Impact of Baseline Characteristics and Parental Risk Factors on CHDs: A Comparative Analysis Study

Temel Özelliklerin ve Ebeveyn Risk Faktörlerinin Doğuştan Kalp Hastalıkları Üzerindeki Etkisi

Ⓘ Sana Ashiq[1,2], Ⓘ Syed Najam Hyder[3], Ⓘ Muhammad Farooq Sabar[4]

[1]Department of Molecular Genetics, Centre for Applied Molecular Biology, University of the Punjab, Lahore, Pakistan
[2]Department of Medical Laboratory Technology, Shalamar School of Allied Health Sciences, Affiliated with University of Health Sciences, Lahore, Pakistan
[3]Department of Paediatric Cardiology, University of Child Health Sciences, The Children's Hospital, Lahore, Pakistan
[4]Department of School of Biochemistry and Biotechnology, University of the Punjab, Lahore, Pakistan

ABSTRACT

Objective: To identify the potential role of the patient's baseline characteristics and assess the association of congenital heart defects (CHDs) with parental risk factors, particularly maternal chronic disease and socioeconomic status.

Methods: This case-control study included 376 subjects. Extensive patient histories, including the subjects' anthropometric parameters and paternal risk factors, were collected from multiple hospitals in Lahore between March 2021 and April 2022. Children's physical parameters, including body mass index, were measured according to the Centre's for Disease Control and Prevention guidelines. Statistical analyses were conducted using R-manager and GraphPad Prism.

Results: In the current study, 65.8% of CHD subjects and 64.9% of healthy subjects were male. The comparative assessment of the patient's anthropometric parameters suggested no significant association with the heart defect. However, compared to healthy subjects, CHD patients were significantly underweight (p < 0.0001). However, the difference was not significant for the comparison between cyanotic and acyanotic CHD groups. The assessment of maternal risk factors showed significant associations for maternal hypertension [3.09 95% confidence interval (CI): 1.64-5.79] and maternal diabetes [2.92 (95% CI: 1.24-6.88)]. In addition, the impact of parental socioeconomic status was substantial: 25.7% and 46.6% of patients were from poor and middle-income families, respectively.

ÖZ

Amaç: Hastanın temel özelliklerinin potansiyel rolünü belirlemek ve doğuştan kalp kusurlarının (DKK) ebeveyn risk faktörleriyle, özellikle annenin kronik hastalığı ve sosyoekonomik durumuyla ilişkisini değerlendirmek.

Yöntemler: Bu olgu-kontrol çalışmasına 376 kişi dahil edildi. Mart 2021 ile Nisan 2022 tarihleri arasında Lahor'daki birçok hastaneden, deneklerin antropometrik parametreleri ve baba risk faktörleri de dahil olmak üzere kapsamlı hasta öyküleri toplandı. Çocukların vücut kitle indeksi de dahil olmak üzere fiziksel parametreleri, Hastalık Kontrol ve Önleme Merkezi kılavuzlarına göre ölçüldü. İstatistiksel analizler R-manager ve GraphPad Prism kullanılarak yapıldı.

Bulgular: Mevcut çalışmada, DKK'lı deneklerin %65,8'i ve sağlıklı deneklerin %64,9'u erkekti. Hastaların antropometrik parametrelerinin karşılaştırmalı değerlendirmesi, kalp kusuru ile anlamlı bir ilişki göstermedi. Bununla birlikte, sağlıklı deneklere kıyasla, DKK hastaları anlamlı derecede düşük kiloluydu (p < 0,0001). Ancak, siyanotik ve asiyanotik DKK grupları arasındaki karşılaştırmada fark anlamlı değildi. Anne risk faktörlerinin değerlendirilmesi, maternal hipertansiyon için anlamlı ilişkiler gösterdi [3,09 (%95 güven aralığı (GA): 1,64-5,79)] ve maternal diyabet için anlamlı ilişkiler gösterdi [2,92 (%95 GA: 1,24-6,88)]. Ayrıca, ebeveynlerin sosyoekonomik durumunun etkisi önemliydi: Hastaların %25,7'si ve %46,6'sı sırasıyla yoksul ve orta gelirli ailelerden geliyordu.

Address for Correspondence/Yazışma Adresi: Sana Ashiq, Department of Molecular Genetics, Centre for Applied Molecular Biology, University of the Punjab, Lahore, Pakistan; Department of Medical Laboratory Technology, Shalamar School of Allied Health Sciences, Affiliated with University of Health Sciences, Lahore, Pakistan

E-mail / E-posta: sanaashiq72@gmail.com
ORCID ID: orcid.org/0000-0003-0418-4022

ABSTRACT

Conclusion: CHD in children was significantly associated with patients' health status, including maternal hypertension and diabetes. However, this relationship was not found between cyanotic and acyanotic patients. In addition, parental socioeconomic status patients' poses a significant burden on patients' families and the healthcare system.

Keywords: CHD, BMI, hypertension, socioeconomic status, congenital heart defect

ÖZ

Sonuç: Çocuklarda DKK, maternal hipertansiyon ve diyabet de dahil olmak üzere hastaların sağlık durumuyla anlamlı derecede ilişkiliydi. Bununla birlikte, bu ilişki siyanotik ve asiyanotik hastalar arasında bulunmadı. Ayrıca, ebeveynlerin sosyoekonomik durumu, hastaların aileleri ve sağlık sistemi üzerinde önemli bir yük oluşturmaktadır.

Anahtar Sözcükler: DKK, BMI, hipertansiyon, sosyoekonomik durum, konjenital kalp kusuru

INTRODUCTION

Globally, congenital heart defects (CHDs) remained the top reason of infant morbidity and mortality. Thus, included as one of the major agendas in the 2015 sustainable development goals of the United States (1). Worldwide, 10% of all births are affected by this disease; however, due to recent advancements in pediatric cardiology treatment, overall mortality has declined. While in comparison to high-income countries (HICs) a higher mortality rate was observed in lower-middle-income countries and lower-income countries with an average of 1.2 deaths per 100,000 cases and 4.9 deaths per 100,000 cases respectively (2). A meta-analysis of 260 studies suggested that overall, after every five years the prevalence of congenital heart malformation increased by 10% due to milder lesions with the highest prevalence in Asian regions as compared to Africa (3). It is a complex birth defect that occurs during cardiogenesis and may involve a complex interaction between genetic and environmental risk factors, particularly maternal factors (4). Depending on the clinical severity of the disease, CHDs can be further classified as mild, moderate, and severe. Moreover, the clinical presentation of patients is further divided into two major categories cyanotic or a-cyanotic (5-7). Although several studies have been conducted to analyze the underlying cause of the disease, the exact mechanism of pathogenesis remains unclear. One poorly understood mechanism in pathophysiology is the role played by modifiable risk factors, including maternal health (particularly during pregnancy), use of medications during pregnancy, a history of stillbirths, smoking, and diabetes mellitus. In addition, these risk factors may vary across different populations and cultures (8,9). Over the past few decades, several studies identified genetic variants and chromosomal abnormalities in syndromic CHD but the etiology of complex non-syndromic CHD needs further studies that can provide us better insights into disease pathogenesis and may provide us a new direction for future prevention of disease (10). To date, the majority of research studies have focused on the genetics of CHD compared with other extrinsic factors, while few extrinsic factors have been studied. This study comprehensively analyzed all the crucial paternal and anthropometric parameters in non-syndromic CHD, which may help us strengthen management guidelines and improve genetic counseling, thereby reducing future disease risk.

MATERIALS AND METHODS

This study was designed as a case-control study to compare the baseline characteristics and maternal risk factors. Ethical approval was obtained from the Punjab University Ethical Committee, Faculty of Economics and Management Sciences, University of the Punjab (approval number: 84/DFEMS, date: 05.04.2021) and Institutional Review Board of The Children's Hospital & The Institute of Child Health, Lahore (approval number: 2021-282-CHICH, date: 18.05.2021). This study includes paediatric cardiologist-confirmed cases of both cyanotic and acyanotic CHD. After obtaining informed consent, all critical information was collected from the study subjects. The information collected from participants was divided into two phases: first, the patient's baseline parameters were studied; second, parental risk-factor analysis was performed and is described in the detailed sections below.

Patient's and Healthy Subjects Characteristics

The baseline parameters from subjects with cyanotic or acyanotic CHDs and control subjects were recorded for comparative evaluation. The following information was collected: age, gender, weight in kg, height in cm, and body mass index (BMI) in kg/m^2. The BMI results were further used to classify the study subjects as underweight, healthy weight, overweight, and obese. BMI was calculated according to the Centers for Disease Control and Prevention (CDC) guidelines. The following cut-off points were used for classification: less than the 5th percentile for underweight, 5th percentile to up to the 85th percentile for healthy subjects, 85th to less than the 95th percentile for overweight, and equal to, or greater than the 95th percentile for obese subjects (11).

Parental Risk Factors

The paternal risk-factor analysis was divided into four major sections: demographics, family history, chronic disease evaluation, and maternal pregnancy complications. The demographic data further include the parental age, and socioeconomic status evaluation according to the Kuppuswamy scale, and data were divided into upper-class, middle-class, poor class, and very-poor class (12,13). Maternal risk factors recorded were smoking, of medicines, a history of chronic disease or complicated pregnancy, and the number of children aborted.

Statistical Analysis

Categorical data were represented as percentages or frequencies, and continuous data as means with standard deviation, respectively. The t-test and chi-square test were used to compare continuous and categorical variables, respectively. The associations were further expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant. The statistical analyses were performed using R-Manager, the Statistical Package for the Social Sciences 22.0, and GraphPad Prism version 5.

RESULTS

A total of 376 subjects were recruited, including 225 cases and 151 controls. Among CHDs, 101 were cyanotic and 124 were acyanotic. The cases had 148 males and 77 females, while the controls had 98 males and 53 females (p = 0.95). The comparative assessment of baseline characteristics between patients with CHDs and healthy subjects revealed no significant differences except for BMI (p < 0.0001, Table 1).

The comparison of health status suggested a significant difference between the two categories: the percentages of healthy, underweight, overweight, and obese individuals were 92.54%, 0%, 4.48%, and 2.98% in controls, and 58.59%, 37.37%, 4.04%, and 0% in cases (Figures 1 and 2).

There was no statistically significant difference in anthropometric parameters between cyanotic and acyanotic CHDs (p > 0.05, Table 1). The percentages of healthy, underweight, overweight, and obese in cyanotic and a-cyanotic groups were 60%, 37.78%, 2.22%, and 0%, and 57.41%, 37.04%, 5.55%, and 0%, respectively (Figure 3). The impact of paternal socioeconomic status was significant in the Pakistani population, as the majority of patients (46.67%) belonged to the middle class and 25.78% to the poor class. Moreover, high-cost treatment strategies were a key reason for the burden on patients' families and the healthcare system. However, in 79.56% of cases, clinical outcomes improved after open-heart, closed-heart, or interventional treatments.

The maternal age was 27.64 ± 5.64 and 26.88 ± 4.51 (p = 0.16), and the paternal age was 30.79 ± 5.35 and 30.37 ± 4.43 (p = 0.42) in congenital heart disease and healthy subjects, respectively. Similarly, there was no statistically significant difference between cyanotic and a-cyanotic CHD for maternal and paternal age (p = 0.51, p = 0.41) (Table 2).

Assessment of underlying maternal chronic disease conditions suggested a significant association between maternal hypertension and CHDs when patients were compared with controls

(OR: 3.09, 95% CI: 1.64-5.79, p = 0.0003). Similarly, maternal diabetes was significantly associated with CHD in children (OR: 2.92, CI: 1.24-6.88, p = 0.01). Child mortality due to maternal pregnancy complications and the use of medicines was non-significant (p = 0.78 and 0.58), respectively. The maternal and paternal histories also showed no significant association with congenital heart disease (p > 0.05) in the Pakistani population (Tables 3 and 4).
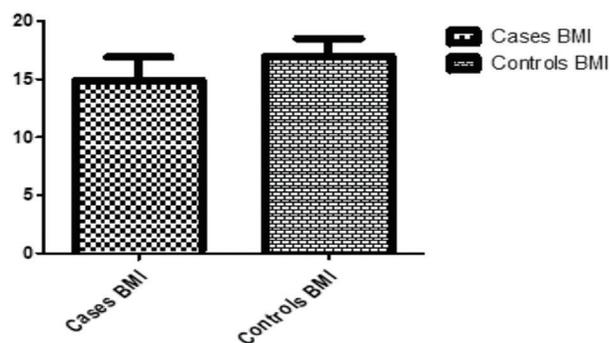
Figure 1. Evaluation of BMI between CHD and control subjects.

CHDs: Congenital heart defects, BMI: Body mass index.
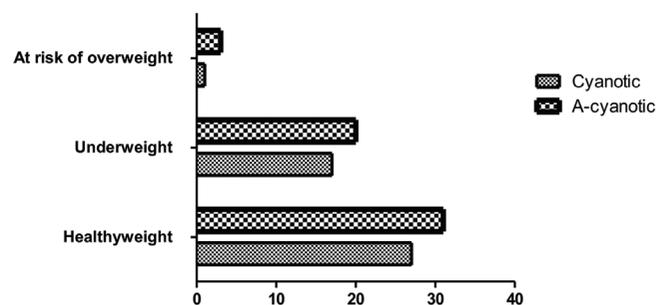
Figure 2. Comparison of health status between cases and controls.

Table 1. Role of baseline characteristics in congenital heart defect and comparative assessment between cyanotic and a-cyanotic CHDs.

Characteristics	CHDs	Controls	p-value	Cyanotic CHDs	A-cyanotic CHDs	p-value
Gender						
Male	148 (65.8%)	98 (64.9%)	0.95	63 (62.4%)	85 (68.5%)	0.33
Female	77 (34.2%)	53 (35.1%)		38 (37.6%)	39 (31.5%)	
Age:						
<1 year (months)	5.27 ± 2.94	5.72 ± 2.66	0.28	5.24 ± 3.25	5.28 ± 2.80	0.95
≥1 year (years)	4.41 ± 3.68	4.06 ± 3.58	0.47	4.24 ± 3.85	4.58 ± 3.51	0.58
Weight (kg)	8.73 ± 5.60	9.31 ± 8.01	0.40	8.89 ± 5.64	8.60 ± 5.58	0.70
<2 year weight	4.92 ± 1.70	4.68 ± 1.25	0.26	5.15 ± 1.81	4.75 ± 1.60	0.19
≥2 year weight	13.58 ± 5.06	15.12 ± 9.07	0.16	13.5 ± 5.33	13.6 ± 4.89	0.92
Height (cm)	72.83 ± 23.39	70.33 ± 24.73	0.32	73.07 ± 23.47	72.21 ± 23.97	0.78
<2 year height	55.83 ± 7.72	54.33 ± 7.71	0.16	56.27 ± 8.05	55.47 ± 7.48	0.56
≥2 year height	94.46 ± 18.18	90.39 ± 24.10	0.21	93.98 ± 19.11	93.91 ± 20.26	0.98
BMI (kg/m²) ≥2 year (years)	14.89 ± 2.03	16.97 ± 1.51	<0.0001*	14.88 ± 1.97	14.90 ± 2.09	0.96

*: p < 0.05.

CHDs: Congenital heart defects, BMI: Body mass index, Kg: Kilogram, cm: Centimeter, Kg/m²: Kilogram/meter².

DISCUSSION

The current study was the first comprehensive report from the Pakistani cohort that comparatively analyzed the role of patients' baseline characteristics and parental risk factors. The results of this study suggested an association between underlying maternal chronic disease conditions, including hypertension and diabetes, and congenital heart disease in children. In addition, the findings of this study indicated that CHD patients had a compromised health status compared with healthy subjects. Furthermore, it posed a
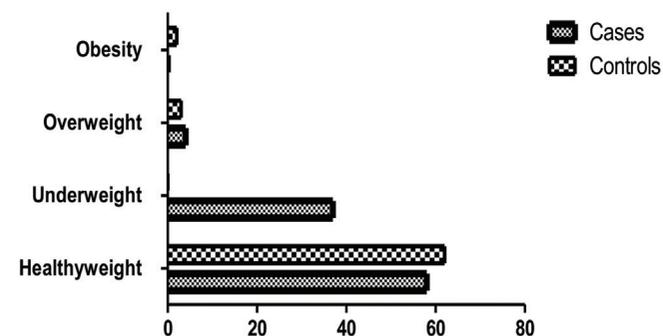
Figure 3. Comparative assessment of health status between cyanotic and a-cyanotic CHD.

CHDs: Congenital heart defects.

substantial burden on patients' families and the healthcare system, as the majority of patients in Pakistan are from middle- or low-income families. The expensive surgical treatments are considered a major challenge for cardiac surgeons, patients' families, and Pakistan's healthcare system.

The low BMI of patients indicates poorer nutritional status compared with healthy subjects. Okoromah et al. (14) also reported severe malnutrition and underweight in congenital heart disease patients as compared to controls.

This study's findings were similar to results from another cohort that reported 21% of CHD patients were underweight (p < 0.001). While cyanotic vs. a-cyanotic CHD analysis showed that cyanotic were more underweight (15).

Xiang et al. (16) reported a 97% survival rate after surgeries of pediatric patients and suggested that middle and low-income families were at high risk of poor prognosis after cardiac surgery. The overall percentage of low and middle-income status patients was 69% (16). A population-based study from California showed a significant association between patient socioeconomic status and environmental triggers with high CHD incidence (17). Maternal occupation and socioeconomic disparities also showed a significant association (p < 0.001) with the disease in Iran (18). Paternal low socioeconomic status and remoteness of residence were associated with high patient mortality and adverse disease outcomes (19).

Table 2. Impact of maternal and parental age.

Parental age	CHDs	Controls	p-value	CHDs		p-value
				Cyanotic	A-cyanotic	
Maternal age	27.64 ± 5.64	26.88 ± 4.51	0.16	27.92 ± 5.57	27.43 ± 5.71	0.51
Paternal age	30.79 ± 5.35	30.37 ± 4.43	0.42	31.11 ± 5.26	30.53 ± 5.43	0.41

CHDs: Congenital heart defects.

Table 3. Comparative assessment of parental risk factors.

Risk factors	CHDs n (%)	Controls n (%)	OR (95% CI)	p-value
Maternal hypertension				
Yes	54 (24%)	14 (9.27%)	3.09 (1.64-5.79)	0.0003*
No	171 (76%)	137 (90.73%)		
Maternal diabetes				
Yes	28 (12.4%)	7 (4.6%)	2.92 (1.24-6.88)	0.01*
No	197 (87.6%)	144 (95.4%)		
Children deceased due to maternal pregnancy complications				
Yes	19 (8.44%)	14 (9.3%)	0.90 (0.43-1.86)	0.78
No	206 (91.6%)	137 (90.7%)		
Medicines used during pregnancy				
Yes	20 (8.89%)	16 (10.6%)	0.82 (0.41-1.64)	0.58
No	205 (91.11%)	135(89.4%)		
Paternal smoking history				
Yes	12 (5.33%)	11 (7.3%)	0.71 (0.30-1.67)	0.43
No	213 (94.67%)	140 (92.7%)		

*: p < 0.05.
CHDs: Congenital heart defects, CI: Confidence interval, OR: Odds ratio.

Table 4. Comparative study of parental risk factors.

Characteristics	CHDs (n = 225)	Controls (n = 151)	Cyanotic CHDs (n = 101)	A-cyanotic CHDs (n = 124)
Maternal hypertension	54 (24%)	14 (9.27%)	26 (25.7%)	28 (22.6%)
Maternal diabetes	28 (12.4%)	7 (4.6%)	14 (13.9%)	14 (11.3%)
Children deceased due to maternal pregnancy complications	19 (8.44%)	14 (9.3%)	11 (10.89%)	8 (6.45%)
Number of children aborted				
One abortion	10 (4.45%)	14 (9.3%)	8 (7.92%)	2 (1.61%)
Two abortions	3 (1.33%)	0 (0%)	0 (0%)	3 (2.42%)
Three abortions	1 (0.44%)	0 (0%)	1 (0.99%)	0 (0%)
No abortions	211 (93.78%)	137 (90.7%)	92 (91.09%)	119 (95.97%)
Medicines used during pregnancy	20 (8.89%)	16 (10.6%)	9 (8.91%)	11 (8.87%)
Maternal smoking history	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Paternal smoking history	12 (5.33%)	11 (7.3%)	4 (3.96%)	8 (6.45%)
Family history	25 (11.11%)	7 (4.64%)	13 (12.87%)	12 (9.68%)

CHDs: Congenital heart defects.

A cohort study reported no significant association between paternal age and CHDs in the Danish population (20). However, findings from the Indian cohort showed an association between maternal and paternal age and heart defects in children (21). This study's results were in accordance with the study of Taylor et al. (22) as they reported a 0.96 OR and 0.85-1.07, 95% CI for paternal smoking (22). Other case-control results suggested a relationship between maternal smoking and the high risk of CHD in children (23). Likewise, maternal hypertension ($p < 0.01$), maternal smoking ($p < 0.01$), and maternal diabetes ($p < 0.01$) were found as strongly associated risk factors for congenital heart malformation in children (24). Hypertensive disorder of pregnancy has been shown to be associated with a threefold increase in CHD (OR 2.51, 95% CI: 2.38-2.64, $p \leq 0.001$), and the OR for maternal diabetes and CHD in children was 5.14 (95% CI: 5.04-5.23, $p \leq 0.001$) (25). The OR for maternal drug use was 2.68 ($p < 0.05$), the OR for family history was 4.14, and for maternal abortions was 1.12 (26). Maternal hypertension, diabetes, preeclampsia, and smoking during pregnancy showed a statistically significant association with CHDs in the pediatric population ($p < 0.001$) (27).

CONCLUSION

The findings of this study suggest a potential role for maternal risk factors, including hypertension, diabetes, and socioeconomic status. Furthermore, the analysis revealed that children with CHD were more likely to be underweight compared with healthy subjects. However, in the cyanotic group, anthropometric parameters, including BMI, were not statistically different from those in the acyanotic group. In addition, maternal and paternal ages did not differ between the CHDs and control groups, and between the cyanotic and a-cyanotic groups. Appropriate measures should be taken to screen for parental risk factors and family history, which may help us strengthen future CHD prevention guidelines. It is further recommended to conduct additional studies with larger cohorts across different subgroups to provide a more definitive conclusion.

REFERENCES

1. Su Z, Zou Z, Hay SI, Liu Y, Li S, Chen H, et al. Global, regional, and national time trends in mortality for congenital heart disease, 1990-2019: an age-period-cohort analysis for the Global Burden of Disease 2019 study. EClinicalMedicine. 2022; 43.

2. Varela-Chinchilla CD, Sánchez-Mejía DE, Trinidad-Calderon PA. Congenital heart disease: the state-of-the-art on its pharmacological therapeutics. J Cardiovasc Dev Dis. 2022; 9: 201.

3. Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol. 2019; 48: 455-63.

4. Ashiq S, Ashiq K, Sabar MF. The role of NKX2-5 gene polymorphisms in congenital heart disease (CHD): a systematic review and meta-analysis. Egypt Heart J. 2021; 73: 72.

5. Jin X, Ni W, Wang G, Wu Q, Zhang J, Li G, et al. Incidence and risk factors of congenital heart disease in Qingdao: a prospective cohort study. BMC Public Health. 2021; 21: 1044.

6. Majiyagbe OO, Akinsete AM, Adeyemo TA, Salako AO, Ekure EN, Okoromah CA. Coagulation abnormalities in children with uncorrected congenital heart defects seen at a teaching hospital in a developing country. PLoS One. 2022; 17: e0263948.

7. Madsen NL, Marino BS, Woo JG, Thomsen RW, Videbæk J, Laursen HB, et al. Congenital heart disease with and without cyanotic potential and the long-term risk of diabetes mellitus: a population-based follow-up study. J Am Heart Assoc. 2016; 5: e003076.

8. Fung A, Manlhiot C, Naik S, Rosenberg H, Smythe J, Lougheed J, et al. Impact of prenatal risk factors on congenital heart disease in the current era. J Am Heart Assoc. 2013; 2: e000064.

9. Smith JM, Andrade JG, Human D, Field TS. Adults with complex congenital heart disease: cerebrovascular considerations for the neurologist. Front Neurol. 2019; 10: 329.

10. Feng Y, Yu D, Yang L, Da M, Wang Z, Lin Y, et al. Maternal lifestyle factors in pregnancy and congenital heart defects in offspring: review of the current evidence. Ital J Pediatr. 2014; 40: 1-7.

11. Andonian C, Langer F, Beckmann J, Bischoff G, Ewert P, Freilinger S, et al. Overweight and obesity: an emerging problem in patients with congenital heart disease. Cardiovasc Diagn Ther. 2019; 9 (Suppl 2): S360.

12. Saif-Ur-Rahman KM, Anwar I, Hasan M, Hossain S, Shafique S, Haseen F, et al. Use of indices to measure socio-economic status (SES) in South-Asian urban health studies: a scoping review. Syst Rev. 2018; 7: 196.

13. Wani RT. Socioeconomic status scales—modified Kuppuswamy and Udai Pareekh's scale updated for 2019. J Family Med Prim Care. 2019; 8: 1846-9.

14. Okoromah CA, Ekure EN, Lesi FE, Okunowo WO, Tijani BO, Okeiyi JC. Prevalence, profile and predictors of malnutrition in children with congenital heart defects: a case-control observational study. Arch Dis Child. 2011; 96: 354-60.

15. Chen CA, Wang JK, Lue HC, Hua YC, Chang MH, Wu MH. A shift from underweight to overweight and obesity in Asian children and adolescents with congenital heart disease. Paediatr Perinat Epidemiol. 2012; 26: 336-43.

16. Xiang L, Su Z, Liu Y, Zhang X, Li S, Hu S, et al. Effect of family socioeconomic status on the prognosis of complex congenital heart disease in children: an observational cohort study from China. Lancet Child Adolesc Health. 2018; 2: 430-9.

17.

18. Peyvandi S, Baer RJ, Chambers CD, Norton ME, Rajagopal S, Ryckman KK, et al. Environmental and socioeconomic factors influence the live-born incidence of congenital heart disease: a population-based study in California. J Am Heart Assoc. 2020; 9: e015255.

19. Amini-Rarani M, Vahedi S, Borjali M, Nosratabadi M. Socioeconomic inequality in congenital heart diseases in Iran. Int J Equity Health. 2021; 20: 1.

20. Olugbuyi O, Smith C, Kaul P, Dover DC, Mackie AS, Islam S, et al. Impact of socioeconomic status and residence distance on infant heart disease outcomes in Canada. J Am Heart Assoc. 2022; 11: e026627.

21. Su XJ, Yuan W, Huang GY, Olsen J, Li J. Paternal age and offspring congenital heart defects: a national cohort study. PLoS One. 2015; 10: e0121030.

22. Abqari S, Gupta A, Shahab T, Rabbani MU, Ali SM, Firdaus U. Profile and risk factors for congenital heart defects: a study in a tertiary care hospital. Ann Pediatr Cardiol. 2016; 9: 216-21.

23. Taylor K, Elhakeem A, Thorbjørnsrud Nader JL, Yang TC, Isaevska E, Richiardi L. Effect of maternal prepregnancy/early-pregnancy body mass index and pregnancy smoking and alcohol on congenital heart diseases: a parental negative control study. J Am Heart Assoc. 2021; 10: e020051.

24. Deng C, Pu J, Deng Y, Xie L, Yu L, Liu L, et al. Association between maternal smoke exposure and congenital heart defects from a case-control study in China. Sci Rep. 2022; 12: 14973.

25. Wu Y, Liu B, Sun Y, Du Y, Santillan MK, Santillan DA, et al. Association of maternal prepregnancy diabetes and gestational diabetes mellitus with congenital anomalies of the newborn. Diabetes Care. 2020; 43: 2983-90.

26. Sanapo L, Donofrio MT, Ahmadzia HK, Gimovsky AC, Mohamed MA. The association of maternal hypertensive disorders with neonatal congenital heart disease: analysis of a United States cohort. J Perinatol. 2020; 40: 1617-24.

27. Saad H, Sinclair M, Bunting B. Maternal sociodemographic characteristics, early pregnancy behaviours, and livebirth outcomes as congenital heart defects risk factors—Northern Ireland 2010-2014. BMC Pregnancy Childbirth. 2021; 21: 1-13.

28. Savla JJ, Putt ME, Huang J, Parry S, Moldenhauer JS, Reilly S, et al. Impact of maternal-fetal environment on mortality in children with single ventricle heart disease. J Am Heart Assoc. 2022; 11: e020299.