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# The birth prevalence, severity, and temporal trends of congenital heart disease in the middle-income country: A population-based study

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## Abstract

**Objectives**: There is limited data on congenital heart disease (CHD) from the lower- and middle-income country. We aim to study the epidemiology of CHD with the specific objective to estimate the birth prevalence, severity, and its trend over time.

**Design**: A population-based study with data retrieved from the Pediatric Cardiology Clinical Information System, a clinical registry of acquired and congenital heart disease for children.

**Setting**: State of Johor, Malaysia.

**Patients**: All children (0-12 years of age) born in the state of Johor between January 2006 and December 2015.

**Intervention**: None.

**Outcome measure**: The birth prevalence, severity, and temporal trend over time.

**Results**: There were 531,904 live births during the study period with 3557 new cases of CHD detected. Therefore, the birth prevalence of CHD was 6.7 per 1000 live births (LB) (95% confidence interval [CI]: 6.5-6.9). Of these, 38% were severe, 15% moderate, and 47% mild lesions. Hence, the birth prevalence of mild, moderate, and severe CHD was 3.2 (95% CI: 3.0-3.3), 0.9 (95% CI: 0.9- 1.1), and 2.6 (95% CI: 2.4-2.7) per 1000 LB, respectively. There was a significant increase in the birth prevalence of CHD, from 5.1/1000 LB in 2006 to 7.8/1000 LB in 2015 ($P < .0001$) due to increase in detection of both mild (1.9/1000 LB in 2006 to 3.9/1000 LB in 2015, $P < .001$) and severe CHD (1.8/1000 LB in 2005 to 2.9/1000 LB in 2015, $P < .001$).

**Conclusions**: The birth prevalence of CHD was 6.7 per 1000 live births, and two in five were severe and significantly associated with syndrome and extracardiac defect. There was a significant increase in the detection of severe lesions in recent years leading to more burden to resources that are already limited in the middle-income country. Therefore, strategic and comprehensive pediatric and congenital heart surgery program is required.

KEYWORDS

birth prevalence, clinical registry, congenital heart disease, lower- and middle-income country, temporal trend

  

## 1 | INTRODUCTION

Congenital heart disease (CHD) is defined as a gross structural abnormality of the heart or intrathoracic great vessels that are actually or potentially of functional significance.[1] It is the most frequent congenital malformation in children with a reported prevalence of 6-13 per 1000 live births (LB).[2-5] The etiology of CHD is multifactorial which include genetic, environmental and maternal illness.[6,7] However, most CHD are isolated, and only 20%-25% are associated with chromosome anomalies or with an extracardiac defect.[8]

Most of the lesions are mild such as small ventricular septal defects which require no intervention or may close spontaneously. However, some are severe or critical such as transposition great arteries which require early intervention or surgery. Severe lesions occurred in 25%-35% of CHD and are associated with significant morbidity and mortality.[9-12] Hence, a good pediatric and congenital cardiac surgery program (PCCSP) requires a highly skilled multidisciplinary team, which often translates into high costs and good infrastructures. However, in most of the low- and middle-income countries (LMIC), the PCCSP are burdened with multiple problems and setbacks that is lack of expertise, equipment, and infrastructure leading to high morbidity and mortality rate.[13-16]

Currently, to the best of our knowledge, there is no population study in Malaysia and insufficient data from the middle-income countries describing the epidemiology and trend in birth prevalence of CHD in relation to its severity. A population study on CHD which reflects the true natural history and disease burden is needed for better planning of PCCSP in resource-limited LMIC. In addition, it will give a better insight into CHD etiology, propelling the development of a disease prevention program.

Therefore, this study aimed to describe the epidemiology features of CHD in Johor, Malaysia in relation to gender, race and associated risks with the specific objective to estimate the birth prevalence of CHD and its trend in relation to its severity from 2006 to 2015.

## 2 | METHODS

Malaysia is located in Southeast Asia and is considered as a middle-income country by the World Bank. It has an estimated population of 30 million and consists of 13 states and 3 federal territories. Johor is located in the southern peninsula of Malaysia with an estimated population of 3.5 million and live births of 50 000 per year. It is a multiethnic state with the majority are Malay (51%), followed by Chinese (34%) and Indian (10%). Meanwhile, during the study period (2006-2015), health services in Johor were mainly delivered by government hospitals. The majority of the infants were born in the government hospital and had a full clinical examination before hospital discharge. Almost all cases of suspected CHD in infants and children either from the government or private facilities were referred to Hospital Sultanah Aminah (HSAJB), a single cardiac center in the state of Johor for confirmation of diagnosis and further management. During the study period, a pulse oximeter for screening critical CHD was not available, meanwhile fetal echocardiography services were available only toward the end of study. The population studied were all children (0-12 years of age) born in the state of Johor from January 2006 to December 2015 with newly diagnosed CHD. The minimal and maximal duration follow- up was at 18 months and 12 years, respectively. Children or infants born from other states of Malaysia were excluded from this study.

Cases of CHD were ascertained from two data sources. Primary information was from the Pediatric Cardiology Clinical Information System (PCCIS), a clinical registry developed in 2004 dedicated for all infants and children with acquired and congenital heart disease in the State of Johor.[11] In brief, the PCCIS contained all demographics, 2D echocardiography, cardiac intervention and surgical data. All the data were entered during the first clinical consultation and follow-up. PCCIS was verified and regularly updated by MNMB. The second source of information was from the National/State under five Mortality Registry (U5MR). Since 2012, it was mandatory in Malaysia to report all deaths in infants and children less than five years of age. This includes cardiac-related death either at home or in any hospital. Death data from U5MR was entered into the PCCIS. Thus, PCCIS ensures statewide inclusion of patients with CHD and their long-term follow-up.

Data retrieved from PCISS were sex, race, and gestational age at birth (term and preterm), age at diagnosis, a cardiac diagnosis, and CHD severity, maternal diabetes during pregnancy, family history of CHD, associated syndrome, chromosomal anomalies, and noncardiac malformation.

CHD was defined as previously published[1] and was confirmed by either 2D echocardiogram, cardiac catheterization, cardiac CT scan, or MRI. All suspected CHD in neonates, infants, and children had a thorough cardiac assessment, including cross-sectional, Doppler and color imaging echocardiography performed by a pediatric cardiologist. Patients with patent foramen ovale, mild branch pulmonary stenosis (PS), isolated dextrocardia, and isolated bilateral superior vena cava, a right arch without other lesions or symptoms of airway obstruction, mitral valve prolapse, and bicuspid aortic valve without significant stenosis or regurgitation were excluded. PDA with spontaneous closure at 6 months of life in premature infants and 3 months of life in term infants were also excluded.

The severity of CHD was divided according to the level of care as described by Hoffman.[2] Briefly, severe CHD involved all severely ill newborns or infants requiring intensive care. This includes all cyanotic CHD and some acyanotic lesions, such as atrioventricular septal defect (AVSD), large ventricular septal defect (VSD), large PDA, critical or severe PS, critical coarctation of the aorta (CoA), and critical or severe aortic stenosis (AS). Meanwhile, in moderate CHD, the patient requires expert care but less intensive than severe CHD. In mild CHD, most patients are asymptomatic, and the lesions may close spontaneously or require no intervention. Patients with multiple

**TABLE 1** Birth prevalence, distribution, associated syndrome and extra-cardiac defect of congenital heart disease in infants and children born in Johor, Malaysia (2006-2015)

| CHD | Total number of persons *n* = 3557 | Isolated CHD *n* = 2843 | Associated syndrome[a] *n* = 620 | Extracardiac defect *n* = 94 | *P* value | Birth prevalence per 1000 live births [95% CI] |
|---|---|---|---|---|---|---|
| VSD | 1181 (33.2) | 969 (34.1) | 190 (30.6) | 22 (23.4) | .03 | 2.22 [2.09, 2.35] |
| PDA | 750 (21.1) | 579 (20.4) | 151 (24.4) | 20 (21.3) | .08 | 1.41 [1.31, 1.51] |
| PS | 358 (10.1) | 315 (11.1) | 35 (5.6) | 8 (8.5) | <.001 | 0.67 [0.60, 0.74] |
| ASD | 199 (5.6) | 146 (5.1) | 50 (8.1) | 3 (3.2) | .01 | 0.37 [0.32, 0.43] |
| TOF | 194 (5.5) | 153 (5.4) | 34 (5.5) | 7 (7.4) | .68 | 0.36 [0.31, 0.42] |
| AVSD | 97 (2.7) | 31 (1.1) | 65 (10.5) | 1 (1.1) | <.001 | 0.18 [0.15, 0.22] |
| TGA | 88 (2.5) | 83 (2.9) | 3 (0.5) | 2 (2.1) | .002 | 0.17 [0.13, 0.20] |
| PAVSD | 77 (2.2) | 56 (2.0) | 16 (2.6) | 5 (5.3) | .07 | 0.14 [0.11, 0.18] |
| Coarctation | 68 (1.9) | 49 (1.7) | 12 (1.9) | 7 (7.4) | <.001 | 0.13 [0.10, 0.16] |
| DORV | 56 (1.6) | 42 (1.5) | 11 (1.8) | 3 (3.2) | .38 | 0.11 [0.08, 0.13] |
| Heterotaxy | 56 (1.6) | 55 (1.9) | 1 (0.2) | 0 (0.0) | .003 | 0.11 [0.08, 0.13] |
| HLHS | 49 (1.4) | 43 (1.5) | 4 (0.6) | 2 (2.1) | .20 | 0.09 [0.07, 0.12] |
| Tricuspid atresia | 45 (1.3) | 38 (1.3) | 7 (1.1) | 0 (0.0) | .49 | 0.08 [0.06, 0.11] |
| PAIVS | 43 (1.2) | 40 (1.4) | 3 (0.5) | 0 (0.0) | .09 | 0.08 [0.06, 0.11] |
| AS | 38 (1.1) | 31 (1.1) | 7 (1.1) | 0 (0.0) | .59 | 0.07 [0.05, 0.09] |
| TAPVD | 35 (1.0) | 31 (1.1) | 4 (0.6) | 0 (0.0) | .37 | 0.07 [0.04, 0.09] |
| Ebsteins anomaly | 32 (0.9) | 28 (1.0) | 3 (0.5) | 1 (1.1) | .48 | 0.06 [0.04, 0.08] |
| Truncus arteriosus | 30 (0.8) | 26 (0.9) | 2 (0.3) | 2 (2.1) | .13 | 0.06 [0.04, 0.08] |
| Mitral atresia | 28 (0.8) | 21 (0.7) | 5 (0.8) | 2 (2.1) | .32 | 0.05 [0.03, 0.07] |
| SV, other | 27 (0.8) | 19 (0.7) | 7 (1.1) | 1 (1.1) | .46 | 0.05 [0.03, 0.07] |
| DILV | 22 (0.6) | 18 (0.6) | 3 (0.5) | 1 (1.1) | .78 | 0.04 [0.02, 0.06] |
| IAA | 17 (0.5) | 11 (0.4) | 4 (0.6) | 2 (2.1) | .04 | 0.03 [0.02, 0.05] |
| ccTGA | 16 (0.4) | 14 (0.5) | 0 (0.0) | 2 (2.1) | .01 | 0.03 [0.02, 0.04] |
| AP window | 11 (0.3) | 11 (0.4) | 0 (0.0) | 0 (0.0) | .25 | 0.02 [0.01, 0.03] |
| RPA absent | 9 (0.3) | 6 (0.2) | 2 (0.3) | 1 (1.1) | .25 | 0.02 [0.01, 0.03] |
| CAF | 7 (0.2) | 7 (0.2) | 0 (0.0) | 0 (0.0) | .41 | 0.01 [0.00, 0.02] |
| Cor triatriatum | 7 (0.2) | 6 (0.2) | 1 (0.2) | 0 (0.0) | .88 | 0.01 [0.00, 0.02] |
| Vascular rings | 7 (0.2) | 6 (0.2) | 0 (0.0) | 1 (1.1) | .09 | 0.01 [0.00, 0.02] |
| ALCAPA | 5 (0.1) | 5 (0.2) | 0 (0.0) | 0 (0.0) | .53 | 0.01 [0.00, 0.02] |
| Others | 5 (0.1) | 4 (0.1) | 1 (0.2) | 1 (1.1) | .04 | 0.01 [0.00, 0.02] |

(*Continues*)

**TABLE 1** (Continued)

| CHD | Total number of persons<br>*n* = 3557 | Isolated CHD<br>*n* = 2843 | Associated syndrome[a]<br>*n* = 620 | Extracardiac defect<br>*n* = 94 | *P* value | Birth prevalence per 1000 live births [95% CI] |
|---|---|---|---|---|---|---|
| Isolated septal defect | 1284 (36.1) | 1038 (36.5) | 224 (36.1) | 22 (23.4) | .03 | 2.41 [2.28, 2.55] |
| Conotruncal | 385 (10.8) | 317 (11.2) | 52 (8.4) | 16 (17.0) | .02 | 0.72 [0.65, 0.80] |
| LVOTO | 137 (3.9) | 110 (3.9) | 21 (3.4) | 6 (6.4) | .37 | 0.26 [0.21, 0.30] |
| RVOTO | 556 (15.6) | 478 (16.8) | 64 (10.3) | 14 (14.9) | <.001 | 1.05 [0.96, 1.13] |
| Severe CHD | 1362 (38.3) | 1020 (35.9) | 293 (47.3) | 49 (52.1) | <.001 | 2.56 [2.42, 2.70] |
| Moderate CHD | 522 (14.7) | 415 (14.6) | 99 (16.0) | 8 (8.5) | .28 | 0.98 [0.90, 1.07] |
| Mild CHD | 1673 (47.0) | 1408 (49.5) | 228 (36.8) | 37 (39.4) | <.001 | 3.15 [2.99, 3.30] |

*Notes*. (%), represent the percentage of total CHD, isolated CHD, associated syndrome or extracardiac defect.
A statistically significant difference within the group if *P* value <.05.
Abbreviations: ALCAPA, anomalous left coronary artery to pulmonary artery; ASD, atrial septal defect; AP, aortopulmonary; AS, aortic stenosis; AVSD, atrioventricular septal defect; CAF, coronary artery fistula; CHD, congenital heart disease; CI, confidence interval; CoA, Coarctation of aorta; DILV, double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; LVOTO, left ventricular outflow obstruction; PAIVS, pulmonary atresia with intact septum; PAVSD, pulmonary atresia with ventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; RVOTO, right ventricular outflow tract; SV, single ventricle; TAPVD, total anomalous pulmonary venous drainage; ccTGA, congenitally corrected TGA; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
[a]Associated syndrome with or without chromosomal abnormality or single gene defect.

**TABLE 2** Syndrome and its associated cardiac lesions

| Syndrome | Frequency | Percentage | Cardiac diagnosis (frequency) |
|---|---|---|---|
| Down | 348 | 56.0 | VSD (118), PDA (100), AVSD (60), ASD (31), TOF (15), PS (7), univentricular (7), DORV (2), ebsteins (2), PAVSD (2), TGA (1), TA (1), PAIVS (1), AS (1) |
| Not recognizable | 64 | 10.3 | PDA (19), VSD (15), ASD (5), PAVSD (5), TOF (4), AVSD (2), CoA (2), MA (2), PS (2), TA (2), TGA (1), TAPVD (1), PAIVS (1), IAA (1), HLHS (1), DORV (1) |
| Edwards | 39 | 6.3 | VSD (23), MA (3), AVSD (2), CoA (2), DORV (2), HLHS (2), TOF (2), AS (1), DILV (1), PAVSD (1) |
| Noonan | 22 | 3.5 | PS (11), VSD (4), ASD (2), PDA (2), TOF (2), PAVSD (1) |
| VACTERL syndrome | 17 | 2.7 | VSD (4), TOF (4), PAVSD (2), AS (1), ASD (1), CoA (1), DILV (1), DORV (1), absent RPA (1), TAPVD (1) |
| Patau | 14 | 2.3 | VSD (4), CoA (2), DORV (2), PAVSD (2), DILV (1), PDA (1), TOF (1), PAIVS (1) |
| Turner | 14 | 2.3 | CoA (3), PDA (3), IAA (2), PS (2), TGA (1), TOF (1), TA (1), VSD (1) |
| Goldenhar | 13 | 2.1 | ASD (2), DORV (2), TOF (2), VSD (2), CoA (1), PAVSD (1), PDA (1), absent RPA (1), TAPVD (1), |
| Congenital rubella | 12 | 1.9 | PDA (9), PS (3) |
| DiGeorge | 8 | 1.3 | VSD (3), PAVSD (2), TOF (1), truncus (1), IAA (1) |
| CHARGE Association | 7 | 1.1 | PDA (3), ASD (1), TOF (1), TA (1), VSD (1) |
| Pierre Robin | 7 | 1.1 | PDA (3), ASD (2), PS (1), VSD (1) |
| Cornelia de Lange | 5 | 0.8 | PDA (2), PS (2), heterotaxy (1) |
| Dandy-Walker | 4 | 0.6 | VSD (2), PS (1), PDA (1) |
| Treacher Collins | 4 | 0.6 | DORV (1), PDA (1), PS (1), TA (1) |
| Williams | 4 | 0.6 | AS (3), PS (1) |
| Alagille | 3 | 0.5 | PS (2), AVSD (1) |
| Holt-Oram | 3 | 0.5 | VSD (3) |
| Wolf-Hirschhorn | 3 | 0.5 | VSD (2), ASD (1) |
| Chromosome 16 disorder | 2 | 0.3 | CoA (1), TAPVD (1) |
| Chromosome 9 disorder | 2 | 0.3 | PDA (1), VSD (1) |
| Mobius | 2 | 0.3 | TOF (1), ebsteins (1) |
| TAR | 3 | 0.5 | PDA (3) |
| Chromosome 3 disorder | 2 | 0.3 | Tricuspid atresia (1), ASD (1) |
| Albinism | 1 | 0.2 | HLHS (1) |
| Apert | 1 | 0.2 | PS (1) |
| Camptomelic | 1 | 0.2 | Truncus (1) |
| Chromosome 14 disorder | 1 | 0.2 | VSD (1) |
| Chromosome 18 disorder | 1 | 0.2 | Cor triatriatum (1) |
| Chromosome 4 disorder | 1 | 0.2 | VSD (1) |
| Chromosome 8 disorder | 1 | 0.2 | VSD (1) |
| Chromosomal other | 1 | 0.2 | VSD (1) |
| Coffin-Siris | 1 | 0.2 | ASD (1) |
| Cri du chat | 1 | 0.2 | VSD (1) |
| Kabuki | 1 | 0.2 | ASD (1) |
| Klinefelter | 1 | 0.2 | ASD (1) |

*(Continues)*

**TABLE 2** (Continued)

| Syndrome | Frequency | Percentage | Cardiac diagnosis (frequency) |
|---|---|---|---|
| Limb-body wall complex | 1 | 0.2 | PS (1) |
| Meckel Gruber | 1 | 0.2 | ASD (1) |
| Poland | 1 | 0.2 | PDA (1) |
| Roberts | 1 | 0.2 | AS (1) |
| Robinow | 1 | 0.2 | VSD (1) |
| Schinzel-giedion | 1 | 0.2 | PDA (1) |

Abbreviations: AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart disease; CoA, coarctation of aorta; DILV, double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; MA, mitral atresia; PAVSD, pulmonary atresia with ventricular septal defect; PAIVS, pulmonary atresia with intact septum; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TA, tricuspid atresia; TAPVD, total anomalous pulmonary venous drainage; TAR, thrombocytopenia with absent radius; ccTGA, congenitally corrected TGA; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

**TABLE 3** Extracardiac defect and associated cardiac lesions

| Type of extracardiac defect | Frequency | Percentage | Cardiac lesions (frequency) |
|---|---|---|---|
| Gastrointestinal system | | | |
| Cleft lip and palate | 29 | 30.9 | VSD (9), PDA (5), PS (4), CoA (3), TOF (2), ASD (1), HLHS (1), IAA (1), PAVSD (1), TGA (1), truncus (1) |
| Anorectal malformation | 14 | 14.9 | VSD (3), PAVSD (3), PDA (2), PS (1), TOF (1), VR (1), ASD (1), DORV (1), HLHS (1) |
| Tracheoesophageal fistula | 8 | 8.5 | PDA (2), TOF (2), VSD (2), DILV (1), MA (1) |
| Duodenal atresia | 5 | 5.3 | VSD (2),ccTGA (1), CoA (1), absent RPA (1) |
| Diaphragmatic hernia | 3 | 3.2 | DORV (1), IAA (1), VSD (1) |
| Gastroschisis | 1 | 1.1 | PDA (1) |
| Omphalocele | 1 | 1.1 | PS (1) |
| Neurological system | | | |
| Congenital hydrocephalus | 4 | 4.3 | ccTGA (1), PAVSD (1), TGA (1), VSD (1) |
| TEF, myelomeningocele | 1 | 1.1 | PS (1) |
| Neural tube defect | 1 | 1.1 | SV, other (1) |
| Urogenital system | | | |
| Cloacal exstrophy, omphalocele, and amniotic band | 1 | 1.1 | PDA (1) |
| Hypospadias | 1 | 1.1 | CoA (1) |
| Absent left kidney | 1 | 1.1 | VSD (1) |
| Musculoskeletal system | | | |
| Skeletal dysplasia | 2 | 2.1 | PDA (1), TOF (1) |
| Bilateral talipes | 1 | 1.1 | PS (1) |
| Sacral agenesis | 1 | 1.1 | Truncus arteriosus (1) |
| Lung/airways | | | |
| Laryngomalacia | 4 | 4.3 | VSD (2), PDA (1), Ebsteins (1) |
| Tracheal stenosis | 1 | 1.1 | DORV (1) |
| Esophageal lung | 1 | 1.1 | RPA to left lung |
| Congenital lobar emphysema | 1 | 1.1 | PDA (1) |
| CCAM | 1 | 1.1 | VSD (1) |
| Bronchomalacia | 1 | 1.1 | ASD (1) |

*(Continues)*

**TABLE 3** (Continued)

| Type of extracardiac defect | Frequency | Percentage | Cardiac lesions (frequency) |
|---|---|---|---|
| Miscellaneous | | | |
| Ectopic cordis | 2 | 2.1 | MA (1), TOF (1) |
| Ptosis | 1 | 1.1 | PDA (1) |
| Congenital anrhinia | 1 | 1.1 | PDA (1) |
| Congenital glaucoma | 1 | 1.1 | CoA (1) |
| Cystic hygromas | 1 | 1.1 | PDA (1) |
| Hemangiomas | 1 | 1.1 | PDA (1) |
| Abdominal cysts | 1 | 1.1 | AVSD (1) |
| Abnormal 3rd toe | 1 | 1.1 | PDA (1) |
| Atretic left ear | 1 | 1.1 | CoA (1) |
| Isolated choanal atresia | 1 | 1.1 | PDA (1) |

Abbreviations: AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CCAM, congenital cystic adenomatoid malformation; CoA, coarctation of aorta; DILV, double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; MA, mitral atresia; PAIVS, pulmonary atresia with intact septum; PAVSD, pulmonary atresia with ventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; RPA, right pulmonary artery; SV, single ventricle; TA, tricuspid atresia; TAPVD, total anomalous pulmonary venous drainage; TEF, tracheoesophageal fistula; ccTGA, congenitally corrected TGA; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

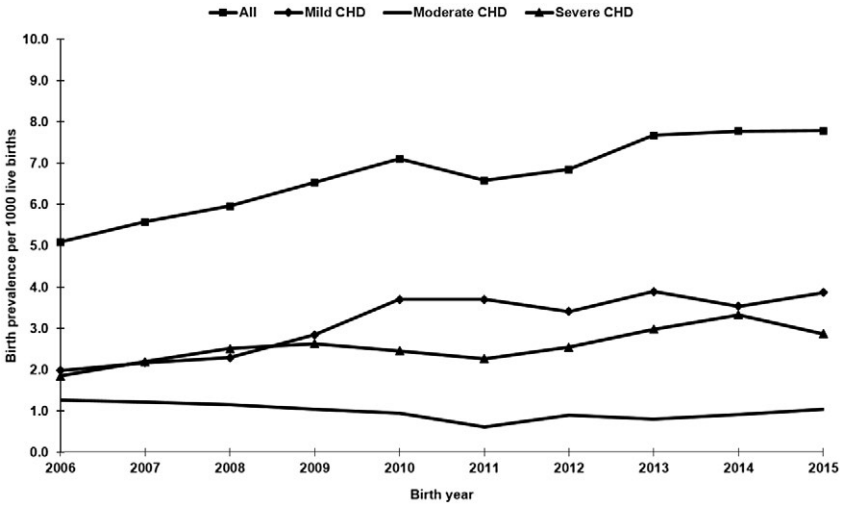


**FIGURE 1** The trend of birth prevalence of congenital heart disease in relation to severity over time in Johor, Malaysia (2006-2015)

lesions had their lesions classified hierarchically as in the Baltimore Washington Infant Study.[17]

CHD was also categorized into three main groups, (1) isolated CHD, (2) associated with an extracardiac defect (ECD), and (3) associated syndrome with or without chromosome abnormality.[5] Also, infants or children with CHD were categorized as having a conotruncal defect, left ventricular outflow tract obstruction (LVOTO) and right ventricular outflow tract obstruction (RVOTO) as used by Botto et al.[18]

We diagnosed ECD with clinical features and supported by radiological examination or intraoperative finding. Meanwhile, the associated syndrome was diagnosed by phenotype features with or without chromosomal analysis. A syndromic patient such as Down syndrome who have ECD (anorectal malformation or duodenal atresia) were categorized as Down syndrome only.

## 2.1 | Statistical analysis

We used SPSS version 11.5 (IBM, Armonk, New York) to analyze the data. As suggested by Mason et al,[19] we used birth prevalence rather than incidence to represent the frequency of CHD in our study. Birth prevalence was calculated by a number of infants or children with CHD divided by a total number of live births for 2006-2015 and described as per 1000 live births. We used the actual number of live-born infants for the appropriate time as the denominator. We used EpiCal2000 to analyze the birth prevalence and its trend over the 10-year period. $P$ value < .05 represents a statistically significant result.

We used the chi-square test to test the association of independent variables (sex, race, associated syndromes, maternal, and

**TABLE 4** Sex and racial distribution in infants and children with congenital heart disease in Johor, Malaysia (2006-2015)

| CHD | Total | Sex | | *P* value | Race | | | | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| | | Male | Female | | Malay | Chinese | Indian | Other | |
| | | n = 1709 | n = 1848 | | n = 2476 | n = 687 | n = 227 | n = 167 | |
| VSD | 1181 | 591 (34.6) | 590 (31.9) | .09 | 824 (33.3) | 237 (34.5) | 66 (29.1) | 54 (32.3) | .51 |
| PDA | 750 | 300 (17.6) | 450 (24.4) | <.001 | 538 (21.7) | 132 (19.2) | 55 (24.2) | 25 (15.0) | .07 |
| PS | 358 | 171 (10.0) | 187 (10.1) | .91 | 242 (9.8) | 76 (11.1) | 19 (8.4) | 21 (12.6) | .41 |
| ASD | 199 | 75 (4.4) | 124 (6.7) | .003 | 145 (5.9) | 34 (4.9) | 11 (4.8) | 9 (5.4) | .77 |
| TOF | 194 | 99 (5.8) | 95 (5.1) | .39 | 129 (5.2) | 42 (6.1) | 9 (4.0) | 14 (8.4) | .20 |
| AVSD | 97 | 34 (2.0) | 63 (3.4) | .009 | 70 (2.8) | 15 (2.2) | 9 (4.0) | 3 (1.8) | .44 |
| TGA | 88 | 63 (3.7) | 25 (1.4) | <.001 | 66 (2.7) | 13 (1.9) | 4 (1.8) | 5 (3.0) | .57 |
| PAVSD | 77 | 42 (2.5) | 35 (1.9) | .25 | 54 (2.2) | 11 (1.6) | 7 (3.1) | 5 (3.0) | .48 |
| CoA | 68 | 42 (2.5) | 26 (1.4) | .02 | 41 (1.7) | 17 (2.5) | 7 (3.1) | 3 (1.8) | .29 |
| DORV | 56 | 32 (1.9) | 24 (1.3) | .17 | 33 (1.3) | 11 (1.6) | 7 (3.1) | 5 (3.0) | .09 |
| Heterotaxia | 56 | 30 (1.8) | 26 (1.4) | .40 | 43 (1.7) | 8 (1.2) | 2 (0.9) | 3 (1.8) | .58 |
| HLHS | 49 | 30 (1.8) | 19 (1.0) | .06 | 32 (1.3) | 10 (1.5) | 4 (1.8) | 3 (1.8) | .89 |
| Tricuspid atresia | 45 | 19 (1.1) | 26 (1.4) | .43 | 31 (1.3) | 12 (1.7) | 0 (0.0) | 2 (1.2) | .24 |
| PAIVS | 43 | 22 (1.3) | 21 (1.1) | .68 | 34 (1.4) | 8 (1.2) | 0 (0.0) | 1 (0.6) | .27 |
| AS | 38 | 24 (1.4) | 14 (0.8) | .06 | 22 (0.9) | 13 (1.9) | 3 (1.3) | 0 (0.0) | .07 |
| TAPVD | 35 | 20 (1.2) | 15 (0.8) | .28 | 21 0.8) | 7 (1.0) | 4 (1.8) | 3 (1.8) | .38 |
| Ebsteins | 32 | 18 (1.1) | 14 (0.8) | .35 | 20 (0.8) | 9 (1.3) | 2 (0.9) | 1 (0.6) | .63 |
| Truncus | 30 | 15 (0.9) | 15 (0.8) | .83 | 21 (0.8) | 7 (1.0) | 1 (0.4) | 1 (0.6) | .85 |
| Mitral atresia | 28 | 17 (1.0) | 11 (0.6) | .18 | 17 (0.7) | 4 (0.6) | 5 (2.2) | 2 (1.2) | .07 |
| SV, other | 27 | 12 (0.7) | 15 (0.8) | .70 | 19 (0.8) | 4 (0.6) | 4 (1.8) | 0 (0.0) | .20 |
| DILV | 22 | 12 (0.7) | 10 (0.5) | .54 | 15 (0.6) | 4 (0.6) | 2 (0.9) | 1 (0.6) | .96 |
| IAA | 17 | 8 (0.5) | 9 (0.5) | .93 | 13 (0.5) | 3 (0.4) | 0 (0.0) | 1 (0.6) | .73 |
| ccTGA | 16 | 7 (0.4) | 9 (0.5) | .73 | 11 (0.4) | 1 (0.1) | 4 (1.8) | 0 (0.0) | .01 |
| AP window | 11 | 6 (0.4) | 5 (0.3) | .66 | 10 (0.4) | 0 (0.0) | 1 (0.4) | 0 (0.0) | .32 |
| RPA absent | 9 | 1 (0.1) | 8 (0.4) | .04 | 5 (0.2) | 2 (0.3) | 0 (0.0) | 2 (1.2) | .08 |
| CAF | 7 | 6 (0.4) | 1 (0.1) | .05 | 6 (0.2) | 1 (0.1) | 0 (0.0) | 0 (0.0) | .77 |
| Cor triatriatum | 7 | 6 (0.4) | 1 (0.1) | .05 | 4 (0.2) | 3 (0.4) | 0 (0.0) | 0 (0.0) | .40 |
| Vascular rings | 7 | 4 (0.2) | 3 (0.2) | .72 | 3 (0.1) | 2 (0.3) | 0 (0.0) | 2 (1.2) | .02 |
| ALCAPA | 5 | 2 (0.1) | 3 (0.2) | 1.00 | 2 (0.1) | 1 (0.1) | 1 (0.4) | 1 (0.6) | .20 |
| Others | 5 | 1 (0.1) | 4 (0.2) | .38 | 5 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | .53 |

*(Continues)*

**TABLE 4** (Continued)

| CHD | Total | Sex | | *P* value | Race | | | | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| | | Male | Female | | Malay | Chinese | Indian | Other | |
| | | n = 1709 | n = 1848 | | n = 2476 | n = 687 | n = 227 | n = 167 | |
| Isolated septal defect | 1284 | 623 (36.5) | 661 (35.8) | .67 | 896 (36.2) | 255 (37.1) | 73 (32.2) | 29 (32.6) | .59 |
| Conotruncal defect | 385 | 218 (12.8) | 167 (9.0) | <.001 | 263 (10.6) | 74 (10.7) | 22 (0.9) | 26 (1.1) | .23 |
| LVOTO | 137 | 84 (4.9) | 53 (2.9) | .002 | 89 (3.6) | 33 (4.8) | 10 (4.4) | 5 (3.0) | .45 |
| RVOTO | 556 | 272 (15.9) | 284 (15.4) | .65 | 382 (15.4) | 116 (16.9) | 28 (12.3) | 30 (18.0) | .33 |
| Severe CHD | 1362 | 697 (40.8) | 665 (36.0) | .003 | 932 (37.6) | 271 (39.4) | 87 (38.3) | 72 (43.1) | .48 |
| Moderate CHD | 522 | 204 (11.9) | 318 (17.2) | <.001 | 392 (15.8) | 85 (12.4) | 28 (12.3) | 17 (10.2) | .03 |
| Mild CHD | 1673 | 808 (47.3) | 865 (46.8) | .78 | 1152 (46.5) | 331 (48.2) | 112 (49.3) | 78 (46.7) | .77 |

*Notes*. (%), represent the percentage of sex or race.

A statistically significant difference within the group if *P* value < .05.

Abbreviations: ASD, atrial septal defect; ALCAPA, anomalous left coronary artery to pulmonary artery; AP, aortopulmonary; AS, aortic stenosis; AVSD, atrioventricular septal defect; CAF, coronary artery fistula; CHD, congenital heart disease; CoA, coarctation of aorta; DILV, double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; LVOTO, left ventricular outflow obstruction; PAIVS, pulmonary atresia with intact septum; PAVSD, pulmonary atresia with ventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; RVOTO, right ventricular outflow tract obstruction; SV, single ventricle; TAPVD, total anomalous pulmonary venous drainage; TGA, transposition of the great arteries; ccTGA, congenitally corrected TGA; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

**TABLE 5** The timing of diagnosis of congenital heart disease in relation to severity

| CHD | Timing of diagnosis | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total CHD | | Antenatal | | 0-28 d | | 1-12 mo | | 1-4 y | | 5-10 y | |
| | N | % | N | % | N | % | N | % | N | % | N | % |
| Mild | 1673 | 47.0 | 22 | 1.3 | 747 | 44.7 | 723 | 43.2 | 148 | 8.8 | 33 | 2.0 |
| VSD | 797 | 22.4 | 17 | 2.1 | 347 | 43.5 | 362 | 45.4 | 59 | 7.4 | 12 | 1.5 |
| PDA | 409 | 11.5 | 0 | 0.0 | 280 | 68.5 | 95 | 23.2 | 24 | 5.9 | 10 | 2.4 |
| PS | 311 | 8.7 | 2 | 0.6 | 75 | 24.1 | 191 | 61.4 | 38 | 12.2 | 5 | 1.6 |
| ASD | 114 | 3.2 | 2 | 1.8 | 30 | 26.3 | 64 | 56.1 | 16 | 14.0 | 2 | 1.8 |
| AS | 22 | 0.6 | 0 | 0.0 | 4 | 18.2 | 8 | 36.4 | 9 | 40.9 | 1 | 4.5 |
| CoA | 9 | 0.3 | 1 | 11.1 | 3 | 33.3 | 1 | 11.1 | 1 | 11.1 | 3 | 33.3 |
| Ebsteins | 6 | 0.2 | 0 | 0.0 | 6 | 100.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Others | 5 | 0.1 | 0 | 0.0 | 2 | 40.0 | 2 | 40.0 | 1 | 20.0 | 0 | 0.0 |
| Moderate | 522 | 14.7 | 3 | 0.6 | 120 | 23.0 | 227 | 43.5 | 130 | 24.9 | 42 | 8.0 |
| PDA | 201 | 5.7 | 0 | 0.0 | 43 | 21.4 | 78 | 38.8 | 70 | 34.8 | 10 | 5.0 |
| VSD | 198 | 5.6 | 2 | 1.0 | 55 | 27.8 | 112 | 56.6 | 23 | 11.6 | 6 | 3.0 |
| ASD | 83 | 2.3 | 1 | 1.2 | 12 | 14.5 | 19 | 22.9 | 29 | 34.9 | 22 | 26.5 |
| PS | 11 | 0.3 | 0 | 0.0 | 2 | 18.2 | 8 | 72.7 | 1 | 9.1 | 0 | 0.0 |
| AS | 8 | 0.2 | 0 | 0.0 | 1 | 12.5 | 6 | 75.0 | 1 | 12.5 | 0 | 0.0 |
| AVSD | 7 | 0.2 | 0 | 0.0 | 1 | 14.3 | 1 | 14.3 | 2 | 28.6 | 3 | 42.9 |
| CoA | 6 | 0.2 | 0 | 0.0 | 2 | 33.3 | 1 | 16.7 | 2 | 33.3 | 1 | 16.7 |
| CAF | 5 | 0.1 | 0 | 0.0 | 3 | 60.0 | 2 | 40.0 | | 0.0 | 0 | 0.0 |
| Others | 3 | 0.1 | 0 | 0.0 | 1 | 33.3 | 0 | 0.0 | 2 | 66.7 | 0 | 0.0 |
| Severe | 1362 | 38.3 | 81 | 5.9 | 790 | 58.0 | 433 | 31.8 | 53 | 3.9 | 5 | 0.4 |
| TOF | 194 | 5.5 | 6 | 3.1 | 94 | 48.5 | 72 | 37.1 | 22 | 11.3 | 0 | 0.0 |
| Large VSD | 186 | 5.2 | 4 | 2.2 | 88 | 47.3 | 90 | 48.4 | 3 | 1.6 | 1 | 0.5 |
| Large PDA | 140 | 3.9 | 0 | 0.0 | 79 | 56.4 | 61 | 43.6 | 0 | 0.0 | 0 | 0.0 |
| AVSD | 89 | 2.5 | 2 | 2.2 | 50 | 56.2 | 29 | 32.6 | 6 | 6.7 | 2 | 2.2 |
| D-TGA | 88 | 2.5 | 4 | 4.5 | 69 | 78.4 | 15 | 17.0 | 0 | 0.0 | 0 | 0.0 |
| PAVSD | 77 | 2.2 | 5 | 6.5 | 45 | 58.4 | 23 | 29.9 | 4 | 5.2 | 0 | 0.0 |
| DORV | 56 | 1.6 | 1 | 1.8 | 35 | 62.5 | 15 | 26.8 | 4 | 7.1 | 1 | 1.8 |
| Heterotaxia | 56 | 1.6 | 11 | 19.6 | 28 | 50.0 | 17 | 30.4 | 0 | 0.0 | 0 | 0.0 |
| CoA | 53 | 1.5 | 1 | 1.9 | 34 | 64.2 | 17 | 32.1 | 1 | 1.9 | 0 | 0.0 |
| HLHS | 49 | 1.4 | 9 | 18.4 | 36 | 73.5 | 4 | 8.2 | 0 | 0.0 | 0 | 0.0 |
| Tricuspid atresia | 45 | 1.3 | 5 | 11.1 | 26 | 57.8 | 13 | 28.9 | 1 | 2.2 | 0 | 0.0 |
| PAIVS | 43 | 1.2 | 7 | 16.3 | 32 | 74.4 | 3 | 7.0 | 1 | 2.3 | 0 | 0.0 |
| Severe PS | 36 | 1.0 | 1 | 2.8 | 23 | 63.9 | 11 | 30.6 | 1 | 2.8 | 0 | 0.0 |
| TAPVD | 35 | 1.0 | 0 | 0.0 | 22 | 62.9 | 12 | 34.3 | 1 | 2.9 | 0 | 0.0 |
| Truncus arteriosus | 30 | 0.8 | 0 | 0.0 | 25 | 83.3 | 4 | 13.3 | 1 | 3.3 | 0 | 0.0 |
| Mitral atresia | 28 | 0.8 | 5 | 17.9 | 16 | 57.1 | 6 | 21.4 | 1 | 3.6 | 0 | 0.0 |
| SV, other | 27 | 0.8 | 4 | 14.8 | 16 | 59.3 | 7 | 25.9 | 0 | 0.0 | 0 | 0.0 |
| Severe Ebsteins | 26 | 0.7 | 9 | 34.6 | 11 | 42.3 | 3 | 11.5 | 2 | 7.7 | 1 | 3.8 |
| DILV | 22 | 0.6 | 3 | 13.6 | 15 | 68.2 | 4 | 18.2 | 0 | 0.0 | 0 | 0.0 |
| IAA | 17 | 0.5 | 1 | 5.9 | 14 | 82.4 | 1 | 5.9 | 1 | 5.9 | 0 | 0.0 |
| ccTGA | 16 | 0.4 | 3 | 18.8 | 8 | 50.0 | 5 | 31.3 | 0 | 0.0 | 0 | 0.0 |

*(Continues)*

**TABLE 5** (Continued)

| CHD | Timing of diagnosis | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total CHD | | Antenatal | | 0-28 d | | 1-12 mo | | 1-4 y | | 5-10 y | |
| | N | % | N | % | N | % | N | % | N | % | N | % |
| AP window | 10 | 0.3 | 0 | 0.0 | 7 | 70.0 | 2 | 20.0 | 1 | 10.0 | 0 | 0.0 |
| Severe AS | 8 | 0.2 | 0 | 0.0 | 6 | 75.0 | 2 | 25.0 | 0 | 0.0 | 0 | 0.0 |
| RPA absent | 7 | 0.2 | 0 | 0.0 | 5 | 71.4 | 2 | 28.6 | 0 | 0.0 | 0 | 0.0 |
| Vascular rings | 7 | 0.2 | 0 | 0.0 | 3 | 42.9 | 4 | 57.1 | 0 | 0.0 | 0 | 0.0 |
| Cor triatriatum | 6 | 0.2 | 0 | 0.0 | 0 | 0.0 | 3 | 50.0 | 3 | 50.0 | 0 | 0.0 |
| ALCAPA | 5 | 0.1 | 0 | 0.0 | 0 | 0.0 | 5 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| Others | 6 | 0.2 | 0 | 0.0 | 3 | 50.0 | 3 | 50.0 | 0 | 0.0 | 0 | 0.0 |
| All CHD | 3557 | 100.0 | 106 | 3.0 | 1657 | 46.6 | 1383 | 38.9 | 331 | 9.3 | 80 | 2.2 |

Abbreviations: ALCAPA, anomalous left coronary artery to pulmonary artery; AP, aortopulmonary; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CAF, coronary artery fistula; CHD, congenital heart disease; CoA, coarctation of aorta; DILV, double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PAIVS, pulmonary atresia with intact septum; PAVSD, pulmonary atresia with ventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; RPA, right pulmonary artery; SV, single ventricle; TAPVD, total anomalous pulmonary venous drainage; ccTGA, congenitally corrected TGA; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

ECD) with specific CHD, phenotypes and its severity. Variables with $P < .005$ in the univariate analyses were entered into the binary logistic regression. Odds ratio (OR) and its 95% confidence interval were calculated.

This study was registered with National Malaysian Reseach Registry [NMRR-16-1746-32473 (IIR)] and approved by the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia. MREC waived complete consent from the parents

## 3 | RESULTS

There were 531,904 live births during the 10-year study period with 3557 were CHD. Therefore, the overall birth prevalence of CHD was 6.7 per 1000 LB (95% confidence interval [CI]: 6.5-6.9). Of these 3557 CHD, 38% were severe, 15% moderate, and 47% mild lesions, hence the birth prevalence for mild CHD was 3.2 (95% CI: 3.0-3.3), 0.9 (95% CI: 0.9- 1.1) for moderate CHD, and 2.6 (95% CI: 2.4-2.7) for severe CHD. Table 1 shows the distribution and birth prevalence of specific CHD and its association with syndromes and ECD. Of 3557 CHD, the majority (80%) were isolated CHD, and there were more RVOTO (1.05 per 1000 LB) than LVOTO (0.26 per 1000 LB). Binary logistic regression shows atrial septal defect (ASD) and AVSD were significantly associated with syndrome with adjusted odds ratio (aOR) of 1.6 (95% CI: 1.2-2.3, $P = .005$) and 10.6 (95% CI: 6.8-16.5, $P < .0001$), respectively. CoA was significantly associated with an ECD with aOR of 4.6 (95% CI: 2.0-10.4, $P < .0001$). Meanwhile, severe CHD was significantly associated with the syndrome (aOR 1.6, 95%CI: 1.3-1.9, $P < .001$) and ECD (aOR 1.9 95%CI: 1.3-2.9, $P < .01$).

Tables 2 and 3 shows specific syndromes, ECD, and their associated cardiac lesions. Of 620 CHD with syndromes, the majority ($n = 348$, 50%) was Down syndrome. The most common lesions in Down syndrome were VSD (34%) followed by PDA (29%) and AVSD (17%). Unfortunately, we were not able to identify the specific syndrome in 10% of patients. Meanwhile, gastrointestinal malformation is the commonest ECD detected with CHD followed by the neurological system.

Figure 1 shows the temporal trend of birth prevalence in relation to CHD severity from 2006 to 2015. There was a significant increase

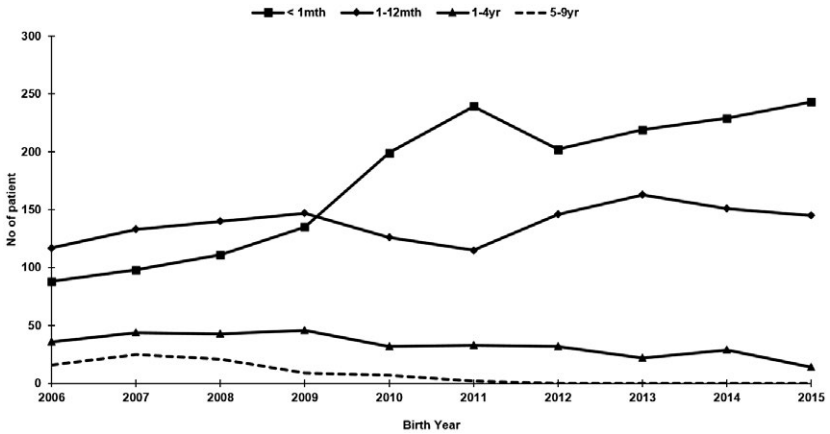


**FIGURE 2** The trend of the timing of diagnosis of congenital heart disease over time in Johor, Malaysia (2006-2015)

**TABLE 6** Maternal diabetes during pregnancy and congenital heart disease

| CHD | Total number of persons | Maternal diabetes during pregnancy | | | | | | *P* value |
|---|---|---|---|---|---|---|---|---|
| | | No maternal DM | | Preexisting DM | | Gestational DM | | |
| | | *N* | (%) | *N* | (%) | *N* | (%) | |
| VSD | 1181 | 1046 | (34.2) | 29 | (27.4) | 106 | (27.2) | .01 |
| PDA | 750 | 614 | (20.1) | 22 | (20.8) | 114 | (29.2) | <.001 |
| PS | 358 | 330 | (10.8) | 4 | (3.8) | 24 | (6.2) | .002 |
| ASD | 199 | 181 | (5.9) | 3 | (2.8) | 15 | (3.8) | .11 |
| TOF | 194 | 159 | (5.2) | 13 | (12.3) | 22 | (5.6) | .007 |
| AVSD | 97 | 83 | (2.7) | 0 | (0.0) | 14 | (3.6) | .13 |
| PAVSD | 77 | 65 | (2.1) | 2 | (1.9) | 10 | (2.6) | .84 |
| TGA | 88 | 64 | (2.1) | 7 | (6.6) | 17 | (4.4) | .001 |
| Coarctation | 68 | 62 | (2.0) | 1 | (0.9) | 5 | (1.3) | .46 |
| DORV | 56 | 48 | (1.6) | 3 | (2.8) | 5 | (1.3) | .52 |
| Heterotaxia syndrome | 56 | 47 | (1.5) | 0 | (0.0) | 9 | (2.3) | .21 |
| HLHS | 49 | 37 | (1.2) | 2 | (1.9) | 10 | (2.6) | .09 |
| Tricuspid atresia | 45 | 37 | (1.2) | 2 | (1.9) | 6 | (1.5) | .73 |
| PAIVS | 43 | 36 | (1.2) | 1 | (0.9) | 6 | (1.5) | .80 |
| AS | 38 | 35 | (1.1) | 2 | (1.9) | 1 | (0.3) | .19 |
| TAPVD | 35 | 33 | (1.1) | 1 | (0.9) | 1 | (0.3) | .30 |
| Ebsteins anomaly | 32 | 28 | (0.9) | 0 | (0.0) | 4 | (1.0) | .59 |
| Truncus arteriosus | 30 | 24 | (0.8) | 3 | (2.8) | 3 | (0.8) | .08 |
| Single ventricle, other | 27 | 23 | (0.8) | 2 | (1.9) | 2 | (0.5) | .35 |
| Mitral atresia | 28 | 22 | (0.7) | 3 | (2.8) | 3 | (0.8) | .05 |
| DILV | 22 | 18 | (0.6) | 1 | (0.9) | 3 | (0.8) | .83 |
| IAA | 17 | 14 | (0.5) | 2 | (1.9) | 1 | (0.3) | .09 |
| ccTGA | 16 | 9 | (0.3) | 3 | (2.8) | 4 | (1.0) | <.001 |
| RPA absent | 9 | 9 | (0.3) | 0 | (0.0) | 0 | (0.0) | .48 |
| AP window | 11 | 8 | (0.3) | 0 | (0.0) | 3 | (0.8) | .19 |
| CAF | 7 | 7 | (0.2) | 0 | (0.0) | 0 | (0.0) | .57 |
| Cor triatriatum | 7 | 7 | (0.2) | 0 | (0.0) | 0 | (0.0) | .57 |
| Vascular rings and slings | 7 | 6 | (0.2) | 0 | (0.0) | 1 | (0.3) | .87 |
| ALCAPA | 5 | 5 | (0.2) | 0 | (0.0) | 0 | (0.0) | .67 |
| Others | 5 | 4 | (0.1) | 0 | (0.0) | 1 | (0.3) | .76 |
| | | | | | | | | |
| Isolated septal defect | 1284 | 1146 | (37.4) | 29 | (27.4) | 109 | (27.9) | <.001 |
| Conotruncal defect | 385 | 309 | (10.1) | 26 | (24.5) | 50 | (12.8) | <.001 |

*(Continues)*

**TABLE 6** (Continued)

| CHD | Total number of persons | Maternal diabetes during pregnancy | | | | | | *P* value |
|---|---|---|---|---|---|---|---|---|
| | | No maternal DM | | Preexisting DM | | Gestational DM | | |
| | | *N* | (%) | *N* | (%) | *N* | (%) | |
| LVOT | 137 | 117 | (3.8) | 6 | (5.7) | 14 | (3.6) | .6 |
| RVOT | 556 | 497 | (16.2) | 9 | (8.5) | 50 | (12.8) | .03 |
| Severe CHD | 1362 | 1148 | (37.5) | 53 | (50.0) | 161 | (41.3) | .01 |
| Moderate CHD | 522 | 477 | (15.6) | 13 | (12.3) | 32 | (8.2) | <.001 |
| Mild CHD | 1673 | 1436 | (46.9) | 40 | (37.7) | 197 | (50.5) | .06 |
| Total | 3557 | 3061 | (100) | 106 | (100) | 390 | (100) | |

*Notes*. (%), the percentage of maternal diabetes.
A statistically significant difference within the group if *P* value < .05.
Abbreviations: ALCAPA, anomalous left coronary artery to pulmonary artery; AP, aortopulmonary; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CAF, coronary artery fistula; CHD, congenital heart disease; CoA, coarctation of aorta; DM, diabetes mellitus; DILV, double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; LVOTO, left ventricular outflow obstruction; PAVSD, pulmonary atresia with ventricular septal defect; PAIVS, pulmonary atresia with intact septum; PDA, patent ductus arteriosus; PS, pulmonary stenosis; RVOTO, right ventricular outflow tract obstruction; TAPVD, total anomalous pulmonary venous drainage; ccTGA, congenitally corrected TGA; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

in the birth prevalence of overall CHD from 5.1 per 1000 LB in 2006 to 7.8 per 1000 LB in 2015, *P* = .001. A significant increase was noted in mild (from 1.9 per 1000 LB in 2006 to 3.9 per 1000 LB in 2015, *P* < .001) and severe CHD (from 1.8 per 1000 LB in 2006 to 2.9 per 1000 LB in 2015, *P* < .001).

Table 4 shows the sex and racial distribution of CHD in our study. There were slightly more females (*n* = 1848) than males (*n* = 1709) with overall birth prevalence for males were 3.21 (95% CI: 3.06-3.37) per 1000 LB and 3.47 (95% CI: 3.32-3.36) per 1000 LB for females. A significant female to male dominance was noted in PDA (1.5:1), AVSD (1.8:1) and ASD (1.6:1). Meanwhile, male to female dominance was observed in TGA (2.5:1), CoA (1.6:1) conotruncal defect (1.3:1), lesions with left ventricular outflow tract obstruction (1.6:1) and severe CHD (1.1:1).

There were 2476 Malay, 687 Chinese, and 227 Indian ethnic group in our study. Hence, the birth prevalence for Malay, Chinese, and Indian ethnic group were 4.6 (95%CI: 4.5-4.8) per 1000 LB, 1.3 (95%CI: 1.2-1.4) per 1000 LB, and 0.4 (95% CI: 0.4-0.5) per 1000 LB, respectively. There was no racial or ethnic dominance for specific or severity of CHD.

Table 5 shows the severity of CHD in relation to the timing of diagnosis. Overall, 3% were detected during the antenatal period with the majority having severe lesions, 50% were detected by 1 month of age, and 88% by 1 year of age. Meanwhile, of the total 1362 with severe CHD, 64% were detected by 1 month of age and 96% by 1 year of age. Figure 2 shows a significant increase in neonatal diagnosis over time. Further analysis shows a significant increase in neonatal diagnosis of mild (from 20 in 2006 to 107 in 2006, *P* < .001) and severe CHD (from 54 in 2006 to 112 in 2015, *P* < .001).

There was a total of 510 (14.3%) premature infants with 172 (34%) were PDA, 145 (28%) were VSD, 67 (13%) were PS and 125 miscellaneous lesions. Of 172 PDA, 34% were severe, 11% were moderate, and the remaining 55% were mild PDA.

Maternal diabetes during pregnancy was noted in 496 (14%) of CHD with 106 preexisting and 390 gestational DM. Table 6 shows the specific CHD and its severity in relation to the type of maternal diabetes during pregnancy. The majority of lesions were PDA and VSD. There was a significant number of the conotruncal defect and severe CHD in preexisting and gestational DM than those without maternal diabetes during pregnancy. Multivariate logistic regression analysis shows gestational DM during pregnancy was significantly associated with PDA with aOR 1.6 (95% CI: 1.3-2.1, *P* < .001), TGA with aOR 2.1 (95%CI: 1.2-3.7, *P* = .006) and ccTGA with aOR 3.5 (95%CI: 1.1-11.5, *P* = .04). Meanwhile, preexisting maternal DM during pregnancy was significantly associated with TOF with aOR of 2.5 (95%CI: 1.4-2.6, *P* = .002), TGA with aOR 3.3 (95%CI: 1.5-7.4, *P* = .004), Mitral atresia with aOR 4.0 (1.2-13.6, *P* = .03), ccTGA with aOR 9.8 (95%CI; 2.6-37.1, *P* = .001), Conotruncal with aOR 2.9 (95%CI; 1.8-4.6), *P* < .001) and severe CHD with aOR 1.6 (95% CI: 1.1-2.4, *P* = .01).

Only 54 (1.6%) of our cohort have a positive family history of CHD with 41 having siblings with CHD (17 VSD, 6 PDA, 5 ASD, 3PAVSD, 2 PS, 1 each for AS, AVSD, CoA, DILV, heterotaxy, mitral atresia, PAIVS, and tricuspid atresia) and 13 with mothers with CHD (8 VSD, 1 each for AVSD, ASD, PDA, PS, and TOF).

## 4 | DISCUSSION

To the best of our knowledge, this is the first study in Malaysia and from the middle-income countries describing the trend in birth prevalence of CHD in relation to its severity. Our study shows the overall birth prevalence of CHD was 6.7 per 1000 live births with a significant increase toward the end of the study, 7.7 per 1000 LB. This rate is within the results of published studies.[2,4] The birth prevalence in this study is slightly lower compared to

the study from Norway[5] (13.7/1000 LB), Taiwan[20] (13.8/1000 LB), China[21] (11.1/1000 LB), and United States of America[22] (10.8/1000 LB). However, it is almost similar to Europe[3] (7.2/1000 LB), Western Australia[23] (7.6/1000 LB), Tunisia[24] (6.8/1000 LB), Turkey[25] (7.7/1000 LB), and Oman[26] (7.2/1000 LB). The slightly low rate in our study could be due to incomplete case ascertainments. Underreporting may occur due to undiagnosed mild lesions, diagnoses made at other states or centers in Malaysia or neighboring country in Singapore, and severe or critical CHD that died prior to diagnosis. With regards to severe cases who died prior diagnosis, our data shows only one case diagnosed at postmortem. Lack of postmortem data in our study was due to nonmandatory of a postmortem for all infant deaths in our country as well as due to cultural and religious beliefs, reluctance from parents to give consent for postmortem, which contribute to underreporting of severe or critical CHD in our study. Another reason for underreporting was a diagnosis of CHD at other cardiac centers in Malaysia or neighboring Singapore. We are aware some parents may move to or seek treatment in other state or center in Malaysia. However, as the only cardiac center in Johor State, most were referred to us for the continuation of care, which reduces the underreporting.

Regarding undiagnosed mild cases, our data shows an increase in neonatal diagnosis of milder cases in the later years of the study. This suggests an underestimation of the mild lesions in the early years of the study. Despite possible underreporting in our study, we believe the result is the best estimate of the birth prevalence of CHD in our state of Johor.

Study on the prevalence of severe CHD is compounded by various definitions of the severe lesion. This includes lesions that require cardiac catheterization and/or surgery or had autopsy,[27] associated with high perinatal mortality rate,[3] the complexity of the lesions,[28] lesions with severe clinical symptoms and need for early intervention or surgery[2] and life-threatening lesions.[29] In a recent review by Miranovic et al, which used a standard set of criteria, only eleven out of 128 publications were included in their analysis.[9] They found the incidence of severe CHD ranging in between 0.4 and 2.3 per 1000 LB. The overall birth prevalence of severe CHD in our study was 2.6 per 1000 LB. It is slightly high due to the inclusion of large VSD, large PDA, critical PS, AS or CoA that require early intervention or surgery. As suggested by Hoffman,[2] the inclusion of these lesions together with all cyanotic CHD will reflect a real burden of CHD in the country. Our study shows 38% of CHD or two in five were severe with the majority TOF, large VSD, and large PDA. Of these severe lesions, 80% are considered suitable for biventricular repair and require early surgery or intervention. Unfortunately, with limited human resources and infrastructure in Malaysia, the mortality rate of the critical lesions is high (34%) with a significant deaths occurring prior and after the surgery or intervention.[11] Currently, there are only one dedicated pediatric and congenital cardiac center, 48 registered pediatric cardiologists, and only five dedicated pediatric cardiac surgeons in Malaysia covering for the 3.5 million population and an estimated 5000 new cases of CHD per year. With two in five of CHD were severe lesions, this adds more burden to already constraints resources.

Our study shows a significant increase in the overall birth prevalence of CHD over time, with a gradual increase from 5.1 per 1000 LB in 2006 to 7.7 per 1000 LB in 2015. The increase in rate is due to increase detection of both mild and severe CHD. This finding is also observed in other studies.[2,4,30] Increased detection of CHD is due to widely available echocardiogram machines and trained personnel in echocardiography in all district hospitals toward the end of the study. As more personnel were able to do an echocardiogram, more asymptomatic neonates with a cardiac murmur had an echocardiogram. This is shown as almost one in two of lesions were detected during the first one month of life. Early echocardiogram in an asymptomatic neonate with cardiac murmur also allows us to diagnose severe, noncyanotic lesions at an early age. Another reason for the increase in detection of CHD was due to widely available fetal echocardiography services toward the end of study (2011-2015). Despite the improvement in fetal diagnosis toward the end of the study, only 3% of CHD detected with the majority were severe lesions. As in other LMIC, these results show that fetal diagnosis of CHD in Malaysia is still in the infancy stage. Currently only limited center and pediatric cardiologist were able to offer fetal echocardiogram services. Hence, much more effort is needed to improve fetal diagnosis, that is training obstetriciano in the high-risk screening of pregnant mothers for CHD.

Previous studies suggested dominant right-sided lesions in the Asian population and low prevalence of left-sided obstructive lesions compared to the western population.[4,20,31] Our result is consistent with population study in an Asian country which shows a high prevalence of right-sided lesions. In a meta-analysis in 2011, Linde et al noted a relatively high rate of the right-sided lesions in Asia could be due to the inclusion of institutional or hospital-based data rather than population data.[4] However, this population study confirmed the high prevalence of right-sided lesions in the Asian population.

This study also shows a low rate of the left-sided lesions, and consistent with studies from the Asian population. The low rate of the left-sided lesions in Asia could be due to genetic variation or underestimation (died before diagnosis or died in utero). Further genetic study may explain the difference.

The presence of a chromosomal anomaly, syndrome, or ECD in a patient with CHD adds additional burden to the health care system. Most of them require more investigations, longer hospitalizations and are associated with poor outcome.[11] In this study, 80% of CHD was not associated with any syndrome or ECD. This result is similar to previous population studies.[3,5,23] The majority of chromosomal anomaly detected in our study was Down syndrome with the most frequent lesions being VSD rather than AVSD. This result is similar to another study from the Asian population.[32] Genetic variation may play a role, and hence further study is warranted to understand this variation. Unfortunately, genetic services in LMIC are limited.

Our study shows that pregnant mothers with preexisting DM are three times more likely to have an infant with a conotruncal defect and two times more likely to have an infant with severe CHD compared to their counterpart. This result is similar to the previous study.[33] However, our study also shows gestational diabetes during pregnancy is also associated with a high risk of having infants with TGA and PDA. This finding supports the observational study by Hunter et al.[34] This highlights the important role of maternal diabetes during pregnancy. Hence, control of diabetes may help in reducing the likelihood of severe lesions and reduce the burden of disease.

### 4.1 | Study limitation

We are aware of a few limitations in our study. Data were collected from a clinical registry. Hence some underreporting may occur especially on the associated syndrome or malformation. This data may or may not represent our national data, thus reflecting a need for a national registry. However, despite this limitation, we believe a clinical registry is another alternative for LMIC to understand the disease burden in their country better.

## 5 | CONCLUSIONS

The birth prevalence of CHD in southern Malaysia was 6.7 per 1000 live births. Two in five CHD were severe and significantly associated with syndrome and extracardiac defect. Furthermore, there was a significant increase in the detection of a severe lesions in recent years leading to increased burden to an already limited-resources health care system in a middle-income country. Therefore, a comprehensive and strategic plan for PCCSP is required in LMIC.

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### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

### AUTHOR CONTRIBUTIONS

MNMB designed the PCCIS, conceptualized the study, carried out the echocardiogram, data entry, and analysis, drafted the initial manuscript, and revised the manuscript.

MHS and MTJ carried out the echocardiogram, data entry, and analysis.

NA, EYA, and NZ analyze the data and critically review the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all the aspects of the work.

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