more.
Yang, 2023[28]	China	Cross sectional study	1,892 cases	AI-Based Auxiliary Diagnosis	A total of 326 patients were assessed by artificial intelligence. The detection rate of ASD was 73.8%, differing significantly from that of auscultation (P = .008). The detection rate for VSD was 78.8%, whereas the detection rate for PDA was 88.9%. A total of 518,258 individuals from 82 towns and 1,220 schools were screened, comprising 15,453 suspected cases and 3,930 confirmed cases (7.58%). The classification accuracy of AI in VSD (P = .007) and PDA (P = .021) was superior to that of auscultation. In typical instances, the recurrent neural network achieved a high accuracy of 97.77% in diagnosing CHD–PAH (P = .032). AI-driven diagnosis is an efficient support mechanism for CHD screening.
Zhang, 2021[29]	China	Prospecti ve study	8,305 NBs	Auscultation and PO	Out of 8305 neonates, 22 cases tested positive for POX exclusively, with 6 diagnosed via echocardiography; 83 cases were positive solely through cardiac auscultation, of which 47 were diagnosed by echocardiography; and 8 cases were positive by both methods, all confirmed by echocardiography. Four further cases were verified during the follow-up. The sensitivity, specificity, and positive and negative predictive values of the combined screening were 93.85%, 99.37%, 53.98%, and 99.95%, respectively.

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Table 2. Critical appraisal of study

Parameters	Atitlan-Gil,2020	Cody, 20204	Dinarti, 2020	Giread a, 2022	Hamilcikan, 2017	Helle, 2020	Tsao, 2023	Yang, 2024	Zhang, 2021
1. Bias related to temporal precedence									
Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Clear cause and effect	Clear cause and effect	Clear cause and effect	Clear cause and effect	Clear cause and effect	Clear cause and effect	Clear cause and effect	Clear cause and effect	Clear cause and effect
2. Bias related to selection and allocation									
Was there a control group?	Control group present	Control group present	Control group present	Control group present	Control group present	Control group present	Control group present	Cross-sectional study, no control group	Control group present
3. Bias related to confounding factors									
Were participants included in any comparisons similar?	Matched for baseline characteristics	Matched for baseline characteristics	Matched for baseline characteristics	Matched for baseline characteristics	Matched for baseline characteristics	Matched for baseline characteristics	Matched for baseline characteristics	Matched for baseline characteristics	Matched for baseline characteristics
4. Bias related to administration of intervention/exposure									
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or	All participants had same screening	All participants had same screening	All participants had same screening	All participants had same screening	All participants had same screening	All participants had same screening	All participants had same screening	All participants had same screening	All participants had same screening

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intervention of interest?									
5. Bias related to assessment, detection, and measurement of the outcome									
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Bias related to participant retention									
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	100% retention, no significant follow-up loss	Complete	Complete	Retention adequate, no significant follow-up loss	Complete	100% retention, no significant follow-up loss	Complete	Complete	100% retention, no significant follow-up loss
7. Statistical conclusion validity									
Was appropriate statistical analysis used?	Appropriate statistical methods, p-values reported	Appropriate statistical methods, p-values reported	Appropriate statistical methods, no p-values	Appropriate statistical methods, p-values reported	Appropriate statistical methods, p-values reported	Appropriate statistical methods, p-values reported	Appropriate statistical methods, p-values reported	Appropriate statistical methods, p-values reported	Appropriate statistical methods, p-values reported

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DISCUSSION

In this review, the results from China, USA, UK, Taiwan, Dublin, Netherlands, Romania, New England, and Singapore included as developed countries. While the results from Mexico, Morocco, India, Romania, Indonesian, and Turkey included as developing countries. Combination of pulse oxymetry (PO) and auscultation, or PO alone were the most common postnatal screening tools in developed and developing countries. [15–17,21,23,26,27,29] For prenatal screening, ultrasound was commonly used.[9,12,18,24] Another screening tools included 12-lead ECG or fetal ECG, genetic testing, echocardiography, checklist-based approach, checklist-based approach, clinical examination, peripheral perfusion index (PIx), and artificial intelligence.[5,8,9,11,13,18–20,25,28,30] Artificial intelligence and genetic testing were only used in developed countries.

Etiology

- **Genetics**

Congenital heart disease is the predominant congenital defect in neonates.[31] It constitutes 3% of neonatal fatalities and 46% of deaths attributable to congenital abnormalities, making it the primary cause of neonatal mortality. The average prevalence of coronary heart disease in Asia is markedly greater than in Africa, leading to an increased burden of healthcare in Asia.[31,32] Causes encompass chromosomal aneuploidies, copy number variations, pathogenic mutations in individual genes, and environmental exposures.[10] The identification of particular genes responsible for lesions, along with some previously recognized genes, is noted. T-box, NK, and GATA transcription factors are linked to several syndromic and isolated congenital heart anomalies. The superfluous functions of NKx 2.5 and NKx 2.7, as well as the relationship between NKx 2.7 and TBx 20, are clarified. Additional categories of transcription factors are also being clarified. Research has been conducted on the 22q11.2

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deletion and microduplication disorders, along with their genetic connections. Recent research emphasizes PTPN11 and NOTCH1 in Noonam syndrome within the genetics of congenital cardiac disease. These genetic connections will significantly enhance the understanding of downstream transcriptional or signaling networks associated with this hereditary illness. Gene therapy aimed at rectifying genetic anomalies in blood may offer essential treatment for CHD in children, adolescents, and adults.[32]

The initial clinical scenario warranting genetic testing in CHD is the existence of a syndromic phenotype. A thorough clinical examination is essential for identifying extracardiac involvement. Typical physical manifestations encompass facial dysmorphia (anomalies of the eyes, ears, mouth, and nose), limb dysmorphia (atrophy and reduction in length), hand and foot dysmorphia (polydactyly, shortened fingers, clinodactyly), and further skeletal irregularities such as scoliosis. Growth delays can be detected through the monitoring of height and weight, while neurological state must be evaluated to diagnose cognitive impairments and learning problems.[33]

- **Maternal Obesity and Diabetes Mellitus**

The processes of maternal diabetes mellitus during crucial phases of heart development are not well understood. The mechanisms suggested to modify cardiac development in maternal diabetes mellitus encompass glucose-induced disruptions in left-right patterning, heightened apoptosis resulting from oxidative stress, deficiencies in nitric oxide signaling, compromised autophagy, and changes in neural crest cell formation and migration. Ex vivo models of heart development have replaced therapy with supraphysiological glucose levels as a surrogate for maternal diabetes mellitus. Nevertheless, the influence of glucose's downstream metabolites on heart development is still largely unexamined. Experimental models of maternal diabetes mellitus have demonstrated the disruption of canonical signaling pathways during mesodermal differentiation and heart development. The multitude of

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suggested cellular models and molecular pathways emphasizes the necessity for additional investigation into the impact of maternal diabetes mellitus on fetal cardiac development.[14]

- **Maternal micronutrient deficiency**

Three investigations evaluated vitamin D levels in cases against controls, revealing considerably lower levels in cases compared to control samples. The average vitamin D levels in both patients and controls were categorized as inadequate, with insufficiency defined as less than 50 nmol/L. Nonetheless, the median vitamin B12 levels reported by Dilli et al. fell within the normal range of established reference values. Folate levels were evaluated in both cases and controls, with all three investigations indicating no significant variation in folate levels. Vitamin A concentrations were evaluated in a limited cohort of 50 patients and 50 controls, revealing no statistically significant difference between the groups. Zinc levels were evaluated in both patients and controls, with hair concentrations revealing no significant differences between the two groups. Copper concentrations were evaluated between patients and controls, revealing elevated levels in cases compared to controls. Selenium levels were higher in cases than in controls, with reduced adjusted chances of coronary heart disease in kids with elevated selenium levels. Ferritin levels were evaluated between cases and controls, revealing significantly lower levels in cases, although being within the normal range according to established reference ranges.[22]

In conclusion, these research yield inconclusive data on the risk factors for CHD in mothers. Some research indicated a heightened adjusted likelihood of CHD associated with vitamin D deficiency, however others found no correlation between lower levels of vitamin B12 or folate in mothers and higher odds of CHD. Additional study is required to enhance comprehension of the factors affecting CHD risk and its implications for maternal health.

- **Maternal lifestye (Smoking, alcohol)**

Smoking is deemed teratogenic, and hemodynamic

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problems generated by smoking may promote morphological or functional anomalies in the embryonic cardiovascular system. Carbon monoxide and nicotine may adversely affect embryonic heart development. A meta-analysis of observational studies comprising 137,574 patients with CHD revealed that maternal active and passive smoking, along with paternal active smoking, elevate the risk of CHD in offspring, indicating that the cessation of parental smoking during the peri-pregnancy period is essential for CHD prevention. Furthermore, subgroup analysis indicated that active maternal smoking, as opposed to passive smoking, correlates with the risk of Autism Spectrum Disorder (ASD) and right ventricular outflow tract obstruction (RVOTO). A subsequent meta-analysis demonstrated a nonlinear dose-response association between parental alcohol intake and the risk of CHD in offspring, indicating that the risk of CHD in offspring escalates progressively with increasing parental alcohol use. Consequently, diminishing parental alcohol use prior to conception and during gestation may aid in the prevention of congenital heart disease in offspring.[32]

Screening

In most of developing countries including Indonesia, systematic screening for pediatric cardiac problems has not yet been implemented.

- **Pulse Oximetry (PO)**

Pulse oximetry is a readily accessible and precise technique for objectively measuring oxygen saturation (SpO2), thereby enabling the detection of clinically undetected hypoxemia prevalent in most neonates with CHD. It is advisable to utilize pulse oximeter devices that are approved for neonatal use, effective in low perfusion conditions, capable of reporting functional oxygen saturation, and tolerant of motion. The establishment of threshold values will dictate the sensitivity and specificity of the screening instrument. When selecting the cutoff value, it is essential to balance the false positive rate with the danger of overlooking CHD. Ewer et al. characterized SpO2 levels below 95%

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in either limb or a discrepancy above 2% between the limbs as abnormal.[34,35] Numerous studies have shown that pulse oximetry screening conducted beyond 24 to 48 hours of life reduces false-positive outcomes, and employing two limbs (the right hand and either foot) optimizes the accuracy of CHD screening.[36]

- **Prenatal Ultrasound**

In the Czech Republic, Canada, and the other developed country, every resident pregnant woman had a nationwide prenatal screening conducted by a local obstetrician/gynecologist between weeks 18 and 21 of pregnancy.[38] The final combined ultrasound diagnostic rate was 76% (95%CI: 50.00%-102%).[29] Limitations include the variety of heart views examined and the operator-dependent quality of ultrasound imaging.[36]

- **Artificial Intelligence**

Vries, et al. (2023)[5]suggested that the suggested technology, which integrates current advancements in non-invasive fetal electrocardiography with artificial intelligence for the automatic detection of congenital heart disease (CHD), attained a detection rate of 63% for all CHD cases and 75% for critical CHD cases. This feasibility research indicates that detection rates of congenital heart disease may enhance by the incorporation of electrocardiography-based screening alongside routine ultrasound-based screening. Yang, et al. (2022)[28] suggested that of the 518,258 individuals tested, 13,126 suspected cases were identified in the artificial auscultation group, whereas 3,120 suspected cases were noted in the AI group. The accuracy of AI in classifying VSD and PDA surpassed that of artificial auscultation, with a statistically significant difference. Furthermore, the total precision of AI screening surpassed that of auscultation screening.

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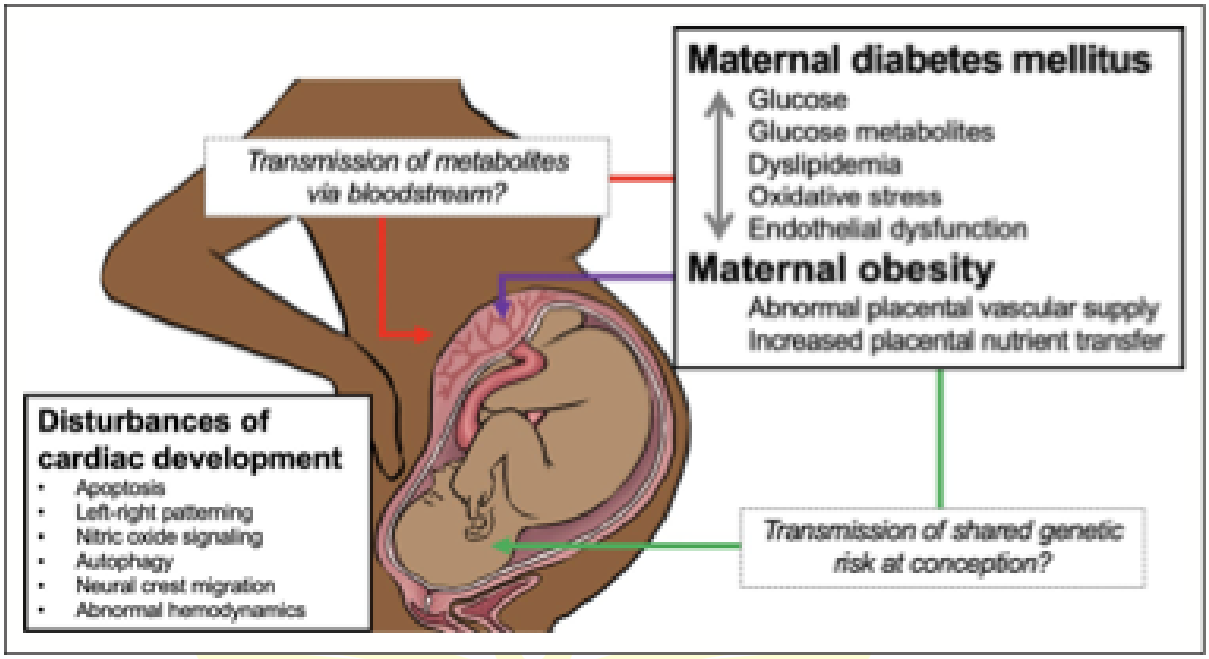


Figure 2. Potential mechanisms for CHD development.[14]

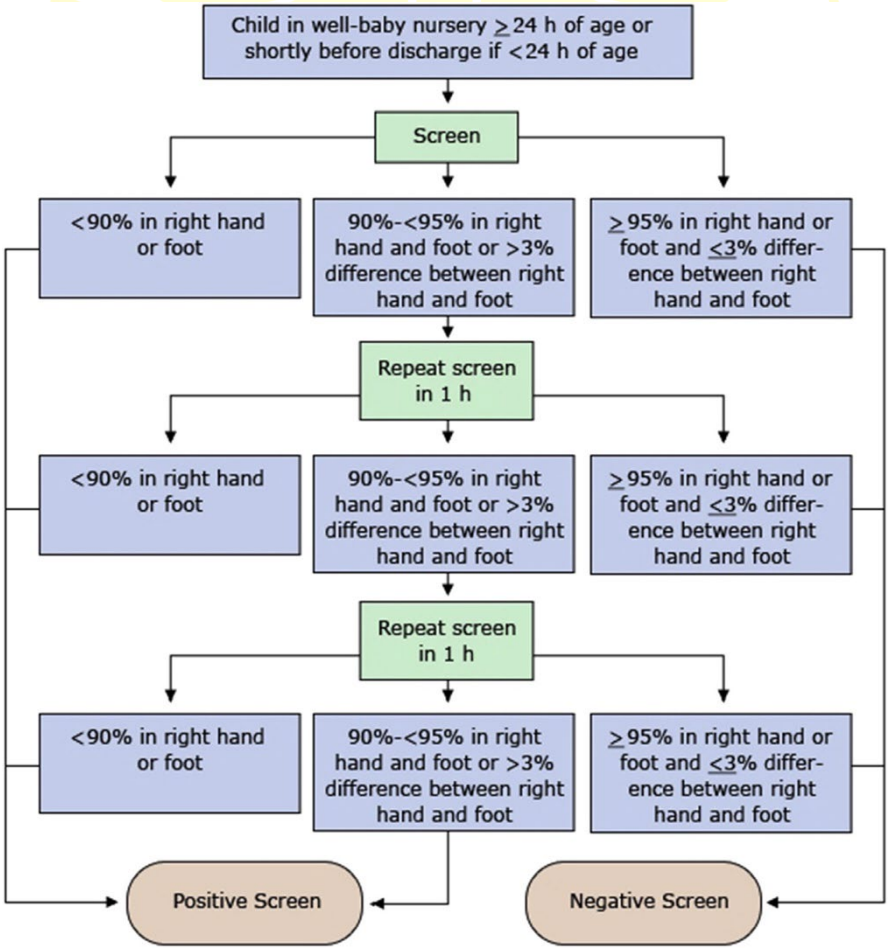


Figure 3. CHD screening algorithm with pulse oximetry.[37]

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CONSCLUSION

The urgent need for affordable early detection of congenital heart disease (CHD) in developing countries cannot be overstated, as it holds the potential to significantly reduce the global burden of this condition. By implementing comprehensive prenatal and postnatal screening programs, we can identify at-risk infants early, enabling timely interventions and improved health outcomes. Addressing this critical issue not only enhances individual lives but also strengthens healthcare systems and fosters healthier communities.

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