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Shanxi province in northern China has one of the highest reported prevalence rates of neural tube defects (NTDs) in the world. The current study selected Heshun, the county with the highest rate of NTDs in Shanxi, as a study area and tested whether residence in a coal mining area was a contributing factor. A NTD cluster was detected in an area within 6 km of the coal mines for almost every year during 1998–2005. Poisson regression analysis revealed that there may be an association between production in coal mines and prevalence of NTDs in coal mine areas. Future work identifying factors independently correlated with NTDs in coal mining regions may provide further insights into the health effects of coal mines on NTDs.

Keywords: neural tube birth defects; small coal mines; spatial filtering; cluster; environmental pollution

Introduction

Neural tube defects (NTDs) are among the most common congenital malformations and are a major cause of stillbirths and infant mortality. The etiology of these birth defects, however, is still unknown and has often been considered multifactorial (Wang et al. 2010). An environmental cause is any non-genetic factor that increases the risk of NTDs for the exposed individual. Such factors include fetal infection (Nørgård et al. 2006), maternal illness (Shaw et al. 1998), nutritional deficiencies (Carrillo-Ponce et al. 2004), drug ingestion (Brender et al. 2004), chemical exposure (Voss et al. 2008) and radiation (Vinceti et al. 2001).

China has been identified as a region with a high occurrence of NTDs. They account for up to one-third of stillbirths and a quarter to a third of neonatal deaths (Li et al. 2006). Based on data collected from a hospital-based surveillance system, the prevalence of NTDs was approximately 27.4 per 10,000 births in 1987. Among the different regions in China, Shanxi province in northern China had the highest rate, with a rate of 105.5 per 10,000 births in 1987 and 60.88 per 10,000 births in 1996–2002 (Gu et al. 2007). A higher NTD incidence in Shanxi is thought to result from, for example, daily passive exposure to cigarette smoke, poor ventilation during heating and excessive consumption of pickled vegetables (Li et al. 2006).

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Another factor to consider, however, is the impact of Shanxi coal mining on the health of the resident population. Since 1999, the coal output in Shanxi province has been sustained at about 250 million tons per year. This represents 25% of the national total output and 5.6% of the world's production (Wei 2003). Coal contains fluorine, cadmium, nickel, mercury and organic compounds, and the mining and cleaning of coal at local processing sites creates large quantities of ambient particulate matter and contaminated water (Hendryx et al. 2008). For example, in Shanxi province, Yu et al. (2007) found drinking water contained high levels of arsenic and indoor spaces were also contaminated from burning coal indoors. Despite a number of epidemiological studies undertaken in Shanxi and elsewhere, a link between coal-mining activities and NTDs has yet to be clearly demonstrated (Li et al. 2006; Gu et al. 2007). The objective of the current study was to further evaluate NTD prevalence in one of the high-risk regions of Shanxi by combining a spatial filtering method and classical statistical methods, such as relative risk and Poisson regression analysis (Haining 2003; Christakos 2005; Wang 2006; Wang et al. 2008), in the hope of determining whether there is an additional effect linked to residence in intensive coal mining areas.

Materials and methods

Study site

The study was carried out in Heshun, a county in the Tai Hang mountain area of Shanxi province. The county consists of 326 administrative villages and has an area of 2,250 km^2. Most of the people in this county are farmers and their living environments seldom change. Furthermore, there has been no large-scale migration of people in the history of this region. The inherited and congenital causes of birth defects are similar among the people in this region, and these factors explain only a small fraction of all of the NTD birth defect cases seen. Most types of birth defects designated by the World Health Organization (WHO) can be found in Heshun, and NTD birth defects predominate in this county (Wu et al. 2004). During 1998–2005, there were 7,880 births in Heshun and 187 had NTDs.

In 1999, the State Family Planning Commission launched the Birth Defect Intervention Project across the country. Heshun was designated as one of the pilot regions for the project carried out in 2001. The intervention work mainly involved dynamic monitoring before and after conception and again following childbirth, and as a result is referred to as a three-tiered intervention. The first-tier intervention service covered newlywed couples and couples who were entitled to have a second child. Before pregnancy, couples were offered counseling and advised to take supplements, including folic acid and iodine. The second-tier intervention covered all pregnant women. During the course of intervention, women in Heshun took a vitamin supplement containing 0.4 mg of folic acid everyday from 3 m before pregnancy to 3 m after pregnancy. Women who had a previous NTD-affected pregnancy took forceval capsules, which contain a combination of 24 vitamins, minerals and trace elements. The third-tier intervention covered effective follow-up treatment for all children who were already affected by birth defects. In this national intervention project, the main measure taken to reduce the risk of NTDs was to counsel women of child-bearing age to take folic acid supplements (Hu 2003).

Heshun is one of China's major coal-producing counties. Heshun has a coal-bearing area of 1,852 km^2, which accounts for 82.3% of the county's total area. The county's coal-bearing area contains total reserves of 156 billion tons, of which 34 billion tons are identified. The coal output in Heshun is 8 million tons per year. In the study period, Heshun had about 80 coal mines according to the materials provided by the Heshun Bureau of Coal Industry. It was noted that most of these coal mines are small town and village coal mines or illegal coal mines. In the rural areas, 48.17% of the population lived within 6 km of the coal mines (i.e. within the coal region) (Figure 1).

Data sources

For this analysis, we included all live and still births occurring in Heshun from 1 January 1998 to 31 December 2005, born to women at the hospital, and who were residents of the county during that time period. The hospitals involved were the county Chinese medicine hospital, the county people's hospital, the maternal and child health hospital of the county, all of the township hospitals and rural medical clinics. We also included all therapeutic abortions in that area where the estimated date of delivery fell in the time period of interest. All NTD cases, regardless of pregnancy outcome, were verified by doctors in hospitals. Records of NTD cases were collected from the local family planning department. The NTDs in the study included anencephaly, spina bifida, encephalocele, and holoprosencephaly, among others.

The local planning department declined to provide identifiers to link substantiated NTD cases to births, so we were unable to conduct the study at an individual level; instead, we conducted an ecological study. Specifically, we used the relationship among NTDs and the environmental characteristics of the villages in which the patients' mothers lived to assess the disease risk.

A geographic information system (GIS) is a computer package used to store, manage, analyze, and map geographic data. It plays a significant role in data processing and has superior advantages over traditional methods. GIS allows the addition of relevant layers that can be used for analyzing the spatial relationships among selected factors (Liao et al. 2010). We used ArcGIS 9.2 as the GIS platform to locate the 326 villages and 80 coal mines. NTDs and populations were aggregated to the geographic centers of the villages.

Spatial filtering method

The spatial filtering method employs non-parametric statistical techniques as an exploratory spatial data analysis tool. It can provide estimates for unknown risk or relative risk without making distributional assumptions (Anselin et al. 2006). In this study, a spatial filtering method was used to explore spatial variations in birth-related morbidity. It provided a way of identifying whether there was an unusually high occurrence of morbidity clustered in coal mining areas.

The statistical software used in the cluster analysis was the Distance Mapping and Analysis Program (DMAP), a public-domain software package available from www.uiowa.edu/ ~ gishlth/DMAP4/, which utilizes the Rushton spatial filtering method. This method was selected because:

(1) It is suitable for rare diseases, such as birth defects, since it can evaluate the disease risk of a specified grid based on its neighbors;

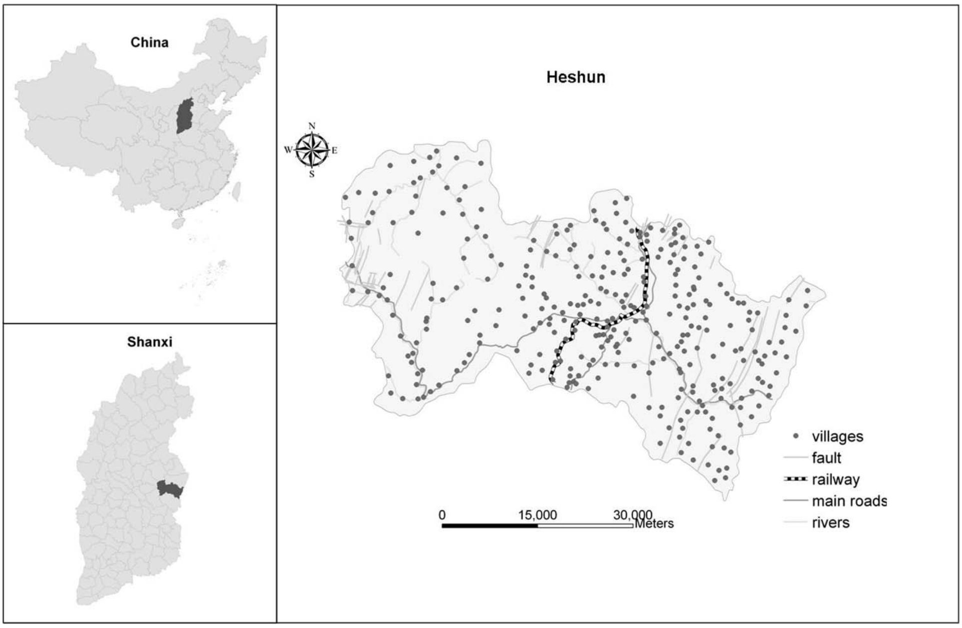

Figure 1. Distribution of coal mines in Heshun.

(2) For diseases whose etiology is imperfectly understood, it incorporates characteristics of individual cases in a GIS database so expert investigators can examine the characteristics of cases that occur in close geographic proximity;
(3) It does not need to specify the size or locations of clusters before analysis (Rushton and Lolonis 1996); and
(4) The isarithmic maps have many advantages in comparison with other conventional thematic maps that provide an indication of the level of a disease by area. They are not constrained by the borders of geographic units and sudden transitions between levels of two neighboring areas are avoided (Ozdenerol et al. 2005).

The Rushton spatial filtering method first creates a series of spatial filter circles centered on point locations on a regular grid that covers the study area. The spatial filter circle surrounding each of these points is the area from which an estimate of the NTD rate is made. For each of the circles, the rate is computed as the crude rate of NTD events compared with all births. After repeating this for a grid of such estimates, the NTD rate can be interpolated as a continuous spatial distribution. Neighboring grid points share circular patterns that overlap, thereby sharing observations. Isarithmic maps with a constant range of values were constructed in a GIS after the estimated rates were assigned to grid points. Given births at these point locations, the Monte Carlo method was then used to test how likely the spatial distribution of NTDs was due to chance alone. Areas that have significantly high NTD rates are regarded as hot spots of the disease.

The DMAP requires four files for input: A grid file, a numerator (case) events file, a denominator (all births/control) events file and an event probability file. In this study, the grid file was automatically created by giving the endpoints of the rectangle and the distance between each grid point. The numerator events file was created from relative information of villages that had NTD cases during the study period. Similarly, the denominator events file was created from information from all villages in Heshun. An event probability file used to operationalize the null hypothesis was created by setting the probability of each village becoming a hot spot. In addition, maximum window radius input was needed during the course of analysis. After analysis, the DMAP provides some useful information, such as NTD rate and statistical significance of the observed disease rates in each grid. The grids whose significance is more than a specified value can be selected as hot spots.

Risk factor analysis

Relative risk (RR) was applied to investigate the association between residences near coal mines and risk of NTDs. Poisson regression was used to test whether there were other influence factors in the coal mine areas. Poisson regression modeled the log of the probability of a NTD as a linear function of socioeconomic and geographic variables. The models included all main effects of the explanatory factors. Based on the fitted model, the adjusted relative risk (ARR) and 95% confidence interval were estimated for each factor. The ARR reflects the independent effect of each factor on NTDs, controlling for the effects of all other explanatory factors (Tang et al. 2006; Archer et al. 2007). The socio-economic factors reported useful information on income (per-capita net income), agricultural chemical exposure (the use of fertilizers and pesticides), crop yields (fruit and vegetable productions), and the production of coal mines of every village in coal mine areas during the 1998–2005 period. The geographic factors included elevation, vegetation coverage (normalized difference vegetation index) and the geological background (distance to faults) of these villages. The source of the NDVI dataset used in the study was the Flemish Institute for Technological Research (VITO), Belgium (http://www.vgt.vito.be). In the Poisson regression model, the number of NTDs and the log value of births were respectively set as the outcome and offset variable. All tests were two-tailed and a P value of 0.05 or less was considered statistically significant. All calculations were performed with SPSS version 17.0 (SPSS Inc) (Table 1).

Results

Spatial analyses

In spatial analysis, the grid interval and filter size are particularly relevant in computing birth defect rates. The window radius should not be so small that no births will be counted, but should be large enough to ensure the sharing of observations between neighboring grid locations (Rushton and Lolonis 1996). By matching the addresses of the birth records to village points, we were able to compute the NTD rates for each location on a grid covering the entire Heshun county area at a resolution of approximately 4.8 km. To be able to make general conclusions about the results of spatial filtering, we used multiple filter sizes, such as 1.6, 2.4, 3.2 and 4 km. Based on the cases and birth data in 1998, we conducted a sensitivity analysis using differing spatial filter sizes. The result (seen from Table 2) showed that the 4 km size appeared to provide the optimal

Table 1. List of risk factors.

Variables	Values	Numbers	Marginal percentage	Variables	Values	Numbers	Marginal percentage
Use of fertilizer (unit: ton)	0–9.58	31	31.3	Annual NDVI (normalized difference vegetation index)	0–102.5451	34	34.3
	9.59–18.38	21	21.2		102.5452–109.3073	28	28.3
	18.39–29.15	11	11.1		109.3074–118.5434	18	18.2
	29.16–47.73	23	23.2		118.5435–126.2691	13	13.1
	More than 47.73	13	13.1		More than 126.2691	6	6.1
Production of vegetable (unit: ton)	0–4.6819	14	14.1	Elevation (unit: m)	1,100–1,250	5	5.1
	4.6820–12.6313	19	19.2		1,251–1,300	30	30.3
	12.6314–24.4812	19	19.2		1,301–1,400	32	32.3
	24.4813–60.7825	19	19.2		1,400–1,500	11	11.1
	More than 60.7825	28	28.3		More than 1,500	21	21.2
Net-income (unit: yuan/year)	0–1001.56	23	23.2	Use of pesticide (unit: ton/year)	0–0.0135	16	16.2
	1001.57–1047.19	4	4.0		0.0136–0.0463	17	17.2
	1047.20–1167.56	8	8.1		0.0464–0.0975	16	16.2
	1167.57–1393.38	5	5.1		0.0976–0.2567	25	25.3
	More than 1393.38	24	24.2		More than 0.2567	25	25.3
Fault buffer (unit: m)	0–2,000	35	35.4	Production of fruit (unit: ton/year)	0–0.0063	68	68.7
	2,001–4,000	27	27.3		0.0064–0.4750	20	20.2
	4,001–6,000	10	10.1		0.4751–4.5938	10	10.1
	6,001–8,000	9	9.1		More than 4.5938	1	1.0
	8,001–10,000	9	9.1	Production of coal mines (unit: ton/year)	0	68	68.7
	10,001–12,000	5	5.1		1,000–20,000	17	17.2
	12,001–14,000	2	2.0		More than 20,000	14	14.1
	14,001–16,000	2	2.0				

Table 2. Detection results for different spatial filter sizes.

Filter sizes	Number of clusters	Number of grids included in clusters
1.6 km	3	3
2.4 km	2	4
3.2 km	2	4
4 km	2	9

distance for this study. Progressively larger spatial filtering of data removes local spatial variability (Esra et al. 2005), which eventually produces an approximately uniform pattern of NTDs.

The approximately 4.8 km distance interval between grid intersections resulted in 204 grid points in Heshun. Meaningful NTD rates were estimated for the grid points that had at least 5 births within a 4.8 km vicinity. The spatial filter circle surrounding each of these points is the area from which an estimate of the NTD rates is made. We counted the normal births and NTDs within the circle and assigned the observed rate to that location. When we repeated this for a grid of such estimates, we were able to interpolate the NTD rates as a continuous spatial distribution. Neighboring grid points share circular patterns that overlap, thereby sharing observations. Isarithmic maps with a constant range of values were constructed in GIS after the estimated rates were assigned to grid points.

For each village, we generated a random number from a uniform distribution in the range of 1 through 999. For each of the 204 grid-point locations, 999 Monte Carlo simulations were run. The simulated and real rates were then rank-ordered. The percent of the simulated rates at each grid location that were less than the observed rate for the same grid location were computed and the levels of statistical significance portrayed as isolines. Because testing the rates against 999 simulations is a form of exploratory spatial analysis, the methods for representing the results are discretionary, and the investigator can adjust the results based on the level of significance. Figure 2 illustrates the NTD clusters for Heshun during 1998–2005. A NTD cluster can be detected in the coal region for almost every year in the series.

Coal mining exposure and NTDs

A total of 187 NTD cases were included for analysis in this study and the prevalence of NTDs in Heshun was 237.31 per 10,000 births (187/7880). Of the births with NTDs, 58.29% lived in the coal region. Stratified according to distance to coal mines, we found that the NTD rates in the area within 6 km of coal mines were 270.74 per 10,000 births (109/4026) and 202.39 per 10,000 births (78/3854) beyond the coal region. We therefore calculated risks for the population in the coal region relative to the reference population by indirect standardization, assuming a common relative risk for all coal mines. The result showed the relative risk of NTDs for residents in the coal region was significantly higher (RR = 1.338, 95% CI = 1.004–1.783).

In addition, it seems that the Birth Defect Intervention Project did not play a role in reducing the incidence of NTDs in coal mine areas. During 1998–2001, the rate of NTDs was 251.00 per 10,000 births. But the rate remained at 273.97 per 10,000 births in 2002–2005.

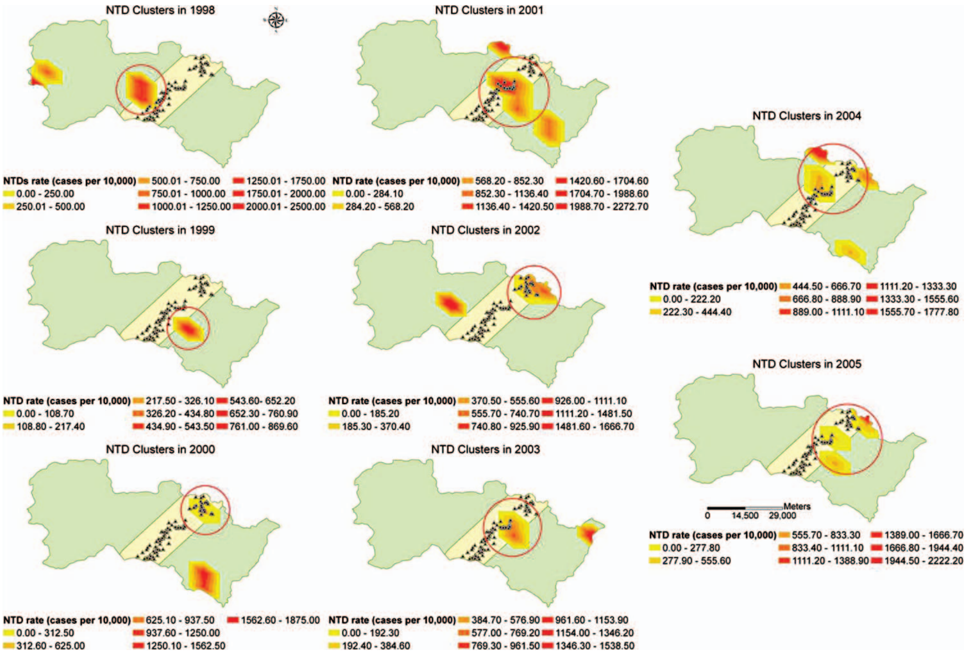

Figure 2. NTD clusters in Heshun during 1998–2005.

Other factors and NTDs

Heshun is classified as a "national-level poverty-stricken" county (McCall 2003), according to the Chinese government and the local economy is comparatively undeveloped. In Heshun, villages are distributed along the main road, so most of the transportation and economic centers of the county are located in the coal region. The natural geologic environment there is relatively simple compared with other areas in the county. The elevation is more than 1,300 m and the variations of slopes are not great. The Qingzhang River passes through the area and there are some fault lines in the north.

The multivariate analysis using the Poisson regression model showed P values of 0.010 for the production of coal mines in coal mine areas. This means that coal mining exposure may be related to the incidence of NTDs in coal mine areas. A clear effect of increasing distance to faults on the incidence of NTDs was observed in the Poisson regression analysis (Table 3).

Discussion

NTD incidence is higher in Heshun because of socio-economic activities, soil type distribution (Wu et al. 2004) and a complicated geological background (Li et al. 2006), and living in the coal region is an additional risk factor. The possibility that environmental contamination from the coal mining industry causes NTDs is consistent with known risks linked to coal. Heshun county has a mine area of 520 km^2 with 7 identified mining coal layers with a total thickness of 12.11 m. Coal products include gas coal, anthracite, lean coal, coking coal and others. The sulfur content of coal there is higher than in other areas, especially the No. 15

Table 3. Results of Poisson regression.

Variables	Values	ARR (adjusted relative risk)	95% Wald Confidence Interval for ARR		Variables	Values	ARR	95% Wald Confidence Interval for ARR	
			Upper	Lower				Upper	Lower
Annual NDVI (normalized difference vegetation index)	0–102.5451	0.648	0.090	4.679	Use of fertilizer (unit: ton/year)	0–9.58	0.563	0.107	2.960
	102.5452–109.3073	0.551	0.077	3.927		9.59–18.38	0.277	0.057	1.334
	109.3074–118.5434	0.726	0.120	4.378		18.39–29.15	0.315	0.071	1.404
	118.5435–126.2691	1.316	0.143	12.135		29.16–47.73	0.549	0.177	1.709
	More than 126.2691	1	.	.		More than 47.73	1	.	.
Use of pesticide (unit: ton/year)	0–0.0135	3.331	0.723	15.353	Production of vegetable (unit: ton/year)	0–4.6819	0.514	0.170	1.550
	0.0136–0.0463	3.890	0.985	15.357		4.6820–12.6313	1.290	0.453	3.675
	0.0464–0.0975	1.845	0.575	5.918		12.6314–24.4812	0.410	0.146	1.154
	0.0976–0.2567	0.640	0.207	1.984		24.4813–60.7825	1.481	0.698	3.140
	More than 0.2567	1	.	.		More than 60.7825	1	.	.
Elevation (unit: m)	1,100–1,250	3.044	0.246	37.638	Net- income (unit: yuan/year)	0–1001.56	0.266	0.062	1.138
	1,251–1,300	5.740	0.646	50.973		1001.57–1047.19	1.397	0.287	6.799
	1,301–1,400	2.744	0.355	21.236		1047.20–1167.56	2.591	0.727	9.239
	1,400–1,500	4.591	0.654	32.235		1167.57–1393.38	1.320	0.440	3.959
	More than 1,500	1	.	.		More than 1393.38	1	.	.
Production of fruit (unit: ton/year)	0–0.0063	1.802	0.310	10.467	Fault buffer (unit: m)	0–2,000	1.947E10	4.065E8	9.321E11
	0.0064–0.4750	1.002	0.104	9.630		2,001–4,000	2.643E10	5.830E8	1.198E12
	0.4751–4.5938	1.610	0.271	9.581		4,001–6,000	7.360E9	1.184E8	4.576E11
	More than 4.5938	1	.	.		6,001–8,000	6.039E10	2.239E9	1.628E12
Production of coal mines (unit: ton/year)	0	0.261	0.094	0.724		8,001–10,000	8.562E10	3.461E9	2.118E12
	1,000–20,000	0.158	0.045	0.549		10,001–12,000	4.414	0.000	.
	More than 20,000	1	.	.		12,001–14,000	5.980E12	0.000	0.000
						14,001–16,000	1	.	.

coal (STD = 36.01%) (Chang et al. 2007). The release of particulate matter and toxins from burning coal may be a NTD risk factor. In addition, human activities around the coal mines have already caused pollution. In Heshun, few coal mines are equipped to treat both mine water and sewage to prevent the seepage of pollutants. Ground water samples from wells showed excess arsenic levels in the Jinzhong basins in which Heshun is located (Yu et al. 2007). Of note, Wlodarczyk et al. (2006) analyzed gene expression in the neural tubes of arsenic exposed mouse embryos and found that there was a significant dysregulation in a group of genes directly involved in the mitochondrial process of energy production. The local government has been developing environmental requirements and accompanying enforcement mechanisms for larger mines, but this case study shows that more needs to be done.

Living in the region may expose residents to pollution from the coal mining industry, or may be associated with additional behavioral or demographic characteristics not captured through other covariates (Hendryx et al. 2008; Wang et al. 2010). The study found that distance to faults was related to NTDs in coal mine areas. Faults indicate intensive geological structural movement. And the concentration of radon in soil, water and air near fault zones were found to be far higher than areas away from faults (Li et al. 2006). However, it needs to be shown in the future whether a fetus *in utero* is at particular risk of damage from radon radiation.

Although we found that coal mining pollution may affect NTD incidence, there are some limitations associated with our choice of methods. A concern is that there may have been a significant amount of under reporting in this area, as some pregnant women would have chosen to have home births rather than hospital births. Therefore, we were limited to the use of data from hospital records and investigations undertaken in the villages. Also, some of the women may have relocated during their pregnancies, so there could be a migration bias in risk factor identification. In addition, our study is limited to an ecological analysis since we were unable to obtain any individual information otherwise required. The measures of coal mining exposure are limited. Causes of individual NTD cases cannot be identified, and the precise pathway between residence in coal mining areas and NTDs is unknown. Future research should improve measures of coal mining processing facilities and identify exposure routes (e.g. air, water and soil), exposure levels, and biological mechanisms of action that can account for a higher NTD incidence in Heshun's coal region.

Regardless of whether causes are environmental, behavioral or economic, it is clear that the population in the coal region is at risk for a host of health problems. Poverty there has been most persistent over time when characterized by single source economies, such as coal production. Based on social inequality models, addressing the health disparities of coal mining communities requires the development of economies that offer more diverse job opportunities at lower environmental cost, enacting and enforcing environmental protection policies, improving support for educational development, and creating environments that are conducive to health and wellness (Hendryx et al. 2008). Although in this study we only had the opportunity to investigate the effects of coal mining to NTDs in Heshun, a rural region in the north of China, the analysis methodology may provide some good ideas for the Chinese government to improve treatment policies and intervention measures for birth defects in the future.

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