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Unveiling associated factors related to congenital heart disease in children: A case-control study

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ABSTRACT

Background: Congenital heart diseases (CHDs) remain a significant global health burden and a leading cause of child mortality. However, limited evidence exists regarding the factors associated with CHDs, particularly in Indonesia. This study aims to identify factors associated with congenital heart defects (CHDs) in children.

Methods: A case-control study was conducted using secondary data from pediatric cardiology patients at Ngoerah Hospital between 2021 and 2023, extracted from pedcardiobali.com. Patients aged 0–18 years who were diagnosed with CHD via echocardiography were included in the case group. Those with normal echocardiographic findings comprised the control group. Patients with incomplete medical records were excluded from the study. A total of 300 eligible subjects were selected, with 150 assigned to each group using a combination of purposive and random sampling methods. Multivariate logistic regression analysis was performed using SPSS version 29.0.

Results: Among the 300 subjects, low birth weight (<2,500 grams) was significantly associated with CHDs (OR 3.365; 95% CI: 1.48–7.65; P = 0.004). Prematurity, maternal alcohol consumption, and congenital anomalies were identified as potential confounding factors (OR 1.19; 95% CI: 0.61–2.35; P = 0.61; OR 1.65; 95% CI: 0.45–6.06; P = 0.45; OR 1.98; 95% CI: 0.56–6.94; P = 0.29, respectively). No significant associations were found with maternal or paternal age, multiparity, multiple gestation, smoking, family history of CHDs, or maternal infection.

Conclusion: Low birth weight is a dominant factor associated with CHDs. Early prenatal care and targeted interventions are crucial in reducing this risk. Further research is warranted to investigate the underlying mechanisms and genetic contributions to coronary heart disease (CHD).

Keywords: *Associated factors, congenital heart disease, children*.
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INTRODUCTION

Congenital heart disease (CHD) is the most common congenital anomaly observed in newborns, representing a significant global public health concern. Congenital heart disease (CHD) is a congenital anomaly that is still a worldwide health issue. The severity of CHDs depended on the structural defect complexity that occurred since the beginning of heart morphogenesis during pregnancy. Heart malformations can include the presence of a hole in the septum, anatomical malpositioning of the heart or its blood vessels, or incomplete or underdeveloped cardiac structures.[1] Congenital heart disease is the most common congenital anomaly observed in newborns, with approximately 1.5 million cases reported globally each year. Asia has the highest prevalence, with 9.3 cases per 1,000 births, including those in Indonesia.[2]

CHD is also one of the leading causes of neonatal and infant mortality, particularly in low- and middle-income countries, where diagnostic limitations and delayed interventions compound the risk. The etiology of CHD is multifactorial, involving a complex interplay between genetic predispositions and environmental exposures during gestation. Several maternal and prenatal risk factors have been implicated, including advanced or very young maternal age, infections during pregnancy, poor nutritional status, exposure to teratogens (e.g., alcohol, tobacco, certain medications), and inadequate prenatal care.[3,4] In many cases, CHD coexists with other congenital anomalies, further complicating clinical outcomes and increasing the risk of mortality and long-term morbidity.

Identifying factors associated with CHD is crucial for precaution both during preparation and throughout pregnancy. Although several international studies have explored these associations, there is a significant lack of region-specific evidence from Indonesia. Existing national data are mostly hospital-based and do not adequately investigate the contextual maternal and perinatal factors contributing to CHD incidence. Moreover, socioeconomic disparities, variations in access to antenatal care, and differences in health-seeking behavior may result in distinct patterns of risk and presentation in Indonesian populations. Therefore, this research aimed to unveil the associated factors of CHD among Indonesian children.

MATERIAL AND METHODS

A case-control study was conducted among pediatric patients suspected of having congenital heart disease (CHD) who visited Ngoerah Hospital between 2021 and 2023. Secondary data was extracted from the pediatric cardiology register website, pedcardiobali.com. The sample size was calculated using the OpenEpi calculator, with a power of 0.8, a minimum detectable odds ratio (OR) of 2.0, and a case-to-control group ratio of 1:1. The minimum sample size was determined to be 276. A mixed sampling technique was used to define inclusion and exclusion criteria through purposive sampling, and the sample was then randomized to achieve the desired number of subjects. Patients aged 0-18 years old who were diagnosed with CHD through echocardiography were included as the case group, and patients who were having normal echocardiography were included as the control group. Incomplete medical records were excluded in this study. Several variables were chosen as associated factor candidates, such as other congenital anomalies, family history of CHD (1st-degree relatives), maternal and paternal age, multiparity, gemelli, maternal infection during the first trimester, maternal smoking, maternal alcohol, low birth weight (<2.500 grams), and prematurity (<37 weeks). Maternal and paternal age, which might affect as an associated factor, were defined as <20 and ≥ 35 years old. Multiparity was described as having given birth to more than one child.

At first, bivariate analysis of variables related to CHD was conducted using the Chi-square test, and variables with a p-value < 0.25 were included as candidates for multivariate analysis using multiple logistic regression with the enter method on SPSS 29.0. The variables were removed individually from the model, starting with the variable with the highest p-value, and it was observed whether the odds ratio (OR) changed by more than 10% for each variable upon removal. Variables that caused more than a 10% change in OR were reinserted into the model and defined as confounding factors related to associated factors and CHD. The final model was analyzed using multiple logistic regression to identify the dominant risk factors associated with coronary heart disease (CHD). This study was approved by the Research Ethics Committee at the Faculty of Medicine, Universitas Udayana/Ngoerah Hospital, Denpasar (2024.03.01.1055).

RESULTS

Among 300 eligible subjects, 150 patients were allocated to each case and control group. There were 52.1% females in the case group and 47.9% in the control group. Acyanotic congenital heart defects (CHDs) were predominantly found in the case group (85%), with 24% of cases involving isolated patent ductus arteriosus (PDA) and 22% involving isolated ventricular septal defects (VSD) (Figure 1).

Bivariate analysis was conducted using chi-square (Table 1). Low birth weight (LBW), prematurity, gemelli, maternal alcohol consumption, and other congenital anomalies were included in a multivariate analysis model with p-values < 0.25 (P < 0.002; P < 0.009; P = 0.156; P = 0.239; P = 0.101; consecutively).

Those variables were analyzed using multiple logistic regression, and low birth weight was found as a dominant associated factor of CHD, with prematurity, maternal alcohol, and other congenital anomalies found as confounding factors that contributed to>10% change in OR (Table 2).

DISCUSSION

Congenital heart diseases (CHDs) remain an essential cause of neonatal mortality.[3,4] This case-control study aimed to identify associated factors of CHD in Indonesian children. Our study revealed no statistically significant association between several parental or familial factors. Some studies have reported conflicting results on the association between advanced paternal and maternal age in increasing CHD risk. A positive association between either younger maternal age (<24 years old) or advanced maternal age (35-44 years old) and increased CHD risk has been reported in a register-based study by Mamasoula et al. (OR 1.16, 95% CI, 1.07–1.25).[5] In contrast to the study, our finding showed that maternal age was not significantly associated with CHD risk (OR 1.00; 95% CI 0.49-2.01; P = 1.00), which is consistent with several studies.[6,7] We also found no significant association between paternal age (<20 years old and > 35 years old) with CHD (OR 1.16; 95%CI 0.63-2.14; *P* 0.693). Meanwhile, a meta-analysis by Joinau-Zoulovits et al. highlighted that advanced paternal age may be a potential risk factor

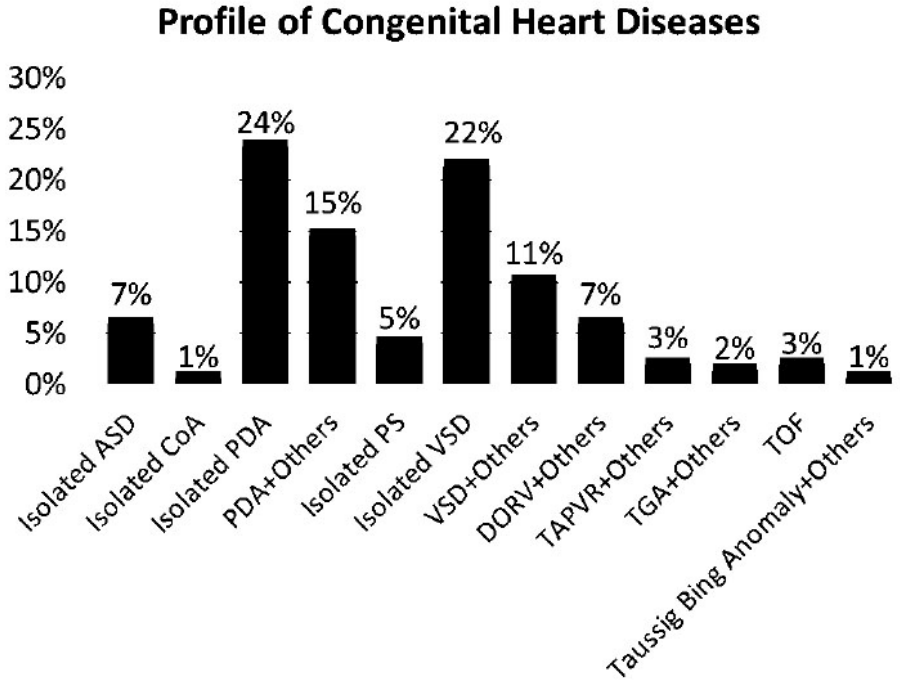

Figure 1. Profile of Congenital Heart Disease in Case Group.

Table 1. Bivariate analysis of associated factor candidates

Variable	CHD (n= 150)		Normal (n=150)		P-value	OR	95% CI	
	n	%	n	%			Min	Max
Low Birth Weight (< 2500gr)	38	76	12	24	<0.001	3.90	1.95	7.82
Prematurity (< 37 weeks)	44	63.8	25	36.2	0.009	2.08	1.19	3.62
Gemelli	9	69.2	4	30.8	0.156	2.33	0.70	7.74
Maternal Age < 20 or > 35 y.o	18	50.0	18	50.0	1.000	1.00	0.49	2.01
Paternal Age < 20 or > 35 y.o	26	53.1	23	46.9	0.693	1.16	0.63	2.14
Family history of CHD	3	50.0	3	50.0	1.000	1.00	0.19	5.04
Multiparity	40	53.3	35	46.7	0.505	1.19	0.71	2.02
Maternal with active smoking	37	55.2	30	44.8	0.332	1.31	0.76	2.26
Maternal with alcohol consumption	8	66.7	4	33.3	0.239	2.06	0.61	6.98
Maternal infection	9	47.4	10	52.6	0.813	0.89	0.35	2.27
Other congenital anomalies	10	71.4	4	28.6	0.101	2.61	0.79	8.51

Table 2. Multivariate analysis final model

Variable	B	S.E.	p-value	OR	95% CI for OR	
					Lower	Upper
Low birth weight	1.213	.419	.004	3.365	1.480	7.649
Prematurity	.176	.346	.612	1.192	.605	2.347
Maternal alcohol	.500	.664	.451	1.649	.449	6.064
Other congenital anomaly	.681	.641	.288	1.976	.563	6.935

*P 0.002, Nagelkerke R square 0.084

for CHD (OR 1.16, 95% CI 1.07-1.25).[8] A family history of CHD was also found not to be significantly related to CHD in our study (OR 1.00; 95% CI 0.19-5.04; P = 1.00), which contradicts the study by Peyvandi et al.[9]

Maternal parity has been reported to be significantly associated with CHD risk, which increases CHD risk by 6% per live birth in higher parity.[10] Although the underlying mechanism remained unclear, it may be caused by nutrient depletion, shorter inter-pregnancy intervals, intrauterine environmental changes, and increased maternal stress associated with multiparity.[10,11] Contradict to those studies, our study found there was no significant association between multiparity and CHD (OR 1.19; 95% CI 0.71-2.02; P 0.505), which might be caused by different study populations, educational level, and prenatal care status.

History of maternal infection during the first trimester and maternal smoking during pregnancy has been reported to be associated with CHD significantly due to increased oxidative stress and inflammation that might affect heart morphogenesis.[12,13] Environmental and behavioral exposures, such as maternal smoking and infection during the first trimester, were also not significantly associated with CHD in our findings. This contrasts with established studies linking these factors to oxidative stress and inflammation during cardiogenesis. Gemelli was also found not to be associated with CHD (OR 2.33; 95% CI 0.70-7.74; P = 0.156), which contradicts the Best and Rankin study.[14] This disparity might be caused by incomplete maternal history or reporting biases. Factors such as nutritional depletion, shorter inter-pregnancy intervals, and physiological stress are commonly hypothesized pathways. However, Indonesian women, particularly in urban areas, may have better access to prenatal care and nutritional support during pregnancy, potentially mitigating this effect.

Interestingly, LBW plays a role as a dominant factor associated with CHD significantly (OR 3.90; 95% CI 1.95-7.82; P < 0.001). It was similar to the case-control study by Giraldo-Grueso (2020), which found that LBW (<2.500g) increased the risk of presenting with CHD (OR 4.13; 95% CI: 3.13-5.44). These findings are consistent with prior research linking LBW to CHD, especially PDA, which, similar to our study, found isolated PDA as the most prevalent case.[15,16] Although the underlying mechanisms remain unclear, the association between low birth weight (LBW) and congenital heart disease (CHD) may involve multiple contributing factors, most notably placental insufficiency.[17] This condition is potentially driven by dysregulation of gene expression affecting the placental–heart axis, whereby impaired placental function leads to fetal hypoxia and reduced nutrient transfer.[18] These disturbances may restrict fetal growth and have an adverse impact on cardiac morphogenesis.[17-19]

Many interrelated factors result in CHD. According to multivariate analysis, prematurity (OR 2.08; 95%CI 1.19-3.62; P 0.009), maternal alcohol (OR 2.06; 95%CI 0.61-6.98; P 0.239), and other congenital anomalies (OR 2.61; 95%CI 0.79-8.51;

P 0.101) might be related to both LBW and CHD (Table 2). Prenatal exposure to alcohol and genetic abnormalities might interfere with heart morphogenesis and could also lead to organ immaturity and LBW.[20,21] The multivariate analysis model could only explain a few factors associated with CHD (R square 0.084). Other potential confounding factors, such as prematurity, maternal alcohol use, and coexisting congenital anomalies, also showed suggestive but statistically non-significant associations with CHD in our multivariate analysis. From a clinical perspective, the findings highlight the importance of early identification of at-risk pregnancies, particularly those with LBW and prematurity, for prompt referral and echocardiographic screening. While some global studies emphasize advanced maternal age or genetic history, our findings highlight the need for context-specific risk assessments in Indonesia, where factors such as nutritional status, access to prenatal care, and environmental exposures may differ significantly from those in high-income countries.

This study has several limitations that should be acknowledged. First, the use of secondary data may have introduced information bias, particularly regarding maternal history, lifestyle behaviors, and environmental exposures. Second, although multiple potential risk factors were analyzed, the explanatory power of our multivariate model was relatively low (R^2 = 0.084), suggesting that other unmeasured variables, such as maternal comorbidities, medication use during pregnancy, exposure to environmental toxins, nutritional status, and contraceptive use, may play a role in CHD pathogenesis but were not captured in the current analysis. Third, recall bias and underreporting may have occurred, especially for sensitive information such as maternal smoking, alcohol consumption, and infections during pregnancy. The absence of data on prenatal care quality and timing may also affect the interpretation of maternal risk factors. Further research is needed to explore the underlying mechanisms, genetic contribution, and any other potential factors related to coronary heart disease (CHD). Also, future research should aim to incorporate a prospective cohort design with more comprehensive and standardized data collection, including detailed maternal history, environmental exposures, and nutritional status. Larger multicenter studies with broader geographic representation across Indonesia are also recommended to enhance the generalizability of findings.

CONCLUSION

Low birth weight is a dominant factor associated with CHDs. Early prenatal care and targeted interventions are crucial in reducing this risk. Further research is warranted to investigate the underlying mechanisms and genetic contributions to coronary heart disease (CHD).

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AUTHOR CONTRIBUTION

All authors contributed equally to the conception, design, data collection, analysis, and preparation of this manuscript. Each author has read and approved the final version of the manuscript and agrees to be accountable for all aspects of the work.

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CONFLICT OF INTERESTS

None.

ETHICAL STANDARDS

This study was approved by the Research Ethics Committee at the Faculty of Medicine, Universitas Udayana/Ngoerah Hospital, Denpasar (2024.03.01.1055).

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