▸ **INTERNATIONAL PERSPECTIVES**

Although most of the information presented in the Journal refers to situations within the United States, environmental health and protection know no boundaries. The Journal periodically runs International Perspectives to ensure that issues relevant to our international constituency, representing over 60 countries worldwide, are addressed. Our goal is to raise diverse issues of interest to all our readers, irrespective of origin.

Arsenic Levels in the Soil and Risk of Birth Defects: A Population-Based Case-Control Study Using GIS Technology

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Abstract **Arsenic is a highly dangerous metal that has been linked to a number of adverse health effects in both adults and children, including birth defects. Yet few epidemiologic studies have examined the relationship between arsenic levels in the soil and the risk of birth defects. The purpose of the authors' study was to examine this association among people exposed to environmental pollution in a developed area of China. The authors used global positioning system to locate the coordinates of 80 villages in 40 towns for soil sampling. Soil samples were analyzed for arsenic content. Logistic regression was used to investigate the relationship between exposure to arsenic and birth defects, controlling for potentially confounding factors. The authors found that exposure to arsenic in any amount increased the risk of birth defects. The positive association found between arsenic exposure and birth defects warrants further study, and future large-scale population-based studies are needed with an emphasis on individual-level exposure and confounding variables.**

Introduction

Arsenic is a widely distributed metalloid occurring in rock, soil, water, and air. It is usually considered along with lead, cadmium, and mercury as a threat to human health (Jarup, 2003). The effects of arsenic on human health are regularly reviewed by international bodies such as the World Health Organization. People are exposed to arsenic mainly through food and drinking water (World Health Organization [WHO], 2009). In some areas, drinking water is a significant source of exposure to inorganic arsenic, which is harmful to health (Lee, Jang, Wang, & Liu, 2007).

Established risk factors for birth defects associated with heredity or environment are very difficult to filter out clearly. Environmental risk factors, such as chemicals, toxins, and environmental pollution, account for varying prevalence of birth defects in different regions (An & Fu, 1995; Bhatt, 2000; Garry et al., 2002; Hutz, Carvan, Baldridge, Conley, & Heiden, 2006; Shaw et al., 2001). Early intervention, including accurate diagnosis and a clear understanding of cause, is important for ameliorating the consequences of birth defects (International Birth Defects Information Systems, 2009). Considerable interest has focused recently on the role of environmental contaminants (e.g., heavy metals such as arsenic, lead, and cadmium) in causing birth defects, although their explicit links are still unknown (Bound, Harvey, Francis, Awwad, & Gatrell, 1997; Sever, 1995; Shalat, Walker, & Finnell, 1996; Vinceti et al., 2008; Wigle et al., 2007).

Some studies suggest that arsenic may be teratogenic. Arsenic received during gestation induces neural tube defects in several animal models (Carpenter, 1987; Ferm & Hanlon, 1986; Morrissey & Mottet, 1983). But the relationship between arsenic exposure and birth defects is less clear (WHO, 2001). Most research has assessed the risk to population health of contamination by arsenic and other trace elements in water (Luu, Sthiannopkao, & Kim, 2009). But in developed regions with sufficient water decontamination and treatment facilities, exposure to arsenic in drinking water should be obviated. For example, Wuxi County, which we examined for our study, is located in the geographic center of the Yangtze River Delta. In 2002, Wuxi County ranked ninth among 35 major cities of China in terms of gross domestic product (People's Government of Wuxi, 2003). Air pollution in this area is not excessive, but water pollution is very serious and has a negative effect on population health. In some parts of the region, people use bottled water for drinking. Although water pollution due to industry and pesticide use in rural villages affects child development and the reproductive health of women (Song & Chen, 2007), the greatest source of

FIGURE 1

The Distribution of Villages and Soil Sample Locations

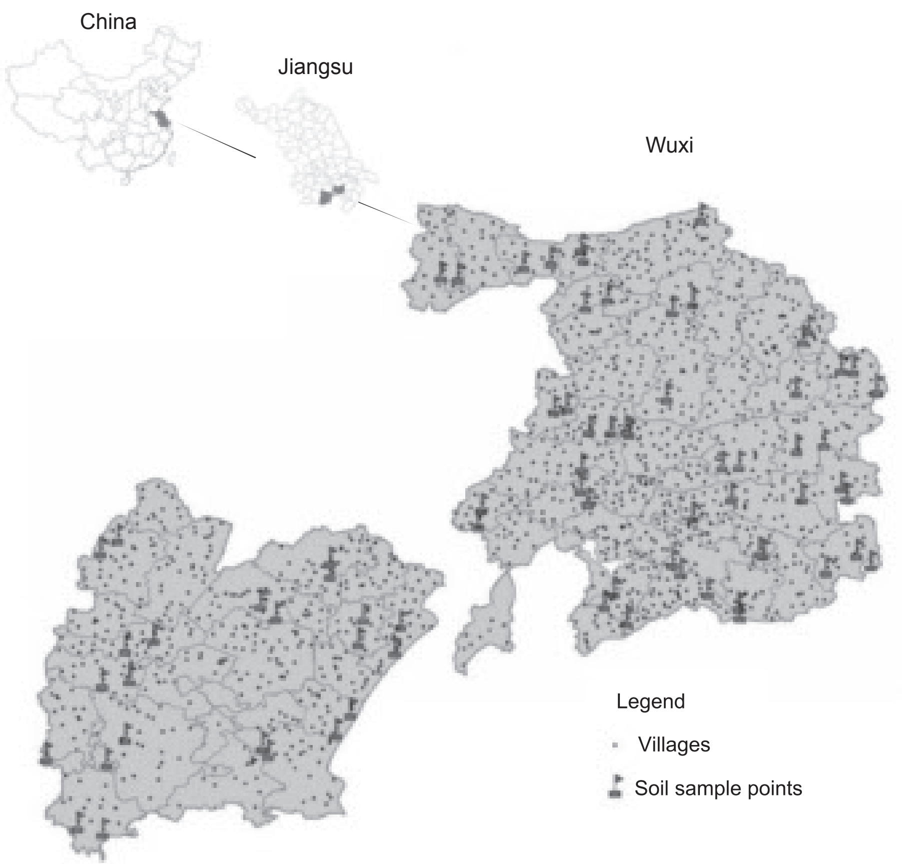

TABLE 1

Demographic Characteristics of Cases and Controls in the Wuxi Area, 2002–2004

Characteristic	Cases (254)		Controls (1183)	
	n	%	*n*	%
Residence				
Rural	156	61.4	579	48.9
Urban	98	38.6	604	51.1
Age				
<25	161	63.4	770	65.1
25–29	78	30.7	372	31.4
30+	15	5.9	41	3.5
Education				
Less than high school	124	48.8	424	35.8
High school	90	35.4	546	46.2
College or more	40	15.8	213	18.0

exposure to arsenic among the people living in Wuxi might be the soil in which they grow their vegetables.

Contaminated soil is a potential source of arsenic exposure (WHO, 2001). But to date, few epidemiologic studies have examined the relationship between arsenic levels in the soil and the risk of birth defects. Therefore, we performed a population-based case-control study focusing on birth defects in Wuxi, a developed region of China characterized by high environmental pollution.

Methods

Study Area

Given its well-developed economy, Wuxi County has a systematic health care system. Birth defects have been monitored in Wuxi since the national survey of birth defects in 1987 (Chen, 2001; Wang, 2005; Zhang, 1997). The prevalence of birth defects in this region is about 5% higher than in developed countries, and the number is increasing in trends (Song & Chen, 2007). Hot-spot analysis with spatial statistics has indicated that pollution is one of the most likely risk factors for birth defects (Wu et al., 2008).

We measured levels of contamination in soil samples from 80 villages in 40 towns in Wuxi County. The soil sampling villages were chosen with two-step selecting. First, there are 96 town-level administrative units in the study area and 31 of them are urban, without cultivated lands. We ordered the other 65 towns according to their population and birth numbers. Forty towns were selected by an interval sampling method. Then within the selected towns, we used a random sampling method to choose two villages for soil sample collection in their cultivated land. Figure 1 shows the distribution of the sample locations and villages. Arsenic levels in the soil samples were measured using inductively coupled plasma quadrupole mass spectrometry as described in Zhang and co-authors (2007).

Selection of Cases and Controls

The data used in our study were collected for a retrospective survey of mothers conducted in 2005 in Wuxi. All respondents were pregnant women who had given birth (stillbirths or live births) in various hospitals in Wuxi from 2002 to 2004, who were residents of

Wuxi, and whose gestational period had been more than 28 weeks. The case group consisted of 254 women whose pregnancies had been affected by birth defects as detected from 28 weeks gestation to seven days after birth by the birth defects monitoring system. The controls were 1,183 women who had had normal live births over the same period (2002–2004). The controls were selected from a representative sample obtained using multistage sampling methods composed of simple sampling and cluster random sampling from 72,232 total births in the same period. After the exclusion of stillbirths, infants born with fetal birth defects, infants who died within seven days of birth, infants with low birth weight, and other abnormal births, 1,183 controls remained. Data were collected through use of a face-to-face questionnaire survey. Mother's residence (urban or rural), age, and education were control variables. Table 1 shows demographic data for cases and controls.

Arsenic Modeling

In general, arsenic has several different pathways of exposure to humans, such as through air, drinking water, and food (meat, fish, and poultry) (Balakumar & Kaur, 2009). Among those, drinking water is a main pathway for arsenic exposure to humans. As Wuxi region is a developed area with heavy pollution in the water (Na, Fang, Zhanqi, Ming, & Cheng, 2006), however, most people living there are used to drinking bottled water from other regions. So it is very hard to measure the association between the quality of drinking water and health effects.

After a careful survey, we found that people living there still have vegetables and rice planted in their cultivated land for food. Therefore we thought this could be a main pathway of exposure of arsenic to people in our study area. Although the arsenic content in the soil samples had been measured accurately (Zhang et al., 2007), individual exposure was not measured but rather estimated from exposure level zones based on predicted concentrations. In our current study we used the Kriging model in the geostatistical modules of ArcGIS 9.2 (Environmental Systems Research Institute, Inc.) to interpolate arsenic levels based on the geocoded sampled data. The Kriging model was originally developed for use in the field of geology and

FIGURE **2**

Levels of Arsenic in the Soil and Rude Birth Defect Rates

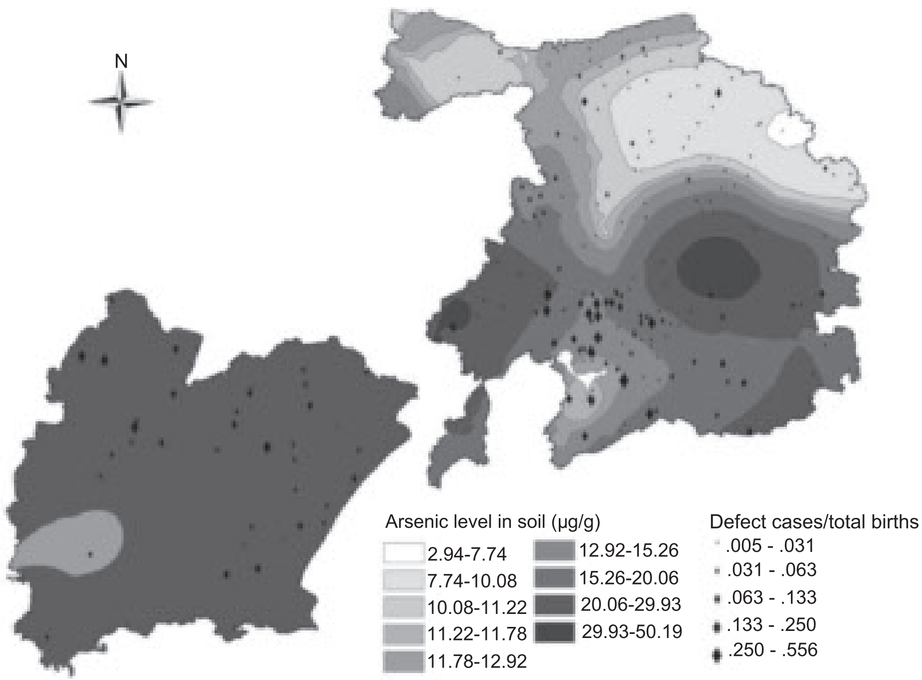

TABLE **2**

Odds Ratios (*OR*) and 95% Confidence Intervals (*CI*) of Birth Defect Risk by Multivariable Logistic Regression Analysis

Characteristic	*B*[a]	SE	*OR*	95% *CI*	Significance
Residence					
Rural	–	–	1.00	–	.000
Urban	–0.531	.168	0.59	0.42–0.82	.002
Age					
<25	–	–	1.00	–	.200
25–29	0.034	.168	1.03	0.75–1.44	.841
30+	0.602	.336	1.83	0.95–3.53	.073
Education					
Less than high school	–	–	1.00	–	.067
High school	–0.388	.167	0.68	0.49–0.94	.020
College or more	–0.242	.237	0.79	0.49–1.25	.307
Arsenic level in the soil (μg/g)					
Low (<12.9)	1.667	.224	5.294	3.41–8.22	.000
Intermediate (12.91–15.1)	–0.044	.245	0.957	0.12–0.29	.000
High (15.11–20.0)	0.238	.211	1.269	0.17–0.35	.000
Very high (>20.01)	–	–	1.00	–	.000

[a]Coefficient of logistic regression analysis.

has since been applied to the study of geography, soil science, and public health (Berke, 2004; Goovaerts, 2006). Figure 2 shows the predicted arsenic levels in the soil in this region and the rude birth defect rates (i.e., with the number of birth defects as the numerator and the total number of births in the same village and period as the denominator). We divided exposure levels into four categories: low (<12.90 μg/g), intermediate (12.91–15.10 μg/g), high (15.11–20.0 μg/g), and very high (>20.01 μg/g). According to China National Standard GB 15618-1995 for the environmental quality of soils, the natural background value of arsenic content in soil is about 15.0 mg/kg (Ministry of Environmental Protection of the People's Republic of China, 1996).

The respective contours of these interpolated levels of arsenic content were digitized and contoured onto the surface of the map using GIS technology. We overlaid a map of the villages onto the interpolated maps to determine the category of each village. From the village codes, we obtained an exposure classification for each case and control.

Statistical Analysis

We calculated crude and adjusted odds ratios and 95% confidence intervals (*CI*) around these estimates to assess the relationship between the estimated maternal exposure to arsenic in soil and the occurrence of birth defects. Logistic regression using SPSS 12.0 was used to adjust the odds ratios for potentially confounding variables: residence (urban or rural), age (younger than 25, 25–29, or 30 or older), and education (less than high school, high school, or college or more) (Table 1).

Results

From 2002 to 2004, a total of 254 cases and 1,183 controls were identified with addresses that enabled geocoding to a soil exposure category. We used conditional logistic regression to calculate odds ratios given residence, age, and education as control variables. Table 2 shows the distributions of birth defect cases by maternal factors and soil arsenic exposure category.

Women living in urban areas had 0.59 times less risk (95% *CI*, 0.42–0.82) than women in rural areas of having a child with a birth defect. Compared to women younger than 25, those 30 and older had a 1.83 times greater risk (95% *CI*, 0.95–3.53) of having a child with a birth defect. Better-educated mothers had less risk, as they usually have more knowledge of health care and available resources. Mothers with a college education or more were 0.79 times less likely than those with less than a high school education to have a child with a birth defect.

Although a significant statistical relationship existed between arsenic levels in the soil and the risk of birth defects, mothers living in areas of low exposure had about 5.3 times higher risk (95% *CI*, 3.41–8.22) of having a child with a birth defect than those living in areas with very high exposure. This indicates that low arsenic content in the soil tends to be neglected more than high levels (Shalat et al., 1996). That is, high levels of arsenic in the soil usually show harmful effects to people's health clearly while low levels of it might be treated with indifference. But a low level of arsenic in the soil has the same poisonous effects after long-term exposure.

Discussion and Conclusion

Overall, our results provide evidence for an association between the level of arsenic in the soil and the risk of birth defects. In our study area, however, the statistical results show that higher arsenic content is not associated with a higher risk of birth defects. This fact might be caused by the local people's awareness about environmental health. Wuxi is a developed region in China with many small industrial enterprises in towns that have brought heavy pollution to the local environment. Those industries have even brought a drinking water crisis in this area (Qin et al., 2010). People living in Wuxi have been paying increasing attention to drinking water and health (Liu & Qu, 2009; Zhang et al., 2010). But low-level arsenic in the soil is easily neglected because of the less direct effect on people's health. Yet with long-term exposure to low levels of arsenic, people there have a higher risk of birth defects.

Our study has a number of strengths. It is a population-based study and involves cases and controls randomly selected from among mothers residing in a defined geographic area. The variables analyzed are reliable characteristics of pregnant women. The use of the Kriging model and GIS tools such as geocoding enabled us to interpolate the sampled data to the whole area to generate arsenic exposure levels, which meant we did not have to measure each individual's unique level of exposure. This method has been used previously in epidemiologic studies to facilitate the analysis of relationships between health data and putative covariates that are typically measured over different spatial supports (Berke, 2004; Goovaerts, 2006). Further study is needed, however, to show that individuals' exposure to arsenic in the soil is a pathway for adverse health effects and a higher risk of birth defects.

The nearly 5-to-1 case-control matching (usually considered to be a good trade-off in terms of statistical power) resulted in fairly precise relative risk estimates. Although some results are opposite of our expectations, the findings confirm the association between exposures to arsenic and effects on reproductive health such as birth defects. Another study showed that women who work or live near metal smelters and near toxic waste sites and incinerators may have an increased risk of miscarriage or stillbirth (Brender et al., 2006). Note, however, that this claim is based entirely on the extensive animal literature, as no corresponding human data are available (Golub, 1994).

Some animal models have proven the teratogenic effects of arsenic on both maternal and embryonic glucose levels and thus the contributory effect on neural tube defects (Hill, Wlodarczyk, Mitchell, & Finnell, 2009). Other research suggests that exposure to even low levels of arsenic during a sensitive time in fetal development can result in birth defects such as spina bifida (Dummer, Dickinson, & Parker, 2003; Wlodarczyk, Bennett, Calvin, & Finnell, 1996). In our study area, environmental management had been carried out on those small-level industrial enterprises for heavy pollution (Qin et al., 2010). Low-level environmental pollution should also be carefully investigated. For example, some pesticides containing organic arsenicals, such as zinc methylarsonate, calcium methanearsonic acid, Tuzet, and others that had been used in this area for rice planting, will bring arsenic into the environment, and this includes the soil of cultivated land. As a high-prevalence area of neutral tube defects (Li et al., 2005; Wu et al., 2008), those pollutions should also be investigated more.

Despite these strengths, our study also has some limitations worth noting. This study was of mixed individual/ecological design, with cases and controls linked to arsenic exposure levels at the village scale. Thus, we set the centers of the villages as the locations of the cases and controls and in this way assigned exposure categories to the participants; therefore, differential exposure and misclassification of individuals cannot be ruled out.

People who live in areas with higher levels of arsenic in the soil are usually more careful about the foods they eat and the drinking water they consume. While surveying, we found that many families had decontamination equipment on the taps from which they got their drinking water. Moreover, low levels of arsenic in the soil usually indicate few nearby enterprises and slow economic development; socioeconomic level also has an effect on the risk of birth defects in this region (Chen, Li, Pei, Zhang, & Zheng, 2008). In addition, many other known risk factors for birth defects exist, including individual behaviors such as smoking, which we were unable to include in our analyses at present. Further studies should also pay more attention to those factors.

Moreover, our study considered a possible threshold effect of arsenic exposure from soil and did not examine dose-response relationships and the exposure routes of arsenic to human health. The relationship between chronic health effects and arsenic exposure has been well proven (Yoshida, Yamauchi, & Fan Sun, 2004). To obtain more precise information about this threshold level, future work needs to include more cases and controls to maintain statistical power.

In conclusion, our study is consistent with existing case-control studies that have found an association between risk of birth defects and socioeconomic factors such as maternal residence, age, education, and exposure to arsenic. The positive association between the level of arsenic in soil and risk of birth defects warrants further study in other regions and populations potentially exposed to arsenic. The small number of cases and controls in this study precludes the consideration of more variables and detailed classifications. When speculating about the effects of arsenic exposure on the risk of birth defects, we must also keep in mind individual and socioeconomic confounding. To obtain new insights into the association between arsenic and the risk of birth defects, future large-scale population-based studies are needed that include assessments of more maternal and parental characteristics, environmental exposures and routes, individual behaviors, and socioeconomic factors. A follow-up investigation in this region should also be considered to discover more about the pathways of exposure and confounding of individual behaviors. Finally, the association found between the level of arsenic in the soil and risk of birth defects warrants further study to understand arsenic in soil and which health effects, if any, in this process might render exposed women more at risk for children with birth defects.

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