Original Article

Prevalence and risk factors for congenital heart defects among children in the Multi-Ethnic Yunnan Region of China

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Background: To determine the congenital heart defect (CHD) prevalence and identify the associated risk factors in children within the multi-ethnic Yunnan Region of China.

Methods: This is a prospective matched case-control screening study. Screening for CHD in children residing within 28 county districts of Yunnan Province during the period of January 2001 to December 2016 was conducted. A total of 2,421 and CHD cohort and 24,210 control cohort were derived from a total population of 400,855 children (under 18 years of age).

Results: A total of 2,421 children were diagnosed with CHD, yielding a CHD prevalence of 6.04 cases per 1,000 children. The prevalence of CHD by sex was 6.54 per 1,000 females versus 5.59 per 1,000 males. The ethnic groups displaying the highest CHD prevalence were the Lisu (15.51 per 1,000), Achang (13.18 per 1,000), Jingpo (12.32 per 1,000), Naxi (9.68 per 1,000), and Tibetan (8.57 per 1,000), respectively. The most common CHD was atrial septal defect, amounting to 1.94 instances per 1,000 children. We identified a number of child-associated parameters that significantly correlated with greater CHD risk, such as lower mass at birth, shorter duration of gestation, and younger age at the time of screening. We also identified a number of maternal and familial risk factors.

Conclusions: This ultrasonic color Doppler imaging study revealed a relatively commonplace prevalence of CHD. Moreover, the prevalence of CHD in Yunnan Region significantly varied with sex and ethnic status. Certain child-associated, maternal, and familial risk factors may contribute to CHD risk.

Keywords: Epidemiology; risk factor; congenital heart defect; congenital heart defect (CHD); Doppler imaging; China

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Introduction

Congenital heart defects (CHD) are among the most frequent birth defects, occurring in as many as 9.3 per 1,000 live births with significant geographical variation (1). Defects can range from asymptomatic to life-threatening, and many cases require surgical or pharmacological intervention at an early stage to prevent adverse outcomes (2). Timely screening is therefore necessary to help identify patients with CHD, diagnose cases early on, and lower mortality rates.

Several citywide and nationwide studies have been performed over the years to estimate the frequency of CHD among live births. An early study in the United Kingdom conducted from 1985 to 1994 screened 377,310 live neonatal births and diagnosed 1,942 instances of CHD, amounting to a prevalence of 0.52% (3). Another early study in the United States, conducted from 1968 to 1997 as part of the Metropolitan Atlanta Congenital Defects Program (MACDP), revealed a CHD prevalence of 0.62%, which was remarkably similar to the UK study (4). CHD screenings in urban China, within the cities of Shanghai in 1987 and Beijing in 2005, identified 6.9 CHD cases and 4.6 CHD cases per 1,000 live neonatal births, respectively (5,6). A more recent meta-analysis revealed a slightly higher CHD rate in Asian populations than in those of Europe or North America (1). Due to this variance, targeting and screening discrete geographic regions may be necessary to obtain accurate information on the CHD rate for a particular population.

Our objective was to determine the CHD prevalence and identify the associated risk factors in children within the multi-ethnic Yunnan Region of China. In this targeted screening study, we estimated the CHD rate for children under 18 years of age residing with Yunnan region and identified the risk factors associated with higher-than-average CHD prevalence in this population. We conducted our whole-population screen using ultrasonic color Doppler imaging, a non-invasive technique that superimposes colored velocity information obtained by Doppler ultrasound over anatomical images in grey-scale obtained by conventional pulse-echo ultrasound (7).

We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-21-371/rc).

Methods

Patient and public involvement

The development of the research question and outcome measures were partly determined based on the unique ethnic constituencies of Yunnan Province and the varying altitude levels at which the residents of Yunnan Province live. Feedback received from the local target populations via the Yunnan Education Bureau and the Health and Family Planning Commission of Yunnan Province was critical to the design of this study. Adult community members were involved in encouraging the recruitment of minors into this study. Following publication, the key results of this study will be disseminated to the local target populations in their local languages by the Yunnan Education Bureau.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study obtained approval from the Ethics Review Committees at The First People's Hospital of Yunnan Province, Kunming, China (No. KHLL2020-KY019) and Yan'an Affiliated Hospital of Kunming Medical University, Kunming, China (No. YYHKM04584). Written informed consent was obtained from all participants' parents or legal guardians prior to their enrollment.

Enrollment for the screening program

Yunnan Province is situated in southern China and, in2010, was home to an estimated 46 million people, making it the 12th largest province in China in terms of population. The Province is sub-divided into a total of 129 county-level districts and has 1,565 cities. Among the country's 56 recognized ethnic groups, 25 are found in Yunnan. Approximately 38% of the province's population are members of ethnic minorities (8). The Congenital Malformation Registry Database of Yunnan Province (CMRD), compiled between January 2001 and December 2016, consists of 400,855 individuals residing within 28 of the province's county-level districts. Prior to conducting this prospective matched case-control screening study, the Yunnan Education Bureau and the Health and Family Planning Commission of Yunnan Province jointly determined the distribution of children (aged 0–18 years) residing within the 28 county districts. After identifying target localities within the 28 districts, the Yunnan Branch of the Red Cross Society of China cooperated in a public relations effort to issue questionnaires within the townships and villages. Local schoolteachers affiliated with the local Education Bureaus (under the administration of the Yunnan Education Bureau) were responsible for educating community members about the screening program and helping participating parents to enroll their children in

the study and complete the screening questionnaire. Every person under 18 years of age, whether exhibiting CHD symptoms or not, was encouraged to enroll in the CMRD through their parents. However, there were several reasons for non-enrollment: (I) the child's parents did not provide their informed consent, (II) the child succumbed to a fatal condition prior to the screen, or (III) the child's records were incomplete.

Collection of relevant health information via questionnaire

After enrollment, parents were provided with a questionnaire that requested the child's details, as follows: (I) date of birth (DOB), (II) weight at delivery, (III) height at delivery, (IV) duration of gestation based on the birth certificate, (V) feeding method (breast milk, formulation, etc.), (VI) health history (i.e., any prior infections or congenital conditions, etc.), and (VII) present health condition. The questionnaire also contained questions related to the parents' details: (VIII) health history and present health condition (e.g., history or presence of CHD hypertension, diabetes, etc.), (IX) lifestyle habits (e.g., alcohol consumption or smoking habits, etc.), and (X) socioeconomic status (e.g., education, occupation, net income, etc.). Finally, the questionnaire asked for details specific to the mother, as follows: (XI) weight-gain from pregnancy, (XII) complications during pregnancy (e.g., gestational diabetes, hypertension, or anemia, infections during pregnancy, medications received during pregnancy, etc.), (XIII) exposure to harmful chemicals (e.g., mercury, lead, benzene, formaldehyde, pesticide, etc.), and (XIV) activities during pregnancy (e.g., home renovation, etc.).

CHD screening procedures

First, a conventional cardiac physical examination by a licensed cardiologist was performed to screen for clinical suspicion of CHD. The cardiologist palpated upper and lower extremity pulses bilaterally and measured blood pressure via sphygmomanometry on the right arm. Jugular venous distension and precordial motion were checked. Cardiac valve areas were auscultated with the patient in a seated position. Typical abnormal signs from physical examination included cyanosis of the lips and nail beds, loud pulmonary valve (P2), murmurs, and splitting of the second heart sound. Quality control (QC) was performed by QC physicians during the screening program. The QC physicians randomly selected 10% of the participants from the physical exam screening and evaluated inter-rater reliability, observing an inter-rater agreement of over 95%.

Second, color Doppler echocardiography was used to confirm the presence of CHD in patients that were clinically suspected of CHD from the physical exam. Philips Sonos 5500 (Philips, Cambridge, MA, USA) color Doppler echocardiograph devices were employed to screen for CHD. An established protocol for CHD detection was employed by a team of trained and certified sonographers, who coordinated the CHD screening effort across Yunnan region.

Patients who were identified as having a CHD by the screening were then referred to a cardiologist, who performed diagnostic testing by heart catheterization to confirm CHD prior to heart surgery. The diagnosed anomalies were as follows: (I) ventricular septal defect (VSD), defined as an opening present in the interventricular septum, (II) atrial septal defect (ASD), defined as an opening present in the interatrial septum (other than a patent foramen ovale (PFO), defined in turn as an opening at the oval fossa measuring less than 5 mm in diameter); (III) patent ductus arteriosus (PDA), defined as a joining between the descending thoracic aorta and the left pulmonary artery, (IV) single ventricle, defined as a larger ventricle dominating a smaller ventricle or as a single ventricle with two atrioventricular valves, (V) pulmonary stenosis, defined as a narrowing or blockage from the right ventricle to the pulmonary artery resulting in elevated blood velocity (>2.0 mm/s), (VI) Ebstein's anomaly, defined as a deviation in the septal and posterior leaflets from the right atrioventricular valve towards the apex of the right cardiac ventricular chamber (with the extent of deviation measured as the distance between the tricuspid valve and mitral valve and deemed significant when longer than 20 mm). For purposes of analysis, in cases where multiple CHD defects were observed, the case was identified by the most severe anomaly. In addition, CHD patients were assessed for the presence of congenital anomalies (e.g., congenital airway anomalies (CAAs), cleft lip/palate, congenital neurologic anomaly, etc.) and genetic syndromes using the diagnostic criteria stated in the International Pediatric and Congenital Cardiac Code (IPCCC) (9).

Selection of matching healthy control cohort

Participants with CHD validated by color Doppler echocardiography were compared to a demographically-matched healthy control cohort derived from the same county-level district to analyze the risk factors for

CHD. The conditions for demographic matching were as follows: (I) participants from the same country-level district and township or village, (II) participants of the same age in years, (III) participants of the same ethnic group, and (IV) participants of the same sex. The healthy control participants did not possess any non-hereditary or congenital diseases. Demographic matching was performed at a 1:10 ratio (i.e., one patient with a CHD was paired with ten healthy control participants). If the participants with a CHD was attending school, 10 healthy control children who were the same age in years, the same ethnicity, and the same sex were selected from the same school grade level as the participant with CHD. If the participant with a CHD was not attending school (e.g., those aged 0–3 years or those unable to attend school), 10 healthy control children who were the same age in years, the same ethnicity, and the same sex were selected from the same township or village as the participant with CHD.

Follow-up on enrollees with CHD

Clinical follow-up was performed on all participants with validated CHD for a period of 1 year. This follow-up included a pre-operative clinical examination (including ultrasound cardiography (UCG), electrocardiography (ECG), chest radiography, liver function, kidney function, and immunological function) as well as post-operative follow-up at 1 week, 3 months, 6 months, and 1 year. Those participants with untreated CHD were also followed-up for a period of 1 year.

Statistical analysis

All statistical tests were conducted with the Predictive Analytics Software suite (PASW, version 20.0, SPSS Statistics 20, IBM, Armonk, NY). Statistically significant results were taken for two-tailed P values of less than 0.05. Significance between the children with CHD and healthy children was computed by two variable tests for nominal data. Significant associations between CHD status and covariate parameters were calculated by logistic regression. The covariate parameters for each child were as follows: age, sex, mass, gestational age, etc. Covariate parameters from the mother were: age at child's birth, body mass index (BMI) before pregnancy, weight, height, pregnancy issues (e.g., gestational diabetes, hypertension, infection, medication, exposure to harmful chemicals during pregnancy, etc.). The covariate parameters for both parents were as follows: health history and present health condition (e.g., CHD, hypertension, diabetes, etc.), lifestyle habits (e.g., alcohol consumption, smoking, etc.), and socioeconomic status (e.g., education, occupation, net income, altitude, etc.). The multiple imputation method was applied for deal with missing data values.

Results

From January 2001 to December 2016, 2,421 out of 400,855 children screened were conclusively diagnosed with CHD by color Doppler echocardiography (*Table 1*). This amounted to a prevalence of 6.04 CHD cases per 1,000 children in Yunnan region. We analyzed the presence of CAAs in this 2,421-member CHD cohort. Bronchomalacia and tracheomalacia were the most commonly found CAAs (Table S1). We also analyzed the presence of genetic syndromes in the CHD cohort, with Trisomy 21 and Turner's syndrome being the most commonly found genetic syndromes (Table S2).

The most frequent CHD condition was ASD, accounting for 1.94 cases per 1,000 children (*Table 2*). VSD was also relatively prevalent, with 1.37 instances per 1,000 children, followed by PFO with 1.29 instances per 1,000 children (*Table 2*). Out of the 2,421 CHD patient cohort, 187 patients (7.72%) possessed multiple CHD defects, with 172 children (7.10%) possessing two CHD defects, 13 children (0.54%) possessing three CHD conditions, 1 child (0.04%) possessing four CHD conditions, and 1 child (0.04%) possessing five CHD conditions.

Of the 2,421 CHD patients, 441 cases (18.22%) displayed elevated moderate-severe pulmonary arterial pressure via color Doppler echocardiography. A total of 337 patients of the 2,421 CHD patient cohort underwent corrective surgery, yielding a treatment rate of 13.92%. Out of the 2,421 CHD patients, a total of 231 children perished during their 1-year follow-up period, yielding a 1-year mortality rate of 9.54% (Table S3). Of these 231 CHD children who died during follow-up, 14/231 (6.06%) underwent corrective surgery, making the one-year mortality rate of operative cases to be 14/337 (4.15%).

Subgroup analysis (*Table 3*) demonstrated a greater prevalence of CHD in female children compared to male children (6.54 per 1,000 females versus 5.59 per 1,000 males). Certain factors related to the children, mothers, and families were also statistically associated with CHD prevalence. The child-related factors that affected the prevalence of CHD were age at screening, birthweight,

Table 1 Clinicopathological characteristics of the CHD and healthy control cohorts

Variable	CHD cohort (n=2,421)	Control cohort (n=24,210)	P value
Sex, n (%)			
Female	1,253 (51.76)	12,530 (51.76)	1.00
Male	1,168 (48.24)	11,680 (48.24)	1.00
Age at screening, (years), n (%)			
0–3	551 (22.76)	5,510 (22.76)	1.00
4–6	488 (20.16)	4,880 (20.16)	1.00
7–18	1,382 (57.08)	13,820 (57.08)	1.00
Comorbidity, n (%)			
Prematurity (<37 weeks)	347 (14.33)	1,892 (7.81)	<0.001
Cleft lip/palate	21 (0.87)	28 (0.12)	<0.001
CAA (Table S1)	97 (4.01)	11 (0.05)	<0.001
Genetic syndrome (Table S2)	238 (9.83)	28 (0.12)	<0.001
Congenital neurological anomaly	3 (0.12)	8 (0.03)	0.04
Congenital gastrointestinal anomaly	2 (0.08)	9 (0.04)	0.29
Congenital genitourinal anomaly	1 (0.04)	14 (0.06)	0.74

CHD, congenital heart defect; CAA, congenital airway anomaly.

Table 2 Prevalence of various CHD defects

CHD defect	n	Prevalence per 1,000
Atrial septal defect	779	1.94
Ventricular septal defect	548	1.37
Patent foramen ovale	516	1.29
Patent ductus arteriosus	278	0.69
Pulmonary stenosis	47	0.12
Tetralogy of Fallot	41	0.10
Atrioventricular septal defect	29	0.07
Aortic stenosis	13	0.03
Single ventricle	4	0.01
Ebstein's anomaly	4	0.01
Compound type	65	0.16
Other lesions	97	0.24

CHD, congenital heart defect.

and duration of gestation. The highest CHD rates were observed in children who were school-aged at screening, weighed less than 2.5 kg at birth, and had a gestational period of less than 37 weeks. Maternal factors that influenced the prevalence of CHD were age, elevated BMI before pregnancy, gestational diabetes, hypertension, anemia, infection, medication, and exposure to harmful chemicals during pregnancy. The greatest frequency of CHD was also observed in babies whose mothers had BMIs greater than 28 kg/m^2 before pregnancy and who were older than 40 years old and younger than 20 years old. Family factors that affected the prevalence of CHD were familial history of CHD, education, family income, dwelling altitude, and ethnicity. CHD prevalence was positively associated with parental history of CHD and dwelling altitude but negatively associated with parental education and income. Notably, the Lisu, Jingpo, Achang, Naxi and Tibetan ethnicities displayed the highest CHD prevalence rates compared to the other Chinese ethnic groups included in the study.

We constructed two models to determine the comparative CHD risk in children (*Table 4*). Model 1 did not adjust for any covariates, while Model 2 adjusted for all covariates. Covariate parameters considered for the child included: sex, age at screening, mass at birth, and duration of gestational period. Covariate parameters considered for the mother included: age at child's birth, BMI before

Table 3 Prevalence of CHD by various subgroups

Variable	Prevalence per 1,000	P value
Child characteristics		<0.001
Sex		
Male	5.59	
Female	6.54	
Age at screening, (years)		<0.001
0–3	4.09	
4–6	6.31	
7–18	7.32	
Birthweight (g)		<0.001
<2,500	11.69	
2,500–<3,000	7.70	
3,000–<3,500	5.86	
3,500–<4,000	5.04	
≥4,000	5.13	
Gestational age (weeks)		<0.001
<37	10.09	
37	8.09	
38	5.59	
39–40	5.68	
≥41	5.53	
Maternal characteristics		
Maternal age at birth (years)		0.001
<20	7.40	
20–24	6.73	
25–29	5.62	
30–34	5.89	
35–39	7.01	
≥40	9.39	
Maternal pre-pregnancy BMI (kg/m^2)		0.036
<18.5	5.71	
18.5–23.9	5.86	
24.0–27.9	6.28	
≥28	7.28	
Prenatal infection		<0.001
No	5.38	
Yes	58.29	
Prenatal contact with toxic substances		0.003
No	6.04	
Yes	18.69	
Prenatal medication use		<0.001
No	5.89	
Yes	13.20	
Gestational hypertension		<0.001
No	5.98	
Yes	9.97	
Gestational diabetes		<0.001
No	5.98	
Yes	10.18	
Prenatal anemia		0.001
No	5.92	
Yes	7.85	
Family characteristics		
History of mother with CHD		<0.001
No	6.01	
Yes	38.57	
History of father with CHD		<0.001
No	6.04	
Yes	30.20	
Education of mother (years)		<0.001
≥16	5.22	
15–16	5.83	
13–14	5.83	
<13	7.61	
Education of father (years)		<0.001
≥16	5.29	
15–16	6.01	
13–14	6.01	
<13	7.25	
Smoking		0.115
None	5.74	
Both mother and father	5.07	

Table 3 (*continued*)

Table 3 (*continued*)

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Prevalence per 1,000	P value
Father	6.37	
Mother	2.72	
Family income (yuan/month)		<0.001
<1,000	10.95	
1,000–2,000	8.30	
2,000–3,000	6.07	
>3,000	3.23	
Altitude (m)		<0.001
<1,000	2.45	
1,000–2,000	5.90	
2,000–3,000	7.25	
>3,000	9.45	
Ethnicity		<0.001
Han	5.19	
Tibetan	8.57	
Bai	6.30	
Dai	5.90	
Hani	8.42	
Yi	7.95	
Zhuang	3.59	
Naxi	9.68	
Lisu	15.51	
Wa	8.43	
Jingpo	12.32	
Keno	5.71	
Miao	7.87	
Hui	5.73	
Achang	13.18	
Yao	0.00	
Pumi	0.00	
Others	6.64	

CHD, congenital heart defect; BMI, body mass index.

pregnancy, gestational diabetes, hypertension, anemia, infection, medication, and exposure to harmful chemicals during pregnancy. Covariate parameters considered for the family included: history of CHD, smoking status, education, family income, altitude, and ethnicity.

The odds ratios (ORs) and 95% confidence intervals (95% CIs) for CHD risk were calculated for both models (*Table 4*). Younger age (0–3 years) at screening (OR =3.71, 95% CI: 2.71–5.07), lower birth mass (<2,500 g) (OR =1.63, 95% CI: 1.29–2.06), and shorter duration (<37 weeks) of gestation (OR =1.18, 95% CI: 0.95–1.47) remained significant factors for CHD compared to the healthy control cohort. There was a greater likelihood of CHD for children whose mothers were 40 years of age or older (OR =1.55, 95% CI: 1.09–2.20), suffered from an infection during pregnancy (OR =14.60, 95% CI: 12.20–17.31), and experienced gestational diabetes (OR =1.82, 95% CI: 1.32–2.48) or hypertension (OR =1.40, 95% CI: 1.04–1.89). There was an increased risk of CHD in children whose parents had CHD (mother, OR =6.45, 95% CI: 3.13–13.26; father, OR =4.35, 95% CI: 1.53–12.29) or for children with mothers having less than 13 years of education (OR =1.33, 95% CI: 1.08–1.65).

Discussion

Out of a cohort of 400,855 children in Yunnan region, 2,421 children were diagnosed with CHD, amounting to a prevalence of 6.04 cases per 1,000 children. There was a statistically significant dependence on sex, with 6.54 CHD cases per 1,000 females within a cohort of 1,253 girls versus 5.59 CHD cases per 1,000 males within a cohort of 1,168 boys. After adjusting for covariates, we found that several infant factors (i.e., age at screening, mass at birth, and duration of gestational period), maternal factors (i.e., BMI before pregnancy, age of mother at child's birth, gestational diabetes, hypertension, and anemia, infection, medication, and exposure to harmful chemicals during pregnancy), and familial factors (i.e., history of CHD, education, and income) significantly influenced the risk of CHD in the children included in the study.

Previous studies have identified similar rates of CHD prevalence in Asian children ranging from 0 to 18 years of age (10,11). That being said, our calculated prevalence of CHD in Yunnan Province children may vary slightly from earlier studies on other populations. Most previous CHD screening programs in China have only enrolled children suspected of possessing a CHD based on signs and symptoms (5,6). In these previous studies, children were initially observed by heart auscultation, and only those individuals exhibiting suspicious signs and symptoms were then examined by non-invasive echocardiography or more invasive cardiac catheterization. However, in our

Table 4 Odd ratios (and 95% CI) of CHD by various factors

Variable	Model 1		Model 2**	
	Odd ratio	95% CI	Odd ratio	95% CI
Child characteristics				
Sex				
Male	1.00		1.00	
Female	1.44	1.31–1.59	1.48	1.34–1.62
P for difference		<0.001		<0.001
Age at screening, (years)				
0–3	4.23	3.13–5.72	3.71	2.71–5.07
4–6	1.16	1.00–1.36	1.18	1.01–1.38
7–18	1.19	1.01–1.39	1.24	1.05–1.44
P for trend		<0.001		<0.001
Birthweight (g)				
<2,500	2.03	1.70–2.44	1.63	1.29–2.06
2,500–<3,000	1.25	1.10–1.42	1.18	1.03–1.36
3,000–<3,500		1.00		1.00
3,500–<4,000	0.84	0.75–0.95	0.86	0.76–0.97
≥4,000	0.96	0.81–1.15	0.97	0.82–1.17
P for trend		<0.001		<0.001
Gestational age (weeks)				
<37	1.79	1.51–2.11	1.18	0.95–1.47
37	1.51	1.27–1.79	1.26	1.06–1.52
38	0.98	0.86–1.12	0.90	0.78–1.03
39–40		1.00		1.00
≥41	0.92	0.80–1.08	0.97	0.83–1.13
P for trend		<0.001		0.032
Maternal characteristics				
Maternal age at birth (years)				
<20	1.26	0.83–1.94	0.95	0.61–1.48
20–24	1.25	1.10–1.41	1.06	0.93–1.22
25–29		1.00		1.00
30–34	1.08	0.96–1.22	1.09	0.97–1.24
35–39	1.22	1.02–1.46	1.11	0.93–1.34
≥40	1.78	1.25–2.50	1.55	1.09–2.20
P for trend		0.001		0.239
Maternal pre-pregnancy BMI (kg/m^2)				
<18.5	1.01	0.82–1.24	0.97	0.78–1.20
18.5–23.9		1.00		1.00
24.0–27.9	1.03	0.90–1.20	1.00	0.85–1.16
≥28	1.23	1.00–1.51	1.15	0.93–1.42
P for trend		0.159		0.454
Prenatal infection				
No		1.00		1.00
Yes	14.08	12.10–16.48	14.60	12.20–17.31
P for difference		<0.001		<0.001
Prenatal contact with toxic substances				
No		1.00		1.00
Yes	3.44	1.50–7.89	1.15	0.47–2.81
P for difference		0.005		0.848
Prenatal medication use				
No		1.00		1.00
Yes	2.39	1.90–2.98	0.91	0.70–1.18
P for difference		<0.001		0.319
Gestational hypertension				
No		1.00		1.00
Yes	1.64	1.24–2.18	1.40	1.04–1.89
P for difference		<0.001		0.016
Gestational diabetes				
No		1.00		1.00
Yes	1.75	1.29–2.36	1.82	1.32–2.48
P for difference		<0.001		<0.001
Prenatal anemia				
No		1.00		1.00
Yes	1.36	1.14–1.62	1.22	1.01–1.45
P for difference		0.002		0.074

Table 4 (*continued*)

Table 4 (*continued*)

Variable	Model 1		Model 2**	
	Odd ratio	95% CI	Odd ratio	95% CI
Family characteristics				
History of mother with CHD				
No		1.00		1.00
Yes	6.84	3.72–12.60	6.45	3.13–13.26
P for difference		<0.001		<0.001
History of father with CHD				
No		1.00		1.00
Yes	5.54	2.19–14.01	4.35	1.53–12.29
P for difference		<0.001		<0.001
Education of mother (years)				
≥16		1.00		1.00
15–16	1.10	0.98–1.26	1.10	0.95–1.28
13–14	1.15	1.00–1.31	1.11	0.92–1.33
<13	1.45	1.29–1.65	1.33	1.08–1.65
P for trend		<0.001		0.016
Education of father (years)				
≥16		1.00		1.00
15–16	1.14	1.00–1.30	1.06	0.91–1.24
13–14	1.13	0.99–1.29	0.98	0.83–1.17
<13	1.38	1.21–1.56	0.97	0.79–1.20
P for trend		<0.001		0.819
Smoking				
None		1.00		1.00
Both mother and father	0.86	0.54–1.39	0.74	0.45–1.22
Father	1.07	0.97–1.18	1.02	0.92–1.14
Mother	0.45	0.07–3.24	0.36	0.05–2.65
P for trend		0.099		0.315
Family income (yuan/month)				
<1,000	1.37	1.15–1.61	1.16	0.97–1.39
1,000–1,999	1.19	1.05–1.33	1.00	0.87–1.15
2,000–2,999	0.99	0.88–1.12	0.92	0.81–1.05
≥3,000		1.00		1.00
P for trend		<0.001		0.173
Altitude (m)				
<1,000		1.00		1.00
1,000–2,000	0.99	0.88–1.11	0.92	0.82–1.05
2,000–3,000	1.18	1.05–1.32	1.00	0.88–1.14
>3,000	1.36	1.15–1.59	1.16	0.97–1.37
P for trend		<0.001		0.179

**, Model 1 did not adjust for any covariates, while Model 2 adjusted for all covariates listed in the above table. CHD, congenital heart defect; BMI, body mass index; CI, confidence interval.

CMRD screening program, all children under 18 years of age—whether exhibiting CHD symptoms or not—were encouraged to enroll through their parents. Therefore, because several instances of CHD have been identified in asymptomatic children, our reported frequency of CHD may be slightly different than those of previous screening programs. Earlier data in nine CHD registries derived from those of specialized cardiology clinics in UK, US, and Sweden from the 1940s to the 1960s, summarized by Hoffman *et al.* found incidence rates of 3.20–6.00 cases of CHD per 1,000 live births (12). Hoffman *et al.* speculates that these early figures were inaccurately low compared to more recent median estimates of 7.00–8.00 CHD cases per 1,000 live births due to knowledge deficiencies in CHD diagnosis among pediatricians, only severe CHD cases being diagnosed and referred to cardiology clinics, and a general reluctance to establish CHD diagnoses by invasive cardiac catheterization due to the unavailability of effective diagnostic echocardiography (13). The CHD prevalence rates reported here fall slightly lower than the current median estimates of 7.00–8.00 CHD cases per 1,000 live births (13). This phenomenon may also be due to a combination of factors alluded to by Hoffman *et al.* or to underlying ethnodemographic differences in the risk of CHD in Western and Chinese populations.

In our study, we found that the CHD prevalence was higher in girls than in boys, which is consistent with reports from other Chinese provinces (14-16). Moreover, CHD prevalence was affected by ethnic status, with the Lisu (15.51 per 1,000), Achang (13.18 per 1,000), Jingpo (12.32 per 1,000), Naxi (9.68 per 1,000), and Tibetan (8.57 per 1,000) ethnicities displaying the highest CHD prevalence relative

to Han Chinese (5.19 per 1,000). Yunnan Province possesses the greatest number of ethnic groups among the provinces and autonomous regions in China (17). Minority ethnicities such as the Lisu, Achang, Jingpo, Naxi, and Tibetan typically do not fully assimilate with the Han Chinese majority population and are less likely to intermarry with other Chinese ethnicities (18); therefore, the odds of consanguineous marriages [a genetic factor contributing to CHD risk (19)] is higher in these minority ethnicities. Moreover, critical socioeconomic factors should also be taken into account; for instance, some minority groups, such as Lisu, Achang, and Jingpo, have significantly lower average incomes than Han Chinese (20). The etiologies of ethnically-based differences in CHD prevalence remain largely unstudied, so further studies should be conducted to illustrate the roles (if any) that genetic susceptibility and socioeconomic factors may play in the risk of CHD.

The most frequent CHD defect in our study was ASD, which occurred at a rate of 1.94 cases per 1,000 children. This rate was lower than in previous CHD screening programs. For example, 10.6 cases per 1,000 Chinese live births was found in 2015 (15), 3.77 cases per 1,000 Brazilian live births was found in 2003 (21), and 3.89 cases per 1,000 Canadian infants was found in 2000 (22). Our rates of ASD may be lower than these studies due to the differentiation of ASD from PFO in our analysis; if we were to merge our ASD and PFO prevalence rates together, then the resulting figure of 3.23 cases per 1,000 children more closely approximates that of previous studies.

The formation of the heart is a complicated developmental process that can be disrupted by a variety of factors, possibly leading to a structural defect (23). A particularly critical developmental period occurs from the second to eighth week of pregnancy (24). For example, contracting a viral infection or receiving medications during the first trimester increases the risk of CHD occurrence (25,26). In addition, the genetic makeup of the fetus is a known risk element for CHD, with the genetic predisposition controlled by a complex gene inheritance pattern (27). Consistent with this theory, we observed a greater predisposition to CHD in children whose mothers and fathers also possessed CHD at birth. Our study also revealed a number of maternal features that correlated positively with CHD prevalence, including advanced age, higher BMI before pregnancy, gestational diabetes, hypertension, and anemia, infection, medication, and exposure to harmful chemicals during pregnancy. These findings largely match those of a previous CHD screening study conducted in Tianjin, China (15). In particular, the relationship between diabetes and CHD risk is a complex one. The prevalence of CHD in the offspring of mothers with diabetes ranges from 3% to 5%, a significantly higher figure than in mothers without diabetes (28). Moreover, CHD survivors possess an increased risk of developing type 2 diabetes after age 30, with cyanotic CHD survivors being at particular risk (29). On a molecular level, we know that gestational diabetes induces Smad2 activation and alters endothelial growth factor expression in areas of the heart most susceptible to CHD (30). With respect to advanced age, older mothers are more likely to harbor *de novo* mutations in transcription factors regulating cardiac formation, while younger mothers have been linked to other kinds of birth anomalies (31). Unfortunately, the precise molecular pathway(s) associated with these maternal risk factor-related CHD defects remain largely unknown and require further investigation.

One interesting finding from our screening program was that the mother's degree of education influenced the prevalence of CHD. It is possible that the lower levels of socioeconomic resources typically available to children with poorly-educated mothers could lead to poorer outcomes due to inferior access to healthcare services and adequate nutrition. Likewise, lower levels of maternal education may lead to inferior lifestyle choices, such as prenatal smoking or alcohol consumption, which contribute to increased CHD risk in her offspring. That being said, improving population-based screening can help alleviate negative outcomes by improving CHD diagnosis rates in at-risk children with these characteristics.

Every child our screening identified as having CHD was referred to a cardiologist in Yunnan region for follow-up care. Out of the original 2,421 children to have been diagnosed with CHD, a total of 231 children (9.54%) perished during their 1-year follow-up period. This relatively high 1-year mortality rate may be attributable to two factors: (I) some children with CHD defects did not receive a timely diagnosis at an earlier point in their life and had progressed to a near-fatal condition at the time of screening; and (II) some families of the patients with CHD had disadvantaged socioeconomic conditions and did not have the ability to medically manage their child's condition.

This study possesses several strengths, including the large cohort size, the use of non-invasive, accurate ultrasonic color Doppler imaging that can detect even small CHD defects, and our application of rigorous statistical analyses. This study also suffers from some limitations. First, risk

factors were evaluated by a transverse study rather than a longitudinal one; therefore, it is not possible to establish causality between risk factors and CHD. Although we attempted to screen the entire population of the CMRD, a portion of children died before performance of the screen; some of these succumbed to acute severe CHD, which means that the morbidity of CHD could be underestimated. As health records become more widely digitized, we may be able to account for these cases in future analyses.

We employed non-invasive ultrasonic color Doppler imaging in a targeted screening study for CHDs among children aged 18 years and under in China's Yunnan region. Our study revealed a CHD prevalence of 6.04 per 1,000 children in Yunnan Province. We also identified several child-associated and maternal risk factors that predisposed children to a higher risk of CHDs in this population, which may help identify at-risk patients in future screening efforts.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-21-371/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-21-371/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-21-371/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study obtained approval from the Ethics Review Committees at The First People's Hospital of Yunnan Province, Kunming, China (No. KHLL2020-KY019) and Yan'an Affiliated Hospital of Kunming Medical University, Kunming, China (No. YYHKM04584). Written informed consent was obtained from all participants' parents or legal guardians prior to their enrollment.

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Supplementary

Table S1 Prevalence of various CAA defects

Airway anomaly	n	%
Bronchomalacia	38	1.57
Tracheomalacia	37	1.53
Laryngomalacia	30	1.24
Others	27	1.12

CAA, congenital airway anomalies.

Table S2 Prevalence of various genetic syndromes

Genetic syndrome	n	%
Trisomy 21	68	2.81
Other syndrome	40	1.65
Turner's syndrome	37	1.53
Holt-Oram syndrome	34	1.40
Marfan syndrome	31	1.28
Noonan syndrome	17	0.70
DiGeoge syndrome	11	0.45

Table S3 Analysis of mortality rates over 1-year follow-up period

Variable	Mortality rate over one-year follow-up	
	n	%
Sex		
Female	125/1,253	9.98
Male	106/1,168	9.08
Age at screening		
0–3 years	90/551	16.33
4–6 years	57/488	11.68
7–18 years	84/1,382	6.08
Comorbidity		
Prematurity (<37 weeks)	55/347	15.85
Cleft lip/palate	2/21	9.52
CAA	38/97	39.18
Genetic syndrome	67/238	28.15
Congenital neurological anomaly	2/3	66.67
Congenital gastrointestinal anomaly	1/2	50.00
Congenital genitourinary anomaly	0/1	0.00

CAA, congenital airway anomalies.

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