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# Review Article

# Noninherited Risk Factors of Congenital Heart Defects in Offspring: A Review

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**Abstract**

*Prognosis of children with congenital heart defects (CHDs) continues to improve with advancement in technology and training in pediatric cardiology and cardiac surgery; however, lack of information about risk factors for malformations in cardiovascular development impeded the prevention of CHDs. Etiology of CHDs are complex and possibly lies within the interaction of environmental exposures and inherited factors. Studies found multiple maternal environmental exposures, including living in newly renovated rooms, residential proximity to main traffic, smoking and maternal occupation as manual worker significantly associated with CHDs. Advanced maternal age, low socioeconomic status, maternal perinatal diseases including maternal fever, diabetes, influenza, maternal certain medication use and alcohol intake were also significantly associated with CHDs. Isolated CHDs and multiple defects have different profiles of risk factors, while subtype of CHDs share common risk factors. Because of differences in methods, these studies are only suggestive. Relatively less information has been reported on noninherited factors that may have an adverse effect on the cardiovascular development, which has made it difficult to create population-based strategies to reduce the burden of illness from CHDs and for couples to choose lifestyles to reduce the risk of delivering a child with CHDs.*

***Keywards:*** *Noninherited, risk factors, congenital heart defects.*

## Introduction

With advances in perinatal care, congenital malformations are emerging as one of the leading cause of neonatal and infant mortality, even in developing countries.[1] CHDs represent approximately one-third of all congenital anomalies and are the leading cause of perinatal mortality.[2] CHDs comprise a wide range of malformations of the heart and great vessels, reflecting the complexity of developmental processes and potential disturbances in morphogenesis of the cardiovascular system. CHDs affecting almost 1% of live births throughout the world.[3] Improvement in perinatal care, diagnosis and orientation or awareness among general pediatrician and early referral has resulted in an increase of reported prevalence of CHDs in Bangladesh also.[4,5] Although advancement in pediatric cardiology and pediatric cardiac surgery have improved long term outcome and promised better quality of life, the etiology of most congenital heart defects are still unknown. Several chromosomal anomalies, certain maternal illnesses, and prenatal exposures to specific therapeutic drugs are recognized risk factors. It is difficult to establish the role of a single factor because the cause of a defect is believed to be multifactorial in many cases, including the combination of environmental teratogens with genetic and chromosomal conditions.[6] The prognosis of children with CHDs continues to improve with advancing surgical techniques; however, lack of information about modifiable risk factors for malformations in cardiovascular development impeded the prevention of CHDs. Clinicians and basic scientists

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have understood the sources of these cardiovascular developmental errors, and there is wide acceptance of the opinion that the etiology of CHD is complex and possibly lies within the interaction of environmental exposures and inherited factors.[7]Although CHDs can occur in the setting of multiple birth defects as part of a syndrome, most are found as isolated defects with no syndromic association. Over the past decade, a multitude of research studies have identified both chromosomal and gene mutations as causation for the syndromic heart malformation.[8,9] Despite a strong heritable basis, a genetic etiology is identified in less than 20% of CHD cases.[10] This reflects a combination of the low sensitivity of routine cytogenetic testing at detecting rare or de novo mutations associated with isolated CHD, and the unmeasured contribution of complex gene environment interactions to CHD.[11] Oyen et al[12] estimated recurrence risk ratios and found that among first-degree relatives, the recurrence risk ratio was 79.1 for heterotaxia, 11.7 for conotruncal defects, 24.3 for atrioventricular septal defect, 12.9 for left ventricular outflow tract obstruction, 48.6 for right ventricular outflow tract obstruction, 7.1 for isolated atrial septal defect and 3.4 for isolated ventricular septal defect. The overall recurrence risk ratio for the same defect was 8.15, whereas it was 2.68 for different heart defects. Fung et al[13] found parental consanguinity in 3.5% of cases with CHD which was comparable to controls. The lesions most strongly associated with a positive family history were left heart lesion, PDA and right heart lesion. Twenty three percent of cases with a positive family history underwent genetic testing; overall positive yield was 32% (i.e. 32% of all cases tested showed abnormalities). Fung et al[13] also described advanced parental age and association of CHD. They found association of CHDs and older maternal age (OR: 1.18 [1.06 to 1.30] per 10 year increase in age at conception, p=0.002). Advanced parental age was associated with increased odds of CHD was limited to CHD patients with genetic abnormalities (OR: 1.10 [1.01 to 1.20] per 10 year increase in age at conception, p=0.02).

However, lack of enough information about modifiable risk factors for malformations in fetal heart development has impeded the prevention of CHDs. Moreover, CHDs include several distinct subtypes (e.g., conotruncal defects, left ventricular outflow track defects, and septal defects) and there is a potential for etiologic heterogeneity. Therefore, it is not surprising that studies for categories of CHDs report different or opposite results.

Maternal prepregnancy body mass index, maternal urinary tract infections, type 1 diabetes and exposure to nonfertility medications during pregnancy. Later year of birth, family history of CHD, presence of major Extra Cardiac Anomalies (ECAs), maternal smoking during pregnancy, and maternal medication exposure were associated with increased odds of CHD.[13] One recent study in China showed that multiple maternal environmental exposures, including living in newly renovated rooms, residential proximity to main traffic, paternal smoking, and maternal occupation as manual worker, were significantly associated with CHDs with ORs ranging 1.30-9.43. Maternal perinatal diseases (including maternal fever, diabetes, influenza and threatened abortion), maternal medication use (antibiotic use), advanced maternal age, low socioeconomic status and paternal alcohol intake were also significantly associated with CHDs, with ORs ranging 1.60-3.96. Isolated CHDs and multiple defects have different profiles of risk factors, while subtype of CHD shares common risk factors.[14]

Recent epidemiologic studies have demonstrated an association between maternal lifestyle factors, specifically smoking, alcohol, illicit drugs use, caffeine use, body mass index and psychological factors and the risk of CHDs in offspring.[15] More recently, classification of CHDs to account for variation of phenotypes based on the complexity of cardiac lesions present (ie, simple, associations, complex) and for the presence of disorders in other organ systems (ie, isolated or multiple/complex pattern), further developed.[16] These developments in nomenclature and classification, in turn, have facilitated more reliable assessments of trends in population-based prevalence of specific phenotypes of CHDs[17] and standardized research methods for the purpose of identifying modifiable risk factors and potential prevention interventions for CHDs. An exploration of the contribution of noninherited risk factors that are potentially modifiable is particularly important in the context of the growing health burden of CHD.[18]

Reports linking environmental exposures to birth defects have steadily increased. However, a failure to routinely ascertain environmental exposures during pregnancy, difficulty in quantifying these exposures and maternal recall bias limit the ability to determine causality.[19]

While the origin of non-syndromic CHD that accounts for most of congenital cardiac abnormalities is still under the veil waiting to be further uncovered. Relatively less information has been reported on noninherited factors that may have an adverse effect on the cardiovascular development, which has made it difficult to create population-based strategies to reduce the burden of illness from CHDs and for couples to choose lifestyles to reduce the risk of delivering a child with CHDs. This review therefore performed a comprehensive analysis of literatures for environmental risk factors of CHD.

**Maternal socioeconomic status (SES) and lifestyle factors and CHD**

SES is customarily determined by educational achievement, family income and occupational prestige. Studies reported association between maternal lifestyle factors during pregnancy and the risk of offspring with CHDs. Children born in low SES had significantly higher rates of CHDs (rate ratio = 1.20; 95% confidence interval [CI] = 1.15-1.24).[20] Study provides evidence of an association between low SES and an increased risk of CHDs, including maternal educational attainment, family income and maternal occupational prestige. No clear relationship was found between socioeconomic status and CHDs in developed countries.[21] An epidemiological case-control study was conducted in Kaunas city during 1999-2005, showed that low and moderate maternal education significantly increased the risk of congenital heart defects (OR=3.43; 95% CI, 1.54-7.64). The housewives and workers had a higher risk of delivering a newborn with CHDs than the office workers (OR=2.34; 95% CI, 1.34-4.10 and OR=1.28; 95% CI, 0.79-2.07, respectively).[22]

Yu et al[21] reviewed more than 50,000 cases for risk factors of CHDs. They concluded that lower degree of maternal socioeconomic status is modestly associated with an increased risk of CHDs. In regard to family income and occupational prestige, results showed that the lowest income category and occupation levels increased the risk of CHDs compared with the highest. Many factors could explain this finding. First, poor education is always accompanied by smoking[23] and diabetes mellitus[24] which have both been shown to be associated with an increased risk of CHDs.[25]

Possible associations between maternal lifestyle factors and CHDs, we must remember that such associations from observational studies may be due to the exposures or factors of interest, but they may also be a result of chance, bias or confounding. Because of differences in methods most of the studies are suggestive. An observational study can yield an association as a result of sampling variation of the controls or multiple comparisons in an exploratory study. Since the assessment of exposure to many factors is often based on parental recall after the birth of the child, recall bias should be concerned.[18] The mechanisms by which maternal lifestyle factors may result in CHDs still remain unknown. However, further prospective studies are needed to confirm the association.

**Effects of environmental chemical contamination in congenital heart disease**

There is compelling evidence that prenatal exposures to environmental xenobiotics adversely affect human development. A growing number of studies have indicated the potential role of environmental agents as risk factors in CHD occurrence. In particular, maternal exposure to chemicals during the first trimester of pregnancy represents the most critical window of exposure for CHDs. Specific classes of xenobiotics (e.g. organochlorine pesticides, organic solvents, air pollutants) have been identified as potential risk factors for CHD.[26] Nonetheless, the knowledge gained is currently still incomplete as a consequence of the frequent heterogeneity of the methods applied and the difficulty in estimating the net effect of environmental pollution on the pregnant mother.

***Maternal occupational exposure to chlorinated solvents, aromatic solvents and stoddard solvent and CHD:*** Evidence of association between CHDs in offspring and estimated maternal occupational exposure to chlorinated solvents, aromatic solvents and Stoddard solvent during the period from 1 month before conception through the first trimester was found in a study. Exposure to any solvent and any chlorinated solvent with perimembranous ventricular septal defects (OR 1.6, 95% CI 1.0 to 2.6 and OR 1.7, 95% CI 1.0 to 2.8, respectively). Associations were observed for: any solvent exposure with aortic stenosis (OR 2.1, 95% CI 1.1 to 4.1) and Stoddard solvent exposure with d-transposition of the great arteries (OR 2.0, 95% CI 1.0 to 4.2), right ventricular outflow tract

obstruction defects (OR 1.9, 95% CI 1.1 to 3.3) and pulmonary valve stenosis (OR 2.1, 95% CI 1.1 to 3.8).[27] In a case-control study using an assessment of occupational tasks, women's occupational exposures to dyes and pigments and insecticides increased risks of delivering infants with conotruncal defects (Odds ratios of 1.5).[28]

***Trichloroethylene-contaminated drinking water and CHD:*** The organic solvent trichloroethylene (TCE) is a metal degreasing agent and an intermediate in the production of fluorochemicals and polyvinyl chloride. TCE is also a common, persistent drinking water contaminant. Several epidemiological studies have alleged links between TCE exposure during pregnancy and offspring health problems including CHDs; however, the results of these studies are inconsistent, difficult to interpret and involve several confounding factors.[29]

***Lead exposure:*** Maternal lead exposure may be harmful to fetal development. However, sufficient evidence is lacking about the risk on cardiac development in offspring. To explore the association between maternal lead exposure and risks of CHDs occurrence in fetuses, a case-control study was adopted during pregnant women making antenatal examinations. Maternal lead exposure is associated with the risk of some subtypes of CHDs occurrence in offspring. The potential dose-response relationship is also presented.[30]

***Arsenic exposure:*** In several studies, chronic exposure to arsenic through drinking water is linked to developmental anomaly of CHDs. Jin et al[31] found arsenic concentrations ≥62.03 ng/g were associated with increased risk for almost every CHD subtype, with a dose-response relationship. Rudnai et al[32] showed an increased risk of congenital heart anomalies among infants whose mother was exposed to drinking water with arsenic content above 10 micro g/L during pregnancy.

**Maternal exposure to housing renovation and offspring with CHD**

Housing renovations are a newly recognized source of indoor environmental pollution that is detrimental to health. Research suggests that maternal occupational exposure to renovation materials may be associated with an increased risk of giving birth to fetuses with CHD. A multi-hospital case-control study investigate the association between maternal periconceptional housing renovation exposure and the risk of CHD for offspring and found that the risk for CHD in offspring was significantly associated with maternal exposure to housing renovations (AOR: 1.89, 95% CI: 1.29-2.77). Maternal housing renovation exposure may increase the fetus' risk of suffering from conotruncal defect or anomalous venous return. There were significant risks for cardiac defects if the pregnant woman moved into a new house within one month after decoration at either 3 months before pregnancy (AOR: 2.38, 95% CI: 1.03 to 5.48) or during first trimester (AOR: 4.00, 95% CI: 1.62 to 9.86).[33]

**Evidence of maternal psychological factors and CHD**

Maternal stress is measured by maternal reports of divorce, separation, job loss or death of a close relative or friend. A large registry-based study reported maternal emotional stress may be a risk factor for CHDs in infants. The association was most for infants of mothers who had lost a partner or child (OR =1.32, 1.04-1.67).[34] Maternal mental stress during early pregnancy was significant associated with aggregate cardiac defects in a hospital-based Case-control study (OR, 3.93; 95% CI, 1.94-7.94).[35] Adams et al[36] showed increased risks associated with maternal stress related to job loss, divorce, separation or death of a close friend or relative and a history of a sibling with a cardiac defect (odds ratio 4.8; 90% confidence interval 2.2 to 10.5). Maternal stress could affect fetal development by several plausible mechanisms, such as catecholamine production and corticosteroid production, which may be associated with the development of birth defects. Another potential mechanism is that stress may lead to harmful coping behaviors (e.g., increased substance use or cigarette smoking or decreased dietary quality) and therefore affect development indirectly.

**Evidence of maternal body mass index during pregnancy and CHD**

Now a days, obesity rates has an increasing tendency, since the incidence of obesity in both developed and developing countries is still rising over the years. Numerous studies have shown that obese women appear to be at a higher risk of pregnancy

complications, as well as adverse fetal and neonatal outcomes, such as congenital heart defect. A meta-analysis of 18 studies found an association of maternal obesity with an increased risk of cardiovascular anomalies (OR, 1.30; 95% CI, 1.12-1.51) and septal anomalies (OR, 1.20; 95% CI, 1.09-1.31).[37] A recent meta-analysis of 14 epidemiological studies demonstrated an association between overweight, moderate obesity and severe obesity and all CHD combined (OR, 1.08, 95% CI, 1.02-1.15; OR, 1.15, 95% CI, 1.11-1.20; and OR, 1.39, 95% CI, 1.31-1.47, respectively) as well as some individual defects such as pulmonary valve stenosis, hypoplastic left heart syndrome and outflow tract defects, with the highest risk of tetralogy of Fallot for obese mothers for (OR, 1.94; 95% CI, 1.49-2.51).[38] Being underweight did not increase the risk of any of the aforementioned CHDs but did increase the risk of aortic valve stenosis (OR, 1.47; 95% CI, 1.01-2.15). In a more recent Case-control study that evaluated the risk of congenital anomalies with different doses of maternal pre-pregnancy obesity in Florida, five CHD phenotypes showed evidence of a dose-response pattern with increasing severity of maternal obesity corresponding to increased odds of each defect.[39]

**Ambient air pollution and risk of CHD**

Ritz et al[40] found carbon monoxide (CO), nitrogen dioxide, ozone and particulate matter <10 microm in aerodynamic diameter, have increased Odds ratios for cardiac ventricular septal defects in a dose-response fashion with increasing second-month CO exposure [Odds ratio (OR)(2nd quartile) CO = 1.62, 95% confidence interval (CI): 1.05, 2.48; OR(3rd quartile) CO = 2.09, 95% CI: 1.19, 3.67; OR(4th quartile) CO = 2.95, 95% CI: 1.44, 6.05]. Similarly, risks for aortic artery and valve defects, pulmonary artery and valve anomalies and conotruncal defects increased with second-month ozone exposure. Confirmation by further studies is needed.

**Smoking and CHD**

Active maternal smoking during pregnancy is well recognized as a cause of fetal mortalityand morbidity. Smoking during pregnancy has been associated also with increased risks of congenital malformations, particularly heart defects, limb-reduction defects, kidney/urinary tract defects, and cleft lip and palate defects.[41] However, Lee et al[25] confirmed the association between maternal smoking and increased risk of CHDs by meta-analysis. Maternal smoking during pregnancy tended to increase the risk of congenital heart defects by 48% (OR=1.48; 95% CI, 0.82-2.67). Malik et al[42] found association between maternal cigarette smoking and CHDs. Alberman et al[43] was one of the first to report the association between maternal cigarette smoking and CHDs. However, the evidence since then has been mixed, with some studies showing positive associations and others providing null results. To date, a total of three meta-analyses have investigated the association between maternal smoking during pregnancy and CHDs in offspring. The first meta-analysis published in1999 found no association for all CHDs combined (OR, 1.07; 95% CI, 0.98-1.17) and mixed results for analyses of specific groups or phenotypes.[44] The second meta-analysis by Hackshaw et al[45] estimated the effects of maternal smoking across a spectrum of birth defects including heart defects (OR, 1.09; 95% CI, 1.02-1.17). However, the study did not evaluate the effects of maternal smoking on CHD subtypes and dose-response relationships (i.e., increasing levels of smoking) were not assessed. A latest meta-analysis of studies published between 1971 and 2011 found positive association for all CHDs combined (RR, 1.11; 95% CI, 1.02-1.21). According to analysis, as for specific groups, women who smoked during pregnancy were more likely to give birth to a child with 12 of 17 CHD subtypes analyzed compared with nonsmoker. The highest risk was for septal defects as a group (RR, 1.44; 95% CI, 1.16-1.79).[42] After that, a recent study reported that only valvar pulmonary stenosis (VPS) was highly associated with mothers who smoked 20 cigarettes or more per day (p = 0.03). When both mother and father consumed at least 20 cigarettes per day, VPS and coarctation of the aorta would have a significant p-value (0.03 and 0.02 respectively).[46]

Secondhand smoke involves exposure to the same range of tobacco smoke toxins experienced by active smokers, although at lower levels, it is likely that exposure to secondhand smoke also causes some or all of these complications but with lower levels of relative risk. However, the effect of maternal secondhand smoke exposure on other fetal outcomes, including mortality and congenital malformations, is less widely known. A recent meta-analysis showed pregnant women who are exposed to secondhand smoke are estimated to be 23% more likely to experience stillbirth and 13% more likely give birth to a child with a congenital malformation. Because the timing and mechanism of this effect is not clear, it is important to prevent secondhand smoke exposure in

women before and during pregnancy.[47] Findings have shown that maternal smoking has adverse effects on the developing fetus, including hypoxia caused by carbon monoxide, nicotine and reduction in the supply of essential nutrients to the embryonic tissues.[48]

**Evidence of maternal caffeine use during pregnancy and CHD**

Caffeine is a natural component of coffee, tea, cocoa and cola products. It is teratogenic in animal studies when administered at high concentrations.[49] In human, caffeine and its metabolites easily cross the placenta and reach the fetus.[50] Most studies on the human teratogenicity of caffeine have not shown an important effect. In a systematic review investigating the association between maternal exposure to caffeine and risk of congenital anomalies, slight elevations were observed for associations between coffee intake and cardiovascular malformations (OR, 1.10; 95%CI, 0.90-1.50), but not for the association between tea and cardiovascular malformations (OR, 1.00; 95%CI, 0.90-1.20).[51] Fixler et al[50] observed an OR of 0.75 (95% CI, 0.39-1.44) for the occurrence of cardiac defects with coffee consumed daily and an OR of 0.89 (95% CI, 0 .42-1.88) for consumption of caffeine in general.

**Evidence of maternal illicit drug use during pregnancy and CHD**

***Exposure to asthma medication in the first trimester of pregnancy and CHD:*** Exposure during the first trimester of pregnancy has the potential to increase the risk of congenital anomalies. Pregnant women with asthma often have to continue their medication during pregnancy. Asthma treatment today is mainly administered by inhalation therapy, which reduces the systemic effects of the medications. Meta-analysis of aggregated data from three cohort studies conducted in Wales, Norway, Denmark found that for severe congenital heart defects, an increased OR (1.97; 1.12-3.49) was associated with exposure (from 91 days before to 91 days after the pregnancy start date) to combination treatment with inhaled corticosteroids and long-acting beta-2-agonists.[52]

***Exposure to trimethoprim-sulfamethazin in pregnancy and association of CHD:*** Czeizelet al[53] found a higher rate of multiple congenital abnormalities was found in case infants born to mothers with cotrimoxazole treatment during the second-third months of pregnancy. In addition, a higher rate of cardiovascular malformations occurred in cases born to mothers with cotrimoxazole treatment and trimethoprim-sulfamethazine treatment during the second-third months of pregnancy, respectively.

***Folic acid antagoinst:*** A study was conducted on exposure to folic acid antagonists that act as dihydrofolatereductase inhibitors and to certain antiepileptic drugs. The relative risks of cardiovascular defects in infants whose mothers were exposed to dihydrofolatereductase inhibitors during the second or third month after the last menstrual period, as compared with infants whose mothers had no such exposure, were 3.4 (95 percent confidence interval, 1.8 to 6.4). The relative risks of cardiovascular defects, after maternal exposure to antiepileptic drugs were 2.2 (95 percent confidence interval, 1.4 to 3.5). Use of multivitamin supplements containing folic acid diminished the adverse effects of dihydrofolatereductase inhibitors, but not that of antiepileptic drugs. Folic acid antagonists, which include such common drugs as trimethoprim, triamterene, carbamazepine, phenytoin, phenobarbital and primidone, may increase the risk not only of neural-tube defects, but also of cardiovascular defects.[54] A meta-analysis of the association between maternal folic acid supplementation and CHDs provide evidence that maternal folate supplementation is associated with a significantly decreased risk of CHDs (RR = 0.72, 95% CI: 0.63-0.82).[55] Homocysteine acts as folic acid antagonist and increased levels of maternal serum homocysteine are associated with increased risk of occurrence of CHDs in their offsprings as altered homocysteine metabolism may play role in CHDs.[56]

**Multivitamin** use has been associated with lower risks for some birth defects. Febrile illness with no multivitamin use was associated with generally increased risk for the defects (cardiac outflow tract defects, ventricular septal defects, atrial septal defects) and the combined group (odds ratio = 1.5, 1.9, 2.9 respectively). With multivitamin use, however, the risk estimates associated with febrile illness were generally lower (Odds ratio = 0.0, 1.5, 0.0 respectively).[57] Botto et al[58] in another study found regular use of multivitamins from 3 months before pregnancy through the first 3 months of pregnancy was associated with a reduced risk for nonsyndromic

cardiac defects in the offspring (odds ratio (OR) = 0.76; 95% confidence interval (CI): 0.60, 0.97) with no use during the same time. The risk reduction was strongest for outflow tract defects (OR = 0.46; 95% CI 0.24, 0.86) and ventricular septal defects (OR = 0.61; 95% CI: 0.38, 0.99). No risk reduction was evident when multivitamin use was begun after the first month of pregnancy. If these associations are causal, the results suggest that approximately one in four major cardiac defects could be prevented by periconceptional multivitamin use.

***Maternal use of bupropion:*** Bupropion is an antidepressant medication used to treat major depressive disorder and seasonal affective disorder. A positive association was found between early pregnancy and bupropion use and left outflow tract heart defects. Mothers of infants with left outflow tract heart defects were more likely to have reported taking bupropion than mothers of control infants (adjusted odds ratio, 2.6; 95% confidence interval, 1.2-5.7; P = .01).[59]

***Clomiphene citrate:*** A population-based, multi-site case-control study of major birth defects in USA showed an increased adjusted odds ratios (aOR) with Clomiphene citrate for septal heart defects (1.6, 1.1-2.2), muscular ventricular septal defect (4.9, 1.4-16.8) and coarctation of aorta (1.8, 1.1-3.0).[60]

***Marijuana, hashish, cocaine, hallucinogens, heroin, and methadone:*** Williams et al[61] in Atlanta reported maternal cannabis use, was associated with a two-fold increased risk of VSD. Self-reported cannabis use for fewer than three days per week resulted in a similar OR, while use three or more days per week resulted in an almost four-fold increased risk (OR, 3.73; 95% CI, 1.56- 8.96). A Case-control study using data from the Baltimore-Washington Infant Study (BWIS) examined the association between maternal cocaine use and isolated membranous ventricular septal defects (VSD). An OR of 2.99 for maternal cocaine use dropped to 2.15 when taking into account paternal cocaine use (a change of 28%) and to 2.52 when paternal marijuana use was considered (a change of 16%).[62] Cocaine or marijuana, a vasoconstrictor, has been investigated as a potential teratogen because exposure may result in vascular disruptions and hypoperfusion.[63] vascular disruption, increased homocystine levels and oxidative stress are potential mechanisms for various congenital malformations.[64] Further studies are warranted to elucidate the possible association of illicit drug use with CHDs in offspring.

**Evidence of maternal alcohol consumption during pregnancy and CHD**

Ever since the first description of the fetal alcohol syndrome by Jones and Smith in 1973, many observational studies have been published on the topic of alcohol consumption in pregnant women and the effects on the development of their fetus and child, including cardiac defects. Recently, several studies investigate the association between maternal alcohol consumption during the pregnancy and CHDs. A population-based Case-control study of California births indicated that compared with nonconsumers, women who consumed alcohol less than once a week had a 1.3 fold higher risk of having infants with a conotruncal heart defect (95% CI, 1.00- 1.90), and women who consumed alcohol once a week or more had a 1.9 fold increase in risk (95% CI, 1.00- 3.40).[65] In another population-based Case-control study among a cohort of California births between July 1999 and June 2003, maternal consumption of alcohol less than one day per week was associated with a 2.1 fold increased risk of d-transposition of the great arteries (95% CI, 1.10- 3.20).[66] According to a cohort study including 80,346 pregnant women enrolled into the Danish National Birth Cohort, exposure to low-to-moderate levels of alcohol on a weekly basis during pregnancy was not significantly increased risk of isolated ventricular septal defect (VSD) and atrial septal defect(ASD) in offspring.[67] A recent meta-analysis observed a null association between maternal alcohol consumption during pregnancy and the risk of CHDs. Even in the analysis of different trimesters of pregnancy, they found little association between the two.[68] However, these statistics do not intend to say that maternal drinking is safe; the fact is that even low levels of prenatal alcohol exposure, such as in a single dose, can produce the birth defect termed fetal alcohol syndrome (FAS) and as many as 54 % of live-born children with FAS present with some form of cardiac anomalies[69] that can lead to developmental challenges, ongoing medical care and death. The mechanisms by which alcohol consumption may result in CHDs remain to get confirmed, even though its etiology has been the focus of much study, especially the cellular and molecular mechanisms.[70] Additionally,

findings have shown that alcohol consumption during pregnancy may affect the Wnt/$\alpha$-catenin signaling which allows normal gene activation and cardiogenesis.[61] Cell death is a hypothesized mechanism for muscular VSD formation and alcohol exposure has been shown to result in abnormal cell development and cell death.[72]

**Pregnant women with diabetes mellitus and CHD**

Women with diabetes mellitus have considerably higher risks of adverse pregnancy outcomes, including birth defects, than nondiabetic women.[73] And pregestational maternal diabetes mellitus is the only relatively prevalent population risk factor for congenital heart defects (CHDs).[18] Even though the association of pregestational diabetes mellitus with CHD has been known for decades, it is not clear if this knowledge has resulted in a substantive impact of the reduction of pregnancies complicated by diabetes mellitus or in the proportion of births with CHDs attributable to pregestational diabetes mellitus. Maternal diabetes mellitus may be associated with specific types of CHD, yet epidemiological studies published to date have not focused specifically, finding the effect of diabetes mellitus to differ across sections of the embryonic heart corresponding to cardiac phenotypes.[74] Maternal pregestational diabetes mellitus (type 1 and type 2) was associated with a 4-fold increased offspring CHD risk.[71] A case-control study was conducted to investigate maternal risk factors for conotruncal cardiac defects showed increased risks associated with maternal diabetes (odds ratio 5.6; 90% confidence interval 2.5 to 15.6).[36] Vascular disruption, increased homocysteine levels and oxidative stress associated with hyperglycemia are potential mechanisms for various congenital malformations.[64] For the same reason, women who are obese might have diabetes mellitus, which appears to be an important pathogenetic factor that is associated with a wide spectrum of CHDs.[76] Experimental studies suggest that hyperglycemia during early embryogenesis may alter gene expression in key cellular components of the developing heart, in particular, the embryonic heart's outflow sections; however, the mechanism producing this altered gene expression is unclear.[16,17]

**Maternal infection during pregnancy and CHD**

Frequency of maternal urinary tract infections during pregnancy (5% to 9%, EST: +0.5% [+0.2%, +0.7%]/ year, $P$<0.001) is associated with CHD.[13] Prenatal maternal fever or influenza may be associated with right-sided obstructive lesions in all infants and with atrioventricular septal defects in infants with Down syndrome. There were significant associations between fever and influenza and specific CHDs, namely right-sided obstructive defects (fever: OR, 2.04; 95% CI, 1.27 to 3.27; influenza: OR, 1.75; 95% CI, 1.16 to 2.62) and atrioventricular septal defects in infants with Down syndrome (fever: OR, 1.92; 95% CI, 1.10 to 3.38; influenza: OR, 1.66; 95% CI, 1.04 to 2.63). Maternal antipyretic use in the setting of fever or influenza tended to decrease these associations.[77]

**At risk situation for CHDs in Bangladesh**

Bangladesh is one of the world's most densely populated country and has also faced rapid population growth throughout the last century although the population growth rate has somewhat decreased to a moderate level in recent times. In Bangladesh, 31.5% of the population lives below the national poverty line and current literacy rate is 61.5% and among female it is 58.5%.[78,79] The country is going to witness a rapid spread of urbanization over the next decade. The already acute slum population is growing further, contributing to serious human problems. The present environmental condition of Bangladesh is not at all in equilibrium. Severe air, water and noise pollution are threatening human health and ecosystems. There is a good reason to worry about the Air Quality in Dhaka, as Bangladesh ranks 169$^{th}$ (out of 178 countries) at the Environmental Performance Index for Air Quality (2014 score).[80] Air pollution caused due to increasing population, burning fossil fuels, industrialization, associated motorization and rapid urbanization of major cities. The water resource of Bangladesh becomes a major health hazard due to arsenic contamination, inadequate solid waste and industrial effluent management. Environmental degradation of Bangladesh is also caused due to poverty and over-population.[81] The Global Adult Tobacco Survey (GATS) founds that in Bangladesh use of smoked tobacco products was far greater among males (45.6%) than females (3.1%). Use of smokeless tobacco products in Bangladesh was approximately the same among males (26.4%) and females (27.9%).[82] Khan et al[83] recently found large number of female tobacco user both smoker and chewer in their study. In Bangladesh, the consumption of alcohol is strictly prohibited both

as a social function and as a religious rite by most of the religions. Yet, the problem of alcoholism is becoming a threat to the nation's welfare. Although the problem is more serious in urban areas of the country (probably due to easy accessibility of alcoholic beverages), there are indications that it is emerging at an increasing rate in rural areas. A survey conducted by Kasimuddin et al[84] among residential students of higher educational institutions in Dhaka City by) found that 13.73% of males and 3.07% of females abused alcohol. Foods adulteration became a major health concern now a days.[85] A lack of awareness among consumers and the callous attitude of a large section of physicians have turned many lifesaving drugs into silent killers. Unlike in developed countries, Bangladesh does not have any strict regulations regarding over the counter (OTC) sales of drugs including antibiotics. All these indicate that large number of population is exposed to risk of developing congenital anomalies including CHDs.

**Conclusion**

This review summarizes the current state of knowledge of noninherited factors that may increase the likelihood of CHDs in offspring. However, more prospective studies are needed to further investigate the association between these factors and CHDs. To date, no public policies or interventions are specifically directed at reducing the public health impact of congenital heart defects in Bangladesh. Findings of this review could make public health advocacy measures to reduce modifiable risk factors like maternal education, socioeconomic status, advanced maternal age, smoking, alcohol, obesity, diabetes, exposure to industrial chemical, air and water pollution, chemical exposure due to food adulteration and medication use during pregnancy to develop population based prevention strategies to reduce the incidence and burden of CHDs.

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