

Preplanned Studies

Prevalence and Trends of Birth Defects — Five Counties, Shanxi Province, China, 2003–2022

Duoduo Wang^{1,2}; Zhijiao Song³; Yali Zhang^{1,2}; Le Zhang^{1,2}; Lei Jin^{1,2}; Aiguo Ren^{1,2}; Zhiwen Li^{1,2}; Jufen Liu^{1,2,#}

Summary

What is already known about this topic?

The Shanxi Province, located in northern China, holds the highest prevalence of birth defects (BDs) across the country. Following the implementation of a nationwide folic acid supplementation program in 2009, a significant reduction of 53.89% in the prevalence of neural tube defects (NTDs) was observed in Shanxi from 2012 to 2017. However, despite this decrease, the prevalence rate for congenital heart defects (CHDs) in 2017 was over four times that of the 2012 rate. Since 2014, CHDs have emerged as the most predominant BD in Shanxi.

What is added by this report?

The present study has identified a marked reduction in the prevalence of both total BDs and NTDs in five counties within Shanxi over the past two decades. As of 2017–2022, NTDs continue to be the most prevalent BDs recorded in this region. Contrarily, there has been a noteworthy increase in the prevalence of CHDs, ranking them among the top five most common BDs in the region between 2017 and 2022, though their rate remains below the national average. Additionally, the proportion of external anomalies remains high. Nevertheless, due to constrained access to primary healthcare services and diagnostic facilities, the early detection rate for internal anomalies, particularly CHDs, may be underestimated in the region.

What are the implications for public health practice?

The results of this study underscore the necessity for augmented efforts in promoting folic acid supplementation as a preventive measure for NTDs. Moreover, improvements in the distribution of medical resources within this region are recommended, particularly the introduction and enforcement of local training programs aimed at enhancing CHD screening and diagnostic processes in these respective counties.

Birth defects (BDs) present a substantial clinical and public health concern, notably contributing to infant mortality rates (1). Shanxi Province, in northern China, exemplifies this challenge, displaying the highest prevalence rate for BDs in the country and the highest incidence of neural tube defects (NTDs) worldwide (2). Nevertheless, the initiation of a folic acid supplementation program yielded a 52.49% reduction in NTDs within a span of five years across five counties in Shanxi (3). In contrast, the prevalence of congenital heart defects (CHDs) elevated from 13.23 per 10,000 in 2012 to 58.27 per 10,000 in 2017, and has remained the most common BDs in Shanxi since 2014 (4).

Our study scrutinized the prevalence trends of total BDs, NTDs, and CHDs from 2003 to 2022 in five counties of Shanxi Province, leveraging data from a population-based BD surveillance system. We documented a marked decrease in total BDs and NTDs over the past two decades. Yet, NTDs, with a prevalence of 20.09 per 10,000, continued to be the most prevalent BDs in the region from 2017 to 2022. Moreover, while remaining below the national average, the incidence of CHDs notably increased from 1.24 per 10,000 in 2003 to 13.43 per 10,000 in 2022 and ranked among the top five most common BDs from 2017 to 2022.

Notwithstanding, the study observed a high proportion of external anomalies. Consequently, owing to restricted access to primary healthcare services and diagnostic facilities, the region's early diagnosis rates for internal anomalies, especially CHDs, may be underestimated. As such, it is crucial to enhance the screening and diagnostic procedures for CHDs in these counties.

The data for this study originates from a population-based BD surveillance system in five counties — Pingding, Xiyang, Taigu, Zezhou, and Shouyang — in Shanxi Province. BD diagnosis was conducted by local maternal-fetal medicine specialists and later confirmed by pediatricians at Peking University. Practice quality was assessed in 2004 by a survey, which confirmed that

95.6% of births were included in this dataset, with no underreporting of NTDs (5). We have detailed the system in a prior publication (3).

This surveillance encompasses all pregnant women who have lived in the study area for over a year. It recorded all live births or stillbirths that occurred at 28 or more complete gestational weeks, along with terminations of pregnancies at any gestational age following the prenatal diagnosis of BDs. Data collected covered BD diagnostic criteria (coded in accordance with the 10th Edition of the International Statistical Classification of Diseases and Related Health Problems), sex, gestational weeks, birth outcomes, and maternal residential data. We previously described the classification of BD types in this surveillance (6). The study protocol was examined and approved by the Institutional Review Board of Peking University.

The study's prevalence denominator encompassed all live and still births of 28 or more complete gestational weeks, whereas the numerator included all live births, stillbirths, and pregnancy terminations that presented BDs. BDs categorized as perinatal were defined as incidences at 28 or more complete gestational weeks, while pre-perinatal BDs referred to cases identified prior to the 28-week gestational threshold and, subsequently, induced labor. The Joinpoint Regression Program (Version 5.0.2., 2023; Information Management Services, Inc., Calverton, MD, USA) was utilized to create a Joinpoint regression model, thereby estimating the average annual percentage change (AAPC) in the prevalence of total BDs, NTDs, and CHDs. The comparison of gestational week group, diagnosis, outcome, sex, and residence of CHDs and NTDs was accomplished using Chi-square tests and Fisher's exact tests in the SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). Additionally, perinatal and pre-perinatal proportions, denoting cases of 28 or more and fewer than 28 gestational weeks, respectively, were calculated. Three distinct intervals were defined following population policy and public strategy. In the conducted analysis, a *P*-value less than 0.05 indicated statistical significance.

Between 2003 and 2022, the system logged a cumulative total of 288,987 births with 4,436 instances of BDs. This led to a prevalence rate of 153.50 per 10,000. A significant decline of 40.35% in the total prevalence of BDs was observed over the past two decades, with rates reduced from 195.81 per 10,000 in 2003 to 116.81 per 10,000 in 2022 [AAPC=−2.84%, 95% confidence interval (CI):

−3.90%, −1.77%, *P*<0.001]. Further analysis of the joinpoint regression model in Table 1 pointed out a marked declining trend from 2003 to 2014 [annual percentage change (APC)=−4.39%, 95% CI: −5.66%, −3.11%, *P*<0.001]. However, a subsequent decrease in prevalence was observed from 2014 to 2022, though without statistical significance (APC=−0.66%, 95% CI: −2.78%, 1.51%, *P*=0.523). Moreover, external anomalies still constituted a significant proportion, with the five most prevalent BDs between 2017 and 2022, as displayed in Table 2, being: NTDs (20.09 per 10,000), polydactyly (22.25 per 10,000), cleft lip with or without cleft palate (11.12 per 10,000), external ear malformation (9.13 per 10,000), and CHDs (8.63 per 10,000).

Table 1 illustrates a substantial decline in the prevalence of NTDs, from 116.75 per 10,000 in 2003 to 18.80 per 10,000 in 2022. This decline proved to be statistically significant, with an AAPC of −9.58% (95% CI: −12.92%, −6.12%, *P*<0.001). Furthermore, the proportion of pre-perinatal NTDs exhibited a significant increase over the final three time periods, as depicted in Figure 1. Over the past two decades, all three subtypes of NTDs — primarily anencephaly and spina bifida — demonstrated a downward trend. NTD prevalence by subtype from 2000 to 2019 is detailed in

TABLE 1. Trends in the prevalence of total BDs, NTDs, and CHDs in five counties in Shanxi Province from 2003 to 2022, as determined by Joinpoint analysis.

Types of BDs	Period	APC (95% CI)	P
Total BDs			
Trend 1	2003–2014	−4.39 (−5.66, −3.11)	<0.001
Trend 2	2014–2022	−0.66 (−2.78, 1.51)	0.523
AAPC	2003–2022	−2.84 (−3.90, −1.77)	<0.001
NTDs			
Trend 1	2003–2011	−8.37 (−12.18, −4.39)	0.001
Trend 2	2011–2019	−14.41 (−18.75, −9.84)	<0.001
Trend 3	2019–2022	1.01 (−16.86, 22.72)	0.913
AAPC	2003–2022	−9.58 (−12.92, −6.12)	<0.001
CHDs			
Trend 1	2003–2012	5.35 (−4.82, 16.59)	0.291
Trend 2	2012–2022	20.63 (10.63, 31.53)	<0.001
AAPC	2003–2022	13.13 (6.45, 20.23)	<0.001

Note: Data from only four counties — Zezhou, Pingding, Taigu, and Shouyang — are presented for the year 2003. However, data from five counties are available for all other years.

Abbreviation: BDs=birth defects; NTDs=neural tube defects; CHDs=congenital heart defects; APC=annual percentage change; AAPC=average annual percentage change; CI=confidence interval.

TABLE 2. Prevalence of the top ten BDs in five counties of Shanxi Province from 2003 to 2022 (reported as prevalence per 10,000 births).

Ranking	2003–2009	2010–2016	2017–2022	Total
Number of births	129,824	98,923	60,240	288,987
First	NTDs (98.60)	NTDs (47.92)	NTDs (20.09)	NTDs (64.88)
Second	CL/P (19.95)	CL/P (20.32)	Polydactyly (20.25)	CL/P (18.24)
Third	Polydactyly (13.40)	Polydactyly (15.37)	CL/P (11.12)	Polydactyly (15.50)
Fourth	Congenital hydrocephalus (8.94)	Congenital hydrocephalus (6.57)	External ear malformation (9.13)	Congenital hydrocephalus (6.96)
Fifth	External ear malformation (4.54)	External ear malformation (5.36)	CHDs (8.63)	External ear malformation (5.78)
Sixth	Limb reduction defects (4.31)	Limb reduction defects (4.45)	Syndactyly (6.47)	Limb reduction defects (4.15)
Seventh	Congenital talipes equinovarus (3.39)	CHDs (3.64)	Down syndrome (4.32)	CHDs (3.91)
Eighth	Hypospadias (3.31)	Hypospadias (2.43)	Congenital hydrocephalus (3.32)	Syndactyly (3.15)
Ninth	Anorectal atresia or stenosis (without anus) (2.70)	Syndactyly (2.43)	Limb reduction defects (3.32)	Congenital talipes equinovarus (2.84)
Tenth	Syndactyly (2.16)	Congenital talipes equinovarus (2.12)	Congenital talipes equinovarus (2.82)	Hypospadias (2.77)

Note: Three distinct periods were demarcated based on changes in population policies and public strategies: 2003–2009, prior to the initiation of folic acid supplementation; 2010–2016, following folic acid supplementation but preceding the implementation of the universal two-child policy; and 2017–2022, following the implementation of the universal two-child policy.

Abbreviation: BDs=birth defects; NTDs=neural tube defects; CL/P=cleft lip with or without cleft palate; CHDs=congenital heart defects.

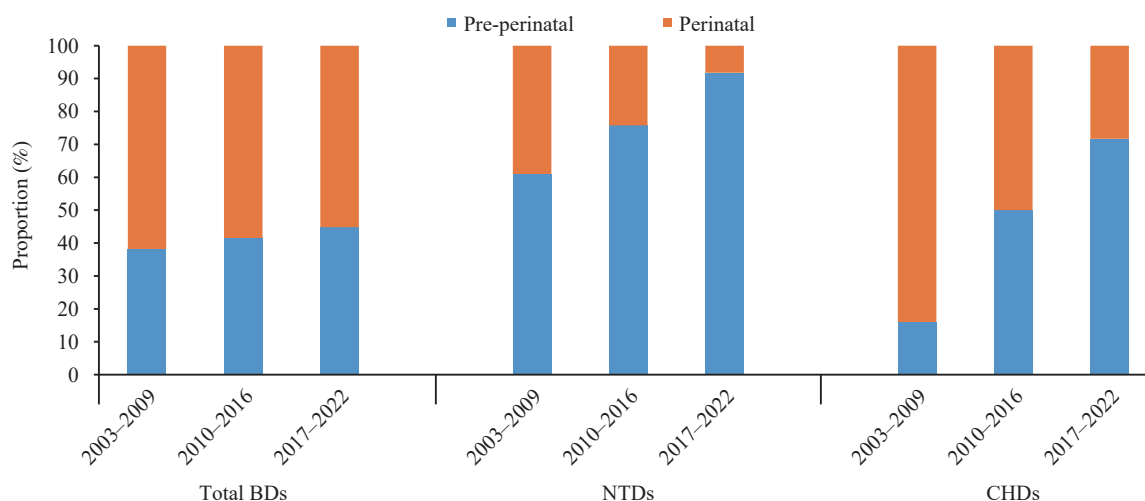


FIGURE 1. Proportion of BDs by gestational weeks and periods across five counties in Shanxi Province, 2003–2022.

Note: Three distinct periods were demarcated based on changes in population policies and public strategies: 2003–2009, prior to the initiation of folic acid supplementation; 2010–2016, following folic acid supplementation but preceding the implementation of the universal two-child policy; and 2017–2022, following the implementation of the universal two-child policy.

Abbreviation: BDs=birth defects; NTDs=neural tube defects; CHDs=congenital heart defects.

* Data pertaining to the gestational week for total BDs was unavailable for four cases, accounting for 0.09% of the data.

a prior publication (6).

Figure 2 presents a decline in the prevalence of the four types of outcomes among NTDs, along with a decreasing proportion of deaths within seven days. A joinpoint regression analysis identified three distinct trends in NTD prevalence. Initially, a notable statistical annual reduction from 116.75 per 10,000 in 2003 to 69.59 per 10,000 in 2011 was observed

(APC=−8.37%, 95% CI: −12.18%, −4.39%, $P=0.001$). Subsequently, a sharp decrease from 69.59 per 10,000 in 2011 to 16.39 per 10,000 in 2019 was recorded (APC=−14.41%, 95% CI: −18.75%, −9.84%, $P<0.001$). This was then followed by a marginal fluctuation from 2019 to 2022 (APC=1.01%, 95% CI: −16.86%, 22.72%, $P=0.913$).

On the contrary, there was a significant ascending

trend in the prevalence of CHDs (AAPC=13.13%, 95% CI: 6.45%, 20.23%, $P<0.001$). The Joinpoint regression analysis, as outlined in Table 1, showed two distinct trends in the prevalence of CHDs. From 2003 to 2012, a relatively low level was observed with no significant trends (APC=5.35%, 95% CI: -4.82%, 16.59%, $P=0.291$), which was then followed by a steep and significant incline, from 0.64 per 10,000 in 2012

to 10.97 per 10,000 in 2022 (APC=20.63%, 95% CI: 10.63%, 31.53%, $P<0.001$). Figure 1 illustrates a considerable rise in the proportion of pre-perinatal CHDs during the last three periods.

Table 3 reveals that CHDs have a higher incidence of perinatal cases at or beyond 28 gestational weeks (47.37% vs. 33.28%, $P=0.001$) and mortality within seven days (39.22% vs. 18.93%, $P<0.001$), compared

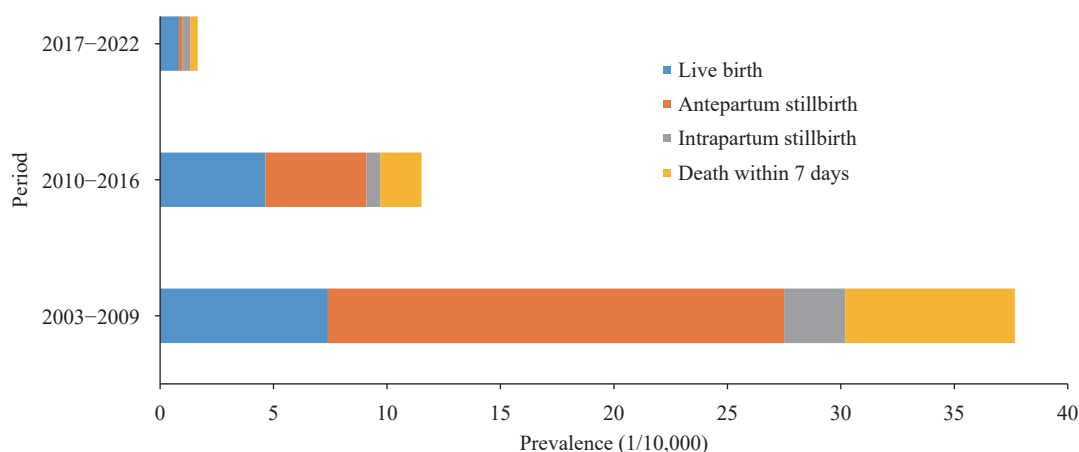


FIGURE 2. Prevalence of perinatal neural tube defects by outcomes and periods across five counties in Shanxi, 2003–2022. Note: Three distinct periods were demarcated based on changes in population policies and public strategies: 2003–2009, prior to the initiation of folic acid supplementation; 2010–2016, following folic acid supplementation but preceding the implementation of the universal two-child policy; and 2017–2022, following the implementation of the universal two-child policy.

TABLE 3. Comparison of characteristics between NTDs and CHDs in five counties of Shanxi Province, 2003–2022 (n , %).

Variables	NTDs	CHDs	P-value
No. of cases	1,875 (42.27)	114 (2.57)	
Gestational weeks			0.002
<28 weeks	1,251 (66.72)	60 (52.63)	
≥28 weeks	624 (33.28)	54 (47.37)	
Diagnosed by ultrasound*	1,223 (99.27)	49 (98.04)	0.333
Outcome†			<0.001
Live birth	148 (23.95)	20 (39.22)	
Antepartum stillbirth	310 (50.16)	8 (15.69)	
Intrapartum stillbirth	43 (6.96)	3 (5.88)	
Death within 7 days	117 (18.93)	20 (39.22)	
Male§	847 (45.20)	61 (54.46)	0.054
Residence¶			<0.001
Urban	240 (12.80)	31 (27.43)	
Rural	1,635 (87.20)	82 (72.57)	

Abbreviation: NTDs=neural tube defects, CHDs=congenital heart defects.

* Diagnostic data were only procured for cases with a pre-perinatal age of less than 28 weeks; however, this information was unavailable for 22 cases, which represents 1.68% of the total cases studied.

† Outcome data were not available for nine cases, accounting for 1.33% of total instances.

§ For 3 cases (0.15%), sex data were unavailable, while 45 cases (2.40%) remained unidentified in terms of sex for NTDs.

¶ Data on residence were not available for 1 case (0.05%).

to NTDs. Both NTDs and CHDs were predominantly diagnosed using ultrasound (99.27% *vs.* 98.04%, $P=0.333$) and were predominantly found in women from rural areas (87.20% *vs.* 72.57%, $P<0.001$).

DISCUSSION

Our research uncovered a significant decline in the prevalence of BDs in select regions of Shanxi Province over the past two decades. This trend suggests that the area's comprehensive strategies for managing and preventing BDs were successful. The observed average prevalence rate of BDs from 2003 to 2022 was 153.50 per 10,000, mirroring the national average of 154.98 per 10,000 reported from 2010–2016 (7). The prevalence decreased substantially from 2003 to 2014 and then became stable from 2014 to 2022, which could be attributed to recent changes in China's birth policy. The Chinese government introduced a partial two-child policy in November 2013 and a universal two-child policy in January 2016. Following these changes, the incidence of high-risk pregnancies rose from 19.4% in 2013 to 24.7% in 2016, an increase from the 15.7% reported in 2008 (8). Additionally, the high rate of external anomalies signals that further improvements are needed in Shanxi's prenatal diagnostic capabilities.

Shanxi Province in northern China has the highest global prevalence of NTDs (2). NTD prevalence documented within this BD surveillance system saw a significant decline from 2011–2019 due to a comprehensive folic acid supplementation program implemented in 2009. Despite this, fluctuations were observed between 2019 and 2022, potentially resulting from a decrease in regional births mirroring the national trend (9), or signaling a plateau following the implementation of NTD reduction measures. Notably, NTD prevalence in this region exceeded the national average (1.45/10,000 in 2020) (10), with 20.09 per 10,000 in 2017–2022. This disparity might stem from inadequate adherence to folic acid intake during the periconceptional period. Although the number of women supplementing increased, rural women in the high-prevalence Shanxi population showed continued disparities compared to the low-prevalence Jiangsu population, possibly due to impeded preventive action prompted by late supplementation initiation (11). Consequently, an emphasis on health education is necessary to promote adherence to folic acid recommendations. Other factors, such as folic acid resistance, need to be investigated in future studies as

potential contributors to NTD incidence.

CHD prevalence in our study area has seen a substantial increase over the past two decades, positioning it among the top five BDs in 2017–2022. Indeed, there has been a significant increase in pre-perinatal CHDs detected before 28 gestational weeks, despite the majority occurring at or after 28 gestational weeks. The rise in CHD prevalence may be attributed to improved detection methods, revisions in diagnostic standards, and the augmentation of neonatal CHD screening in China since 2018 (12). However, regional CHD prevalence falls short of national prevalence and that of other Chinese regions. Nationally, CHD incidence significantly escalated from 11.40 per 10,000 in 2000 to 173.20 per 10,000 in 2020 — significantly higher than the global average (94/10,000) — indicating CHDs as the most common BDs since 2010 in China (10,13). Economic and medial resource disparities among regions may have resulted in this difference.

The substantial prevalence of external anomalies highlights the need for improving prenatal diagnostic capabilities. CHD prevalence may be influenced by prenatal diagnostic quality and neonatal physical examination techniques, which are affected by local perinatal healthcare availability and diagnostic tech proficiency (7). Coastal provincial-level administrative divisions (PLADs) have established CHD screening networks, but in economically deprived regions, many children with CHDs are undiagnosed or untreated. In Shaanxi Province, CHDs have the highest prevalence (77.32/10,000) among BDs, an economically worse-off and less medically developed region (14). On the other hand, the economically prosperous and medically advanced Zhejiang Province saw an increase in overall CHD incidence from 127 per 10,000 in 2014 to 206 per 10,000 in 2018 (12). The local primary healthcare's insufficient capacity may be the reason why early CHD diagnoses are underestimated in Shanxi Province. It is crucial that diagnostic capabilities for internal anomalies, especially CHDs, be improved for perinatal infants in this region.

Our study boasts several key strengths. Primarily, the population-based BD surveillance system employed herein encompasses both perinatal and pre-perinatal BDs, offering a broader scope than the majority of studies, which frequently only report perinatal BDs at or beyond 28 gestational weeks within a hospital-based surveillance system. The incorporation of BDs prior to 28 weeks of gestation is fundamental in accurately

determining the true incidence of BDs, thereby establishing a robust foundation for evaluating the real-time effects of primary prevention measures. Furthermore, it serves to stimulate health authorities at all tiers to prioritize the enhancement of primary prevention strategy implementation in the future. Additionally, the span of two decades of consistent surveillance data encapsulates durable trends of change.

This study, however, presented several limitations. Primarily, the limited selection area, comprising predominantly rural counties in Shanxi Province, may constrain the applicability of our conclusions on a more expansive geographic scale, such as the entire PLADs or the nation as a whole. For more complete subsequent investigations, the inclusion of extensive individual exposure data is crucial to delve deeper into the origins of BDs.

In summary, the region has witnessed a marked decline in total BD prevalence over the past two decades, attributable to holistic preventive measures rolled out in the area. Importantly, the folic acid supplementation program, initiated broadly in 2009, resulted in a significant decrease in NTDs. This highlights the critical role of persistent folic acid supplementation promotion in forestalling NTDs. Alternatively, the region has seen a substantial rise in CHD prevalence. Less than optimal access to primary healthcare services and diagnostic facilities likely leads to an underestimation of early diagnosis rates for internal anomalies, particularly CHDs, in the region. Therefore, an immediate reallocation strategy favoring improved medical resources is vital, with particular emphasis on setting up local training programs geared towards enhancing internal anomaly screening and diagnostic capabilities, with a primary focus on CHDs in these counties.

Acknowledgements: We would like to express our appreciation to all the participants of the study. We express our profound gratitude to all hospital staff who collaborated with us from Pingding, Xiyang, Taigu, Zezhou and Shouyang counties. We'd like to acknowledge Prof. Gabriel L. Galea, Developmental Biology and Cancer Department, Institute of Child Health, University College London, for his critical suggestions and feedback for the manuscript.

Funding: National Key Research and Development Program, Ministry of Science and Technology of the People's Republic of China (No. 2021YFC2701101), and National Natural Science Foundation of China (No. 82373582).

doi: 10.46234/ccdcw2023.153

Corresponding author: Jufen Liu, liujufen@bjmu.edu.cn.

¹ Institute of Reproductive and Child Health / National Health Commission Key Laboratory of Reproductive Health, Peking University, Beijing, China; ² Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China; ³ Department of Health Education, Shanxi Women and Children Health Hospital, Taiyuan City, Shanxi Province, China.

Submitted: August 11, 2023; Accepted: September 02, 2023

REFERENCES

- Feldkamp ML, Carey JC, Byrne JLB, Krikov S, Botto LD. Etiology and clinical presentation of birth defects: population based study. *BMJ* 2017;357:j2249. <http://dx.doi.org/10.1136/bmj.j2249>.
- Gu X, Lin LM, Zheng XY, Zhang T, Song XM, Wang JF, et al. High prevalence of NTDs in Shanxi Province: a combined epidemiological approach. *Birth Defects Res Part A Clin Mol Teratol* 2007;79(10):702 – 7. <http://dx.doi.org/10.1002/bdra.20397>.
- Liu JF, Zhang L, Li ZW, Jin L, Zhang YL, Ye RW, et al. Prevalence and trend of neural tube defects in five counties in Shanxi province of Northern China, 2000 to 2014. *Birth Defects Res Part A Clin Mol Teratol* 2016;106(4):267 – 74. <http://dx.doi.org/10.1002/bdra.23486>.
- Zhang ZL, Hu XM, Fan HX, Zhang J, Li YF, Song ZJ, et al. Epidemiological analysis of the surveillance data of birth defects among perinatal infants in Shanxi Province, 2012–2017. *Chin Gen Pract* 2020;23(10):1298 – 304. <http://dx.doi.org/10.12114/j.issn.1007-9572.2019.00.708>. (In Chinese).
- Li ZW, Ren AG, Zhang L, Ye RW, Li S, Zheng JC, et al. Extremely high prevalence of neural tube defects in a 4-county area in Shanxi Province, China. *Birth Defects Res Part A Clin Mol Teratol* 2006;76(4):237 – 40. <http://dx.doi.org/10.1002/bdra.20248>.
- Liu JF, Wang LL, Zhang YL, Zhang L, Jin L, Li ZW, et al. Selected structural birth defects — Shanxi Province, China, 2000-2019. *China CDC Wkly* 2020;2(37):718 – 22. <http://dx.doi.org/10.46234/CCDCW2020.196>.
- Zhou TJ, He LK, Zhao ZL, Liu WX, Luo M, Li XY. Incidence of birth defects in Sichuan Province from 2010 to 2018. *J Chongqing Med Univ* 2021;46(10):1206 – 10. <http://dx.doi.org/10.13406/j.cnki.cyx.002616>. (In Chinese).
- Liu J, Song L, Qiu J, Jing WZ, Wang L, Dai Y, et al. Reducing maternal mortality in China in the era of the two-child policy. *BMJ Glob Health* 2020;5(2):e002157. <http://dx.doi.org/10.1136/bmjgh-2019-002157>.
- Chen ZZ, Wang YL, Lan FY, Li S, Wang JH. An expanded view of infertility: the challenge of the changing profiling of major birth defects in China. *Biosci Trends* 2023. <http://dx.doi.org/10.5582/BST.2023.01160>.
- Department of Maternal and Child Health and Community Health, Ministry of Health. National Maternal and Child Health Surveillance and Annual Report Newsletter (2022). Available online at: <http://www.mchscn.cn>. (accessed August, 2022). (In Chinese).
- Liu JF, Jin L, Meng QQ, Gao LL, Zhang L, Li ZW, et al. Changes in folic acid supplementation behaviour among women of reproductive age after the implementation of a massive supplementation programme in China. *Public Health Nutr* 2015;18(4):582 – 8. <http://dx.doi.org/10.1017/S1368980014000950>.
- Zhang XH, Sun Y, Zhu JJ, Zhu YN, Qiu LQ. Epidemiology, prenatal diagnosis, and neonatal outcomes of congenital heart defects in eastern China: a hospital-based multicenter study. *BMC Pediatr* 2020;20(1):416. <http://dx.doi.org/10.1186/s12887-020-02313-4>.
- Liu YJ, Chen S, Zühlke L, Black GC, Choy MK, Li NX, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol* 2019;48(2):455 – 63. <http://dx.doi.org/10.1093/ije/dyz009>.
- Pei LL, Kang YJ, Cheng Y, Yan H. The association of maternal lifestyle with birth defects in Shaanxi province, northwest China. *PLoS One* 2015;10(9):e0139452. <http://dx.doi.org/10.1371/journal.pone.0139452>.