

Changes in the Incidence of Birth Defects in Sichuan Province, Southwest China from 2006 to 2019: A Retrospective Analysis Based on Hospital Birth Defect Monitoring

Tianjin Zhou

Sichuan Provincial Maternity and Child Health Care Hospital

Weixin Liu

sichuan provincial maternity and child health care hospital

Ziling Zhao (✉ 344399976@qq.com)

sichuan provincial maternity and child health care hospital

Gang Zhang

sichuan provincial maternity and child health care hospital

Jingtao Liu

sichuan provincial maternity and child health care hospital

Linkun He

sichuan provincial maternity and child health care hospital

Min Luo

sichuan provincial maternity and child health care hospital

bingzhong su

sichuan provincial maternity and child health care hospital

Research article

Keywords: Hospital birth defect monitoring, perinatal infants, birth defects, change trend, retrospective analysis

Posted Date: February 25th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-271811/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: As a province with a large population in Southwest China, Sichuan has a relatively high incidence of birth defects (BDs), but the current status and characteristics of BDs are unclear. This study aimed to analyse the changing trends of BDs in the past 14 years and propose countermeasures.

Methods: Data were obtained from the Sichuan Provincial Birth Defects Hospital Surveillance Network (SPBDHSN); the surveillance objects were perinatal infants (PIs) and BD infants who were hospitalized in the surveillance hospital from 2006 to 2019. SPSS 22.0 software was used for relevant statistics and analysis; descriptive and chi-square test analyses were used to calculate the incidence of BDs in the whole province, region of the mother, sex of the baby and maternal age.

Results: From 2006 to 2019, 1,799,914 PI cases were monitored, and 26,797 newborns were diagnosed with BDs. The average incidence of BDs was 148.88 per 10,000 births. The average incidence of BDs based on region (urban, rural) and sex (male, female) was 237.01, 87.6, 166.4, and 129.63 per 10,000 births, respectively. The average rates of birth defects for maternal age (<20, 20-25, 25-30, 30-35, >35 years) were 142.77, 133.01, 147.96, 170.39 and 180.37 per 10,000, respectively. P values according to the chi-square test for the incidence of BDs by region, sex of the baby, and maternal age were all less than 0.01, with significant differences. The incidence of BDs in the province varied from year to year, with the first deformity gradually transitioning from body surface deformity to visceral deformity.

Conclusions: The prevention and treatment of BDs in Sichuan has achieved remarkable results, and the incidence of birth defects has begun to show a downward trend in recent years. However, due to the imbalance of economic and social development between regions in the province, the prevention and treatment of birth defects still faces huge challenges.

Background

Birth defects (BDs) can lead to foetal death as well as infant death and disability, which not only affects the life of the individual but also brings a heavy spiritual and economic burden to the family and society. In recent years, the global incidence of BDs has been increasing yearly. BDs have become a serious social problem and a public health issue recognized to be of great importance in countries all over the world. China is a country with a high incidence of BDs. According to the "China Birth Defect Prevention Report (2012)", it is estimated that the total incidence of BDs in China is approximately 5.6%. China's annual direct economic loss due to neural tube defects exceeds 200 million yuan, the total economic burden of the life cycle of newborn Down syndrome exceeds 10 billion yuan, and the total economic burden of the life cycle of new congenital heart disease exceeds 12.6 billion yuan. BDs seriously affect the quality of our population and bring heavy burdens to families and society^[1-3].

Sichuan Province is located in the southwestern region of China. The population of the province ranks fourth in China and first in the western part. In 2001, Sichuan Province established a hospital-based monitoring system covering the whole province. The monitoring objects were from 28 weeks of pregnancy to 7 days after delivery. As a province with a large population, Sichuan as a high BD incidence, and the overall economic level is lower than in other provinces. There are more poor counties and poor population, and the cost of treatment and rehabilitation due to BDs is huge. Many families return to poverty due to illness. poverty alleviation has become a major focus. With the development of medical technology and the improvement of health care, the detection rate and accuracy of BD have increased, but for various reasons, the incidence of BD remains high. The BD rate in the province has nearly doubled in the past 19 years, from 65.4 per 10,000 in 2001 to 136.93 per 10,000 in 2019, an increase of 109.37%. In recent years, the incidence of BD has been at a high level. With the full implementation of the two-child policy, the proportion of women with high-risk pregnancies has increased, the number of newborns is large each year; the risk of BDs has also increased, as may their occurrence. The task of prevention and treatment of BD is daunting, and intervention for the prevention and treatment of BDs is imminent^[4-5].

This study aimed to analyse the situation of BDs in Sichuan Province over the past 14 years, evaluate the current situation of prevention and treatment, analyse current problems in prevention and treatment, and propose countermeasures that will effectively reduce BD incidence in Sichuan Province and improve quality of life among the population. It is of great practical significance to promote sound and rapid economic development.

Methods

Data source

The data were obtained from a network of birth defect monitoring hospitals established in Sichuan Province that covers 21 cities (prefectures) across the province. Ninety-five monitoring hospitals reported through the Sichuan Maternal and Child Health Information Platform (SCMCHI). The monitoring subjects were perinatal newborns and those with birth defects who were hospitalized in the hospital from 2006 to 2019 using a time frame of 28 weeks of gestation to 7 days after birth. There were 23 types of birth defects monitored, including anencephaly, spina bifida, encephalocele, hydrocephalus, cleft palate, cleft lip, cleft lip with palate, anotia/microtia, congenital ear malformations (not anotia/microtia), oesophageal atresia/stenosis, anorectal atresia/stenosis, hypospadias, club foot, polydactyly, syndactyly, limb reduction defects, omphalocele, gastroschisis, conjoined twins, Down syndrome, and congenital heart disease, among others.

Data Collection

The monitoring hospitals were responsible for monitoring staff to regularly learn about birth defects, such as diagnostic criteria. Every newborn in the monitoring hospital was checked by a trained professional after birth. Relevant clinical experts were required to confirm each case of deformity to ensure

quality and avoid misdiagnosis and missed diagnosis. If a baby with a deformity was found and diagnosed, the medical institution's birth defect card in the Sichuan Maternity and Child Health Information Platform (SCMCHI) was filled in; the monitoring hospital counted the perinatal data on a quarterly basis and fill in the quarterly report on the number of perinatals. County-level maternal and child health care institutions collect data from monitoring hospitals in their jurisdictions and reviewed the reported data level by level according to the administrators of county-city-provincial maternal and child health care institutions. On-site quality control of the reported data was performed every quarter at the county-level maternal and child health care institutions, every six months at the municipal maternal and child health care institutions, and every year at the provincial maternal and child health care institutions. The quantity and quality of data collection were highly guaranteed.

Statistical analysis

Epidata3.1 was used to establish a database. SPSS22.0 software was used to carry out relevant statistics and analysis, and the chi-square test was applied to analyse the incidence of birth defects based on the region of the mother (urban, rural), the sex of the baby (male, female), and the maternal age (< 20, 20–25, 25–30, 30–35, > 35 years). A descriptive analysis was carried out on the trend of change in the rate of BDs in the province, sex of the baby (male, female), region of the mother (urban, rural), maternal age (< 20, 20–25, 25–30, 30–35, > 35 years) and first birth defect from 2006 to 2019^[6–9].

Results

A total of 1799914 perinatal cases were monitored in Sichuan Province in the 14 years from 2006 to 2019; of these, 26,797 birth defects were diagnosed between 28 weeks of pregnancy and 7 days after birth, with an average birth defect rate of 148.88 per 10,000. The average rates of birth defects in the region of the mother (urban, rural) and sex of the baby (male, female) were 237.01, 87.63, 166.47 and 129.63 per 10,000, respectively. The average rates of birth defects for maternal ages of < 20, 20–25, 25–30, 30–35, > 35 years were 142.77, 133.01, 147.96, 170.39 and 180.37 per 10,000, respectively. The P values of the chi-square test for sex of the baby, region of the mother and maternal age were less than 0.01, which was significantly different. (Table 1)

Table 1
Analysis of the occurrence of BD in the province

	Number of perinatal babies	Number of birth defects	total	Chi-square value	P values
Whole province	1799914	26797	148.88	—	—
Maternal region				6624.62	< 0.001
urban	738230	17497	237.01		
rural	1061642	9303	87.63		
Sex				415.63	< 0.001
male	937116	15600	166.47		
female	862426	11180	129.63		
Maternal age (years)				30057.25	< 0.001
< 20	57924	827	142.77		
20-	504533	6711	133.01		
25-	696004	10298	147.96		
30-	364108	6204	170.39		
> 35	177303	3198	180.37		

The incidence of BDs in the province from 2006 to 2019 gradually increased to a peak and then steadily declined. It rose from 111.28 per 10,000 in 2006 to 182.97 per 10,000 in 2009 and then gradually decreased to 136.93 per 10,000 in 2019. The incidence of BDs in urban areas rose from 131.76 per 10,000 in 2006 to 284.96 per 10,000 in 2015, gradually decreased and then stabilized at approximately 280.86 per 10,000 in 2019. The incidence of BDs in rural areas rose from 94.06 per 10,000 in 2006 to 148.42 per 10,000 in 2009 and then gradually dropped to 61.09 per 10,000 in 2019. The incidence of BDs in males rose from 11.302 per 10,000 in 2006 to 221.28 per 10,000 in 2009 and then gradually decreased to 1,446.4 per 10,000 in 2019. The incidence of BDs in females rose from 106.65 per 10,000 in 2006 to 170.58 per 10,000 in 2009 and then gradually decreased to 127.69 per 10,000 in 2019. The BD incidence among mothers under 20 years of age rose from 117.65 per 10,000 in 2006 to 187.16 per 10,000 in 2009 and then fell to 111.38 per 10,000 in 2019. The incidence of BDs among mothers aged 20–25 increased from 103.15 in 2006. The rate of BDs in mothers aged 25–30 years increased from 109.95 per 10,000 in 2006 to 195.58 per 10,000 in 2009 and then decreased to 2019, and that in mothers aged 30–35 years increased from 111.15 per 10,000 in 2006 to 235.90 per 10,000 in 2014 and then decreased to 156.86 per 10,000 in 2019. BD in maternal age over 35 years The incidence rate rose from 136.45 per 10,000 in 2006 to 216.19 per 10,000 in 2015 and then dropped to 178.62 per 10,000 in 2019^[10–15] (Table 2 and Figs. 1–3).

Table 2
The incidence of BDs by characteristics in the province from 2006 to 2019 (1/10,000)

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Whole province	111.28	123.42	152.71	182.97	172.86	160.91	157.21	154.41	144.6	162.57	140.88	137.57	137.07	136.93
Maternal region														
urban	131.76	145.52	189.71	260.90	271.48	211.42	206.31	225.84	251.79	284.96	259.03	246.63	257.52	280.86
rural	94.06	102.25	119.91	148.42	91.62	119.96	115.50	99.91	69.30	77.80	64.47	68.13	65.62	61.09
Sex														
male	113.02	131.81	167.50	221.28	188.76	173.31	174.27	171.46	165.31	187.65	162.05	158.16	150.91	144.64
female	106.65	111.01	131.71	170.58	151.75	143.47	137.69	134.14	121.98	134.87	116.64	113.08	121.26	127.69
Maternal age (years)														
<20	117.65	122.57	125.41	187.16	183.7	129.78	149.73	145.9	142.12	104.45	190.39	128.01	105.83	111.38
20-	103.15	118.75	142.63	156.12	154.82	146.09	147.59	136.79	120.54	120.82	130.70	103.02	117.13	107.05
25-	109.95	117.5	155.01	195.58	171.86	161.64	151.62	158.72	124.95	169.78	148.71	131.25	123.44	130.50
30-	111.15	136.26	153.62	205.16	187.79	174.74	175.72	164.29	235.90	194.91	136.63	164.00	161.20	156.86
>35	136.45	131.02	182.87	192.01	209.85	196.7	184.72	177.39	180.73	216.19	123.16	174.08	177.95	178.62

The incidence of BD in the province varied from year to year. Major deformity gradually transitioned from body surface deformities to visceral deformities, and the primordial deformity transitioned from congenital ear malformation (CEM) in 2006–2012 to congenital heart disease (CHD) in 2013–2019. The incidence of BD in urban areas transitioned from CEM in 2006–2011 to CHD in 2012–2019. The incidence of birth defects in rural areas transitioned from cleft lip with or without cleft palate in 2006 to CEM in 2008 and then to polydactyly in 2014–2019. The incidence of birth defects in males transitioned from CEM in 2006 to CHD in 2013–2019; that in females transitioned from CEM 2006–2011 to CHD in 2012–2019 (Table 3). The first occurrence of BDs in the province changed mainly among CEM, polydactyly, and CHD (Figs. 1–3).

Table 3
The first occurrence of BD in the province from 2006 to 2019 (1/10,000)

years	The province's first order deformity	first order deformity in urban areas	first order deformity in rural areas	first order deformity in males	first order deformity in females					
2006	CEM	18.26	CEM	26.74	CLP	17.41	CEM	18.13	CEM	18.44
2007	CEM	22.07	CEM	33.25	Polydactyly	17.09	Polydactyly	25.25	CEM	20.05
2008	CEM	25.69	CEM	34.28	CEM	18.07	CEM	24.94	CEM	26.07
2009	CEM	40.28	CEM	57.12	CEM	26.46	CEM	41.26	CEM	38.82
2010	CEM	37.51	CEM	63.02	CEM	16.50	CEM	39.48	CEM	35.37
2011	CEM	31.61	CEM	43.87	CEM	21.67	CEM	33.20	CEM	29.71
2012	CEM	26.95	CHD	40.40	CEM	20.49	CEM	28.48	CHD	26.04
2013	CHD	34.42	CHD	64.66	CEM	16.41	CHD	34.35	CHD	34.23
2014	CHD	33.12	CHD	70.12	Polydactyly	12.34	CHD	35.41	CHD	30.50
2015	CHD	48.75	CHD	103.66	Polydactyly	15.09	CHD	51.43	CHD	45.87
2016	CHD	36.80	CHD	84.84	Polydactyly	13.28	CHD	35.75	CHD	37.94
2017	CHD	27.72	CHD	64.01	Polydactyly	13.38	CHD	26.63	CHD	28.68
2018	CHD	30.66	CHD	69.44	Polydactyly	14.70	CHD	27.45	CHD	33.99
2019	CHD	38.87	CHD	94.07	Polydactyly	14.79	CHD	39.93	CHD	38.40

Discussion

With joint efforts of all departments at all levels of the province, the rate of BDs in our province decreased from 182.97 in 2009 to 136.93 per 10,000 in 2019; overall, the continuous increase in the rate of BDs in the province is being effectively curbed. In the past 10 years, as the province's prevention and control of BDs has been strengthened, the incidence of some fatal and severely disabling birth defects that are sensitive to interventions has gradually decreased. At the same time, the perinatal detection rate of some birth defects such as congenital heart disease has increased due to the gradual rise in medical and health care

institutions' ability to diagnose birth defects such as visceral malformations. First-order malformation in the province has gradually transitioned from malformations of the outer ear to congenital heart disease, and congenital heart disease has been the primary birth defect for 7 consecutive years. Monitoring data show that the total rate of birth defects in our province is still at a high level, but some serious defects, such as neural tube defects, hydrocephalus, and limb short deformities, have exhibited a downward trend, indicating that the implementation of targeted interventions can effectively reduce the rate of birth defects^[16-19].

This study shows that the birth defect rate in urban areas is higher than that in rural areas; this is related to the higher level of medical technology in urban areas, which has a direct impact on the detection rate and diagnostic accuracy; it is also related to factors such as environmental pollution in urban areas, which increase the risk of birth defects. The incidence of birth defects among pregnant women over 35 years of age was higher than that of other age groups. After the implementation of the comprehensive two-child policy in the province in 2015, the number of births gradually declined after peaking in 2016. Nonetheless, if prevention and control efforts are not further strengthened, the increase in the proportion of older mothers, the decline in fertility, assisted reproduction, pregnancy complications, and complications of birth defects and other factors that increase the risk of birth defects will lead to an rise in the total number of birth defects.

Due to the unbalanced economic development throughout our province, provinces and cities (states) in the country continue to introduce relevant laws and regulations and local supporting policies; however, in most areas, the corresponding localization policy is not implemented in a timely manner to prevent and control birth defects, and free screening and treatment of birth defect-related policies are seriously lagging. Therefore, Sichuan Province has yet to formulate laws and regulations related to the prevention and treatment of birth defects and other policies. Sichuan Province invests huge financial funds each year to increase investment in birth defect prevention and control resources; with the development of secondary and third-level prevention and screening work, a large number of children diagnosed with birth defects will create the need for a huge amount of rehabilitation costs. The cost of diagnosis and treatment of most of the diseases of children with birth defects has not been clarified, in turn affecting the diagnosis, treatment and rehabilitation of these children. How to integrate medical insurance, civil assistance and other resources is a problem that needs serious consideration. Sichuan Province's birth defect information system has high connectivity, and our province has begun to establish a regional maternal and child case information platform in Chengdu, Zigong City, Leshan City. The use of real-time, dynamic, accurate and efficient collection of maternal and child health service case information on-line and the establishment of exploratory maternal and child health service management information databases through the platform to obtain information on childbirth outcomes can improve the accuracy and timeliness of birth defect information collection.

Strengths And Limitations

Birth defect monitoring is usually adopted to understand the level of birth defects in a country or region. In accordance with the requirements of the "Sichuan Province Birth Defects Monitoring Program", monitoring hospital-county-city-provincial maternal and child health care institutions cooperate with each other after reporting and reviewing information, and the quantity and quality of data sources are highly guaranteed.

At present, the hospital-based birth defect monitoring network in our province only monitors the birth defects found and reported by the hospital and does not carry out large-scale population-based birth defect monitoring. The monitoring time limit is 28 weeks of pregnancy to 7 days after birth, which fails to account for the 28 weeks before of pregnancy and 7 days after birth in the diagnosis of birth defects, which does not reflect the true level of birth defects in our province.

Conclusions

In recent years, due to the hard work of institutions at all levels and the majority of health care workers, the prevention and treatment of birth defects in our province has achieved remarkable results, and the incidence of birth defects has begun to show a downward trend. However, because of the imbalance of economic and social development between regions in the province, the prevention and treatment of birth defects still faces huge challenges. Sichuan women and children's health causes are facing a rare development opportunity. With the implementation of the national medical reform policy, maternal and child health, as an important part of public health, will receive increasing attention; moreover, financial investment will increase, and the prevention and treatment of birth defects will also receive more policy support. Sichuan will make full use of favourable domestic and provincial development opportunities, promote further reform of the medical and health system, strive to achieve the goals of the Sichuan Women and Children Development Program, effectively reduce the rate of birth defects in our province, and make new and greater contributions to the overall improvement of the health of women and children in Sichuan Province^[20-22].

Abbreviations

Birth Defects (BDs)

Sichuan Provincial Birth Defects Hospital Surveillance Network (SPBDHSN)

Perinatal infants (PIs)

Sichuan Maternal and Child Health Information Platform (SCMCHI)

Congenital ear malformations (CEM)

Congenital heart disease (CHD)

Declarations

Ethics Approval and Consent to Participate

This study has been approved by the Research Ethics Board boards from Sichuan Provincial Maternity and Child Health Care Hospital. This study was deemed exempt from obtaining consent by the Research Ethics Boards.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that there are no conflicts of interest.

Funding

This project was supported by the National Key R&D Program of China (grant no. 2017YFC0907304).and by the Science & Technology Project of Science and Technology Department of Sichuan Province (No. 2018JY0647). The funder of the study had no role in study design, data collection, analysis, interpretation, or writing of the report.

Authors' contributions

TZ performed the statistical work and drafted the manuscript. WL and GZ designed the research plan and revised the manuscript. ZZ and JL performed the statistical work. LH and ML checked and prepared the data. JZ supervised the birth defect surveillance programme and provided data accession. All authors read and approved the final manuscript.

Acknowledgements

We thank the birth defect monitoring hospitals across the province for their strong support for this research.

Authors' information

TZ is an assistant researcher, a master's degree student and mainly engaged in research on maternal and child health. ZZ is an associate researcher and doctoral student who is mainly engaged in maternal and child health management. GZ is a professor of medicine and a doctoral student who is mainly engaged in maternal and child health management.

Author details

¹Sichuan Provincial Maternity and Child Health Care Hospital/The Affiliated Women's and Children's Hospital of Chengdu Medical College, No. 290, ShaYan West Second Street, Jin Yang Road, WuHou District, Chengdu Sichuan 610045, China

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Harris BS, Bishop KC, Kemeny HR, et al Risk Factors for Birth Defects. *Obstet Gynecol Surv.* 2017 Feb;72(2):123–135. doi: 10.1097/OGX.0000000000000405. PMID: 28218773.
2. Mai CT, Isenburg JL, Canfield MA. et al. National Birth Defects Prevention Network. National population-based estimates for major birth defects,2010–2014. *Birth Defects Res.* 2019 Nov 1;111(18):1420–1435. doi:10.1002/bdr2.1589. Epub 2019 Oct 3. PMID: 31580536; PMCID: PMC7203968.
3. Kirby RS. The prevalence of selected major birth defects in the United States. *Semin Perinatol.* 2017 Oct;41(6):338–344. doi:10.1053/j.semperi.2017.07.004. PMID: 29037343.
4. Tuan RS. Birth Defects: Etiology, screening, and detection. *Birth Defects Res.* 2017 Jun 1;109(10):723–724. doi: 10.1002/bdr2.1066. PMID: 28568741.
5. Lupo PJ, Mitchell LE, Jenkins MM. Genome-wide association studies of structural birth defects: A review and commentary. *Birth Defects Res.* 2019 Nov 1;111(18):1329–1342. doi: 10.1002/bdr2.1606. Epub 2019 Oct 25. PMID: 31654503; PMCID: PMC7250002.

6. Brender JD, Weyer PJ. Agricultural Compounds in Water and Birth Defects. *Curr Environ Health Rep.* 2016 Jun;3(2):144–52. doi:10.1007/s40572-016-0085-0. PMID:27007730.
7. Feldkamp ML, Carey JC, Byrne JLB. et al. Etiology and clinical presentation of birth defects: population based study. *BMJ.* 2017 May 30;357:j2249. doi: 10.1136/bmj.j2249. PMID: 28559234; PMCID: PMC5448402.
8. Tinker SC, Gilboa SM, Moore CA. et al. National Birth Defects Prevention Study. Specific birth defects in pregnancies of women with diabetes: National Birth Defects Prevention Study, 1997–2011. *Am J Obstet Gynecol.* 2020 Feb;222(2):176.e1-176.e11. doi: 10.1016/j.ajog.2019.08.028. Epub 2019 Aug 24. PMID: 31454511; PMCID: PMC7186569.
10. Carstairs SD. Ondansetron Use in Pregnancy and Birth Defects: A Systematic Review. *Obstet Gynecol.* 2016 May;127(5):878 – 83. doi: 10.1097/AOG.0000000000001388. PMID: 27054939.
11. San Agustin JT, Klena N, Granath K. et al. Genetic link between renal birth defects and congenital heart disease. *Nat Commun.* 2016 Mar 22;7:11103. doi: 10.1038/ncomms11103. Erratum in: *Nat Commun.* 2016 Jun 08;7:11910. PMID:27002738; PMCID: PMC4804176.
12. Benjamin RH, Littlejohn S, Mitchell LE. Bariatric surgery and birth defects: A systematic literature review. *Paediatr Perinat Epidemiol.* 2018 Nov;32(6):533–44. doi:10.1111/ppe.12517. Epub 2018 Oct 11. PMID: 30307630; PMCID: PMC6261675.
13. Zambelli-Weiner A, Via C, Yuen M. et al. First trimester ondansetron exposure and risk of structural birth defects. *Reprod Toxicol.* 2019 Jan;83:14–20. doi:10.1016/j.reprotox.2018.10.010. Epub 2018 Oct 29. PMID:30385129.
14. Liberman RF, Getz KD, Heinke D. Assisted Reproductive Technology and Birth Defects: Effects of Subfertility and Multiple Births. *Birth Defects Res.* 2017 Aug 15;109(14):1144–1153. doi: 10.1002/bdr2.1055. Epub 2017 Jun 21. PMID: 28635008; PMCID: PMC5555800.
15. Mumphe-Mwanja D, Barlow-Mosha L, Williamson D, et al. A hospital-based birth defects surveillance system in Kampala, Uganda. *BMC Pregnancy Childbirth.* 2019 Oct 22;19(1):372. doi:10.1186/s12884-019-2542-x. PMID: 31640605; PMCID: PMC6805492.
16. Mirfazeli A, Kaviani N, Hosseinpoor K. et al. Birth Defects in Northern Iran (2008–2013). *Iran J Public Health.* 2018 Mar;47(3):413–417. PMID: 29845030; PMCID: PMC5971179.
17. Howley MM, Feldkamp ML, Papadopoulos EA, Fisher SC, Arnold KE, Browne ML. National Birth Defects Prevention Study. Maternal genitourinary infections and risk of birth defects in the National Birth Defects Prevention Study. *Birth Defects Res.* 2018 Nov 15;110(19):1443–1454. doi: 10.1002/bdr2.1409. Epub 2018 Nov 6. PMID: 30402975; PMCID: PMC6543540.
18. Davies MJ, Rumbold AR, Marino JL. et al. Maternal factors and the risk of birth defects after IVF and ICSI: a whole of population cohort study. *BJOG.* 2017 Sep;124(10):1537–44. doi:10.1111/1471-0528.14365. Epub 2016 Oct 17. PMID:27748040.
19. Andersen SL, Lönn S, Vestergaard P. et al. Birth defects after use of antithyroid drugs in early pregnancy: a Swedish nationwide study. *Eur J Endocrinol.* 2017 Oct;177(4):369–78. doi:10.1530/EJE-17-0314. Epub 2017 Aug 5. PMID: 28780518.
20. Parker SE, Van Bennekom C, Anderka M, Mitchell AA. National Birth Defects Prevention Study. Ondansetron for Treatment of Nausea and Vomiting of Pregnancy and the Risk of Specific Birth Defects. *Obstet Gynecol.* 2018 Aug;132(2):385–394. doi: 10.1097/AOG.0000000000002679. PMID: 29995744.
21. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC. et al. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. *Cochrane Database Syst Rev.* 2015 Dec 14;(12):CD007950. doi: 10.1002/14651858.CD007950.pub3. PMID: 26662928.
22. Honein MA, Dawson AL, Petersen EE. et al. Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy. *JAMA.* 2017 Jan 3;317(1):59–68. doi: 10.1001/jama.2016.19006. PMID: 27960197.
23. Kirby RS, Browne ML. Population-based birth defects surveillance, epidemiology, and public health practice. *Birth Defects Res.* 2018 Nov 15;110(19):1381–2. doi:10.1002/bdr2.1412. Epub 2018 Nov 6. PMID: 30403010.

Figures

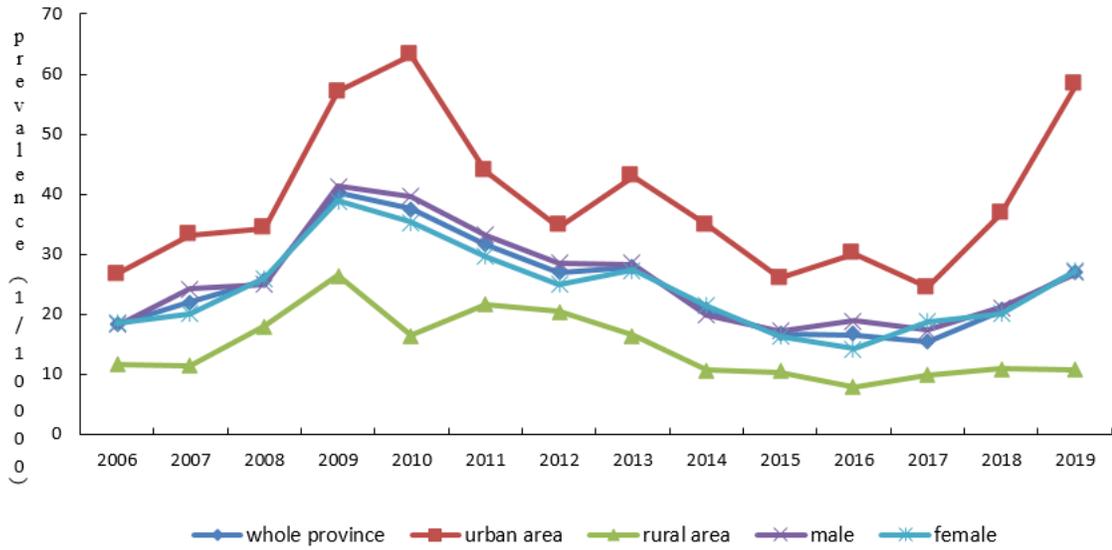


Figure 1

Trends in the incidence of CEM (1/10,000) from 2006 to 2019

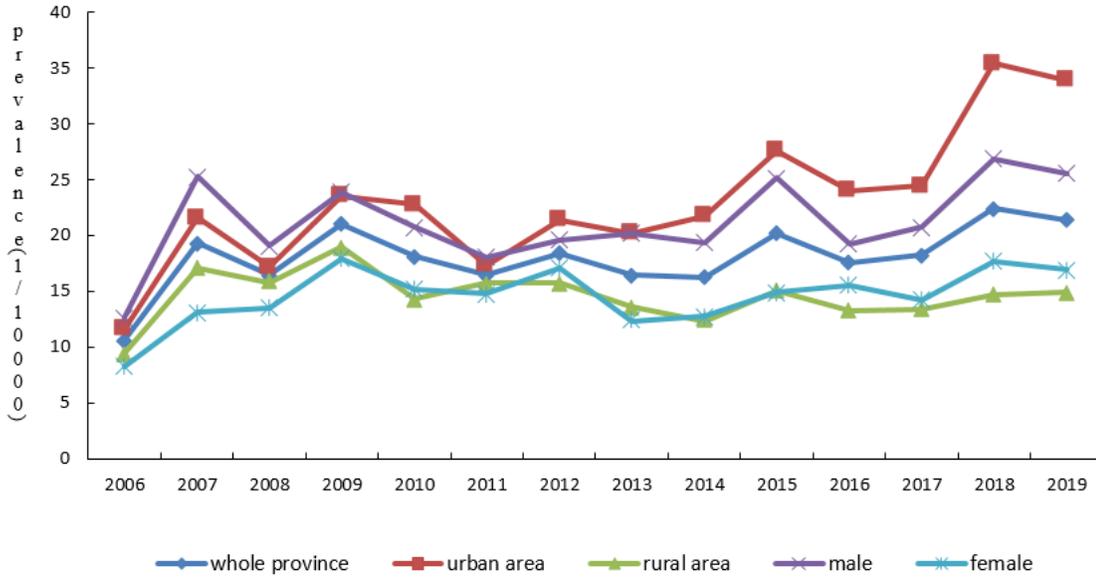


Figure 2

Trends in the incidence of polydactyly (1/10,000) from 2006 to 2019

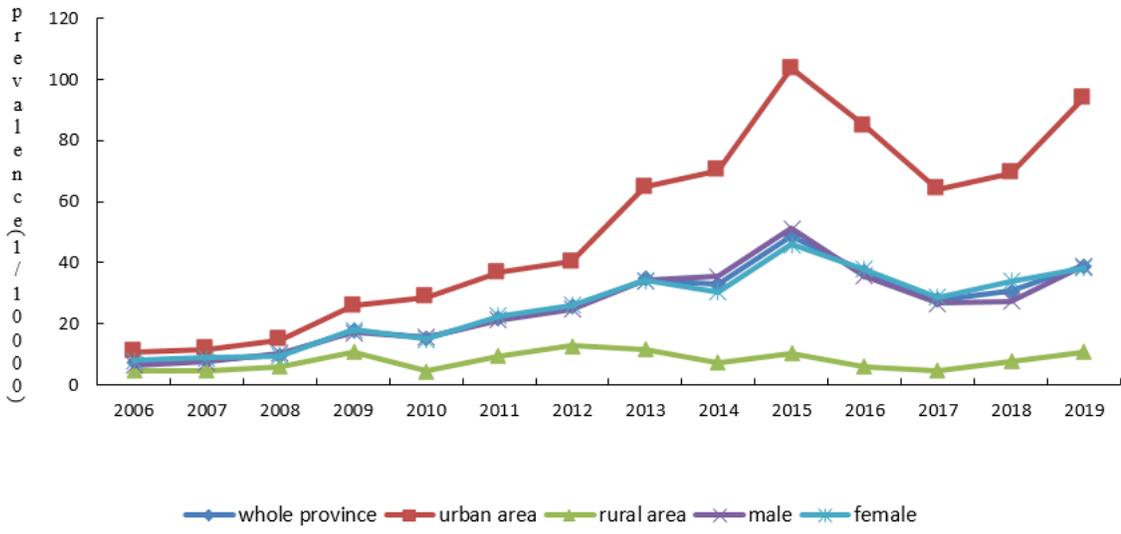


Figure 3

Trends in the incidence of CHD (1/10,000) from 2006 to 2019