Risk Factors for Congenital Heart Disease among Infants and Children in Baghdad
A Case-Control Study

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ABSTRACT

Background: Congenital heart disorders represent 25% of all congenital anomalies. They significantly contribute to morbidity and mortality in pediatric populations.
Objectives: To define the probable risk factors implicated in the etiology of congenital heart disorders.
Methods: From 15 May 2024 to February 2025, Al-Mahmoudia General Hospital, a prospective case control study on 250 babies and children. One hundred children were diagnosed by chest x-ray, ECG, and echocardiography. The remaining 150 were randomly selected from the consultant clinic. Mothers and other relatives answered a specifically developed form and provided verbal approval. Data collection includes age, gender, maternal, and paternal characteristics.
Results: Of 100 children with congenital heart disorders enrolled, ventricular septum defect was the most common defect (40%). Residency, birth order, family history of congenital heart disorders, maternal age, history of reproductive problems, use of hormones, sedative drugs and maternal diseases were the factors significantly affect CHD ($P<0.05$). Four factors were significant independent risk factors for CHD. These factors were lack of folic acid during pregnancy (OR= 2.07), maternal age ≥ 35 years (OR= 4.71), positive family history (OR= 5.18), and gestational diabetes (OR= 3.22).
Conclusions: The birth order, family history of congenital heart disorders, maternal age, history of reproductive problems, use of drugs, and maternal diseases during pregnancy can affect congenital heart disorders incidence.

Keywords: Children, Infants, Congenital heart diseases, Risk factors.
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Birth defects affecting the heart or the adjacent blood vessels that manifest in early childhood or later on are known as congenital heart disorders (CHDs). The pattern of CHD varies by geo-graphic location, and the prevalence of CHD has been reported to differ worldwide[1]. The prevalence of CHDs is approximately 8 per 1,000 live births; however, only 2-3% of these cases develop symptoms within the first year of life[2]. Asia ranks as the region with the highest cases of CHD (9.3/1000 live births), followed by Europe (8.2/1000 live births) and lowest rate is in Africa (1/1000 live births).

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Since 2010, there has been an approximately 5% increase in CHD prevalence every five years, which is likely due to increased detection and diagnosis of milder CHD lesions, as well as greater usage of echocardiography with improved technique. The mortality rate for CHD is extremely high: by the end of the first week, 29% of new-born die, 42% die by the first month, and 87% by the first year[3].

Genetic and environmental risk factors are both believed to be involved in the multifactorial aetiology of CHD. Although there is no definitive inheritance pattern due to the different types of CHD and multiple environmental factors that predispose to CHD, it is possible that a two-hit pathogenesis is present in which the genetic predisposition and further non-

genetic risk factors, such as maternal diabetes and obesity, can increase the fetus's risk of developing CHD. Additionally, parental consanguinity has been found to be a risk factor for CHD, particularly in regions where endogamy is a popular practice[4]. The development of CHD is influenced by a variety of modifiable and non-genetic risk factors. These include the use of certain medications during pregnancy, such as lithium, anti-epileptics, antibiotics, and alcohol, hypertension, smoking, infectious diseases especially maternal infection with Rubella (congenital rubella syndrome), and maternal diabetes (including pre-gestational and gestational versions), as well as older maternal age. It is more important to identify modifiable risk factors at an early stage in order to prevent the development of CHD in the neonate[5]. The prognosis for patients with CHDs is highly variable, ranging from spontaneous cure to death. This is partially attributable to the variations in the severity of CHD. Surgical (corrective or palliative) and interventional catheterization are the most commonly performed interventional treatment modalities. Reoperation is necessary for approximately 15% of patients with CHD who undergo corrective surgery. In terms of complexity and severity, cyanotic conditions, including tetralogy of Fallot (ToF), transposition of the great arteries (TGA), and single ventricle, demonstrate a wide range of surgical interventions[6].

Methods

A case-control study was carried out in Al-Mahmoudia General Hospital, which is located about 20 kilometers southern to Baghdad, during the period from 15th of May 2024 till the end of February 2025.

Two-hundred and fifty infants and children were included in this study who have been admitted to pediatric wards, NCIU or referred to echocardiography clinic at Al-Mahmodya General Hospital, excluding those with chromosomal abnormalities like (Down syndrome and multiple congenital anomalies). Their ages ranged from one-day to 14 years old.

Of those 250 participants, one-hundred patients were diagnosis by chest x-ray finding, electrocardiogram (ECG), and echocardiography (which is a definitive diagnosis of CHD). The remaining 150 apparently healthy infants and children randomly selected from those consulting the outpatient department suffering from illnesses unrelated to cardiac disease (upper respiratory tract infection or diarrhea), within the same age and sex of patient group (exclusion of CHD done by Echo).

A specially designed form was used to collect the information from mothers, grandmothers, and other relatives, verbal consent was taken from family. Data collection includes the following:

- Demographic information: include; age, sex, residence (rural, urban) and date of birth. Other information such as gestational age, birth order, birth weight, family history of CHD, presenting symptom (dyspnea, cyanosis, feeding difficulty, sweating, failure to thrive, and murmur).
- Maternal factors: include; age, reproductive history, illnesses and diseases (pre-gestational diabetes mellitus type 1 or 2), gestational diabetes mellitus, fever, influenza (flu-like illness), epilepsy, rubella (fever and rash), and drug intake during pregnancy.
- Paternal factors: include; age, occupation, habits (smoking).

Data was fed to the computer and analyzed using the available statistical package of SPSS-25 (Statistical Packages for Social Sciences- version 25). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of the difference in different percentages (qualitative data) was tested using the Pearson Chi-square test. A level of p-value less than 0.05 was considered significant.

Al-Mahmoudia General Hospital Ethical Committee gave the research permission to proceed, and parents or guardians gave

their verbal agreement, ensuring confidentiality and voluntary participation.

Results

A total of 250 children were enrolled, of them 100 patients had cardiovascular disease (case group) and 150 healthy children (control group), furtherly 49% patients in the case group were females.

Type of CHD observed in this study were ventricular septal defect (VSD) in 40% of patients, patent duct arteriosus (PDA) in 26%, atrial septal defect (ASD) in 17%, tetralogy of Fallot (TOF) in 7%, transposition of the greater arteries in 4% had. Other common CHDs, accounting for 6%, (Figure 1).

Table 1 shows the comparison of sociodemographic characteristics between the study groups. The rate of CHDs was higher among patients of rural mothers (62%). There is a statistically significant difference between the two groups regarding residency, birth order of children and family history of CHDs (P = 0.001 for each). No statistically significant difference in children's age and sex between the study groups (P ≥ 0.05).

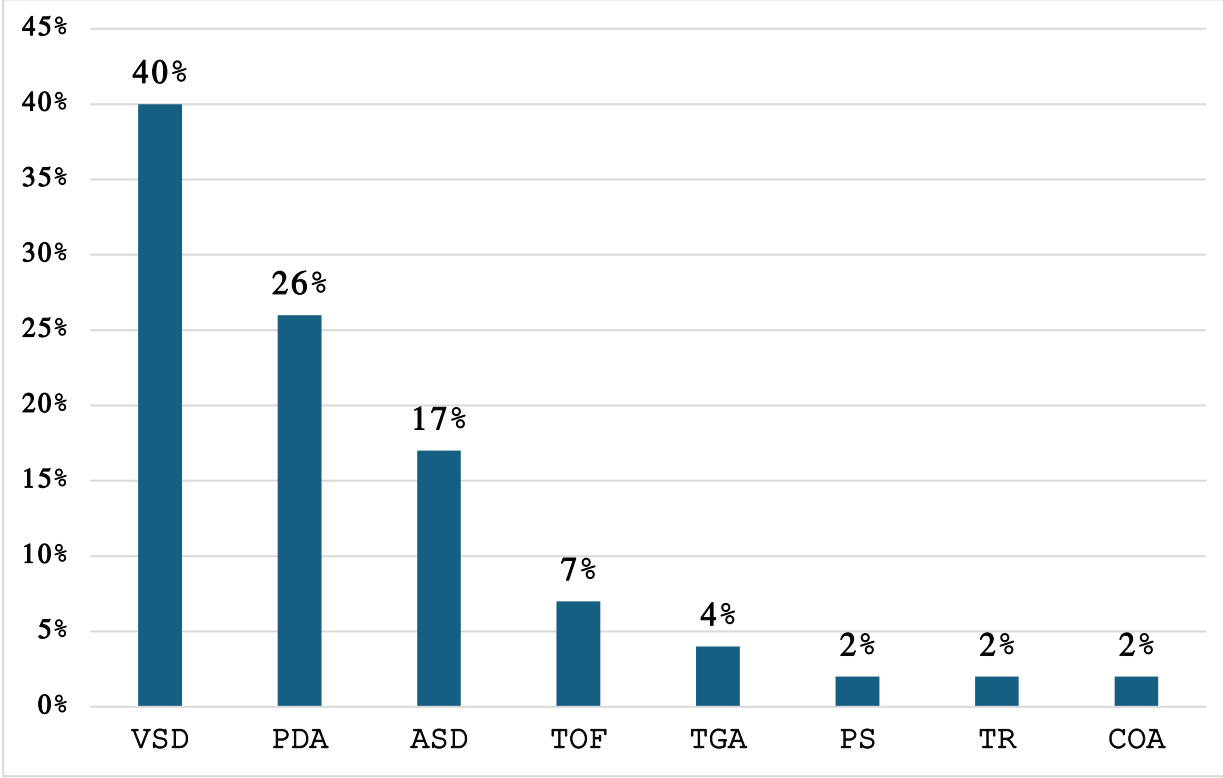

Figure 1: Distribution of the case group by type of congenital heart disease.

VSD; Ventricular Septal Defect, **PDA**; Patent Ductus Arteriosus. **ASD**; atrial septal defect, **TOF**; Tetralogy of Fallot; **TGA**; Transposition of the Great Arteries, **PS**; Pulmonary Stenosis, **TR**; Tricuspid Regurgitation, COA; Coarctation of the Aorta.

Table 1: Comparison between study groups according to sociodemographic characteristics of children.

Variables		Study groups		P -value
		Case (n= 100) No. (%)	Control (n= 150) No. (%)	
Age (years)	< 1	52 (52.0)	83 (55.3)	**0.604**
	1 – 4	34 (34.0)	41 (27.3)	
	5 – 9	8 (8.0)	22 (14.6)	
	10 – 14	6 (6.0)	4 (2.6)	
Gender	Male	51 (51.0)	86 (57.3)	**0.324**
	Female	49 (49.0)	64 (42.6)	
Residency	Urban	38 (38.0)	117 (78.0)	**0.001**
	Rural	62 (62.0)	33 (22.0)	
Birth order	1st	6 (6.0)	28 (18.7)	**0.001**
	2nd	8 (8.0)	23 (15.3)	
	3rd	9 (9.0)	21 (14.0)	
	4th	12 (12.0)	14 (9.3)	
	5th	13 (13.0)	12 (8.0)	
	≥ 6th	52 (52.0)	52 (34.7)	
Family history of CHDs	No	81 (81.0)	141 (94.0)	**0.001**
	Siblings	7 (7.0)	5 (3.3)	
	Mother	5 (5.0)	3 (2.0)	
	Father	7 (7.0)	1 (0.7)	

Table 2 summarizes the comparison between the two groups according to maternal characteristics. In the present study, the rate of CHDs was significantly higher among patients whose mothers were aged 20 – 34 years (52%, P = 0.001), patients of mothers with history of reproductive problems (27%, P = 0.001) and patients of mothers didn't take folic acid during the pregnancy (86%, P < 0.001).

Concerning maternal drug use, mothers of children with CHDs showed a significantly higher intake of ibuprofen (8%, P=0.004) and clomiphene (22%, P=0.004), while there was no statistically significant difference concerning aspirin, diclofenac sodium, corticosteroids, metronidazole, and phenobarbital intake between the two groups. On the other hand, diabetes, fever, influenza, epilepsy, and preeclampsia were reported at a significantly higher rate among mothers of children with CHDs, compared to the control group (P < 0.001).

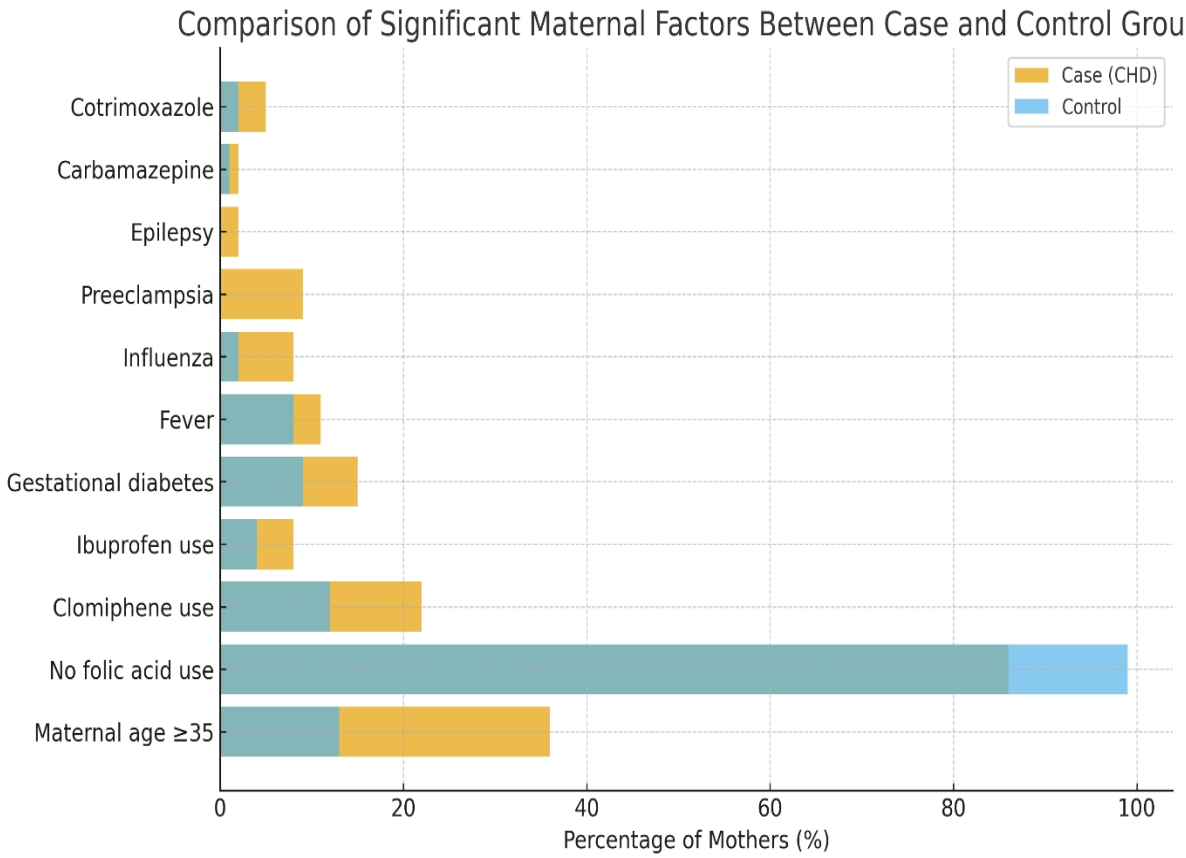

Figure 2: Comparison of significant maternal factors between case and control groups.

The comparison of paternal characteristics (age and smoking habits) between the two groups (Table 3). This study found that the rate of CHDs was significantly higher among children whose paternal age was 35 – 39 years (30%, P = 0.016). No significant difference was seen between the case and control group regarding smoking status (P = 0.06).

Logistic regression analysis was applied (Table 4) using presence of congenital heart disease as the dependent variable and the variables that showed significant association in the binary analysis as the independent variables. Four factors were found to be significant independent risk factors for greater likelihood of congenital heart disease. These factors were lack of folic acid during pregnancy (OR= 2.07), maternal age ≥ 35 years (OR= 4.71), positive family history of CHD (OR= 5.18), and gestational diabetes (OR= 3.22).

Table 2: Comparison between the study groups according to sociodemographic maternal characteristics.

Variables		Study groups		P-value
		Case (n=100) No. (%)	Control (n=150) No. (%)	
Maternal age (years)	< 20	12 (12.0)	9 (6.0)	**0.001**
	20–34	52 (52.0)	128 (85.3)	
	≥ 35	36 (36.0)	13 (8.6)	
Reproductive history	No problems	73 (73.0)	126 (84.0)	**0.001**
	Miscarriage	16 (16.0)	14 (9.3)	
	Stillbirth	3 (3.0)	4 (2.6)	
	Preterm birth	8 (8.0)	6 (4.0)	
Folic acid use	Yes	14 (14.0)	51 (34.0)	**< 0.001**
	No	86 (86.0)	99 (66.0)	
Maternal drug use	No drugs	47 (47.0)	104 (69.3)	**> 0.05**
	Aspirin	4 (4.0)	6 (4.0)	**> 0.05**
	Diclofenac sodium	2 (2.0)	5 (3.3)	**> 0.05**
	Ibuprofen	8 (8.0)	4 (2.6)	**< 0.004**
	Clomiphene	22 (22.0)	12 (8.0)	**< 0.004**
	Phenobarbital	4 (4.0)	3 (2.0)	**> 0.05**
	Carbamazepine	2 (2.0)	1 (0.6)	**< 0.004**
	Cotrimoxazole	5 (5.0)	2 (1.2)	**< 0.004**
	Metronidazole	4 (4.0)	8 (5.3)	**> 0.05**
	Corticosteroids	2 (2.0)	5 (3.3)	**> 0.05**
Maternal illnesses	Fever	11 (11.0)	8 (5.3)	**< 0.001**
	Influenza	8 (8.0)	2 (1.3)	**< 0.001**
	Gestational diabetes	15 (15.0)	9 (6.0)	**< 0.001**
	Pre-gestational diabetes – type 1	0 (0.0)	0 (0.0)	**< 0.001**
	Pre-gestational diabetes – type 2	2 (2.0)	2 (1.3)	**< 0.001**
	Epilepsy	2 (2.0)	0 (0.0)	**< 0.001**
	Preeclampsia	9 (9.0)	0 (0.0)	**< 0.001**

Table 3: Comparison between the study groups according to paternal characteristics.

Variables		Study groups		P-value
		Case (n=100) No. (%)	Control (n=150) No. (%)	
Paternal age	< 25	11 (11.0)	19 (12.6)	0.016
	25–29	23 (23.0)	36 (24.0)	
	30–34	29 (29.0)	66 (44.0)	
	35–39	30 (30.0)	16 (10.6)	
	40–44	5 (5.0)	7 (4.6)	
	≥ 45	2 (2.0)	6 (4.0)	
Paternal smoking habits	No smoking	72 (72.0)	123 (82.0)	0.06
	< 20/day	16 (16.0)	12 (8.0)	
	20–40/day	8 (8.0)	9 (6.0)	
	> 40/day	4 (4.0)	6 (4.0)	

Table 4: Logistic regression analysis for association of various risk factors with development of congenital heart disease among infants and children.

Variables	Odd's ratio	95% C.I for odd's ratio
Lack of folic acid during pregnancy	2.07	1.05 – 3.14
Maternal age ≥ 35 years	4.71	2.77 – 12.5
Positive family history of CHD	5.18	2.1 – 24.4
Gestational diabetes	3.22	1.21 – 7.32

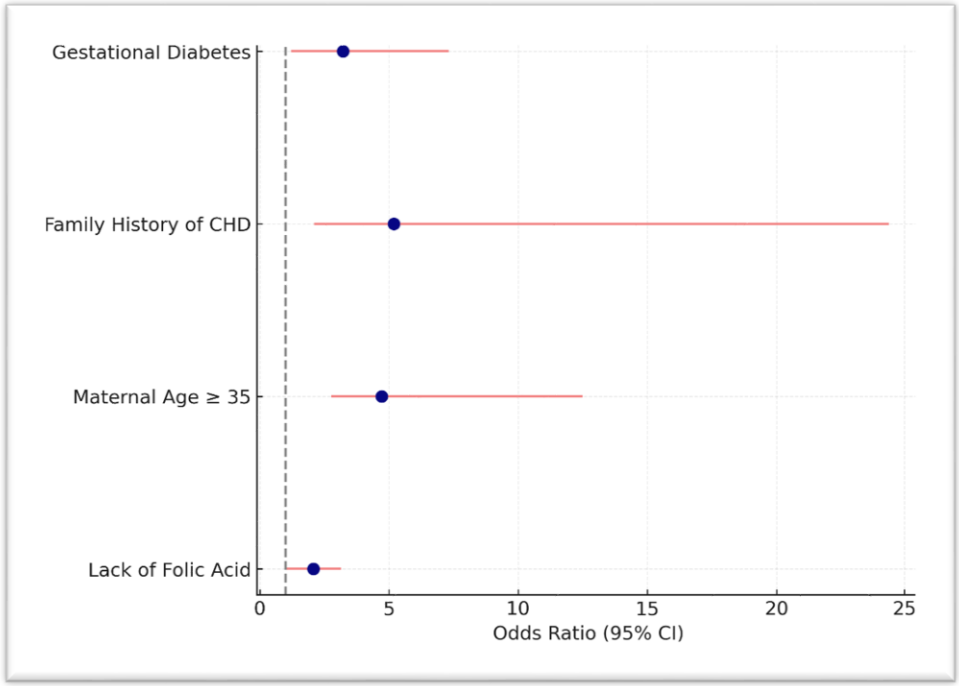

Figure 3: Independent risk factors CHD.

Discussion

Congenital heart disorders (CHDs) are structural, functional, or positional abnormalities of the heart and associated blood arteries present at birth, recognizable in infancy or later. CHDs are observed in over 90% of people with trisomy 18, half of people with trisomy 21, and 40% of individuals with Turner syndrome[7]. The formation of the heart is a complicated developmental process that can be disrupted by a variety of factors, possibly leading to a structural defect. Type of CHD observed in this study was VSD in 40% of patients, which agreed to the results published in Mohammed et al study[2], Almasri et al study[3], and Tuky et al study[8], in which VSD was most prevalent type of CHD observed in 28%, 34.2% and 38.3%, respectively. The predominance of VSD among CHDs likely results from its increased vulnerability throughout cardiac development, widespread identification using contemporary diagnostic methods, correlation with genetic and maternal risk factors, and incorporation of spontaneously healing lesions in epidemiological statistics[1].

The current study reported a significant difference between both groups regarding residency, family history of CHDs and birth order of children, which may be due to maternal depletion of micronutrients and exposure to environmental or age-related risks in subsequent pregnancies[9], while no significant difference in children's age and sex. In a different manner, age and gender of infants were significantly associated with the prevalence of CHD among 2,421 children screened for CHD in Cao et al study. Other factors significantly related were residency, gestational age and familial history of CHD[10]. Similarly, in Mohammed et a study and Mecklin et al study[11], there was no significant difference between cases and controls regarding their age and gender[2]. Differently, studies done in China by Li et al [12], and Pie et al, found that majority of the cases were living in urban area. Anyway, there was no significant difference regarding the residence of the participants of those studies and the rate of CHDs[13]. Mohammed et al study had observed that the relationship between CHDs and family history of CHDs was found to be significant and odds ratio was calculated to be 3.22[2]. This is consistent with the result of Al-Hyali et al study, which found that there was significant relationship between CHDs and family history of CHDs with odd's ratio of 3.4[14]. The results of both studies mean that parents with family history of CHDs were three-times more likely to have offspring with CHDs compared to those without. The variations in the reported effect of age, gender, and family history on the prevalence of CHD in children are probably attributable to a combination of diagnostic methodologies, study design, genetic heterogeneity, and the quality of healthcare systems. Although family history is a persistent risk factor, the influence of age and gender frequently indicates methodological disparities rather than real biological differences.

In fact, higher birth order may increase the risk of CHD due to maternal depletion of micronutrients and exposure to environmental or age-related risks in subsequent pregnancies, as observed in epidemiologic studies regardless of parental age.

In the present study, the rate of CHDs was significantly associated with age of mothers, history of reproductive problems, use of folic acid during the pregnancy, higher intake of ibuprofen and clomiphene, diabetes, fever, influenza, epilepsy, and preeclampsia. This agreed to the results of Cao et al study, as reported that maternal factors significantly influenced the rate of CHD were maternal age, high BMI before pregnancy, gestational diabetes, hypertension, anemia, infection, medication, and exposure to harmful chemicals during pregnancy[10]. Ahmadi and colleagues observed that history of obesity in mother before pregnancy, history of abortion, parental consanguinity, exposure to cigarette smoke during pregnancy, exposures to teratogens in the first trimester of the pregnancy, and,

maternal diseases, family history of CHD and use of medicine during pregnancy were the factors significantly influenced the rate of CHD[15]. Wu and other co-authors found that there was a significant association between CHD rate and obesity in pregnancy, smoking in pregnancy, maternal diabetes, and exposure to organic solvents, while no correlations were revealed between CHD susceptibility and advanced maternal age[16]. The current study contradicts the results of Mohammed et al study, as observed that fever, headache, hypertension, diabetes, abortion, hormonal therapy, aspirin use, and consanguinity failed to achieve a significant association with the rate of CHDs among their participants[2].

In terms of advanced age, older mothers are more likely to have de novo mutations in transcription factors that regulate cardiac formation, whereas younger mothers have been associated with other types of birth anomalies. Unfortunately, the exact molecular pathway(s) underlying these maternal risk factor-related CHD defects are still largely unknown and necessitate further investigation. Moreover, the relationship between diabetes and CHD risk is a complex one. The prevalence of CHD in the offspring of mothers with diabetes ranges from 3% to 5%, a significantly higher figure than in mothers without diabetes[17].

The main limitation of the current study is that it was conducted as a single-center, hospital-based case-control study with a small sample size, dependent on self-reported maternal and paternal histories, which may lead to recall and selection bias and may limit the generalizability of the findings to other regions or healthcare settings, hence limiting the applicability of the results. Multi-center studies with larger and more diverse populations are recommended to validate these results.

The strength of this study is attributed to its clearly defined case-control design, its incorporation of both clinical and echocardiographic verification of congenital heart disease (CHD) diagnosis, a thorough evaluation of various maternal and paternal risk factors, and the application of multivariate logistic regression analysis to ascertain independent predictors of congenital heart disease.

In conclusion, this study shows that among all fetal and maternal factors as well as demographic and socioeconomic factors, birth order of children family history of CHDs, maternal age, history of reproductive problems, use of folic acid during the pregnancy and maternal diseases during pregnancy could affect the incidence of CHD. Based on the results of this study, it seems necessary to improve pregnancy health care, lowing consanguineous marriage, prompt treatment of maternal disease, and decreasing exposure to cigarette smoke and teratogens during pregnancy.

Conflict of interest: The authors have no conflicts of interest to declare.

Author Contributions: Author 2 conceived the idea and designed the study. Author 1 conducted the experiments and collected the data. Data analysis was performed by author 1 and author 2. The manuscript was written by author 1 and revised by author 2. All authors read and approved of the final manuscript.

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Policies and interventions to create healthy school food environments

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