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Mini Review

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Biomarkers in Congenital Heart Disease: Current Evidence and Future Directions

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Abstract

Congenital heart diseases (CHDs) are the most prevalent congenital anomalies worldwide and are a leading cause of infant morbidity and mortality, particularly in low- and middle-income countries. Despite advances in fetal imaging and pediatric cardiac care, most CHDs are diagnosed only after structural defects have formed, limiting opportunities for prevention. This narrative review synthesizes evidence on established and emerging biomarkers for early detection, risk stratification, and prevention of CHD. Studies published between 2000 and 2025 in PubMed were reviewed, focusing on metabolic, nutritional, immunological, molecular, and imaging biomarkers from maternal, fetal, and postnatal contexts. Advances in omics technologies—including metabolomics, proteomics, transcriptomics, and epigenomics—have revealed alterations in pathways related to one-carbon metabolism, oxidative stress, lipid metabolism, hypoxia signaling, immune regulation, and chromatin remodeling in CHD-affected pregnancies and patients. Biomarkers such as homocysteine, acylcarnitines, branched-chain amino acids, natriuretic peptides, inflammatory cytokines, microRNAs, and epigenetic regulators show potential for reflecting early pathogenic processes and disease severity. However, heterogeneity across studies and limited longitudinal validation currently restrict clinical translation. Overall, evidence supports a multimodal biomarker approach integrated with imaging and clinical assessment, with early risk identification during the periconceptional and early gestational periods offering the greatest opportunity to reduce the global burden of CHD.

Keywords: Congenital heart disease; Biomarkers; Maternal-fetal interface; Periconceptional period; Preventive cardiology; Prognostics.

Introduction

Congenital heart diseases (CHDs) are the most common congenital anomalies worldwide, accounting for nearly 28% of all birth defects. The global incidence is estimated at approximately 9 per 1,000 live births, translating to about 1.35 million affected newborns annually, including ~240,000 cases in India.[1] Owing to their clinical heterogeneity, complex etiological architecture, and substantial contribution to infant morbidity and mortality, CHDs represent a major public health burden, particularly in low- and middle-income countries.[2]

CHDs encompass a broad anatomical and physiological spectrum. Acyanotic lesions include ventricular septal defect, atrial septal defect, patent ductus arteriosus, and obstructive lesions such as pulmonary stenosis, aortic stenosis, and coarctation of the aorta. Cyanotic defects include tetralogy of Fallot, tricuspid atresia, truncus arteriosus, and transposition of the great arteries.[3] Disease severity ranges from simple defects that may resolve spontaneously to complex malformations requiring staged surgical interventions and lifelong surveillance.[4]

Despite advances in pediatric cardiac surgery and catheter-based therapies, CHDs remain a leading cause of infant mortality, with up to 18–25% of affected infants dying within the first year of life, particularly in resource-limited settings.[2,5] Survivors often face long-term complications, including neurodevelopmental impairment, growth restriction, recurrent hospitalizations, and psychosocial challenges, imposing sustained healthcare and socioeconomic burdens.[6]

The etiology of CHD is multifactorial and incompletely elucidated. Genetic variants, epigenetic dysregulation, and environmental exposures collectively contribute to disease risk, yet these factors explain only a subset of cases and may vary across populations.[7–9] Increasing evidence underscores the importance of the maternal intrauterine environment during early gestation, particularly the first 6–8 weeks

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when cardiogenesis occurs.[10] Disruptions in key transcription factors (e.g., *NKX2-5, GATA4*), developmental signaling pathways (Notch, Wnt/β-catenin), chromatin-remodeling complexes, and cilia-related genes have been implicated in abnormal cardiac morphogenesis.[7] Currently, CHD diagnosis largely occurs after structural abnormalities have developed. Prenatal detection through fetal echocardiography has improved considerably, with sensitivities ranging from approximately 70–90%, while postnatal screening tools such as pulse oximetry help identify 80% of critical CHDs, and chest radiography demonstrates diagnostic accuracy ranging from 60–80%.[11–13] Advanced imaging modalities, including cardiac magnetic resonance imaging (MRI) and computed tomography (CT), provide valuable anatomical detail but remain costly and limited in accessibility.[14] However, these approaches primarily detect established anatomical defects, highlighting the need for strategies that identify early biological disturbances preceding structural malformations.

In this context, biomarkers have emerged as promising tools for early detection, risk stratification, and potential prevention of CHDs. Biomarkers are measurable indicators of biological processes and ideally should be non-invasive, reproducible, cost-effective, and demonstrate high sensitivity and specificity.[15] Advances in omics-based technologies, including metabolomics, proteomics, transcriptomics, and epigenomics, have expanded the CHD biomarker landscape. Studies have reported alterations in maternal metabolites such as homocysteine, branched-chain amino acids, phosphatidylcholines, and acylcarnitines, reflecting disruptions in one-carbon metabolism, oxidative stress, and energy pathways. Proteomic analyses of maternal plasma have also identified dysregulated proteins related to extracellular matrix organization, immune signaling, and myocardial structure that may distinguish CHD pregnancies from unaffected controls.[16]

Accordingly, this narrative review provides evidence (2000–2025) from PubMed on established and emerging biomarkers in CHD, with emphasis on their potential roles in early diagnosis, risk prediction, and prevention, while highlighting current translational challenges and future research priorities.

Biological indicators of congenital heart defects

Preconceptional health plays a crucial role in shaping maternal physiological adaptation and fetal developmental outcomes, including the risk of CHD.[17] Factors such as maternal age, body mass index, interpregnancy interval, micronutrient sufficiency, and iron status influence early embryonic development.[18] Epidemiological studies report a higher incidence of congenital anomalies—including cardiovascular defects—among teenage pregnancies, particularly in mothers ≤19 years, likely due to biological immaturity, suboptimal nutrition, and limited antenatal care.[19,20]

Maternal nutritional status is a key modifiable determinant of fetal health. Optimization of nutrition prior to conception reduces adverse outcomes such as preterm birth, intrauterine growth restriction, low birth weight, and congenital anomalies.[21] Anemia affects over 500 million women of reproductive age (15–45 years) globally, predominantly due to iron deficiency.[22] Iron deficiency during early gestation impairs oxygen transport and exacerbates fetal hypoxia, a recognized disruptor of normal cardiogenesis.[23]

Emerging evidence also highlights paternal contributions to CHD risk. Advanced paternal age has been associated with an increased risk of patent ductus arteriosus in offspring,[24] potentially mediated by telomere shortening, accumulation of de novo mutations, and epigenetic instability in sperm.[25] Paternal exposures to smoking, alcohol, and environmental toxins before conception may further increase CHD risk through oxidative stress, hormonal dysregulation, genomic instability, and epigenetic alterations.[26]

Metabolomic studies have identified early biochemical disturbances associated with CHD. Elevated maternal levels of acylcarnitine, ethanol, and acetone reflect impaired fatty acid oxidation and altered energy metabolism during early pregnancy.[27] Differential levels of metabolites such as valine, glucose, glutamine, creatinine, and polyunsaturated fatty acids have also been reported in CHD-affected pregnancies.[28] Urinary metabolomic profiling highlights methionine as a significantly altered metabolite, implicating disturbances in one-carbon metabolism.[29]

Additional metabolite signatures—including 4-hydroxybenzeneacetic acid, 5-trimethylsilyloxy-n-valeric acid, propanedioic acid, hydracrylic acid, and uric acid—derived from short-chain fatty acids and aromatic amino acid pathways have been associated with CHD risk.[16] Pathway analyses further indicate disruptions in aldosterone synthesis, nicotinate and nicotinamide metabolism, and drug metabolism pathways.[30]

Metabolic biomarkers

Metabolic biomarkers encompass biochemical indicators reflecting myocardial injury, hemodynamic stress, and systemic metabolite alterations. Early studies focused on cardiomyocyte injury markers such as myoglobin, cardiac troponins, lactate dehydrogenase, and creatine phosphokinase.[31] Although clinically relevant, these markers typically rise only after myocardial damage has occurred.

Subsequent research emphasized biomarkers of cardiac stress and inflammation. B-type natriuretic peptide (BNP) and N-terminal pro-BNP correlate with heart failure severity and ventricular function.[32,33] Inflammatory markers such as high-sensitivity C-reactive protein, interferon-γ, interleukins-6 and 10, tumor necrosis factor-α, and soluble Fas have been implicated in systemic inflammation and vascular dysfunction in pediatric CHD.[34] In addition, elevated maternal apolipoprotein A1 and triglyceride levels during early pregnancy are associated with increased odds of CHD in offspring.[35]

Recent studies highlight low-molecular-weight biomarkers capable of detecting pathological changes. Circulating microRNAs have emerged as promising candidates due to their stability, tissue specificity, and regulatory role in cardiac development and remodeling.[36] Blood-derived biomarkers are minimally invasive and provide quantitative measures of early disease processes, complementing imaging-based diagnostics.[37]

Hypoxia-related metabolic pathways also contribute to CHD pathogenesis.[38] Increased expression of vascular endothelial growth factor, hypoxia-inducible factor-1α, and superoxide dismutase-1 has been observed in CHD fetuses, reflecting adaptive responses to intrauterine hypoxia and

their roles in outflow tract remodeling and coronary vasculogenesis.[39–41] Cardioprotective proteins, including heat shock protein-70, protein kinase C-ε, and endothelial nitric oxide synthase, are essential for myocardial resilience; their dysregulation may predispose the developing heart to ischemia-reperfusion injury later in life.[42]

Maternal metabolic and nutritional biomarkers

Maternal conditions such as infection, substance use, environmental pollution, anemia, hemoglobinopathies, abnormal placentation, pre-eclampsia, and umbilical cord compression can exacerbate fetal hypoxia and disrupt normal cardiac development.[43] Population-based studies report a significant association between maternal anemia and increased CHD incidence.[44]

Maternal serum, urine, and amniotic fluid represent key biological matrices for biomarker discovery. Altered levels of acylcarnitine, sphingomyelins, and other lipid metabolites have been observed in CHD pregnancies.[45] Maternal dyslipidemia, characterized by elevated apolipoproteins A1 and B, triglycerides, and cholesterol fractions, has also been associated with increased CHD risk in offspring.[35] Urinary metabolomic analyses have identified 23 altered metabolites, with methionine showing the most pronounced change.[46]

Micronutrient status is another critical determinant. Elevated maternal homocysteine levels, reflecting impaired folate and vitamin B12 metabolism, have been consistently associated with pregnancies affected by CHD.[47,48]

Immunological biomarkers

Immunological dysregulation contributes to CHD pathophysiology. Reduced granulocyte activity, altered complement levels, and impaired T- and B-cell function have been reported in association with structural cardiac defects. Alterations in immunoglobulin levels (IgA and IgG) and increased suppressor T-cell activity are particularly evident in syndromic CHDs.[49]

Chronic inflammation may also influence disease progression. Elevated levels of high-sensitivity C-reactive protein and interferon-γ have been reported in patients with Eisenmenger syndrome.[50] Children with CHD frequently exhibit increased susceptibility to infections and impaired cellular immunity, particularly following bronchopneumonia.[51]

Integrated metabolomic-immunologic analyses have demonstrated correlations between metabolites—including 3-D-hydroxybutyrate, acetone, acetoacetate, citrate, lactate, creatine, creatinine, and alanine—and disease severity as well as postoperative outcomes, aligning with clinical indices such as the risk adjustment for congenital heart surgery (RACHS) scores, pediatric organ dysfunction scores, and intensive care unit (ICU)-free days.[52]

Molecular biomarkers

Genetic and epigenetic factors play a major role in CHD etiology. Single-gene disorders, chromosomal abnormalities, and copy number variations account for nearly 40% of cases,[7] while genetic contributions may be implicated in up to 90% of CHD overall.[53]

Whole-exome sequencing studies have identified de novo mutations in genes involved in chromatin remodeling, transcriptional regulation, and cardiac morphogenesis, including *HSP90AA1, ROCK2, IQGAP1,* and *CHD4*, many of which are also linked to neurodevelopmental impairment.[54,55] Epigenetic investigations have revealed differential DNA methylation patterns and dysregulated microRNAs associated with abnormal cardiogenesis. High rates of de novo mutations in histone-modifying genes further highlight the role of epigenetic dysregulation in CHD pathogenesis.[56]

Imaging biomarkers

Non-invasive imaging has transformed CHD diagnosis and management. Transthoracic echocardiography remains the cornerstone of evaluation due to its availability, portability, and diagnostic accuracy, while cardiac CT and MRI provide complementary anatomical and functional insights in complex lesions.[57]

Fetal echocardiography is the most effective modality for prenatal CHD detection. The transition from basic four-chamber views to extended protocols incorporating outflow tract and three-vessel trachea views has significantly improved diagnostic yield. Despite high specificity (up to 99.9%), sensitivity remains moderate and operator-dependent, with diagnostic discrepancies reported in approximately 13.5% of cases.[58,59] Nonetheless, fetal echocardiography remains indispensable for early detection and timely intervention.

Biomarkers for CHD: A clinical update

Over the past two decades, substantial advances have improved the understanding, diagnosis, and management of pediatric CHDs. Nevertheless, CHDs remain clinically challenging due to their marked anatomical heterogeneity, lesion-specific hemodynamics, and long-term morbidity. Abnormal pressure and volume loading, cyanosis, and pulmonary hypertension trigger complex biological cascades involving neurohormonal activation, inflammatory cytokine release, fibroblast proliferation, and endothelial dysfunction. These processes drive maladaptive cardiac remodeling, myocardial hypertrophy, thrombosis, cellular injury, and cardiomyocyte death, ultimately influencing disease progression and outcomes.[32]

The clinical utility of a biomarker in CHD lies in its ability to reflect underlying pathophysiological processes and predict clinically meaningful endpoints. In CHD, no single biomarker can capture the diverse mechanisms underlying different phenotypes, age groups, and disease stages.[60] Biomarkers therefore function primarily as surrogate indicators of specific biological processes rather than standalone diagnostic tools. Circulating cytokines, chemokines, adipocytokines, soluble receptors, and other immune activation markers have thus gained attention as indicators of myocardial stress, inflammation, and remodeling.[61] However, robust prognostication in pediatric CHD remains limited by heterogeneous study designs, small cohorts, and a lack of long-term longitudinal datasets.

Among cardiac biomarkers, BNP and soluble suppression of tumorigenicity-2 (ST2) are increasingly used for diagnosis, monitoring, and outcome prediction in pediatric heart disease.[32,62,63] These markers reflect myocardial wall stress, fibrosis, and adverse remodeling—central features of CHD pathophysiology. Their interpretation in children, however, must consider age-dependent physiological variability and lesion-specific hemodynamics.[64]

Biomarkers are also valuable for understanding disease

biology and identifying potential therapeutic targets. Risk factors such as obesity, alcohol consumption, smoking, and substance abuse have been consistently associated with increased CHD risk, likely mediated through metabolic dysregulation, oxidative stress, and epigenetic modification.[9,65] Accordingly, biomarkers reflecting parental metabolic, nutritional, and reproductive health have emerged as an important area of investigation (Tables 1 and 2).[3,16,27,28,32–34,51,66–86]

Hemodynamic assessment through echocardiography, cardiac MRI, and cardiac catheterization remains the cornerstone of CHD evaluation. Circulating biomarkers increasingly complement these modalities. Since the discovery of natriuretic peptides by de Bold in the 1970s, BNP has been extensively studied as a marker of volume overload and myocardial stress across cardiac and non-cardiac conditions.[87] In non-pregnant populations, BNP reliably predicts adverse cardiovascular outcomes.[88] During pregnancy, although echocardiography provides valuable structural and functional information, it cannot fully capture maternal cardiovascular adaptation or early fetal stress. Circulating cardiovascular biomarkers may therefore enhance early risk stratification when combined with imaging.

Maternal health before and during pregnancy plays a decisive role in fetal cardiac development. The placenta functions as the primary interface for oxygen, nutrient, and metabolic exchange during gestation.[89] Periconceptional deficiencies of folic acid, ferritin, vitamin B12, and vitamin D represent modifiable risk factors associated with congenital anomalies.[90] Diets high in fat and animal protein during early conception may increase oxidative stress in the follicular environment, impair oocyte quality, and contribute to gestational diabetes mellitus, an established risk factor for CHD.[91] Maternal anemia further exacerbates fetal hypoxia, disrupting embryogenesis and increasing susceptibility to both congenital and later-life cardiovascular disease.[23,92]

Cardiac morphogenesis is largely completed by the eighth week of gestation, underscoring the importance of very early biomarker assessment.[93] Physiological hypoxia is a normal feature of embryonic development and regulates differentiation through hypoxia-inducible signaling pathways. However, excessive or prolonged hypoxia disrupts these finely tuned processes and contributes to abnormal cardiogenesis. Biomarkers reflecting hypoxic stress, oxidative imbalance, and metabolic dysregulation may therefore provide predictive signals well before anatomical defects become detectable by imaging.[94]

Current clinical detection strategies remain largely imaging-based. Structural cardiac anomalies are typically detected after 20 weeks of gestation using fetal echocardiography,[95] which identifies approximately 68.5–90% of simple and complex CHDs in expert hands, although diagnostic discrepancies persist, particularly for complex lesions and in the presence of maternal comorbidities.[59] Invasive procedures such as amniocentesis carry procedural risks and are unsuitable for population-level screening, reinforcing the need for non-invasive biomarker-based approaches.[96]

Postnatally, several biochemical and immunological biomarkers, including C-reactive protein, interleukins, interferon-γ, CK-MB, myoglobin, and BNP, have demonstrated diagnostic and prognostic relevance in CHD.[49,97] Biomarkers also show promise in predicting postoperative outcomes following congenital heart surgery.[98] Limited evi-

Table 1. Predictive biomarkers in congenital heart disease

Biomarker category	Region	Participants	Sample size	Type of sample	Assessed biomarkers	Methodology	Findings	Reference
Genetic and molecular biomarker	Asian	Pregnant mothers (22–42 years) of gestational age (25–31 weeks)	n = 602 cases	Amniotic fluid	Single nucleotide polymorphism (SNP)	Chromosomal microarray analysis	Pathogenic chromosomal abnormalities were detected in 48.9% of CHD cases	Wang *et al.*[66]
	North-central Chinese	Children (4–7 years)	n = 30 cases; n = 30 controls	Cardiac tissue	miR-145, miR-182, and FXN (frataxin)	Gene expression microarray, and RT-qPCR	Altered expression of FXN due to binding of miR-145 at the 3′ UTR region was confirmed and may regulate the development of CHD	Wang *et al.*[67]
	West Chinese	Mothers (<28 years) of gestational ages (24–25 weeks)	n = 27 cases; n = 27 controls	Serum	miR-19b, miR-22, miR-29c, and miR-375	mirVana PARIS Kit, SOLiD sequencing, and qRT-PCR	All markers were significantly upregulated, and were more efficient, when combined, for prenatal detection of fetal CHD (AUC = 0.813)	Zhu *et al.*[68]

(continued)

Table 1. *(continued)*

Biomarker category	Region	Participants	Sample size	Type of sample	Assessed biomarkers	Methodology	Findings	Reference
	Han Chinese	Children (26 months) and Mothers (20–35 years)	n = 201 cases; n = 201 controls	Placenta tissues and umbilical cords	ABCB1 gene C3435T polymorphism, and maternal periconceptional toxicants	Genotyping/sequencing, cDNA synthesis, and western blotting	ABCB1 mRNA expression was significantly higher in the TT genotype than in the CC genotype. Fetal C3435T polymorphism increased the risk of CHD when mothers were exposed to phthalates and alkylphenolic compounds	Wang *et al.*[69]
Maternal biomarker	USA (Hispanic and non-Hispanic)	Liveborn infants and their mothers	n = 569 families	Buccal cell swabs	RFC1, MGMT, and GSTA3 genes	Illumina Golden Gate Custom SNP genotyping, whole genome amplification, and TaqMan RNase Assay	Four SNPs (rs6812588, rs1762430, rs9296695, and rs4712023) identified in genes RFC1, MGMT, and GSTA3 are involved in DNA methylation, cellular defense, and DNA replication	Patel *et al.*[70]
	Eastern Chinese	Mothers (23–34 years)	n = 71 cases; n = 149 controls	Amniotic fluid	Uric acid	Gas chromatography/time-of-flight-mass spectrometry (GC-TOF/MS)	Elevated uric acid levels ($P < 0.001$) in amniotic fluid may serve as a potential biomarker for CHD	Li *et al.*[71]
	Central-coast Chinese	Mothers (20–43 years)	n = 230 cases; n = 381 controls	Blood	Triglyceride, apolipoprotein-A1, and apolipoprotein-B	Lipid multivariate analysis	Maternal Apo-A1 levels were significantly higher in CHD cases ($P = 0.02$), whereas Apo-B levels were not significant ($P = 0.27$)	Cao *et al.*[32]
	Shaanxi Chinese	Mothers (≥ 30 years)	n = 474 cases; n = 948 controls	Dietary pattern analysis	Extrinsic factors: alcohol, smoking, lower iron dose, medication, and folate supplements	Global Diet Quality Score (GDQS), and Mediterranean Diet Score (MDS)	Maternal GDQS and MDS demonstrated good predictive value for fetal CHD (AUC ≈ 0.8), and were inversely associated with CHD	Yang *et al.*[72]

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Table 1. *(continued)*

Biomarker category	Region	Participants	Sample size	Type of sample	Assessed biomarkers	Methodology	Findings	Reference
	Southwestern Chinese	Mothers (<30 years)	n = 70 cases; n = 70 controls	Urine	4-hydroxybenzeneacetic acid, 5-trimethylsilyloxy-n-valeric acid, propanedioic acid, hydracrylic acid, and uric acid	GC-MS, Wilcoxon-Mann-Whitney test	During the second and third trimesters, short-chain fatty acids and aromatic amino acid metabolism may be associated with CHD	Xie *et al.*[16]
	Northwestern Portugal	Newborns (Gestational ages: 37–40 weeks)	n = 34 cases; n = 20 controls	Umbilical cord blood and plasma	Troponin I, myoglobin, and creatine kinase-MB mass (CK-MB)	Architect i2000 automated analyzer	Troponin I and myoglobin levels were similar between newborn groups; however, variations in plasma CK-MB levels were identified as marker for surgery	Neves *et al.*[3]
	Caucasian, African American, Asian	Mothers (<30 years)	n = 27 cases; n = 59 controls	Serum	C3-OH (hydroxypropionyl carnitine), C5:1-DC (glutaconyl carnitine), C14:2-OH (hydroxytetradecadienyl carnitine)	MS, and nuclear magnetic resonance (NMR) spectroscopy	During the first trimester, these metabolites showed significant elevation of acylcarnitines, with a sensitivity and specificity of 67.9% and 67.8%, respectively	Bahado-Singh *et al.*[27]
	Dutch native, Western immigrant, Non-Western immigrant (Netherlands)	Mothers (24–41 years)	n = 261 cases; n = 325 controls	Blood	Apolipoprotein B, homocysteine, and triglycerides	Immunoturbidometric assay, liquid chromatography, and Cobas Mira auto analyzer	Apolipoprotein B levels above 85.0 mg/dL were strongly associated an increased CHD risk	Smedts *et al.*[73]

ABCB1, ATP-binding cassette subfamily B member 1, AUC, area under curve, CHD, congenital heart disease, DNA, deoxyribonucleic acid, GC-TOF, gas chromatography-time of flight, *GSTA3*, glutathione S-transferase alpha 3, *MGMT*, O-6-methylguaning-DNA methyltransferase, MS, mass spectroscopy, PCR, polymerase chain reaction, *RFC1*, replication factor C subunit 1, SOLiD, supported oligonucleotide ligation and detection, UTR, untranslated region.

Table 2. Diagnostic and prognostic biomarkers in congenital heart disease

Biomarker category	Region	Participants	Sample size	Type of sample	Assessed biomarkers	Methodology	Findings	Reference
Diagnostic biomarker								
Metabolic biomarker	North Indian	Children (0–20 years)	n = 35 cases; n = 15 controls	Serum	Glucose, valine, acetone, glutamine, creatinine, and PUFA	High-resolution 1D ^{1}H CPMG, and NMR spectroscopy	Patients with CHD showed a significantly decreased concentration of glutamate/glutamine ($P < 0.01$)	Vimal *et al.*[28]
	Japanese	Children (mean age = 11 years), adults (mean age = 24 years)	n = 197 children as cases; n = 102 adults as controls	Serum	Uric acid	Clinical, laboratory variables, and Kaplan-Meier survival curves	Elevated uric acid levels are associated with increased cardiovascular risk ($P < 0.001$)	Ohuchi *et al.*[74]
	Northern UK	Children (4–18.9 months)	n = 28 cases; n = 15 controls	Blood	3-D-hydroxybutyrate, acetone, acetoacetate, citrate, lactate, creatine, creatinine, and alanine	NMR Spectroscopy	Metabolites were directly associated with surgical and CHD severity	Correia *et al.*[75]
Immunological biomarker	Chinese	Patients (4–65 years)	n = 28 cases; n = 6 controls	Serum	Whole proteome spectrum	MS, immunohistochemistry, and Western blotting	Expression of filamin A, caveolin and glutathione S-transferase M1 was significantly decreased in the irreversible CHD-pulmonary arterial hypertension (PAH) group ($P < 0.05$)	Huang *et al.*[51]
	Ankara Turkey	Children (<17 years)	n = 50 cases; n = 20 controls	Plasma	Intercellular adhesion molecules-1 (ICAM-1)	Enzyme linked immunosorbent assay (ELISA) assay	Increased serum levels of VCAM-1 and ICAM-1 ($P = 0.002$) were observed and may serve as markers of endothelium dysfunction and damage associated with CHD	Oguz *et al.*[76]
	Egyptian	Children (<4 years)	n = 120 cases; n = 30 controls	Serum	Tumor necrosis factor (TNF-a), interleukin-6 (IL-6), C-reactive protein (CRP), vascular endothelial growth factor (VEGF), troponin T, CK-MB, and caspase 3	ELISA assay	Level of IL-6, CRP, TNF-alpha were significantly increased in cyanotic CHD as compared with acyanotic CHD	Nassef, *et al.*[77]

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Table 2. *(continued)*

Biomarker category	Region	Participants	Sample size	Type of sample	Assessed biomarkers	Methodology	Findings	Reference
Cardiac biomarker	Southern Swedish	Neonates	n = 34 cases; n = 81 controls	Blood	N-terminal B-type natriuretic peptide (NT-proBNP)	NT-proBNP assay	NT-proBNP testing alone identified 71% of all CHD and 68% of critical CHD (AUC = 0.96, $P < 0.05$)	Clausen *et al.*[78]
	North-western Japan	Children (>3 years)	n = 59 cases	Blood	Troponin, amino-terminal procollagen type III peptide (PIIIP), and B-type natriuretic peptide (BNP)/NT-proBNP	NT-proBNP assay	BNP and NT-proBNP levels showed a strong correlation with myocardial damage and heart failure severity. In atrial and ventricular septal defects, highly sensitive troponin I and PIIIP levels were elevated ($P < 0.01$)	Sugimoto *et al.*[34]
	Japanese	Children (<10 years)	n = 163 cases; n = 42 controls	Serum	PIIIP	Immuno-radiometry, (IRMA) kit	PIIIP levels were significantly elevated in CHD patients ($P < 0.001$)	Sugimoto *et al.*[79]
Imaging biomarker	North Indian	Children	-	Organ examination	Imaging analysis	2D, and 3D echo-cardiography	Echocardiography is a non-invasive tool for assessing the structural and functional characteristics of the heart	Tomar *et al.*[80]
	France	Children	-	Organ examination	Imaging analysis	Cardiac magnetic resonance imaging (cMRI), computed tomography (CT) scan	Advanced imaging screening improved patient life expectancy and lifestyle outcomes	Dacher *et al.*[81]
	USA	Newborns	-	Oxygen level examination	Oxygen saturation analysis	Pulse oximetry	Infants with positive pulse oximetry screening results should undergo diagnostic echocardiography	Harold *et al.*[82]

(continued)

Table 2. *(continued)*

Biomarker category	Region	Participants	Sample size	Type of sample	Assessed biomarkers	Methodology	Findings	Reference
Prognostic biomarker								
Prognostic biomarker	Eastern Chinese	Children (mean age = 6 years)	n = 65 cases; n = 17 deceased cases used as controls	Blood	B7-H3 (CD276)	ELISA	Higher serum levels of B7-H3 ($P < 0.001$) were significantly associated with major cardiovascular events (heart muscle disease and arrhythmias), and increased mortality in CHD patients	Zhang *et al.*[83]
	Netherlands	Adults	n = 59 cases; n = 12 deceased cases used as controls	Blood	Cystatin C	Electrochemiluminescence immunoassay (Elecsys 2010 analyzer)	Elevated cystatin C levels ($P < 0.001$) predicted long-term mortality and adverse clinical events in PAH-CHD patients	Blok *et al.*[84]
	Spain	Children (<14 years)	n = 40 cases	Plasma	NT-proBNP	Electrocardiogram, chest X-ray, NYHA scale, and 2D-SSFP sequence	In surgically corrected tetralogy of Fallot patients, NT-proBNP levels were associated with right ventricular dilatation	Valverde *et al.*[85]
	Chinese	Children (1 month–18 years)	n = 77 cases; n = 81 controls	Plasma	Vitamin B12, homocysteine, and hydrogen sulfide	Fluorescence polarization immunoassay, ELISA, and radioimmunoassays	Elevated homocysteine levels and reduced hydrogen sulfide levels ($P < 0.001$) were negatively correlated in PAH associated with CHD, suggesting a role in prognosis and quality of life outcomes	Sun *et al.*[86]
	Germany	Children (mean age = 6 years)	n = 288 cases; n = 152 controls	Venous blood	BNP	Sandwich immunoassay (Triage BNP assay)	Normal BNP levels cannot exclude cardiac pathology but may reflect a compensated cardiac condition	Koch *et al.*[33]

AUC, area under curve, CHD, congenital heart disease, CPMG, Carr-Purcell-Meiboom-Gill, MS, mass spectroscopy, NMR, nuclear magnetic resonance, NT-proBNP, N-terminal pro-B type natriuretic peptide, PUFA, polyunsaturated fatty acid.

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dence suggests that markers such as galectin-3, ST2, NT-proBNP, and glial fibrillary acidic protein improve prediction of unplanned readmission and mortality when combined with clinical risk models.[99,100] Nonetheless, these findings require validation in larger, multicenter cohorts before routine clinical implementation.

Conclusions

Although substantial progress has been made in identifying biomarkers associated with CHD, the search for an ideal biomarker that is feasible, reproducible, cost-effective, and clinically actionable remains ongoing. Current evidence supports a multimodal approach integrating metabolic, molecular, immunological, and imaging biomarkers rather than reliance on a single indicator. Early identification of risk, particularly during the periconceptional and early gestational periods, holds the greatest promise for reducing the global burden of CHD. Continued advances in omics technologies, coupled with well-designed longitudinal studies, are likely to accelerate the translation of biomarker research into effective prevention, diagnosis, and personalized management strategies for CHD.

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Conflict of interest

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Author contributions

SA is the sole author of the manuscript.

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