Incidence and Risk Factors of Congenital Heart Disease in Qingdao: A Prospective Census Study

Xiao Jin  
Qingdao University

Wei Ni  
Qingdao Women and Children's Hospital

Guoju Li  
Qingdao Women and Children's Hospital

Guolan Wang  
Qingdao Women and Children's Hospital

Qin Wu  
Qingdao Women and Children's Hospital

Jun Zhang  
Qingdao Women and Children's Hospital

Na Jiao  
Qingdao Women and Children's Hospital

Wenjing Chen  
Qingdao University

Qing Liu  
Qingdao University

Li Gao  
Qingdao University

Quansheng Xing  
xingqs0532@163.com  
Qingdao Women and Children's Hospital

Research article

Keywords: congenital heart disease, epidemiological analysis, incidence, prospective, birth defect

DOI: https://doi.org/10.21203/rs.3.rs-74090/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Background The incidence of congenital heart disease (CHD) were greatly inconsistent among many studies with a range from 4/1,000 to 50/1,000. A large prospective population study was performed to investigate the incidence and find risk factors of congenital heart disease (CHD) during fetal and neonatal period.

Methods A prospective cohort study was conducted in Qingdao, China, from August 1, 2018 to April 30, 2019. All local registered pregnant were continuously investigated and followed from the first trimester to delivery, collecting the characteristics of pregnant and their newborns. A Poisson regression model was applied to assess the association between CHD and possible risk factors.

Results The incidence of fetal CHD and neonatal CHD are 15.84 per 1000 fetuses and 7.32 per 1000 live births, respectively. Results from Poisson regression indicated that, countryside (0.821; 95% CI, 0.730-0.920) and first gestation (0.890; 95% CI, 0.813-0.975) was negatively associated with CHD. However, paternal factors such as multi-fetal infants (RR: 1.631, 95% confidence interval, CI: 1.276-2.036), greater than high school degree (1.390; 95% CI, 1.129-1.701), illness in 1st trimester (1.214; 95% CI, 1.080-1.359), family history of CHD (2.480; 95% CI, 1.362-3.967), and having a baby with birth defect before (1.780; 95% CI, 1.300-2.345) were positive associated with CHD.

Conclusion The incidence of CHD in Qingdao was similar to existing research. Compared with neonate, the incidence of CHD is higher in fetal. Multi-fetal infants, greater than high school degree, illness in 1st trimester, family history of CHD and having a baby with birth defect before were correlated with an increased risk of CHD. This prospective study would provide great implications for on CHD intervention.

Introduction

Congenital heart disease (CHD) is typically defined as a structural abnormality of the heart and/or great vessels during the embryonic period, also known as congenital heart malformation.\textsuperscript{1} Since the beginning of the 21st century, CHD has been the most frequent form of congenital anomaly in newborn infants all over the world, which accounted for one-third of all anomalies with high mortality.\textsuperscript{2} Updated systematic review and meta-analysis of 260 studies revealed that between 1970 and 2017, the prevalence of CHD globally increased by 10% every 5 years.\textsuperscript{3}

Until now, many studies have been conducted to assess the incidence of CHD, however, results were greatly inconsistent among these studies with a range from 4/1,000 to 50/1,000.\textsuperscript{4} In Japan, researchers described the prevalence of circulatory system malformations that was 3.6/1,000 births, from a prefecture-wide hospital-based birth cohort at the beginning of 12 weeks gestation.\textsuperscript{5} In North America, a prevalence of 6.9 per 1,000 live births (95% CI: 6.7–7.1) was reported in the CHD cases.\textsuperscript{2} Recently, CHD was identified in 1103 neonates, with an updated overall prevalence of 8.98 per 1000 in 18 hospitals in China, including the eastern and western regions.\textsuperscript{6} In addition, it revealed that the difference of CHD
incidence in different areas may be attributed to geographical, demographic, socio-economic variations. Genetic and environmental factors are the two most important factors independently affecting the risk of CHD. Strikingly, more and more data revealed the different incidences of CHD in different areas. We think that the main reason why these incidences of CHD were different maybe attributed to study methods, just as sampling monitor, which could make bias obtaining the inaccurate data. However, in order to assess the accurate incidence of CHD, we conducted a municipal census and prospective cohort study, involving all the pregnant women in Qingdao.

To our best knowledge, this has been the first study evaluating the incidence of CHD and detecting associated risk factors through a census and prospective cohort study. Additionally, we achieved a full time tracking for CHD, from the first trimester to the neonatal stage. This prospective study would improve the knowledge of CHD in China, and provide great implications for CHD intervention.

Methods

Study design and data collection

Data collection

The prospective census-based cohort was defined as a birth cohort enrolling all registered pregnant women (15-20 weeks of gestation) during August 1, 2018 and April 30, 2019 in Qingdao. All these registered pregnant women were observed continuously from the first trimester to newborn, to track the fetus and newborn CHD cases. The study is carried out by Qingdao Municipal Center for Birth Defect Control and Prevention (QMCBDCP), and Qingdao Women and Children's Hospital (QWCH). We used the dataset of the cohort from August 1, 2018 to April 30, 2019, enrolling 64763 registered pregnant women in 15-20 weeks of gestation. Pregnant women use their ID number as the unique identification number linking information in different stages of gestation. Antenatal care is provided by the maternal and child health care system. This system includes 64 delivery hospitals, 65 prenatal screening blood collection hospitals, 10 district-level women and children's health centers and a municipal women and children's health care center (Qingdao Women and Children's Hospital). Qingdao Women and Children's Hospital is the coordination institution of the Women and Children's Health Care System. The 65 prenatal screening blood collection hospitals are the antenatal care providers (Down's screening-a test for prenatal detection of Trisomy 21 (Down's syndrome)) for pregnant women. This system includes detailed information about all pregnant women in Qingdao until their delivery.

Definitions

In our study, we identified all CHD cases from fetus to birth. All fetal CHD cases are diagnosed by fetal ultrasound scan, and neonatal CHD cases are diagnosed by echocardiography, cardiac catheterization and magnetic resonance angiography (MRA) in need. Prenatal cardiac ultrasound allows identification of most types of congenital heart disease in second trimester. The screening of perinatal infants for CHD is conducted by the obstetric and pediatric professionals. Generally, Pulse oximetry
screening, clinical observation, physical examination and echocardiography detect are the main methods to confirm CHD in newborns, but auxiliary examinations such as X-ray, electrocardiography, are applied when necessary. A fractional (as opposed to functional) oxygen saturation of $\geq 94\%$ was accepted as normal.\textsuperscript{14-16} A suspected case is defined as any newborns with SpO2 (Saturation) <94% in room air or visible cyanosis, abnormal fetal echocardiography, unexplained congestive heart failure, murmur, abnormal ECG, abnormal heart sounds, abnormal blood pressure, differential peripheral pulses, and abnormal chest x-ray. The accuracy of our screening method has been proven to be satisfactory.\textsuperscript{17} Isolated interatrial shunt (including secundum atrial septal defects and patent foramen ovale), patent ductus arteriosus among fetal and neonates <28 days of life were excluded because they are normal fetal and neonatal findings. This study was approved by the Ethics Commission of Qingdao Women and Children's Hospital (QFFLL-KY-2020-11) and written informed consent was obtained from involved patients prior to enrollment. To minimize bias among hospitals, investigators and echocardiographers, we provide systematic training for the staffs committed to the survey.

**Data statistical analysis**

Continuous and categorical variables were presented as mean (standard deviation, SD) or median (interquartile range, IQR) where appropriate. In order to detect the independent factors of CHD, the univariate and multivariate analysis were performed. Mann-Whitney U test, Chi-square test or Fisher's exact test were first conducted with a total of 16 factors between CHD and no CHD groups. Poisson regression model was then performed with significant factors selected by univariate analysis to test out the independent factors for CHD. The association between independent factors and CHD was quantified by relative risk (RR). Meanwhile, sensitivity analysis was conducted to guarantee robust results through logistic analysis. A p value less than 0.05 (two-tailed) was considered statistically significant. Analysis was performed using R software (version 3.6.2).

**Results**

**Characteristics of included population**

Of the total of 64,763 pregnant with 15-20 weeks of gestation at the time of entry into the cohort, we were able to identify 805 (1.24%) pregnant with termination of pregnancy, abortion or stillbirth, and 63,844 (99.82%) of pregnant delivering newborns. Outcome from 114 (0.18%) of pregnant were missing in the neonatal stage. The median age of pregnant was 30.62 years old (IQR:28-33), the median age of partner was 31.59 years old (IQR:28-35). Detailed characteristic information and significant P value of factors was represented in Table 1.

**Outcome**

Among all pregnant, 1,026 were identified as abnormal fetal echocardiogram, and a fetal CHD incidence was calculated as 15.84 per 1000 fetuses. 114 of them chose to terminate their pregnancy due to fetal CHD, and 912 of them delivered the newborns. Of the 912 delivered newborns, there were 426 live births
diagnosed as CHD, and 372 were diagnosed as CHD, followed by 114 without data of outcome. Moreover, of the 63,958 live births, 468 newborns were diagnosed as CHD, including 426 cases identified in fetal stage and 42 cases only identified in birth. The neonatal CHD incidence was 7.32 per 1000 live births. The detailed outcome information from fetal to neonatal stages was shown in Figure 1.

Among all the CHD cases, including fetuses and newborns, the incidence of CHD was classified by ICD-11. As shown in Table 2, the CHD cases were classified to thirty categories, based on separately groups of fetuses, terminations and newborns. The predominant types of CHD in fetal stage were congenital tricuspid regurgitation (29.43%), ventricular septal defect (26.71%), multiple structural developmental anomaly of heart or great vessels (8.19%), and vascular ring (7.50%). In neonatal stage, the predominant types of CHD were ventricular septal defect (34.40%), congenital tricuspid regurgitation (18.80%), multiple structural developmental anomaly of heart or great vessels (13.25%), and vascular ring (11.54%). The main types of CHD in termination were multiple structural developmental anomaly of heart or great vessels (24.56%), Tetralogy of Fallot (16.67%), ventricular septal defect (10.53%) and Structural developmental anomaly of heart or great vessels, unspecified (8.77%). The incidence of the main tapes of CHD in fetal and neonatal stage are shown directly in Figure 2.

Factors associated with CHD

We evaluated the effect of each factor on CHD by Mann-Whitney U test, Chi-square test or Fisher’s exact test. Fetus, BMI (Body Mass Index) and educational level of pregnant women, living location, assisted reproduction, fertility history and the number of pregnancy, any illness in 1st trimester pregnancy, history of having a child with birth defects, history of birth defect in pregnant women, family history of birth defect and CHD, folic acid intake, history of husband smoking before pregnancy were significantly related to CHD . Multivariate Poisson regression was then performed with the significant factors selected by univariate analysis. Poisson regression model was then performed with significant factors selected by univariate analysis to test out the independent factors for CHD. Figure 3 summarized the results of multivariate analysis, which showed that multi-fetal infants (RR: 1.631, 95% CI: 1.276-2.036), greater than high school degree (RR: 1.390; 95%CI: 1.129-1.701), illness in 1st trimester (RR: 1.214; 95% CI: 1.080-1.359), family history of CHD (RR 2.480; 95% CI: 1.362-3.967), and having a baby with birth defect before (RR: 1.780; 95% CI: 1.300-2.345), countryside (RR: 0.821; 95% CI: 0.730-0.920) and first gestation (RR: 0.890; 95% CI: 0.813-0.975) were independently associated with CHD, suggesting that multi-fetal infants, high school degree or college degree, illness in 1st trimester, family history of CHD and having a baby with birth defect before would increase the risk of CHD but countryside and first gestation decreasing the risk.

Sensitivity analysis was conducted to guarantee robust results. As shown in Figure 4, the logistic regression analysis was performed to quantify the association between these significant factors detected by univariate analysis and CHD event.

Discussion
Previous studies from different areas in China have reported various incidence of CHD, which ranged from 6.87 to 76.00 per 1000 children.\(^5,18–23\) To our best knowledge, this has been the first time that performed a prospective census-based cohort study investigating all local pregnant and their newborns to respectively evaluate incidence and type of CHD during fetal and neonatal period, and analyze the potential risk factors, which provides new knowledge of CHD control and prevention. Our study indicates that the incidence of CHD in fetuses is twice for that in newborns. Of the 64,763 participants, 1,026 (15.84‰) had fetal congenital heart disease. Of the 63,958 live births (including 114 newborns of missing birth record), 468 (7.32‰) newborns were diagnosed CHD. The highest incidence of fetal CHD is congenital tricuspid regurgitation accounting for 29.43% (304/1,026), followed by malformations of ventricular septal defect 26.71% (274/1,026). However, the highest incidence of neonatal CHD is ventricular septal defect 34.40% (161/468), followed by congenital tricuspid regurgitation 18.8% (88/468). The type with highest incidence in our study is consist with the previous reported by Egbe A, et al.\(^5\) However, the type with second high incidence is different, which is atrial septal defect detected by Egbe A. For this difference, the main reason maybe that isolated patent foramen ovale and patent ductus arteriosus are excluded in our study because they are normal neonatal findings during fetal and neonatal period. Compared with previous studies, our study could evaluate more accurate incidence of CHD on the basis of conducting the prospective census-based cohort study. The higher incidence of CHD in fetuses than newborns, indicates that prenatal screening and diagnosis are significantly important for CHD control and prevention. Moreover, our findings provide some important implications for the prevention and management of CHD. First of all, abortion and stillbirth should be extremely concerned for pregnant with critical CHD fetuses. Moreover, it should be avoided that pregnant with light and mild cardiac abnormality select termination. Last but not least, even if fetuses identified as CHD, they still have a chance to become health when they are born, due to the subsequent development of tissues and organs. Overall, fetal CHD screening is very important for the early detection and intervention of CHD.

As previous studies have suggested, the variation in CHD incidence was attributed to cases of minor CHD, but severe CHD remained stable.\(^4\) In our report, 114 of 1,026 pregnant women with fetal CHD chose to terminate their pregnancy. CHD classified as simple, moderate, complex. Among these terminated cases, sample CHD cases, moderate and complex CHD accounted for 24.56% (28/114 fetuses), 17.54% (20/114 fetuses), 49.12% (56/114 fetuses) respectively. 10 of 114 terminated cases were cardiac abnormal but not identify the type of fetal CHD. Meanwhile, the vast majority of fetuses with congenital tricuspid regurgitation are more likely to repair itself when they are born, as well as about half of fetuses with ventricular septal defects. Additionally, there were 42 newborns with CHD who have no cardiac abnormality during the fetal period. It indicated that the screening of fetal echocardiography in CHD may cause missed diagnosis and overdiagnosis, which may lead to over induction. In our country, most pregnant women and families lack of the knowledge of CHD, reacting strongly to CHD in pregnancy, and eventually chose to give up due to severe psychological burden. Actually, several induction cases including congenital tricuspid regurgitation, small ventricular septal defects and left superior caval vein, maybe self-heal or effectively cured by surgery in later stage, and do not affect quality of life. For these
pregnant with fetal CHD, the ethics committee should strengthen management and strictly control the blind choice of induction.

We observed that pregnant women who have given birth to a child before have effect on the occurrence of CHD have less risk of having CHD in their offspring in comparison to the pregnant women who has never had a child before. (RR: 0.890; 95% confidence interval, CI, 0.813–0.975). We suspected that pregnant women who have given birth to a child before have more experience to take care of themselves in terms of diet, health and pre-pregnant check during pregnancy. Those pregnant women or their relatives had history of congenital heart disease increase odds ratio of having CHD in their offspring (RR, 2.480; 95% CI, 1.362–3.967), which is similar to the study done by Yokouchi-Konishi T, et al. Some studies showed no association between maternal education level with CHD. However, others have found that the occurrence of CHD was inversely associated with the mother's education level, and that there was a dose–response relationship between them. In our study, as compared with maternal educational level group less than high school degree, in maternal educational level group high school or college degree, odds of having CHD is 1.342 (RR, 1.390;95% CI, 1.129–1.701). In China today, adolescents are becoming much more sexually liberated. Premarital sex and unplanned pregnancies among teenagers are increasing, especially in the group of high school degree or college degree, thereby indirectly raising the occurrence of CHD. These findings also highlight the need to improve the healthcare and sex educational opportunities for teenagers, particularly for those with high school or college education. We found that those pregnant women who live in countryside induce odds ratio of having CHD in their offspring (RR, 0.821; 95% CI, 0.730–0.920). The main reason may be the complex industrial/urban scenario emission such as SO2. If pregnant women are influenced by environmental factors during this period (early trimester of pregnancy), the fetus easily suffers from CHD. In this study, we conduct a prospective cohort study of pregnant women and find that the odds of having CHD to be 1.214 (RR, 1.215;95% CI, 1.080–1.359) with a history of illness in 1st trimester, which is similar to the study done by Liang Q, et al. Poisson regression analysis indicated that twin and multi-fetal infants are more likely to suffer from CHD than singleton infants (RR: 1.631, 95% CI: 1.276–2.036). The study can examine the risk of CHD in twins compared with singletons. This is consistent with the study done by Best, K. and J. Rankin. Our study found that the relative ratio of having CHD to be 1.780 (95% CI, 1.300-2.345) with birth defect in the firstborn child. The results indicate that the increased risk of CHD not only associate with the history of having a CHD sibling, but also with the history of having a birth defect sibling. Possible explanations for increased CHD risk in siblings of children with birth defect include shared genes, shared environmental factors, or a combination.

Due to the registration process of the total pregnant women in Qingdao, we need multi-center cooperation to complete information collection throughout their pregnancy. There are more than 60 prenatal ultrasound institutions and many ultrasound physicians in the city. Owing to the widely different levels of experience of examiners, there is a large discrepancy in study results of second trimester ultrasound screening for fetal malformations, which is a result of varying levels of obstetric scanning expertise prevalent at the reporting center.
Conclusions

In conclusion, CHD among fetuses and infants are serious health problem in Qingdao, China, and the incidence of CHD was similar to existing research in Qingdao. Compared with neonate, the incidence of CHD is higher in fetal. Multi-fetal infants, greater than high school degree, illness in 1st trimester, family history of CHD and having a baby with birth defect before were correlated with an increased risk of CHD. Moreover, the risk factors were identified in our study, and our findings may have great implications of public health policy for CHD intervention in China.

List Of Abbreviations

CHD
congenital heart disease, QMCBDCP = Qingdao Municipal Center for Birth Defect Control and Prevention, QWCH = Qingdao Women and Children's Hospital, MRA = magnetic resonance angiography, SD = standard deviation, IQR = interquartile range, BMI = Body Mass Index, CI = confidence interval, RR = Relative ratio, NSFC = The National Natural Science Foundation of China

Declarations

Ethics: This study was approved by the Ethics Commission of Qingdao Women and Children's Hospital (QFFLL-KY-2020-11) and written informed consent was obtained from involved patients prior to enrollment.

Consent for publication: All authors provided critical feedback and approved the publication.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

Conflict of Interest: none declared.

Funding: This work was supported by The National Natural Science Foundation of China (NSFC) [Grant number 81770315]; and Distinguished Taishan Scholars (2019).

Author Contributions: Q-SX, WN and G-JL designed the study and conceptualised the paper. XJ, WN, G-JL, G-LW, QW, JZ, NJ, WJC, QL and LG collected the epidemiological and clinical data. XJ summarised the data and conducted statistical analysis. XJ, WN and G-JL wrote the initial draft of the manuscript. All authors provided critical feedback and approved the final version. The corresponding author has full access to all data in this study and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Acknowledgement: We are deeply thankful to all workers involved in data collection and diagnosis of fetuses in Qingdao.
References

1. Qiang S. Cardiothoracic surgery. In: Ning S, Shan Z, editors. Pediatric surgery (in Chinese). China: People's medical publishing house; 2015. P. 541-604.

2. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011; doi: 10.1016/j.jacc.2011.08.025.

3. Liu Y, Chen S, Zühlke L, Black GC, Choy M-k, Li N, et al. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol 2019; doi: 10.1093/ije/dyz009.

4. Hoffman JI, Kaplan S. The incidence of congenital heart disease. Journal of the American College of Cardiology 2002; doi: 10.1016/s0735-1097(02)01886-7.

5. Hanaoka T, Tamura N, Ito K, Sasaki S, Araki A, Ikeno T, et al. Prevalence and risk of birth defects observed in a prospective cohort study: The Hokkaido study on environment and children's health. J Epidemiol 2018; doi: 10.2188/jea.JE20160108.

6. Zhao Q-M, Liu F, Wu L, Ma X-J, Niu C, Huang G-Y. Prevalence of congenital heart disease at live birth in China. J Pediatr 2019; doi: 10.1016/j.jpeds.2018.08.040.

7. Egbe A, Lee S, Ho D, Uppu S. Effect of race on the prevalence of congenital malformations among newborns in the united states. Ethnicity & disease 2015; 25(2): 226-231.

8. Gelb BD, Chung WK. Complex genetics and the etiology of human congenital heart disease. CSH PERSPECT MED 2014; doi: 10.1101/cshperspect.a0139539.

9. Liu S, Liu J, Tang J, Ji J, Chen J, Liu C. Environmental risk factors for congenital heart disease in the Shandong Peninsula, China: a hospital-based case–control study. J EPIDEMIOL 2009; doi: 10.2188/jea.JE20080039

10. Mir A, Jan M, Ali I, Ahmed K, Radhakrishnan S. Congenital heart disease in neonates: Their clinical profile, diagnosis, and their immediate outcome. 2019; doi: 10.4103/heartindia.heartindia_3_19.

11. Prakash A, Torres AJ, Printz BF, Prince MR, Nielsen JC. Usefulness of Magnetic Resonance Angiography in the Evaluation of Complex Congenital Heart Disease in Newborns and Infants. Digest of the World Core Medical Journals 2007; doi: 10.1016/j.amjcard.2007.03.090.

12. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA; Sklansky MS; Abuhamad A; et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation 2014; doi: 10.1161/01.cir.0000437597.44550.5d.

13. Wong KK, Fournier A, Fruitman DS, Graves L, Human DG, Narvey M et al. Canadian Cardiovascular Society/Canadian Pediatric Cardiology Association position statement on pulse oximetry screening in newborns to enhance detection of critical congenital heart disease. Canadian Journal of Cardiology 2017; doi: 10.1016/j.cjca.2016.10.006.

14. Hiatt PW, Mahony L, Tepper RS. Oxygen desaturation during sleep in infants and young children with congenital heart disease. The Journal of pediatrics 1992; doi: 10.1016/s0022-3476(05)81193-x.
15. Reddy VK, Holzman IR, Wedgwood JF. Pulse oximetry saturations in the first 6 hours of life in normal term infants. Clin Pediatr 1999; doi: 10.1177/000992289903800204.

16. Usen S, Weber M, Mulholland K, Jaffar S, Oparaugo A, Omosigho C, et al. Clinical predictors of hypoxaemia in Gambian children with acute lower respiratory tract infection: prospective cohort study. BMJ 1999; doi: 10.1136/bmj.318.7176.86.

17. Liu WT, Ning SB, Hua BJ, Chen YT, Zhou SY, Guo AL, et al. The incidence and characteristics of children's congenital heart disease in Yangpu and Xuhui districts of Shanghai (in Chinese). Chin J Pediatr 1995; doi: 10.1007/s00246-005-0981-9.

18. Liu WT, Ning SB, Hua BJ, Chen YT, Zhou SY, Guo AL, et al. The incidence and characteristics of children's congenital heart disease in Yangpu and Xuhui districts of Shanghai (in Chinese). Chin J Pediatr 1995; doi: 10.1007/BF02007173.

19. Qu Y, Liu X, Zhuang J, Chen G, Mai J, Guo X, et al. Incidence of congenital heart disease: the 9-year experience of the Guangdong registry of congenital heart disease, China. PloS one 2016; doi: 10.1371/journal.pone.0159257.

20. Yang M, Zhang S, Du Y. Epidemiology characteristics of birth defects in Shenzhen city during 2003 to 2009, China. The journal of maternal-fetal & neonatal medicine 2015; doi: 10.3109/14767058.2014.932767.

21. Wu MH, Chen HC, Lu CW, Wang, JK, Huang SC, Huang SK et al. Prevalence of congenital heart disease at live birth in Taiwan. The Journal of pediatrics 2010; doi: 10.1016/j.jpeds.2009.11.062.

22. Sun PF, Ding GC, Zhang MY, He SN, Gao Y, Wang JH et al. Prevalence of congenital heart disease among infants from 2012 to 2014 in Langfang, China. Chinese medical journal 2017; doi: 10.4103/0366-6999.204923.

23. Pei L, Kang Y, Zhao Y, Yan H. Prevalence and risk factors of congenital heart defects among live births: a population-based cross-sectional survey in Shaanxi province, Northwestern China. BMC pediatr 2017; doi: 10.1186/s12887-017-0784-1.

24. Yokouchi-Konishi T, Yoshimatsu J, Sawada M, Shionoiri T, Nakanishi A, Horiuchi C, et al. Recurrent Congenital Heart Diseases Among Neonates Born to Mothers with Congenital Heart Diseases. Pediatr cardiol 2019; doi: 10.1007/s00246-019-02083-6.

25. Carmichael, SL, Nelson V, Shaw GM, Wasserman CR, Croen LA. Socio-economic status and risk of conotruncal heart defects and orofacial clefts. Paediatric and perinatal epidemiology 2003; doi: 10.1046/j.1365-3016.2003.00498.x.

26. Liu SW, Liu JX, Tang J, Ji JF, Chen JW, Liu CY et al. Environmental risk factors for congenital heart disease in the Shandong Peninsula, China: a hospital-based case–control study. Journal of epidemiology 2009; doi: 10.2188/jea.JE20080039.

27. Wang B, Hertog S, Meier A, Lou C, Gao E. The potential of comprehensive sex education in China: findings from suburban Shanghai. Int Fam Plan Perspect 2005; doi: 10.1363/3106305.

28. Gianicolo EAL, Mangia C, Cervino M, Bruni A, Andreassi MG, Latini G. Congenital anomalies among live births in a high environmental risk area—A case-control study in Brindisi (southern Italy). Environ
29. Liang Q, Gong W, Zheng D, Zhong R, Wen Y, Wang X. The influence of maternal exposure history to virus and medicine during pregnancy on congenital heart defects of fetus. Environ Sci Pollut R 2017; doi: 10.1007/s11356-016-8198-4.

30. Best, K, Rankin J. Increased risk of congenital heart disease in twins in the North of England between 1998 and 2010. Heart 2015; doi: 10.1136/heartjnl-2015-307826.

31. Brodwall K, Greve G, Leirgul E, Tell GS, Vollset SE, Øyen N. Recurrence of congenital heart defects among siblings—a nationwide study. Am J Med Genet A 2017; doi: 10.1002/ajmg.a.38237.

Tables

Table 1 Risk factors of congenital heart defects on univariate analysis
| Risk factors                        | CHD | No CHD | P value |
|-----------------------------------|-----|--------|---------|
| Twinning                          | 1031| 62559  | <0.001  |
| Yes                               | 37  | 1136   |         |
| Maternal age (years)              |     |        |         |
| < 35                              | 869 | 50782  | 0.186   |
| ≥35                               | 199 | 12913  |         |
| Maternal body mass index (BMI)    |     |        | <0.001  |
| <18.5                             | 105 | 5164   |         |
| 18.5-25                           | 668 | 36534  |         |
| >25                               | 179 | 11424  |         |
| Living location                   |     |        | <0.001  |
| City                              | 775 | 39499  |         |
| Countryside                       | 199 | 15125  |         |
| Assisted reproduction             | 949 | 53878  | 0.005   |
| Yes                               | 24  | 765    |         |
| Maternal educational level        |     |        | <0.001  |
| < High school                     | 150 | 11807  |         |
| High school degree or college degree | 748 | 39857  |         |
| > College degree                  | 76  | 2967   |         |
| Eating habits                     |     |        | 0.595   |
| Not partial                       | 823 | 46586  |         |
| Eating less meat                  | 124 | 6316   |         |
| Eating less vegetable             | 26  | 1721   |         |
| Paternal age (years)              |     |        | 0.762   |
| ≤30                               | 463 | 25712  |         |
| >30                               | 510 | 28884  |         |
| Number of previous pregnancies    |     |        | 0.007   |
| Fertility history | 0 | 341 | 17159 |
|------------------|---|-----|-------|
| >1               | 283 | 17730 |
| History of having a child with birth defect | 0 | 513 | 25508 |
| Yes             | 950 | 54065 |
| History of illness in 1st trimester | 0 | 795 | 46981 |
| Yes            | 23 | 581 |
| Family history of birth defect | 0 | 960 | 54262 |
| Yes             | 14 | 384 |
| Family history of CHD | 0 | 967 | 54554 |
| Yes             | 7 | 92 |
| History of folic acid intake | 0 | 0.009 |
| Don't eating folic acid | 0 | 49 | 3374 |
| Eating folic acid 3 months before or 3 months after pregnancy | 0 | 639 | 37044 |
| Eating folic acid 3 months before and 3 months after Pregnancy | 0 | 286 | 14228 |
| History of husband smoking before | 0 | 0.015 |
| 0              | 635 | 33466 |
| <10            | 167 | 10507 |
| 10-19         | 114 | 6945 |
| ≥20           | 58 | 3728 |

**Table 2** Prevalence of congenital heart disease in fetus and newborns by major ICD-11 categories according to fetal echocardiography and pregnancy outcomes in Qingdao prospective study
| Congenital heart disease                                      | ICD-11 code | Fetus n (%) | Termination n (%) | Newborns n (%) |
|---------------------------------------------------------------|-------------|-------------|-------------------|---------------|
| Transposition of the great arteries                           | LA85.1      | 4 (0.39%)   | 4 (3.51%)         | 0 (0.00%)     |
| Double outlet right ventricle                                 | LA85.2      | 3 (0.29%)   | 2 (1.75%)         | 1 (0.21%)     |
| Common arterial trunk                                         | LA85.4      | 1 (0.10%)   | 1 (0.88%)         | 1 (0.21%)     |
| Left superior caval vein                                     | LA86.0      | 14 (1.36%)  | 1 (0.88%)         | 8 (1.71%)     |
| Partial anomalous pulmonary venous connection                 | LA86.21     | 0 (0.00%)   | 0 (0.00%)         | 1 (0.21%)     |
| Other specified anomalous pulmonary venous connection         | LA86.2Y     | 37 (3.61%)  | 2 (1.75%)         | 21 (4.49%)    |
| Congenital tricuspid regurgitation                            | LA87.00     | 302 (29.43%)| 4 (3.51%)         | 88 (18.80%)   |
| Ebstein's anomaly                                             | LA87.0Y     | 1 (0.10%)   | 1 (0.88%)         | 0 (0.00%)     |
| Congenital mitral regurgitation                               | LA87.10     | 7 (0.68%)   | 0 (0.00%)         | 3 (0.64%)     |
| Atrioventricular septal defect                                | LA87.20     | 9 (0.88%)   | 6 (5.26%)         | 1 (0.21%)     |
| Tetralogy of Fallot                                           | LA88.2      | 29 (2.83%)  | 19 (16.67%)       | 4 (0.85%)     |
| Ventricular septal defect                                     | LA88.4      | 274 (26.71%)| 12 (10.53%)       | 161 (34.40%)  |
| Hypoplastic right heart syndrome                              | LA88.Y      | 3 (0.29%)   | 2 (1.75%)         | 0 (0.00%)     |
| Hypoplastic left heart syndrome                               | LA89.3      | 4 (0.39%)   | 4 (3.51%)         | 0 (0.00%)     |
| Functionally univentricular heart, unspecified                | LA89.Z      | 6 (0.58%)   | 6 (5.26%)         | 0 (0.00%)     |
| Congenital pulmonary valvar stenosis                          | LA8A.00     | 23 (2.24%)  | 3 (2.63%)         | 9 (1.92%)     |
| Congenital pulmonary regurgitation                            | LA8A.01     | 53 (5.17%)  | 0 (0.00%)         | 22 (4.70%)    |
| The dysplastic pulmonary valve                                | LA8A.0Y     | 2 (0.19%)   | 1 (0.88%)         | 1 (0.21%)     |
| Congenital pulmonary atresia                                  | LA8A.1      | 1 (0.10%)   | 0 (0.00%)         | 1 (0.21%)     |
| Congenital aortic regurgitation                               | LA8A.21     | 2 (0.19%)   | 0 (0.00%)         | 1 (0.21%)     |
| Bicuspid aortic valve                                         | LA8A.22     | 1 (0.10%)   | 0 (0.00%)         | 1 (0.21%)     |
| Coarctation of aorta                                          | LA8B.21     | 17 (1.66%)  | 1 (0.88%)         | 17 (3.63%)    |
| Interrupted aortic arch                                       | LA8B.22     | 2 (0.19%)   | 1 (0.88%)         | 0 (0.00%)     |
| Condition                                                                 | CODE  | COUNT | PERCENTAGE  |
|---------------------------------------------------------------------------|-------|-------|-------------|
| Vascular ring                                                             | LA8B.2Y | 77    | 7.50%       |
| Congenital anomaly of great arteries including arterial duct, unspecified | LA8B.Z | 9     | 0.88%       |
| Congenital coronary arterial fistula                                      | LA8C.2 | 3     | 0.29%       |
| Divided left atrium                                                       | LA8G.0 | 1     | 0.10%       |
| Restricted oval                                                           | LA8E.Y | 12    | 1.17%       |
| Multiple structural developmental anomaly of heart or great vessels       | LA8Y   | 84    | 8.19%       |
| Structural developmental anomaly of heart or great vessels, unspecified   | LA8Z   | 45    | 4.39%       |
| Total                                                                     | LA80-LA8Z | 1026 | 100%        |

|                        |      |       |             |
| Total                  | 1026 | 114   | 468         |