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Association between risk of birth defects occurring level and arsenic concentrations in soils of Lvliang, Shanxi province of China

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ABSTRACT

The risk of birth defects is generally accredited with genetic factors, environmental causes, but the contribution of environmental factors to birth defects is still inconclusive. With the hypothesis of associations of geochemical features distribution and birth defects risk, we collected birth records and measured the chemical components in soil samples from a high prevalence area of birth defects in Shanxi province, China. The relative risk levels among villages were estimated with conditional spatial autoregressive model and the relationships between the risk levels of the villages and the 15 types of chemical elements concentration in the cropland and woodland soils were explored. The results revealed that the arsenic levels in cropland soil showed a significant association with birth defects occurring risk in this area, which is consistent with existing evidences of arsenic as a teratogen and warrants further investigation on arsenic exposure routine to birth defect occurring risk.

1. Introduction

Birth defects refer to any abnormality in functions, structures and metabolism of fetus when developed in the maternal uterus, occur in approximately 3% of all live births (Canfield et al., 2006). They are becoming the leading causes of infant mortality and one of the important key public health problems in the world (Chen et al., 2009; Yoon et al., 2001). There are many surveys carried out with hospital or population based surveillance of birth defects for the prevalence, public health burden and prevention efforts study (Lisi et al., 2010; Parker et al., 2010).

Existed knowledge known the causes of birth defects include both genetic and environmental factors (Finnell et al., 2000; Sever, 1995). But the specific genetic and environmental factors involved in the etiology of birth defects usually eluded the identification due to lack of consideration of gene–environment interactions on disease risk, and there are no conclusive proofs of environmental risk factors (Andrieu and Goldstein, 1998). Some studies suggested that a combination of genetic and environmental factor is important in the etiology of many birth defects (Lie et al., 1994). More, heavy metal elements in the environment or maternal exposure to arsenic cadmium, lead etc. are suggested to be associated with birth defects and congenital anomalies. However, reviews in lectures shown that some studies reported that these elements might also be teratogens in animal models (Robinson et al., 2011) or by case-control study (Brender et al., 2006), while some studies failed to verify the correlation between them (Carrillo-Ponce Mde et al., 2004). It is difficult to identify clearly which is the determinate one in epidemiologic perspective as the biologic mechanisms still are not legible. Those conflicted results usually related to small defects cases, limited types of metal elements tested and with different estimated birth defects rates.

China has been identified as a region with a high occurrence of neural tube defects (NTDs), the common congenital malformations that occur during early embryogenesis and result in miscarriage and infant death (Gu et al., 2007). As high prevalence of NTDs usually indicates high birth defects occurring risk, the present study selected two counties (Zhongyang and Jiaokou) in Lvliang mountain area of Shanxi province of China, where the prevalence of birth defects were found as high as about 193.64–333.33 per 10,000 births (Li et al., 2003). The birth records data were collected based on population while geocoded the geographical locations of villages, then followed the soil samples collected in each village. Existing research results indicated there some association between geochemical elements of environmental and rates of birth defect occurring (Yu and Zhang, 2011). The purpose of the present study

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was to compare the estimated differences of risk level among village's birth defects occurring and elemental concentration levels in soils and examine the relationship between them. There are two advantages in this study as relative stable risk differences estimation with large samples from high prevalence of birth defect occurring, and 15 types of elements tested from two types of soils samples, namely, cropland and woodland soils.

2. Materials and methods

2.1. Birth data collection and quality control

In this study, the data collection and quality control followed the steps described in the study by Gu et al. (2007). Briefly, the birth data were recorded by including all live-and stillbirths occurring from January 1, 2002 to December 31, 2004, to women who gave birth at hospital or at home, and who were residents of the two counties during that three years. All cases, regardless of pregnancy outcome, were verified by trained doctors in the hospitals. All information of the cases, regarding the birth defect cases and health birth babies, and various factors of the villages were stored in a GIS database, joined by spatial coordinates of the villages. There are about 6420 birth numbers with 538 defect cases (5 birth records without address were excluded when geocoding to village address).

2.2. Soil sampling and analysis

Following the epidemiological survey of birth defects, cropland soil (0–20 cm depth, indicate common exposure to human, such as agricultural activities) and woodland soil samples (20 cm–50 cm depth, indicate parent material of soil and less exposure level) were collected in all villages of the study area in January 2005 (Fig. 1).

The quality control followed the steps described in the study by Yu and Zhang (2011). Briefly, each sample was a composite sample consisting 4 to 5 subsamples from different directions of the village's scope. The samples were air dried in laboratory. The dried samples were ground and sieved with a 100 mesh sieve. An amount of 0.1 g of each soil sample was then mixed with 3 ml nitric acid, 1 ml perchloride acid and 1 ml hydrofluoric acid. Then they were placed in an oven for digestion for 5 h, and removed and heated on an electric heating board for about 1–2 h. After the liquid had evaporated to leave beads, pure water was added to the samples to bring the volume to 10 ml for analysis. Contents of 15 elements in the samples, namely, aluminum(Al), arsenic (As), calcium (Ca), copper (Cu), iron (Fe), potassium (K) magnesium (Mg), molybdenum (Mo), natrium (Na), nickel (Ni), lead (Pb), tin (Sn), strontium (Sr), vanadium (V), and zinc (Zn) were determined using ICP-OES.

2.3. Statistical analysis

As the birth defect cases are events with small probability occurring, the Poisson distribution modeling was applied to estimate the difference of risk of occurring level of birth defects for each village. The normality of chemical element concentrations in soils was tested using Kolmogorov–Smirnov test. Correlation analysis and cluster analysis were performed for risk differences of birth defects occurring level and chemical elements concentrations in soils.

1) The Differences of Risk Levels Estimation.

There are 129 villages surveyed in this period with birth records. The frequencies of birth and defects cases in villages as shown in Table 1.

As the measured frequency of birth defects within each village is generally low and hardly estimated the stabilized risk level on each village, we adopted a Poisson model to this data for the calculation of the differences of risk level of birth defects occurring (Griffith and Haining, 2006). Namely Poisson log-linear regression model conditional on the intensity parameters $\{\lambda(i)\}$, $i = 1,\ldots,n$, and given by:

$$\mathrm{Ln}[E(Y(i))] = \mathrm{Ln}[\lambda(i)] = \mathrm{Ln}[E(i)] + \beta_0 + \beta_1 X_1(i) + \ldots + \beta_k X_k(i) \quad i = 1,\ldots,n$$

where, $Y(i)$ represents the actual count of birth defect cases in village i, $E(i)$ is the expected count in each village without any covariates factors as $X_1,\ldots,X_k$ among the villages. $\lambda(i)$ is "intensity parameters" representing the expected count for each village when covariates are taken into account. As nearly common environment exposure in those villages, birth numbers and defects cases in a given village might relate to those in adjacent villages. We re-specified the above model in a standard Bayesian hierarchical conditional spatial autoregressive (CAR) model to account for potential spatial autocorrelation in the data and estimate the different risk level of birth defect occurring for each village (Besag et al., 1991; Best et al., 2005). Namely,

$$\mathrm{Ln}[E(Y(i))] = \mathrm{Ln}[\lambda(i)] = \mathrm{Ln}[E(i)] + \beta_0 + \beta_1 X_1(i) + \ldots + \beta_k X_k(i) + S(i)$$

where, $\{S(i)\}$ are spatially auto-correlated random variables. The CAR model estimates a spatial interaction parameter ρ and accounts for the spatial distribution of villages through a contiguity matrix (W) (Haining et al., 2009), as given by:

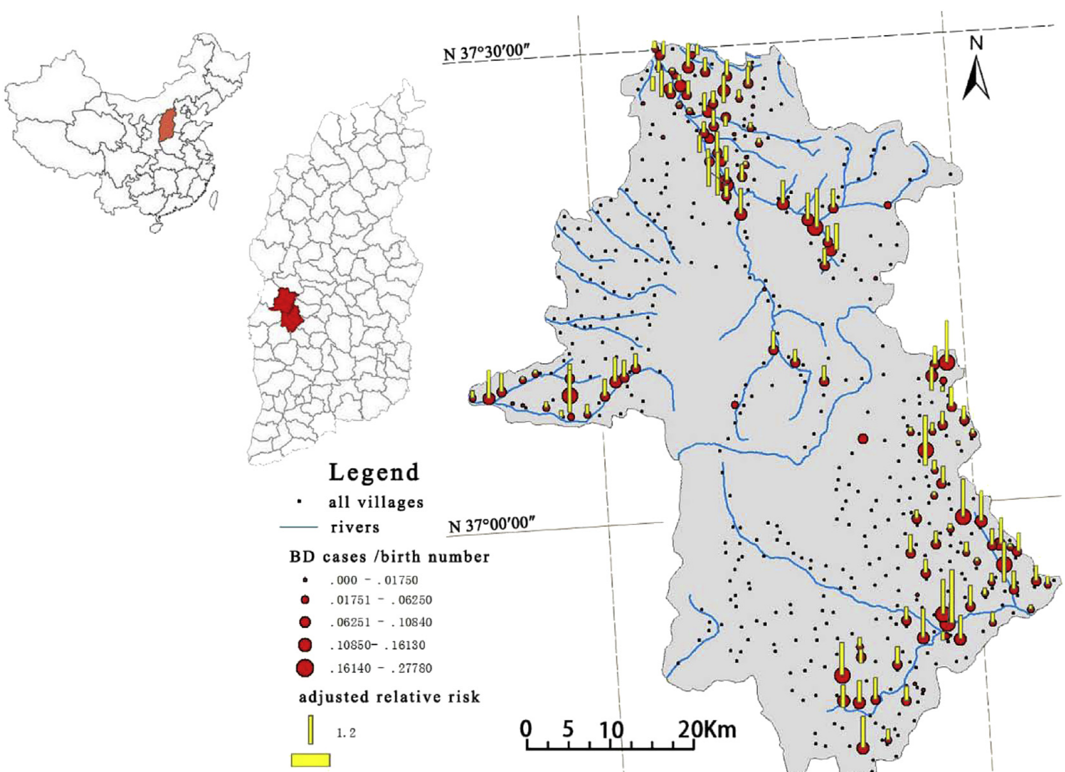

Fig. 1. Study area and the villages of sampled locations with the birth defects distribution and adjusted relative risk of birth defects occurring.

Table 1
Summary statistics of birth numbers and defects cases in each village of study area (2002–2004).

	Total (129 villages)	Minimum	25%	75%	Maximum	Means	Std. deviation
Birth Number	6415[a]	10	31	57.5	223	49.73	30.40
Defect cases	538	0	2	5	21	4.17	3.93
Crude birth defects rate	0.0839	0.839	2.600	4.822	18.702		
Adjusted relative risk of birth defects occurring		0	0.619	0.899	2.47	0.68	0.53

[a] 5 cases (without any defects) without addresses were excluded.

$$\text{prob}\{S(i) = s(i)|S(j) = s(j),\ j\neq i,\ j \text{ is a neighbor of } i\} \sim N\left(\rho\sum_{j\neq i} w(i,j)s(j), w_s^2(i)\right).$$

We used distance between villages to define the adjacency matrix. When the distance between villages i and j was less than 8 km (the median distance among villages), they are considered adjacent, i.e., $w_{ij} = 1$; otherwise, $w_{ij} = 0$. The covariates factor $X(i)$ we used total birth number in each village. And the difference of birth defect occurring risk among villages were estimated as $\exp(\beta_0 + \beta_1 {*} X(i) + S(i))$. The parameter estimation was performed using WinBugs software (Thomas et al., 2004), which Monte Carlo Markov Chain (MCMC) method based on Gibbs sampling was used to obtain the marginal posterior distributions for the parameters without analytical approximations. After we specified the model and adjacency matrix, we initialized values for MCMC method. The inference process was based on a sample of 1,000,000 values after a burn-in of 4000 iterations form a single chain. The program was listed in Appendix.

2) Test for normality of chemical elements in soil and data transformation

For the chemical element concentrations in both cropland and woodland soil samples, we firstly tested their probability distributions prior to further association analysis with the village's differences of risk level of birth defects occurring. For those chemical elements which do not follow the normal distribution among villages, we tried to use logarithmic transformation firstly, and then normal score of the chemical element in soil using Tukey's Formula would be used if they still could not pass the normal test.

3) Correlation and cluster analyses of the village's differences of risk level of birth defects occurring and chemical concentrations in soils

The relationship between the village's differences of risk level of birth defects occurring and chemical elements in both cropland and woodland soils were revealed using Pearson correlation analysis and cluster analysis. All statistical calculations were carried out using the software of SPSS version 20.

3. Results

3.1. Basic statistics of chemical element concentrations in soils

Table 2 shows the basic statistics of the chemical elements concentrations in soil samples. And the comparison with other areas is shown in the Table 3. Data of Shanxi province, China and USA data are from Shi et al. (1996) and Wei et al. (1991). Both tables show that the concentrations of As, Mo, Zn, Pb and Ni in the study area are higher than the average levels of Shanxi province and China.

3.2. Correlation analysis

The Pearson's correlation coefficients were calculated to test the relationships between the village's differences of risk level of birth defects occurring and chemical element concentrations in both cropland and woodland soils, following data transformation towards normality if needed (Table 4). It was found that As, Mg (logarithmic transformed) and Na (following a normal score transformation) in cropland soils, and only Sn (following a normal score transformation) in woodland soils showed statistically significant correlations with the village's differences of risk level of birth defects occurring ($p < 0.05$).

The scatter plot between As (logarithmic transformed) in cropland soils and the village's differences of risk level of birth defects occurring showed the association between them, even though the relationship is still weak (Fig. 2).

3.3. Cluster analyses

To further investigate the relationships between the relative risk of birth defects and chemical element concentrations in soils, the cluster analysis was performed, using correlation coefficients as the measure and furthest neighbor as the cluster method. Namely, the relationship between chemical element contents and birth defects relative risk among those sampled villages were checked. The results showed that heavy metals and most other elements belonged to a different group, while the village's differences of risk level of birth defects occurring and logarithmic transformed As are linked

Table 2
Basic statistics of chemical element concentrations in cropland soils and comparison with other regions (surface soils).

	Min	Max	Median	Mean (s.d.)	K–S test (sig.)**	Shanxi province	China	USA
Sn	1.55	9.31	3.58	3.76 (1.22)	1.091 (0.185)	0.90	2.6	1.3
As	7.86	91.59	17.12	**20.29** (11.52)	1.545 (*0.017*)	9.10	11.2	7.2
Mo	4.95	20.82	11.74	**12.25** (3.09)	1.179 (0.124)	0.50	2.0	0.97
Zn	57.55	261.70	107.70	**110.12** (42.52)	1.114 (0.167)	63.5	74.2	60
Sr	109.17	404.80	272.20	264.31 (73.42)	0.784 (0.571)	207	–	–
Pb	32.77	104.56	54.02	**56.14** (11.43)	0.842 (0.477)	14.7	26	19
Ni	27.89	61.39	40.62	**41.38** (6.39)	0.705 (0.703)	29.9	26.9	19
Fe*	1.889	5.151	3.320	3.284 (0.581)	0.518 (0.951)	2.95#	2.94	2.6
Mg*	0.199	1.647	0.348	0.494 (0.335)	1.713 (*0.006*)	1.25#	0.78	0.90
V	65.78	120.70	85.72	85.98 (9.64)	0.897 (0.397)	63.4	82.4	80
Ca*	0.629	8.723	5.339	5.198 (1.633)	1.216 (0.104)	4.15#	1.54	2.40
Cu	16.44	47.04	22.93	23.42 (3.65)	1.246 (0.090)	22.9	22.6	25
Al*	0.378	6.334	3.661	3.473 (0.952)	1.477 (*0.025*)	6.35#	6.62	7.2
Na*	0.438	1.823	1.307	1.318 (0.216)	0.608 (0.854)	1.22#	1.02	1.2
K*	1.068	2.281	1.674	1.686 (0.221)	0.581 (0.888)	1.81#	1.80	1.5#
Ln(As)	2.06	4.52	2.84	2.90 (0.45)	1.115 (0.166)	–	–	–
Ln(Mg)	5.30	9.71	8.16	8.27 (0.71)	0.905 (0.386)	–	–	–

Note: * Units of Fe, Mg, Ca, Al, Na and K are in %, others are in μg/g; ** Significance is in 2 tailed. # Values are geometric means, study areas and other values are arithmetic means. The figures in bold were echoing the word in the paper as those elements were higher than the average levels of Shanxi province and China. The italic figures show the significance in 2 tailed test below 0.05.
Data source: unit is μg/g and samples = 97 in study area, Shanxi data from Shi et al., 1996, and China & USA data from Wei et al., 1991.

Table 3
Comparison of chemical element concentrations in woodland soils and comparison with other regions (parent soils).

	Min	Max	Median	Mean (s.d.)	K–S test (sig.)**	Shanxi province	China	USA
Sn	2.69	9.14	4.33	**5.11** (1.93)	1.864 (*0.002*)	0.90	2.6	1.3
As	9.60	74.40	20.42	**22.00** (9.94)	1.733 (*0.005*)	9.10	11.2	7.2
Mo	4.33	17.73	13.14	**12.59** (2.74)	0.818 (0.515)	0.50	2.0	0.97
Zn	48.79	335.90	70.62	79.64 (36.25)	1.821 (*0.003*)	63.5	74.2	60
Sr	86.60	413.80	247.18	248.06 (69.57)	0.473 (0.979)	207	–	–
Pb	27.38	73.58	48.52	**48.66** (10.09)	0.788 (0.565)	14.7	26	19
Ni	29.38	52.48	39.85	**39.54** (5.84)	0.777 (0.583)	29.9	26.9	19
Fe*	1.464	5.914	2.914	3.553 (1.247)	2.115 (*0.000*)	2.95#	2.94	2.6
Mg*	0.172	1.511	0.922	0.935 (0.286)	0.468 (0.981)	1.25#	0.78	0.90
V	62.08	113.15	81.69	82.66 (8.69)	0.852 (0.462)	63.4	82.4	80
Ca*	0.540	10.150	5.320	5.162 (2.074)	1.162 (0.134)	4.15#	1.54	2.40
Cu	16.03	30.07	20.45	20.58 (2.08)	0.542 (0.930)	22.9	22.6	25
Al*	0.809	5.850	4.194	3.991 (1.262)	0.797 (0.550)	6.35#	6.62	7.2
Na*	0.444	1.832	1.482	1.436 (0.191)	1.075 (0.198)	1.22#	1.02	1.2
K*	1.030	2.2260	1.798	1.774 (0.202)	0.965 (0.309)	1.81#	1.80	1.5#
Ln(Zn)	3.89	5.82	4.26	4.32 (0.30)	1.257 (0.085)			

Note: * Units of Fe, Mg, Ca, Al, Na and K are in %, others are in μg/g; ** Significance is in 2 tailed. # Values are geometric means, study areas and other values are arithmetic means.
The figures in bold were echoing the word in the paper as those elements were higher than the average levels of Shanxi province and China. The italic figures show the significance in 2 tailed test below 0.05.
Data source: unit is μg/g and samples = 82 in study area, Shanxi data from Shi et al., 1996, and China & USA data from Wei et al., 1991.

together in the same group (Fig. 3), which indicated that their correlation is more statistical significant than other chemical elements, in other words, their distribution is similar among those villages.

4. Discussion and conclusions

There are some exploratory analyses for environmental risk factors to birth defects, such as geological factors (Wu et al., 2004) and environmental pollution (Liao et al., 2010; Vinceti et al., 2001). According to the dualism of the balance between the environment and human beings, the chemical compositions of human being's blood are consistent with those in the lithosphere. If this balance is broken, diseases will break out (An and Fu, 1995). There are some studies on arsenic exposure and risk of reproductive health, such as stillbirth and infant mortality (Kwok et al., 2011; Rahman et al., 2010), which indicate the relationship between environmental chemical elements exposure and risk of birth defects. Those researches support a putative conclusion that the abnormity of chemical elements distribution is related to the differences risk of birth defects occurring among people.

For study the relationship between population health and chemical elements level in soil, there are some researches have shown the relationship between background concentrations of soil elements and human health, such as longevity (Liu et al., 2013b) and cancer (Türkdoğan et al., 2003). As for birth defects research, the key issues include the estimation of the prevalence and risk levels of defect occurring and elements tested. Existed studies usually classified:

1) Investigated the association between exposure to heavy metals and birth defects occurring by case-control study design, such as prenatal exposure (Liu et al., 2013a), maternal exposure by urinary elements tests (Brender et al., 2006) and blood elements levels tests (Zeyrek et al., 2009), or various animal models (Hassan et al., 2012; Thompson et al., 2005).
2) Examined the relationship between maternal proximity to hazardous waste sites or industrial facilities which are

Table 4
Correlations coefficients between the differences of risk of birth defects occurring and chemical elements in soils.

	Cropland soils			Woodland soils	
	Pearson correlation	Sig. (2-tailed)		Pearson correlation	Sig. (2-tailed)
Sn	−0.056	0.583	NS(Sn)	−0.237	0.032*
Ln(As)	0.239	0.019*	NS(As)	−0.114	0.308
Mo	0.132	0.199	Mo	−0.148	0.185
Zn	−0.081	0.431	Ln(Zn)	0.142	0.204
Sr	−0.090	0.379	Sr	−0.102	0.362
Pb	0.004	0.967	Pb	0.003	0.980
Ni	−0.036	0.729	Ni	−0.022	0.845
Fe	0.025	0.808	NS(Fe)	0.174	0.118
Ln(Mg)	0.220	0.031*	Mg	−0.105	0.349
V	−0.007	0.943	V	0.069	0.536
Ca	−0.018	0.864	Ca	−0.111	0.323
Cu	0.002	0.987	Cu	0.099	0.375
NS(Al)	0.167	0.102	Al	−0.062	0.578
Na	0.238	0.019*	Na	−0.134	0.230
K	0.195	0.055	K	−0.193	0.082

Note: NS( )#—Normal Score of the chemical element in soil using Tukey's Formula. * $p < 0.05$.

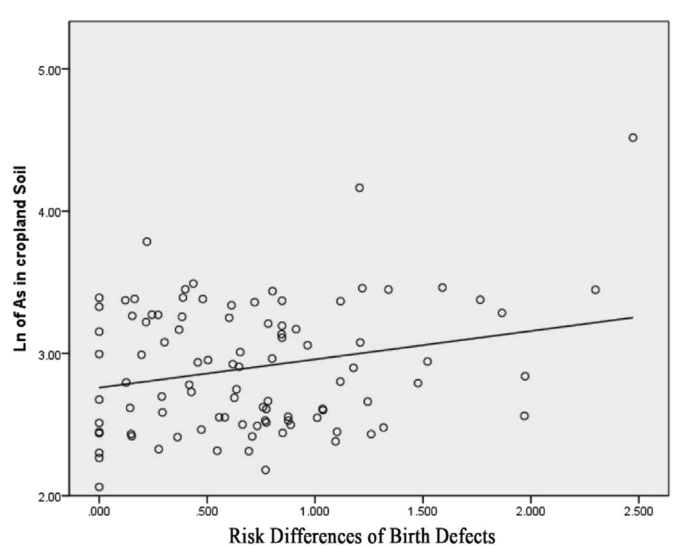

Fig. 2. Scatter plot between As in cropland soils and the relative risk of birth defects.

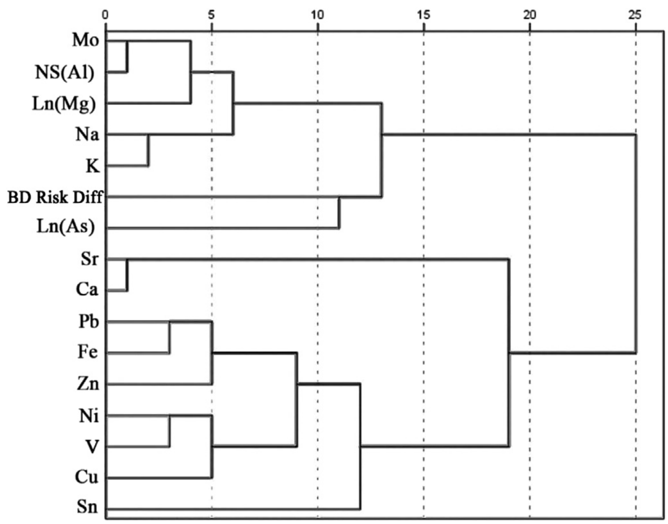

Fig. 3. Results of cluster analysis of relative risk of birth defects occurring and chemical elements in cropland soils.

postulated increase the risk of birth defects occurring. For example, maternal exposure so hazardous wastes site and risk of neural tube defects in offspring by case-control design (Suarez et al., 2007), and risk of congenital anomalies after the opening of landfill sites (Palmer et al., 2005).

Those two type studies sometimes have conflicted results on chemical elements exposure to risk of birth defects occurring as lack of data on specific individual-level exposures, which related to socioeconomic and lifestyle factors. However, this study was designed for population based birth defects occurring risk and chemical elements distributions on two types of soil samples. For good estimation of the birth defects occurring risk, we chose a highest prevalence region of neural tube defects in the world (Gu et al., 2007) with large number of birth records and defects cases. More, as usual procedure on mapping the crude disease rate across different geographical regions may not be meaningful, especially for small areas as it does not take into account spatial patterns or high variability for different population sizes (Maiti, 1998). We estimated the relative risk level of those villages by a standard Bayesian hierarchical conditional spatial autoregressive model, which was a better and stable estimation of risk than directly calculated by traditional methods (Liao et al., 2011). More, 15 types of chemical elements in two types of soil samples, cropland and woodland soils, indicated the different exposure routines by of human activities.

The results of correlation analysis revealed that more elements in the cropland soils showed statistically significant correlations with the village's differences of risk level of birth defects occurring, including logarithmically transformed As and Mg level and the normal score of Na. This suggests that the cropland soil has an overall better association with the village's differences of risk level of birth defects occurring in the study area. The difference between the woodland materials and cropland soils indicates that birth defects in the study area may be more related to external processes other than something natural in the study area. Environment pollution and human behaviors on the risk of birth defects should be paid more attention (Wang et al., 2010b).

Cluster analysis of the village's differences of risk level of birth defects occurring and chemical element concentrations in cropland soils pinpointed associations between birth defects and the level of As (logarithmic transformed) in the study area. Epidemiological studies have linked environmental As exposure to increased risk factor for neural tube defects, the second most common structural birth defects (Hill et al., 2009). With respect to birth defects research, there were few studies on correlations between estimated risk levels and soil As concentrations. The results in this study are consistent with the etiology research (Robinson et al., 2011; Wlodarczyk et al., 1996), and agreed with the results of studies on population health associated with arsenic exposure by different routines, such as water (Hopenhayn-Rich et al., 2000; Sohel et al., 2010). However, Jin et al. (2013) failed to find a significant association between placental concentrations of As and neural tube defects in similar population with case-control design. The study looked at biological measures to assess exposure level while some study shown different capacity for secondary methylation of As between children and adults when exposed to the same concentrations of inorganic arsenic (iAs) (Sun et al., 2007). We used soil metal concentrations as a surrogate for exposure and found the significant association was agree with the associations estimated residential soil arsenic concentrations and community-level environmental measures with mother-child health conditions in South Carolina (Aelion et al., 2012), and similar with worldwide review on studies on spontaneous pregnancy loss in humans and exposure to low-moderate iAs in drinking water exposure (Bloom et al., 2010).

It needs to be acknowledged that this study investigated only limited number of soil samples and limited number of chemical components. The potential influences of other environmental factors cannot be ruled out, and the results in this study should only be regarded as an initial finding. So, the association between As in cropland soils and the village's differences of risk level of birth defects occurring need carefully understanding and explaining, as there is a possibility of external factors, such as whether there are possible high exposure of As and other risk factors from agricultural activities in cropland, which requires further investigations. And more specifically and advanced methods should also be adopted for the risk assessment, such as geographical detectors (Wang et al., 2010a) and spatial multilevel regression analysis (Ren et al., 2013).

In conclusion, the study was characterized with stabilized estimation of differences risk level among villages using large samples of birth and defect cases in high prevalence region and two types of soil samples for different exposure routines to human being. The results revealed that the arsenic levels in cropland soil showed a relatively strong association with the higher risk of birth defects occurring in the study area. The future study should focus on the pathology of arsenic in cropland soil and its exposure pathways to human beings. The finding in this study is consistent with some existing evidences as arsenic might be a teratogen and warrants further investigation on arsenic exposure to potential effects on birth defects and population health research.

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Appendix. Hierarchical Bayesian model definition in WinBUGS

```
model {
# Likelihood
    for (i in 1 : N) {                    # N is the number of villages
        O[i]   ~ dpois(mu[i])
        log(mu[i]) <- log(E[i]) + alpha0 + alpha1 * X[i] + b[i]    # Area-specific
relative risk (for maps)
        RR[i] <- exp(alpha0 + alpha1 * X[i] + b[i])
    }
# CAR prior distribution for random effects:
    b[1:N] ~ car.normal(adj[], weights[], num[], tau)     # adj and num respectively
indicate the geo-codes and number of all neighbors of every villages
    for(k in 1:sumNumNeigh) {      # sumNumNeigh is the sum of neighbors of all
villages
        weights[k] <- 1
    }
# Other priors:
    alpha0   ~ dflat()
    alpha1 ~ dnorm(0.0, 1.0E-5)
    tau   ~ dgamma(0.5, 0.0005)                     # prior on precision
    sigma <- sqrt(1 / tau)                  # standard deviation
   b.mean <- sum(b[])
}
```

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