Analysis of the Seasonal Trend of Congenital Heart Defects

Yuanyuan Dong, MS[1,*], Yunting Zhang, PhD[1,*], Shilu Tong, PhD[2,3], Zhongyi Jiang, BS[1], Zhiwei Xu, PhD[2], Xinyue Li, MS[4], and Wei Wang, MD, PhD[5]

Objective To determine the seasonal trend of congenital heart defects (CHDs) in China using hospital-based clinical data.

Study design We included 40 501 patients with CHD hospitalized at the Shanghai Children Medical Center between 2006 and 2017. The birth rate of CHD in each month was adjusted by sex, year of birth, and monthly birth rate of the general population. Negative binomial regression models were used to assess the seasonal trend of CHD.

Results The included patients consisted of 22 600 boys (55.8%), resulting in a male-to-female ratio of 1.26:1. Among subtypes of CHDs, ventricular septal defects and atrial septal defects were the most common, accounting for 39.7% and 12.6%, respectively. A statistically significant seasonal trend in the monthly birth rate of patients with CHDs was found; the highest relative rate of CHD was found in October and the lowest in April. After adjusting for the potential confounders, the highest relative rate of CHD was found in October and the lowest in November.

Conclusions There seems to be a significant monthly birth rate variation of CHDs in China. The highest relative rate of CHDs occurred in October, suggesting possible maternal exposure to environmental hazards from January to March. These hazards may include air pollution, virus infection, and unhealthy lifestyle behaviors during the Spring Festival. *(J Pediatr 2019;207:29-33)*.

Congenital heart defects (CHDs), are structural problems that arise from abnormal formation of the heart or major blood vessels during fetal development.[1] The defects can involve the walls of the heart, the valves, or the arteries or veins near the heart. The incidence of CHDs in different countries varies from about 4/1000 to 10/1000 live births. In the United States, the incidence was reported to be approximately 8/1000 live births, whereas the incidence of CHDs in Europe and Asia was 6.9/1000 and 9.3/1000 live births, respectively.[2,3] CHD accounts for nearly one-third of all major congenital anomalies and is the most common cause of infant deaths resulting from birth defects.[3-6] Cardiovascular death ranks sixth in causes of death in patients aged from 1 to 19 years.[7] In addition, the annual healthcare costs related to CHDs are estimated to be $5.6 billion, accounting for 15.1% of total pediatric hospitalization costs.[8] In China, the total economic burden of CHDs exceeds 12.6 billion RMB.[9]

CHDs are associated with chromosome abnormalities, gene mutations, and maternal exposure to infectious agents, alcohol, smoking, medications, or illicit drugs during pregnancy.[10-12] In most cases, the diseases are caused by multifactorial inheritance and both genetic and environmental factors are involved. Epidemiologic studies have suggested the possible association of maternal exposure to outdoor air pollutants such as ozone and particles with diameters of 10 μm or less (PM_{10}) during the first trimester of gestation with ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus.[12,13] Other studies also reported the links between maternal exposure to nitrogen dioxide and sulfur dioxide and coarctation of the aorta and tetralogy of Fallot, and between exposure to the particles with diameters of 2.5 μm or less ($PM_{2.5}$), PM_{10} or traffic-related air pollution and increased risk of CHDs and birth defects.[14-16] Although studies provide evidence that air pollution is associated with CHDs,[17] other indoor environmental pollutants, viral infections, and lifestyle behaviors that are related to the seasonal variation may also contribute to the disease.[18,19] Caton et al examined whether the occurrence of birth defects varied by month of conception using the population-based New York State Congenital Malformations Registry, and found a statistically significant seasonal variation in the incidence of VSD.[20] Similarly, Luteijn et al investigated the seasonality of 65 764 nonchromosomal and 12 682 chromosomal congenital anomalies in Europe,

ASD	Atrial septal defect
CHD	Congenital heart defect
$PM_{2.5}$	Particles with diameters of 2.5 μm or less
PM_{10}	Particles with diameters of 10 μm or less
RRR	Relative rate ratio
VSD	Ventricular septal defect

From the [1]Child Health Advocacy Institute, Shanghai Children's Medical Center, Shanghai Jiaotong University, School of Medicine, Shanghai, PR China; [2]School of Public Health and Social Work, Queensland University of Technology, Brisbane, Australia; [3]Department of Clinical Epidemiology and Biostatistics, Shanghai Children's Medical Center, Shanghai Jiaotong University, School of Medicine, Shanghai, PR China; [4]Department of Biostatistics, School of Public Health, Yale University, New Haven, CT; and [5]Department of Thoracic and Cardiovascular Surgery, Shanghai Children's Medical Center, Shanghai Jiaotong University, School of Medicine, Shanghai, PR China

*Contributed equally.

Supported by the Shanghai Municipal Commission of Health and Family Planning (The fourth round of Three-Year Public Health Action Plan, 2015-2017, GWIV-25 [to Z.J.]; and National Science Foundation of China (81670372 [to W.W.]); the Science and Technology Commission of Shanghai Municipality (18411951600 [to S.T.]). The authors acknowledge Shanghai Synyi Medical Technology Co, Ltd. The study sponsor had no role in any process of the study. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2018.12.024

and found a statistically significant seasonal trend of VSD.[21] However, a study by Egbe et al found that there was no geographic or seasonal variation in CHD incidence.[4]

The information on the birth month of children with CHDs is important, because it can reflect the period of fetal heart development during pregnancy. The major objectives of this study were to determine whether there was seasonal variation in the occurrence of CHDs using a large hospital-based clinical dataset and to provide clues for further identifying causes and/or risk factors of CHDs.

Methods

We retrieved and reviewed the data on all patients with CHDs diagnosed in the department of Cardiac Surgery and Cardiology at Shanghai Children's Medical Center from January 1, 2006, to June 30, 2017, based on unique CHD *International Classification of Diseases*, 10th edition codes.[4] A CHD was defined as "a gross structural abnormality of the heart or intrathoracic great vessels present at birth that is actually or potentially of functional significance."[22]

In this study, the ages of the children were between 0 and 18 years old and the study was approved by the ethical review board of Shanghai Children's Medical Center. The inclusion criteria for cases diagnosed as a CHD include that the patient must have a complete medical record including sex, birth date, and date of diagnosis. Patients admitted to the hospital several times were only included once. The exclusion criteria included patients with the following cardiac defects: peripheral pulmonic stenosis, patent ductus arteriosus in preterm neonates, isolated persistent foramen ovale, isolated persistent left superior vena cava, isolated dextrocardia, heart tumor, cardiomyopathy, cardiac arrhythmias, and isolated bicuspid aortic. We also excluded patients who were born before January 1, 2000, or after December 31, 2016, because there were very few cases outside the period of 2000-2016. All data entries were checked item by item by trained medical research staff for completeness and accuracy.

Population-based Birth Data

Because there is no strict referral system in China, children with CHDs can be treated in any hospital. The patients with CHDs included in this study came from all over China; we used the general birth population of national fifth and sixth censuses from the China National Bureau of statistics website (http://www.stats.gov.cn). The population-based birth data in this study collected from November 1, 1999, to October 31, 2000, and from November 1, 2009, to October 31, 2010, respectively.

Statistical Analyses

First, we calculated the monthly percentage of newborns in all collected patients with CHDs and expected cases estimated from the general birth population. The birth month distributions of patients with CHDs and of the general population were compared by calculating percentages of births per month and the ratio of observed over expected cases. Second, the seasonal variation of CHD was investigated in 2 separate negative binomial regression models. Both models were adjusted for sex and birth year, and in one of them the birth counts of the whole population in China were additionally included to account for the birth month distribution in the national reference population. Then, the relative rate ratio (RRR) and 95% CI were estimated based on the relative rate of CHDs in a month as compared with that in the reference month. The statistically significant level was set at $P \leq .05$ (2 tailed). Negative binomial regression models were performed using Stata 14.0 statistical software (StataCorp, College Station, Texas) and all other statistical analyses in this study were conducted using SPSS 22.0 (SPSS Inc, Chicago, Illinois).

Negative binomial regression models were also used to analyze the monthly variation of the CHD subtypes with the largest number of cases, and were conducted by sex, different years of birth, and 2 different periods (2000-2008 and 2009-2016) to verify the overall CHD results.

Results

Demographic Characteristics

Of 43 977 pediatric patients with CHDs reviewed, 40 501 cases met the inclusion criteria: **Table I** shows the demographic characteristics. The patients consisted of 22 600 boys (55.8%), resulting in a male-to-female ratio of 1.26:1.00. The trend of the number of hospitalized patients and the percentages of female patients increased year by year in general from January 2006 to June 2017 (**Table I**). The average age at the time of diagnosis was 2.1 years (SD, 2.4). Among subtypes of CHDs (**Appendix**; available at www.jpeds.com), VSD and ASD were the most common, accounting for 39.7% and 12.6% of cases, respectively. The number of patients in this study accounted for about 3.5% of the patients with CHDs in the country.[9] However, data on the proportion of preterm births were unavailable in our sample.

Table I. Characteristics of the study population by year of treatment

Years	n	Male, %	Female, %	Mean age (SD)
2006	2250	61.10	38.90	1.8 (1.7)
2007	2583	58.70	41.30	2.0 (1.9)
2008	3137	58.70	41.30	2.0 (1.9)
2009	3114	55.80	44.20	2.0 (2.0)
2010	3374	56.30	43.70	2.0 (2.1)
2011	3592	58.00	42.00	2.1 (2.4)
2012	3879	57.00	43.00	2.1 (2.5)
2013	4186	54.70	45.30	2.1 (2.5)
2014	4187	54.40	45.60	2.1 (2.6)
2015	4233	53.60	46.40	2.1 (2.5)
2016	3954	51.80	48.20	2.4 (2.8)
2017	2012	52.70	47.30	2.4 (2.6)
Total	40 501	55.80	44.20	2.1 (2.4)

Seasonal Trend of CHDs

The occurrence of CHDs was the highest for infants born in October (9.5%) and lowest in April (7.4%) during the period from January 2006 to June 2017. Using China's birth population data, we estimated that the relative rate of CHDs was similar from January to October (6.80%-8.68%), with more infants born in the months between November and December (13.07% and 11.6%, respectively; **Figure**). By comparing the observed and expected numbers of cases of CHDs based on the general birth rates from 2000 to 2010, we found that the ratio of observed/expected cases was highest in October, and lower in February, March, November, and December (**Table II**).

Negative binomial regression models revealed a clear seasonal trend of CHDs. The RRRs in different months were 6.7%-28.2% higher than that in the reference month of April, with the highest RRR in October (1.282; 95% CI, 1.209-1.360). After adjusting for birth rates in different months and sex of the general population, we found that the RRRs in July to October were 14.9%-25.5% higher than that in the reference month, with the highest RRR in October (1.255; 95% CI, 1.183-1.332). In contrast, the RRRs in February, November, and December were 7.0%-33.1% lower, with the lowest RRR in November (0.669; 95% CI, 0.630-0.710; **Table III**).

In this study, the subtype with the largest number of cases was septal defects (21 180 [52.30%]). The results of negative binomial regression models showed that there were similar seasonal trends between septal defects and the overall CHDs (**Table IV**; available at www.jpeds.com). Similarly, there were the same seasonal trends between 2 different periods (2000-2008 and 2009-2016; **Table V** and **Table VI**; available at www.jpeds.com).

Discussion

In this study, we found a variation in the month of birth of patients with CHDs. The greatest number of children with CHDs were born in October and the lowest in April. However, after adjustment for the general birth population, the highest relative monthly rate of CHDs was in October and the lowest was in November.

Some studies on the seasonality of CHDs have been conducted, but the results were inconsistent. Dai et al reported that 1095 children were diagnosed with CHDs from 2009 to 2012 in 14 counties and cities in China.[23] By performing circular distribution method, they found that the peak birth month were in September and October.[23] Grech et al investigated all live births from 1990 to 1994 in Malta, and identified 231 patients with CHDs.[24] They found that the peak birth month for patients with CHDs and lesions requiring intervention was in September. Environmental factors such as a maternal viral infection or the treatment of such infections during the first trimester of pregnancy were thought to contribute to CHDs.[24] Another study examined seasonality of 302 cases with VSD in New England, in the United States, and found a moderate peak in summer, which was attributed to a strong tendency for complex VSD in the summer.[25] The difference in the seasonality of the occurrence of patients with CHDs between different studies might be due to

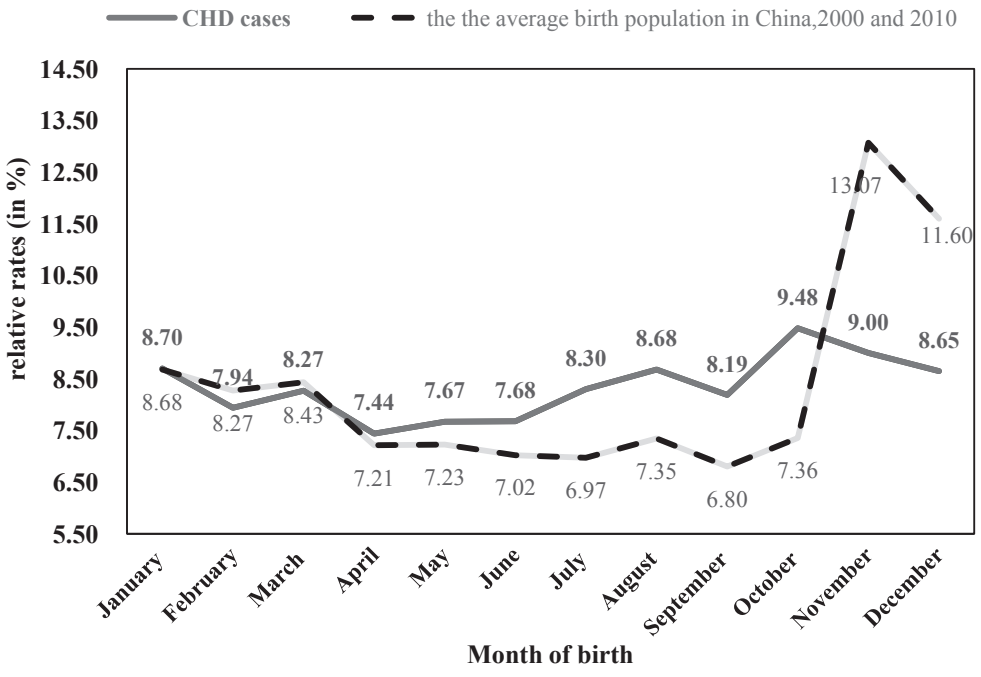

Figure. Relative rate of birth months of CHD cases (n = 40 501) and the general population in China.

Table II. Comparison of observed and expected monthly birth numbers of CHD cases and relative rate in each month*

Months	Observed CHD cases (O)	Relative rate of CHD cases, %	Expected CHD cases† (E)	Relative rate of general population, %	O/E
January	3523	8.70	3515	8.68	1.002
February	3216	7.94	3351	8.27	0.960
March	3351	8.27	3415	8.43	0.981
April	3015	7.44	2922	7.21	1.032
May	3105	7.67	2927	7.23	1.061
June	3109	7.68	2844	7.02	1.093
July	3362	8.30	2825	6.97	1.190
August	3514	8.68	2975	7.35	1.181
September	3318	8.19	2755	6.80	1.204
October	3839	9.48	2979	7.36	1.289
November	3644	9.00	5293	13.07	0.688
December	3505	8.65	4698	11.60	0.746
Total	40 501	100.00	40 501	100.00	1.000

*Monthly birth numbers from 40 501 CHD cases and the average monthly birth relative rate of general population in Chinese fifth and sixth censuses, 2000 and 2010.
†Expected CHD cases = 40 501 × relative rate of general population.

different populations, various approaches used, variable climatic conditions, and distinct socioenvironmental conditions across different regions. Although these studies provided valuable information about the seasonality of CHD incidence, most of them did not adjust for the confounding effects of sex, year of birth, and monthly birth population. We believe that the adjustment by birth population is important, because unadjusted rates may result in bias.[26]

The heart usually forms in the early pregnancy, the critical period of fetal heart and embryo development is 3-8 weeks of gestation.[27] In our study, the birth month of patients with CHDs was highest in October, which indicates maternal exposure to environmental hazards from January to March. Air pollution in winter is more severe; the cold weather means that more coal and other fossil fuels are burned during this time of the year. Central heating, which is powered by coal, is used in individual homes as well as commercial businesses during these months. The demands for energy usually soar in the colder months, and smog is particularly frequent and intense in this time of the year.[28] Second, during the Spring Festival, in late January and early February, centralized fireworks and firecrackers affect the urban air quality in China.[29,30] The China National Environmental Monitoring Centre reports that more than 60% cities in China have excessive air pollution during the Spring Festival holiday. The fireworks and firecrackers can cause the concentration of pollutants such as PM_{10} and $PM_{2.5}$ in the air to increase by as much as 10-fold; there are also significant increases of elements such as K, Ba, Pb and Cu in $PM_{2.5}$.[31] The $PM_{2.5}$ found in the air on smoggy days are small enough to penetrate deep into the blood stream through the lungs and such nanoparticles have been known to cross the placental barrier and cause health problems.[32]

Table III. RRR of the impact of birth month on CHD risk based on data from 40 501 CHD cases in China diagnosed between 2006 and 2017

	Without adjusting for population at risk*			With adjusting for population at risk†		
Months	RRR	95% CI	*P* value	RRR	95% CI	*P* value
January	1.170	1.102-1.242	<.001	0.972	0.916-1.032	.357
February	1.067	1.004-1.133	.037	0.930	0.875-0.988	.019
March	1.110	1.045-1.178	.001	0.949	0.894-1.010	.091
April		Reference			Reference	
May	1.029	0.968-1.094	.353	1.028	0.967-1.092	.380
June	1.034	0.973-1.099	.286	1.062	0.999-1.129	.053
July	1.115	1.050-1.184	<.001	1.153	1.086-1.225	<.001
August	1.170	1.102-1.242	<.001	1.149	1.082-1.220	<.001
September	1.104	1.039-1.173	.001	1.170	1.101-1.243	<.001
October	1.282	1.209-1.36	<.001	1.255	1.183-1.332	<.001
November	1.213	1.143-1.287	<.001	0.669	0.630-0.710	<.001
December	1.165	1.097-1.236	<.001	0.724	0.682-0.769	<.001

*The RRR along with 95% CI and *P* values from negative binomial regression models adjusted only for gender and birth year.
†Additionally adjusted for the general birth population.

In China, influenza activity often begins to increase in November; influenza A activity exhibits a single annual peak in January and February in Northern China (latitude ≥33°N), whereas influenza B activity predominates in colder months throughout most provinces in China,[33] which is consistent with the teratogenic window of 3-8 gestational weeks.

During the Spring Festival, almost every Chinese citizen has at least a 7-day holiday. Pregnant women, possibly being unaware of their pregnancies, may be exposed to smoking in closed building or rooms in winter.[34-37] The pregnant women may also be exposed to alcohol.[38,39]

This study has several strengths. In this study, we adjusted for a range of confounding factors, including sex, the year of birth and the monthly birth population. A statistical approach, (ie, negative binomial regression model), was used to assess the seasonal trend of CHDs. However, our study also has several limitations. First, it is a single-center study and, therefore, the generalizability of our data is limited as only patients with CHDs who arrived at their hospital were included, and a number of patients with mild CHDs (eg, small ASD) might have missed. Second, the study was not stratified by socioeconomic class, race, or cultural background because these data were unavailable and such factors might be related CHDs. Third, the national birth population was used as a reference in the model and the possibility of residual confounding by local birth population could not be ruled out. Fourth, CHDs may be related to preterm birth, which is also affected by seasonal factors. However, no preterm birth data were available in this study. Finally, we cannot calculate the incidence of CHDs because this is only a hospital-based clinical epidemiological study.

Our data suggest that the causes of the CHDs might be related to outdoor/indoor air pollution, virus infection, and unhealthy lifestyle during the Spring Festival. Further studies are warranted to confirm our findings and determine which risk factor plays a key role. ■

Submitted for publication Sep 4, 2018; last revision received Dec 5, 2018; accepted Dec 6, 2018.

Reprint requests: Wei Wang, MD, PhD, Department of Thoracic and Cardiovascular Surgery, Shanghai Children's Medical Center, Shanghai Jiaotong University, School of Medicine, 1678 Dongfang Rd, Shanghai, PR China, 200127. E-mail: wangweicpb@163.com

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Table IV. RRR of the impact of birth month on CHD risk based on data from 21 180 septal defects cases in China diagnosed between 2006 and 2017

	Without adjusting for population at risk*			With adjusting for population at risk†		
Months	RRR	95% CI	*P* value	RRR	95% CI	*P* value
January	1.189	1.102-1.284	<.001	1.456	1.353-1.566	<.001
February	1.135	1.051-1.226	.001	1.458	1.354-1.570	<.001
March	1.157	1.072-1.250	<.001	1.458	1.354-1.569	<.001
April		Reference		1.472	1.365-1.589	<.001
May	1.075	0.994-1.162	.070	1.580	1.466-1.703	<.001
June	1.022	0.945-1.106	.580	1.547	1.434-1.668	<.001
July	1.141	1.056-1.232	.001	1.738	1.614-1.871	<.001
August	1.123	1.141-1.328	<.001	1.779	1.654-1.914	<.001
September	1.149	1.064-1.241	<.001	1.793	1.665-1.930	<.001
October	1.292	1.198-1.139	<.001	1.862	1.732-2.001	<.001
November	1.232	1.142-1.329	<.001		Reference	
December	1.233	1.143-1.330	<.001	1.129	1.050-1.214	.001

*The RRR along with 95% CI and *P* values from negative binomial regression models adjusted only for gender and birth year.
†Additionally adjusted for the general birth population.

Table V. RRR of the impact of birth month on CHD risk based on data from 15 256 cases in China bored between 2000 and 2008

	Without adjusting for population at risk*			With adjusting for population at risk†		
Months	RRR	95% CI	*P* value	RRR	95% CI	*P* value
January	1.185	1.076-1.306	.001	1.323	1.207-1.450	<.001
February	1.039	0.941-1.147	.453	1.216	1.107-1.336	<.001
March	1.106	1.003-1.219	.044	1.270	1.157-1.394	<.001
April		Reference		1.449	1.221-1.476	<.001
May	1.050	0.952-1.159	.330	1.408	1.282-1.547	<.001
June	1.045	0.947-1.154	.379	1.442	1.313-1.584	<.001
July	1.131	1.025-1.246	.014	1.570	1.431-1.723	<.001
August	1.241	1.128-1.367	<.001	1.637	1.494-1.793	<.001
September	1.189	1.076-1.306	.001	1.687	1.539-1.850	<.001
October	1.464	1.332-1.608	<.001	1.923	1.760-2.102	<.001
November	1.351	1.228-1.485	<.001		Reference	
December	1.317	1.198-1.449	<.001	1.010	1.005-1.204	.039

*The RRR along with 95% CI and *P* values from negative binomial regression models adjusted only for gender and birth year.
†Additionally adjusted for the general birth population.

Table VI. RRR of the impact of birth month on CHD risk based on data from 25 245 cases in China bored between 2009 and 2016

	Without adjusting for population at risk*			With adjusting for population at risk†		
Months	RRR	95% CI	*P* value	RRR	95% CI	*P* value
January	1.160	1.082-1.243	<.001	1.547	1.445-1.656	<.001
February	1.085	1.012-1.164	.022	1.518	1.418-1.627	<.001
March	1.112	1.037-1.193	.003	1.527	1.426-1.636	<.001
April		Reference		1.449	1.496-1.721	<.001
May	1.018	0.948-1.093	.617	1.631	1.521-1.749	<.001
June	1.027	0.957-1.103	.457	1.693	1.580-1.815	<.001
July	1.107	1.032-1.187	.004	1.838	1.716-1.968	<.001
August	1.126	1.050-1.207	.001	1.774	1.657-1.900	<.001
September	1.055	0.983-1.132	.136	1.794	1.674-1.922	<.001
October	1.172	1.094-1.256	<.001	1.841	1.720-1.969	<.001
November	1.130	1.054-1.211	.001		Reference	
December	1.074	1.001-1.152	.047	1.070	1.000-1.148	<.001

*The RRR along with 95% CI and *P*-values from negative binomial regression models adjusted only for gender and birth year.
†Additionally adjusted for the general birth population.