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Review Article

Risk factor profiling in congenital heart disease: maternal and foetal determinants

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ABSTRACT

Congenital heart defects (CHDs) pose a substantial challenge to global public health, significantly impacting infant morbidity and mortality rates. This investigation seeks to examine the environmental factors, such as air and water pollution, and workplace exposures, that may influence the occurrence of CHDs in the area. The study evaluated mothers' exposure to various environmental contaminants, lifestyle choices, maternal health, and local industrial activities. Initial results indicate that exposure to high concentrations of air and water pollutants, especially from nearby mining and agricultural operations, may be strongly associated with a higher incidence of CHDs. Moreover, socioeconomic conditions, consanguineous marriages, and insufficient access to prenatal care were identified as important contributing factors.

Keywords: Congenital heart disease, Environmental and genetic risk factors, Maternal health, Socioeconomic condition, Consanguinity

INTRODUCTION

Congenital heart disease (CHD), a birth defect, affects the normal functioning of the heart and major blood vessels. It is a significant global health concern, affecting nearly 1% of live births worldwide, or approximately 8-10 per 1,000 live births, resulting in approximately 1.35 million affected infants each year, with vast regional differences.[1] The incidence and prevalence of CHD vary considerably across various regions owing to the influence of genetic predispositions, environmental influences, and healthcare access. It is important to comprehend these disparities when formulating regionally focused healthcare strategies and improving outcomes for affected individuals.

Globally, the incidence of CHD is estimated to be 9 per 1000 live births, as reported in the 2017 Global Burden of Diseases, Injury and Risk Factor (GBDIRF) study conducted through the Bill & Melinda Gates Foundation. Higher incidence rates are observed in Africa and Asia (9.3 per 1,000), whereas Europe (8.2 per 1,000) and North America (6.9 per 1,000) report to have lower rates. The global incidence remains unchanged while in some developed countries such as Germany and France increasing rates are reported.[2] South America, with its high birth rate, faces a substantial CHD burden, though specific prevalence data is limited.[3] Reported CHD prevalence has increased over time, from 0.6 per 1,000 live births in 1930-1934 to 9.1 after 1995, stabilizing in recent years. Geographical variations may be attributed to differences in access to healthcare, diagnostic facilities, and genetic, environmental, socioeconomic, or ethnic factors.[4]

CHD is responsible for 28% of all congenital defects and almost 200,000 children are born with CHD annually in India.[5] Incidence rates in India range from 8 to 10.13 per 1,000 live births, accounting for around 10% of infant mortality. Additionally, the prenatal incidence of foetal cardiac anomalies was found to be 8.8 per 1,000.[6]

Studies in Western Rajasthan have reported varying prevalence rates of CHD, including 8.4 per 1,000 and 35.20 per 1,000 population.[7,8] Another research from North-Western Rajasthan found an incidence of congenital malformations at 12.3 per 1,000, with a significant proportion attributed to CHDs.[9]

TYPES OF CONGENITAL HEART DISEASE AND THEIR PREVALENCE

Congenital heart defects are categorized into acyanotic and cyanotic types. Acyanotic defects, accounting for approximately 70% of cases, involve left-to-right shunts and include ventricular septal defect (VSD), Atrial Septal Defect (ASD), patent ductus arteriosus (PDA), and atrioventricular septal defect (AVSD). Cyanotic defects, making up around 25%, involve right-to-left shunts or structural abnormalities and include tetralogy of fallot (TOF), transposition of the great arteries (TGA), tricuspid atresia, and total anomalous pulmonary venous return (TAPVR). VSD and ASD are the most common types, affecting 50% of all CHDs (Figure 1 and 2).[10]

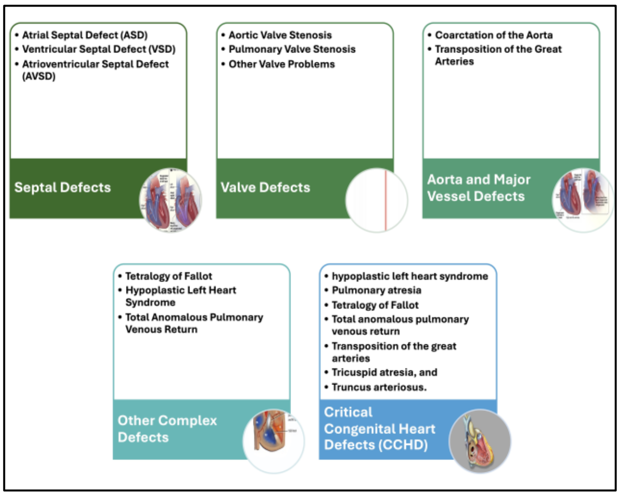

Figure 1: Types of congenital heart disease.

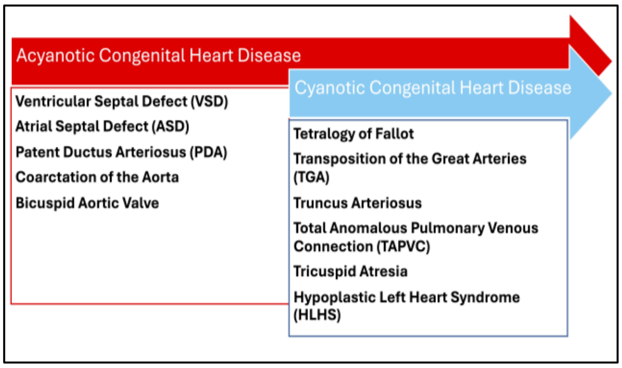

Figure 2: Acyanotic and cyanotic congenital heart disease.

RELATION OF CHD WITH OTHER MALFORMATION AND BODY ORGANS

CHD elevates the likelihood of developing various cancers, including leukaemia, lymphoma, hepatoblastoma, lung cancer, skin cancer, and brain tumours.[11] Individuals with CHD have a structural abnormality that affects pulmonary circulation, making them more susceptible to recurring respiratory infections compared to those without CHD.[12] CHD also increases the risk of pulmonary complications, such as pulmonary arterial hypertension and Eisenmenger syndrome, and liver dysfunction.[13,14]

RISK FACTORS

This review aggregates research literature addressing environmental and genetic risk factors, quality of life, neurocognitive and psychopathological adjustment, examining variables that can potentially affect their development and overall wellbeing (Figure 3).

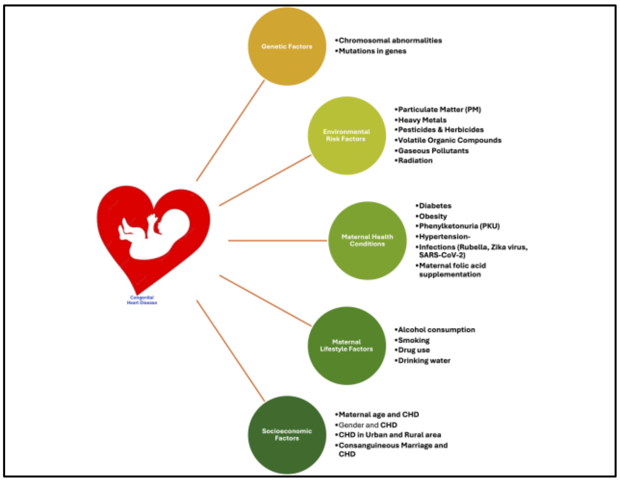

Figure 3: Risk factors for congenital heart disease.

Genetic factors

Some babies develop heart defects due to genetic or chromosomal changes. Studies have identified key transcriptional regulators, signalling molecules, and structural genes essential for cardiac morphogenesis. Furthermore, multiple genes regulated by these conserved molecular pathways have been discovered. Research suggests that genetic factors play a crucial role in the aetiology of CHD, with many genes potentially contributing to its development. Approximately 80% of CHD cases result from a combination of genetic and environmental factors, while around 20% are attributed to genetic factors alone (Table 1 and 2).[15]

Chromosomal abnormalities

Approximately 40% of CHD cases have identifiable genetic risk factors, with chromosomal variations playing a significant role.[16] Chromosomal abnormalities are frequently observed in foetuses with CHD, with trisomy 18 being the most prevalent. The likelihood of detecting chromosomal abnormalities increases in pregnancies complicated by CHD, particularly in older mothers. While simple foetal CHD generally has a favourable outcome, complex CHD and cases involving additional extracardiac anomalies are associated with a poorer prognosis.[17]

Aneuploidy and microdeletion conditions are also associated with non-CHD malformations, including NTD, Urinogenital, Psychomotor development etc. Affected individuals may also exhibit a distinct cognitive profile and unexplained hypercalcemia.[18]

Mutations in genes

Approximately 400 genes, including more than 50 well-characterized human genes, are involved in CHD.[19] Cilia and cilia-mediated signalling pathways, particularly Hedgehog signalling, have been found to play crucial roles in the pathogenesis of CHD. Genetic screens identified cilia-related genes linked to congenital heart disease (CHD). These genes are involved in Hedgehog signalling, which plays a role in left-right patterning and heart development.[20]

Aberrant Epigenetic changes and mutations in transcription factors (TF) (like GATA and T-box proteins) can contribute to congenital heart disease (CHD). Recent findings highlight potential biomarkers for diagnosis and treatment, and shed light on how adverse intrauterine environments may play a role.[21] Mutations in GATA6 are associated with CHD involving the outflow tract, while mutations in T-box transcription factors like TBX5 and TBX20 are linked to various cardiac defects and abnormal heart development.[22]

Genetic alterations in transcription factors and signalling molecules, such as TBX5, GATA4, NKX2-5, and CRELD1, have been associated with CHD, highlighting the importance of genetic studies in understanding the disease.[23]

Genes linked to CHD include GATA4, TBX5, and NKX2-5, crucial for heart chamber formation and septum development.13 Other genes involved are PTPN11, KRAS, SOS1, RAF1, NRAS, BRAF, SHOC2, CBL, and RIT1, which can lead to CHD and distinctive facial features.[32] Additionally, genes like CASZ1, DNAJC18, PDE4DIP, RNF38, and TMEM161B have been identified in mouse studies as playing roles in heart development.[24]

Environmental risk factors

Environmental risk factors for CHD include pollution (air and chemical), maternal health behaviours (smoking, alcohol, poor nutrition), and socioeconomic conditions. Exposure to air pollution, particularly particulate matter (PM), during pregnancy is linked to increased risk of heart defects, such as coarctation of the aorta, atrial septal defect, and TOF.[25] A significant correlation exists between PM exposure and CHD risk, with a notable association with TOF (Table 3).[26]

Heavy metals present in air pollution also contribute substantially to foetal cardiac abnormalities. A large-scale study in South Korea found that prenatal exposure to airborne heavy metals, such as mercury and lead, increases the likelihood of CHDs. Additionally, elements like tungsten (W) and chromium (Cr) have been implicated in cardiac malformations.

Notably, toxic emissions from burn pits used during military operations in Iraq and Afghanistan have been identified as a major source of heavy metal exposure among U.S. veterans, further underlining the environmental risks.[27]

Exposure to pesticides and herbicides is another environmental factor associated with congenital anomalies, including CHDs. These exposures can be occupational or environmental and have been linked to various birth defects. For instance, studies have connected pesticide exposure to neural tube defects, secundum atrial septal defects, and hypoplastic left heart syndrome.[28]

Volatile organic compounds (VOCs), commonly found indoors, especially in newly renovated homes, also pose a serious risk. For example, pregnant women exposed to high levels of VOCs from sources like paint or adhesives, solvents, and building materials have been found to have a sevenfold increase in the risk of CHDs in their offspring.[29]

Gaseous pollutants, such as sulphur dioxide (SO_2) and nitrogen dioxide (NO_2), are additionally linked to specific heart defects. Early pregnancy exposure to these gases has been associated with increased risks of coarctation of the aorta, ventricular septal defects, and pulmonary valve abnormalities. These gases, typically emitted from industrial processes and vehicular exhaust, are common in urban air pollution.[25]

Finally, radiation exposure-particularly during paediatric cancer therapy-has long-term cardiovascular implications. Each 10-Gy increase in cardiac radiation dose correlates with significantly elevated hazard ratios for coronary artery disease (approximately 2.01) and heart failure (approximately 1.87). Although advancements in radiation therapy techniques have reduced these risks, individuals exposed to older treatment protocols remain vulnerable.[30]

Maternal health conditions

Research shows that maternal conditions and environmental exposures significantly impact CHD risk in offspring. Factors such as maternal diet, health conditions, medication use during pregnancy, and pre-existing diabetes or obesity are associated with heart defects in the baby. Conception through assisted reproductive technologies also influences CHD.[31]

Diabetes

A thorough review of multiple studies revealed that maternal gestational diabetes mellitus is associated with a 32% greater probability of CHD in offspring, with certain defects, such as atrial ventricular septal defects and ductus arteriosus occurring more frequently.[32]

Obesity

The intrauterine environment, influenced by maternal obesity, can result in unfavourable cardiac remodelling and increase the likelihood of cardiovascular diseases in later life. Research shows that offspring of obese mothers have an elevated risk of hypertension, coronary artery disease, and CHD compared to those born to mothers of normal weight. Maternal obesity has also been found to increase the thickness of the interventricular septal wall and alter cardiac function in offspring.[33]

Phenylketonuria

Foetal cardiac development is profoundly affected by maternal phenylketonuria, resulting in various heart defects at birth and long-term cardiovascular problems. When maternal phenylalanine levels are elevated, especially if unmanaged, the foetal heart and pulmonary system may develop structural and functional abnormalities, including persistent pulmonary hypertension. Research indicates that 14% of children born to mothers with high phenylalanine concentrations (exceeding 900 µM) developed CHD.[34]

Hypertension

Maternal hypertension disrupts normal blood flow, affecting blood and oxygen delivery to the foetus. Poor placental development and blood vessel abnormalities can restrict foetal growth, causing irregular cardiac development. Studies indicate that foetuses in hypertensive environments are more prone to heart structure defects and altered cardiac function.[35]

Infections

These pathogens can directly impact foetal heart development, resulting in structural abnormalities. To combat this issue, immunization and preventative strategies are crucial in reducing the occurrence of these infections and their subsequent effects on foetal growth. The prevalence of CHD rose to 5.46% in 2023, suggesting a correlation between maternal COVID-19 infection during pregnancy and adverse cardiac outcomes in infants.[36]

Maternal folic acid supplementation

Studies indicate that higher maternal folate levels are associated with lower incidences of CHD, suggesting a protective effect of folic acid.[37]

Table 1: Chromosomal abnormalities and their association with CHD.

Chromosomal location	Syndrome/ condition	Cardiac anomalies	Description	Citation
Trisomy 18	Edward syndrome	VSD	Hole in the wall between the heart's ventricles	53
		ASD	Hole in the wall between the heart's atria	
		Double outlet right ventricle (DORV)	Both arteries arise from the right ventricle	
		Tetralogy of fallot (TOF)	Combination of VSD, pulmonary stenosis, right ventricular hypertrophy, and an overriding aorta	
		Coarctation of the aorta (CoA)	Narrowing of the aorta	
		Hypoplastic left heart syndrome (HLHS)	Underdeveloped left side of the heart	
Trisomy 21	Down syndrome	AVSD	Defect in the septum between the heart's chambers and valves	
		ASD	Hole in the wall between the heart's atria	
		VSD	Hole in the wall between the heart's ventricles	
		TOF	Combination of VSD, pulmonary stenosis, right ventricular hypertrophy, and an overriding aorta	
Trisomy 13	Patau syndrome	Septal defect	Defect in the septum between the heart's chambers	54
		Patent ductus arteriosus (PDA)	Failure of a normal foetal connection to close after birth	

Continued.

Chromosomal location	Syndrome/ condition	Cardiac anomalies	Description	Citation
1p21.2	-	Septal defect	Defect in the septum between the heart's chambers	
1p21.2	-	PDA	Failure of a normal foetal connection to close after birth	
5q22.2	-	Septal defects	Defects in the septum between the heart's chambers	55
7q11.23	Williams syndrome	Supravalvular aortic stenosis (SAS)	Narrowing of the aorta above the valve	56
		Peripheral pulmonic stenosis (PPS)	Narrowing of the pulmonary arteries	
16p11.2 Deletion	-	VSD	Hole in the wall between the heart's ventricles	53
17q21.32	-	Anomalies of thoracic arteries and veins (ATAV)	Abnormal development of arteries and veins in the chest	55,57
20p12.1	-	Transposition of the great arteries (TGA)	Reversed positions of the two main arteries	
22q11.2	DiGeorge syndrome, velo-cardio-facial syndrome	TOF	Combination of VSD, pulmonary stenosis, right ventricular hypertrophy, and an overriding aorta	18,58
		Conotruncal defects	Defects in the development of the outflow tracts of the heart	
		Interrupted aortic arch	Disruption or absence of a segment of the aortic arch	

Table 2: Cardiac anomalies, associated genes, and gene function (grouped format).[15]

Cardiac anomaly	Associated genes	Gene function
Atrial septal defect (ASD)	NKX2-6, GATA4,6, TBX20, CITED2, ZIC3, MYH6,7,11, ACTC1	TF, SP
Tetralogy of fallot (TOF)	NKX2-6, GATA4,6, CITED2, ZFPM2, FOXH1, JAG1, VEGFA, GJA1,5	TF, MG, GJP
Ventricular septal defect (VSD)	NKX2-6, GATA4,6, TBX1,5, TBX20, CITED2, ZIC3, FOXH1, ACTC1	TF
Heterotaxy	ZIC3, NODAL, CFC1	
Transposition of the great arteries (TGA)	CITED2, ZIC3, NODAL, CFC1	
Patent ductus arteriosus (PDA)	TFAP2B, MYH6,7,11	TF, SP
Hypoplastic left heart syndrome (HLHS)	NKX2-6, HAND1, GJA1,5	TF, GJP
Aortic stenosis (AS)	NOTC1	MLR
Pulmonary stenosis (PS)	GATA4,6, ZIC3, JAG1	TF
Interrupted Aortic Arch (IAA)	TBX1,5	
Aortic arch anomalies	TBX1,5	
Left ventricular outflow tract obstruction (LVOTO)	TBX20	
Total anomalous pulmonary venous return (TAPVR)	ZIC3	
Atrioventricular septal defect (AVSD)	ZIC3, CREL1	TF, MCP
Ebstein anomaly	NKX2-6, MYH6,7,11	TF, SP
Supravalvular aortic stenosis (SVAS)	ELN	STP
Double outlet right ventricle (DORV)	NKX2-6, GATA4,6, CFC1	TF
Bicuspid aortic valve (BAV)	NOTC1	MLR
Dextrocardia	CREL1	MLR

Transcription factor–TF, Sarcomeric protein–SP, Mitogen – MG, Gap junction protein–GJP. Membrane ligand-receptor–MLR, Matricellular protein–MCP, Structural protein–STP. *Note that some genes are associated with multiple functions, and some cardiac anomalies are associated with multiple genes with different functions. This table is not exhaustive in terms of gene function for each cardiac anomaly but rather provides a general overview.

Table 3: Pollutant, their source and effect on heart.

Pollutant category	Pollutant(s)	Effect on heart	Source of exposure
Particulate matter (PM)	PM1	Heart disease	Construction sites, wildfire, wood burning, dusty roads
	PM2.5	Tetralogy of Fallot (TOF)	
	PM10	Heart disease	
Heavy metals	Arsenic, Cadmium, Mercury, Lead, Chromium, Tungsten	Heart disease	Toxic burn pit emissions
Pesticides & herbicides	Neonicotinoids, Dichlorophenoxy acid/ester, Paraquat dichloride	Secundum atrial septal defect, Hypoplastic left heart syndrome	Agricultural operations, forestry management
Volatile organic compounds	Formaldehyde, benzene, toluene, xylene etc	Heart defect	Newly renovated homes
Gaseous pollutants	Sulphur Dioxide (SO_2)	Coarctation of the Aorta (COA), ventricular septal defect (VSD)	Burning of coal and oil
	Nitrogen Dioxide (NO_2)	COA, pulmonary valve stenosis	Burning of gasoline
Radiation	2.01 Gy	Coronary artery disease	Nuclear power, weapons, medical diagnostics/treatment
	1.87 Gy	Heart failure	

MATERNAL LIFESTYLE FACTORS

Alcohol consumption

A study of over 5.8 million births found maternal alcohol-related diagnostic codes linked to a 33% to 84% increased CHD risk. Periconceptional alcohol consumption can affect offspring's cardiovascular health, with female offspring exposed to ethanol showing reduced cardiac output and increased gene expression.

This suggests that the impact of alcohol varies with consumption levels and other factors, highlighting the complexity of maternal alcohol use and CHD relationship.[38]

Smoking

Smoking mothers nearly double the risk of CHD including atrioventricular canal and atrial septal defect. Passive smoking also poses a potential risk, indicating that non-smoking mothers exposed to second-hand smoke also face heightened risks for their offspring. Adverse foetal development linked to maternal smoking might result from diminished oxygen supply and harmful chemical exposure, disrupting normal cardiac formation.[39]

Drug use

Mothers using antidepressants and ovulatory drugs show a higher risk of CHD in their offspring. A study found that 52.78% of neonates born to mothers abusing illicit drugs had abnormal echocardiographic findings, with 48.61% exhibiting mild CHD. Use of assisted reproductive technology also demonstrated moderate associations.[40]

Drinking water

Review of literature suggests that drinking water with arsenic, mercury and cadmium is associated with CHD, while magnesium, selenium have a protective effect. Chlorine used in water treatment can produce disinfection by-products, which have been associated with CHD.[41]

SOCIOECONOMIC FACTORS

Maternal age

Lower maternal socioeconomic status, including reduced educational attainment, income, and occupational status, is associated with an increased risk of CHD in offspring. Environmental factors, such as exposure to pollutants, and social deprivation also contribute to higher CHD incidence. Prenatal diagnosis of critical CHD is more likely among patients with private insurance and higher socioeconomic position. However, the relationship between socioeconomic status and CHD development remains inconclusive, with some studies finding no association. Maternal comorbidities partially explain the relationship between social deprivation, environmental exposure, and CHD incidence.[42]

A study conducted in Europe from 1995 to 2015 produced mixed results, with certain trends indicating a higher prevalence of CHD in both younger and older mothers A study in Guangxi, China found a positive correlation between maternal age and CHD. Mothers aged 35 and above face increased risks of delivering preterm babies and infants that are small for gestational age, particularly if the mothers themselves have CHD. Chromosomal abnormalities are more likely to be detected in pregnancies involving older mothers with CHD.[17] In cases of Down syndrome, maternal age influences the type of CHD, with atrioventricular septal defect (AVSD) being more frequent in mothers aged 20 years or younger and VSD being more common in mothers over 45.[43]

Gender differences

Research on CHD reveals significant gender differences in prevalence, outcomes, and experiences. Notably, males are at a higher risk of being born with severe CHD, predominantly involving the outflow tract, whereas females are more likely to have milder CHD subtypes affecting the inflow tract of the heart.[44]

Females may have a slightly higher prevalence at birth, but males have higher surgical mortality rates in adulthood. Women face higher risks of pulmonary hypertension and reduced quality of life, while having lower risks of aortic issues, endocarditis, and need for implantable cardioverter-defibrillators.[45]

Urban and rural differences

CHD prevalence and outcomes can vary significantly between urban and rural areas due to differences in healthcare access, socioeconomic factors, and environmental influences. The prevalence and mortality in rural communities is higher compared to urban areas. Postnatal diagnosis is more frequently observed in rural regions.[46]

In China, CHD mortality increased by 62.4% from 2003 to 2010, with a more significant rise in urban areas (154.5%) compared to rural areas (5.3%). Conversely, in Bangladesh, a study found that 64% of CHD patients were from rural areas. In India, the prevalence of CHD was slightly higher in urban (10.8/1000) than rural (9.3/1000) school children. VSD and ASD were identified as the most common types of CHD.[47]

Consanguinity

Consanguinity, or unions between biologically related individuals, increase the risk of genetic disorders in offspring, including autosomal recessive conditions and congenital anomalies. This practice, common in some regions like South India and among certain communities, is often driven by cultural, economic, and religious factors.[48] Parental consanguinity increases the risk of CHDs in South India. The study found that 40.3% of families with CHD had consanguineous parents, compared to only 15.5% in the control group. However, the degree of risk depends on the degree of relatedness, family genetic history, and other factors, including environmental influences and access to healthcare.[49]

First-cousin consanguineous marriages are associated with a 1.8-fold greater likelihood of having a child diagnosed with CHD at birth. Moreover, such marriages are strongly linked to an increased risk of specific conditions, including VSD, atrial septal defect (ASD), hypoplastic left heart (HLH), and single ventricle (SV), compared to children born to non-related parents.[50]

Research across various countries, including Turkey, Saudi Arabia, Lebanon, Indonesia, Bangladesh, Israel, and India, has consistently shown a direct association between consanguineous marriages and an increased risk of CHDs in offspring.[51,52]

CONCLUSION

CHD is a significant health challenge globally and in India, affecting 8-12 per 1,000 live births. In India, particularly in Rajasthan, CHD contributes to high infant morbidity and mortality due to socio-economic disparities, limited access to specialized care, and lack of awareness. Rajasthan, in particular, faces unique challenges due to socio-economic disparities, inadequate access to specialized paediatric cardiac care, and limited awareness at the primary healthcare level.

To address this, India needs state-level CHD registries, universal newborn screening programs, and trained primary healthcare providers. Strengthening maternal health services, developing regional paediatric cardiac centres, and investing in infrastructure and awareness campaigns can help reduce CHD-related mortality and improve outcomes. A coordinated effort from policymakers, healthcare providers, and the community is crucial for equitable access to quality care.

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