Obravnava novorojenčkov s prirojenimi srčnimi napakami v severovzhodnem delu Slovenije: enocentrična retrospektivna raziskava

Management of Newborns with Congenital Heart Defects in Northeast Slovenia: A Single-Center Retrospective Study

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Izvleček

Namen: *Primerjati epidemiološke in klinične lastnosti med bolniki s kritičnimi in nekritičnimi prirojenimi srčnimi napakami (PSN), ob tem pa primerjati še stopnjo prepoznave PSN, čas ukrepanja in izide zdravljenja z obstoječimi podatki iz literature.*

Metode: *Izvedli smo retrospektivno opazovalno raziskavo novorojenčkov s PSN, ki so se rodili v porodnišnici Univerzitetnega kliničnega centra Maribor od leta 2018 do konca leta 2022, kar je skupno 353 bolnikov. Podatki so bili zbrani iz podatkovne zbirke zdravstvene obravnave bolnikov Univerzitetnega kliničnega centra Maribor in iz osebnih kartotek bolnikov. Primerjali smo lastnosti mater in otrok med skupino kritičnih in nekritičnih PSN ter čas prepoznave*

Abstract

Purpuse: *To compare the epidemiological and clinical characteristics between critical and noncritical congenital heart defects (CHD), and the detection rate of CHD, time of intervention, and outcomes in Slovenia and globally.*

Methods: *We performed a retrospective observational study of 353 neonates with CHD who were born in the maternity ward at the University Medical Center Maribor between 2018 and 2022. Data were collected from the database at the University Medical Center Maribor and from personal patient files. We compared maternal and infant characteristics between critical and noncritical CHD. The detection rate of CHD, time of intervention, treatment options, and outcomes were also compared among infants*

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PSN, vrsto zdravljenja in izide zdravljenja glede na podatke iz literature.

Rezultati: *Skupna incidenca kritičnih PSN je bila 1,75/1.000 živorojenih otrok in incidenca pomembnih PSN 4,4/1.000 živorojenih otrok. Genetske nepravilnosti so bile najdene pri 21,4 % (n = 3) otrok s kritičnimi PSN. Kritične PSN so bile prepoznane pred odpustom iz porodnišnice v 85,7 % (n = 12), po odpustu iz porodnišnice pa v 14,3 % (n = 2). Vse kritične PSN so bile prepoznane na podlagi klinične slike in potrjene z ultrazvokom srca, nobena kritična PSN ni bila prepoznana na podlagi presejalnega testa s pulzno oksimetrijo. 27,5 % (n = 97) nosečnic, ki so rodile otroka s PSN, je imelo nosečnostno sladkorno bolezen.*

Zaključek: *Obravnava novorojenčkov s PSN zahteva ustrezno izobražen multidisciplinarni zdravstveni tim, saj zgodnja prepoznava zmanjšuje obolevnost in umrljivost otrok s PSN. Večina PSN je prepoznanih na podlagi klinične slike in potrjenih z ultrazvokom srca. Stopnja prepoznave PSN je zadovoljiva, kljub temu pa še vedno nekaj novorojenčkov s kritičnimi PSN ob odpustu iz porodnišnice ostane neprepoznanih. Delež neprepoznanih kritičnih PSN bi se lahko še povečal, v kolikor se bo nadaljeval trend zgodnjega odpusta novorojenčkov iz porodnišnice.*

with CHD.

Results: *The overall incidence of critical CHD was 1.75/1,000 live births, while the incidence of major CHD was 4.4/1,000 live births. Genetic abnormalities were found in 21.4% (n = 3) of children with critical CHD. Critical CHD was identified prior to the patient being released from the maternity ward in 85.7% (n = 12) and after discharge in 14.3% (n = 2). All critical CHD cases were identified based on clinical condition and confirmed by echocardiography. The absence of a heart defect was detected by newborn pulse oximetry screening. A total of 27.5% (n = 97) of pregnancies were affected by gestational diabetes (GDM).*

Conclusions: *The management of newborns with CHD requires a trained multidisciplinary medical team, as early recognition improves morbidity and prevents mortality. Most CHDs are detected based on clinical conditions, with the diagnosis being confirmed by echocardiography. While the detection of CHD was satisfactory, some newborns with critical CHD were undiagnosed and discharged from the maternity ward. The proportion of undetected infants with CHD may increase in the future if the trend toward earlier discharge continues.*

INTRODUCTION

Congenital heart defects (CHD) are some of the most common congenital anomalies. However, the incidence of CHD depends on what types of congenital anomalies are included in patient analyses and on the level of development of the country in regards to the availability of perinatal diagnostics (1). In newborns, CHDs manifest with signs of heart failure, cyanosis, or only as a heart murmur. However, CHDs can also occur without clinical symptoms (2). The timely diagnosis of CHD is essential, otherwise morbidity and mortality can occur (3). According to published data, the incidence of major (significant) CHD is 6–8 per 1,000 live births, and the incidence of all CHD is up to 75 per 1,000 live births, depending on the availability of ultrasound diagnostics (4).

Complex heart defects with more than one defect represent 10–15% of all CHD cases. CHD accompanied by other congenital anomalies also occurs in the same proportion (5). Approximately a quarter of major defects are critical heart defects that require surgical or cardiological interventional treatment in the first year of life. Risk factors for the occurrence of CHD are chromosomal anomalies and environmental factors, such as gestational diabetes (GDM), rubella virus infection, or reduced folic acid levels (6). An important risk factor is also a positive family history for CHD, such as the presence of CHD in siblings or parents, and especially in the mother (7).

Pulse oximetry screening is a part of the state screening program for newborns in Slovenia, and is performed 24 hours after birth or at least before hospital discharge. Screening consists of measuring arterial blood oxygen saturation using pulse oximetry in two locations, including on the right hand (pre-ductal saturation) and on one leg (post-ductal saturation) (8, 9). The aim of the screening program is the early recognition of significant CHD. Despite all of the screening tests that are performed before or immediately after birth, a large proportion of CHD remains undiagnosed until the development of a critical, life-threatening condition (2). Fetal ultrasound and fetal heart ultrasound monitor heart defects during pregnancy and identify fetuses with CHD that will require delivery in a tertiary center with possible intervention immediately after birth. We must consider the risk of hemodynamic instability, the presence of obstetric complications, and the ability to provide appropriate care in the maternity hospital when we plan the birth of a child with CHD (10).
Neonates with prenatally diagnosed CHD, without expected hemodynamic instability after birth, do not require special preparations; the child is managed in an outpatient clinic. Hemodynamic instability is not expected immediately after birth in the ductal-dependent CHD, but after the closure of ductus arteriosus, which typically occurs 48–72 hours after birth. In ductal-dependent CHD cases, we introduce therapy with prostaglandin E1 (PGE1) and transport the patient to the main tertiary center. The deliveries of newborns with prenatally detected CHD who require immediate intervention after birth should occur in a tertiary center where a neonatologist, a pediatric cardiologist, and a cardiac surgeon are available with the ability for PGE1 administration and the performance of cardiosurgical or cardiological interventional treatment. A newborn with CHD can be delivered vaginally, or by cesarean section; the method of delivery has no effect on the Apgar score or mortality (11, 12). Newborns with CHD who are born close to their due date have fewer complications than those born earlier (12). The objectives of this study were to compare the epidemiological and clinical characteristics between critical and noncritical CHD. We also compared the detection rate of CHD, time of intervention, and outcomes to previous research in Slovenia and globally.

MATERIALS AND METHODS

This retrospective study contained epidemiological and clinical data from neonates with CHD who were born in the maternity ward of the University Medical Center Maribor between 2018 and 2022. We obtained data from the database of the University Medical Center Maribor and from the personal files of patients managed at the University Medical Center Maribor and at the University Medical Center Ljubljana, where cardiosurgical and cardiological interventional treatment of children with CHD occurs. All children underwent echocardiography with precise assessments of cardiac morphology and cardiac function. We classified CHD according to the standard anatomical nomenclature, based on the main morphological features. Major (significant) CHDs were defined as structural abnormalities of the heart or great vessels that have existing or potential functional significance. Among those, CHDs that required intervention in the first year were defined as critical. Premature children with a gestational age of less than 35 weeks who had persistent ductus arteriosus (PDA) or persistent foramen ovale (PFO) as an isolated CHD as part of prematurity without the need for treatment were excluded from the study. The data of 353 patients were reviewed retrospectively. For each patient, we defined the sex, gestational age, birth weight for gestational age, maternal age, presence of GDM, Apgar at 5 minutes, need for respiratory support, need for vasoactive or inotropic support, time of diagnosis, type of CHD, genetic abnormalities, treatment with prostaglandin E1, time of intervention (cardiac catheterization or surgical treatment), and the treatment outcome. Data from the prenatal cardiological assessment and genetic testing were limited in one third of cases. Clear data for fetal echocardiography were available in two cases, and genetic testing was performed prenatally in five cases and postnatally in 14 cases.
Statistical analysis of the data was performed with

IBM SPSS Statistics Standard version 28.0 (IBM Corporation, Armonk, NY, USA) using basic statistical methods, including descriptive statistics, mean values with standard deviations for normally distributed variables, median with confidence interval (95% CI) for non-normally distributed variables, contingency tables, Pearson's chi-square test for descriptive variables and Fisher's correction for small samples, non-parametric Mann-Whitney U test, non-parametric Kruskal-Wallis rank sum test, and post hoc tests with Bonferroni correction. A $p < 0.05$ was considered statistically significant.

RESULTS

During the four-year period, 8,014 children were born in the maternity ward of the University Medical Center Maribor. CHD was identified in 353 cases, of which 51.8% were male and 48.2% were female. The incidence of all CHD was 44/1,000 live births. A total of 24.8% (n = 91) of CHD were significant. When muscular ventricular septal defects (VSD) were excluded, which some studies do, 9.9% (n = 35) of CHD were significant. The incidence of significant CHD was 11/1,000 live births. When cases of muscular VSD were not considered, the incidence of CHD decreased to 4.4/1,000 live births. A total of 4% (n = 14) of cases were critical CHD that needed intervention during the first year of life, 1.7% (n = 6) required intervention during the first month after birth. The overall incidence of critical CHD was 1.75/1,000 live births, while the incidence of critical CHD with intervention in the first month after birth was 0.75/1,000 live births. During the study period, there were 54 stillbirths, of which 59.3% (n = 32) were feticides, and 40.7% (n = 22) were intrauterine fetal demises. In six cases, feticide was performed due to significant CHD (three cases of hypoplastic left heart syndrome (HLHS), one case of univentricular heart, one case of significant aortic stenosis, and one case involving an unspecified complex heart defect). If those cases were added to critical CHD analyses, their incidence would be 2.50/1,000 births. A total of 1.7% (n = 6) of CHD cases were defined as cyanotic and 98.3% (n = 347) were defined as acyanotic. Within the critical CHD cases, 42.9% (n = 6) were cyanotic and 57.1% (n = 8) were acyanotic (Figure 1).

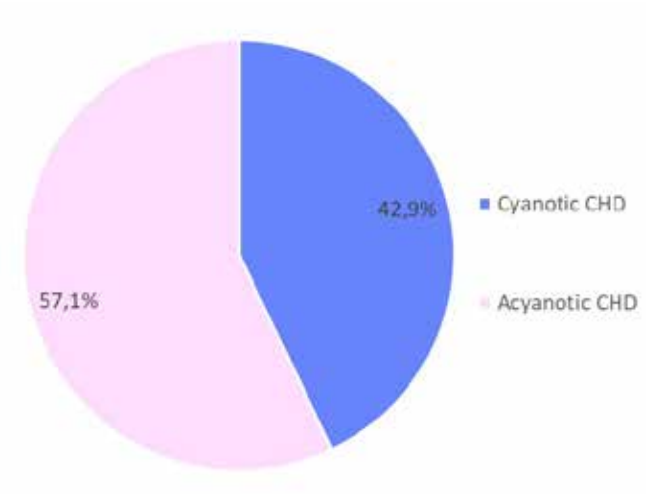

Figure 1. *The percentage of cyanotic and acyanotic congenital heart defects (CHD) within the critical CHD group.*

The distribution of individual acyanotic and cyanotic CHD within the critical and non-critical CHD groups is shown in Table 1.

Therapy with PGE1 for ductal-dependent CHD was necessary in 42.9% (n = 6) of critical CHD cases. The outcome of the treatment of critical CHD was complete repair in 92.9% (n = 13) of patients and staged surgical repair (palliative surgery) in 7.1% (n = 1) of patients. We observed only one death among non-critical CHD patients, which occurred due to complications of extreme prematurity. Genetic abnormalities were identified in 2.5% (n = 9) of children with CHD and in 21.4% (n = 3) of children with critical CHD. The types of genetic abnormalities in individual CHD cases are shown in Table 2.

Critical CHD was identified prior to discharge from the maternity ward or prenatally in 85.7% (n = 12) of cases, and after discharge from the maternity ward in 14.3% (n = 2) of cases (Table 3). All critical CHD cases were identified based on clinical assessments and confirmed by echocardiography. No heart defect was detected by newborn pulse oximetry screening.

Table 1. The distribution of individual acyanotic and cyanotic congenital heart defects (CHD) within the critical and non-critical CHD groups

		Non-critical CHD (N)	Critical CHD (N)
Acyanotic CHD[1]			
Defect type	N (%)	339	8
ASD[2]	133 (37.7)	133	0
VSD[3]	71 (20.1)	68	3
PDA[4]	28 (7.9)	27	1
ASD and PDA	101 (28.6)	101	0
AVSD[5]	0	0	0
PuSt[6]	4 (1.1)	3	1
AoSt7	3 (0.8)	3	0
CoA[8]	1 (0.3)	0	1
Other (MI[9], TI[10], PI[11], CAAs[12])	6 (1.7)	4	2
Cyanotic CHD			
Defect type	N (%)	0	6
ToF[13]	1 (0.3)	0	1
Tricuspid atresia	0	0	0
Pulmonary atresia	0	0	0
Critical PuSt	1 (0.3)	0	1
HLHS[14]	0	0	0
IAA[15]	0	0	0
Critical AoSt	0	0	0
d-TGA[16]	3 (0.8)	0	3
TAPVR[17]	0	0	0
Truncus arteriosus	0	0	0
DORV[18]	1 (0.3)	0	1

[1]CHD – congenital heart defects, [2]ASD – atrial septal defect, [3]VSD – ventricular septal defect, [4]PDA – patent ductus arteriosus, [5]AVSD – atrioventricular septal defect, [6]PuSt – pulmonary stenosis, [7]AoSt – aortic stenosis, [8]CoA – coarctation of the aorta, [9]MI – congenital mitral insufficiency, [10]TI – congenital tricuspid insufficiency, [11]PI – congenital pulmonary insufficiency, [12]CAAs – coronary artery anomalies, [13]ToF – tetralogy of Fallot, [14]HLHS – hypoplastic left heart syndrome, [15]IAA – interrupted aortic arch, [16]d-TGA – transposition of the great arteries, [17]TAPVR – total anomalous pulmonary venous return, [18]DORV – double outlet right ventricle

Table 2. Genetic abnormalities in congenital heart defects (CHD)

Genetic disorder	N	Defect type
Down syndrome	5	DORV[1], ASD[2], VSD[3], ASD and PDA[4]
Noonan syndrome	1	PuSt[5]
DiGeorge syndrome	1	ToF[6]
Sturge-Weber syndrome	1	VSD and PDA
Partial trisomy 16q syndrome	1	Stenosis of pulmonary artery branches

[1]DORV – double outlet right ventricle, [2]ASD – atrial septal defect, [3]VSD – ventricular septal defect, [4]PDA – patent ductus arteriosus, [5]PuSt – pulmonary stenosis, [6]ToF – tetralogy of Fallot

Table 3. Timing of the detection of critical congenital heart defects (CHD)

Time of detection	Critical CHD[1]		
	Acyanotic CHD[1] in N (%)	Cyanotic CHD[1] in N (%)	All in N (%)
Prior to discharge	6 (75)	6 (100)	12 (85.7)
After discharge	2 (25)	0	2 (14.3)

[1]CHD – congenital heart defects

The median time to identify non-critical CHD was 4 days (95% CI: 4–5), while the median time to recognize critical CHD was 3 days (95% CI: 1–6; mode of 1 day; U = 1949.5, p = 0.252). The median time to recognize acyanotic CHD was 4 days (95% CI: 4–5), while the median time to recognize cyanotic CHD was 1 day. The difference in the cyanotic and acyanotic CHD recognition times was statistically different (U = 51.0, p < 0.001).

The median gestational age of non-critical CHD was 37 weeks (95% CI: 37–38), while the median gestational age of critical CHD was 38 weeks (95% CI: 36–40). The difference in gestational age in critical and non-critical CHD was not statistically different (U 2666.0, p = 0.430). The median gestational age of

acyanotic CHD was 37 weeks (95% CI: 37–38), while the median gestational age of cyanotic CHD was 39 weeks (95% CI: 35–39). The difference in gestational age in acyanotic and cyanotic CHD was not statistically different (U 1149.5, p = 0.659).

Apgar at 5 minutes was significantly lower in critical CHD (p < 0.007), in which the Apgar was less than 7 in 21.4% (n = 3) of cases. Neonates with critical CHD needed respiratory support in 50% (n = 7) of cases, including invasive mechanical ventilation in 42.8% (n = 6) of cases, and the addition of oxygen in inhaled air in 7.2% (n = 1) of cases. Vasoactive or inotropic support was necessary in 28.6% (n = 4) of neonates with critical CHD.

In the investigated group of patients from the entire study, 73.9% (n = 261) of newborns were appropriate for gestational age, 15.6% (n = 55) were small for gestational age, and 10.5% (n = 37) were large for gestational age (Figure 2).

A total of 27.5% (n = 97) of pregnancies were affected by GDM in the investigated group of patients from the entire study. There was no statistically significant difference in the incidence of GDM or the adequacy of birth weight for gestational age between critical and non-critical CHD (p = 0.344 and p = 1.000, respectively). No statistically significant difference in the incidence of GDM or in the adequacy of birth weight for gestational age was observed between acyanotic and cyanotic CHD (p = 0.503 and p = 0.482, respectively).

The average age of mothers was 30.9 ± 5.5 years in the investigated group of patients from the entire study. No statistically significant difference in maternal age was observed between critical and non-critical CHD or between acyanotic and cyanotic CHD (U = 2504.5, p = 0.725 and U = 1310.5, p = 0.276, respectively). In the investigated group of patients from the entire study, gestational age was not statistically significantly different relative to the maternal age (r = –0.68, p = 0.200). However, we observed a statistically significant difference in the maternal age according to the history of GDM (H = 7.779, p < 0.020). The average age of mothers was higher in the group of pregnancies affected by GDM, compared to pregnancies without GDM, which was of limited significance as it reflected the established association between advanced maternal age and the higher incidence of GDM.

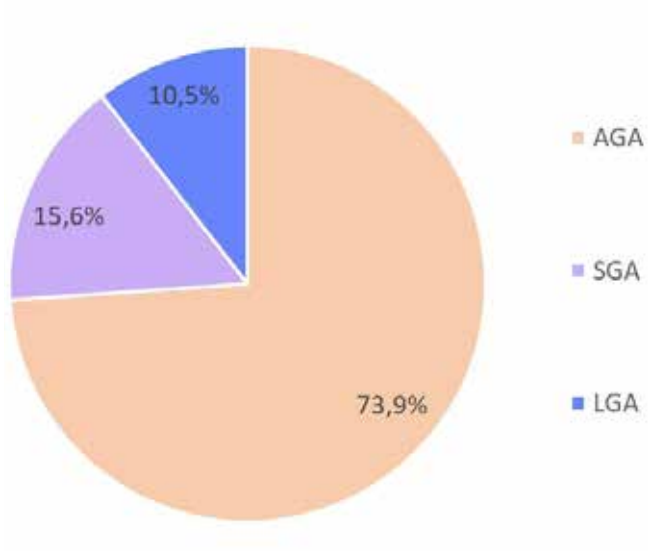

Figure 2. *The percentage of newborns who were appropriate for gestational age (AGA), small for gestational age (SGA), or large for gestational age (LGA) in the investigated group of children with congenital heart defects (CHD) from the entire study.*

DISCUSSION

This study was conducted to evaluate the management of neonates with CHD at the second-largest Slovenian hospital, the University Medical Center Maribor, and to compare treatment outcomes with the existing literature and other studies. The management of newborns with CHD depends on the type of CHD and the time of recognition. We strove to detect significant CHD as soon as possible to plan the childbirth and to provide the best possible obstetric and perinatal care by coordinating work among a multidisciplinary team, including a perinatologist, a neonatologist, and a pediatric cardiologist. Rapid diagnosis and appropriate treatment of newborns with suspected CHD are essential for better outcomes (2, 3).

This retrospective study found a incidence of all CHD in the maternity ward of the University Medical Center Maribor (44/1000 live births) compared to

the existing literature (up to 75/1,000 live births) (4). The incidence of major (significant) CHD (11.4/1,000 live births or 4.4/1,000 live births, if muscular VSDs were excluded) was comparable to data reported in the literature (6–8/1,000 live births) (4, 13). The incidence of critical CHD (1.75/1,000 live births) was slightly lower than that reported in the literature (2.5/1,000 live births) (13, 14), which was most likely due to CHD cases of feticide (30% reduced incidence), and partly due to the management of pregnancies and deliveries with antenatally diagnosed significant CHD at University Medical Centre Ljubljana, where surgical and cardiological interventional treatments are performed.

The proportion of CHD recognized on time (85.7%) was comparable to that reported in a prior Slovenian study (around 90%) (15) and was slightly higher than the European and American average (70–82%) (16-19). We recorded two cases of late recognition, including a combination of coarctation of the aorta and Scimitar syndrome, which manifested at 21 days of age in the form of a blood flow obstruction of the left heart structures. Such an event is also the most common mechanism of unrecognized CHD (20). The second case was a coronary artery anomaly (ALCAPA syndrome), which manifested at two and a half months of age in the form of advanced heart failure. In both cases, the early course after birth was uneventful, and therefore, echocardiography was not performed. All CHD cases were recognized based on the clinical condition, and none were recognized from pulse oximetry screening, which should be further improved and validated.

Genetic abnormalities were observed in 21.4% of critical CHD cases, which was consistent with the literature and other studies (21). Several genetic syndromes are associated with CHD, including Down's syndrome, Noonan syndrome, DiGeorge syndrome, and others, which were also observed in our retrospective study. In the investigated group of children from the entire study, 27.5% of pregnancies were affected by GDM, which was more than that observed in the general population of pregnant women (~10%) (22) and confirmed the correlation between GDM and the increased risk of CHD (23, 24). In developed countries, the prevalence of newborns that are small for gestational age is ~10% (25, 26). In the investigated group of children from the entire study, the percentage of such children was higher at 15.6%, which was also consistent with the other studies (27, 28).

During the study period, screening strategies to detect CHD in Slovenia were based on prenatal fetal ultrasound and physical examinations with echocardiographic confirmation. Pulse oximetry is also performed as an additional screening method for the detection of CHD in all maternity hospitals. The current pre-discharge detection rate of critical CHD is satisfactory at our institution. However, some of the affected neonates still leave the maternity ward undetected.

The main limitations of this study were associated with the centralized management of pregnancies with prenatally known CHD, which affected the incidence of major (significant) and critical CHD outside the capital city. The incidence of CHD was also affected by increasingly developed and accessible prenatal diagnostics and pregnancy terminations. Thus, we must emphasize that in a third of cases, we did not have clear data on prenatal cardiological assessments and genetic testing.

CONCLUSIONS

The management of newborns with CHD requires a trained multidisciplinary medical team, as early recognition improves morbidity and prevents mortality. Most CHD cases are detected based on the clinical condition, and the diagnosis is confirmed by echocardiography. Furthermore, pulse oximetry screening is performed in maternity hospitals nationwide to improve the early detection of critical CHD.

Our study had some limitations, including the small sample size of critical CHD cases. Some of the results were also affected by the redirection of prenatally recognized significant CHD to the main tertiary medical center in Slovenia, the University Medical Center Ljubljana. However, the results of this retrospective study provided insight into the current

state of the treatment of newborns with CHD. Most results were consistent with the existing literature. The detection of CHD was satisfactory, although some newborns with critical CHD were discharged from the maternity ward undiagnosed. The proportion of undetected infants with CHD may increase in the future if the trend toward earlier discharge is continued. There are several possibilities to improve the early detection and management of critical CHD, such as more educated and properly trained medical staff, better ultrasound equipment, standardized screening methods, and efficient cooperation between medical centers. Future research should highlight different types of early medical care for newborns with CHD and record the treatment outcomes nationally. Moreover, the future objective should also be to recognize and expose additional prenatal risk factors for the occurrence of CHD, especially those specific to our environment (pollutants, infections, and maternal substance abuse).

AUTHOR CONTRIBUTIONS:

Conceptualization, T.S.K., T.B. and M.M.; methodology, T.S.K. and M.M.; software, T.S.K. and M.M.; validation, T.S.K. and M.M.; formal analysis, T.S.K; investigation, T.S.K, T.B. and M.M.; resources, T.S.K. and M.M.; data curation, T.S.K. and M.M.; writing the original draft preparation, T.S.K., T.B. and M.M.; writing, review and editing, T.S.K.; visualization, T.S.K.; supervision, M.M. All authors read and approved the final manuscript.

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INFORMED CONSENT STATEMENT:

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CONFLICTS OF INTEREST:

The authors declare no conflict of interest.

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