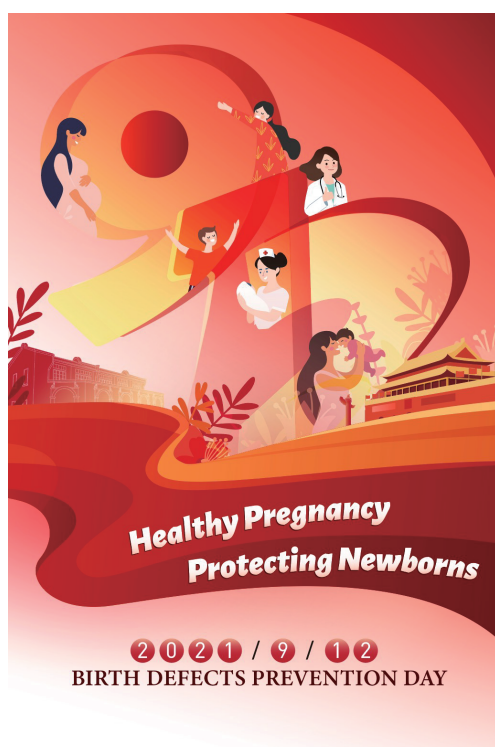


CHINA CDC WEEKLY



Vol. 3 No. 37 Sep 10, 2021

中国疾病预防控制中心周报



BIRTH DEFECTS PREVENTION DAY ISSUE

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ISSN 2096-7071



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Cover Image: Adapted from a poster published by the Department of Maternal and Child Health of the National Health Commission of China and the March of Dimes Birth Defects Foundation of China (MDBDFC).
This week's issue was organized by Guest Editors Zhiwen Li and Jiangli Di.

Foreword

Prevention and Control of Birth Defects in China: Achievements and Challenges

Birth defects, including congenital structural or functional abnormalities, remained a primary cause of child mortality and morbidity and represented a significant clinical and public health challenge. Annually, 3%–6% of infants, nearly 8 million newborns, were born worldwide with a serious birth defect, among those more than 90% are in low and middle-income countries (1).

In China, birth defects affected an estimated 5.6%, approximately 900,000, newborns each year and were the leading cause of infant mortality and a major cause of morbidity (2). To raise awareness of birth defects, to develop and implement primary prevention programs, and to expand referral and care services, the Chinese government declared the September 12 as the “National Birth Defects Prevention Day” at the Second International Conference on Birth Defects and Disabilities in the Developing World which held in Beijing in 2005.

China has continuously improved the laws and regulations and has carried out a series of major projects related to the prevention and control of birth defects. As a result, the preventive measures to prevent birth defects have been continuously strengthened. Nearly 102 million childbearing women took folic acid free of charge from 2009 to 2018, 83.49 million planned pregnancy couples received free pre-pregnancy health examinations in 2010–2018. The screening rate for neonatal genetic or metabolic diseases reached 97.5% in 2017. As of 2018, about 1.65 million couples in 10 southern provincial-level administrative divisions (PLADs) had received free thalassemia screening. The treatment of 72 types of major birth defects such as congenital heart disease has been incorporated into critical illness insurance program. Through unremitting efforts, the prevention and treatment of birth defects has achieved remarkable achievements.

The child mortality rate caused by birth defects has also decreased significantly. For example, the birth defects induced mortality rate of children under 5 years of age reduced from 3.5‰ in 2007 to 1.6‰ in 2017. The incidence of some major birth defects is decreasing year by year. For example, the incidence of perinatal neural tube defects decreased from 27.4 per 10,000 in 1987 to 1.5 per 10,000 in 2017, a decrease of 94.5%. The incidence of fetal edema syndrome (severe α thalassemia) in Guangdong and Guangxi dropped from 21.7 and 44.6 per 10,000 in 2006 to 1.93 and 3.15 per 10,000 in 2017, respectively, a decrease of 91% and 93%, respectively (3).

With close attention and strong support from the Chinese government, opportunities to prevent birth defects are abundant in China, but there are also many challenges in the process. The incidence of some major birth defects did not show a significant decrease, such as in congenital heart defects and oral facial clefts (4). In some northern regions, the incidence of neural tube defects remained higher than levels worldwide (5). Although the rate of folic acid use increased dramatically, the percentage of correct use was still low (6). Macrosomia accounted for a high proportion of adverse birth outcomes due to maternal overnutrition and insufficient exercise before and during pregnancy (7). Meanwhile, the impacts of socioeconomic and environmental changes on child health needed more attention, including pollution following modern industrialization and the increasing number of women of advanced maternal age following the three-child policy. Therefore, government officials, healthcare workers, researchers, and public health practitioners in this field should put more effort into prevention, and comprehensive and integrated efforts need to be taken to accelerate and improve postnatal care, surgical correction, rehabilitation, and social support.

doi: 10.46234/ccdcw2021.191

Submitted: August 31, 2021; Accepted: September 06, 2021

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Preplanned Studies

Orofacial Clefts in High Prevalence Area of Birth Defects — Five Counties, Shanxi Province, China, 2000–2020

Jufen Liu^{1,2}; Yali Zhang^{1,2}; Le Zhang^{1,2}; Linlin Wang^{1,2}; Lei Jin^{1,2}; Nicholas D E Greene³; Zhiwen Li^{1,2,#}; Aiguo Ren^{1,2}

Summary

What is already known on this topic?

The prevalence of structural birth defects, especially neural tube defects, decreased after national folic acid (FA) supplementation initiation.

What is added by this report?

The prevalence of orofacial clefts (OFCs) in five counties of Shanxi Province in northern China, including most subtypes except cleft palate, showed a downward trend in the past two decades. In this study, pre-perinatal prevalence increased due to earlier detection.

What are the implications for public health practice?

Periconceptional supplementation with FA may contribute to the decline in OFCs prevalence, while the effect on the OFCs subtype needs further investigation. Continuing to advocate for earlier supplementation (3 months before conception) and increased supplementation frequency (daily consumption) could promote further reduction in the prevalence of OFCs. Specific surveillance of this effect in the era of universal three-child policy is warranted.

Orofacial clefts (OFCs) are among the most common human congenital malformations worldwide, and the majority of OFCs are non-syndromic (1). Although most OFCs are not fatal, children born with non-syndromic cleft lip, with or without cleft palate (NSCL/P), may have low intelligence and/or impaired speech/language development (2). In addition, OFCs also impose significant social, financial, and public health burdens. Periconceptional folic acid (FA) supplementation could help reduce the risk of neural tube defects (NTDs) (3) and other selected structural birth defects, including OFCs (4). However, the effect on different subtypes of OFCs has not been thoroughly evaluated. Similarly, the effect of policy changes, including the change from mandatory pre-marital health examination to voluntary examinations, release of the two-child population policy, and the subsequent

update to the ongoing three-child policy, have not yet been explored. The current study examined the trend of OFCs in 5 counties based on data from a population-based birth-defect surveillance system in a high prevalence area of northern China from 2000 to 2020. The prevalence of OFCs in the 5 counties in Shanxi Province decreased significantly in the past two decades. Periconceptional supplementation with FA may have contributed to the decline in OFC prevalence.

The data used in the current study came from a population-based birth-defect surveillance system in Shanxi Province. Details of the system have been described in our previous publication (3). In summary, all livebirths or stillbirths of 28 or more complete gestational weeks and pregnancy terminations at any gestational age following the prenatal diagnosis of birth defects among pregnant women who reside in five counties located in Shanxi Province (Pingding, Shouyang, Taigu, Xiyang, and Zezhou) for more than 1 year were included. OFCs were coded Q35–37 according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) as different types of birth defect collected in the system (Table 1). The birth prevalence of OFCs by year, period, type, and gestational week's group was compared using chi-squared tests. Two-tailed $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS Statistics for Windows (Version 24.0. IBM Corp., Armonk, NY, USA).

From 2000 to 2020, a total of 302,101 births and 712 cases of OFCs were recorded in the system, resulting in a total prevalence of 23.57/10,000 births. The proportion of perinatal OFCs with ≥ 28 gestational weeks accounted for 100% in 2000 and 41.7% in 2020 (Figure 1A) while the proportion of pre-perinatal OFCs with < 28 gestational weeks accounted for 0% in 2000 and 58.3% in 2020. The perinatal prevalence decreased dramatically, from more than 30/10,000 in 2002 to merely 5.9/10,000 in 2020 (chi-squared: 39.922, $P < 0.05$) (Figure 1B). The

TABLE 1. Prevalence of orofacial clefts (OFCs) by subtype and gestational weeks in 5 counties of Shanxi Province, 2000–2020.

ICD-10 code	Gestational weeks					
	<28 weeks		≥28 weeks		Total	
	n	Prevalence, 1/10,000	n	Prevalence, 1/10,000	n	Prevalence, 1/10,000
Cleft palate (Q35)	4	0.13	98	3.24	102	3.38
Cleft lip (Q36)	38	1.26	249	8.24	287	9.50
Cleft lip with cleft palate (Q37)	48	1.59	275	9.10	323	10.69
Total	90	2.98	622	20.59	712	23.57

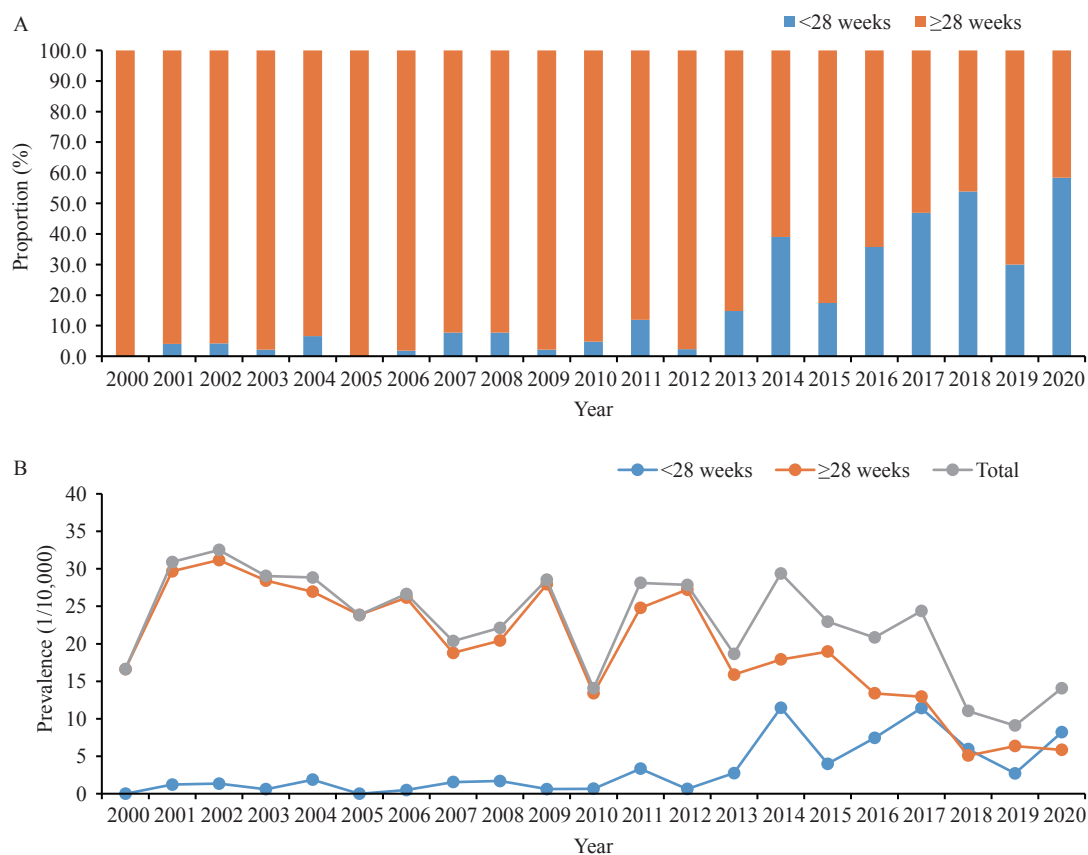


FIGURE 1. Orofacial clefts (OFCs) by gestational week and year in 5 counties, Shanxi Province, China, 2000–2020. (A) Proportion of OFCs; (B) Prevalence of OFCs.

Note: Perinatal prevalence (cases of 28 or more gestational weeks), pre-perinatal prevalence (cases before 28 gestational weeks), and total prevalence (all cases regardless of gestational age) were calculated. Significant time points and corresponding population policy and public strategies are as follows: 2003, canceled mandatory pre-marital physical check-ups; 2009, national campaign for FA supplementation; 2012, population policy transition; and 2016, release of universal two-child policy.

decreasing trend in overall OFCs was also reflected in decreasing frequency of OFCs detected at perinatal stage (Figure 2A) (chi-squared: 120.001, $P < 0.05$). While the pre-perinatal OFCs showed an upward trend during the past two decades due to early detection.

Cleft lip with cleft palate was the most common type among all OFCs, followed by cleft lip alone, and

isolated cleft palate was the third most common type. The rate of cleft lip with cleft palate was 10.69 per 10,000 births and accounted for 45% of OFCs in this population. The prevalence of OFCs detected at the perinatal stage (20.59/10,000) was higher than that detected at pre-perinatal stage (2.98/10,000) (Table 1).

Among all types of OFCs, the prevalence of cleft lip decreased the most (Figure 2B): from 15.15 per 10,000

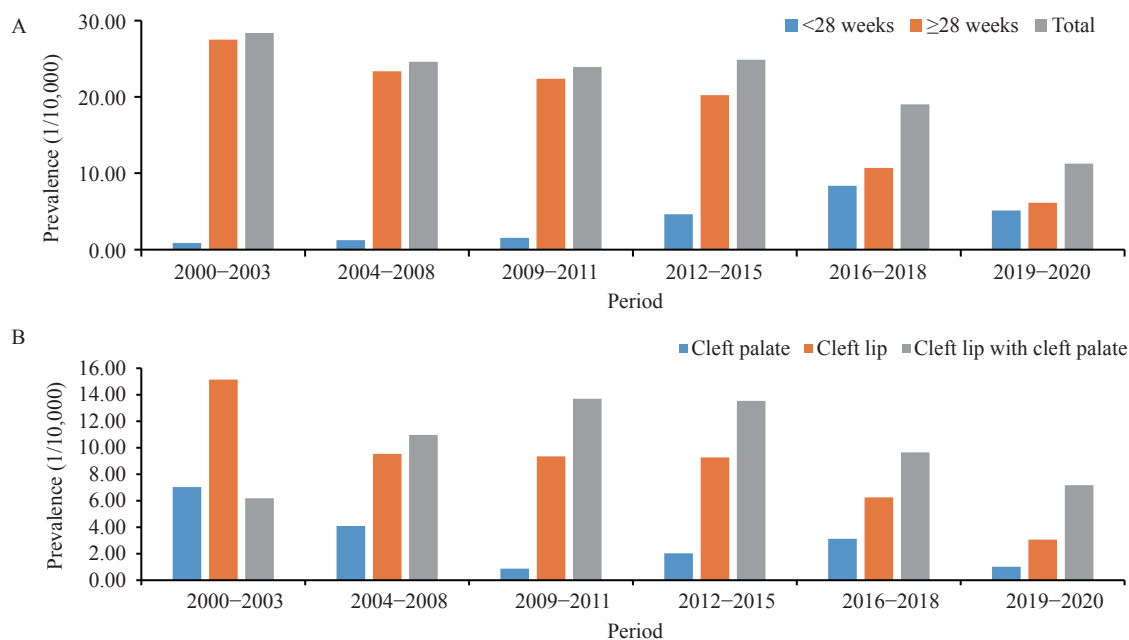


FIGURE 2. Prevalence of orofacial clefts (OFCs) by period in 5 counties of Shanxi Province, 2000–2020. (A) pooled OFCs by gestational weeks; (B) OFCs by subtype.

Note: Perinatal prevalence (cases of 28 or more gestational weeks), pre-perinatal prevalence (cases before 28 gestational weeks), and total prevalence (all cases regardless of gestational age) were calculated. The 6 periods were divided according to population policy and public strategy, i.e., 2000–2003 (Period before voluntary pre-marital physical check-ups), 2004–2008 (Period of voluntary pre-marital physical check-ups and before FA supplementation), 2009–2011 (Period of after FA supplementation), 2012–2015 (Period of population policy transition), 2016–2018 (Period of universal two-child policy), and 2019–2020.

live births between 2000–2003 to 9.35 per 10,000 live births between 2009–2011; from 6.26 per 10,000 live births between 2016–2018 to 3.08 per 10,000 live births between 2019–2020; an overall reduction of 80% in the past 2 decades (Overall reduction, chi-squared: 28.526, $P < 0.05$). Cleft lip with cleft palate increased from 6.19 per 10,000 live births to as high as 13.70 per 10,000 live births between 2000–2011 and decreased to 7.18 per 10,000 live births between 2019–2020 (Overall reduction, chi-squared: 21.356, $P < 0.05$). Cleft palate showed a decreasing trend from 7.04 to 0.87 per 10,000 live births during the first decade and slightly increased to 2–3 per 10,000 live births after that (Overall reduction, chi-squared: 34.837, $P < 0.05$).

DISCUSSION

This population-based birth defect surveillance system showed that the overall prevalence of OFCs in the 5 counties in Shanxi Province decreased significantly from 30.9 per 10,000 births to 14.1 per 10,000 in the past two decades. We hypothesize that the introduction of periconceptional supplementation

with FA may have contributed to this decline. In this case, continuing to advocate for earlier supplementation with FA, which should start from at least 3 months before conception, and increased frequency of supplementation (daily consumption) may promote further reduction of OFCs. The overall prevalence of OFCs showed a continuous decreasing trend when live births significantly declined in China. Specifically monitoring the prevalence of OFCs in the era of the universal three-child policy is warranted.

The prevalence of OFCs in these 5 counties of Shanxi Province was still high, with 14.1 per 10,000 births in 2020, which was significantly higher than the national average and Guangdong Province (7.55 per 10,000 births), Cuba (7.8 per 10,000 births), and the United States (10.0 per 10,000 births). Risk factors for OFCs have been extensively explored. Genetic mutations that disrupt folate metabolism and transportation pathways, including methylenetetrahydrofolate reductase (MTHFR), and reduced folate carrier (RFC1) were studied among the Chinese population (5). A moderate association between MTHFR C677T polymorphism with NSCL/P was revealed in a population from northern

China, and there was a higher incidence associated with the T allele in the north than in the south (6). Future studies of the genetic basis of OFCs are required among northern Chinese populations.

OFCs have a complex etiology resulting from genetic variants combined with environmental exposure factors. Socioeconomic improvements, including higher earnings and higher education levels, would likely better prevent birth defects. Environmental factors including nutrition, medication use, and chemical exposures could also influence the risk for OFCs. FA fortification may have beneficial effects on non-syndromic OFCs (RR=0.88; 95% CI: 0.81–0.96) (7). Our study revealed a continuous decline in the prevalence of OFCs after the initiation of comprehensive FA supplementation among Chinese pregnant women, similar to the trend observed for neural tube defects (4). The nationwide FA supplementation program started from rural areas since 2009; our study showed that the prevalence of OFCs after 2009 was significantly lower than that before 2009, especially cleft lip with/without cleft palate. Therefore, women residing in the 5 counties in this study may have benefited from the program providing free FA supplements. The effect of OFCs on cleft palate requires further investigations as suggested by a recent case-control study (8). As FA supplementation has a strong impact on plasma folate concentrations, earlier supplementation and increased supplementation frequency could potentially promote further reduction of birth defects (9). Our previous study revealed that *in utero* exposure to As, Cd, Pb, and Ni might increase the risks of OFCs in newborns, and a dose-response relationship between risks for total OFCs and different types of OFCs, and the aforementioned heavy metals was observed (10). A further two-stage study revealed that exposure to Pb increased the risk for NSCL/P and this may partly be explained by hypermethylation of WNT3A (11). Besides DNA methylation, other epigenetic modifications, such as histone modifications and microRNA expressions, are emerging mechanisms of importance for orofacial development.

Cleft lip with or without cleft palate decreased significantly during the past two decades. In our study, although the total prevalence of OFCs decreased with time, pre-perinatal OFCs increased. The improvement of the detection method could have contributed to this increase. With the implementation of FA supplementation, more women understood the importance of the pre-natal screening program and went to have prenatal checks earlier. Modern

ultrasound technology assists obstetricians and gynecologists to identify structural malformations such that the proportion of OFCs discovered before 28 weeks increased. Early prenatal examination still needs to be applied more widely in the future.

The number of live births in the study areas have declined since 2016, especially between 2019–2020, which coincided with a decreased fertility rate and may be related to the changing population structure, so further studies are still needed to explore the possible effect of population policy changes as well as fertility transitions. The total number of live births was as high as 20,000 around 2004–2006 but only 8,528 in 2020. As advanced maternal age (AMA) is associated with an overall increased risk for major anomalies, following the enactment of the universal three-child policy in 2021, the risk for OFCs due to AMA may deserve more attention in the near future.

The strength of the current study resides in the population-based surveillance data which included all birth defects regardless of gestational weeks. Our study could provide a more accurate estimation than that provided by hospital-based surveillance data (which only included birth defects detected at more than 28 gestational weeks). Secondly, we collected data over a period of more than 20 years which enabled the analysis of long-term trends.

This study was subject to some limitations. There was a lack of detailed information on the details of NSCL/P, for example whether cleft was bilateral or unilateral, located in hard or soft palate. The study areas were located in Shanxi Province and only limited counties were included, which only reflected the situation of high prevalence of birth defects. Furthermore, no gender effect was considered.

Acknowledgements: Collaborating hospital staff from Pingding, Shouyang, Taigu, Xiyang, and Zezhou counties.

Funding: This study is supported by the National Key Research and Development Program, Ministry of Science and Technology from P.R. China (Grant No. 2016YFC1000501), Natural Science Foundation of China (No.81973056) and Medical Research Council (Grant Ref: MR/T003847/1) from UK.

doi: 10.46234/ccdcw2021.192

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Submitted: August 08, 2021; Accepted: September 01, 2021

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Preplanned Studies

Passive Smoking During the Periconceptional Period and Risk for Neural Tube Defects in Offspring — Five Counties, Shanxi Province, China, 2010–2016

Yali Zhang^{1,2}; Jufen Liu^{1,2}; Le Zhang^{1,2}; Lei Jin^{1,2}; Nicholas D E Greene³; Zhiwen Li^{1,2,*}; Aiguo Ren^{1,2}

Summary

What is already known about this topic?

Passive smoking during pregnancy, which is prevalent in China, has been reported to be associated with an increased risk for neural tube defects (NTDs) in five counties of Shanxi Province in northern China.

What is added by this report?

After 4 years since the implementation of the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) in China, 59.4% of mothers of NTDs cases and 29.4% of mothers of healthy controls reported passive smoking during the periconceptional period. The association between periconceptional passive smoking and an increased risk for NTDs remains in the study population.

What are the implications for public health practice?

It's urgent to take measures to prevent passive smoking among pregnant women to minimize the harmful effects on offspring.

Neural tube defects (NTDs) are severe congenital malformations in the central nervous system, which include anencephaly, spina bifida, and encephalocele. Research has confirmed that folic acid supplementation during the periconceptional period has a protective effect (1–2). Nonetheless, some NTDs are not preventable by folic acid supplementation. Periconceptional exposure to passive smoking has been reported to increase the risk of NTDs (3–4). The adverse effects of maternal passive smoking as a potential risk factor for NTDs is getting more attention (5). China is the largest producer and consumer of tobacco products in the world, with more than 300 million smokers and 740 million nonsmokers exposed to second-hand smoke (6). Since the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) officially took effect in China in 2006, China has taken strong measures to

ban smoking in public places. This study aimed to investigate the effect of maternal passive smoking exposure on the risk of NTDs in offspring in five counties within Shanxi Province of China after 4 years of FCTC implementation. The results showed that there was an association between periconceptional passive smoking and an increased risk for NTDs. Measures need to be taken to prevent passive smoking among pregnant women to minimize the harmful effects on offspring.

Data were analyzed from an ongoing case-control study based on population-based birth-defect surveillance system that covered five counties (Xiyang, Pingding, Taigu, Shouyang, and Zezhou) in Shanxi Province. The surveillance system monitors major external structural birth defects that were diagnosed prenatally or neonatally. When one case with any major external structural birth defect including NTDs was identified, one healthy newborn infant of the same sex in the same region and with the closest date of conception to the case was selected as the healthy control. Information was collected through in-person interviews by trained healthcare workers before discharge from the hospital within 10 days after delivery, using a structured questionnaire including demographics, gravidity history, lifestyle behaviors, maternal active smoking, and passive smoking. For the current study, we included the subjects investigated from 2010 to 2016. The study excluded 12 women (1.5%) who reported active smoking and 27 women (3.4%) whose active or passive smoking status were missing. This study defined passive smoking as exposure to secondhand smoke at least once per week and at least one cigarette each time on average in their environment (such as at home, in the workspace or other public places) from 1 month before to 2 months after pregnancy. The study was approved by the Institutional Review Board of Peking University. Written informed consent was provided by all participants.

Logistic regression was used to evaluate the association between maternal passive smoking and risk for NTDs by crude odds ratio (OR) including 95% confidence intervals (95% CIs) and adjusted OR including 95% CIs after adjusting for potential confounders. The confounding variables included maternal age, pre-pregnancy body mass index (BMI), education, fever or flu in early pregnancy, nausea and vomiting during pregnancy (NVP), periconceptional folic acid use, and history of birth defect-affected pregnancy. All analyses were performed using SPSS package (Version 24.0. IBM Corp., Armonk, NY, USA).

A total of 224 NTD cases and 523 controls were included in analyses from 2010 to 2016. The case group comprised 78 cases of anencephaly, 121 of spina bifida, and 25 of encephalocele. Among 224 NTDs cases, 16 cases (7.1%) had other malformations, such as orofacial clefts or gastroschisis. Compared with healthy control mothers, case mothers had lower education levels, higher gravidity, higher frequency of history of pregnancy affected by birth defects, higher prevalence of contracting fever or flu or having NVP, and lower rates of periconceptional folic acid use. In addition, case mothers were more likely than control mothers to be ≥ 30 years of age and to be overweight (Pre-pregnancy BMI ≥ 25 kg/m², Table 1).

Overall, 59.4% (133/224) of case mothers reported exposure to passive smoking during the periconceptional period, compared with 29.4% (154/523) of control mothers. In 2013, we started collecting data on places where passive smoking occurs (e.g., at home, work, or in other public places). There were 87 women who reported the information, of whom 62.1% were exposed to smoke at home. The crude OR of NTDs for passive smoking exposure was 3.502 (95% CI: 2.527–4.853). After adjusting for maternal age, pre-pregnancy BMI, education, fever or flu in early pregnancy, NVP, periconceptional folic acid use, and history of birth defect-affected pregnancy, there was a still strong association, with the adjusted OR being 3.227 (95% CI: 2.213–4.704). Positive dose-response patterns between exposure frequency and risk of NTDs were found, and the adjusted ORs were 1.878 (95% CI: 1.115–3.163), 2.584 (95% CI: 1.348–4.954), and 6.114 (95% CI: 3.673–10.178) for exposure frequency of 1–3, 4–6, and >6 times per week respectively ($P_{\text{for trend}} < 0.001$, Table 2). Analysis of sub-types of NTDs separately showed that anencephaly, spina bifida, and encephalocele were also significantly associated with

maternal passive smoking exposure after adjusting for potential confounders (Table 3).

DISCUSSION

This study indicated an association between maternal passive smoking during the periconceptional period and an increased risk for both total NTDs and subtypes in offspring of the nonsmoking women, with a significant dose-response relationship. A previous study reported that periconceptional exposure on partner smoking might increase the risk of NTDs in the offspring in same regions from 2002 to 2007 (OR=1.7; 95% CI: 1.3–2.4) (3). Another population-based case-control study consisting of 175 cases and 221 controls among Mexican American women found a similar association between secondhand smoke exposure and NTDs (OR=2.6; 95% CI: 1.6–4.0) (7). Recently, a meta-analysis reported that maternal passive smoking conferred an approximately two-fold risk increase of NTDs (adjusted OR=1.898; 95% CI: 1.557–2.313) (5). These findings were consistent with our study, but the effect was weaker than what we observed in our study (adjusted OR=3.227; 95% CI: 2.213–4.704). This study clarified that higher exposure levels of maternal passive smoking were associated with improved risk for NTDs in offspring, with evidence of a dose-response pattern in nonsmoking women. Most notably, the risk for NTDs rapidly increased to a high level when the exposure frequency was >6 times per week (adjusted OR=6.114; 95% CI: 3.673–10.178).

Maternal exposure to passive smoking during pregnancy increases the risk of adverse pregnancy outcomes (8). In China, female passive smoking is widespread and severe due to the high smoking rates among men, particularly in rural areas. A Chinese study reported the passive smoking exposure rate was 44.9% among 75,107 adults aged ≥ 40 years (9). The passive smoking exposure proportions recorded in this study were 59.4% in the case group and 29.4% in the control group. The harmful constituents in cigarette smoke can pass through the placenta, including nicotine, carbon monoxide, and polycyclic aromatic hydrocarbons (10). However, most participants are not aware of the health dangers of passive smoking. The WHO FCTC was signed and put into effect in 2006, but unfortunately, tobacco control policies in China are poor and a large gap exists from the FCTC requirements (6). This study suggests that control measures should be taken to prevent tobacco smoke pollution from affecting pregnant women, particularly

TABLE 1. Demographic and lifestyle characteristics of NTDs cases and controls in five counties, Shanxi Province, China, 2010–2016.

Characteristic	NTDs cases (n=224) *		Controls (n=523)*		P
	Number	%	Number	%	
Maternal age (years)					0.005
<25	82	37.6	253	49.3	
25–29	71	32.6	161	31.4	
30–34	43	19.7	71	13.8	
≥35	22	10.1	28	5.5	
Prepregnancy BMI (kg/m ²)					<0.001
<18.5	21	9.7	50	9.7	
18.5–24.9	124	57.4	364	70.8	
≥25	71	32.9	100	19.5	
Occupation					0.094
Farmer	169	75.4	362	69.2	
Others	55	24.6	161	30.8	
Education					<0.001
Primary school or lower	18	8.1	24	4.6	
Junior high school	150	67.3	284	54.6	
Senior high school	37	16.6	107	20.6	
College or higher	18	8.1	105	20.2	
Gravidity					0.004
1	88	39.6	247	47.8	
2	75	33.8	186	36.0	
≥3	59	26.6	84	16.2	
Parity					0.323
Primiparas	120	57.1	305	61.1	
Multiparas	90	42.9	194	38.9	
History of birth defect-affected pregnancy					<0.001
Yes	12	5.5	5	1.0	
No	208	94.5	507	99.0	
Fever or flu in early pregnancy					<0.001
Yes	84	38.7	84	16.6	
No	133	61.3	421	83.4	
Nausea and vomiting of pregnancy					0.001
Yes	53	24.5	73	14.2	
No	163	75.5	442	85.8	
Maternal alcohol consumption					0.078
Yes	23	10.3	34	6.5	
No	201	89.7	487	93.5	
Periconception folic acid use					0.043
Yes	129	58.1	337	65.9	
No	93	41.9	174	34.1	

* Values may not sum to the total numbers because of missing information for some subjects.

Abbreviations: NTDs=neural tube defects; BMI=body mass index.

TABLE 2. Association between periconceptional passive smoking and risk for fetal NTDs in five counties, Shanxi Province, China, 2010–2016.

Passive smoking exposure	Case	Control	Crude OR (95% CI)	Adjusted OR* (95% CI)
No	91	369	1.0	1.0
Yes (any exposure)	133	154	3.502 (2.527–4.853)	3.227 (2.213–4.704)
1–3 times/week	37	75	2.000 (1.268–3.155)	1.878 (1.115–3.163)
4–6 times/week	24	37	2.630 (1.499–4.617)	2.584 (1.348–4.954)
>6 times/week	72	42	6.951 (4.458–10.840)	6.114 (3.673–10.178)

* Adjusted for maternal age, pregnancy BMI, education, fever or flu in early pregnancy, nausea and vomiting during pregnancy (NVP), periconception folic acid use and history of birth defect-affected pregnancy; $P_{\text{trend}} < 0.001$.

Abbreviations: NTDs=neural tube defects; OR=odds ratio; CI=confidence interval; BMI=body mass index.

TABLE 3. Association between periconceptional passive smoking and risk for fetal NTDs subtypes in five counties, Shanxi Province, China, 2010–2016.

Groups	Number	Number of passive smoking exposure	Crude OR (95% CI)	Adjusted OR* (95% CI)
Control	523	154	1.0	1.0
Anencephaly	78	42	2.795 (1.724–4.532)	2.497 (1.433–4.352)
Spina bifida	121	78	4.346 (2.864–6.596)	3.907 (2.404–6.348)
Encephaloceles	25	13	2.596 (1.158–5.817)	2.540 (1.043–6.188)

*Adjusted for maternal age, prepregnancy BMI, education, fever or flu in early pregnancy, nausea and vomiting during pregnancy (NVP), periconception folic acid use and history of birth defect-affected pregnancy.

Abbreviations: NTDs=neural tube defects; OR=odds ratio; CI=confidence interval; BMI=body mass index.

exposure at home, to minimize the harmful effects of passive smoking exposure in offspring.

This study had several strengths. It was based on a population-based birth-defect surveillance system with a high prevalence of NTDs and a high participation rate. The case and control participants were from the same source population. The passive smoking exposure level was graded, which helped us to assess the association between different exposure levels and the risk of NTDs. Only nonsmoking mothers were selected in the current study, and the effect of passive smoking exposure was unconfounded by maternal active smoking.

This study was also subject to some limitations. Maternal passive smoking was reported mainly by pregnant women and reporting or recall bias may have potential impacts on the results due to the case-control design. It is worth further investigating with deeper passive smoking exposure assessments, especially through biochemical markers such as nicotine levels in maternal urine or umbilical cord blood. Studies that also considered potential gene-environment interaction may be necessary to understand the role of passive smoking exposure in NTDs etiology.

Acknowledgements: The participants of the study, and the staff of the five hospitals from Xiyang, Pingding, Taigu, Shouyang, and Zezhou counties.

Funding: National Natural Science Foundation of

China (No. 81973056); Medical Research Council (Grant Ref: MR/T003847/1) from UK.

doi: 10.46234/ccdcw2021.193

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Submitted: August 10, 2021; Accepted: September 02, 2021

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Preplanned Studies

Rate of Correct Use of Folic Acid Supplementation Among Pregnant Women — Beijing Municipality, China, 2017–2019

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Summary

What is already known on this topic?

Neural tube defects can be effectively prevented by folic acid supplementation. However, compliance with the recommendations for supplementation is still low in China.

What is added by this report?

This study investigated the rate of correct use of folic acid supplementation and its risk factors among pregnant women in Beijing. Women who took folic acid correctly only comprised less than 50% of the total, possibly due to unexpected pregnancy.

What are the implications for public health practice?

Given the low rate in Beijing, an area with high health literacy, the rate may also be low in other areas in China. Regulations for mandatory fortification of food with folic acid are recommended in China.

Some studies have reported unsatisfactory compliance with folic acid supplementation recommendations in China. In a study encompassing several regions of China, only 38.4% women initiated folic acid supplementation at least 3 months before conception (whether the intake after conception was sufficient was unclear) (1), which was significantly less than the target of 70% set by the National Health Commission (NHC) of the People's Republic of China (2). Beijing has similar socioeconomic characteristics to various developed countries and may reflect future conditions in China. Based on the baseline survey of a cohort study, this study aimed to determine the rate of correct use of folic acid consumption (sufficient not only before but also after conception) among pregnant women in Beijing and to understand its risk factors. A structured questionnaire was administered to 3,988 pregnant women; 97.2% of the women reported taking folic acid supplements (folic acid alone or multivitamin tablets with folic acid), but only 24.2% were compliant with the recommended dose and duration of folic acid supplementation. Unexpected pregnancy was a major

risk factor associated with the correct use of folic acid. The evidence from this study suggests that regulations for mandatory fortification of food with folic acid are required in China.

Data were obtained from a baseline survey of an ongoing prospective cohort study. The participants included 3,988 pregnant women at or before 16 weeks of gestation when enrolling through convenience sampling (selected from a prenatal health checkup and the maternity school) at the Haidian Maternal and Child Health Hospital, China, between August 2017 and November 2019. Among them, 132 women were excluded because their folic acid intake was unclear; therefore, 3,856 women were included in the final analysis. Data collected via the three-part structured questionnaire were entered twice into EpiData software (version 3.1, EpiData Association, Odense, Denmark). This study was approved by the institutional review board, and all participants provided written informed consent.

In pregnant women, the correct use of folic acid could be achieved by the intake of no less than 24 capsules of folic acid per month, from 3 months before to 3 months after conception. The rate of correct use of folic acid supplementation was calculated as the percentage of pregnant women who consumed an adequate dose of folic acid for over the period delineated above. Crude odd ratios (cORs) and adjusted odd ratios (aORs) were calculated to evaluate risk levels of factors. Chi-square and Fisher's tests were used to compare categorical variables, and logistic regression was performed with adjustment for confounding factors including survey year, age at recruitment, education, pregnancy planning, and parity. *P*-values <0.05 were considered statistically significant. SPSS Statistics software (version 24.0; IBM Corp., Armonk, NY, USA) was used for data analysis.

The mean age of the participants was 31 years (range: 21–49 years); 73.5% had a bachelor's degree or higher, 82.0% lived in urban areas, 79.1% were nulliparas, 29.3% were unexpected pregnancies, and 97.2% took folic acid supplements. Only 24.2% of

women started taking folic acid supplements at the recommended dosage 3 months before conception (Table 1).

The results of single-factor analysis (Table 2) showed that the percentage of women taking folic acid correctly differed significantly by age, education, pregnancy planning, and parity (all $P < 0.05$). Correct use of folic acid supplementation was observed in 4.1% of unexpected pregnancies, far lower than planned pregnancies (32.5%). In addition, unexpected pregnancy occurred in 36.9% (992 out of 2,685) of women who took folic acid incorrectly. Pregnant women with planned pregnancies [aOR: 10.31; 95% confidence interval (CI): 7.44–14.29] and nulliparas (aOR: 1.48; 95% CI: 1.15–1.90) were more likely to take folic acid correctly (Table 3). Between 2017 and 2019, the rate of correct use of folic acid supplementation significantly increased (aOR: 1.42; 95% CI: 1.12–1.80). Pregnant women aged ≤ 25 years were more likely to take folic acid incorrectly (aOR: 0.43; 95% CI: 0.26–0.72).

DISCUSSION

The results of this study revealed that among pregnant women in a knowledge-intensive area of

Beijing, 97.2% took folic acid supplementation, but only 24.2% took supplementation correctly. If using the less stringent United States Preventive Services Task Force standard (at least 24 capsules of folic acid per month from 1 month before to 3 months after conception), the rate of correct use of folic acid supplementation just marginally increased to 40.3%. The rate in Beijing was similar to that in Western countries (42.2%) (3) but was still very low. Importantly, this rate likely reflected future conditions in China. Although the rate of correct use of folic acid supplementation increased over time, it was still significantly below the NHC target (70%).

In this study, 29.3% of pregnant women were unexpected pregnancies. Unexpected pregnancies occurred in more than a third of women who took folic acid incorrectly and were associated with a significantly increased risk of incorrect use of folic acid. Unexpected pregnancies were common in China, ranging from 20.6% to 39.6% of all (4–6). Women with unexpected pregnancies often miss the best time for folic acid supplementation, which makes it one of the major risk factors for the correct use of folic acid throughout the world. Furthermore, the one-child policy was abolished in China in 2016, which may increase the likelihood of unexpected pregnancies over

TABLE 1. Folic acid supplementation among pregnant women in Haidian District, 2017–2019.

Variable	Participants (number)	Percentage (%)
Whether or not folic acid was taken		
Yes	3,748	97.2
No	108	2.8
When folic acid supplementation began*		
3 months before conception	1,090	29.1
2 months before conception	350	9.3
1 month before conception	431	11.5
Within 1 month after conception	749	20.0
Later than 1 month after conception	1,030	27.5
Unknown	98	2.6
Frequency of folic acid intake*		
24 capsules or more per month	2,833	75.6
15–23 capsules per month	610	16.3
Fewer than 15 capsules per month	129	3.4
Unknown	176	4.7
Correct use of folic acid		
Yes	880	24.2
No	2,763	75.8

* Among pregnant women who had taken folic acid.

TABLE 2. Single-factor analysis of risk factors of correct use of folic acid among pregnant women in Haidian District, 2017–2019.

Variable	Correct use, n (%)	Incorrect use, n (%)	P
Year			
2017	194 (22.3)	675 (77.7)	0.006
2018	438 (23.2)	1,454 (76.8)	
2019	248 (28.1)	634 (71.9)	
Age, years			
≤25	28 (11.2)	223 (88.8)	<0.001
26–30	474 (24.9)	1,426 (75.1)	
31–35	298 (27.6)	781 (72.4)	
>35	75 (18.8)	325 (81.2)	
Education			
High school or lower	45 (16.5)	228 (83.5)	0.005
Undergraduate	568 (24.2)	1,778 (75.8)	
Master's degree or higher	265 (26.0)	755 (74.0)	
Residence			
City area	698 (24.1)	2,195 (75.9)	0.786
Near suburbs	157 (25.2)	466 (74.8)	
Far outskirts	2 (18.2)	9 (81.8)	
Unexpected pregnancy			
Yes	42 (4.1)	992 (95.9)	<0.001
No	816 (32.5)	1,693 (67.5)	
Parity			
Nulliparas	734 (26.4)	2,050 (73.6)	<0.001
Multiparas	117 (16.0)	614 (84.0)	

time, leading to a lower rate of correct use of folic acid supplementation. In this study, nulliparas were significantly more likely to take folic acid correctly than multiparas. Compared to nulliparas, multiparas pay less attention to folic acid supplementation because of their previous experience with pregnancy. In 2019, more than 60% of births in China were of a second child and above (7). This proportion and the proportion of unexpected pregnancies are likely to increase due to the recently announced three-child policy. As a result, the rate of correct use of folic acid supplementation may decrease, which will delay attainment of the NHC target. Compared to the effects of unexpected pregnancies and parity, the impact of education on correct folic acid supplementation was found to be limited in the high-educated sample.

The US Food and Drug Administration was the first public health body to mandate folic acid supplementation in 1997, which proved to be a successful strategy to reduce birth defects (8). At

present, 88 countries and regions have mandated folate fortification in cereal grains to ensure adequate folic acid consumption in women of childbearing age (9). In a district of Beijing, the prevalence of neural tube defects (NTDs) at ≥28 weeks of gestation (a commonly used indicator) was 73.0% lower than the prevalence of NTDs throughout pregnancy (11/10,000 population) because severe defects often lead to termination of pregnancy before 28 weeks of gestation (10). With such a severe situation, folic acid supplementation is important for NTDs prevention at all times in China. Despite the large number of implemented programs, the rate of correct use of folic acid supplementation was still far below the NHC target, even in the most developed Chinese city. Therefore, besides improved health literacy in underdeveloped areas, mandatory folate fortification supplementation is urgently required all over China.

This study was subject to at least two limitations: convenience sampling provides a less representative sample (overrepresenting nulliparas), and self-reported

TABLE 3. Logistic regression analysis of risk factors of correct use of folic acid among pregnant women in Haidian District, 2017–2019.

Variable	cOR (95% CI)	P	aOR (95% CI)	P
Year				
2017	1		1	
2018	1.05 (0.87–1.27)	0.632	1.12 (0.91–1.38)	0.280
2019	1.36 (1.10–1.69)	0.005	1.42 (1.12–1.80)	0.004
Age, years				
≤25	0.54 (0.34–0.87)	0.011	0.43 (0.26–0.72)	0.002
26–30	1.44 (1.10–1.89)	0.008	0.98 (0.71–1.36)	0.917
31–35	1.65 (1.24–2.20)	0.001	1.16 (0.84–1.60)	0.368
>35	1		1	
Education				
High school or lower	1		1	
Undergraduate	1.62 (1.16–2.26)	0.005	1.51 (1.02–2.25)	0.039
Master's degree or higher	1.78 (1.25–2.52)	<0.001	1.46 (0.97–2.20)	0.072
Unexpected pregnancy				
No	11.38 (8.27–15.68)	<0.001	10.31 (7.44–14.29)	<0.001
Yes	1		1	
Parity				
Nulliparas	1.88 (1.52–2.33)	<0.001	1.48 (1.15–1.90)	0.002
Multiparas	1		1	

Abbreviations: cOR=crude odd ratio; aOR=adjusted odd ratio; CI=confidence interval.

questionnaires may inevitably cause information bias. Nevertheless, based on the low rate of correct use of folic acid supplementation in Beijing, an area with high health literacy, it can be speculated that folic acid supplementation and voluntary fortification of folic acid might not be effective for preventing NTDs in China. Regulations for mandatory fortification of food such as cereal grains with folic acid might be necessary to prevent NTDs.

Conflicts of Interest: No conflict of interest exists in the submission of this manuscript.

Acknowledgements: Families participating in this study; the workers at the Haidian Maternal and Child Health Hospital.

Funding: The National Natural Science Foundation of China (No. 81973056, and 81673177).

doi: 10.46234/ccdcw2021.194

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Submitted: August 11, 2021; Accepted: September 06, 2021

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Vital Surveillances

Incidence of Macrosomia in Rural Areas — Henan Province, China, 2013–2017

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ABSTRACT

Introduction: Macrosomia has short-term and long-term adverse health effects and is thus an important public health concern. Recent decades have witnessed increasing incidence of macrosomia in many countries.

Methods: The present study used a large population-based birth cohort study to depict incidence of macrosomia among live births in rural areas of Henan Province of China from 2013 to 2017.

Results: Among the 1,262,916 births, 82,353 were cases of macrosomia. The overall incidence of all types of macrosomia, of macrosomia with birth weight <4,500 g, and of macrosomia with birth weight ≥4,500 g were 6.52%, 5.30%, and 1.22%, respectively. From 2013 to 2017, the incidence of macrosomia decreased by 31.3% from 7.96% in 2013 to 5.47% in 2017 ($\chi^2_{trend}=946.96$, $P_{trend}<0.001$). Male infants and infants ≥42 gestational weeks had significantly higher incidence of macrosomia than that of female infants and infants <42 gestational weeks ($P<0.001$).

Conclusion: Gestational weight control through nutrition management and physical activities during pregnancy are needed to reduce incidence of macrosomia.

INTRODUCTION

Macrosomia refers to livebirths with birth weight ≥4,000 g and is an important public health concern. A wealth of evidence has indicated that macrosomia is associated with risk of infant and maternal complications and long-term morbidities in infants (1), which carries emotional and economic costs to families and society. Recent decades witnessed rising trends in incidence of macrosomia in many developing countries (2). Due to lack of a national vital statistics system with detailed information on birth indicators, China's secular and temporal changes in macrosomia incidence were unclear, with large variations across years and

regions in different reports (3–4). Earlier research has found significant differences in macrosomia incidence between urban and rural areas (5), yet most studies were mainly based on hospital data in urban areas, especially in southern or northern regions. Henan, located in central China, was among the largest populated and agricultural provinces in China with over 109 million people, while its incidence of adverse pregnancy outcomes including macrosomia was scarcely reported. The aim of the present study was to use a large population-based birth cohort study to depict the incidence of the macrosomia among live births in rural areas of Henan Province of China from 2013 to 2017.

METHODS

The study data came from the National Free Pre-Pregnancy Check-Up Project (NFPCP) in Henan Province. The NFPCP has been providing free health examinations and counselling services for couples intending to become pregnant, especially in rural areas, and following up with pregnancy outcomes since 2010. Basic sociodemographic information of participants, including maternal age and educational level were collected at baseline. Healthcare workers then interviewed women face-to-face or by telephone from beginning of pregnancy to delivery or termination of pregnancy, recording their pregnancy outcomes (normal birth, miscarriage, induced abortion, or stillbirth, etc.), delivery date, gestational weeks, and newborn information (gender and birth weight, etc.) Detailed design of the project was described elsewhere (6). A total of 1,262,916 pregnant women delivered live births in 2013–2017 and were thus included in our analysis. The study protocol was reviewed and approved by Ethics Committee of Henan Institute of Reproductive Health Science and Technology, and written informed consent was obtained from all participants.

Birth indicators were measured by trained obstetricians. Macrosomia was defined as live births

with $\geq 4,000$ g birth weight. Subgroups of macrosomia were also analysed, including term macrosomia (gestational weeks ≥ 37 and < 42), post-term macrosomia (≥ 42 gestational weeks), macrosomia with birth weight $< 4,500$ g, and macrosomia with birth weight $\geq 4,500$ g. The incidence of macrosomia was calculated by using total number of macrosomia as the numerators and all live births as the denominators. We used chi-squared tests to compare incidence (denoted as χ^2) and chi-squared trend tests to examine the

trends of incidence across years (denoted as χ^2_{trend}). The significance level of tests was < 0.05 . R software (version 4.0.2, R Development Core Team, Vienna, Austria) was used for the analysis.

RESULTS

Among the 1,262,916 births, 82,353 were cases of macrosomia (Table 1). The total incidence of macrosomia was 6.52%. The incidence of macrosomia

TABLE 1. Incidence of macrosomia in rural areas of Henan Province from 2013 to 2017.

Item	Births n	Macrosomia					
		Total		<4,500 g		$\geq 4,500$ g	
		n	Incidence, %	n	Incidence, %	n	Incidence, %
Total	1,262,916	82,353	6.52	66,988	5.30	15,365	1.22
Year							
2013 [*]	56,816	4,524	7.96	3,615	6.36	909	4.60
2014	314,403	22,142	7.04	17,771	5.65	4,371	1.39
2015	320,878	22,638	7.06	18,782	5.85	3,856	1.20
2016	333,564	20,061	6.01	16,322	4.89	3,739	1.12
2017	237,255	12,988	5.47	10,498	4.42	2,490	1.05
P_{trend}			< 0.001		< 0.001		< 0.001
Maternal age (years)							
15–19	12,364	781	6.32	644	5.21	137	1.11
20–24	385,873	26,190	6.79	21,448	5.56	4,742	1.23
25–29	628,185	40,620	6.47	33,013	5.26	7,607	1.21
30–34	168,905	10,656	6.31	8,578	5.08	2,078	1.23
35–39	52,306	3,157	6.04	2,528	4.83	629	1.20
40–49	14,807	916	6.19	750	5.07	166	1.12
P			< 0.001		< 0.001		0.648
Maternal education							
College and above	104,252	7,319	7.02	5,703	5.47	1,616	1.55
Senior high school	196,481	13,144	6.69	10,676	5.43	2,468	1.26
Junior high school	918,954	58,779	6.40	48,155	5.24	10,624	1.16
Primary school and below	11,368	718	6.32	574	5.05	144	1.27
P			< 0.001		< 0.001		< 0.001
Gender							
Male	645,042	56,079	8.69	46,753	7.25	9,326	1.45
Female	621,982	26,211	4.21	20,187	3.25	6,024	0.97
P			< 0.001		< 0.001		< 0.001
Gestational weeks							
< 41	1,195,938	75,652	6.33	61,596	5.15	9,326	0.78
≥ 42	66,978	6,701	10.0	5,392	8.05	6,024	8.99
P			< 0.001		< 0.001		< 0.001

* Only part of study areas were included.

with birth weight <4,500 g and macrosomia with birth weight $\geq 4,500$ g were 5.30% and 1.22%, respectively. Male infants have significantly higher incidence of macrosomia than that of female infants regardless of birth weight ($P < 0.001$). Incidence of macrosomia with ≥ 42 gestational weeks was much higher than that of <42 gestational weeks regardless of birth weight ($P < 0.001$). Figure 1 showed the incidence trend of macrosomia from 2013 to 2017. The incidence of total macrosomia decreased by 31.28% overall from 7.96% in 2013 to 5.47% in 2017 ($\chi^2_{trend} = 946.96$, $P_{trend} < 0.001$). The term macrosomia subgroup also showed similar decreases, yet post-term macrosomia rose from 0.27% in 2013 to 0.60% in 2015 and dropped to 0.45% in 2017 ($\chi^2_{trend} = 4.64$, $P_{trend} < 0.05$).

Figure 2 showed incidence of macrosomia subgroups by maternal age. The incidence of macrosomia <4,500 g increased from age 15–19 (5.21%) to age 20–24 (5.56%), decreasing afterwards until age 35–39 (4.83%) and then increasing slightly at age 40–49 (5.07%, $\chi^2 = 94.73$, $P < 0.001$). There was no significant changes in incidence of macrosomia with $\geq 4,500$ g by maternal age ($\chi^2 = 3.34$, $P = 0.648$).

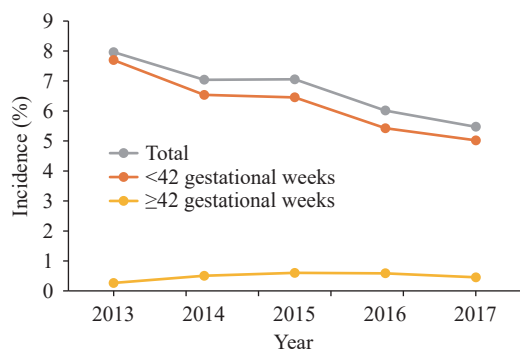


FIGURE 1. Incidence of macrosomia in rural areas of Henan Province from 2013 to 2017.

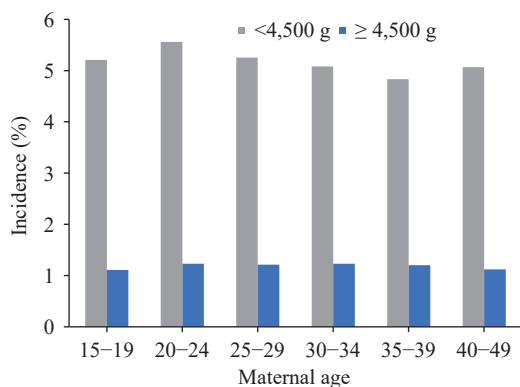


FIGURE 2. Incidence of macrosomia by maternal age in rural areas of Henan Province from 2013–2017.

Figure 3 showed incidence of macrosomia subgroups by maternal education. Significant differences existed across maternal education levels in both macrosomia subgroups. The incidence of macrosomia with $\geq 4,500$ g subgroup in college and above education group was the highest (1.55%), followed by primary and below and senior high school (1.27% and 1.26%, respectively), and the lowest incidence was in junior high school (1.16%) ($\chi^2 = 127.25$, $P < 0.001$). While the incidence of <4,500 g subgroup monotonously decreased with declining maternal education level ($\chi^2 = 127.25$, $P < 0.001$, respectively).

DISCUSSION

This study described the distribution characteristics of macrosomia in a large population-based cohort study in rural areas of Henan Province of central China between 2013 and 2017. The total incidence of macrosomia was 6.52%, consistent with results in a population-based survey also in rural areas in two counties in Shanxi (6.45%) in 2007–2012 (7) and another sample survey in rural areas of 14 provincial-level administrative divisions (PLADs) in 2006 (6.3%) (5). Previous research has reported relatively large variations of macrosomia incidence across regions. For example, a sample survey in 23 PLADs from 2010 to 2014 reported macrosomia's incidence to be 8.7% (4), yet another survey covering 14 PLADs reported the rate to be 7.3% in 2011 (3). A regional survey in Foshan City, Guangdong Province reported the incidence at 2.5% (8), while another survey in Beijing Municipality reported 7.6% (9). These large disparities

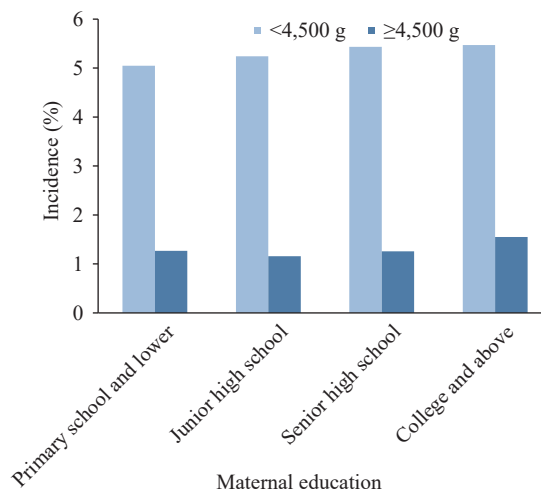


FIGURE 3. Incidence of macrosomia by maternal education in rural areas of Henan Province from 2013–2017.

in macrosomia incidence could come from “true” differences due to different demographic, socioeconomic, and medical characteristics in different regions and years (10–11), but could also come from different ways and accuracies in estimating gestational age and birth weight, sampling errors, and whether the data were at the hospital or population level.

Our study observed that although there were signs of decrease, the incidence of macrosomia in rural Henan Province was still high. Our previous study indicated the macrosomia comprised 41% of all adverse pregnancy outcomes (7). A body of literature has revealed macrosomia to be pertinent to hypertension and metabolic syndrome from childhood to adulthood (1). Gestational weight gain and maternal age are the most crucial drivers of macrosomia (12). With spread of healthcare education, nutrition intervention and weight control for pregnant women, the incidence of macrosomia has been found to reduce in urban areas (9,13), while in rural areas, such healthcare services are less available and the traditional perception of weight gain during pregnancy — “the bigger and heavier, the better” — are still popular. Our study thus suggests the local government and people implement targeted measures to reduce occurrences of macrosomia. For example, education and nutrition consultation should be strengthened among women preparing for pregnancy or who are currently pregnant, especially in rural areas. Besides, local pregnancy nutrition clinics can be established for accurate intervention on gestational weight management.

This study showed disparities in occurrences of macrosomia across different maternal ages and education levels, yet diverse patterns of these disparities were observed in different macrosomia subgroups. Past literature has confirmed an association between macrosomia and maternal sociodemographic factors, but specifics are still unclear as different patterns were observed in different populations (11). Understanding the underlying mechanisms behind relationship between macrosomia and sociodemographic factors would help take targeted measures in different sub-populations.

This study had some strengths. First, the large sample involving more than 1.2 million live births in our study made it possible for us to calculate stable and reliable incidence rate of macrosomia across different sub-populations. Second, as all couples preparing for pregnancy got free check-up in the project, our study was at the population level, thus reducing selection bias.

This study was also subject to some limitations. First, gestational age and birth weight were self-reported by women and thus there might be recall bias. Second, because only those preparing for pregnancy would participate in the Pre-Pregnancy Check-Up Project, our research could not cover unplanned pregnancies. As planned pregnancies have been found to be associated with lower risks of adverse birth outcomes (14), this could partly explain the lower incidence rate in our study.

In conclusion, the present study used a large population-based cohort data to describe the variations of macrosomia incidence in a rural central China PLAD, providing a baseline indication for the researchers and decisionmakers to understand the status of macrosomia. Our findings suggested incidence of macrosomia in Henan Province generally decreased, yet the incidence was still high. Given the short-term and long-term impacts on population quality caused by macrosomia, our study thus calls for maternal healthcare personnel and pregnant women paying attention to nutrition and weight management during pregnancy, especially in rural areas.

Funding: This study was supported by grants from the National Key Research and Development Program of China (2018YFC1004303); National Natural Science Foundation of China (41871360); and the National Health Commission Key Laboratory of Birth Defects and Prevention, Henan Province (ZD202002).

doi: 10.46234/ccdcw2021.196

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Submitted: August 27, 2021; Accepted: September 07, 2021

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The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).



Vol. 3 No. 37 Sep. 10, 2021

Responsible Authority

National Health Commission of the People's Republic of China

Sponsor

Chinese Center for Disease Control and Prevention

Editing and Publishing

China CDC Weekly Editorial Office
No.155 Changbai Road, Changping District, Beijing, China
Tel: 86-10-63150501, 63150701
Email: weekly@chinacdc.cn

CSSN

ISSN 2096-7071
CN 10-1629/R1