Prevalence of Congenital Heart Disease at Live Birth in China

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Objective To investigate the prevalence of congenital heart disease (CHD) in China based on a large prospective multicenter screening study.

Study design A total of 122 765 consecutive infants born at 18 hospitals throughout China between August 1, 2011, and November 30, 2012, were included. Cases of CHD were identified by echocardiography, clinical assessment, and telephone follow-up.

Results The overall prevalence of CHD was 8.98 per 1000 live births (critical, 1.46; serious, 1.47; significant, 5.00; nonsignificant, 1.07), including 7.15 in male infants and 11.11 in female infants. The most common CHD was ventricular septal defect (3.3), followed by atrial septal defect (1.7), patent ductus arteriosus (0.78), pulmonary stenosis (0.73), tetralogy of Fallot (0.47), and transposition of the great arteries (0.35). Female predominance was observed for all CHD and mild CHD (significant and nonsignificant), and male predominance was observed for the critical CHDs. The proportion of preterm newborns was substantially higher among the major CHD cases (critical and serious) compared with normal newborns. There were appreciably more low birth weight infants among the critical CHD cases compared with normal newborns. Significantly higher rates of ventricular septal defect and atrioventricular septal defect were found in infants born to mothers aged ≥35 years. Extracardiac anomalies were found in 9.3% of CHD cases. The risk of CHD was increased by approximately 3-fold when a first-degree relative had CHD.

Conclusions Our estimates are concordant with data from Western studies. This screening study may provide more accurate and complete information on the overall prevalence of CHD in China. *(J Pediatr 2019;204:53-8).*

The reported prevalence of congenital heart disease (CHD) ranges from 4 to 50 per 1000 live births.[1] The variation in prevalence is related primarily to the age at diagnosis, the definition of CHD, and the screening modalities used. The current prevalence of CHD estimates in Western countries is based on data from population-based birth defect registries.[2] However, variations in the diagnostic criteria among the participating hospitals inevitably leads to some bias in the estimates, and information about undiagnosed CHD is difficult to obtain, especially in developing countries.[3]

Previous studies investigating the prevalence of CHD in specific regions of China are not representative of the national level.[4-7] China's national congenital anomaly surveillance system obtains data from designated surveillance sites in each province; however, because of large migrant populations and the fact that diagnosis and treatment of CHD in China are disproportionately undertaken at a small number of large tertiary centers,[8] data from each designated surveillance might not be truly reflective of actual CHD prevalence. As such, the Chinese National Report on Birth Defects in 2012 reported an overall CHD prevalence in China of 4.1‰ or per 1000,[9] significantly lower than prevalence in western countries. We aimed to investigate the prevalence of CHD based on a large prospective national multicenter newborn screening study,[10] which may be more representative of the Chinese newborn population.

Methods

This was a cross-sectional observational study. A multicenter prospective screening study was conducted between August 31, 2011, and November 30, 2012, in 18 hospitals in China, including 12 hospitals in the eastern region of the country and 6 hospitals in the western region. Four were tertiary care hospitals and 14 were secondary care hospitals. These hospitals were selected as representative of birthing facilities in China. Sixteen of the 18 hospitals (89%) had echocardiography capabilities onsite,

ASD	Atrial septal defect
AVSD	Atrioventricular septal defect
CHD	Congenital heart disease
HLHS	Hypoplastic left heart syndrome
PA	Pulmonary atresia
PDA	Patent ductus arteriosus
TAPVC	Total anomalous pulmonary venous connection
TGA	Transposition of the great arteries
ToF	Tetralogy of Fallot
VSD	Ventricular septal defect

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and in the other 2 hospitals, referral for cardiology consultation in a nearby facility was immediately available as needed. All consecutive newborn babies were eligible for inclusion in the prevalence estimate.

Four types of CHD cases were included: (1) newborns with prenatally diagnosed CHD; (2) CHD cases in a symptomatic cohort (ie, those with tachypnea or cyanosis) identified using routine echocardiography; (3) CHD cases in an asymptomatic cohort (eg, without tachypnea or cyanosis) identified by pulse oximetry or clinical assessment; and (4) late-presenting CHD cases in an asymptomatic cohort identified by clinical follow-up at age 6 weeks, in combination with feedback from parents and telephone follow-up at age 1 year or later.

The following conditions were not included in the scope of CHD: (1) patent ductus arteriosus (PDA) that closed spontaneously within 3 months, (2) atrial septal defect (ASD) <5 mm in diameter after 3 months, (3) physiological pulmonary branch stenosis that had resolved at follow-up, (4) pulmonary stenosis or aortic stenosis with a pressure gradient of <20 mmHg with no further deterioration during follow-up, and (5) simple patent foramen ovale. The cardiac diagnoses were arranged in accordance with the nomenclature of the International Pediatric and Congenital Cardiac Code of the Nomenclature Working Group.[11]

Definitions of severity were essentially the same as in the previous study[12]: critical, defects causing death or needing intervention before age 28 days; serious, defects necessitating intervention before age 1 year; significant, defects persisting beyond age 6 months, but not classified as critical or serious; and nonsignificant, defects not physically appreciable and not persisting after age 6 months. We classified critical and serious cases of CHD as major CHD and significant and nonsignificant cases as minor CHD. In combined cardiac defects, either the most hemodynamically significant structural anomaly or the defect necessitating the earliest intervention was considered the predominant diagnosis.

Along with developing uniform standards, we took steps to ensure consistency in screening and diagnostic criteria across the different hospitals. Meetings were held at the launch of the screening program and at the midpoint of the program, at which time hospital leads and screening staff of the 18 participating hospitals underwent training in screening methods and diagnostic criteria. The first author continued to maintain close contact with hospitals to assess and guide the resolution of problems in the screening and diagnosis process. Adherence to screening methods and diagnostic criteria was ensured by means of unannounced inspections at the participating hospitals by the first author.

Statistical Analyses

The clinical characteristics are summarized as count and percentage, mean with SD, and median with range, depending on the type of variable. The prevalence estimates are reported per 1000 live births. Differences between groups were compared using the χ^2 test for categorical variables and the t test for continuous variables. A P value < .05 was considered significant.

This study was approved by the Ethics Committee of Children's Hospital of Fudan University. Verbal informed consent was obtained from the participating infants' parents.

Results

A total of 122 765 deliveries were eligible for our CHD prevalence analysis (54.8% males; 11.4% preterm births). Of these, 122 738 newborns were screened using the study protocol,[10] and 27 newborns with major CHD (20 critical and 5 serious) were prenatally diagnosed and verified with immediate postnatal echocardiography. The mean birth weight was 3220 ± 540 g, median gestational age was 39 weeks (range, 26-43 weeks), and echocardiography was performed at a median age of 43 hours (range, 6-72 hours).

CHD was identified in 1103 neonates (43.5% male), for an overall prevalence of 8.98 per 1000 (critical, 1.46; serious, 1.47; significant, 5.00; nonsignificant, 1.07) (**Tables I** and **II**). These cases included 457 (41.4%) with a single defect and 646 (58.6%) with multiple defects. The most common subtype of CHD was ventricular septal defect (VSD; **Table III**), at a prevalence of 3.3 per 1000, followed by ASD (1.7), PDA (0.78), PS (0.73), tetralogy of Fallot (ToF; 0.47), transposition of the great arteries (TGA; 0.35), pulmonary atresia (PA; 0.33), single ventricle (0.25), atrioventricular septal defect (AVSD; 0.23), coarctation of the aorta (0.18), total anomalous pulmonary venous connection (TAPVC; 0.18), and double-outlet right ventricle (0.16).

Table II shows a female predominance in total cases of CHD ($P < .001$) and mild CHD ($P < .001$), especially for VSD

Table I. Baseline clinical characteristics of newborns with CHD of different severities compared with those without CHD

Characteristics	CHD (N = 1103)					No CHD (N = 121 662)
	Critical (N = 179)	Serious (N = 180)	Significant (N = 613)	Nonsignificant (N = 131)	All (N = 1103)	
Males/females, n	124/55*	107/73	218/395*	32/99*	480/623*	66 790/54 872
Preterm (<37 wk), n (%)	36 (20.1)*	30 (16.7)*	75 (12.2)	17 (13.0)	158 (14.3)*	13 836 (11.4)
Birth weight <2500 g, n (%)	32 (17.9)*	17 (9.4)*	35 (5.7)	8 (6.1%)	92 (8.3)*	7421 (6.1)
Maternal age >35 y, n (%)	9 (5.0)	10 (5.6)	33 (5.4)	6 (4.6)	58 (5.3)	5718 (4.7)
Family history of CHD, n (%)†	0	2 (1.1)	1 (0.16)	0	3 (0.27)	99 (0.08)
Extracardiac anomalies, n (%)	29 (16.2)*	33 (18.3)*	39 (6.4)*	1 (0.76)*	102 (9.2)*	128 (0.11)

*$P < .05$ compared with newborns without CHD.
†First-degree relative (parent or siblings).

Table II. Spectrum of the 1103 cases of CHD and their corresponding severities

Predominant defect	Description	Number*	Severity†
ASD	Remained >5 mm after 6 mo	144	C
	<5 mm or spontaneously closed within 6 mo	63	D
VSD	Underwent surgery or died within 12 mo	40	B
	Untreated within 12 mo (mild)	318	C
	Spontaneously closed within 6 mo	44	D
PDA	Underwent surgery during the neonatal period	7	B
	Spontaneously closed after 3-6 mo	18	D
	Remained open after 6 mo	71	C
AVSD	NA	28 (3 PD)	B
Pulmonary stenosis	Underwent surgery during the neonatal period	10	A
	Underwent surgery or catheterization within 1-12 mo	10	B
	Existed but was untreated at 12 mo	70	C
ToF	Underwent surgery during the neonatal period	10 (1 PD)	A
	Underwent surgery or died between 1 and 12 mo	48 (2 PD)	B
Truncus arteriosus	Underwent surgery during the neonatal period	5	A
	Underwent surgery or died between 1 and 12 mo	3	B
SV (+complex)‡	Underwent surgery or died during the neonatal period (5 TA)	21 (10 PD)	A
	Underwent surgery or died between 1 and 12 mo (2 TA)	10	B
PA/VSD	Underwent surgery or died during the neonatal period	24 (3 PD)	A
	Underwent surgery or died between 1 and 12 mo	4	B
PA/IVS	NA	12	A
TGA	TGA/VSD	26 (5 PD)	A
	TGA/IVS	17	A
DORV (+complex)	Underwent surgery or died during the neonatal period	9	A
	Underwent surgery or died within 1-12 mo	11	B
Ebstein	With no clinical signs or symptoms	2	C
	With clinical signs and symptoms	7	B
HLHS	NA	10 (3 PD)	A
CoA (+complex)	Underwent surgery during the neonatal period	7	A
	Underwent surgery between 1 and 12 mo	7	B
	Untreated within 12 mo (mild)	8	D
IAA	NA	6	A
TAPVC	Underwent surgery during the neonatal period	19	A
	Underwent surgery between 1 and 12 mo	3	B
Aortic stenosis	Underwent catheterization during the neonatal period	3	A
	Underwent surgery or catheterization within 12 mo	2	B
	Untreated within 12 mo (mild)	6	C

CoA, coarctation of the aorta; *DORV*, double-outlet right ventricle; *IAA*, interruption of the aortic arch; *IVS*, intact ventricular septum; *NA*, not available; *PD*, prenatal diagnosis; *SV*, single ventricle.
*Based on the number of affected newborns.
†Classification of severity: A, critical; B, serious; C, significant; D, nonsignificant.
‡Includes mitral atresia, tricuspid atresia, double-inlet left ventricle, double-inlet right ventricle, and heterotaxia syndrome.

($P < .001$), ASD ($P < .001$), and PDA ($P < .001$). A male predominance was seen in cases of critical CHD ($P < .001$), especially for ToF ($P = .003$) and TGA ($P = .02$). The proportion of preterm births (gestational age <37 weeks) was substantially higher among the newborns with major CHD (critical and serious) compared with those without CHD ($P = .001$ and 0.021, respectively), especially in cases of AVSD ($P < .001$), TAPVC ($P = .001$), hypoplastic left heart syndrome (HLHS; $P = .015$), and PA ($P = .002$). The prevalence of low birth weight infants (<2500 g) was appreciably higher in the patients with critical CHD ($P < .001$), and low birth weight was significantly associated with TGA ($P < .001$), TAPVC ($P < .001$), HLHS ($P < .001$), and PA ($P = .008$). A higher prevalence of maternal age ≥35 years was found in all infants with CHD as a group, although the difference was not statistically significant. The prevalences of VSD ($P = .017$) and AVSD ($P = .004$) were significantly higher with a maternal age ≥35 years. In total, 102 affected infants (9.3%) had an extracardiac anomaly, including 30 with cleft lip, 24 with polydactyly, 17 with external ear malformation, 15 with ankylodactylia, 9 with hypospadias, 4 with neural tube defects, 2 with esophageal atresia, 2 with anal atresia, and 1 with gastroschisis. Three newborns with CHD had at least 1 first-degree relative with similar conditions (OR, 3.36; 95% CI, 1.07-10.63).

Discussion

Although the Chinese government began to monitor birth defects in 1986,[8] it is difficult to obtain convincing epidemiologic data regarding CHD prevalence using the national birth defects surveillance system, for several reasons. First, the detection rate of CHD can be greatly affected by variations in definitions, selection criteria, diagnostic methods, and skills of physicians at the different participating hospitals.[13] Second, the narrow window in which diagnosis usually occurs (mostly within 7 days after delivery) makes it difficult to identify CHDs with symptoms that develop after discharge.[6] Third, echocardiography is not available in most birthing facilities, and the data for newborns with suspected CHD who were transferred to another medical center for diagnosis were not

Table III. Prevalence of CHD by sex, gestational age, birth weight, and maternal age

Characteristics	All CHD	Left-to-right shunts				Cyanotic CHD						Left heart obstructive defects				Right heart obstructive defects	
		VSD	ASD	PDA	AVSD	ToF	TGA	SV	DORV	TAPVC	Truncus	Ebstein	CoA	AS	HLHS	IAA	PS	PA
Number	1103	402	207	96	28	58	43	31	20	22	8	9	22	11	10	6	90	40
Prevalence†	89.8	32.7	16.9	7.8	2.3	4.7	3.5	2.5	1.6	1.8	0.7	0.7	1.8	0.9	0.8	0.5	7.3	3.3
Males/females	481/622	155/247*	74/133*	31/65*	13/15	39/19*	31/12*	19/12	10/10	11/11	4/4	4/5	11/11	6/5	6/4	2/4	43/47	22/18
Preterm/term	159/944	47/355	30/177	17/79	10/18*	3/55	7/36	3/28	5/15	8/14*	0/8	0/9	2/20	0/11	4/6*	0/6	12/78	11/29*
Birth weight <2500 g/≥2500 g	93/1010	29/373	15/192	10/86	3/25	0/58	9/34*	3/28	0/20	6/16*	1/7	0/9	0/22	0/11	4/6*	2/4	4/86	7/33*
Maternal age <35 y/≥35 y	60/1043	30/372	7/200	2/94	5/23	1/57	3/40	2/29	0/20	2/20	0/8	0/9	1/21	0/11	2/8	1/5	1/89	3/37

AS, aortic stenosis; *PS*, pulmonary stenosis.
*$P < .05$ compared with newborns without CHD.
†Estimated prevalence per 10 000 live births.

documented by the surveillance system. Given these factors, the surprisingly low prevalence of CHD (1.7-5.2 per 1000) derived from the surveillance system data in China is understandable.[5,6,9] Despite this, based on our previous study,[14] the total prevalence of CHD and the prevalence of clinically detectable CHD in Shanghai were 26.6 per 1000 and 12.1 per 1000, respectively. However, data from the National Birth Defects Report covering the same period reported a CHD prevalence of 2.7 per 1000 in urban areas.

Compared with previous studies in China,[4-7] this study overcame the aforementioned limitations by conducting a large prospective multicenter screening program in 18 participating hospitals located in geographically diverse regions of urban and rural China and included both tertiary and secondary facilities, eliminating referral bias. The accuracy of our screening method has been proven to be satisfactory.[10] More importantly, neonates who screened negative were followed up via telephone at or beyond 1 year of age. Extensive follow-up modalities allowed us to obtain true prevalence values in our study population.

The overall CHD prevalence in our study (8.98 per 1000) is generally consistent with that reported in other studies.[15-19] As previous studies have suggested, the variation in CHD prevalence has been attributed to cases of minor CHD, but the prevalence of severe CHD remained stable.[1] However, several studies found that with increases in prenatal detection of CCHD and abortions, the prevalence of CCHD in live births decreased.[19-21] In contrast, Pfitzer et al found a growing number of cases of registered major CHD in Germany over the last decade.[22]

The rate of major CHD in this study was 7.5% (27 per 359), and there were no cases in which the pregnancy was terminated. Therefore, we speculate that, at least in the near future, prenatal diagnosis will not have a significant effect on the prevalence of CHD and major CHD. Our study also found a prevalence of critical CHD (1.46 per 1000) close to that reported in an echocardiographic screening study (1.16 per 1000)[14] and in studies from Taiwan (1.42 per 1000)[19] and Western countries (1.30-1.56 per 1000).[16,18,23] In contrast, the prevalence of mild CHD in the echocardiographic screening study was much higher than our findings (17.70 per 1000 vs 6.04 per 1000). Consistent with other studies,[2,15,16,18,19] the 3 most common CHDs that we observed were VSD, ASD, and PDA. We found more right-side obstructive lesions and fewer left-side obstructive lesions than reported in Western studies,[15,16,18] a difference that may be explained by genetic differences or by different environmental exposures.

The sex-related CHD patterns identified in our study are similar to those reported in the literature.[15,16,18] Most report that males are more likely to have critical CHD, whereas females are more likely to have mild CHD. We also found slightly higher prevalences of TGA and ToF in males and of ASD, PDA, and VSD in females. Although no statistically significant association was found between maternal age ≥35 years and any of the CHD severity categories, a significantly increased risk with advanced maternal age was observed for VSD and AVSD. These findings are consistent with those of other studies.[15,23]

Previous studies have reported that the prevalence of CHD in preterm infants is 2-3 times that seen in term infants.[24] We also observed this significant association (OR, 1.3), which was even more obvious in the infants with critical and serious CHD (OR, 2.0 and 1.6, respectively). We further noted that the patients with AVSD, TAPVC, HLHS, and PA were more frequently born preterm compared with patients with other types of CHD, confirming previous observations.[15] Low birth weight, which is associated with prematurity, was also more common in the total CHD group and those with critical CHD (OR, 1.4 and 3.4, respectively), corresponding with the results of other studies.[25,26]

Extracardiac abnormalities have been reported in approximately 20% of CHD cases[27,28]; however, the incidence in our study is lower (9%), possibly because CHD was assessed early in our sample (within 72 hours of age), and extracardiac abnormalities identified after discharge were not included in our data. Nonetheless, the most common associated extracardiac abnormalities observed in this investigation were nearly identical with the findings of other studies.[27,28]

Although our findings accurately reflect the prevalence of CHD in 122 738 neonates and to some extent represent a diverse population within China, it is still not a population-based study, which is the ideal research method for an epidemiologic study. However, carrying out a population-based study throughout China would be extremely difficult because data are typically inaccessible between institutions for infants who may be seen at multiple hospitals. In addition, there is no national congenital anomaly registry, and autopsy data are not available to verify causes of infant death possibly related to CHD. We hope that the National Congenital Anomaly Registry can cooperate with pediatric cardiac centers and increase the detection rate of later-presenting CHD cases to obtain more complete epidemiologic data.

At present, the standard of CHD diagnosis and treatment in China has reached the level seen in developed countries. Many coastal cities and provinces have established CHD screening, treatment, and surveillance networks. However, due to disparities in economic and medical resources, many children with CHD in deprived areas in western China are still not diagnosed and treated in a timely manner.[13] We recommend that the National Health Commission develop policies to address the epidemiology of CHD in deprived areas of western China to better allocate medical resources and to develop local training programs to screen and diagnosis CHD in these areas. A national CHD screening network and a so-called "green channel" network are also needed to improve the diagnosis rate of CHD in these areas and to establish follow-up and treatment plans. With the implementation of these recommendations, morbidity and mortality due to CHD can be reduced at the national level.[29] ■

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50 Years Ago in *The Journal of Pediatrics*

Detection of Bacteriuria in Children

Dodge WF, West EW, Fras PA, Travis LB. J Pediatr 1969;74:107-10.

Kunin et al[1] found the point prevalence of asymptomatic bacteriuria to be 1.1% in girls and 0.04% in boys among nearly 10 000 schoolchildren in Virginia. Further long-term studies showed that girls having asymptomatic bacteriuria in the past were at high risk of developing symptomatic infection later, and those having recurrences of bacteriuria post-treatment were at risk of pyelonephritis. This prompted clinicians to advocate screening programs to detect asymptomatic bacteriuria in girls. Fifty years ago, Dodge et al assessed the screening ability of a miniature culture method, testuria, in detecting bacteriuria and considered it to be a good tool for the periodic screening of schoolgirls and pregnant women. This paper was considered timely, with implications on policy and practice for detecting asymptomatic bacteriuria, especially in girls.

Later, Savage et al[2] reported that it was rare for the children with covert (asymptomatic) bacteriuria to develop symptoms of acute urinary tract infection/pyelonephritis or progress to severe renal disease. They raised concern regarding the justification for prescriptive screening for covert bacteriuria and remarked that therapy may well have little effect on what would be a relatively benign disease. The question regarding the need for screening for asymptomatic bacteriuria remained controversial, and even as late as in the 1990s, there was no clarity about the utility of screening or treating. The issue was settled by a Cochrane review published in 2012 that concluded that there was no evidence that covert bacteriuria affected kidney growth in radiologically normal kidneys in the absence of antibiotic prophylaxis.[3] The American Academy of Pediatrics also recommends against routine screening for asymptomatic bacteriuria in children because it is caused by bacterium of low virulence that colonizes the urinary tract and does not damage the kidney. Asymptomatic bacteriuria should not be treated, as this may do more harm than good. The current concept regarding asymptomatic bacteriuria thus is a complete U-turn from the concept published 50 years ago.

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