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Maternal Nutritional and Metabolic Determinants of Congenital Heart Disease in Punjab: A Narrative Review and Prevention Framework

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Abstract: Congenital heart disease (CHD) is considered to be the most common clinically significant congenital anomaly in the world. Nearly one-third of all major birth defects and neonatal mortality can be attributed to CHD. While genetic and chromosomal defects may explain a proportion of cases, most evidence indicates that non-genetic, modifiable maternal factors determine fetal cardiac development. This review aims to evaluate the biological, contextual, and epidemiological evidence on maternal nutrition and metabolic factors associated with CHD, with an emphasis on the state of Punjab, India. The Punjab region in India is popular for agricultural profusion, recurring insufficiency of maternal nutrition, and associated maternal metabolic disorders. Examination of current research that connects maternal micronutrient deficiencies, such as vitamin B12, folate, and zinc, and disorders such as maternal obesity and gestational diabetes to the heightened risk and severity of CHD is the major focus of this review. It further delves into the mechanistic pathways, particularly the impaired one-carbon metabolism, epigenetic dysregulation, oxidative stress, and fuel-mediated teratogenesis, which disrupt the early cardiogenesis during the critical window of 3 to 8 weeks of gestation. These biological mechanisms are situated within the social, cultural, and health ecosystem of Punjab, identifying gaps in care for preconception, dietary diversity supplementation, continuity, and early CHD detection. Finally, the review proposes an integrated framework for care prevention that spans the preconception, antenatal, and postnatal stages. This review emphasizes viewing food security through a broader perspective of nutritional security and maternal health throughout life to initiate discussions on targeted public health approaches to reduce the burden of CHD in agrarian settings.

Keywords: *Maternal Malnutrition, Congenital Heart Disease (CHD), Micronutrient Deficiency, Gestational Diabetes Mellitus, One-Carbon Metabolism, Fetal Cardiogenesis, Preventive Cardiology.*

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I. INTRODUCTION

Neonatal morbidity and mortality are largely governed by the existence of congenital anomalies throughout the world. Congenital heart disease (CHD) is considered to be the most common birth defect that's consequential[1]. One-third of all congenital abnormalities can be attributed to CHD after evaluating the results from the meta-analysis that covers over 24 million live births all over the world. Studies typically estimate a global birth prevalence of CHD in the range of 8-12 per 1,000 live births (with many analyses converging near 9 per 1,000), with reported prevalence in South Asia ranging from 7-10 per 1,000 live births, likely underestimated due to underdiagnosis [2], [3]. This translates to approximately 1.3-1.4 million newborns entering the world with CHD each year, of whom over 90% are born in low- and middle-income countries, according to the analysis of global birth data. Despite these concerning statistics, CHD is under-recognized and under-resourced, especially in countries where low- and middle-income groups dwell. Constraints in infrastructure for diagnosis, delayed identification of disorders, and disparate access to cardiac care of infants and newborns constitute the staggering public health burdens resulting in detrimental long-term outcomes [4], [5].

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The state of Punjab in India is a leading agricultural state, contributing to national food security and rural livelihoods. Though it's considered the nation's breadbasket, there lies an alarming, largely overlooked public health challenge[5]. A sizeable section of Punjab's agrarian communities suffers from nutritional insufficiency. Surveys of women within the reproductive age report deficiencies in folate (20 to 40%), vitamin B_{12} (40 to 70%), and zinc (over 30%). This is the paradox in Punjab, worth pondering. Following a diet with limited diversity, traditional monoculture cropping, and economic inequality in society suggest that caloric intake need not always equate to micronutrient adequacy[6],[7]. These concerns over nutrition can pose challenges to maternal and child health. In this scenario, it highlights nutritional vulnerability, a condition in which individuals have adequate caloric intake yet are prone to inadequate micronutrient intake or to the unavailability of micronutrients essential for physiological and developmental functions[8].

Fetal organogenesis may be disrupted by imbalanced nutrition, leading to critical delays in cardiac development. The risk for CHD may be elevated within regions of agricultural surplus, which has the potential to translate into a few thousand CHD-affected births annually at the state level, though available documentation is limited. A major blind spot in the public health map of Punjab is highlighted by the notion that agricultural sumptuousness can coexist with a high prevalence of prenatal nutritional risk[9]. Here, the assumption that food availability would consistently ensure maternal and fetal nutrition and well-being remains challenged, suggesting the need for a shift in paradigm towards nutritional security rather than food security (International Institute for Population Sciences (IIPS) and ICF. 2021, National Family Health Survey (NFHS-5), India, 2019-21: Punjab. Mumbai: IIPS).

In this context, a systematic analysis of CHD regions, such as Punjab, is vital to quantify the burden of CHD at the state and district levels. A thorough assessment of maternal micro- and macronutrient status among pregnant women in agrarian communities is important. The associations between maternal nutrition and CHD outcomes in newborns have to be assessed. Such approaches would not only help identify modifiable risk factors for public health interventions but also facilitate evidence-based policymaking on antenatal care, maternal nutrition, and congenital disease surveillance. This narrative review aims to collect existing evidence on the role of maternal nutritional and metabolic factors in the development of CHD. It intends to aid in identifying the association between CHD and important micronutrient deficiencies, such as vitamin B_{12} and zinc deficiencies. It also explores how maternal metabolic conditions, such as obesity and gestational diabetes, are linked to CHD. The perturbations in one-carbon metabolism, epigenetic regulation, and oxidative stress pathways, as well as the effects of these exposures on the impairment of fetal cardiac genesis, are explored. A comprehensive, context-specific preventive framework is designed for Punjab to transform current evidence into practical public health protocols.

II. METHODS

The existing literature on maternal, nutritional, and metabolic determinants, with a contextual focus on the state of Punjab in India, was selected for review. Delving through PubMed, Scopus, and Google Scholar helped identify relevant literature. A combination of keywords, including congenital heart disease, maternal nutrition, micronutrient deficiency, folate, vitamin B_{12}, zinc, gestational diabetes, maternal obesity, epigenetics, and Punjab, was used to generate relevant data. Research results were refined with Boolean operators such as AND and OR. Articles published within the last 15 years gained priority in the search. An extensive search for evidence from systematic reviews, meta-analyses, large cohort studies, and population-based investigations was conducted. Tracking citations from relevant articles helped gather valuable information. Reports from national health agencies were unavoidable, as they added to the epidemiological and contextual comprehension for the review. Though this study does not employ formal systematic review protocols, it aims to synthesize and interpret existing evidence to provide a comprehensive overview and propose a conceptual framework to prevent CHD in Punjab. As more studies are observational, findings are reported as associations. These observational studies are heterogeneous, and the reported risk estimates illustrate general trends rather than conclusive effect sizes. The National Family Health Survey-5 (NFHS-5) helped to derive information pertinent to Punjab regarding maternal malnutrition and CHD. NFHS-5 is a nationally representative, population-based survey that provides population-level estimates of health and nutrition (International Institute for Population Sciences (IIPS) and ICF, 2021, National Family Health Survey (NFHS-5), India, 2019-21: Punjab. Mumbai: IIPS). NFHS-5 includes indicators such as anemia prevalence, body mass index (BMI), and blood glucose levels, which are effective proxies for nutritional and metabolic status. Biochemical assessments of micronutrients are absent from the survey. Although anemia is used to indicate micronutrient deficiency, gaps in the survey hinder its ability to analyze the spectrum of micronutrient inadequacies.

III. MATERNAL MALNUTRITION AND METABOLIC STRESS AS MODIFIABLE DRIVERS OF CHD

There's enough literature that attributes CHD to genetic and chromosomal abnormalities. Recent research highlights the significant role of non-genetic, modifiable maternal features in shaping fetal cardiac development [10]. Maternal nutritional status encompasses micro and macronutrient sufficiency, dietary quality, and metabolic health and is among the most addressable determinants of CHD risk [10]. Epidemiological studies that rely on case-control and cohort designs report approximately a 1.5- to 3-fold increase in risk of CHD with specific micronutrient deficiencies [10]. The metabolic and nutritional influences are amenable to population-level interventions, unlike genetic traits. Such an agreeable impact

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makes it pertinent from both mechanistic and public health points of view.

A sequence of molecular and cellular events occurs within 8 weeks of gestation, even before the pregnancy is clinically diagnosed [11], [12]. It is a crucial period during which the embryo is completely dependent on nutrients supplied by the mother, which leads to the support of the synthesis of nucleic acids, the multiplication of cardiomyocytes, the migration of neural crest cells, the maintenance of the redox balance, and the assistance in the structural patterning of the components of the heart. Even mild but chronic deficiencies at conception can therefore exert disproportionate effects; significant increases in risk have been reported across multiple observational studies on cardiac morphogenesis involving micronutrients [13], central regulators of one-carbon metabolism, nucleotide biosynthesis, and epigenetic methylation processes that govern gene expression during cardiogenesis[14], [15]. Experimental and mechanistic studies suggest that insufficient maternal intake may alter DNA methylation pathways. Human observational studies have reported associations between low folate or vitamin B_{12} levels and an increased risk of CHD. Zinc deficiency impairs transcription factor activity, cellular proliferation, and oxidative stress regulation, with experimental and epidemiological studies linking zinc insufficiency to a broad spectrum of structural cardiac malformations in agrarian regions such as Punjab [14], [16]. Substantial zinc deficits are associated with cereal-based, low-diversity diets, partly influenced by predominantly vegetarian dietary patterns[17].

Parallel to micronutrient inadequacy, Punjab bears one of the highest liabilities of maternal obesity and gestational diabetes mellitus in India, with gestational diabetes (typically diagnosed during pregnancy), which may be reflected at earlier stages[18]. The metabolic dysregulation estimates range from 10% to 30%, and overweight or obesity affects more than one-quarter of pregnant women. Hyperglycemia during early pregnancy is among the most potent and non-genetic teratogens affecting cardiac development, mainly during the period of cardiac morphogenesis[19]. Oxidative stress is induced by excess lipids and maternal glucose, which can disrupt essential mitochondrial functions. This results in alterations in apoptotic signals, which impair the survival and migration of neural crest cells [20]. Maternal obesity, even when hyperglycemia is absent, carries the risk of prolonged inflammation and altered lipid metabolism [21]. Such metabolic dysregulations and micronutrient inadequacies converge on developmental pathways, even when they originate through different routes. Estimates suggest that at least 30% of women entering pregnancy in Punjab (where there is coexistence of micronutrient insufficiency and excess metabolic determinants) are exposed to the depleting methyl-donor effect during chromatin regulation and intensified oxidative stress. Overlapping biological pathways arise from co-occurring exposures that lead to epigenetic dysregulation and oxidative stress, increasing the overall risk of abnormal heart development [22]. A broader phenomenon of the dual burden of malnutrition is manifested in these co-occurrences, characterized by energy-dense yet micronutrient-poor diets. The dietary patterns dependent on wheat-based staples, inadequate intake of dietary fiber from fruit and vegetables, vegetarianism without ensuring adequate implementation, sedentary lifestyles, and intergenerational nutritional stress contribute to a contradictory state in which women enter pregnancy being overweight and micronutrient-deficient [23].

Diversifying the diet with micronutrient- and fiber-rich foods, food fortification, and targeted supplementation could reduce the burden of maternal malnutrition. Essential screening for metabolic factors and sustained care throughout the antenatal and preconception stages hold considerable potential to mitigate the incidence of CHD [24]. These measures are beyond the realm of academic interest and strictly concern advancing preventive cardiology and upgrading maternal-child health policies, particularly in regions facing the dual burden of malnutrition, even when there's apparent agricultural prosperity.

- *Epigenetic Mechanisms in Micronutrient Deficiency*

Epigenetic marks that control early embryonic development are realized by micronutrients that are actively involved in one-carbon metabolism [25], [26]. These nutrients render the methyl groups, which are used in the synthesis of S-adenosylmethionine (SAM). SAM is regarded as the universal methyl donor for DNA, histone, and RNA methylation [27]. During morphogenesis of the heart, epigenetic regulation ensures the precise temporal and spatial activation of genes, supporting cell lineage specification and associated migration, proliferation, and structural patterning [28]. During the early stages of pregnancy, if there's a micronutrient deficiency, epigenetic processes are disrupted, resulting in defective heart development.

The most serious consequence of micronutrient deficiency is DNA hypomethylation[29], with studies reporting reduced global DNA methylation levels; however, in human populations, these measurements are typically derived from surrogate tissues, such as maternal or cord blood[30]. A reduction in SAM availability may lead to global and gene-specific hypomethylation, particularly in the promoters of genes essential for cardiac development[31]. Experimental studies have shown that key transcription factors such as NKX2-5 and GATA4 can be expressed under conditions of disrupted methylation; however, direct evidence of such alterations in human fetal cardiac tissue remains limited[32]. Genes involved in neural crest cell migration and outflow tract development are dysregulated, increasing susceptibility to septal defects and conotruncal abnormalities. These methylation changes, well-illustrated in experimental systems, are thought to be particularly relevant during early organogenesis, although direct evidence in human populations remains limited. The methylation changes were especially damaging because they occur during early organogenesis (week 3 to 6 of gestation, when over 80% of cardiac structural

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patterning is established), when epigenetic marks are newly established and are highly sensitive to environmental inputs. Alterations in histone modifications resulting from micronutrient deficiency disrupt chromatin accessibility to genes. Inadequate availability of methyl donors disrupts the activation and repression of histone markers, such as H3K4me3 and H3K27me3. This leads to inappropriate opening of silenced chromatin regions that contain cardiac developmental genes [33]. Micronutrient deficiency can lead to imprecise boundaries of gene expression and impaired coordination of signaling pathways required for normal heart formation. Specifically, the zinc deficiency disturbs the zinc-finger transcription by disturbing the binding of GATA and Krüppel-like family members, which are essential to ensure the proper formation of the heart [34].

The regulatory microRNA that ensures cardiomyocyte proliferation, differentiation, and apoptosis is affected by micronutrient inadequacy [35]. The altered microRNA results in perturbing the equilibrium between cell growth and predetermined cell death, resulting in impaired cardiac tissue formation. The adaptable strategy to prevent CHD is the intake of adequate micronutrients at all stages of pregnancy. It is worth noting that much of the human evidence linking maternal micronutrient status to epigenetic modifications is derived from accessible surrogate tissues, such as maternal peripheral blood or cord blood. Indirect investigation of epigenetic changes in human embryonic or fetal cardiac tissue is inherently limited by ethical and technical constraints. Thus, many mechanistic comprehensions into gene regulation throughout cardiogenesis are inferred from experimental models and should be interpreted with appropriate caution when extrapolated to human development.

IV. OXIDATIVE STRESS AND FUEL-MEDIATED TITRATOR GENESIS IN MATERNAL DIABETES

Maternal diabetes, particularly preexisting (pregestational) diabetes, is among the most significant non-genetic risk factors for CHD, especially when associated with hyperglycemia during the earlier stages of pregnancy[36]. It is important to distinguish between pre-existing diabetes and gestational diabetes mellitus (GDM) in the context of fetal cardiac development. Cardiac morphogenesis occurs primarily during the first 3 to 8 weeks of gestation, during which pre-existing hyperglycemia has the most direct impact on embryonic development. Although GDM is typically diagnosed during the second trimester, around 24 to 28 weeks, indications suggest that metabolic dysregulation and mild hyperglycemia may be present earlier in pregnancy but remain undetected. Thus, some pregnancies classified as GTM may involve early gestational exposure to hyperglycemia, which could influence cardiac development. Its petrogenetic and teratogenic effects arise from a complex metabolic setting termed "fuel-mediated teratogenesis," in which readily accessible maternal glucose, lipids, and ketone bodies readily cross the placenta and directly perturb embryonic development, as the early embryo has limited metabolic flexibility and immature antioxidant defenses.

Diabetes-induced CHD is governed by an oxidative stress mechanism[37]. Hyperglycemia is associated with increased generation of reactive oxygen species (ROS), as observed in experimental and animal studies. A striking link to CHD is provided by human studies pointing to GDM. Hyperglycemia is responsible for ROS generation in embryonic tissues, which extends to mitochondrial dysfunction. Causing oxidative damage to DNA and interrupting redox-sensitive signaling pathways are other manifestations. Certain developmental processes of the heart are disrupted, altering the gene expression patterns essential for normal heart formation. The neural crest cells of the heart are sensitive to oxidative and metabolic stress, yet a direct observation of these processes in human embryos is limited. In pregnancies with GDM, ROS-mediated apoptosis and faulty migration of these cells have been associated with anomalies in conotruncal development, thereby increasing the risk of defects[38]. Developmental regulators, including PAX3, HAND2, and Sonic Hedgehog, further disrupt cardiac patterning and structural integration[39]. Additional mechanisms are quite capable of complicating the teratogenic environment. Altered nitric oxide synthesis weakens nitric oxide signaling, affecting vasculogenesis and endocardial cushion formation, which are decisive for heart formation [40]. When oxidative stress remains persistent, it compromises the functioning of mitochondria and may lower ATP availability, thereby failing to support the rapid proliferation and differentiation of the cardiac cells[41]. Population-based evidence collected from Punjab accentuates the consequence of these mechanisms, with population screening studies targeting tens of thousands of pregnancies [42].

V. INTEGRATED EPIGENETIC AND METABOLIC PATHWAYS IN THE PATHOGENESIS OF CHD

The successful prevention and screening of CHD in Punjab is challenged by tangled systemic, cultural, and clinical barriers. Most women enter pregnancy without proper preconception care, including evaluation of nutritional status. This facilitates the development of micronutrient deficiencies, even in the presence of obesity or insulin resistance. There are implementation challenges beyond continuity, including differences in coverage across the state's supplementation programs. Inadequate counseling and insufficient attention to micronutrients, particularly in a predominantly vegetarian population, compound these challenges. Voids exist in determining CHD through the course of prenatal and postnatal stages, including lower rates of early abdominal scans, low access to echocardiography of the fetus, delaying the early screening, and seeking care due to a lack of awareness. These systemic weaknesses that compile socio-cultural perceptions and clinical limitations contribute to delayed diagnosis and augmented illness rates, leading to the inability to assess the

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true CHD burden within Punjab. It leads to a situation in the state in which nutrition- and metabolism-linked CHD persists despite its structural and agricultural advancements.

It is obvious that the strategies adopted in Punjab against CHD must start much before pregnancy by supporting primary prevention through a structured preconception care. The proposed framework, discussed below, identifies the need to reduce risk factors before disease onset, to detect disease early, to improve clinical outcomes, and to provide long-term management. It is proposed as a conceptual, evidence-informed model based on existing literature and is anticipated to guide future research and policy development, as well as public health strategies, rather than to demonstrate clinical effectiveness.

The primary prevention includes routine screening of women of reproductive age for nutritional deficiencies, obesity, and metabolic risk (Kaur, R. (2018). Sorry State of women Health In Punjab. Amity International Journal of Legal & Multidisciplinary Studies). This works alongside the intermittent folic acid and iron supplementation and targeted vitamin B12 and zinc support. Dietary patterns rely on food-based approaches, including wheat flour fortification and programs that support weight management. Family planning counseling and careful interventions are essential to lessen internal risk. The primary healthcare and available nutrition platforms within the state should disseminate these services and monitor by implementing measurable indicators. Secondary prevention is focused on the pregnancy stage, with early risk detection and mitigation during acute periods of fetal development. Early antenatal registration, universal screening for gestational and pregestational diabetes, timely initiation of folic acid and micronutrient supplementation, context-specific nutrition counseling, and strengthened parental education skills need to be imparted[43]. Early detection of CHD can be realized through anomaly scans in time and following referral pathways for fetal echocardiography. Essential integration with existing antenatal services offered within the state and participation in nationwide programs offered by the national health ministry are important. Careful capacity-building interventions for sonographers and clinicians would improve quality and progress, as evidenced by early registration rates, glycemic control, and completion of recommended scans. Tertiary prevention is offered after birth and is critical for reducing CHD-related mortality and long-term disability through early detection, referral, and sustained care. It is understood that 60 to 80% of critical CHDs can be identified with universal newborn pulse oximetry screening. Postoperative follow-up, nutritional recovery, and monitoring of the neurodevelopmental model are essential. Strategies to implement programs to offer financial and psychosocial support for families can further improve outcomes. This is where effective coordination among governmental schemes, primary health centers, and insurance schemes becomes pertinent. The existing and ongoing research and scrutiny should yield district-level evidence on nutritional status, metabolic risk, and CHD incidence. The factors that can undermine the benefits of these strategies for grassroots populations have to be identified. The strategies suggested are cohesive and measurable, helping transform Punjab's agricultural and nutritional possibilities to reduce CHD burden and improve maternal and child health.

Table 1. Maternal Nutritional and Metabolic Indicators in Punjab (NFHS-5)

Indicator	Value (Punjab, NFHS-5)	Population Group	Interpretation
Anemia prevalence	59%	Women aged 15-49 years	Indicates a high burden of iron deficiency and overall micronutrient vulnerability
Overweight/Obesity (BMI ≥25 kg/m²)	~40%	Women aged 15-49 years	Reflects rising metabolic risk and dual burden of malnutrition
Underweight (BMI <18.5 kg/m²)	~9-10%	Women aged 15-49 years	Suggests persistent undernutrition in a subset of the population
Elevated blood glucose levels	~8 -10%	Women aged 15-49 years	Proxy for diabetes or prediabetes; indicates metabolic dysregulation
Antenatal care (≥4 visits)	~58-60%	Pregnant women	Moderate healthcare access; gaps remain in maternal monitoring
Institutional deliveries	~95%	Recent births	High healthcare utilization at delivery stage
Iron supplementation during pregnancy	~30-35% (≥100 days)	Pregnant women	Suboptimal compliance with recommended supplementation

Table 1 juxtaposes exposure frequency with effect size and highlights why moderate risk elevations may translate into a significant CHD burden in high-exposure settings such as Punjab (NFHS-5). Though maternal anemia and the growing prevalence of metabolic disorders in Punjab[44], [45] impose a dual burden of malnutrition, direct biochemical data on key micronutrients remain an important limitation for population-level nutritional assessment. This scenario also highlights the need for more comprehensive biomarker-based assessments in future population health services. To ensure regional specificity and data consistency, the summary table has been restricted to indicators reported in NFHS-5 for Punjab (International Institute for Population Sciences (IIPS) and ICF. 2021, National Family Health Survey (NFHS-5), India, 2019-21: Punjab.

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Mumbai: IIPS), while micronutrient deficiencies not directly captured in the survey are discussed separately based on available literature.

VI. CONCLUSIONS

The illness and death among infants in Punjab are largely associated with CHD yet are inadequately addressed. The Indian state of Punjab experiences a paradox in which agricultural abundance is accompanied by profound maternal nutritional vulnerability and the co-occurrence of micronutrient insufficiency. This escalates the epidemic of maternal obesity and GDM and is associated with an adverse intrauterine ecosystem affecting pregnancies to some extent. Such adversity may elevate the risk of structural cardiac deformities. There is substantial experimental and epidemiological evidence for the biological pathways underlying these risks. When the fetal heart is sensitive to distress, epigenetic dysregulation, impaired one-carbon metabolism, oxidative stress, and fuel-mediated teratogenesis are obvious. However, these risks remain largely manageable, accentuating the potential to implement preventive measures. Existing challenges in Punjab can create gaps in both the health system and social determinants, leading to delays in identifying CHD risk factors. In such a scenario, the transition from the existing pregnancy-centered care to a prospective life-course approach that highlights women's metabolic and nutritional health and well-being before conception while reinforcing antenatal screening, ensuring dietary variety and continuous micronutrient availability, and enhancing fetal and newborn CHD detection capabilities. An all-inclusive tiered prevention model spanning primary, secondary, and tertiary postnatal strategies targeting pre-pregnancy, pregnancy, and post-pregnancy, respectively, offers a logical trail forward. The implementation of these strategies will require coordinated efforts across all sectors of health, agriculture, and community systems, supported by robust surveillance and evidence-driven policymaking. These practices may help Punjab mitigate the burden of CHD through targeted, evidence-informed approaches.

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