Evaluating an intervention for neural tube defects in coal mining cites in China: a temporal and spatial analysis

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Received 30 October 2019; revised 23 February 2020; editorial decision 7 June 2020; accepted 3 September 2020

\textbf{Background:} Neural tube defects (NTDs) are congenital birth defects of the central nervous system that affect 0.5–2 per 1000 pregnancies worldwide. Therefore effective interventions for birth defects, especially NTDs, are very important.

\textbf{Methods:} Yuanping City is a coal mining city in Shanxi Province, China, with a high incidence of NTDs. This study evaluates the effects of NTD interventions in this city after adjusting for covariates that characterize the native environment. The number of NTD cases and births for the 18 towns in Yuanping City from 2007 to 2014 were included in the study. A shared–component zero-inflated Poisson regression was applied to analyse the temporal–spatial variance among the incidence rates of NTDs in Yuanping City before and after the interventions.

\textbf{Results:} The results showed that existing interventions to mitigate birth defects, such as folic acid supplementation, reduced the incidence of NTDs by 53.5% in coal mining areas in Yuanping City. However, the NTD risk in areas near coal mines, especially unrestored coal mines, was still high, even after the intervention.

\textbf{Conclusions:} The government should focus on health hazards related to mining and agricultural production and should provide education and resources to reduce environmental exposure. Reducing environmental risks should be regarded as an early intervention strategy to mitigate birth defects.

\textbf{Keywords:} coal mining city, neural tube defects, prevention and control, shared component model, temporal and spatial analysis.

\textbf{Introduction}

Birth defects are congenital anomalies that present in infancy or later in life and are induced by events preceding birth; they may be inherited or acquired.\textsuperscript{1} According to the World Health Organization, birth defects were the fifth leading cause of child death globally from 2000 to 2013.\textsuperscript{2} The incidence of birth defects in China is approximately 5.60% and approximately 900 000 infants are affected.\textsuperscript{3} Among birth defects, neural tube defects (NTDs) have the highest incidence rate and are associated with the most severe consequences. NTDs are congenital birth defects that affect the central nervous system and prevent the neural tube from completely closing. They result in anencephaly, spina bifida and encephalocele, among other conditions.\textsuperscript{4} China has the highest incidence of NTDs worldwide and the province of Shanxi, the largest coal mining base in China, has the highest incidence of NTDs in China.\textsuperscript{5,6}

A national project for the prevention of birth defects in China was initiated in 2000. The national project mainly involves dynamic monitoring before and after pregnancy and following childbirth. The most widely used method for the prevention and control of NTDs is vitamin supplements, specifically folic acid, for the pregnant mother,\textsuperscript{7,8} with the addition of other complex vitamins.\textsuperscript{9} However, the incidence of birth defects in perinatal infants in China increased from 109.79 to 153.23 per 10 000 infants between 2000 and 2011. Moreover, with the implementation of the

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two-child policy in China, the rate of birth defects in infants born to mothers >35 y of age reached 9.29% in 2013, which is nearly three times higher than that in 2000 (3.90%). There is an urgent need to evaluate the effects of existing preventative measures and explore possible changes in birth defect intervention policies in China.10,11

Most research methods for evaluating the effects of government interventions are simple, merely comparing the rates of NTDs before and after the intervention. A significant decline in the NTD rate indicates that the intervention is effective. For example, Barboza-Arguello et al.12 calculated the NTD rate in Costa Rica from 1987 to 2012 during the pre-folic acid fortification period (1987–1991, 1996–1998), the fortification period (1999–2002) and the post-fortification period (2003–2012) and found that NTD morbidity declined. Similarly, Williams et al.13 estimated the pre-fortification and post-fortification NTD morbidity rates in different racial groups in the USA using data from 19 population-based birth defect surveillance programs and found that the NTD rate among all groups decreased following the introduction of folic acid fortification. However, this method can show only the overall decline across all areas under surveillance; it cannot provide an in-depth understanding of the differences in the effects of interventions across different social strata or in different geographic regions. Agha et al.14 found that in Canada, after the introduction of food fortification, the NTD morbidity rate decreased significantly between 1994 and 2009 in Ontario hospitals. On this basis, they further studied the effect of intervention measures among people of differing socio-economic statuses and found that food fortification could not effectively eliminate the disparity in NTDs in different socio-economic groups. Liu et al.15 examined potential sex and subtype differences in the preventive effects of folic acid supplementation on NTD prevalence in northern China based on a large cohort study in a public health campaign from 1993 to 1996. Folic acid supplementation reduced the rates of anencephaly and total NTDs to a greater degree in females than males. Liao et al.16 applied Ripley’s K-function and spatial filtering methods to analyse the temporal and spatial changes in NTD risk in some coal mining regions in China with increased rates of NTDs after the implementation of the intervention and found that clusters of NTDs were consistently present before and after the intervention near the roads used for coal transport. The researchers suggested that it is necessary to use different interventions in different regions and that the key to preventing NTDs is to strengthen the environmental restoration of coal production and transport areas.17,18

The evaluations of NTD prevention and control described above were more targeted than previous methods, but there are many risk factors for NTDs. To evaluate the effect of an intervention in different geographic regions, it is necessary to control for the effects of the native environment of the study area to obtain a better understanding of the real effects of the intervention, which will then allow more precise suggestions for control and prevention.19

To evaluate the effect of the existing intervention on NTDs in coal mining cities in China, this study used Yuanping City, a coal mining city in Shanxi Province with a high prevalence of birth defects, as the experimental area. We identified temporal and spatial variations in the NTD prevalence in Yuanping City before and during the intervention. In the study, covariates, such as native environmental factors that are associated with high incidence rates of NTDs, were controlled, which allowed us to focus on the effect of the intervention.

### Materials and methods

#### Data and study area

Yuanping City, Shanxi Province, China, has a high incidence of NTDs.9 There are 18 towns in Yuanping City, with a combined area of 2560 km² and a total population of approximately 497 600. Yuanping City has 14 coal sites and a coal production area of 400 km², which accounts for 15.6% of the city’s total area. According to the materials provided by the Yuanping Bureau of Coal Industry, the largest coal site in Yuanping City maintains 1.12 billion tons of coal reserves. In addition, Yuanping City is one of the key transfer stations on China’s main coal transportation railway.

Registered NTD cases and birth records from the 18 towns in Yuanping City from 2007 to 2014 were provided by the local family planning department and verified by doctors in the hospitals. In 2009, Yuanping City began distributing folic acid supplements during pre-pregnancy to all women who were actively trying to become pregnant and in the first trimester of pregnancy in an effort to reduce NTDs. Therefore the study period was divided into two periods: before the state intervention in 2009 (2007–2009) and after the state intervention (2010–2014).16 Figure 1 shows the location of Yuanping City and Table 1 summarizes the corresponding NTD and birth data.

In previous work, NTDs were found to be associated with geographic factors, such as elevation and distance from a fault.16,20,21 Therefore elevation and distance from a fault were included in our model to adjust for the influence of the native environment. Data regarding elevation were collected from the geospatial data cloud (http://www.gscloud.cn/) and the resolution was 100 m. The average elevation of each township and the distance from the centre of the township to the nearest fault were calculated as the input data. Table 2 shows the descriptive statistics of these two covariates and their distributions are displayed in Figure 2.

#### Shared component model (SCM)

In this study, an SCM was applied to analyse the temporal–spatial variance in the incidence rates of NTDs in Yuanping City. The basic SCM was proposed by Knorr-Held and Best.22 Its premise is to jointly model the relative risk (RR) of two diseases by using separate components, including components common to both diseases, that can represent the underlying exposure risk factors and residual variation components that are specific to each disease. This enables information about both diseases to be shared. The primary applications of SCM are joint analyses of two objects that share a spatial distribution pattern (e.g. two diseases or two genders).23–25 This model has been extended by incorporating covariates,26 increasing the number of diseases considered27 and including temporal trends.28

Most SCMs use a standard Poisson likelihood, which is appropriate for rare and non-contagious diseases. However, when area-specific count data are particularly sparse, an alternative
formulation allowing for excess zero counts may be preferable. The NTD case data in Yuanping City are sparse, with some zero data. Therefore we applied a shared component zero-inflated Poisson (ZIP) model. In the ZIP model, the zero counts were separated into excess (those above what is expected in a Poisson distribution) and non-excess zeros (those expected in a Poisson distribution). The model was applied within a Bayesian context and can be expressed as follows:

$$O_{1i} \sim \text{Poisson}((1 - \mu_{1i})E_{1i}\theta_{1i})$$

$$O_{2i} \sim \text{Poisson}((1 - \mu_{2i})E_{2i}\theta_{2i})$$

(1)

where $O_{1i}$ and $O_{2i}$ are the observed NTD counts for the two periods (before the intervention and after the intervention); $i = 1, 2, \ldots, 18$ towns; $E_{1i}$ and $E_{2i}$ are the expected counts for each period; $\theta_{1i}$ and $\theta_{2i}$ are the RRs; and $\mu_{1i}$ and $\mu_{2i}$ are the probabilities of zero in the ZIP model.

The log RR was then modelled as follows:

$$\log (\theta_{1i}) = \alpha_1 + u_i \times \delta_1 + v_{1i} + \epsilon_{1i}$$

$$\log (\theta_{2i}) = \alpha_2 + u_i \times \delta_2 + v_{2i} + \epsilon_{2i}$$

(2)

where $\alpha_1$ and $\alpha_2$ are the period-specific intercept, which refers to the average NTD rate in different periods; $u_i$ is a latent variable that is consistently associated with the NTD rates over the two periods or a surrogate risk factor that is common to both periods that can capture the shared spatial pattern of NTDs across time; $\delta_1$ and $\delta_2$ are scaling factors representing the relative strength of the association between $u_i$ and outcomes between periods, where $\delta_1\delta_2 = 1$; $v_{1i}$ and $v_{2i}$ are component/latent variables that
Table 2. Descriptive statistics of the covariates

| Covariates          | Maximum | Minimum | Median | Interquartile range |
|---------------------|---------|---------|--------|---------------------|
| Elevation (km)      | 1.75    | 0.81    | 1.01   | 0.92–1.21           |
| Distance from fault (km) | 19.65  | 0.87    | 2.58   | 1.77–6.59           |

Figure 2. Maps of the two covariates: (a) elevation; (b) faults.

capture the period-specific variability; and $\varepsilon_1$ and $\varepsilon_2$ are terms that allow for overdispersion.

This Bayesian approach assumes that all parameters and random effects have unknown quantities that require the specification of prior distribution. For the shared pattern determined by $u_i$, a spatially structured distribution was modelled using the conditional autoregressive normal prior, $u_i \sim \text{CARNormal}(W, \tau_u)$, which considers the weight of neighbouring areas. For $v_1$ and $v_2$, normal distributions $N(0, \tau_{v_1})$ and $N(0, \tau_{v_2})$ were assumed, with $\tau_{v_1}$ and $\tau_{v_2}$ as the precision parameters. Finally, the hyperprior specifications were $\alpha_1, \alpha_2 - \text{dflat}(\log(\delta_1 - N(0.5, 0.88)), \sigma_v = 1/\tau_v$, $\sigma_{v1} = 1/\tau_{v1}, \sigma_{v2} = 1/\tau_{v2}$, and $\tau = \gamma(0.5, 0.00005)$.

Selection of the covariates

To evaluate whether the two covariates (elevation and distance from a fault) were associated with the incidence of NTDs in our study area, they were included in the model. The model of the RR with one covariate is as follows:

$$\log(\theta_i) = \alpha_1 + u_i \times \delta_1 + v_1 + \beta_1 X_i + \varepsilon_1,$$

$$\log(\theta_i) = \alpha_2 + u_i \times \delta_2 + v_2 + \beta_2 X_i + \varepsilon_2,$$

where $\beta_1$ and $\beta_2$ are the coefficients of the covariate $X_i$. A non-informative prior $N(0, 1000)$ was assigned to the regression coefficients $\beta_1$ and $\beta_2$. The settings of other parameters were the same as those used for the above SCM, without covariates.

Table 3 shows the estimated coefficients of the two covariates when they were included in the model. According to the results, distance from a fault was not included in the model and elevation was only included for period 1. The final SCM model with covariates is as follows:

$$\log(\theta_i) = \alpha_1 + u_i \times \delta_1 + v_1 + \beta_1 X_i + \varepsilon_1,$$

$$\log(\theta_i) = \alpha_2 + u_i \times \delta_2 + v_2 + \beta_2 X_i + \varepsilon_2,$$

where $X_i$ is the average elevation of each township and $\beta_1$ is the coefficient of this covariate.

This study applied Bayesian inference using Markov chain Monte Carlo (MCMC) simulations in WinBUGS version 3.2.2 software. We ran two MCMC chains with 20,000 iterations for each model. The deviance information criterion (DIC) proposed by Spiegelhalter et al. was used to evaluate the model.

Results

SCM results without covariates

In this study we applied a shared component ZIP model to analyse the common and specific spatial patterns of the NTD
Table 3. Coefficients of covariates

| Covariates               | Period 1 (2007–2009)       | Period 2 (2010–2014)       |
|--------------------------|-----------------------------|-----------------------------|
| Elevation, median (95% CI)| $-2.229 (-4.186$ to $-0.55)$ | $-1.206 (-2.737$ to $0.023)$ |
| Distance from fault, median (95% CI) | $-0.02 (-0.07$ to $0.02)$ | $-0.02 (-0.06$ to $0.02)$ |

CI: confidence interval.

Table 4. SCM results without covariates

| Covariates               | Period 1 (2007–2009)       | Period 2 (2010–2014)       |
|--------------------------|-----------------------------|-----------------------------|
| Fraction of total variations, mean (90% CI) | | |
| Shared component ($u$), % | 88 (54.11 to 99.9) | 94.4 (88.8 to 99.9) |
| Specific component ($v_1$, $v_2$), % | 12 (0.1 to 45.89) | 5.6 (0.1 to 11.2) |
| Model fit criteria       |                             |                             |
| DIC (total DIC=118.9)    | 65.1                        | 53.43                       |

CI: confidence interval.

Table 5. SCM results with covariates

| Covariates               | Period 1 (2007–2009)       | Period 2 (2010–2014)       |
|--------------------------|-----------------------------|-----------------------------|
| Fraction of total variations, mean (90% CI) | | |
| Shared component ($u$), % | 88.63 (54.11 to 99.9) | 95.39 (87.18 to 99.9) |
| Specific component ($v_1$, $v_2$), % | 11.37 (0.1 to 45.89) | 4.61 (0.1 to 12.88) |
| Model fit criteria       |                             |                             |
| DIC (total DIC=113.6)    | 58                          | 55.6                        |

CI: confidence interval.

incidence rates for two time periods in Yuanping City. The results of the SCM without covariates are shown in Table 4. Approximately 88% of the spatial variation in period 1 was captured by the shared term ($u$), leaving 12% of the variability attributable to the specific pattern. This shared term captured slightly more of the total spatial variation in period 2 (94.4%), leaving only 5.6% of the variability attributable to the specific component. Hence fewer risks were partitioned into the specific component, suggesting a strong common spatial pattern between the two periods.

SCM results with covariates

The results of the SCM with covariates and adjusted for covariates are shown in Table 5. After adjusting for elevation in period 1, the effect of the native environment could be eliminated. Approximately 88.63% of the spatial variation in period 1 was captured by the shared term ($u$), leaving 11.37% of the variability attributable to the specific pattern. This shared term captured more of the total spatial variation in period 2 (95.39%) than in period 1, leaving only 4.61% of the variability attributable to the specific component. There was more shared variation between the two periods in the SCM without covariates than in the SCM with covariates. This indicates that, after adjusting for elevation, the spatial pattern of NTDs was similar for both periods. Figure 3 shows the spatially structured common component (posterior mean estimates of $eu$) for the two time periods.

Figure 3(a) is the shared pattern without covariates and Figure 3(b) is the shared pattern with the covariates for the two periods. Figure 3(c) shows the different RRs for period 1 and period 2. Compared with Figures 3(a) and (b), the town of Changliang-gou (located in the western area) and the town of Xizhen (in the central area) were identified as consistently high-risk areas in the SCMs both with and without covariates. This indicates that the RRs in these areas were still high even after the intervention. However, Figure 3(c) shows that after adjusting for the effect of elevation,
the risks decreased greatly in these areas. The results without covariates may exaggerate the RRs in these areas, and the actual RRs were not as high after adjustment. In addition, the RRs are overvalued in the flat areas, even in Figure 3, although the common spatial pattern was similar before and after adjusting for elevation. Therefore, apart from the influence of elevation, the spatial heterogeneity of NTD risk decreased.

In this study, the different patterns of NTD incidence rates for the two periods were captured. As shown in Figures 4(a) and 4(b), as a result of efficient intervention, the NTD incidence rate decreased in period 2. The period-specific patterns for both periods are consistent with the rates of NTDs in period 1 and period 2. In period 1, the town of Xizhen (in the central region of the city) and the town of Sulongkou (in the eastern region of the city) had high RRs. However, those two high-RR areas in period 1 became low-RR areas in period 2. These patterns explain a small proportion of the variance (Table 5), indicating that the spatial pattern of NTDs did not change much between the two periods and that the period-specific pattern was weak.

Discussion
In contrast with existing studies evaluating the efficacy of NTD interventions, this study provided a novel approach for adjusting for the native environment and it focused on other factors that can be controlled during evaluations of the effects of interventions in coal mining cities in China. The study quantitatively extracted the
common and period-specific patterns of NTDs before and after the intervention. In addition, after adjusting for the effect of elevation, the authentic shared pattern for both periods (Figure 3(b)) and the period-specific patterns (Figures 4(c) and 4(d)) were obtained. These patterns suggest ways to focus on non-native environmental factors that can be controlled during interventions in different regions. According to the results of this study, control and prevention policies for NTDs in Yuanping City have been accurately applied.

A 53.5% reduction in the NTD incidence after the intervention in Yuanping City was found in this study. In addition, the number of towns in Yuanping City with an NTD incidence > 60 per 10,000 births was reduced from eight before the intervention to four after the intervention. Similarly, Liu et al.33 also found that the prevalence of NTDs in five counties in Shanxi Province decreased continuously, from 120.00 per 10,000 births in 2004 to 31.5 per 10,000 births in 2014, after the folic acid supplementation program was introduced. Therefore the national intervention for NTDs has successfully reduced the incidence of NTDs in some coal mining cities in China. From 2009 to 2018, the Chinese government freely provided folic acid supplements to all women with a rural household registration who planned to become pregnant. The incidence of NTDs in perinatal infants in China also decreased, from 27.40 to 1.50 per 10,000 infants between 1987 and 2017.34

Although existing interventions for birth defects, such as folic acid supplementation, have obviously reduced the risk of birth defects in many coal mining sites in China, environmental pollution from coal mining and agricultural production has
influenced the effect of the intervention. In the past, large-scale coal mining has had a serious impact on the ecosystems in those regions. Therefore environmental restoration work around coal mines in China is urgently required. However, according to the 13th Five-Year Environmental Protection Plan of Shanxi Province, comprehensive environmental management has taken place at only 35% of the abandoned mines the province. Environmental pollution from coal mining remains harmful to local health and affects the implementation of interventions for NTDs.16 The town of Changlianggou is located in the western mountains of Yuanping City and is far from the city capital. The town has the highest density of coal mines in Yuanping City. Traditional industry and mining comprise the mainstay of the local economy. The results show that the NTD risk in Yuanping City was still high, even after the intervention. Therefore, in areas near coal mines, especially unrestored coal mines, the government should focus on the remediation of environmental pollution. A reduction in the potential adverse health effects of environmental exposure should be a main goal of the intervention.

In the coal mining cities of China, ecological agriculture has developed. Through ecological agriculture reclamation in coal mining areas, agricultural land has undergone a reasonable progression from traditional agriculture involving only farming to modern agriculture, which includes forestry, animal husbandry and related disciplines, fish integration, planting and breeding support.35 Although ecological agriculture can increase the income of residents, the overuse of fertilizers and the disposal of farmyard manure from agricultural production will lead to the pollution of surface water and groundwater sources.16 These types of agricultural pollution degrade the physical independence of inhabitants who are exposed to environmental toxins associated with birth defects. In the study, three townships located in the modern, efficient agro-industrial belt of Yuanping City became high-risk areas for NTDs after the intervention. The three townships are all close to rivers and aquaculture areas, and new farms are being developed there. With the increasing production of poultry products, the storage and disposal of raw poultry manure has become an environmental hazard to residents. Therefore the government should focus on the health hazards of agricultural production and provide education and resources to reduce environmental exposure.

This research has some limitations. First, only two native environmental covariates were considered in this study and we referred to previous studies of the risk factors for NTDs to determine the covariates. If other factors are found to influence NTDs in the future, our study should be extended. Second, we only collected data at the hospital level; thus we only used aggregated data rather than individual birth location data. If data on home births are made available in the future, they should be included in future studies. In addition, only one city was used as a case to assess the effect of a national NTD prevention project in the study. More sample cities should be included in intervention evaluations in the future.

Conclusions
Yuanping City is typical of coal mining cities in northern China. In the process of urbanization in China, a large number of rural areas in coal mining cities are undergoing economic transition and areas with high NTD risks are facing the same problems and challenges as Yuanping City. Thus our research may be of value for promoting interventions in these areas.

When evaluating the effects of interventions in coal mining cities, the native environment should be considered and adjusted to ensure that the risks of NTDs are estimated correctly. In addition to providing comprehensive folic acid supplementation for NTD prevention and control, industrial and mining towns should particularly focus on prevention. Although changes in the dominant industries have led to improved control of pollution in these areas, long-term environmental damage continues to have an impact on NTD rates. Moreover, in areas with recent agricultural development, the environmental burden has gradually increased, which may lead to increased NTD risks in these areas, thus the government should be proactive in implementing prevention programs in these areas.

Authors’ contributions: YL designed the research project and analysed the research results. NZ implemented the research and wrote the paper. ZR assisted in analysing the research results.

Acknowledgments: None.

Competing interests: None declared.

Ethical approval: Not required.

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